HEPATOLOGY

A clinical textbook

Wedemeyer, Mauss, Berg, Keitel, Rockstroh, Sarrazin

11th Edition **2024–2025**

Wedemeyer, Mauss, Berg, Keitel, Rockstroh, Sarrazin

Hepatology – A clinical textbook

Eleventh Edition, 2024-2025

HEPATOLOGY

A clinical textbook

11th Edition **2024–2025**

Editors

Heiner Wedemeyer

Stefan Mauss

Thomas Berg

Verena Keitel

Jürgen Rockstroh

Christoph Sarrazin

Disclaimer

Hepatology is an ever-changing field. The editors and authors of Hepatology – A Clinical Textbook have made every effort to provide information that is accurate and complete as of the date of publication. However, in view of the rapid changes occurring in medical science, as well as the possibility of human error, this book may contain technical inaccuracies, typographical or other errors. Readers are advised to check the product information currently provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating physician who relies on experience and knowledge about the patient to determine dosages and the best treatment for the patient. The information contained herein is provided "as is" and without warranty of any kind. The editors disclaim responsibility for any errors or omissions or for results obtained from the use of information contained herein.

Design: Hanno Schaaf | Schaafkopp.de

Foreword

11th Edition (2024–2025)

Liver diseases remain **dramatically underestimated worldwide.** At some point in life, almost everyone will experience **elevated liver enzymes,** and millions of people are affected by **abnormalities in ALT or AST levels.** More than **100 million individuals** globally are living with **liver cirrhosis,** highlighting the enormous burden of liver diseases on healthcare systems. Despite these staggering numbers, awareness of liver diseases remains low, and many patients are diagnosed only at advanced stages when therapeutic options are limited.

In recent years, **hepatology has undergone profound transformations,** with rapid progress in both **therapeutic and diagnostic advancements.** The introduction of **novel antiviral therapies for hepatitis B, C and D, targeted treatments for liver and bile-duct cancer, and innovations in metabolic and autoimmune liver diseases** has reshaped the field. Furthermore, **personalized medicine and non-invasive diagnostic tools** have revolutionized clinical practice, enabling earlier and more precise disease detection and management. These developments emphasize the need for **up-to-date, comprehensive educational resources** to support clinicians in making informed decisions for their patients.

Against this backdrop, we are pleased to continue the success of the **Hepatology – A clinical textbook,** now in its **11th edition (2024–2025).** This latest volume once again provides **a complete overview of the most recent developments** across the entire spectrum of hepatology, covering **viral hepatitis, steatotic liver disease (SLD), rare liver diseases, cirrhosis-related complications, and hepatocellular carcinoma (HCC).** The continuous evolution of the textbook reflects the dynamic nature of the field and ensures that it remains a **reliable and relevant reference** for clinicians, researchers, and students.

This edition is the result of a **collaborative effort by numerous internationally renowned experts** from leading hepatology centers in Germany and beyond. Their expertise and dedication have made it possible to **update existing chapters and contribute entirely new sections,** ensuring that this textbook remains an essential resource for those dedicated to the care of patients with liver diseases.

We extend our **deepest gratitude** to all contributors for their commitment to this project. We hope that this new edition will serve as a **trusted guide** in clinical hepatology and contribute to **improving patient care worldwide.**

Again, the book is available as a free download at
www.hepatologytextbook.com

The Editors

Heiner Wedemeyer
Thomas Berg
Jürgen Rockstroh
Stefan Mauss
Verena Keitel
Christoph Sarrazin

Preface of the first edition

Hepatology is a rapidly evolving field that will continue to grow and maintain excitement over the next few decades. Viral hepatitis is not unlike HIV 10 or 15 years ago. Today, hepatitis B viral replication can be suppressed by potent antiviral drugs, although there are risks regarding the emergence of resistance. Strategies to enhance the eradication rates of HBV infection still need to be developed. On the other hand, hepatitis C virus infection can be eradicated by treatment with pegylated interferon plus ribavirin, although the sustained virologic response rates are still suboptimal, particularly in those infected with genotype 1. Many new antiviral drugs, especially protease and polymerase inhibitors, are currently in clinical development, and the data from trials reported over the last few years provide optimism that the cure rates for patients with chronic hepatitis C will be enhanced with these new agents, and even that all-oral regimens are around the corner! In other areas of hepatology, e.g., hereditary and metabolic liver diseases, our knowledge is rapidly increasing and new therapeutic options are on the horizon.

In rapidly evolving areas such as hepatology, is the book format the right medium to gather and summarise the current knowledge? Are these books not likely to be outdated the very day they are published? This is indeed a challenge that can be convincingly overcome only by rapid internet-based publishing with regular updates. Another unmatched advantage of a web-based book is the free and unrestricted global access. Viral hepatitis and other liver diseases are a global burden and timely information is important for physicians, scientists, patients and health care officials all around the world.

The editors of this web-based book – Thomas Berg, Stefan Mauss, Jürgen Rockstroh, Christoph Sarrazin and Heiner Wedemeyer – are young, bright, and internationally renowned hepatologists who have created an excellent state-of-the-art textbook on clinical hepatology. The book is well-written and provides in-depth information without being lengthy or redundant. I am convinced that all five experts will remain very active in the field and will continue to update this book regularly as the science progresses. This e-book should rapidly become an international standard.

Stefan Zeuzem – Frankfurt, Germany, January 2009

Therapeutic options and diagnostic procedures in hepatology have quickly advanced during the last decade. In particular, the management of viral hepatitis has completely changed since the early nineties. Before nucleoside and nucleotide analogues were licensed to treat hepatitis B and before interferon α + ribavirin combination therapy were approved for the treatment of chronic hepatitis C, very few patients infected with HBV or HCV were treated successfully. The only option for most patients with end-stage liver disease or hepatocellular carcinoma was liver transplantation. And even if the patients were lucky enough to be successfully transplanted, reinfection of the transplanted organs remained major challenges. In the late eighties and early nineties discussions were held about rejecting patients with chronic hepatitis from the waiting list as posttransplant outcome was poor. Today, just 15 years later, hepatitis B represents one of the best indications for liver transplantations, as basically all reinfection can be prevented. In addition, the proportion of patients who need to be transplanted is declining – almost all HBV-infected patients can nowadays be treated successfully with complete suppression of HBV replication and some well-selected patients may even be able to clear HBsAg, the ultimate endpoint of any hepatitis B treatment.

Hepatitis C has also become a curable disease with a sustained response of 50–80% using pegylated interferons in combination with ribavirin. HCV treatment using direct HCV enzyme inhibitors has started to bear fruit (we draw your attention to the HCV chapters).

Major achievements for the patients do sometimes lead to significant challenges for the treating physician. Is the diagnostic work-up complete? Did I any recent development to evaluate the stage and grade of liver disease? What sensitivity is really necessary for assays to detect hepatitis viruses? When do I need to determine HBV polymerase variants, before and during treatment of hepatitis B? When can I safely stop treatment without risking a relapse? How to treat acute hepatitis B and C? When does a health care worker need a booster vaccination for hepatitis A and B? These are just some of many questions we have to ask ourselves frequently during our daily routine practice. With the increasing number of publications, guidelines and expert opinions it is getting more and more difficult to stay up-to-date and to make the best choices for the patients. That is why Hepatology – A Clinical Textbook is a very useful new tool that gives a state-of-the art update on many aspects of HAV, HBV, HCV, HDV and HEV infections. The editors are internationally-known experts in the field of viral hepatitis; all have made significant contributions to understanding the pathogenesis of virus-induced liver disease, diagnosis and treatment of hepatitis virus infections.

Hepatology – A Clinical Textbook gives a comprehensive overview on the epidemiology, virology, and natural history of all hepatitis viruses including hepatitis A, D and E. Subsequent chapters cover all major aspects of the management of hepatitis B and C including coinfections with HIV and liver transplantation. Importantly, complications of chronic liver disease such as hepatocellular carcinoma and recent developments in assessing the stage of liver disease are also covered. Finally, interesting chapters on autoimmune and metabolic non-viral liver diseases complete the book.

We are convinced that this new up-to-date book covering all clinically relevant aspects of viral hepatitis will be of use for every reader. The editors and authors must be congratulated for their efforts.

Michael P. Manns – Hannover, January 2009

Contributing Authors

Julian Allgeier
Medical Department and Polyclinic II
Ludwigs Maximilians University
Munich, Germany
julian.allgeier @med.uni-muenchen.de

Akif Altinbas
Department of Medicine
UConn Health
University of Connecticut
Farmington, USA
altinbas@uchc.edu

Matthias J. Bahr
Ammerland-Klinik GmbH
Academic Educational
Hospital for MHH
Westerstede, Germany
matthias.bahr@ammerland-klinik.de

Heike Bantel
Department of Gastroenterology,
Hepatology, Infectious Diseases and
Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
bantel.heike@mh-hannover.de

Lea Marie Bartsch
Department of Gastroenterology,
Hepatology, Infectious Diseases and
Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
bartsch.leamarie@mh-hannover.de

Patrick Behrendt
Department of Gastroenterology,
Hepatology, Infectious Diseases and
Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
behrendt.patrick@mh-hannover.de

Thomas Berg
Medical Department II
University of Leipzig
Leipzig, Germany
thomas.berg@medizin.uni-leipzig.de

Christoph Boesecke
Department of Medicine I
University Hospital Bonn
Bonn, Germany
christoph.boesecke@ukb.uni-bonn.de

Kathrin van Bremen
Medical Care Center for Internal Medicine
Cologne, Germany
kathrin.vanbremen@ukbonn.de

Ali Canbay
Department of Internal Medicine
University Hospital
Knappschaftskrankenhaus Bochum
Ruhr University Bochum
Bochum, Germany
ali.canbay@ruhr-uni-bochum.de

Markus Cornberg
Department of Gastroenterology,
Hepatology, Infectious Diseases and
Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
cornberg.markus@mh-hannover.de

Katja Dinkelborg
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
dinkelborg.katja@mh-hannover.de

Ursula Ehmer
Department and Polyclinic of Internal Medicine II
Technical University of Munich
Munich, Germany
ursula.ehmer@mri.tum.de

Andreas Geier
Medical Department and Polyclinic II
University of Würzburg
Würzburg, Germany
geier_a2@ukw.de

Juliana Gödiker
Medical Department B
University of Münster
Münster, Germany
juliana.goediker@ukmuenster.de

Christiana Graf
Medical Department and Polyclinic II
Ludwigs Maximilians University
Munich, Germany
christiana.graf@med.uni-muenchen.de

Marie Griemsmann
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
griemsmann.marie@mh-hannover.de

Katharina Hupa-Breier
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
hupa.katharina@mh-hannover.de

Verena Keitel-Anselmino
Department of Gastroenterology, Hepatology and Infectious Diseases
Otto von Guericke University
Magdeburg, Germany
verena.keitel-anselmino@med.ovgu.de

Theresa Kirchner
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
kirchner.theresa@mh-hannover.de

Andreas E. Kremer
Department of Gastroenterology and Hepatology
University of Zürich & University Hospital Zürich
Zürich, Switzerland
andreas.kremer@usz.ch

Christian M. Lange
Medical Department and Polyclinic II
Ludwigs Maximilians University
Munich, Germany
christian.lange@med.uni-muenchen.de

Benjamin Maasoumy
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
maasoumy.benjamin@mh-hannover.de

Jens U. Marquardt
Department of Medicine I
University Medical Center Schleswig-Holstein
Lübeck, Germany
jens.marquardt@uksh.de

Stefan Mauss
Center for HIV and Hepatogastroenterology
Düsseldorf, Germany
stefan.mauss@center-duesseldorf.de

Uta Merle
Department of Gastroenterology, Hepatology and Infectious diseases
University Hospital Heidelberg
Heidelberg, Germany
uta.merle@med.uni-heidelberg.de

Claus Niederau
Department of Internal Medicine
St. Josef Hospital
Oberhausen, Germany
claus.niederau@yahoo.de

Jörg Petersen
Liver Unit, IFI Institute for Interdisciplinary Medicine
Asklepios Klinik St Georg Hamburg
Hamburg, Germany
petersen@ifi-medizin.de

Sven Pischke
Department of Medicine I
University Medical Centre Hamburg-Eppendorf (UKE)
Hamburg, Germany
s.pischke@uke.de

Josef Pospiech
Department of Internal Medicine
University Hospital
Knappschaftskrankenhaus Bochum
Ruhr University Bochum
Bochum, Germany
josef.pospiech@ruhr-uni-bochum.de

Michael Praktiknjo
Medical Department B
University of Münster
Münster, Germany
michael.praktiknjo@ukmuenster.de

Jürgen K. Rockstroh
Department of Medicine I
University Hospital Bonn
Bonn, Germany
juergen.rockstroh@ukb.uni-bonn.de

Heinrich Rodemerk
Medical Department II
University of Leipzig
Leipzig, Germany
heinrich.rodemerk@medizin.uni-leipzig.de

Elke Roeb
Department of Internal Medicine
Justus Liebig University & University Hospital Gießen
Gießen, Germany
elke.roeb@innere.med.uni-giessen.de

Lisa Sandmann
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
sandmann.lisa@mh-hannover.de

Christoph Sarrazin
Medical Department II
St. Josefs-Hospital Wiesbaden
Wiesbaden, Germany
CSarrazin@joho.de

Johannes Sauter
Medical Department and Polyclinic II
Ludwigs Maximilians University
Munich, Germany
johannes.sauter@med.uni-muenchen.de

Andrea Schneider
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
schneider.andrea@mh-hannover.de

Christian P. Strassburg
Medical Department and Polyclinic I
University Hospital Bonn
Bonn, Germany
christian.strassburg@ukbonn.de

Pavel Strnad
Medical Clinic III
University Hospital RWTH Aachen
Aachen, Germany
pstrnad@ukaachen.de

Richard Taubert
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
taubert.richard@mh-hannover.de

Jonel Trebicka
Medical Department B
University of Münster
Münster, Germany
jonel.trebicka@ukmuenster.de

Florian van Bömmel
Medical Department II
University of Leipzig
Leipzig, Germany
florian.vanboemmel@medizin.uni-leipzig.de

Michelle Walkenhaus
Medical Clinic III
University Hospital RWTH Aachen
Aachen, Germany
mwalkenhaus@ukaachen.de

Heiner Wedemeyer
Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology
Hannover Medical School (MHH)
Hannover, Germany
wedemeyer.heiner@mh-hannover.de

Tobias J. Weismüller
Department of Gastroenterology, Hepatology and Oncology
Vivantes Humboldt Hospital
Berlin, Germany
tobias.weismueller@vivantes.de

Table of Contents

1. Hepatitis A

Sven Pischke, Heiner Wedemeyer

Epidemiology

Hepatitis A virus (HAV) infections occur worldwide, either sporadically or in epidemic outbreaks (Van Damme 2023). An estimated 1.4 million cases of HAV infections occur each year. HAV is usually transmitted and spread via the fecal-oral route (Lemon 1985). Thus, infection with HAV occurs predominantly in areas of lower socio-economic status and reduced hygienic standards, especially in developing, tropical countries. Not surprisingly, a study investigating French children confirmed that travel to countries endemic for HAV is indeed a risk factor for anti-HAV seropositivity (Faillon 2012). But hepatitis is not only a travel disease, but also endemic in countries of the western world. In industrialised countries like the US or Germany the number of reported cases has decreased markedly in the past decades, according to official data published by the Centers for Disease Control and Prevention (CDC, Atlanta, USA) and the Robert Koch Institute (RKI, Berlin, Germany) (Figure 1). This decrease is mainly based on improved sanitary conditions and anti-HAV vaccination. Vaccination programmes have also resulted in fewer HAV infections in various endemic countries including Argentina, Brazil, Italy, China, Russia, Ukraine, Spain, Belarus, Israel and Turkey (Hendrickx 2008).

Despite of the overall decrease in the frequency of hepatitis A in industrialised countries HAV outbreaks still occur. For example, HAV outbreaks have been described both in Europe and the US that were linked to frozen berries (Guzman Herrador 2014, Fitzgerald 2014) or imported pomegranate arils (Collier 2014).

HAV is transmitted fecal-orally either by person-to-person contact or ingestion of contaminated food or water. Usually HAV infection is restricted to humans and hepatitis A is no zoonosis. However, recently experimental HAV infection of pigs has been demonstrated (Song 2015, Migueres 2021).

Five days before clinical symptoms appear, the virus can be isolated from the feces of patients (Dienstag 1975). The hepatits A virus stays detectable in the feces up to two weeks after the onset of jaundice. Fecal excretion of HAV up to five months after infection can occur in children and immunocompromised persons. A recent study from Brasil evaluated the risk of household HAV transmission within a cohort of 97 persons from 30 families (Rodrigues-Lima 2013). Person-to-person transmission was seen in

six cases indicating a relevant risk for relatives of patients with hepatitis A. On the other hand, there was no evidence of HAV transmission in another incident by an HAV-infected foodhandler in London (Hall 2014). Further studies are necessary to evaluate the use of HAV vaccination of relatives at risk in this setting.

Risk groups for acquiring an HAV infection in Western countries are health care providers, military personnel, psychiatric patients and men who have sex with men. Parenteral transmission by blood transfusion has been described but is a rare event. Mother-to-fetus transmission has not been reported (Tong 1981). Distinct genetic polymorphisms including variants in ABCB1, TGFB1, XRCC1 may be associated with a susceptibility to HAV (Zhang 2012).Regarding the severity of HAV infections an uncommon phenomenon has been described: it has been shown that the number of reported HAV infections in the USA decreased from 6 cases/ 100000 in 1999 to 0.4 cases/ 100000 in 2011 while the percentage of hospitalisations due to hepatitis A increased from 7.3% to 24.5% indicating that hepatitis A is getting rare but is causing still severe courses, particularly in elderly and patients with underlying liver diseases (Ly 2015).

Virology and diagnostics

Hepatitis A is an inflammatory liver disease caused by infection with the hepatitis A virus (HAV) (Van Damme 2023). HAV is a single-stranded 27 nm non-enveloped, icosahedral RNA virus, which was first identified by immune electron microscopy in 1973 (Feinstone 1973). The virus belongs to the hepadnavirus genus of the Picornaviridae. Recent structure-based phylogenetic analysis placed HAV between typical picornavirus and insect picorna-like viruses (Wang 2014). HAV uses host cell exosome membranes as an envelope which leads to protection from antibody mediated neutralisation (Feng 2013). Of note, only blood but not bile HAV shows host-derived membranes.

Seven different HAV genotypes have been described, of which four are able to infect humans (Lemon 1992).

The positive-sense single-stranded HAV RNA has a length of 7.5 kb and consists of a 5' non-coding region of 740 nucleotides, a coding region of 2225 nucleotides and a 3' non-coding region of approximately 60 nucleotides.

Acute hepatitis A is associated with a limited type I interferon response (Lanford 2011), which may be explained by cleavage of essential adaptor proteins by an HAV protease-polymerase precursor (Qu 2011). A dominant role of CD4+ T cells to terminate HAV infection has been established in HAV infected chimpanzees (Zhou 2012). However, in humans strong HAV-specific CD8 T cells have also been described, potentially contributing to resolution of infection (Schulte 2011). A failure to maintain these HAV-specific T cell responses could increase the risk for relapsing hepatitis A.

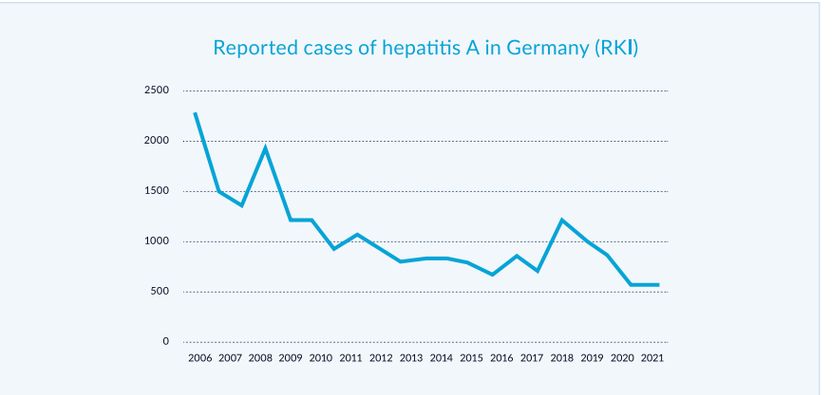

Figure 1. Number of reported cases of HAV infections in Germany over the last two decades (Source: Robert Koch Institut through 04/2023)

Diagnosis of acute HAV infection is based on the detection of anti-HAV IgM antibodies or HAV RNA. The presence of HAV IgG antibodies can indicate acute or previous HAV infection. HAV IgM and IgG antibodies also become positive early after vaccination, with IgG antibodies persisting for at least two to three decades after vaccination. Available serological tests show a very high sensitivity and specificity. Recently, a study from Taiwan revealed that HIV-infected patients develop protective antibody titres after HAV vaccination less frequently than healthy controls (Tseng 2012). In addition a study examining the immune response to HAV vaccination in 282 HIV-infected patients (Mena 2013) demonstrated that male sex or HCV coinfection were associated with lower response rates. The clinical relevance of these findings needs to be investigated in further studies.

A large study investigatied 183 adolescents (age 15- 16 years) who had initiated a two-dose HAV vaccination at age of 6, 12 or 15 months. Within these subgroups patients who got the vaccine during the earlier childhood at an age of 6 months and patients who got passively transferred maternal anti-HAV antibodies but were vaccinated at month 12 or 15 had a lower likelihood of carrying anti-HAV antibodies at the age of 15 or 16 years (Spradling 2015). This study demonstrates that HAV vaccination should not be vaccinated against HAV before 12 months of age, which is in line with the US recommendations. Delayed seroconversion may occur in immunocompromised individuals, and testing for HAV RNA should be considered in immunosuppressed individuals with unclear hepatitis. HAV

RNA testing of blood and stool can determine if the patient is still infectious. However, it has to be kept in mind that various in-house HAV RNA assays may not be specific for all HAV genotypes and thus false negative results can occur.

Elevated results for serum aminotransferases and serum bilirubin can be found in symptomatic patients (Tong 1995). ALT levels are usually higher than serum aspartate aminotransferase (AST) in non-fulminant cases. Increased serum levels of alkaline phosphatase and gamma-glutamyl transferase indicate a cholestatic form of HAV infection. The increase and the peak of serum aminotransferases usually precede the increase of serum bilirubin. Laboratory markers of inflammation, like an elevated erythrocyte sedimentation rate and increased immunoglobulin levels, can also frequently be detected.

Recently within a small pilot study, examining 10 patients with acute hepatitis A, saliva of HAV infected patients has been shown to contain HAV RNA in 8/10 (80%) and anti HAV IgM in 10/10 (100%) (Armado Leon 2014). The relevance of this finding and the potential value of testing of saliva needs to be studied in larger cohorts.

Natural process and surveillance

The clinical course of HAV infection varies strongly, ranging from asymptomatic, subclinical infections to cholestatic hepatitis or life-threatening fulminant liver failure (Figure 2) (Van Damme 2023).

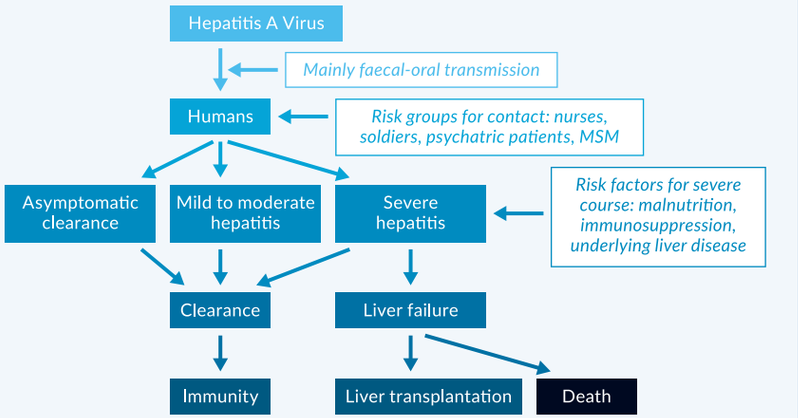

Figure 2. Possible courses of HAV infection

Most infections in children are either asymptomatic or unrecognised, while 70% of adults develop symptomatic hepatitis A with jaundice and hepatomegaly.

The incubation time ranges between 15 and 49 days with a mean of approximately 30 days (Koff 1992). Initial symptoms are usually non-specific and include weakness, nausea, vomiting, anorexia, fever, abdominal discomfort, and right upper quadrant pain (Lednar 1985). As the disease progresses, some patients develop jaundice, darkened urine, uncoloured stool and pruritus. The prodromal symptoms usually diminish when jaundice appears.

Approximately 10% of infections take a biphasic or relapsing course. In these cases the initial episode lasts about 3-5 weeks, followed by a period of biochemical remission with normal liver enzymes for 4-5 weeks. Relapse may mimic the initial episode of the acute hepatitis and complete normalisation of ALT and AST values may take several months. (Tong 1995). A recent investigation in two HAV-infected chimpanzees demonstrated that the CD4 count decreased after clinical signs of hepatitis A disappeared (Zhou 2012). Eventually an intrahepatic reservoir of HAV genomes that decays slowly in combination with this CD4 response may explain the second phase of disease, but further observations on human patients are required to verify this.

Cases of severe fulminant HAV infection leading to hepatic failure occur more often in patients with underlying liver disease (Patterson 2020). Conflicting data on the course of acute hepatitis A have been reported

for patients with chronic hepatitis C. While some studies showed a higher incidence of fulminant hepatitis (Vento 1998), other studies do not confirm these findings and even suggest that HAV superinfection may lead to clearance of HCV infection (Deterding 2006). Other risk factors for more severe courses of acute hepatitis A are age, malnutrition and immunosuppression. Severity of liver disease during acute hepatitis A has recently been shown to be associated with a distinct polymorphism in TIM1, the gene encoding for the HAV receptor (Kim 2011). An insertion of 6 amino acids at position 157 of TIM1 leads to more efficient HAV binding and greater NKT lytic activity against HAV infected liver cells.

In contrast to hepatitis E, there are no precise data on the outcome of HAV infection during pregnancy. Some data suggest an increased risk of gestational complications and premature birth (Elinav 2006).

HAV infection has a lethal course in 0.1% of children, in 0.4% of persons aged 15-39 years, and in 1.1% in persons older than 40 years (Lemon 1985). In contrast to the other fecal-orally transmitted hepatitis, hepatitis E, no chronic courses of HAV infection have been reported so far.

In contrast to other hepatitis virus infections extrahepatic manifestations are really uncommon in HAV (Pischke 2007). If they occur, they usually show an acute onset and disappear upon resolution of HAV infection in most cases. Possible extrahepatic manifestations of acute HAV infection are arthralgia, diarrhoea, renal failure, red cell aplasia, generalised lymphadenopathy, and pancreatitis. Arthralgia can be found in 11% of patients with hepatitis A.

Very uncommon are severe extrahepatic manifestations like pericarditis and/or renal failure. An association of hepatitis A with cryoglobulinaemia has been reported but is a rare event (Schiff 1992). Furthermore, cutaneous vasculitis can occur. In some cases, skin biopsies reveal anti-HAV-specific IgM antibodies and complements in the vessel walls (Schiff 1992). In contrast to hepatitis B or C, renal involvement is rare, and there are very few case reports showing acute renal failure associated with HAV infection (Pischke 2007). Recently it has been shown that approximately 8% of hepatitis A cases are associated with acute kidney injury (Choi 2011).

Therapy

There is no specific antiviral therapy for treatment of hepatitis A (Migueres 2021). However a *in vitro* analysis of a cell culture system for HAV infection revealed efficient inhibition of HAV replication by cyclosporin A and silibinin (Esser-Nobis 2015). The clinical value of this *in vitro* observation still needs to be determined.

A study from the Netherlands investigated the use of post-exposure HAV vaccination or prophylaxis with immunglobulins in patients with household contact with HAV. In this study none of the patients who received immunoglobulins developed acute hepatitis A in contrast to some patients who received the vaccine. The study revealed that HAV vaccination post-exposure might be a sufficient option in younger patients (<40 years) while older patients (>40 years) might benefit from immunglobulins (Whelan 2013). The disease usually takes a mild to moderate course, which requires no hospitalisation, and only in fulminant cases is initiation of symptomatic therapy necessary. Prolonged or biphasic courses should be monitored closely. HAV may persist for some time in the liver even when HAV RNA becomes negative in blood and stool (Lanford 2011), which needs to be kept in mind for immunocompromised individuals. Acute hepatitis may rarely proceed to acute liver failure; liver transplantation is required in few cases. In the US, 4% of all liver transplantations performed for acute liver failure were due to hepatitis A (Ostapowicz 2002). In a cohort of acute liver failures at one transplant centre in Germany approximately 1% of patients suffered from HAV infection (Hadem 2008). The outcome of patients after liver transplantation for fulminant hepatitis A is excellent. Timely referral to liver transplant centres is therefore recommended for patients with severe or fulminant hepatitis A.

References

Armado Leon La, de Almeida AJ, de Paula VS et al. Longitudinal Study of Hepatitis A Infection by Saliva Sampling: The Kinetics of HAV Markers in Saliva Revealed the Application of Saliva Tests for Hepatitis A Study. PLOS One 2015; 10(12)

Centers for Disease Control and Prevention. Viral Hepatitis Surveillance – United States 2010. Hepatitis A virus, http://www.cdc.gov/hepatitis/Statistics/index.htm, accessed 26 January 2013.

Choi HK, Song YG, Han SH, et al. Clinical features and outcomes of acute kidney injury among patients with acute hepatitis A. J Clin Virol 2011;52:192-7.

Collier MG, Khudyakov YE, Selvage D, et al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. Lancet Infect. Dis. 2014; 10: 976-981.

Deterding K, Tegtmeyer B, Cornberg M, et al. Hepatitis A virus infection suppresses hepatitis C virus replication and may lead to clearance of HCV. J Hepatol 2006;45:770-8.

Dienstag JL, Feinstone SM, Kapikian AZ, Purcell RH. Faecal shedding of hepatitis-A antigen. Lancet 1975;1:765-7.

Elinav E, Ben-Dov IZ, Shapira Y, et al. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. Gastroenterology 2006;130:1129-34.

Esser-Nobis K, Harak C, Schult P, et al. Hepatology 2015, 62: 397-408

Faillon S, Martinot A, Hau I, et al. Impact of travel on the seroprevalence of hepatitis A in children. J Clin Virol. 2013 Jan;56(1):46-51. doi: 10.1016/j.jcv.2012.10.004.

Feinstone SM, Kapikian AZ, Purceli RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. Science 1973;182:1026-8.

Feng Z, Hensley L, McKnight KL, Hu F, Madden V, Ping L, et al. A pathogenic picornavirus acquires an envelope by hijacking cellular membranes. Nature. 2013;496(7445):367-71.

Fitzgerald M, Thornton L, O'Gorman J, et al. Outbreak of hepatitis A infection associated with the consumption of frozen berries, Ireland, 2013 - linked to an international outbreak. Euro Surveill. 2014;19(43):pii=20942.

Guzman-Herrador B, Jensvoll L, Einöder-Moreno M, et al. Ongoing hepatitis A outbreak in Europe 2013 to 2014: imported berry mix cake suspected to be the source of infection in Norway . Euro Surveill. 2014;19(15):pii=20775.

Hadem J, Stiefel P, Bahr MJ, et al. Prognostic implications of lactate, bilirubin, and aetiology in German patients with acute liver failure. Clin Gastroenterol Hepatol 2008;6:339-45.

Hall V, Abrahams A, Tubitt D, et al. No evidence of transmission from an acute case of hepatitis E in a foodhandler: follow-up of almost 1000 potentially exposed individuals, Lonndon, United Kingdom, April 2012Euro Surveill. 2014; 19 (30)

Hendrickx G, Van Herck K, Vorsters A, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat 2008;15 Suppl 2:1-15.

Kim HY, Eyheramonho MB, Pichavant M, et al. A polymorphism in TIM1 is associated with susceptibility to severe hepatitis A virus

infection in humans. J Clin Invest. 2011;121:1111-8.

Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. Vaccine 1992;10 Suppl 1:S15-7.

Lanford RE, Feng Z, Chavez D, et al. Acute hepatitis A virus infection is associated with a limited type I interferon response and persistence of intrahepatic viral RNA. Proc Natl Acad Sci U S A 2011;108:11223-8.

Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. Am J Epidemiol 1985;122:226-33.

Lemon SM, Jansen RW, Brown EA. Genetic, antigenic and biological differences between strains of hepatitis A virus. Vaccine 1992;10 Suppl 1:S40-4.

Lemon SM. Type A viral hepatitis. New developments in an old disease. N Engl J Med 1985;313:1059-67.

Ly KN, Klevens RM. Trends in disease and complications of hepatitis A virus infection in the United States 199-2011: a new concern for adults. J. Infect. Dis. 2015, 58; 40-49

Mena G, García-Basteiro AL, Llupià A, Factors associated with the immune response to hepatitis A vaccination in HIV-infected patients in the era of highly active antiretroviral therapy. Vaccine. 2013;12;31(36):3668-74.

Migueres M, Lhomme S, Izopet J. Hepatitis A: Epidemiology, High-Risk Groups, Prevention and Research on Antiviral Treatment. Viruses. 2021;13(10):1900.

Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947-54.

Patterson J, Hussey HS, Silal S, et al. Systematic review of the global epidemiology of viral-induced acute liver failure. BMJ Open. 2020;10(7):e037473.

Pischke S, Vogel A, Jaeckel E, Manns MP. Immunopathogenesis of Extrahepatic Manifestations in HAV, HBV, and HCV Infections. In: Liver Immunology. Totowa, New Jersey: Humana Press, 2007:209-17.

Rodrigues-Lima L, De Ameilda AJ, dos Santos Tourinho R, et al. Evidence of Hepatitis A Virus Person-to-Person Transmission in Household Outbreaks. PLOS One 2013, Vol. 9, Issue 7.

Qu L, Feng Z, Yamane, et al. Disruption of TLR3 signaling due to cleavage of TRIF by the hepatitis A virus protease-polymerase processing intermediate, 3CD. PLoS Pathog. 2011 Sep;7(9):e1002169.

Schiff ER. Atypical clinical manifestations of hepatitis A. Vaccine 1992;10 Suppl 1:S18-20.

Schulte I, Hitziger T, Giugliano S, et al. Characterisation of CD8+ T-cell response in acute and resolved hepatitis A virus infection. J Hepatol. 2011;54:201-8.

Song YJ, Park WJ, Park BJ, et al. J. Med. Virol. 2015, epub ahead of print

Spradling PR, Bulkow LR, Negus SE, et al. Persistence of seropositivity among persons vaccinated for hepatitis A during infancy by maternal antibody status: 15 year follow-up- Hepatology 2015, epub ahead of print

Tseng YT, Chang SY, Liu WC, et al. Comparative effectiveness of two doses versus three doses of hepatitis a vaccine in HIV-infected and HIV-uninfected men who have sex with men. Hepatology. 2012 Dec 19. doi: 10.1002/hep.26210. [Epub ahead of print]

Tong MJ, el-Farra NS, Grew MI. Clinical manifestations of hepatitis A: recent experience in a community teaching hospital. J Infect Dis 1995;171 Suppl 1:S15-8.

Tong MJ, Thursby M, Rakela J, McPeak C, Edwards VM, Mosley JW. Studies on the maternal-infant transmission of the viruses which cause acute hepatitis. Gastroenterology 1981;80:999-1004.

Van Damme P, Pintó RM, Feng Z, Cui F, Gentile A, Shouval D. Hepatitis A virus infection. Nat Rev Dis Primers. 2023;9(1):51.

Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338:286-90.

Wang X, Ren J, Gao Q, et al. Hepatitis A virus and the origin of picornaviruses. Nature 2014; epub ahead of print

Whelan J, Sonder GJ, Bovee L, et al. Evaluation of hepatitis A vaccine in post-exposure prophylaxis, The Netherlands, 2004-2012. PLoS One 2013, 17: e78914.

Zhou Y, Callendret B, Xu D, et al. Dominance of the CD4(+) T helper cell response during acute resolving hepatitis A virus infection. J Exp Med. 2012 Jul 30;209(8):1481-92. doi: 10.1084/jem.20111906. Epub 2012 Jul 2.

Zhang L, Yesupriya A, Hu DJ, et al. Variants in ABCB1, TGFB1, and XRCC1 genes and susceptibility to viral hepatitis A infection in Mexican Americans. Hepatology. 2012; 55:1008-18.

2. Hepatitis B – treatment

Heinrich Rodemerk, Thomas Berg, Florian van Bömmel

Introduction

Treatment of Hepatitis B is a complex and dynamic field. Since the approval of the first interferon-based treatment for Hepatitis B in the late 20th century, new antiviral substances, such as nucleos(t)ide analogues have been introduced and further developed. An even wider range of possible new therapeutic options is currently being investigated in studies.

A subgroup of patients with a chronic HBV infection progresses to chronic Hepatitis B (CHB). Those patients carry an elevated risk for liver-related mortality and morbidity. Identifying the patients that benefit most from antiviral therapy is crucial for reducing the risk of fibrosis, cirrhosis, decompensation and hepatocellular carcinoma (HCC) development. Several factors influence the choice of the optimal treatment out of available options. Regular monitoring of patient-related and viral factors should accompany any therapeutic action. Although a sterile and complete cure for Hepatitis B is not yet possible, different therapeutic endpoints can be reached with current treatment. Novel approaches, such as treatment cessation after long-term application of nucleos(t)ide analogues or combination of new substances may induce functional cure.

Before commencing any form of treatment, some main questions need to be considered:

1) Why treat?
2) Who to treat?
3) How to treat?
4) How to monitor treatment?
5) When to stop?

This chapter aims to provide an overview of therapeutic options and may help to answer some of the questions above. However, an individualised and patient-centred approach should be maintained and all relevant factors in the clinical situation need to be considered. Hepatitis B care, including antiviral treatment, should be delivered according to regularly updated guidelines. There are different regional and international guidelines reflecting the current state of the art for Hepatitis B care (see Table 1). Several context factors can influence the clinical decision, so other guidelines may be relevant in different parts of the world, even if not listed here.

Table 1. Guideline overview

Institution	Year	Full Name	Reference
World Health Organization (WHO)	2024	Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection	(WHO 2024)
European Association for the Study of the Liver (EASL)	2017*	EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection	(EASL 2017)
American Association for the Study of Liver Diseases (AASLD)	2018	Update on Prevention, Diagnosis, and Treatment and of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance	(Terrault 2018)
Asian Pacific Association for the Study of the Liver (APASL)	2016	Asian-Pacific clinical practice guidelines on the management of hepatitis B	(Sarin 2016)
The Korean Association for the Study of the Liver (KASL)	2022	KASL clinical practice guidelines for management of chronic hepatitis B	(KASL 2022)
Turkish Association for the Study of the Liver (TASL)	2017	Diagnosis, management and treatment of hepatitis B virus infection: Turkey 2017 Clinical Practice Guidelines	(Tabak 2017)
German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS)	2021	S3 Guideline of the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) on the Prophylaxis, Diagnosis, and Treatment of Hepatitis B Virus Infection	(Cornberg 2021)

*Update to be published in 2025

Treatment goals (Why treat?)

Hepatitis B is still a major public health threat. The overall rationale for Hepatitis B testing, treatment and care is to lower the disease burden on a population level. Besides public health approaches that mainly focus on prevention, current treatment strategies are designed to reach therapeutic endpoints that reduce the individual risk for liver-related mortality and morbidity. To date, the full eradication of HBV (sterile cure) is impossible to achieve by available treatment options. This is due to the persistence of episomal covalently closed circular DNA (cccDNA), a template of the HBV genome located in the nucleus of infected hepatocytes (Rehermann 1996). Thus, the main treatment goal is to improve the patient's survival and quality of life by preventing disease progression, hepatocyte and parenchyma damage, complications and consequently HCC development. Reducing the risk of HBV transmission is an additional goal of antiviral therapy (EASL 2017; Terrault 2018; WHO 2024). Reactivation of an HBV infection may occur in certain circumstances from the nuclear reservoirs even decades after HBsAg loss. Prophylactic antiviral therapy should be used in patients undergoing (induced) immunosuppression to prevent reactivation. In patients with acute Hepatitis B, preventing the risk of acute liver failure is the main treatment goal.

Future therapeutic options aim to cure CHB by eliminating all replicative forms of HBV. The ultimate goal is the global elimination of HBV infection by various strategies, including vaccination, treatment and prevention of transmission (Sarin 2016).

Forms of cure and therapeutic endpoints

Different categories of "cure" have been defined, and they serve as endpoints that should be reached by CHB treatment:

- Virological cure: Suppression of HBV DNA to undetectable levels
- HBeAg loss: seroconversion from detectable HBeAg to anti-HBe
- Functional cure: HBsAg loss +/- seroconversion to anti-HBs
- Partial functional cure: inactive carrier state with low levels of HBsAg and HBV DNA, off-treatment
- Sterile cure: no form of HBV-DNA detected, including integrated forms and cccDNA

Virological cure refers to the suppression of the HBV replication to undetectable levels. It is one major goal in treatment. The continuous suppression of serum HBV DNA over several years shows a time-dependent reversion of liver fibrosis as well as a decrease in the HCC risk. The regression of liver fibrosis during antiviral treatment was impressively demonstrated in a subanalysis of two trials with patients who underwent biopsies before and after five years of TDF monotherapy (Marcellin 2013). 88% of the patients experienced an improvement in overall liver histology. Of patients who had cirrhosis at the start of therapy, 73% experienced regression of cirrhosis, and 72% had at least a two-point reduction in fibrosis scoring. The positive effect of antiviral treatment on liver histology was also shown in a subgroup of patients from a rollover study including two phase III trials on the efficacy of ETV in treatment-naïve patients. Liver biopsies taken at baseline and after a median treatment duration of 6 years showed a substantial histologic improvement in 96% of the patients (Chang 2010b). Ongoing viral replication is a key risk factor for HCC development. Antiviral treatment reduces that risk by 30% (in cirrhosis) up to 80% (in non-cirrhosis), as first shown for Asian cohorts (Papatheodoridis 2015). The decrease in HCC incidence during antiviral treatment was illustrated by

the results of a retrospective analysis comparing HBV-infected Taiwanese either being treated with antivirals or not. Among the patients receiving treatment with NAs, the incidence rate of HCCs over 7 years of follow-up was 7.3 % compared to 22.9% in patients without antiviral treatment (Wu 2014). However, the HCC risk is not affected immediately after the initiation of antiviral treatment. Thus, the incidence of HCCs was shown to start decreasing after 5 years of effective HBV DNA suppression by either Entecavir or Tenofovir (Papatheodoridis 2017). After eight years of treatment, it was similar to individuals without HBV infection in a multicentric European cohort (Papatheodoridis 2018). The presence of liver cirrhosis strongly determines the remaining HCC risk. However, also patients with liver cirrhosis show a decreasing incidence of HCC development following treatment (Su 2016). Overall, these data indicate that with potent NAs, the HCC risk can be reduced but not eliminated.

HBeAg loss. HBeAg seroconversion is another treatment endpoint, as long as HBV replication remains durably suppressed to low levels. In HBeAg-positive patients, seroconversion from HBeAg to anti-HBe was found to be a reliable surrogate marker for prognosis of chronic HBV infection leading in many cases to an inactive HBsAg carrier state. In these patients, HBsAg remains detectable but HBV replication continues at low or even undetectable levels and transaminases are generally within normal ranges. HBeAg seroconversions that appear during antiviral treatment can be considered a lasting immune response in the majority of patients. In a meta-analysis, in 76% of patients, the HBeAg seroconversion was stable after treatment discontinuation (Papatheodoridis 2016b). However, long-term observations reveal that HBeAg seroconversion cannot always be taken as a guarantee of long-term remission. A reactivation of the disease with "sero-reversion" (HBeAg becoming detectable again) as well as a transition to HBeAg-negative CHB with increased and often fluctuating HBV DNA levels may occur in 30-50% of patients (Hadziyannis 2001; Hadziyannis 2006a; van Hees 2018). Therefore, HBeAg seroconversion should only be regarded as a treatment endpoint in conjunction with durable and complete suppression of HBV replication. There is an ongoing discussion about whether and how long a consolidation treatment (6-12 months) should be maintained following HBeAg seroconversion. As a result, Asian guidelines recommend stopping treatment immediately after HBeAg seroconversion, whereas American and European guidelines favour treatment continuation, but allow discontinuation in selected patients with close subsequent monitoring.

HBsAg loss. Since HBsAg loss or seroconversion is associated with a complete and definitive remission of disease activity and an improved long-term outcome, it is currently regarded as a "functional cure" and a stable remission of HBV infection, although HBV cccDNA persists in infected hepatocytes and reactivations may occur. Unfortunately, HBsAg loss can be induced in only a limited number of patients by treatment (in up to 10% of HBeAg-positives and in <1% of HBeAg-negatives) (Moini 2022). The probability of HBsAg seroclearance during therapy with NAs is linked to a decrease in HBsAg levels during the early treatment period. As HBsAg levels remain unchanged in most patients during the first years of treatment it seems therefore unlikely that a longer duration of NA treatment will further increase rates of HBsAg loss (Marcellin 2011). Due to a greatly reduced risk in most hepatic outcomes on morbidity and mortality, HBsAg loss can be regarded as the most important endpoint (Morais 2023).

Partial functional cure/Sustained immune control. The term "sustained immune control" can be used to describe a stage that follows the discontinuation of treatment for Hepatitis B, either in NA- or PegIFN-based treatments. It describes the "absence of virological treatment indication" and refers to a stage with low HBV replication (ideally < 2.000 IU/mL) and normal ALT levels but detectable HBsAg (and possibly HBeAg). However, the durability of this immune control is not guaranteed due to the fluctuating course of HBeAg-negative CHB. For treatment with PEG-IFN α in both HBeAg-positive and -negative patients, inducing an immune control status, characterised by persistent suppression of viral replication with HBV DNA levels below 2, 000 IU/mL and normalisation of ALT levels was defined as a treatment endpoint (Marcellin 2009). If this condition is maintained over time, it increases the probability of HBsAg loss and reduces the development of liver fibrosis and HCC. Late relapse beyond 6 months post-treatment has been described, but a sustained response at one year post-treatment appears to be durable through long-term follow-up (Marcellin 2009). However, the immune control status needs to be regularly monitored, and treatment has to be reintroduced in cases with an increased HBV replication. Immune control defined as the "absence of treatment indication" was recently shown to be an important endpoint after discontinuation of long-term antiviral treatment in HBeAg-negative patients (Berg 2017). For patients presenting any signs of liver fibrosis or a family history of HCC, immune control should not be regarded as a treatment endpoint but rather the complete suppression of HBV replication.

Sterile cure: This term refers to the complete absence of HBV DNA and its integrates in hepatocytes. With currently used antivirals this endpoint is not achievable. In difference to functional cure with loss of HBsAg, there is no suspected risk of reactivation. Patients would have a similar HBV-attributable liver-related mortality as individuals who have never been infected.

Indication for antiviral therapy (Who to treat?)

Acute hepatitis B

Acute Hepatitis B resolves spontaneously in 95-99% of cases (McMahon 1985; Tassopoulos 1987; EASL 2017). Therefore, treatment of acute HBV infections with the currently available drugs is generally not indicated. In a study from India, treatment with LAM in patients with acute Hepatitis B showed no significantly greater biochemical and clinical improvement compared to placebo (Kumar 2007). However, in patients with a potentially life-threatening disease course as severe or fulminant acute Hepatitis B, antiviral treatment should be at least considered. There are observations suggesting that antiviral treatment might reduce mortality in patients experiencing fulminant hepatitis during acute HBV infection. Thus, in a trial comparing treatment with LAM 100mg once daily versus no treatment in Chinese patients with fulminant Hepatitis B, a mortality of 7.5% was found in patients receiving LAM treatment compared to 25% in the control group. The earlier the treatment was initiated, the better the results obtained (Yu 2010). Several case reports from Europe also indicate that patients with severe and fulminant Hepatitis B may benefit from early antiviral therapy with LAM or other NAs by reducing the need for high-urgency liver transplantation (Tillmann 2006). NAs appear to be safe in patients with fulminant Hepatitis B and do not increase the risk for chronification (Jochum 2016). As a result, antiviral treatment of fulminant or severe acute Hepatitis B with NAs is recommended by current treatment guidelines (Sarin 2016; EASL 2017; Terrault 2018; WHO 2024). Interferon therapy is generally not recommended in patients with acute HBV infection due to the risk of liver failure by increasing the inflammatory activity. The endpoint of treatment of acute HBV infections is HBsAg clearance (Su 2016; EASL 2017).

Chronic hepatitis B

Due to the large interindividual differences in the natural course of HBV infection, it is necessary to identify patients with a higher risk for HBV-related mortality. Those patients benefit from specific antiviral therapy. All individuals with HBV viraemia should initially be considered as potential candidates for antiviral therapy due to the oncogenic potential of HBV (Chen 2006; Iloeje 2006; EASL 2017; Terrault 2018). However, a new nomenclature was introduced to distinguish patients with ongoing inflammation and a higher risk from those with a less active form of infection. Most guidelines base their recommendations on who to treat on this differentiation. While patients with signs of active chronic Hepatitis B, defined by high viraemia, increased transaminases and/or (non-invasive) indicators of tissue damage should usually be treated, patients with chronic HBV infection are usually subject to regular monitoring. Table 2 shows the main differences between chronic Hepatitis B and chronic HBV infection.

Table 2. Hepatitis B nomenclature

	HBeAg-positive		HBeAg-negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/ Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	≥ 107 IU/mL	104-107 IU/mL	< 2,000 IU/mL*	≥ 2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated**
Liver disease	None/ minimal	Moderate/ severe	None	Moderate/ severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

*HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis
**Persistently or intermittently. Adapted from: (EASL 2017)

There is widespread agreement that the decision on whether to initiate treatment should be made on the following criteria (Sarin 2016; EASL 2017; Tabak 2017; Terrault 2018; Cornberg 2021; KASL 2022; WHO 2024):

1) serum HBV-DNA levels,
2) ALT elevation
3) histologic changes in liver tissue

In Table 3, the key recommendations for treatment initiation from different guidelines are listed. It is important to note, that the defined upper limit of normal (ULN) of alanine aminotransferase (ALT) levels varies geographically, therefore different guidelines have set different cut-offs. The WHO guidelines define a cut-off at 30 IU/L for men and boys and 19 IU/L for women and girls, almost similar to the AASLD guidelines, whereas the KASL guidelines define 34 IU/L for males and 30 IU/L for females as ULN. In the EASL and APASL guidelines, 40 IU/L is set as ULN for both sexes.

Besides the assessment of inflammation, indication for treatment should also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations. The HBeAg-status is not necessary

anymore for treatment indication, although concerning the choice of the appropriate antiviral drug (NAs vs. Interferon α), this criterium may still be useful.

Table 3. Recommendation upon treatment initiation

Guideline	Treat all HBsAg-positive patients with:
WHO	• Signs of fibrosis (non-invasive) or cirrhosis • HBV DNA >2000 IU/ml and ALT above ULN • Presence of co-infections, family history of HCC, immune suppression, comorbidities or extrahepatic manifestations • Persistently abnormal ALT levels
EASL	• HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis • Patients with compensated or decompensated cirrhosis, with any detectable HBV DNA level • HBV DNA >20,000IU/ml and ALT >2xULN
AASLD	• ALT ≥2x the ULN or evidence of significant histologic disease plus elevated HBV DNA above 2,000 IU/mL (HBeAg negative) or above 20,000 IU/mL (HBeAg positive). • Cirrhosis, if HBV DNA is >2,000 IU/mL
APASL	• Positive HBeAg, HBV DNA >20,000 IU/ml, ALT > 2xULN • Negative HBeAg, HBV DNA >2,000 IU/ml, ALT > 2xULN • Signs of severe necroinflammation or significant fibrosis • Severe reactivation of CHB • Decompensated cirrhosis with any detectable HBV DNA • Compensated cirrhosis with HBV DNA >200IU/ml
KASL	• Elevated HBV DNA, ALT ≥2x ULN, significant fibrosis or inflammation (non-invasive or in liver biopsy) • Decompensated cirrhosis with any detectable HBV DNA • Compensated cirrhosis with HBV DNA >200IU/ml
TASL	• Life-threatening liver diseases • Risk of developing liver failure/HCC in the short-term interval • Compensated cirrhosis with detectable serum HBV DNA • Risk for progressive liver disease • Patients with a persistently serum HBV DNA levels >20.000 IU/mL and ALT > 2x ULN, regardless of the level of fibrosis
DGVS	• HBV DNA > 2,000 IU/ml and inflammatory activity (elevated ALT) and risk for complications or HCC

Important note: The guidelines use different ALT cut-offs as ULN, m=male, f=female. WHO: m: 30 IU/L, f: 19 IU/L; EASL/APASL: m/f: 40 IU/L, AASLD: m: 35 IU/L, f: 25 IU/L, KASL m: 34 IU/L, f: 30 IU/L

While treatment recommendations vary slightly among the different guidelines, in the majority of them, the most important factor for a decision to initiate treatment has shifted from histologically proven disease activity to the serum levels of HBV DNA. Thus, most guidelines recommend antiviral treatment for patients with HBV DNA levels >2, 000 IU/mL (corresponding to >10, 000 copies/mL) in association with a sign of ongoing hepatitis (elevated ALT levels) or liver fibrosis demonstrated by liver histology greater than A1/F1. If available, non-invasive tools such as liver elastography or serologic algorithms should be used, especially if patients are reluctant to have a liver biopsy (EASL 2017; WHO 2024). The treatment algorithm from the EASL guidelines is displayed in Figure 1.

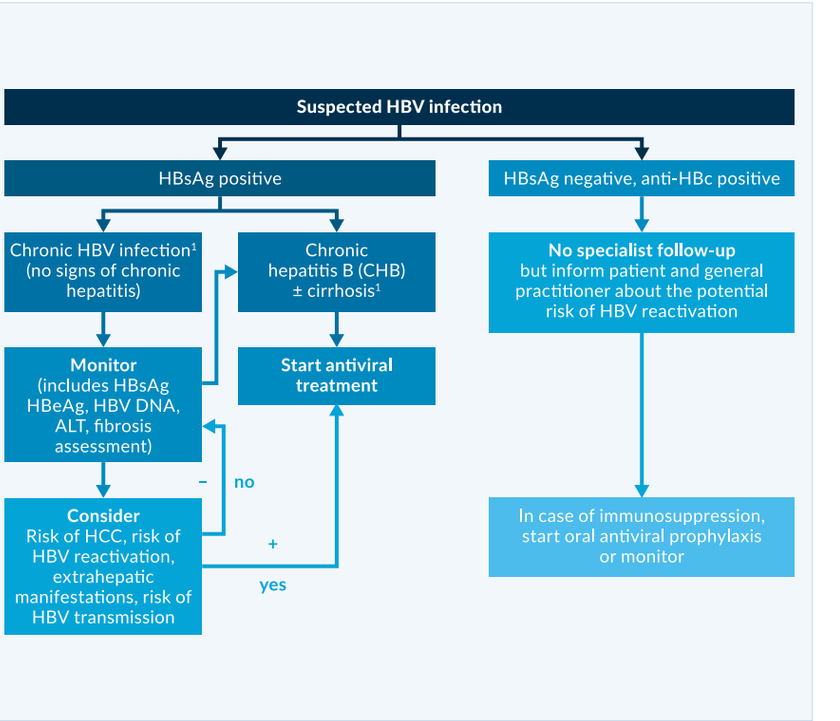

Figure 1. Hepatitis B treatment algorithm from EASL Clinical Practices Guidelines (EASL 2017).

Treatment of HBV infections in special populations

Cirrhosis

In patients with liver cirrhosis and detectable HBV DNA, treatment is recommended in most guidelines, regardless of serum HBV DNA levels or ALT elevation (EASL 2017; Cornberg 2021; KASL 2022; WHO 2024). Other guidelines include a strong recommendation for antiviral treatment only in decompensated cirrhosis but suggest considering treatment in compensated cirrhosis with low-level viraemia (Terrault 2018). In patients with decompensated cirrhosis with Child-Pugh-Score B or C, standard or pegylated Interferon-α is contraindicated.

HBeAg-negative HBV infection

It is yet under debate if there is a benefit in treating all patients with detectable viraemia, even without signs of hepatitis. In HBeAg-negative HBV infection (former "inactive HBsAg carriers") characterised by positive anti-HBe, HBV DNA levels below 2, 000 IU/mL and serum aminotransferases within normal ranges, therapy is currently not recommended by most guidelines (Sarin 2016; EASL 2017; Terrault 2018; Cornberg 2021). The risk of liver-related mortality in patients without biochemical or histological signs of hepatitis or parenchyma damage was not elevated in European HBsAg carriers compared to uninfected individuals (Manno 2004). The current WHO guideline regards low viraemia as only one factor to be considered. Treatment is also recommended in HbsAg-positive patients with any form of fibrosis or any of the following co-factors: coinfection (e.g. HIV, HDV, HCV), family history of liver cancer or cirrhosis, immune suppression, comorbidities (e.g. diabetes, metabolic dysfunction-associated steatotic liver disease) or extrahepatic manifestations (e.g. glomerulonephritis or vasculitis). If quantitative HBV DNA assays are unavailable, any ALT above ULN is seen as a treatment indication (WHO 2024). See Figure 2 for the updated WHO treatment algorithm. These recommendations apply to a much broader range of patients. In addition, the REVEAL study demonstrated, that patients with HBeAg-negative HBV infection still had a substantial risk for HCC (Chen 2010).

The differentiation between true inactive chronic HBV infection and patients with chronic HBeAg-negative hepatitis may be difficult in some cases. Elevated transaminases are no reliable parameter for assessing the stage of liver fibrosis and long-term prognosis of HBV-infected individuals. Even in patients with normal or only slightly elevated aminotransferases, there can be a significant risk for the development of HBV-associated complications (Chen 2006; Iloeje 2006; Chen 2010). HBsAg levels are useful for predicting the risk of HBV reactivation with subsequent replication and inflammatory activity (Martinot-Peignoux 2013; Tseng 2013). Newer biomarkers, such as quantitative HBV RNA may help to distinguish patients with a true inactive HBV infection from those with a higher risk for reactivation (Testoni 2024). Antiviral treatment reduces the risk of HBV-related mortality if used in early phases with high viraemia, but does not affect endpoints when serum HBV-DNA levels are low (Huang 2023; Choi 2024). Furthermore, antiviral treatment can't fully eliminate the risk of HCC. Therefore, the benefits of antiviral therapy must be carefully weighed against the higher off-treatment chance of spontaneous HBsAg loss and the relevant side effects of long-term NA treatment (Yip 2024).

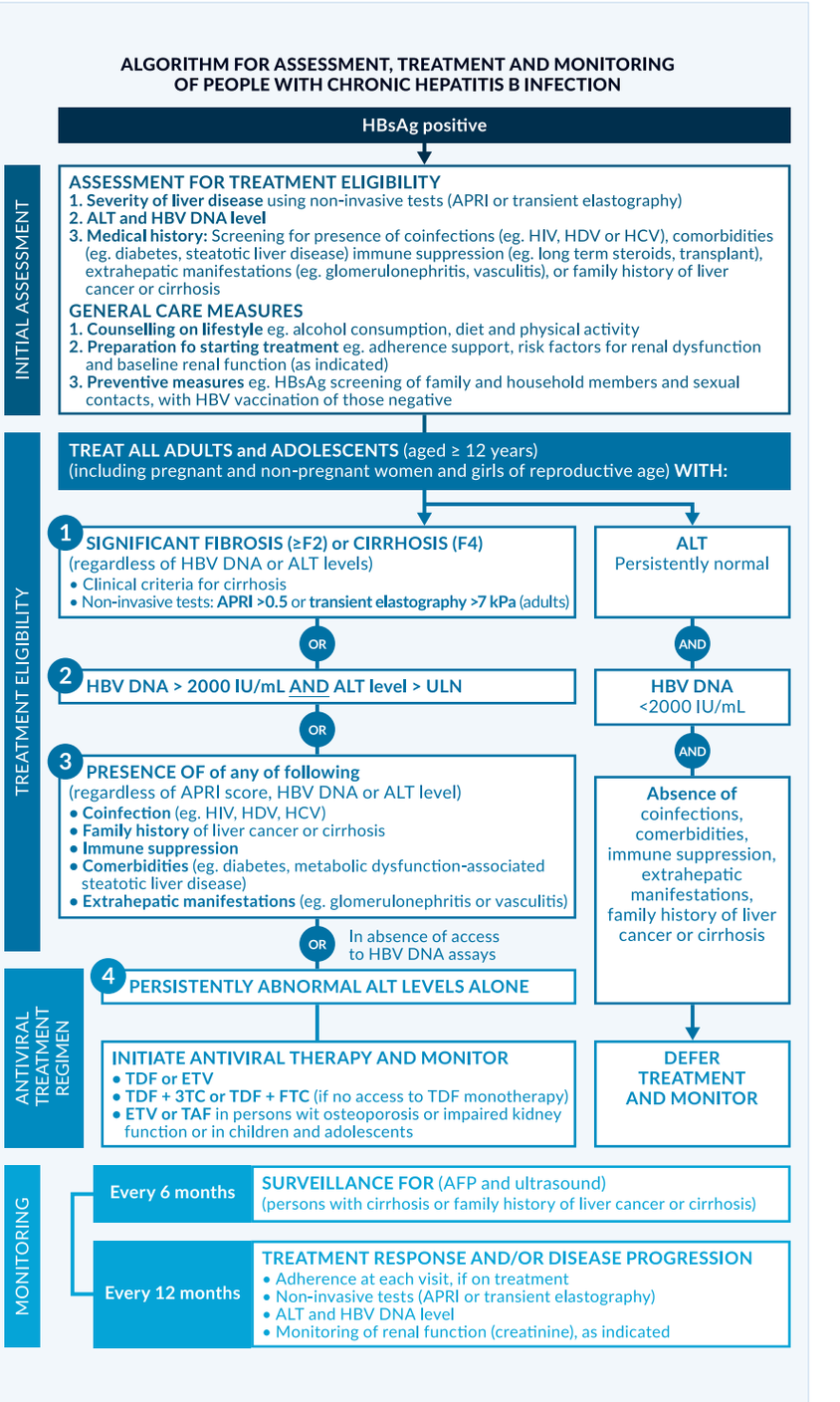

Figure 2. Algorithm for assessment, treatment and monitoring of people with chronic Hepatitis B infection, reproduced from WHO guidelines. ALT ULN: male: 30 IU/L, female: 19 IU/L (WHO 2024).

Pregnancy

Globally, vertical transmission from the mother to the newborn is the most frequent cause of HBV infection. The highest risk occurs during delivery, especially if the maternal viraemia is high in HBeAg-positive Hepatitis B. To prevent transmission, guidelines recommend the active Hepatitis B vaccination of the newborn infant as soon as possible, preferably within the first 12-24 hours (WHO 2024), followed by 2 to 3 additional doses in a routine scheme. A combination of Hepatitis B immunoglobulin may further reduce the risk of transmission to less than 5% (Veronese 2021). Still, for a neonate born to a mother with high levels of HBV DNA (over 200, 000 IU/mL), the risk of perinatal transmission is considerable. Therefore, antiviral treatment is generally recommended in these women (EASL 2017; Terrault 2018; Cornberg 2021; WHO 2024). PEG-IFN α is contraindicated. In pregnant women with high levels of HBV DNA, LAM treatment during the last trimester of pregnancy was reported to reduce the risk of intrauterine and perinatal transmission of HBV if given in addition to passive and active vaccination (van Zonneveld 2003). Due to its high antiviral potency, TDF is often considered the treatment of choice. The risk of teratogenicity of NAs is assessed by a classification based on data gathered in clinical trials as well as through the FDA Pregnancy Registry. TDF and LAM are listed as pregnancy category B drugs, whereas ADV and ETV are category C drugs. However, side effects on the newborn cannot completely be ruled out. A recent study reported that bone mineral content in infants of HIV-infected mothers exposed to TDF was 12% lower than in non-exposed (Siberry 2015). In a comparative study, LdT, TDF and TAF were similarly very effective in preventing mother-to-child transmission. However, in the TAF group, a higher amount of cardiac abnormalities was observed (Pan 2024b). The benefits of maternal treatment in preventing mother-to-child transmission must be carefully weighed against potential risks for maternal and infant health. A recent meta-analysis found no relevant safety concerns in NA treatment (Pan 2024a). As exacerbations of the HBV infection may occur, women with HBV should be monitored closely after delivery (Borg 2008).

Immunosuppression

During immunosuppressive treatment, an asymptomatic or inactive HBV infection may reactivate in 20% to 50% of patients (Lau 2021). These reactivations can occur in both inactive chronic HBV infections and in patients with functional cures (HBsAg-negative, but anti-HBc-positive patients). They are characterised by an increase in HBV replication followed by signs of liver inflammation during immune reconstitution resulting in liver damage or even liver failure in some patients (Artz 2010; Roche 2011). Immunosuppressive therapies with the highest risk of HBV reactivation are chemotherapeutic treatment for cancer and advanced anti-autoimmune and antirheumatic treatment. This includes anti-CD20 therapies (rituximab), treatment with corticosteroids and TNF-α inhibitors (i.e. infliximab, etanercept, adalimumab), tyrosine kinase inhibitors (i.e. imatinib) or other biologicals (i.e. abatacept, anakinra, tocilizumab) and stem cell transplantation. Some cases of HBV reactivation have also been observed in other forms of immunosuppression, such as trans-arterial chemoembolisation for HCC or immunosuppressive therapy after solid organ transplantation (Moses 2006; Vassilopoulos 2007; Lau 2021). Prior to initiating immunosuppressive therapies, screening for HBV infection is recommended (EASL 2017; Lau 2021). Pre-emptive therapy should be considered for:

- all patients with active Hepatitis B before any immunosuppressive treatment
- HBsAg-positive chronic HBV infections receiving moderate to aggressive immunosuppression, depending on the individual risk
- anti-Hbc-positive, HBsAg-negative patients when therapy with a high risk of reactivation is planned (i.e. rituximab or human stem cell transplantation)

If available, highly potent antivirals, such as ETV or TDF, should be used for pre-emptive treatment. Termination of antiviral therapy can be considered 6 months after the end of immunosuppression (Lau 2021).

Treatment options and choice (How to treat?)

Currently, there are two main options for medical treatment of CHB: pegylated Interferon (PEG-IFN) or nucleoside/nucleotide analogues (NAs). The option of PEG-INF α-treatment may be considered for all patients in the first line, however, there are many contraindications, making them unsuitable for several subgroups of CHB patients. In contrast, NAs can be used in almost all clinical situations. Factors influencing the decision on which drug to use will be discussed under the subheading “Choosing the right treatment option”.

Interferons

INF α is a naturally occurring cytokine with immune modulatory, antiproliferative and antiviral activity. During treatment, the therapeutic efficacy of INF α can often be clinically recognised by a self-limited increase of ALT levels to at least twice the baseline levels. These ALT flares are frequently associated with virologic response. The main goal of INF α treatment is to induce long-term remission after a finite treatment duration. Response to IFN α can be either HBeAg seroconversion or durable suppression of HBV DNA to low or undetectable levels. In these responders, the chance for HBsAg loss in the long-term is relatively high.

Table 4. Interferon overview

Treatment Option	Dosage	Advantage/disadvantage
Standard INF α	5-10 Mio. IU 3x/ week	+ first approved CHB treatment
		– subcutaneous injection every other day
PEG-INF α	180 µg/week	+ application once weekly + high rates of HBe seroconversion + high rates of sustained virological suppression after termination + high rates of sustained virological suppression after termination
		– many side effects – a considerable amount of non-responders – not useful in certain clinical situations (cirrhosis, prophylaxis, pregnancy)

Standard INF α. Standard IFN α was approved for the treatment of CHB in 1992. IFN α is applied in dosages ranging from 5 million units (MU) to 10 MU every other day or thrice weekly. In a meta-analysis, a significant improvement in endpoints was shown in patients with HBeAg-positive chronic Hepatitis B being treated with standard IFN compared to untreated patients (Craxì 2003). Complete remission of fibrotic changes was observed in some patients and the loss of HBsAg occurred comparatively often. Furthermore, there was a trend towards less hepatic decompensation (treated 8.9% vs. untreated 13.3%), hepatocellular carcinoma (1.9% vs. 3.2%), and liver-associated deaths (4.9% vs. 8.7%) (Craxì 2003). A significant decrease in ALT and HBV DNA serum levels was also shown for standard IFN α in the treatment of HBeAg-negative CHB (Brunetto 2003). However, a high percentage of these patients relapse after the end of treatment showing elevation of ALT levels and a return of HBV DNA levels. The relapse rate seems to be higher when treatment duration is short (16 to 24 weeks) compared to longer treatment (12 to 24 months). A retrospective comparison of IFN therapies lasting from 5 to 12 months showed, that prolonged treatment increased the chance of a long-term response, concerning ALT normalisation and HBV DNA suppression. The overall response rates were 54% at the end of therapy, 24% at 1 year after therapy, and 18% 7 years after therapy (Manesis 2001). Patients with long-term response to treatment have a more favourable outcome for progression to liver cirrhosis, liver-associated deaths and development of hepatocellular carcinoma than patients who were untreated, unresponsive, or had a relapse (Brunetto 2003; Lampertico 2003). However, due to higher antiviral efficacy, PEG-IFN α should be preferred to standard IFN α.

PEG-INF α. The addition of a polyethylene glycol molecule to the interferon resulted in a significant increase in half-life, thereby allowing administration once weekly. Two types of subcutaneously administered PEG-IFN α were developed: PEG-IFN α-2a and PEG-IFN α-2b. PEG-IFN α-2a was licensed for the treatment of chronic HBV infections in a weekly dose of 180 µg for 48 weeks in both HBeAg-positive and HBeAg-negative patients. Both forms show similar efficacy. After one year of treatment with PEG-IFN α-2a and α-2b, 22% to 27% of patients were reported to achieve HBeAg seroconversion (Janssen 2005; Lau 2005) The safety profiles of standard IFN α and PEG-IFN α are similar. After termination of therapy, a relatively high relapse rate can be expected (>50%). The dose of 180 µg per week applied for 48 weeks was shown to exert a stronger antiviral efficacy compared to administration for 24 weeks or to the administration of 90 µg per week (Manesis 2001; Liaw 2011). Treatment for longer than 48 weeks is not recommended in current guidelines.

PEG-IFN α in HBeAg-positive patients. Several randomised, controlled studies investigating the efficacy of PEG-IFN α in HBeAg-positive patients have been conducted (Chan 2005; Janssen 2005; Lau 2005). These studies compared 180 µg PEG-INF α per week to standard IFN, LAM, and/or combination treatment with PEG-INF α + LAM for 48 weeks. Sustained HBeAg seroconversion at the end of follow-up (week 72) was significantly higher in patients treated with PEG-IFN α-2a alone or in combination with LAM than in patients treated with LAM alone (32% and 27% versus 19%) (Marcellin 2004).

PEG-IFN α in HBeAg-negative patients. The efficacy and safety of 48 weeks of treatment with 180 µg PEG-IFN α-2a once weekly, with LAM 100 mg daily and the combination of LAM and PEG-IFN α-2a was compared in HBeAg-negative patients. After 24 weeks of follow-up, the percentage of patients with normalisation of ALT levels or HBV DNA levels below 20,000 copies/mL was significantly higher with PEG-IFN α-2a monotherapy and a combination of PEG-IFN α-2a plus LAM than with LAM monotherapy. The rates of sustained suppression of HBV DNA below 400 copies/mL were 19% with PEG-IFN α-2a monotherapy, 20% with combination therapy,

and 7% with LAM alone (Lau 2005). Prolongation of PEG-IFN α treatment beyond 48 weeks may increase sustained response rates in HBeAg-negative patients. This was found in an Italian study with HBeAg-negative patients who were randomised to either treatment with 180 µg PEG-IFN α-2a per week for 48 weeks or additional treatment with PEG-IFN α-2a 135µg per week for another 48 weeks. As a result, 48 weeks after the end of treatment, 26% of patients who had received a longer treatment course showed HBV DNA suppression below 2, 000 IU/mL as compared to only 12% of the patients who had received PEG-IFN α-2a for 48 weeks only. Combination with LAM showed no additional effect (Lampertico 2013). However, the prediction of response and management of side effects during prolonged treatment with PEG-IFN α has not yet been established and it is not recommended for clinical practice. Importantly, it was shown that PEG-IFN α obviously induces immune modulatory effects which lead to considerable HBsAg clearance rates during the long–term follow-up period after treatment termination. In a study, HBeAg-positive patients with chronic HBV infection who had received treatment with standard IFN α were retrospectively analysed for a median period of 14 years. During the observation period, almost a third of this cohort lost HBsAg (Moucari 2009).

Nucleoside and nucleotide analogues

NAs inhibit HBV replication by competing with the natural substrate deoxyadenosine triphosphate (dATP) and therefore causing termination of the HBV DNA chain prolongation. They represent two different subclasses of reverse transcriptase inhibitors: while both are based on purines or pyrimidines, acyclic nucleotide analogues have an open (acyclic) ribose ring that confers greater binding capacity to resistant HBV polymerase strains. The optimal treatment duration for NAs is not yet defined, but treatment cessation after application of these agents for 48 weeks is associated with prompt relapse in viraemia, so they should be administered for longer periods. The treatment efficacy of NAs is defined by a complete suppression of HBV DNA levels in serum. This should be achieved within at least 6-12 months if agents with moderate to high risk for resistance development, such as LAM, ADV, and LdT, are used. Cumulative data concerning resistance rates in NAs are displayed in Figure 3. Effective and durable control of HBV replication with NAs is associated with a reduction of long-term complications such as liver cirrhosis and the development of HCC, especially in patients with liver cirrhosis (Toy 2009; Hosaka 2013). Studies with different NAs have demonstrated that suppression of HBV replication is associated with a significant decrease in histologic inflammatory activity and fibrosis, including partial reversion of liver cirrhosis (Mommeja-Marin 2003; Chang 2010b; Schiff 2011). With increasing treatment duration, HBeAg seroconversion rates increase, but even after 8 years of treatment they rarely exceed 40-50% of treated patients (Xing 2017). There is also evidence that effective inhibition of HBV replication can reduce HBV cccDNA, possibly parallel to the decline in serum HBsAg levels (Werle-Lapostolle 2004). As treatment of HBeAg-negative patients with NAs does not result in an endpoint in most patients even after more than a decade of therapy, new concepts are assessed. Discontinuation of long-term NA treatment may represent a novel approach to induce sustained immune control and serologic response in a significant proportion of HBeAg-negative patients (van Bömmel 2018).

As displayed in Table 5, over the last years, several NAs were approved for Hepatitis B therapy: Lamivudine (LAM), Adefovir dipivoxil (ADV), Telbivudine (LdT), Entecavir (ETV) and Tenofovir, as Tenofovir disoproxil (TDF) and Tenofovir alafenamide (TAF).

Table 5. Nucleos(t)ide analogues overview

Treatment Option	Dosage	Advantage/Disadvantage
Lamivudine (LAM)	100mg/d	+ cheap, generic + good availability + long-term clinical experience
		– high rates of resistance
Adefovir (ADV)	10mg/d	+ active in LAM-resistant HBV variants
		– weaker antiviral activity – low genetic resistance barrier – marketing license withdrawn
Telbivudine (LdT)	600mg/d	+ high antiviral activity + high rates of induced HBeAg loss
		– cross-resistance to LAM and ADV – low genetic resistance barrier – marketing license withdrawn
Entecavir (ETV)	0.5mg/d 1mg/d in LAM-experienced patients	+ high resistance barrier + renal safety + cheap, generics available
		– cross-resistance to LAM
Tenofovir disoproxil (TDF)	245mg/d	+ high resistance barrier + high antiviral activity + part of HIV antiviral regimens
		– potential long-term side effects on renal function and bone density
Tenofovir alafenamide (TAF)	25mg/d	+ high antiviral activity + part of HIV antiviral regimens + less renal toxicity
		– costly, no generics available to date

Lamivudine (LAM). LAM, a (-) enantiomer of 2' -3' dideoxy-3'-thiacytidine, is a nucleoside analogue that was approved for the treatment of chronic HBV infection in 1988 with a daily dose of 100 mg. This dose was chosen based on a preliminary trial showing that 100 mg LAM was more effective than 25 mg and similar to 300 mg in reducing HBV DNA levels (Dienstag 1995). LAM exerts its therapeutic action when phosphorylated in the cell. By inhibiting the RNA- and DNA-dependent DNA polymerase activities, the synthesis of both the first and the second strand of HBV DNA is interrupted. Long-term LAM treatment is associated with an increasing rate of antiviral drug resistance reaching approximately 70% after 5 years in patients with HBeAg-positive HBV infections. Therefore, in many guidelines, LAM is not recommended as a first-line agent anymore. However, LAM may still play a role in combination regimens or patients with mild CHB expressing low levels of HBV DNA. An early and complete virologic response to LAM within 6 months of therapy, reaching less than 400 copies/mL is a prerequisite for long-term control of HBV infection without the risk of resistance development.

Adefovir dipivoxil (ADV). Adefovir dipivoxil was approved for the treatment of chronic Hepatitis B in the US in 2002 and in Europe in 2003. It is an oral diester prodrug of adefovir, an acyclic nucleotide adenosine analogue. It is active in its diphosphate form. ADV was the first substance with simultaneous activity against wild-type, pre-core mutated and LAM-resistant HBV variants. In vitro, it shows activity against various DNA viruses other than HBV and retroviruses (i.e. HIV). The dose of 10 mg per day was derived from a study comparing 10 mg versus 30 mg/d. The higher dosage results in stronger suppression of HBV DNA levels but is also associated with renal toxicity and an increase in creatinine levels (Marcellin 2003). ADV was the first acyclic nucleotide that was widely used in the treatment of LAM-resistant HBV infections. However, the antiviral efficacy of ADV in the licensed dosage of 10 mg/day is weaker in comparison to other available antivirals, making it more vulnerable to HBV resistance (Hadziyannis 2006b). Thus, ADV should not be used as first-line monotherapy.

Telbivudine (LdT). Telbivudine is a thymidine analogue with activity against HBV, but it is at least in vitro not active against other viruses, including HIV and Hepatitis C Virus (HCV). LdT at 600 mg/day expresses higher antiviral activity than LAM at 100 mg/day or ADV at 10 mg/day. More patients achieve HBeAg loss within 48 weeks compared to other NAs. LdT was reported to have a good safety profile at a daily dose of 600 mg/day, being non-mutagenic, non-carcinogenic, non-teratogenic, and causing no mitochondrial toxicity (Lai 2007; Hou 2008). However, elevations in creatine kinase (CK) levels were observed more often than in the group treated with LAM and neurotoxicity may be an issue when LdT is administered in combination with PEG-INF α (Fleischer 2009). Higher CK levels were also observed in the GLOBE trial comparing LdT to LAM. However, rhabdomyolysis was not seen in patients and overall treatment efficacy was higher in LdT (Liaw 2009). High rates of peripheral neuropathy were reported in patients who received combination therapy of PEG-INF α and LdT but not in patients who received LdT monotherapy (Marcellin 2015). Resistance to LdT occurs in up to 20% of patients after 2 years of treatment, predominantly in those who did not achieve undetectable HBV DNA within 6 months (Zeuzem 2009). LdT shows cross-resistance to LAM and ETV. It should not be used in LAM or ETV refractory patients. Currently, LdT is not available in most areas, since the marketing authorisation is discontinued by the FDA and the EMA at the request of the manufacturer.

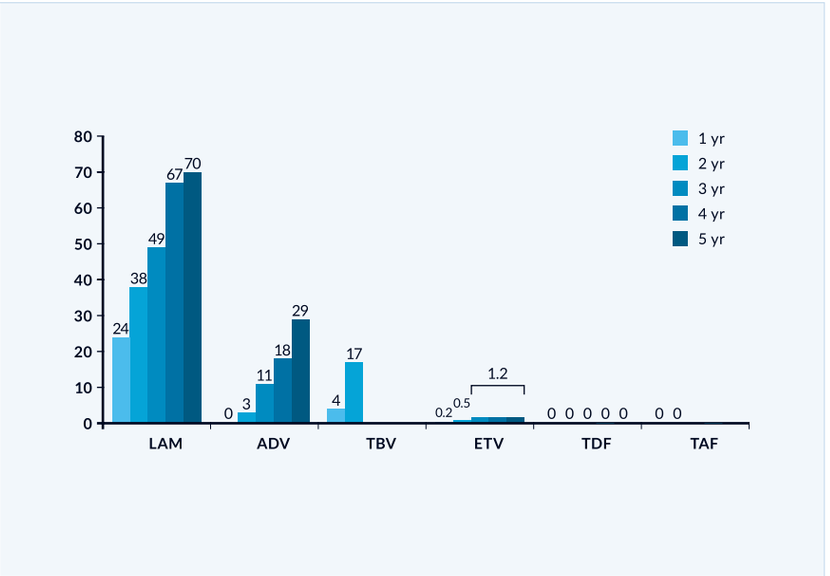

Figure 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) after several years of treatment (Collation of available data). Figure reproduced from EASL Clinical Practice Guidelines (EASL 2017).

Entecavir (ETV). Entecavir, a cyclopentyl guanosine nucleoside analogue, is a selective inhibitor of HBV replication and was approved in 2006. Entecavir blocks all three polymerase steps involved in the replication process of the Hepatitis B virus: base priming, reverse transcription of the negative strand from the pregenomic messenger RNA and synthesis of the positive strand of HBV DNA. ETV is more efficiently phosphorylated to its active triphosphate compound by cellular kinases than other NAs. It is a potent inhibitor of wild-type HBV but is less effective against LAM-resistant

HBV mutants. Therefore, ETV was approved at a dose of 0.5 mg per day for treatment-naïve HBeAg-positive and HBeAg-negative patients, but at a dose of 1 mg per day for patients with prior treatment with LAM (Chang 2005; Sherman 2008). Treatment-naïve HBeAg-positive patients achieved undetectable HBV DNA levels in 67%, 74% and 94% after one, two and five years of therapy, respectively (Chang 2010a). A virological response can be induced in over 90% of patients within one year (Lampertico 2010) and maintained in most patients over time (Hou 2020). So far, the rate of resistance at six years of treatment is estimated to be approximately 1.2% for treatment-naïve patients (Tenney 2009). Loss of HBsAg occurs in approximately 5% of treatment-naïve individuals after two years of ETV therapy (Gish 2010). In LAM-resistant patients, ETV is less potent. Fewer than 50% of patients with LAM resistance achieve undetectable HBV DNA levels after one or two years of treatment (Sherman 2008). Due to that cross-resistance, up to 45% of patients with LAM resistance develop resistance against ETV after 5 years of treatment (Tenney 2009). ETV has a favourable tolerability profile and can be easily adjusted to renal function. However, ETV may cause severe lactic acidosis in patients with impaired liver function and a MELD score of 18 points or more (Lange 2009).

Tenofovir (TFV). Tenofovir is available in two different formulas. It is an acyclic nucleoside phosphonate, or nucleotide analogue, structurally closely related to ADV. TFV has selective activity against retroviruses and hepadnaviruses and is approved for the treatment of HIV and HBV infection.

Tenofovir disoproxil fumarate (TDF), an ester prodrug form of Tenofovir (PMPA; (R)-9-(2-phosphonylmethoxypropyl) showed marked antiviral efficacy over eight years in almost all treatment-naïve HBeAg-negative and -positive patients. HBeAg loss and HBeAg seroconversion were found in 54% and 40% of patients respectively. Of the HBeAg-positive patients remaining under observation, 11.8% experienced HBsAg loss (Buti 2015). Other clinical studies show high efficacy of TDF in LAM-resistant HBV (van Bömmel 2010). Due to a possibly existing cross-resistance to ADV, the efficacy of TDF might be lowered by the presence of ADV resistance in patients with high HBV viraemia; however, a breakthrough of HBV DNA during TDF treatment in patients with previous ADV failure or in treatment-naïve patients has not been observed (van Bömmel 2010; Berg 2014). TDF is generally well tolerated and not associated with severe side effects. Renal safety during TDF monotherapy was investigated in several studies. Long-term TDF application was not associated with severe adverse outcomes concerning renal function (Heathcote 2011; Woldemedihn 2023). However, surrogate parameters of renal function changed in around 1% of patients treated with TDF, especially in patients with preexisting renal impairment (Buti 2015). In addition, effects on bone density are observed in real-world cohorts of people treated with TDF (Yip 2024).

Tenofovir alafenamide fumarate (TAF or (9-[®-2-[[(S)-[[(S)-1-(isopropoxycarbonyl) ethyl]amino] phenoxyphosphinyl]methoxy]propyl] adenin), was approved for the treatment of HBV infections in 2016. TAF follows a novel pro-drug mechanism of action and has a higher bioavailability and increased plasma stability compared to TDF. As a result, a lower daily dose of 25 mg (vs. 245 mg for TDF) is as effective as the TDF formulation in patients, regardless of the HBeAg status. The TAF formulation of Tenofovir is associated with fewer negative effects on bone and kidney biomarkers (Buti 2016; Agarwal 2018; Da Wang 2023). A switch from TDF to TAF may improve these biomarkers (Chan 2024). However, the clinical relevance of this observation remains under debate. To date, generic forms of TAF are not yet available.

Choosing the right treatment option

Interferon or NA

Initially, all patients with HBV viraemia can be considered potential candidates for interferon therapy. Because of limited tolerability and more adverse events, these patients need to be carefully selected. PEG-interferon should be preferred over standard IFN, due to its easier handling. Current guidelines recommend the use of PEG-IFN only in mild to moderate CHB (EASL 2017; Terrault 2018). Contraindications for PEG-IFN therapy include decompensated liver cirrhosis, acute Hepatitis B, autoimmune disease, uncontrolled psychiatric disease, cytopenia, severe cardiac disease or uncontrolled seizures (Terrault 2018). The potential benefit of PEG-IFN is a higher rate of HBeAg loss, HBsAg loss and long-term sustained suppression of HBV replication compared to NAs. The treatment duration of PEG-IFN is limited to 48 weeks, the benefits of the therapy often occur after treatment discontinuation. However, if a patient does not fulfil the criteria for a higher likelihood of response to treatment with PEG-INF α, has contraindications or is intolerant to PEG-INF α, long-term therapy with an NA is recommended.

Which NA?

NAs are orally administered and can achieve suppression of HBV DNA in almost all patients, but they have to be used for an undefined period unless one of the endpoints is achieved. Planned discontinuation of long-term NA treatment represents a novel approach to induce immune control in HBeAg-negative patients. The efficacy of NAs can be hampered by the emergence of HBV resistance. If an NA is chosen, several parameters have to be considered prior to therapy: the antiviral efficacy of the drug,

the resistance barrier, potential side effects and the stage of liver disease. Table 5 provides an overview of the advantages and disadvantages of each NA. The preferred regimens are ETV, TDF or TAF as monotherapies. These first-line treatments are recommended in guidelines due to their strong antiviral efficacy and low rate (ETV) or to date even absence (TDF, TAF) of reported resistance (Sarin 2016; EASL 2017; Terrault 2018; WHO 2024). LAM is still licensed, but due to its weaker antiviral performance and substantial risk of resistance development, it is no longer recommended for treating CHB. The approval for LdT and ADV by EMA and FDA was withdrawn at the manufacturer's request due to economic reasons, therefore these substances are hardly available now. Both substances should not be used in clinical routine. If a patient is already on treatment with good virological response, shows no signs of disease progression and has good adherence, the continuation of a LAM therapy can be considered, however, current guidelines give no formal recommendation for this (WHO 2024).

ETV, TDF or TAF?

Except for patients with cirrhosis, the HCC risk reduction in older and newer NAs is comparable, but ETV, TDF and TAF have a higher resistance barrier. Due to possible cross-resistance, Entecavir should be used at a higher dose of 1mg/day in LAM-experienced patients. However, if LAM resistance is confirmed, TAF or TDF should be preferred. Both formulas of Tenofovir perform equally in their antiviral activity (Lim 2023), in terms of HCC risk reduction, they are superior to ETV (Choi 2023), see Figure 4. Due to rare adverse outcomes in renal function and bone density under long-term TDF therapy, TAF or ETV should be considered in patients with present renal dysfunction or bone diseases, such as an increased risk for osteoporosis (WHO 2024). Due to the currently indefinite treatment period for many patients, therapy costs may play a role: ETV and TDF are available as generics.

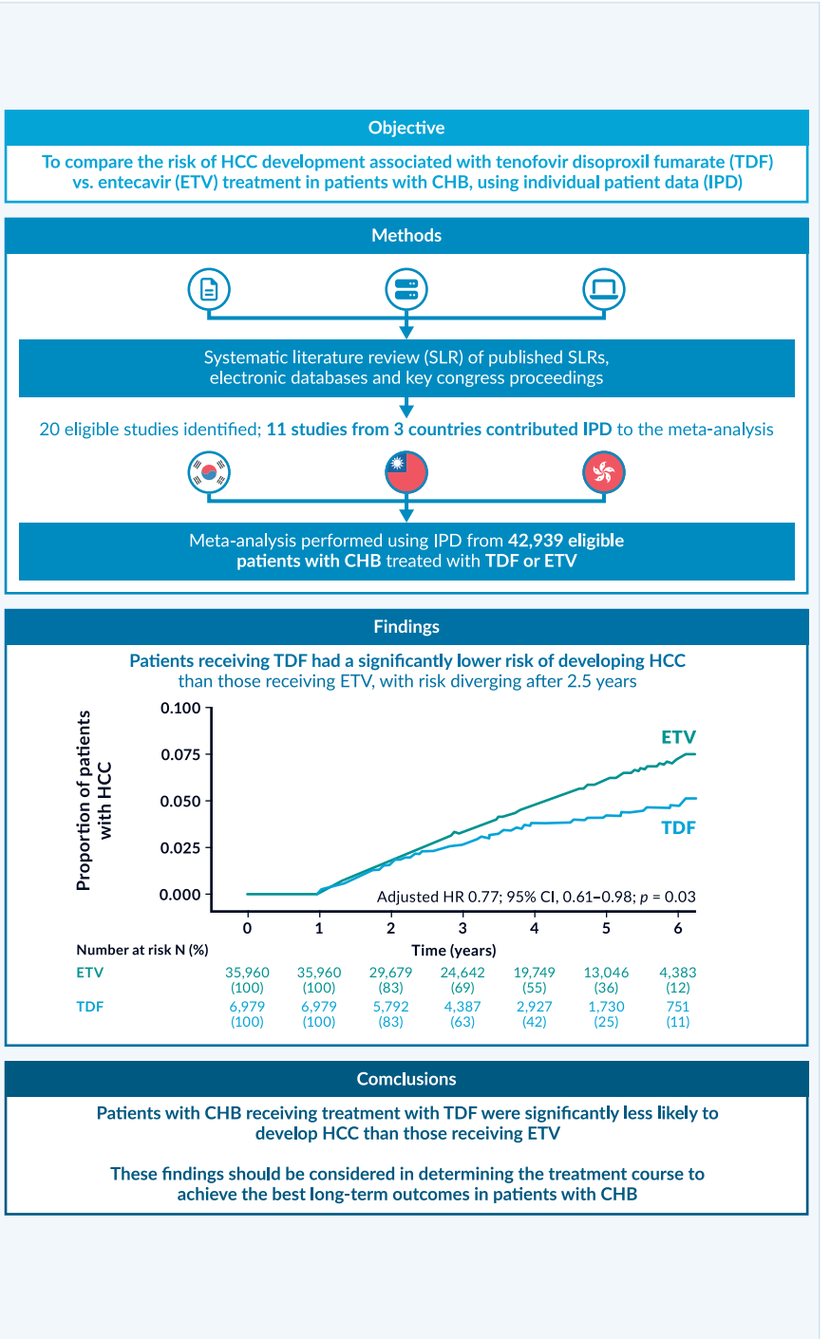

Figure 4. Comparison of HCC risk in patients treated with Tenofovir disoproxil (TDF) or Entecavir (ETV). The risk in the TDF group was significantly lower, especially for HBeAg-positive patients. Figure reproduced from a metanalysis with 40,000 Asian patients (Choi 2023).

Combination therapy

Combination treatments with different NAs or NAs with PEG-IFN α were studied in various patient cohorts. However, in most trials, combinations were not superior to monotherapies, and due to insufficient knowledge of how to select patients who will benefit from first-line combination treatments, they are currently not recommended by guidelines.

NA+NA

Combining two (or more) nucleos(t)ide analogues is not superior to available monotherapies. Studies investigating combinations of LAM with ADF or LdT showed no difference in virological or biochemical response (Lai 2005; Sung 2008). In another trial, treatment-naïve patients were randomised to receive either ETV 0.5 mg/day as monotherapy or in combination with TDF. By week 96, a higher proportion of patients in the combination therapy arm showed HBV DNA suppression, the subgroup of HBeAg-positive patients with a high baseline viraemia benefited most (Lok 2012). The addition of Emtricitabine to TDF led to a higher proportion of patients with complete HBV DNA suppression in HBeAg-positive patients. However, HBeAg seroconversion or HBsAg loss was reported in only a few patients, and this was not different across both groups (Chan 2014). In ADV pre-treated patients, TDF monotherapy was as effective as the combination of TDF and Emtricitabine (Berg 2010). Although combination therapy theoretically may be useful for certain patients, especially those with incomplete response to first-line antivirals, it is currently not recommended for de-novo treatment (EASL 2017; Terrault 2018). However, the WHO guideline acknowledges that in some countries the availability of TDF plus Emtricitabine or LAM is better than TDF monotherapy due to cheaper supply as part of subsidised HIV treatment programmes. In this case, those combinations may be used for first-line therapy (WHO 2024).

NA+IFN

Although a combination of NAs and PEG-IFN α theoretically represents a more promising approach as two different mechanisms of action could potentially be synergistic, the results from clinical studies do not fully support this strategy. A stronger on-treatment virologic response at week 48 of treatment was observed with combination therapy compared to LAM or PEG-IFN α alone in one study (Chan 2005). However, a combination of LAM plus PEG-IFN α failed to demonstrate serologic or clinical benefit when evaluated at the end of follow-up in most studies (Janssen 2005). Combination therapies of PEG-IFN α with more potent NAs such as ETV or TDF may be more attractive. A combination treatment of ETV and PEG-IFN 2α after 4 years of complete response to ETV was superior to the continuation of ETV treatment by HBeAg and HBsAg loss and seroconversion rates (Ning 2014). A randomised study investigating the efficacy of either PEG-IFN α or TDF alone or in combination showed that patients treated with TDF plus PEG-IFN 2α for 48 weeks achieved significantly higher rates of HBsAg loss at week 72 (9.1%) than patients treated with either TDF (0%) or PEG-IFN 2α (2.8%) (Marcellin 2016). Despite the few promising results, evidence on combination treatment is still scarce and the risk of adverse events is higher in those therapeutic regimens, therefore current guidelines do not recommend a de-novo combination of NA and IFN (EASL 2017; Terrault 2018; Cornberg 2021).

Management of HBV resistance

Resistance development. NAs perform their antiviral action by competitive inhibition of the HBV polymerase. During treatment with these substances, HBV variants bearing mutations within the HBV polymerase gene may be selected from the HBV quasispecies, a phenomenon defined as genotypic resistance. In contrast, phenotypic resistance is defined as decreased susceptibility (in vitro testing) to inhibition by antiviral drugs associated with genotypic resistance. Cross-resistance of HBV to antiviral treatment has been described within the groups of nucleoside and nucleotide analogues. If a resistant HBV quasispecies predominates due to selective advantage, treatment might fail and a viral breakthrough during treatment may appear. This is associated with severe and sometimes fatal reactivation (Zoulim 2012). Theoretically, all available NAs may select resistant HBV strains, but resistance is rare in treatment-naive patients who receive substances with strong antiviral activity, i.e., TDF or ETV. Resistance rates against LdT, ADV and especially LAM are significantly higher. For patients treated with TDF, problems with resistance have not been reported yet, even in patients who were pretreated with ADV, although ADV resistance-associated mutations might slightly decrease response to TDF (van Bömmel 2012; Berg 2014). Global monitoring for Tenofovir resistance is necessary for the early detection of emerging TDF-resistant strains (Lumley 2024).

Detection of HBV resistance. Generally, a confirmed relapse of HBV DNA over 1 log10 from nadir during treatment with nucleoside/nucleotide analogues is considered a potential viral breakthrough caused by HBV resistance. Genotypic resistance testing is not available to most treating physicians and is generally not recommended in the first place. If available, molecular resistance testing might be considered for individuals with suspected resistance to any first-line antiviral treatment. It should

be performed by a reference laboratory (Terrault 2018; Cornberg 2021; WHO 2024). It should be considered that most viral breakthroughs in treatment-naive patients receiving ETV or TDF are the result of adherence issues. Therefore, patient adherence should be assessed before genotypic resistance testing.

Avoidance of HBV resistance. HBV resistance occurs most frequently in patients treated with LAM, LdT or ADV, therefore many guidelines discourage physicians from using these NAs in first-line treatment. The selection of resistant HBV strains is more likely if HBV DNA levels are not suppressed to undetectable levels within 6 months of treatment. Therefore, in patients undergoing treatment with these substances, who show detectable HBV DNA after 6 to 12 months of treatment, the treatment should be adjusted (EASL 2017). First-line treatment with ETV or TDF/TAF is recommended by many guidelines to avoid HBV resistance (EASL 2017; Terrault 2018; WHO 2024).

Treatment of HBV resistance. Generally, resistance against a nucleoside analogue should be treated with a nucleotide analogue and vice versa. In real life, treatment with TDF has shown effectiveness against most kinds of HBV variants associated with resistance against either nucleoside or nucleotide analogues. Thus, a switch to monotherapy with TDF was shown to be very effective in patients with resistance to LAM and also in patients with resistance to ADV in European and Asian patients (van Bömmel 2010; Huang 2017). In a randomised study, patients with resistance to LAM did not show a better response to a combination treatment of TDF plus Emtricitabine compared to TDF monotherapy (Fung 2014). In another study, it was observed that monotherapy with TDF was superior to Entecavir-Adefovir combination treatment in NA-resistant patients with suboptimal response to Lamivudine-Adefovir (Lee 2018). Thus, most guidelines recommend a switch to TDF or TAF in patients with treatment failure due to resistance (EASL 2017; WHO 2024), see Table 6. The combination of TDF with a nucleoside analogue might be useful in patients with multiple pre-treatments who have accumulated different resistance mutations (Petersen 2012; van Bömmel 2012). If a Tenofovir resistance is suspected, the addition of ETV may be considered, however, due to the rarity of this event in real-world settings, evidence about the efficacy is scarce.

Table 6. Management of patients with NA resistance. Recommendations on alternative regimes (switching). Table reproduced from EASL Clinical Practices Guidelines (EASL 2017).

Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADF resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistance: switch to TDF or TAF If HBV DNA plateaus: add ETV*** or switch to ETV
TDF or TAF resistance**	If LAM-naïve: switch to ETV If LAM-R: add ETV*
Multidrug resistance	Switch to ETV plus TDF or TAF combination

ETV = entecavir; TDF = tenofovir disoproxil fumarate; TAF = tenafovir alafenamide; LAM = lamivudine; ADV = adefovir, TBV = telbivudine.

* The long-term safety of these combinations is unknown.
** Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile.
*** Especially in patients with ADV resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted.

Treatment Monitoring (How to monitor treatment?)

Baseline

Prior to the initiation of therapy, baseline parameters should be measured. The number of recommended tests varies among different guidelines and needs to be adjusted according to local circumstances (EASL 2017; Cornberg 2021; KASL 2022; WHO 2024).

Virological tests

- Quantitative HBV DNA levels, measured with a highly sensitive assay
- HBsAg, ideally with a quantitative assay
- HBeAg
- Anti-HBe
- Anti-HBs and anti-HBc may play a role in the initial diagnosis of HBV infection
- Screening for concomitant viral infections (HIV, HCV, HDV)

HBV genotyping is only recommended in patients who are considered candidates for treatment with IFN. HBV resistance testing can be useful in patients with prior failure to more than one NA, but this is not a standard diagnostic approach.

General lab tests

- Serum levels of alanine transaminase (ALT) and other liver function tests
- Kidney function tests
- complete blood count
- Assessment of liver parenchyma status
- Ultrasound imaging
- Non-invasive fibrosis assessment: transient elastography, APRI-Score
- Liver biopsy and histology: no routine use

Under therapy

During therapy, HBV DNA, ALT and creatinine levels should be measured after 4 to 6 weeks and later every 3 months. The early identification of viral resistance is crucial to adjust the therapy if necessary. Patients with a stable suppression of HBV replication to levels below 300 copies/mL (60 IU/mL) and no signs of severe liver damage may be scheduled at 6-month surveillance intervals. HBsAg and, in HbeAg-positive patients, HBeAg and anti-HBe should also be measured once HBV DNA levels have become undetectable, to detect serologic response and therapeutic endpoints. When using TDF as a therapeutic regime, renal function tests and regular assessment of bone density might be helpful to detect long-term side effects of treatment.

HCC risk

The risk for HCC development remains increased even in patients with complete viral suppression during long-term treatment with NA. However, identifying those patients with a greater risk and the necessity for more regular monitoring remains challenging. Scoring systems can help estimate the individual risk of HCC development. Several scoring systems have been proposed to monitor the HCC risk during NA treatment including the HCC-Rescue, CAMD and mREACH-B score. Most risk scores were developed and tested using Asian cohorts, they perform almost equally. However, a recent meta-analysis favoured the HCC-Rescue score in terms of clinical practicability and risk group discrimination (Xu 2023). For European individuals, the PAGE-B score, which is based on different parameters, seems to allow a more precise prediction as compared to the other scores (Papatheodoridis 2016a). The newly developed aMAP score underwent a validation process with patient groups of different ethnicities and with different forms of hepatitis. Even non-viral hepatitis was included. It showed a good discriminatory ability and calibration and could therefore be useful in various clinical settings worldwide (Fan 2020). A comparison of selected risk scores can be found in Table 7. The scores with their corresponding cut-offs may help to determine, which CHB patients have an elevated risk for HCC development. These patients, along with other high-risk subgroups (cirrhosis, family history of HCC) should be subject to regular screening, including ultrasound imaging and measuring of AFP levels (WHO 2024).

Table 7. HCC risk scores (under treatment)

Score	Parameters	Cohorts	Cut-Off*	Publication
HCC-Rescue	age, sex, presence of cirrhosis	Asian patients	65/85	(Sohn 2017)
APA-B	age, AFP, platelet count	Asian patients	6/10	(Chen 2017)
mREACH-B	age, sex, ALT, liver stiffness, HBeAg status	Asian patients	–	(Lee 2014)
PAGE B	age, sex platelet count	European patients	10/18	(Papatheodoridis 2016a)
CAMD	age, sex, presence of diabetes mellitus, presence of cirrhosis	Asian patients	8/14	(Hsu 2018)
aMAP	age, sex, albumin, total bilirubin, platelet count	Asian and European patients, also treated HCV patients	50/60	(Fan 2020)

Data overview in courtesy of Rong Fan (Guangzhou, China). This list is not comprehensive. *Cut-off values between low and intermediate (left) and intermediate and high-risk groups (right).

Prognostic factors and treatment response

Effective treatment of HBV ideally reaches defined endpoints and results in a reduction of overall disease burden. It is important to assess the treatment response, regardless of the form of treatment used.

Criteria for treatment response:

Virologic response

- Sustained decrease of HBV DNA, to at least <2,000 IU/mL (corresponding to <10,000 copies/mL), ideally to <60 IU/mL (<300 copies/mL)
- Sustained HBeAg seroconversion in former HBeAg-positive patients
- Ideally: loss of HBsAg with or without the appearance of anti-HBs

Biochemical response

- Sustained ALT normalisation

Histologic response

- Reduction of fibrosis (histological staging)
- Reduction of inflammatory activity (histological grading).

Potential long-term effects

- Avoidance of cirrhosis, hepatocellular carcinoma (HCC), transplantation and death

Baseline factors: Several factors are associated with long-term remission and may help to guide treatment decisions. Pre-treatment factors predictive of HBeAg seroconversion are low viral load, high ALT levels (above 2-5 x ULN) and high histological grading (Wong 1993; Perrillo 2002; Flink 2006; Lai 2007; Yuen 2007; Buster 2009). These general baseline predictors are particularly relevant for treatment regimens with PEG-IFN α but may be in part also for NAs. A pooled analysis from the two largest trials using PEG-IFN α-2a or -2b in CHB tried to calculate a score predicting successful interferon therapy based on an individual patient's characteristics (viral load, ALT level, HBV genotype, age, gender). However, this approach may only be feasible in HBeAg-positive patients. (Buster 2009).

HBV genotypes: HBV genotypes are associated with IFN α treatment success. Patients with HBV genotype A, prevalent in northern Europe and the US, show a much higher rate of HBeAg and HBsAg seroconversion than patients with HBV genotype D, prevalent in the south of Europe, or the HBV genotypes B or C originating from Asia (Flink 2006; Keeffe 2007). During treatment with nucleos(t)ide analogues, suppression of HBV replication and induction of HBeAg loss can be achieved regardless of the present genotype. However, HBsAg loss was almost exclusively observed in patients with genotypes A or D.

HBV DNA: During antiviral therapy, the decrease of HBV DNA levels from baseline is the most important tool in monitoring treatment efficacy. A complete response to antiviral therapy is defined as the suppression of HBV DNA below the limit of detection as measured by a sensitive real-time PCR assay. Incomplete suppression is characterised by persistent HBV replication despite antiviral therapy. Ongoing HBV replication in the presence of the drug should be avoided to prevent the selection of resistant HBV strains in the so-called "plateau phases". A breakthrough of HBV DNA during continuous NA treatment may be caused by viral resistance; however, if NAs with high genetic barriers against resistance such as ETV or TFD are used, non-adherence to the antiviral treatment is more likely. Measuring HBV DNA kinetics early during therapy will help guide antiviral treatment and establish early stopping rules or add-on strategies to avoid antiviral failure.

An incomplete or partial virologic response to NAs is defined as a decrease of HBV DNA of more than 1 log10 IU/mL but remaining measurable (Lavanchy 2004). The timespan to reach HBV DNA suppression depends on the type of treatment: for agents with a high genetic barrier against resistance (ETV or TDF), a partial response is defined after 12 months and for substances with a low genetic barrier like LAM or LdT, after 6 months of monotherapy. In case of partial response to a drug with a low genetic barrier, an appropriate rescue therapy should be initiated. It was recently shown that patients with partial response to LAM or ADV have a high probability of responding to TDF monotherapy, without risking the development of resistance (van Bömmel 2010; Heathcote 2011; Berg 2014). For patients with partial response to a drug with a high genetic barrier such as ETV or TDF, current guidelines recommend considering the initiation of a combination treatment. However, this might be necessary only in a minority of patients, as published long-term studies have shown that the continuation of a first-line monotherapy with ETV or TDF increases the percentage of patients with undetectable HBV DNA over time without leading to resistance development (Chang 2010b; Buti 2015). Therefore, in case of incomplete viral suppression at week 48, a continuation of monotherapy with TDF or ETV 1 mg is advisable as long as HBV DNA levels decrease continuously. However, the debate on whether to switch treatment or add a second drug for optimal management is not yet resolved.

Timepoint of HBeAg-loss. In patients who were treated with PEG-IFN α-2b as monotherapy or in combination with LAM, the loss of HBeAg within the first 32 weeks of treatment was shown to be an on-treatment predictor for HBsAg loss during a mean period of 3.5 years after the end of treatment. HBsAg loss was found in 36% of the patients with early HBeAg loss and only in 4% of the patients with HBeAg loss after 32 weeks of treatment (Buster 2009).

HBsAg levels: The response of HBeAg-positive and HBeAg-negative patients to PEG-IFN treatment can be predicted by measuring HBsAg levels before and changes in HBsAg levels during treatment. During PEG-IFN treatment for HBeAg-positive chronic HBV infection, an absence of a

decline in HBsAg levels at week 12 of treatment reduced the probability of response to less than 5% in one study (Sonneveld 2010). In the NEPTUNE trial investigating the predictive value of HBsAg levels in HBeAg-positive patients receiving PEG-IFN α -2a over 48 weeks, it was shown that in patients achieving suppression of HBsAg to levels below 1, 500 IU/mL after 12 weeks of treatment, the chance of reaching HBeAg seroconversion, suppression of HBV DNA to undetectable levels and HBsAg loss 6 months after treatment was higher. In patients still showing HBsAg levels over 20, 000 IU/mL after 12 weeks of treatment, none of the endpoints was achieved (Liaw 2011). Also, in HBeAg-negative patients, the decrease of HBsAg after 12 weeks of PEG-IFN α treatment can predict long-term response. This prediction can be made even more precise regarding the kinetics of both HBsAg and HBV DNA (Moucari 2009).

Treatment cessation (When to stop?)

Treatment duration and stopping rules

Treatment with modern and potent NAs usually results in a quick and durable suppression of HBV DNA replication. While there is widespread agreement among the guidelines on who to treat, it is yet under debate how long the therapy should last. The duration of NA therapy was primarily set to an indefinite length, due to the observed relapse in disease activity after short-term NA application. However, treatment discontinuation may be a novel approach to induce functional cure in a subset of patients. The recommendations about when to discontinue treatment depend on the treatment endpoint the patients have reached.

Patients with HBsAg loss

Treatment with NAs can safely be withdrawn in patients who reach the endpoint of functional cure, i.e. HBsAg loss or seroconversion to anti-HBs. This status is durable and clinical or virological reversion is rare in these patients and usually without complications (Kim 2014). The HCC risk in patients who achieve HBsAg loss under therapy seems to be much lower than those only achieving virological suppression (Yip 2019).

HBeAg seroconversion

Treatment-induced HBeAg loss or seroconversion in previously HBeAg-positive patients is one of the treatment endpoints. The seroconversion is seen as a surrogate marker for silencing HBV transcriptional activity. Current guidelines recommend a consolidation phase of at least another 12 months before stopping NAs in these patients to reduce the risk of sero-reversion (EASL 2017; Terrault 2018).

HBeAg-negative patients with detectable HBsAg

As previously described, induced HBsAg loss occurs in only around 1% of HBeAg-negative patients on treatment with NAs. Unable to reach a defined endpoint, these patients may therefore undergo an almost lifelong treatment. Although the safety of modern NAs has been proven, long-term side effects and treatment costs may be of concern in some settings. An off-treatment "cure" is desired by both patients and clinicians. While practical details are still under debate, newer guidelines acknowledge this novel approach as a possible strategy for eligible patients. Treatment discontinuation leads to a relapse in HBV replication in almost all patients, often in combination with signs of disease activity, such as increased ALT levels (Ghany 2020). Those relapses are in fact associated with a reactivation of the previously "hibernating" immune system. Some patients lose their HBsAg in the course of this immune reactivation (Tout 2021). The potential of this approach was demonstrated in the FINITE trial, where 43% of non-cirrhotic patients did not require re-therapy after TDF discontinuation, either by achieving HBsAg loss or remaining in a status with low viraemia (Berg 2017). In a randomised controlled trial (STOP-NUC), comparing NA discontinuation to ongoing treatment, 10% of the patients lost their HBsAg and 40% remained in virological remission in the discontinuation arm (van Bömmel 2023). A typical disease course after NA cessation is shoen in Figure 5.

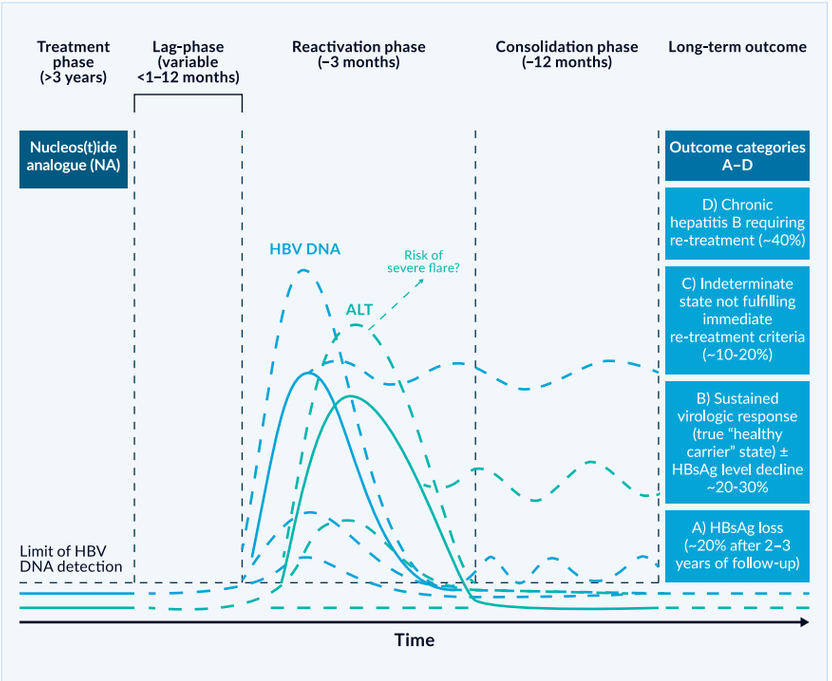

Figure 5. Dynamics of HBV DNA and ALT levels after NA treatment cessation in HBeAg-negative patients, following a period of treatment for at least 3 years. Different long-term outcomes are listed. Figure reproduced from the report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference (Cornberg 2020).

Who is eligible for a stopping NA?

There is widespread agreement that patients for this approach must be carefully selected and closely monitored, preferably in trials. If monitoring and induction of re-treatment or emergency handling of patients with a severe relapse are not guaranteed, this strategy may not be safe for the patients. The advantages and disadvantages of therapy cessation need to be carefully weighed: on the one hand, there is a higher chance of inducing HBsAg loss and functional cure, in around 10% of the patients. Even more patients proceed to a state with low disease activity, without the need for re-treatment. On the other hand, most patients experience an increase in HBV DNA and ALT levels and excellent patient adherence is required since regular clinical follow-up visits should be performed. In about half of the patients, subsequent re-treatment is necessary (Berg 2021). It is yet difficult to predict the course of the disease and the probability of reaching HBsAg loss in patients with NA discontinuation. As evidence is still scarce, universal stopping rules are not yet defined. The selection of patients that most likely benefit from this approach is currently under investigation in studies, but the first results may help to select those that most likely lose HBsAg or remain virologically suppressed. A low pre-treatment viraemia, a decrease in quantitative HBsAg under therapy and low HBsAg levels upon stopping are positive predictive markers for success (Liu 2019). Newer biomarkers such as HBV RNA and HB core-related antigen (HBcrAg) may help to further stratify the groups on treatment concerning their risk of severe relapse or more beneficial outcomes after cessation (Berg 2021). Due to the risk of severe decompensation, all patients with cirrhosis should remain on infinite NA treatment as long as HBsAg is measurable. In Figure 6, an algorithm for consideration of NA discontinuation is displayed.

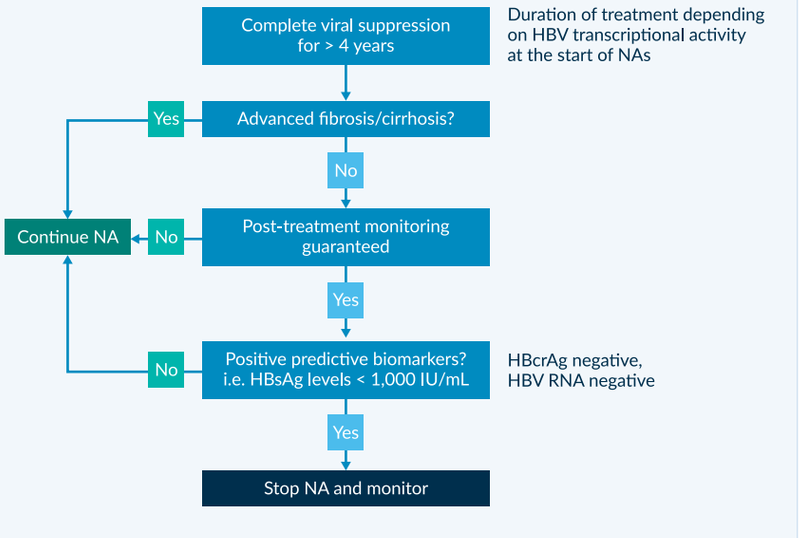

Figure 6. Proposed algorithm and decision aid for an NA treatment discontinuation approach.

PEG-IFN

PEG-IFN α should be administered for 48 weeks in HBeAg-positive and HBeAg-negative patients. If no decrease in HBV DNA or/and in HBsAg levels can be noted after 12 weeks of treatment, further response is unlikely, and treatment may be stopped early in agreement with the patient.

Outlook

In today's world, there are many strategies for preventing Hepatitis B, monitoring patients on and off treatment and finding an appropriate therapy for the vast majority of the infected. However, the complete eradication of HBV from infected individuals cannot be achieved by any of the currently available treatments, this is due to the persistence of HBV cccDNA in the hepatocytes. In the dynamic field of HBV research, many teams are working on the development of a complete, long-lasting and even "sterile" cure. In addition, new biomarkers emerge, which help to predict outcomes for recently developed treatment strategies.

New parameters for treatment monitoring

Currently, most clinicians around the world use quantitative HBV DNA, HBsAg and anti-HBs, as well as qualitative anti-HBc, HBeAg and anti-HBe for Hepatitis B diagnostics and treatment monitoring. The innovation of newer biomarkers can help to gain a deeper understanding of disease dynamics both on and off treatment, see Figure 7. Levels of Hepatitis B core-related antigens (HBcrAg) may help to predict HBsAg seroclearance (Tseng 2023). HBV RNA may act as a parameter to determine cccDNA transcriptional activity (Wang 2016), this could help to predict the outcome in patients where treatment cessation is planned (Seto 2021). The emergence of those and other biomarkers supports clinicians in further individualising and planning therapeutic approaches.

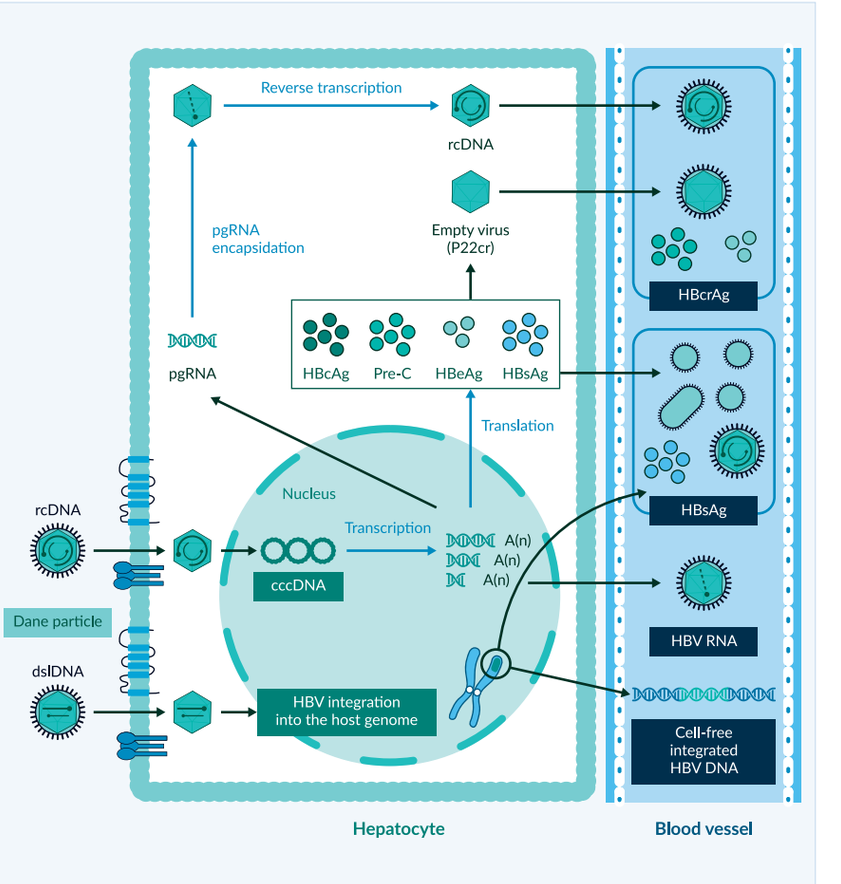

Figure 7. Overview of old and new biomarkers for disease and treatment monitoring in Hepatitis B, both in hepatocytes and bloodstream. Figure taken from KASL clinical practice guidelines for management of chronic hepatitis B (KASL 2022).

New therapeutic strategies

Even after HBsAg loss, the remainder of HBV stays in the body in the form of cccDNA. Although generally rare, HBV reactivation may occur in patients undergoing immunosuppression. In addition, some risk of HCC development remains after seroclearance (Yang 2022). A "sterile" cure with complete elimination of cccDNA is not yet achievable with current therapeutic regimes but remains the ultimate goal in new drug development. In addition, the optimisation of available antiviral options as well as new therapeutic targets to achieve HBsAg loss are similarly important. Different approaches are already being investigated and some potential candidates have reached phase II and III trials (see Table 8, Figure 8).

Table 8. New therapeutic approaches

Drug type	Mode of action
Capsid assembly modulators	Inhibition of capsid assembly, reduction of cccDNA expression
Anti-sense oligonucleotides	Inhibition of HBsAg production
siRNA	Silencing of viral RNA, inference with viral protein production
HBsAg release inhibitors	Inhibition of HBsAg assembly and release
Gene editing	Specific cutting and destruction of HBV DNA
Therapeutic vaccine	Enhancement of host immune system by exposition to antigens
Toll-like receptor agonists	Activation of innate immune system by inducing specific pathways
Checkpoint inhibitors	Reversion of T cell dysfunction
Monoclonal antibodies	Targeted against viral structures

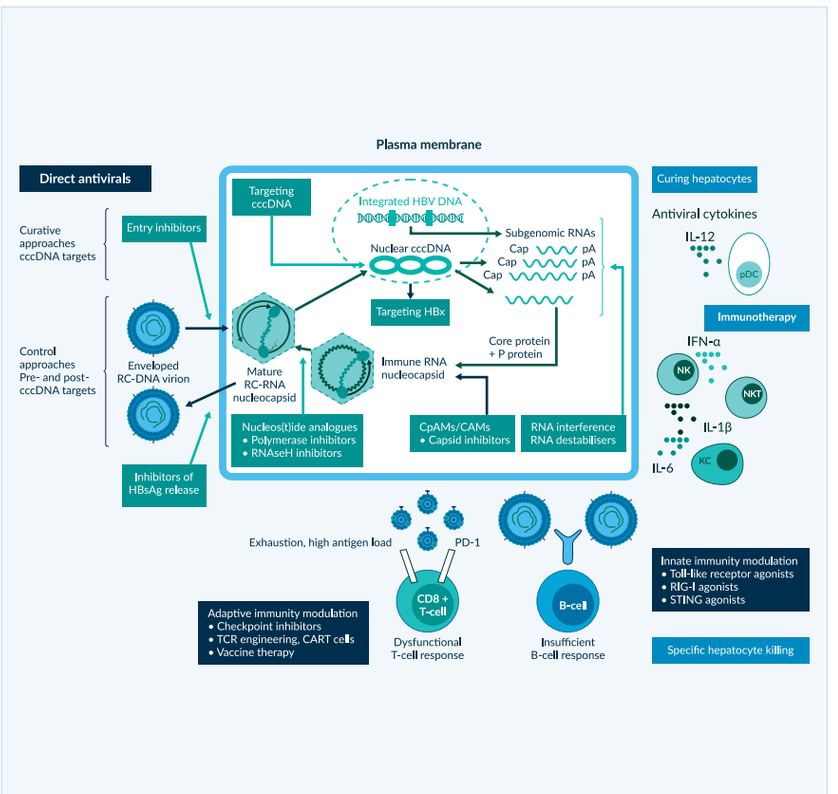

Figure 8. Overview of current and possible future therapeutic targets and corresponding drug classes. Reproduced from a strategy paper on Hepatitis B cure (Revill 2019).

The combination of two or more therapeutic options directed at different targets in the viral lifecycle seems promising in terms of stronger viral suppression and immune stimulation. Complementary strategies may help to reach a functional or even sterilising cure by reducing HBV replication and HBsAg load while simultaneously reinforcing the host immune system to fulfil its role in HBV elimination (Figure 9). While NAs currently remain the backbone of therapy, first trial results of new drugs are promising and may lead to a new era of Hepatitis B treatment. Replication inhibitors, antigen reducers and immune modulators are the main three classes of new therapeutics (Figure 10). The combination of those different mechanisms of action potentially leads to a stronger antiviral activity. However, its superiority to monotherapies and long-term safety must be assessed in future trials (Feld 2023).

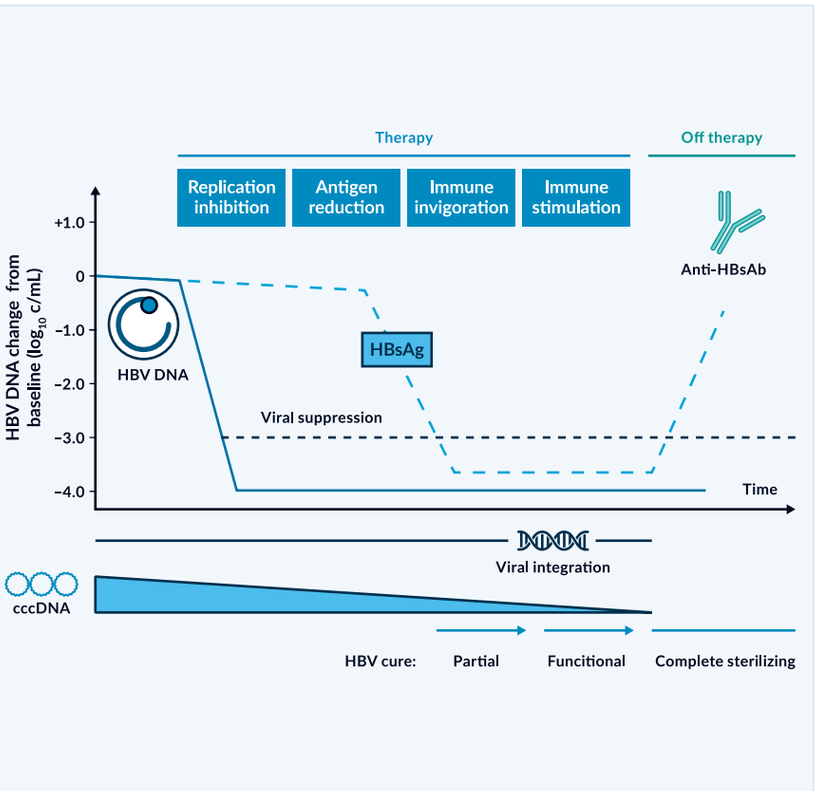

Figure 9. The potential of combination therapy with agents directed at different parts of the viral life cycle and host immune system. Figure reproduced from a review article concerning New Perspectives on Development of Curative Strategies for Chronic Hepatitis B (Feld 2023).

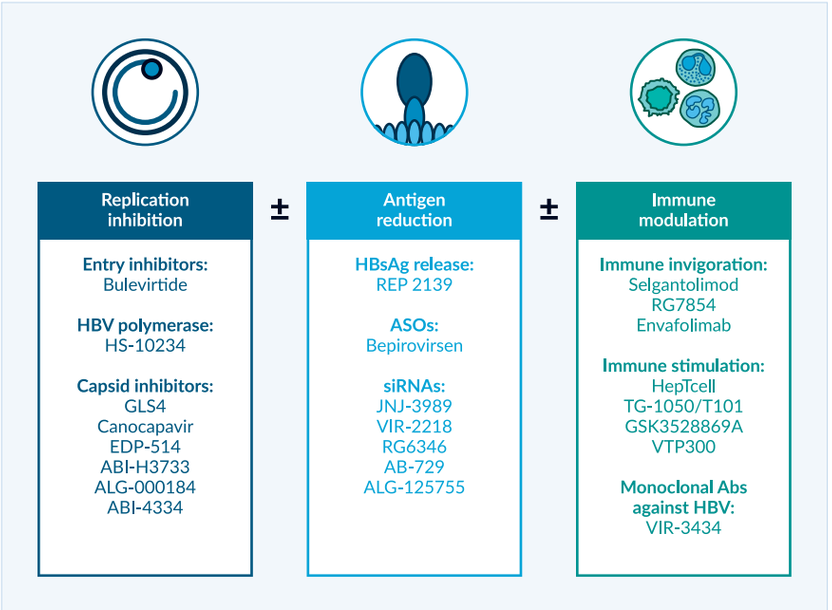

Figure 10. Different classes of new therapeutic agents and an (incomplete) list of substances currently under investigation. Figure reproduced from a review article concerning New Perspectives on Development of Curative Strategies for Chronic Hepatitis B (Feld 2023).

The future importance and clinical value of new therapeutic options is not yet easy to determine. The field of HBV therapy is dynamic and the list of the most promising drug candidates changes fast. Different websites have regularly updated databases on current drug development. Interested readers should pay continuous attention. The Hepatitis B Foundation displays an overview of current trials and candidates: https://www.hepb.org/treatment-and-management/drug-watch/

Elimination of Hepatitis B as a global threat and reason for disease burden remains the ultimate goal that may be achieved by concerted action in the next decades.

References

Agarwal, K., Brunetto, M. & Seto, W. K. et al. (2018) 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. Journal of hepatology 68 (4), 672–681.

Artz, A. S., Somerfield, M. R. & Feld, J. J. et al. (2010) American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. Journal of clinical oncology official journal of the American Society of Clinical Oncology 28 (19), 3199–3202.

Berg, T. & Lampertico, P. (2021) The times they are a-changing - A refined proposal for finite HBV nucleos(t)ide analogue therapy. Journal of hepatology 75 (2), 474–480.

Berg, T., Marcellin, P. & Zoulim, F. et al. (2010) Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. Gastroenterology 139 (4), 1207–1217.

Berg, T., Simon, K.-G. & Mauss, S. et al. (2017) Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study. Journal of hepatology 67 (5), 918–924.

Berg, T., Zoulim, F. & Moeller, B. et al. (2014) Long-term efficacy and safety of emtricitabine plus tenofovir DF vs. tenofovir DF monotherapy in adefovir-experienced chronic hepatitis B patients. Journal of hepatology 60 (4), 715–722.

Borg, M. J. ter, Leemans, W. F., Man, R. A. de & Janssen, H. L. A. (2008) Exacerbation of chronic hepatitis B infection after delivery. Journal of viral hepatitis 15 (1), 37–41.

Brunetto, M. R., Oliveri, F., Colombatto, P., Coco, B., Ciccorossi, P. & Bonino, F. (2003) Treatment of HBeAg-negative chronic hepatitis B with interferon or pegylated interferon. Journal of hepatology 39 Suppl 1, S164-7.

Buster, E. H. C. J., Flink, H. J. & Simsek, H. et al. (2009) Early HBeAg loss during peginterferon alpha-2b therapy predicts HBsAg loss: results of a long-term follow-up study in chronic hepatitis B patients. The American journal of gastroenterology 104 (10), 2449–2457.

Buti, M., Gane, E. & Seto, W. K. et al. (2016) Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. The lancet. Gastroenterology & hepatology 1 (3), 196–206.

Buti, M., Tsai, N. & Petersen, J. et al. (2015) Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Digestive diseases and sciences 60 (5), 1457–1464.

Chan, H. L. Y., Buti, M. & Lim, Y.-S. et al. (2024) Long-Term Treatment With Tenofovir Alafenamide for Chronic Hepatitis B Results in High Rates of Viral Suppression and Favorable Renal and Bone Safety. The American journal of gastroenterology 119 (3), 486–496.

Chan, H. L. Y., Chan, C. K. & Hui, A. J. et al. (2014) Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 146 (5), 1240–1248.

Chan, H. L.-Y., Leung, N. W.-Y. & Hui, A. Y. et al. (2005) A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. Annals of internal medicine 142 (4), 240–250.

Chang, T.-T., Gish, R. G. & Hadziyannis, S. J. et al. (2005) A dose-ranging study of the efficacy and tolerability of entecavir in Lamivudine-refractory chronic hepatitis B patients. Gastroenterology 129 (4), 1198–1209.

Chang, T.-T., Lai, C.-L. & Kew Yoon, S. et al. (2010a) Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology 51 (2), 422–430.

Chang, T.-T., Liaw, Y.-F. & Wu, S.-S. et al. (2010b) Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 52 (3), 886–893.

Chen, C.-H., Lee, C.-M. & Lai, H.-C. et al. (2017) Prediction model of hepatocellular carcinoma risk in Asian patients with chronic hepatitis B treated with entecavir. Oncotarget 8 (54), 92431–92441.

Chen, C.-J., Yang, H.-I. & Su, J. et al. (2006) Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 295 (1), 65–73.

Chen, J.-D., Yang, H.-I. & Iloeje, U. H. et al. (2010) Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology 138 (5), 1747–1754.

Choi, W.-M., Kim, G.-A. & Choi, J. et al. (2024) Non-linear association of baseline viral load with on-treatment hepatocellular carcinoma risk in chronic hepatitis B. Gut 73 (4), 649–658.

Choi, W.-M., Yip, T. C.-F. & Wong, G. L.-H. et al. (2023) Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- vs. entecavir-based regimens: Individual patient data meta-analysis. Journal of hepatology 78 (3), 534–542.

Cornberg, M., Lok, A. S.-F., Terrault, N. A. & Zoulim, F. (2020) Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference‡. Journal of hepatology 72 (3), 539–557.

Cornberg, M., Sandmann, L. & Protzer, U. et al. (2021) S3 Guideline of the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) on the Prophylaxis, Diagnosis, and Treatment of Hepatitis B Virus Infection: S3-Leitlinie der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) zur Prophylaxe, Diagnostik und Therapie der Hepatitis-B-Virusinfektion - (AWMF-Register-Nr. 021-11). Zeitschrift fur Gastroenterologie 59 (7), 691–776.

Craxi, A., Di Bona, D. & Cammà, C. (2003) Interferon-alpha for HBeAg-positive chronic hepatitis B. Journal of hepatology 39 Suppl 1, S99-105.

Da Wang, F., Zhou, J. & Li, L.-Q. et al. (2023) Improved bone and renal safety in younger tenofovir disoproxil fumarate experienced chronic hepatitis B patients after switching to tenofovir alafenamide or entecavir. Annals of hepatology 28 (5), 101119.

Dienstag, J. L., Perrillo, R. P., Schiff, E. R., Bartholomew, M., Vicary, C. & Rubin, M. (1995) A preliminary trial of lamivudine for chronic hepatitis B infection. The New England journal of medicine 333 (25), 1657–1661.

EASL (2017) Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of hepatology 67 (2), 370–398.

Fan, R., Papatheodoridis, G. & Sun, J. et al. (2020) aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. Journal of hepatology 73 (6), 1368–1378.

Feld, J. J., Lok, A. S. & Zoulim, F. (2023) New Perspectives on Development of Curative Strategies for Chronic Hepatitis B. Clinical gastroenterology and hepatology the official clinical practice journal of the American Gastroenterological Association 21 (8), 2040–2050.

Fleischer, R. D. & Lok, A. S. F. (2009) Myopathy and neuropathy associated with nucleos(t)ide analog therapy for hepatitis B. Journal of hepatology 51 (4), 787–791.

Flink, H. J., van Zonneveld, M., Hansen, B. E., Man, R. A. de, Schalm, S. W. & Janssen, H. L. A. (2006) Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. The American journal of gastroenterology 101 (2), 297–303.

Fung, S., Kwan, P. & Fabri, M. et al. (2014) Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 146 (4), 980–988.

Ghany, M. G., Feld, J. J. & Chang, K.-M. et al. (2020) Serum alanine aminotransferase flares in chronic hepatitis B infection: the good and the bad. The lancet. Gastroenterology & hepatology 5 (4), 406–417.

Gish, R. G., Chang, T.-T. & Lai, C.-L. et al. (2010) Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naïve HBeAg-positive patients with chronic hepatitis B. Journal of viral hepatitis 17 (1), 16–22.

Hadziyannis, S. J. & Papatheodoridis, G. V. (2006a) Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Seminars in liver disease 26 (2), 130–141.

Hadziyannis, S. J., Tassopoulos, N. C. & Heathcote, E. J. et al. (2006b) Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 131 (6), 1743–1751.

Hadziyannis, S. J. & Vassilopoulos, D. (2001) Hepatitis B e antigen-negative chronic hepatitis B. Hepatology 34 (4 Pt 1), 617–624.

Heathcote, E. J., Marcellin, P. & Buti, M. et al. (2011) Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic

hepatitis B. Gastroenterology 140 (1), 132–143.

Hosaka, T., Suzuki, F. & Kobayashi, M. et al. (2013) Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 58 (1), 98–107.

Hou, J., Yin, Y.-K. & Xu, D. et al. (2008) Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. Hepatology 47 (2), 447–454.

Hou, J.-L., Zhao, W. & Lee, C. et al. (2020) Outcomes of Long-term Treatment of Chronic HBV Infection With Entecavir or Other Agents From a Randomized Trial in 24 Countries. Clinical gastroenterology and hepatology the official clinical practice journal of the American Gastroenterological Association 18 (2), 457-467.e21.

Hsu, Y.-C., Yip, T. C.-F. & Ho, H. J. et al. (2018) Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B. Journal of hepatology 69 (2), 278–285.

Huang, D. Q., Tamaki, N. & Lee, H. W. et al. (2023) Outcome of untreated low-level viremia versus antiviral therapy-induced or spontaneous undetectable HBV-DNA in compensated cirrhosis. Hepatology 77 (5), 1746–1756.

Huang, M., Lin, G. & Shi, H. et al. (2017) TDF Monotherapy Is Effective Regardless of Prior Nucleos(t)ide Analogue Treatment in Chronic Hepatitis B Patients in China. BioMed research international 2017, 2463197.

Iloeje, U. H., Yang, H.-I., Su, J., Jen, C.-L., You, S.-L. & Chen, C.-J. (2006) Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 130 (3), 678–686.

Janssen, H. L. A., van Zonneveld, M. & Senturk, H. et al. (2005) Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet (London, England) 365 (9454), 123–129.

Jochum, C., Maischack, F. & Anastasiou, O. E. et al. (2016) Therapie der akuten fulminanten Hepatitis B mit Nucleos(t)id-Analogen ist sicher und führt nicht zur Chronifizierung der Hepatitis B. Zeitschrift fur Gastroenterologie 54 (12), 1306–1311.

KASL (2022) KASL clinical practice guidelines for management of chronic hepatitis B. Clinical and Molecular Hepatology 28 (2), 276–331.

Keeffe, E. B., Zeuzem, S. & Koff, R. S. et al. (2007) Report of an international workshop: Roadmap for management of patients receiving oral therapy for chronic hepatitis B. Clinical gastroenterology and hepatology the official clinical practice journal of the American Gastroenterological Association 5 (8), 890–897.

Kim, G.-A., Lim, Y.-S. & An, J. et al. (2014) HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 63 (8), 1325–1332.

Kumar, M., Satapathy, S. & Monga, R. et al. (2007) A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology 45 (1), 97–101.

Lai, C.-L., Gane, E. & Liaw, Y.-F. et al. (2007) Telbivudine versus lamivudine in patients with chronic hepatitis B. The New England journal of medicine 357 (25), 2576–2588.

Lai, C.-L., Leung, N. & Teo, E.-K. et al. (2005) A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 129 (2), 528–536.

Lampertico, P., Del Ninno, E. & Viganò, M. et al. (2003) Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. Hepatology (Baltimore, Md.) 37 (4), 756–763.

Lampertico, P., Viganò, M. & Di Costanzo, G. G. et al. (2013) Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B. Gut 62 (2), 290–298.

Lampertico, P., Viganò, M. & Facchetti, F. et al. (2010) 1009 EFFECTIVENESS OF ENTECAVIR FOR NUC-NAIVE, HBEAG-NEGATIVE CHRONIC HEPATITIS B PATIENTS IN CLINICAL PRACTICE: A 2-YEAR MULTICENTER COHORT STUDY IN 311 PATIENTS. Journal of hepatology 52, S389-S390.

Lange, C. M., Bojunga, J. & Hofmann, W. P. et al. (2009) Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 50 (6), 2001–2006.

Lau, G., Yu, M.-L. & Wong, G. et al. (2021) APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatology International 15 (5), 1031–1048.

Lau, G. K. K., Piratvisuth, T. & Luo, K. X. et al. (2005) Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. The New England journal of medicine 352 (26), 2682–2695.

Lavanchy, D. (2004) Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. Journal of viral hepatitis 11 (2), 97–107.

Lee, H. W., Yoo, E. J. & Kim, B. K. et al. (2014) Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. The American journal of gastroenterology 109 (8), 1241–1249.

Lee, S. H., Cheon, G. J. & Kim, H. S. et al. (2018) Tenofovir disoproxil fumarate monotherapy is superior to entecavir-adefovir combination therapy in patients with suboptimal response to lamivudine-adefovir therapy for nucleoside-resistant HBV: a 96-week prospective multicentre trial. Antiviral therapy 23 (3), 219–227.

Liaw, Y.-F., Gane, E. & Leung, N. et al. (2009) 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology 136 (2), 486–495.

Liaw, Y.-F., Jia, J.-D. & Chan, H. L. Y. et al. (2011) Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. Hepatology 54 (5), 1591–1599.

Lim, Y.-S., Chan, H. L. Y. & Ahn, S. H. et al. (2023) Tenofovir alafenamide and tenofovir disoproxil fumarate reduce incidence of hepatocellular carcinoma in patients with chronic hepatitis B. JHEP reports innovation in hepatology 5 (10), 100847.

Liu, J., Li, T., Zhang, L. & Xu, A. (2019) The Role of Hepatitis B Surface Antigen in Nucleos(t)ide Analogues Cessation Among Asian Patients With Chronic Hepatitis B: A Systematic Review. Hepatology 70 (3), 1045–1055.

Lok, A. S., Trinh, H. & Carosi, G. et al. (2012) Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. Gastroenterology 143 (3), 619-628.e1.

Lumley, S. F., Delphin, M. & Mokaya, J. F. et al. (2024) A systematic review and meta-analysis of the risk of hepatitis B virus (HBV) resistance in people treated with entecavir or tenofovir. Journal of clinical virology the official publication of the Pan American Society for Clinical Virology 174, 105711.

Manesis, E. K. & Hadziyannis, S. J. (2001) Interferon alpha treatment and retreatment of hepatitis B e antigen-negative chronic hepatitis B. Gastroenterology 121 (1), 101–109.

Manno, M., Cammà, C. & Schepis, F. et al. (2004) Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology 127 (3), 756–763.

Marcellin, P., Ahn, S. H. & Ma, X. et al. (2016) Combination of Tenofovir Disoproxil Fumarate and Peginterferon α-2a Increases Loss of Hepatitis B Surface Antigen in Patients With Chronic Hepatitis B. Gastroenterology 150 (1), 134-144.e10.

Marcellin, P., Bonino, F. & Lau, G. K. K. et al. (2009) Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. Gastroenterology 136 (7), 2169-2179.e1-4.

Marcellin, P., Chang, T.-T. & Lim, S. G. et al. (2003) Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. The New England journal of medicine 348 (9), 808–816.

Marcellin, P., Gane, E. & Buti, M. et al. (2013) Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet (London, England) 381 (9865), 468–475.

Marcellin, P., Heathcote, J. E. & Buti, M. et al. (2011) Characterization of HBsAg Kinetics and HBsAg Seroconversion in Patients with Chronic Hepatitis B (CHB) Treated with Tenofovir Disoproxil Fumarate (TDF).

Marcellin, P., Lau, G. K. K. & Bonino, F. et al. (2004) Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. The New England journal of medicine 351 (12), 1206–1217.

Marcellin, P., Wursthorn, K. & Wedemeyer, H. et al. (2015) Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy. Journal of hepatology 62 (1), 41–47.

Martinot-Peignoux, M., Lapalus, M. & Laouénan, C. et al. (2013) Prediction of disease reactivation in asymptomatic hepatitis B e antigen-negative chronic hepatitis B patients using baseline serum measurements of HBsAg and HBV-DNA. Journal of clinical virology the official publication of the Pan American Society for Clinical Virology 58 (2), 401–407.

McMahon, B. J., Alward, W. L. & Hall, D. B. et al. (1985) Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. The Journal of infectious diseases 151 (4), 599–603.

Moini, M. & Fung, S. (2022) HBsAg Loss as a Treatment Endpoint for Chronic HBV Infection: HBV Cure. Viruses 14 (4).

Mommeja-Marin, H., Mondou, E., Blum, M. R. & Rousseau, F. (2003) Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. Hepatology (Baltimore, Md.) 37 (6), 1309–1319.

Morais, E., Mason, L. & Dever, J. et al. (2023) Clinical Consequences of Hepatitis B Surface Antigen Loss in Chronic Hepatitis B Infection: A Systematic Literature Review and Meta-Analysis. Gastro hep advances 2 (7), 992–1004.

Moses, S. E., Lim, Z. Y. & Sudhanva, M. et al. (2006) Lamivudine prophylaxis and treatment of hepatitis B Virus-exposed recipients receiving reduced intensity conditioning hematopoietic stem cell transplants with alemtuzumab. Journal of medical virology 78 (12), 1560–1563.

Moucari, R., Korevaar, A. & Lada, O. et al. (2009) High rates of HBsAg seroconversion in HBeAg-positive chronic hepatitis B patients responding to interferon: a long-term follow-up study. Journal of hepatology 50 (6), 1084–1092.

Ning, Q., Han, M. & Sun, Y. et al. (2014) Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: a randomised open-label trial (OSST trial). Journal of hepatology 61 (4), 777–784.

Pan, C. Q., Zhu, L., Yu, A. S., Zhao, Y., Zhu, B. & Dai, E. (2024a) Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate for Preventing Vertical Transmission in Chronic Hepatitis B Mothers: A Systematic Review and Meta-Analysis. Clinical infectious diseases an official publication of the Infectious Diseases Society of America.

Pan, S., Zhang, Y., Zeng, Y. & Lin, C. (2024b) Comparison of the efficacy and safety of TAF, TDF, and LdT to prevent the transmission of hepatitis B in pregnant women: A retrospective study. Immunity, inflammation and disease 12 (2), e1204.

Papatheodoridis, G., Dalekos, G. & Sypsa, V. et al. (2016a) PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. Journal of hepatology 64 (4), 800–806.

Papatheodoridis, G., Vlachogiannakos, I. & Cholongitas, E. et al. (2016b) Discontinuation of oral antivirals in chronic hepatitis B: A systematic review. Hepatology 63 (5), 1481–1492.

Papatheodoridis, G. V., Chan, H. L.-Y., Hansen, B. E., Janssen, H. L. A. & Lampertico, P. (2015) Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. Journal of hepatology 62 (4), 956–967.

Papatheodoridis, G. V., Idilman, R. & Dalekos, G. N. et al. (2017) The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 66 (5), 1444–1453.

Papatheodoridis, G. V., Sypsa, V. & Dalekos, G. et al. (2018) Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. Journal of hepatology 68 (6), 1129–1136.

Perrillo, R. P., Lai, C.-L. & Liaw, Y.-F. et al. (2002) Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. Hepatology (Baltimore, Md.) 36 (1), 186–194.

Petersen, J., Ratziu, V. & Buti, M. et al. (2012) Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. Journal of hepatology 56 (3), 520–526.

Rehermann, B., Ferrari, C., Pasquinelli, C. & Chisari, F. V. (1996) The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. Nature medicine 2 (10), 1104–1108.

Revill, P. A., Chisari, F. V. & Block, j. M. et al. (2019) A global scientific strategy to cure hepatitis B. The lancet. Gastroenterology & hepatology 4 (7), 545–558.

Roche, B. & Samuel, D. (2011) The difficulties of managing severe hepatitis B virus reactivation. Liver international official journal of the International Association for the Study of the Liver 31 Suppl 1, 104–110.

Sarin, S. K., Kumar, M. & Lau, G. K. et al. (2016) Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatology International 10 (1), 1–98.

Schiff, E. R., Lee, S. S. & Chao, Y.-C. et al. (2011) Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. Clinical gastroenterology and hepatology the official clinical practice journal of the American Gastroenterological Association 9 (3), 274–276.

Seto, W.-K., Liu, K. S. & Mak, L.-Y. et al. (2021) Role of serum HBV RNA and hepatitis B surface antigen levels in identifying Asian patients with chronic hepatitis B suitable for entecavir cessation. Gut 70 (4), 775–783.

Sherman, M., Yurdaydin, C. & Simsek, H. et al. (2008) Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology 48 (1), 99–108.

Siberry, G. K., Jacobson, D. L. & Kalkwarf, H. J. et al. (2015) Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy. Clinical infectious diseases an official publication of the Infectious Diseases Society of America 61 (6), 996–1003.

Sohn, W., Cho, J.-Y. & Kim, J. H. et al. (2017) Risk score model for the development of hepatocellular carcinoma in treatment-naïve patients receiving oral antiviral treatment for chronic hepatitis B. Clinical and Molecular Hepatology 23 (2), 170–178.

Sonneveld, M. J., Rijckborst, V., Boucher, C. A. B., Hansen, B. E. & Janssen, H. L. A. (2010) Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. Hepatology 52 (4), 1251–1257.

Su, T.-H., Hu, T.-H. & Chen, C.-Y. et al. (2016) Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver international official journal of the International Association for the Study of the Liver 36 (12), 1755–1764.

Sung, J. J. Y., Lai, J.-Y. & Zeuzem, S. et al. (2008) Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B. Journal of hepatology 48 (5), 728–735.

Tabak, F., Yurdaydın, C. & Kaymakoğlu, S. et al. (2017) Diagnosis, management and treatment of hepatitis B virus infection: Turkey 2017 Clinical Practice Guidelines. The Turkish Journal of Gastroenterology 28 (Suppl 2), 73–83.

Tassopoulos, N. C., Papaevangelou, G. J., Sjogren, M. H., Roumeliotou-Karayannis, A., Gerin, J. L. & Purcell, R. H. (1987) Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. Gastroenterology 92 (6), 1844–1850.

Tenney, D. J., Rose, R. E. & Baldick, C. J. et al. (2009) Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. Hepatology 49 (5), 1503–1514.

Terrault, N. A., Lok, A. S. F. & McMahon, B. J. et al. (2018) Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67 (4), 1560–1599.

Testoni, B., Scholtès, C. & Plissonnier, M.-L. et al. (2024) Quantification of circulating HBV RNA expressed from intrahepatic cccDNA in untreated and NUC treated patients with chronic hepatitis B. Gut 73 (4), 659–667.

Tillmann, H. L., Hadem, J. & Leifeld, L. et al. (2006) Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. Journal of viral hepatitis 13 (4), 256–263.

Tout, I., Lampertico, P., Berg, T. & Asselah, T. (2021) Perspectives on stopping nucleos(t)ide analogues therapy in patients with chronic hepatitis B. Antiviral research 185, 104992.

Toy, M., Veldhuijzen, I. K., Man, R. A. de, Richardus, J. H. & Schalm, S. W. (2009) Potential impact of long-term nucleoside therapy on the mortality and morbidity of active chronic hepatitis B. Hepatology 50 (3), 743–751.

Tseng, T.-C., Chiang, C. & Liu, C.-J. et al. (2023) Low Hepatitis B Core-Related Antigen Levels Correlate Higher Spontaneous Seroclearance of Hepatitis B Surface Antigen in Chronic Hepatitis B Patients With High Hepatitis B Surface Antigen Levels. Gastroenterology 164 (4), 669-679.e6.

Tseng, T.-C., Liu, C.-J. & Yang, H.-C. et al. (2013) Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. Hepatology 57 (2), 441–450.

van Bömmel, F. & Berg, T. (2018) Stopping long-term treatment with nucleos(t)ide analogues is a favourable option for selected patients with HBeAg-negative chronic hepatitis B. Liver international official journal of the International Association for the Study of the Liver 38 Suppl 1, 90–96.

van Bömmel, F., Man, R. A. de & Wedemeyer, H. et al. (2010) Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology 51 (1), 73–80.

van Bömmel, F., Stein, K. & Heyne, R. et al. (2023) A multicenter randomized-controlled trial of nucleos(t)ide analogue cessation in HBeAg-negative chronic hepatitis B. Journal of hepatology 78 (5), 926–936.

van Bömmel, F., Trojan, J. & Deterding, K. et al. (2012) Evolution of adefovir-resistant HBV polymerase gene variants after switching to tenofovir disoproxil fumarate monotherapy. Antiviral therapy 17 (6), 1049–1058.

van Hees, S., Bourgeois, S. & van Vlierberghe, H. et al. (2018) Stopping nucleos(t)ide analogue treatment in Caucasian hepatitis B patients after HBeAg seroconversion is associated with high relapse rates and fatal outcomes. Alimentary pharmacology & therapeutics 47 (8), 1170–1180.

van Zonneveld, M., van Nunen, A. B., Niesters, H. G. M., Man, R. A. de, Schalm, S. W. & Janssen, H. L. A. (2003) Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. Journal of viral hepatitis 10 (4), 294–297.

Vassilopoulos, D. & Calabrese, L. H. (2007) Risks of immunosuppressive therapies including biologic agents in patients with rheumatic diseases and co-existing chronic viral infections. Current opinion in rheumatology 19 (6), 619–625.

Veronese, P., Dodi, I., Esposito, S. & Indolfi, G. (2021) Prevention of vertical transmission of hepatitis B virus infection. World journal of gastroenterology 27 (26), 4182–4193.

Wang, J., Shen, T. & Huang, X. et al. (2016) Serum hepatitis B virus RNA is encapsidated pregenome RNA that may be associated with persistence of viral infection and rebound. Journal of hepatology 65 (4), 700–710.

Werle-Lapostolle, B., Bowden, S. & Locarnini, S. et al. (2004) Persistence of cccDNA during the natural history of chronic hepatitis B and decline during adefovir dipivoxil therapy. Gastroenterology 126 (7), 1750–1758.

WHO (2024) Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection.

Woldemedihn, G. M., Aberra, H. & Desalegn, H. et al. (2023) Renal Safety of Long-term Tenofovir Disoproxil Fumarate Treatment in Patients With Chronic Hepatitis B. Open Forum Infectious Diseases 10 (8), ofad404.

Wong, D. K., Cheung, A. M., O'Rourke, K., Naylor, C. D., Detsky, A. S. & Heathcote, J. (1993) Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. Annals of internal medicine 119 (4), 312–323.

Wu, C.-Y., Lin, J.-T. & Ho, H. J. et al. (2014) Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 147 (1), 143-151.e5.

Xing, T., Xu, H., Cao, L. & Ye, M. (2017) HBeAg Seroconversion in HBeAg-Positive Chronic Hepatitis B Patients Receiving Long-Term Nucleos(t)ide Analog Treatment: A Systematic Review and Network Meta-Analysis. PLoS ONE 12 (1), e0169444.

Xu, X., Jiang, L., Zeng, Y., Pan, L., Lou, Z. & Ruan, B. (2023) HCC prediction models in chronic hepatitis B patients receiving entecavir or tenofovir: a systematic review and meta-analysis. Virology Journal 20 (1), 180.

Yang, H., Bae, S. H. & Nam, H. et al. (2022) A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance. Journal of hepatology 77 (3), 632–641.

Yip, T. C.-F., Lai, J. C.-T. & Yam, T.-F. et al. (2024) Long-term use of tenofovir disoproxil fumarate increases fracture risk in elderly patients with chronic hepatitis B. Journal of hepatology 80 (4), 553–563.

Yip, T. C.-F., Wong, G. L.-H. & Chan, H. L.-Y. et al. (2019) HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. Journal of hepatology 70 (3), 361–370.

Yu, J.-W., Sun, L.-J., Zhao, Y.-H., Kang, P. & Li, S.-C. (2010) The study of efficacy of lamivudine in patients with severe acute hepatitis B. Digestive diseases and sciences 55 (3), 775–783.

Yuen, M.-F., Fong, D. Y.-T., Wong, D. K.-H., Yuen, J. C.-H., Fung, J. & Lai, C.-L. (2007) Hepatitis B virus DNA levels at week 4 of lamivudine treatment predict the 5-year ideal response. Hepatology 46 (6), 1695–1703.

Zeuzem, S., Gane, E. & Liaw, Y.-F. et al. (2009) Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. Journal of hepatology 51 (1), 11–20.

Zoulim, F. & Locarnini, S. (2012) Management of treatment failure in chronic hepatitis B. Journal of hepatology 56 Suppl 1, S112-22.

3. Hepatitis C

Christoph Sarrazin, Christiana Graf

Epidemiology

Global occurrence

Globally, an estimated 57 million people were living with a hepatitis C virus (HCV) infection in 2020, corresponding to 0.7% of the world's population, with over 70% deriving from low-income and middle-income countries (Polaris Observatory HCV Collaborators 2022). Recent global estimates indicate that 30 countries account for 80% of the disease burden, with the highest prevalence being observed in countries in eastern Europe, certain countries in Africa and Asia, the Middle East and the South Caucasus and Central Africa (Spradling 2024). In contrast, HCV prevalence is observed to be low with <1.0% in most developed countries. Over the past 5 years a considerable decline of 6.8 million HCV infections was observed (Polaris Observatory HCV Collaborators 2022). However, these estimates may rather derive from revised results of prevalence data than from the elimination progress, although country-specific therapeutic and harm reductions programmes have also contributed to a substantial decline (e. g. Egypt)(Polaris Observatory HCV Collaborators 2022, Polaris Observatory HCV Collaborators 2017).

Currently, about 1.5 million new HCV infections are estimated each year with injecting drug use and unsafe health-care injections accounting for most cases (Polaris Observatory HCV Collaborators 2017). Overall, epidemiology of HCV is rapidly changing due to a scale up in screening and prevention measures and high cure rates in the era of interferon free direct acting antiviral (DAA) treatment. The implementation of a routinely screening of donated blood for bloodborne viruses in the early 1990, high-coverage needle and syringe programmes as well as opioid agonist therapy have led to a significant reduction of HCV infections in people who inject drugs (PWID) and of transfusion associated HCV infections. Accordingly, a peak of annual HCV incidence was observed in most countries between 1970 and 2005 followed by a decline in PWIDs in many high-income countries (Morris 2017). Nevertheless, in the USA and some low-income and middle-income countries a sustained high or even increasing incidence has been reported in the last years (Artenie 2023, Liang and Ward 2018, Trickey 2019).

HCV strains are classified into eight major genotypes, with at least 86 subtypes identified to date, whose prevalence and distribution vary

considerably between different regions (Borgia et 2018, Polaris Observatory HCV Collaborators 2017). HCV subtypes 1a and 1b are the most common in Northern America, Europe and Japan, while genotype 2 accounts for most infections in West Africa and in South America (Gower 2014, Messina 2015, Petruzziello 2016). Subtype 3a, which is very common among intravenous drug abusers, is common mainly in Europe, USA, Pakistan and South East Asia, while genotype 4 prevails in North Africa and in the Middle East and genotypes 5 and 6 are endemic, respectively, in South Africa and in South China / South East Asia (Gower 2014, Messina 2015, Petruzziello 2016, Polaris Observatory HCV Collaborators 2017, Zhang 2017).

Transmission

Parenteral exposure to HCV is the most efficient means of transmission. Most common routes include transfusion of unscreened blood products, injection drug use and unsafe skin-penetrating health-care practices. Infrequent modes of transmission are vertical and heterosexual transmission.

It is estimated that most recently acquired infections occur in individuals who have injected illicit drugs. However, HCV infection has also been associated with a history of injecting recreational drugs such as methamphetamine in a sexual context or intranasal cocaine use, presumably due to blood on shared straws or other sniffing paraphernalia. Besides recreational drug use, sexual risk behaviour represents the predominant risk factor for HCV transmission in men who have sex with men (MSM), with increased risk in men with human immunodeficiency virus (HIV) coinfection. In the last decades, observed outbreaks of recently acquired HCV infections in several cities in Europe and the United States among MSM have focused attention on sexual transmission of HCV (Boesecke 2015, Boesecke 2012). Sexual behaviors with HCV acquisition in this population including fisting, anal intercourse without condom, group sex, having many sex partners in a short time period and mucosal damage have been identified as primary risk factors for HCV transmission in MSM (Bradshaw et al., 2020; Newsum et al., 2021). In contrast, HCV transmission by sexual contact is uncommon between heterosexual couples (<0.1% per year in monogamous heterosexual couples)(Terrault 2013). Perinatal transmission of HCV is observed in about 5% of infants born to women with HCV, with increased risk associated with maternal HIV co-infection (10%), higher maternal HCV RNA (≥6.0 $\log_{10}$ IU/mL), amniocentesis, prolonged rupture of membranes and invasive fetal monitoring (Ades 2023, Benova 2014, Deng 2023, Kushner 2022, Ohto 1994, Terrault 2021).

In high-income countries, PWIDs and HIV positive MSM represent the populations at highest risk to acquire HCV infections (Degenhardt 2017, Jin 2010). In middle-income and low-income countries, unsafe health medical procedures are the most commonly identified source of infection, with an increasing burden related to injection drug use.

Clinical presentation and natural history of HCV infection

Recently acquired HCV infection

Most people (>70%) have no symptoms attributable to recently acquired HCV infection, making early diagnosis challenging (Vogel 2009). Symptoms associated with recently acquired infection include jaundice, fever, headache, malaise, anorexia, nausea, vomiting, diarrhoea, and abdominal pain. Aminotransferases become elevated approximately 6-12 weeks after exposure. The elevation of aminotransferases can have a broad range among individuals but tends to be more than 10-30 times the upper limit of normal. HCV antibodies can be found about 6-8 weeks after exposure in most cases. However, in some patients HCV seroconversion can be delayed. Thus, if recently acquired HCV infection is suspected, HCV-RNA testing by PCR is recommended as HCV antibodies might not present yet (Hajarizadeh et al., 2015). Periodic screening for infection may be warranted in certain groups of patients who are at high risk for infection, e. g. HIV positive MSM or persons who use drugs.

Although most people have viral persistence and develop chronic HCV infection, some undergo spontaneous clearance (15–35%), usually within 6 months (Aisyah 2018, Ingiliz 2017, Micallef 2006). Factors, that have been found to be associated with spontaneous clearance of HCV infection, were associated with female gender, younger age at infection, lower HCV RNA load and co-infection with hepatitis B virus (HBV)(Grebely 2014, Martinello 2018, Shin 2016). Immunodeficiency has been observed to reduce the chance of spontaneous clearance (<20%)(Aisyah 2018, Ingiliz 2017).

Introduction of highly efficient DAA agents has led to several changes in management and treatment of patients with recently acquired HCV infections with varying recommendations of international guidelines (EASL 2020, AASLD 2023, EACS 2024). Treatment initiation 4 weeks after HCV has been diagnosed and after spontaneous seroconversion has been ruled out, is recommended by the European AIDS Clinical Society (EACS) guideline and has been shown to be beneficial for patients' outcome, to reduce transmission and to be cost effective (EACS 2024).

Chronic HCV infection

In most individuals chronic HCV infection causes progressive disease, that deteriorate from chronic inflammation to fibrosis and liver cirrhosis. Approximately, 20-30% of chronically infected patients develop liver cirrhosis over a period of 20 to 30 years (Freeman 2001, Thein 2008). It is not clear why HCV results in chronic infection in most cases. The rapid mutation of the virus and its high genetic diversity may allow HCV to escape immune recognition. Host factors such as HCV-specific CD4 T cell and NK cell responses, IL28B gene polymorphisms and specific HLA-DRB1 alleles have been shown to be involved in the ability to spontaneously clear the virus (Lauer and Walker 2001, Rauch 2010, Thomas 2009).

Once liver cirrhosis has been diagnosed, the risk of hepatic decompensation and hepatocellular carcinoma is about 3% and 1-2% per year, respectively (Fattovich 1997). Factors associated with increased risk of hepatocellular carcinoma are elevated bilirubin, male gender, markers of advanced liver cirrhosis and portal hypertension as well as prolonged prothrombin time and thrombocytopenia (Villanueva 2019). Moreover, about 30% to 40% of individuals with chronic HCV infection develop extrahepatic manifestations and diseases such as mixed cryoglobulinemic vasculitis, porphyria cutanea tarda, lichen planus and B-cell non-Hodgkin lymphoma (Zignego and Craxì 2008).

Diagnosis

The standard algorithm for testing HCV involves a two-step process. Serologic tests are sufficient when chronic hepatitis C is expected, with a sensitivity of more than 99% with currently used 3rd generation assays. Positive serologic results require HCV ribonucleic acid (RNA) or with slightly reduced sensitivity HCV core antigen measurement in order to differentiate between chronic hepatitis C and resolved HCV infection in the past. Anti-HCV antibodies are usually detectable within 6 weeks after exposure, although in severely immunocompromised individuals, their detection may be delayed or absent (Netski 2005). Thus, when recently acquired hepatitis C is considered, serologic screening alone is insufficient because anti-HCV antibodies may develop late after transmission of the virus. In contrast, HCV RNA is detectable within a few days of infection, making nucleic acid-based tests mandatory in diagnosing recently acquired hepatitis C. HCV testing is usually conducted by collecting a blood sample and analysing it in a centralised laboratory. The complexity and costs associated with HCV diagnostics pose challenges to large-scale testing. Simplifying the diagnostic process and utilising easily accessible samples could improve testing uptake and enable decentralised care, especially among low-income settings and in key populations. Various approaches, such as dried blood spot testing, point-of-care antibody and RNA testing and reflex RNA testing from HCV antibody positive samples have demonstrated effectiveness in enhancing testing uptake and diagnosis (Cunningham 2022). Point-of-care HCV testing has simplified testing algorithms, increased diagnosis rates, and facilitated linkage to care and treatment. At the point of care, antibody testing can be conducted using fingerstick blood, whole blood, or oral fluid samples, providing results in less than 20 minutes. Similarly, HCV RNA testing can be performed using fingerstick or whole blood samples, with results available within 1 hour. These point-of-care tests have shown excellent diagnostic performance in various populations and settings, including community health centres, drug treatment clinics, prisons, homelessness settings, supervised drug consumption rooms, residential rehabilitation facilities as well as in countries with restricted health care resources.

Management of HCV infection

Indications for treatment: who should be treated?

Generally, all treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection should be considered for HCV treatment, because cure of infection is associated with reductions in the risk of hepatocellular carcinoma (HCC), liver-related and all-cause mortality, improvements in liver fibrosis and quality of life. One further reason for early treatment initiation is the prevention of further HCV transmission especially in patients with high risk of transmitting HCV (PWIDs, MSM with high-risk sexual behaviour, women of childbearing age and prison inmates). Besides early HCV treatment in PWIDs and MSM with high-risk sexual practices, constructive preventive strategies such as raising awareness as well as behavior interventions are necessary to prevent reinfections and further HCV transmission.

Patients with significant liver fibrosis (METAVIR score F2 or F3) or liver cirrhosis (METAVIR score F4), including those with decompensated liver cirrhosis, should be considered for urgent treatment initiation. Further reasons for prompt treatment initiation are clinically significant extrahepatic manifestations (e.g. HCV immune complex-mediated vasculitis, HCV infection related B-cell non-Hodgkin lymphomas (B-NHL), HCV recurrence during or after liver transplantation, patients at risk of rapid progression of liver disease due to concomitant diseases (e. g. patients with coinfections such as HBV or HIV or in recipients of solid organs or stem cells).

Endpoint of HCV therapy

The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. Sustained virologic response (SVR) is the established efficacy endpoint and is defined as undetectable HCV RNA in serum or plasma 12 (SVR12) or 24 (SVR24) weeks after the end of treatment.

In settings, where HCV RNA assays are not available or not affordable, using a HCV core antigen assay with a lower limit of detection corresponding to approx. 4.000 IU/mL HCV RNA can be used as an alternative endpoint. Long-term follow-up studies have shown that in most cases SVR corresponds to a definitive cure of HCV infection (Frías 2019, Sarrazin 2017).

Pretherapeutic assessment of patients

When assessing individuals with hepatitis C (HCV) infection, several key factors should be considered.

Evaluation of liver disease severity is crucial prior to treatment initiation in order to identify the presence or absence of liver cirrhosis or advanced liver fibrosis (METAVIR score F3), because some treatment regimens must be adjusted and post-treatment prognosis as well as surveillance for HCC are dependent on the severity of liver disease. Non-invasive tools should be preferred over liver biopsy to assess advanced liver disease. Liver stiffness measurement obtained with Transient Elastography (TE), point-shear wave elastography (pSWE) or 2D-SWE are well validated tools to determine significant fibrosis or liver cirrhosis (Berzigotti 2021). If possible, liver stiffness measurement should be performed in combination with blood biomarkers such as the aspartate aminotransferase to plated ratio index (APRI) and fibrosis-4 score (FIB-4) in order to improve accuracy (Castéra 2010, Castéra 2005). The need for liver biopsy prior to HCV treatment has become rare and indication to liver biopsy is limited to cases of suspected mixed etiologies (e. g. metabolic syndrome or autoimmunity).

Moreover, relevant comorbidities such as HIV-, or HBV coinfection, renal insufficiency and further causes of liver disease (e. g. metabolic-associated fatty liver disease or alcoholic liver disease) should be systematically investigated.

Beyond that, assessment of factors associated with HCV transmission such as substance abuse or sexual risk behavior and factors associated with liver disease progression, including alcoholic use, obesity and diabetes mellitus should be performed.

Prior to initiating HCV therapy, the presence of viraemia should be verified by detecting HCV RNA or if not available or not affordable HCV core antigen in serum or plasma. Identifying HCV genotype is not mandatory before starting pan-genotypic HCV drug regimens but should be done prior to initiating genotype-specific DAA therapy. In addition, HCV genotype determination is useful, if available, in order to identify HCV subtypes, which are resistant to NS5A inhibitors (i. e. HCV genotype 3c), and to identify patients, who may benefit from an adapted HCV treatment. Figure 1 provides an overview of the treatment process in the case of HCV therapy, from pre-treatment assessment to a simplified therapy with genotype/subtype-free combinations and the post-treatment follow-up.

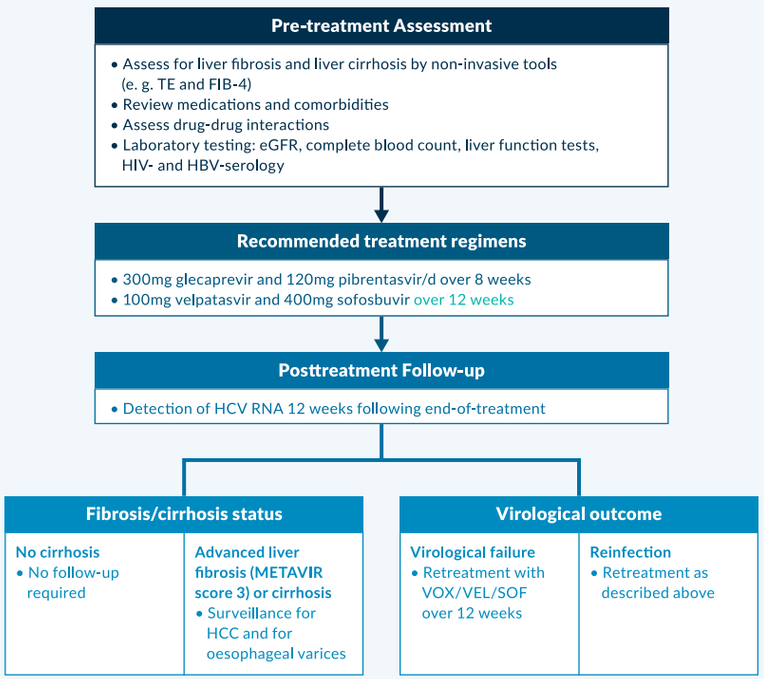

Figure 1. Simplified genotyping-free algorithm for HCV treatment among treatment-naive patients with and without cirrhosis

Direct-acting antiviral therapy

Continuous research on the HCV life cycle enabled the development of a new generation of antiviral substances for treating HCV infection, the direct acting agents (DAAs). In contrast to the rather non-specific treatment with pegylated interferon (peg IFN-α) and ribavirin (RBV), DAAs inhibit specific viral proteins necessary for HCV replication. Based on their molecular mode of action DAAs are classified in NS3/4 protease inhibitors, that prevent the proteolytic processing of the HCV polyprotein between NS3 and NS4A, non-nucleoside and nucleotide analogue NS5B RNA-dependent RNA-polymerase inhibitors, which target the NS5B, and NS5A inhibitors, that bind to the NS5A domain 1 and prevent RNA from binding, therefore disrupting RNA replication (Gottwein 2018, Powdrill 2010). The introduction of these IFN-free DAAs has revolutionised and simplified clinical management in the past decade.

With the approval of the nucleotide analogue sofosbuvir in December 2013 in the USA and in January 2014 in Europe, the first IFN-free therapy became widely available. The first interferon-free regimens were the dual combinations of ledipasvir-sofosbuvir (LDV/SOF) and sofosbuvir plus simeprevir, which were approved for genotype 1 HCV infection 2014. With the approval of the fixed-dose combination of the second-generation pan-genotypic NS5A inhibitor velpatasvir with sofosbuvir in summer 2016, the first pan-genotypic fixed-dose combination regimen was available. Today, four pangenotypic fixed-dose combination regimens are available: velpatasvir-sofosbuvir (VEL/SOF), daclatasvir-sofosbuvir (DAC/SOF), glecaprevir/pibrentasvir (GLE/PIB) and voxilaprevir/velpatasvir/sofosbuvir (VOX/VEL/SOF)(Bourlière 2017, Brown 2020, Feld 2015, Foster 2015, Kwo 2017, Sulkowski 2014, Wyles 2017, Zeuzem 2018). The triple fixed-dose dose combination of VOX/VEL/SOF was approved in 2017 and enables re-treatment of patients failing DAA therapy. Moreover, the non-pangenotypic combination of grazoprevir and elbasvir is possible in settings, where available HCV genotype and subtype determination enables the identification of patients infected with HCV genotype 1b (Jacobson 2017). Table 1 and 2 give an overview of the recommended first-line treatment schedules and treatment durations in patients with compensated liver disease, depending on whether genotype/subtype determination is available. All approved IFN-free DAAs have an excellent safety and efficacy profile (SVR≥95%, including patients with compensated liver cirrhosis), short treatment duration and low resistance-related failure.

Table 1. Overview of genotyping/subtyping-free antiviral combinations in DAA-naïve patients with compensated liver disease

Genotype	Cirrhosis status	Prior treatment	Glecaprevir-pibrentasvir	Velpatasvir-sofosbuvir
All genotypes	No cirrhosis	Treatment-naïve	8 weeks*	12 weeks**
		Peg-IFN+RBV		
	Compensated cirrhosis	Treatment-naïve		
		Peg-IFN+RBV	12 weeks*	

Abbreviations: DAA, direct-acting antiviral agent.
*In cases of HCV GT3 and treatment experience meaning pre-treatment with (PEG-) interferon ± ribavirin, sofosbuvir with (PEG-)interferon + ribavirin or sofosbuvir + ribavirin, extended treatment duration over 16 weeks is recommended.
**In patients with liver cirrhosis, additional treatment with ribavirin should be considered.

Table 2. Overview of antiviral combinations in DAA-naïve patients with compensated liver disease if genotype is available

Genotype	Cirrhosis status	Prior treatment	Glecaprevir-pibrentasvir	Sofosbuvir-velpatasvir	Grazoprevir-elbasvir	Voxilaprevir-velpatasvir-sofsobuvir
1b	No cirrhosis	Treatment-naïve	8 weeks	12 weeks*	12 weeks	No
		Peg-IFN+RBV				
	Compensated cirrhosis	Treatment-naïve				
		Peg-IFN+RBV	12 weeks			
1a, 2, 4, 5, 6	No cirrhosis	Treatment-naïve	8 weeks	12 weeks*	No	No
		Peg-IFN+RBV				
	Compensated cirrhosis	Treatment-naive				
		Peg-IFN+RBV	12 weeks			
3	No cirrhosis	Treatment-naive	8 weeks	12 weeks*	No	No
		Peg-IFN+RBV	12-16 weeks			No
	Compensated cirrhosis	Treatment-naïve	8 weeks	12 weeks*		12 weeks
		Peg-IFN+RBV	16 weeks			12 weeks

Abbreviations: DAA, direct-acting antiviral agent.
**In patients with liver cirrhosis, additional treatment with ribavirin should be considered.

If genotype determination is not available or affordable, simplified treatment algorithms are feasible in most cases: the only information needed to start treatment with the genotyping/subtyping-free treatment regimens VEL/SOF or GLE/PIB in treatment-naïve patients with compensated liver disease (no liver cirrhosis or compensated liver cirrhosis Child-Pugh A), who

are treatment-naïve or treatment-experienced with an IFN-based regimen, is the presence of HCV replication and possible drug-drug interactions. Evidence from several clinical trials as well as real-world studies exists and supports that treatment with GLE/PIB over 8 weeks or VEL/SOF over 12 weeks is effective if genotype/subtype determination is not available (EASL 2020)(Table 1). However, in many middle- and low-income countries, the recommended pan-genotypic DAA combinations are not available. In these cases, the generic combination of daclatasvir and sofosbuvir (DAC/SOF) is safe and provides high SVR rates at a relatively low price (Pawlotsky 2020). If this combination is also not accessible, the use of older DAA combinations or, in rare cases, treatment with IFN-based therapy is necessary (Zeng 2020). For detailed information on older treatment regimens such as the dual treatment with Peg-IFN+RBV and triple treatment regimens including Peg-IFN+RBV plus protease inhibitors, we refer to the previous edition of the textbook dating from 2015. For detailed information on older DAA combinations sofosbuvir + ribavirin, simeprevir + sofosbuvir, daclatasvir + sofosbuvir and for the 3D combination (ombitasvir, paritaprevir/r + dasabuvir) we refer to the textbook dating from 2016.

Management of HCV in special epidemiological groups

HCV treatment in children and adolescents

A systematic review updated in 2016 on the prevalence of HCV viraemia in children and adolescents aged 1-19 years, revealed an overall burden of 3.5 million cases or 0.15% of the global population (Indolfi 2019). Clinical trial data evaluating DAA regimens in children and adolescents have allowed the expanded use of these safe and well-tolerated HCV therapies in the paediatric population. Generally, HCV treatment in children and adolescents is based on the recommendations for adults.

Based on representative study results, GLE/PIB was approved as a pan-genotypic therapy for children and adolescents in 2019 (Jonas 2020). For children aged 12 and over, the effectiveness, dosage and treatment duration of therapy correspond to those approved for adults. Regarding the administration of GLE/PIB in children aged 3-11 years, dosage adjustment is required depending on age and body weight (Table 3). Based on positive study results, VEL/SOF has also been approved for paediatric patients aged ≥3 years in June 2021 (Jonas 2019). The recommended dose of VEL/SOF in patients aged 3 to less than 18 years is based on weight. Following positive results of two clinical trials, genotype-specific therapy of LED/SOF was approved for paediatric patients aged 3 years and older infected with HCV genotype 1, 4, 5 and 6 (Murray 2018, Schwarz 2020). DAC/SOF is not approved in children and adolescents but is recommended by WHO based on real-world data and pharmacokinetic modelling for the use in this population in low-income and middle-income countries (Pawlotsky 2020).

Table 3. Overview of genotyping/subtyping-free antiviral combinations in DAA-naïve patients with compensated liver disease

Treatment regimen	Usual dose
GLE + PIB	
Adults and adolescents (≥12 years) ≥ 45kg	300mg GPR + 120mg PBR/day in 1 dose
Children (3-11 years) ≥ 30 to < 45kg	250mg GPR and 100mg PBR/day in 1 dose
Children (3-11 years) ≥ 20 to < 30kg	200mg GPR and 80 PBR/day in 1 dose
Children (3-11 years) < 20 kg	150mg GPR and 60mg PBR/day in 1 dose
VEL + SOF	
Adults and adolescents (≥12 years) ≥30 kg	100mg VEL + 400mg SOF/day in 1 dose
Children (3-11 years) ≥17 to <30 kg	50mg VEL + 200mg SOF/day in 1 dose
Children (3-11 years) <17 kg	37.5mg VEL + 150mg SOF/day in 1 dose
GZR + ELB	
Adults and adolescents (≥12 years) ≥30 kg	100mg GZR + 50mg ELB/day in 1 dose
VOX + VEL + SOF	
Adults and adolescents (≥12 years) ≥ 45kg	100mg VOX + 100mg VEL + 400mg SOF/day in 1 dose

Abbreviations: DAA, direct-acting antiviral agent; ELB, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; PIB, pibrentasvir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

HCV treatment in pregnancy

Data situation is still limited regarding the teratogenic risk of DAAs. Thus, safe contraception should be recommended during antiviral treatment. Antiviral therapy during pregnancy and breastfeeding is currently not recommended. However, real world data on different DAA regimens (i.e. VEL/SOF, DAC/SOF) used in pregnancy showed no adverse effects on pregnancies and newborns and a prospective study for the use of VEL/SOF during pregnancy is ongoing (AbdAllah 2021, Ades 2023, Chappel). In HCV-monoinfected patients, the risk of vertical transmission is approx. 5%, a caesarean section does not reduce the risk of transmission (Yeung 2014). HCV-infected mothers are not advised against breastfeeding. Diagnosis of HCV infection in newborns is uncertain during the first weeks and spontaneous resolution is not infrequent until the age of 3 years.

HCV treatment in people with hepatocellular carcinoma

In patients with chronic hepatitis C and hepatocellular carcinoma (HCC), a coordinated approach and multidisciplinary tumour board decision is required. The indication for antiviral therapy should be made individualised in an experienced centre, taking into account tumour stage, treatment concept and the overall prognosis. If a curative treatment approach exists for HCC, antiviral therapy is generally indicated in those patients. DAA interactions with immunotherapies for hepatocellular carcinoma are not a concern. However, in contrast to HBV-associated HCC, where antiviral suppression therapy has a clinical significance in palliative treatment, no reliable and confirmed analogous data exist for the palliative treatment of HCV-associated HCC (Zhang and Guo 2015).

Post-treatment surveillance

After achieving SVR12, patients with normal liver enzymes and without advanced liver disease (advanced liver fibrosis METAVIR F3 or liver cirrhosis) require no further follow-up. HCV infection can be considered as definitely cured in these patients.

Patients with persistently elevated liver parameters post SVR12 should be examined for further hepatopathies. Individuals with advanced liver fibrosis (METAVIR score F3) or liver cirrhosis (F4) should remain under surveillance for HCC by ultrasound and for clinically significant portal hypertension. Long-term post-SVR follow-up studies revealed that the risk of developing HCC is significantly reduced compared to untreated patients post SVR but it remains (Arase 2013, Carrat 2019, Nahon 2017, van der Meer 2012). Thus, duration of HCC surveillance in patients with advanced fibrosis or liver cirrhosis is indefinite despite SVR and potential normalisation of non-invasive liver fibrosis assessment tools. However, a recent meta-analysis showed good correlation between declined values for transient elastography 24 weeks after the end-of-treatment and a lower risk for HCC development, although a specific cut-off cannot be determined so far (Esposto 2024). In line with these results, discontinuation of surveillance for clinically significant portal hypertension can be considered if improvement can be observed following SVR (liver stiffness measurement <12 kPa and platelet count >150x10^9 /L)(de Franchis 2022, Semmler 2024).

Remaining challenges

Tremendous progress in DAA therapy, that resulted in pan-genotypic fixed-dose combinations, solved most of the remaining challenges in anti-HCV treatment. Today, IFN-free DAA combinations enable HCV cure quite easily and safe without any relevant adverse effects. However, some patients still fail to cure.

Treatment of patients with virological failure after pan-genotypic DAA therapy

With currently available highly efficacious pangenotypic DAA regimens, treatment failure is rare. However, some difficult-to-treat subgroups remain, who fail not only first-line therapy but also retreatment with VOX/VEL/SOF (Bourlière 2017, Vermehren 2020). Studies have shown that virologic treatment failure to VOX/VEL/SOF is primarily observed in patients with difficult-to-treat cofactors such as HCC, liver cirrhosis and HCV genotype 3 (Degasperi 2019, Graf 2024, Llaneras 2019). In contrast, clinical trials as well as real-world studies have shown that RASs as well as rare genotypes and chimera have no impact on cure in patients retreated with VOX/VEL/SOF (Bourlière 2017, Degasperi 2019, Graf 2024, Llaneras 2019).

In these cases, rescue therapy with GLE/PIB+SOF over 24 weeks or retreatment with VOX/VEL/SOF + RBV over 16-24 or weeks is recommended (Pawlotsky 2020). However, only limited clinical experience consisting of case series involving fewer than 25 patients supports this recommendation (Bernhard and Stickel 2020, Dietz 2021, Fierer and Wyles 2020, Martin 2021).

Treatment of patients with decompensated liver disease

Patients with decompensated liver cirrhosis including those after TIPS implantation represent a further subgroup which is still difficult to treat even in the age of DAAs. Due to its hepatic metabolisation, NS3/4 protease inhibitors are contraindicated in these patients, which limits treatment option to NS5A inhibitors, sofosbuvir and RBV. Thus, the European Association for the Study of the Liver (EASL) recommends the combination of VEL/SOF over 12 weeks as the treatment of choice in patients with decompensated liver cirrhosis (Child Pugh B or C) or with compensated liver cirrhosis (Child Pugh A) and prior episodes of decompensation (Pawlotsky 2020).

This recommendation is based on the results of the ASTRAL-4 study, which demonstrated high SVR rates in patients with a Child Pugh class B

liver cirrhosis treated with VEL/SOF with weight-based RBV (Curry 2015). Due to the observed benefit of adding RBV, add-on administration should be started at a dose of 600mg in patients with decompensated liver cirrhosis and should be adjusted depending on tolerance (Curry 2015, Lu 2019). In cases of contraindications of the use of RBV or poor tolerance to RBV on treatment, the fixed dose combination of VEL/SOF should be administered over 24 weeks.

It is still not clear until which stage of liver cirrhosis patients benefit from an antiviral treatment and when to defer HCV treatment to after liver transplantation (Samur 2018). Several studies assessed whether achieving SVR prior to liver transplantation would lead to a benefit for patients with decompensated liver cirrhosis. Most of them demonstrated that HCV cure led to substantial improvement in liver function, portal hypertension and potential delisting in patients with a MELD <20 (Deterding 2015, El-Sherif 2018, Mandorfer 2016). Data on HCV patients with a MELD score >20 are rare, but existing studies demonstrate that above a MELD of 20 the risk of adverse events and death during treatment was higher and life expectancy benefit of treating was less than 1 year. Moreover, the likelihood of substantial enhancement in liver function and removal from the transplant list was minimal at this stage of disease was minimal. Accordingly, studies have shown that pre-liver transplantation treatment was only observed to be cost-effective for patients with a MELD score <20 (Chhatwal 2017, Cortesi 2018). Accordingly, current EASL guidelines recommend HCV treatment of patients with decompensated liver cirrhosis (Child Pugh B or C) and a MELD score < 18-20 prior to liver transplantation.

Treatment of patients with rare HCV subtypes

Due to a reduced susceptibility to current DAA therapies, some HCV sub-types represent a further challenge in treating and eliminating HCV infection. The hepatitis C virus is incredibly diverse, with subtypes distributed variably around the world. These viral genotypes fall into two categories: epidemic subtypes, which are prevalent globally, and endemic subtypes, mainly found in Africa and Asia. The high genetic diversity of endemic strains raises the possibility of resistance to pan-genotypic direct-acting antiviral regimens. While many endemic subtypes respond well to these therapies, others (such as genotypes 1l, 3b, and 4r) do not perform as predicted (Dietz 2024, Wei 2020, Wei 2019). Several genotypes, rare in high-income countries but common elsewhere, have not yet undergone comprehensive clinical trials. Further sequencing and clinical studies in sub-Saharan Africa and Asia are essential to monitor treatment response and support the World Health Organization's 2030 elimination strategy.

References

AbdAllah, M., Alboraie, M., Abdel-Razek, W., et al. 2021. Pregnancy outcome of anti-HCV direct-acting antivirals: Real-life data from an Egyptian cohort. Liver Int. Off. J. Int. Assoc. Study Liver 41, 1494–1497.

Ades, A.E., Gordon, F., Scott, K., et al. 2023. Spontaneous Clearance of Vertically Acquired Hepatitis C Infection: Implications for Testing and Treatment. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 76, 913–991.

Aisyah, D.N., Shallcross, L., Hully, A.J., O'Brien, A., Hayward, A., 2018. Assessing hepatitis C spontaneous clearance and understanding associated factors-A systematic review and meta-analysis. J. Viral Hepat. 25, 680–698.

Arase, Y., Kobayashi M., Suzuki, F., et al. 2013. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. Hepatol. Baltim. Md 57, 964–973.

Artenie, A., Stone, J., Fraser, H., et al., HIV and HCV Incidence Review Collaborative Group, 2023. Incidence of HIV and hepatitis C virus among people who inject drugs, and associations with age and sex or gender: a global systematic review and meta-analysis. Lancet Gastroenterol. Hepatol. 8, 533–552.

Benova, L., Mohamoud, Y.A., Calvert, C., Abu-Raddad, L.J., 2014. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 59, 765–773.

Bernhard, B., Stickel, F., 2020. Successful fourth line treatment of a relapse patient with chronic hepatitis C virus infection genotype 3a using sofosbuvir, glecaprevir/pibrentasvir, and ribavirin: a case report. Z. Gastroenterol. 58, 451–455.

Berzigotti, A., Tsochatzis, E., Boursier, J., et al. 2021. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. J. Hepatol. 75, 659–689.

Boesecke, C., Grint, D., Soriano, V., et al. 2015. Hepatitis C seroconversions in HIV infection across Europe: which regions and patient groups are affected? Liver Int. Off. J. Int. Assoc. Study Liver 35, 2384–2391.

Boesecke, C., Wedemeyer, H., Rockstroh, J.K., 2012. Diagnosis and treatment of acute hepatitis C virus infection. Infect. Dis. Clin. North Am. 26, 995–1010.

Borgia, S.M., Hedskog, C., Parhy, B., et al. 2018. Identification of a Novel Hepatitis C Virus Genotype From Punjab, India: Expanding Classification of Hepatitis C Virus Into 8 Genotypes. J. Infect. Dis. 218, 1722–1729.

Bourlière, M., Gordon, S.C., Flamm, S.L., et al., POLARIS-1 and POLARIS-4 Investigators, 2017. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N. Engl. J. Med. 376, 2134–2146. https://doi.org/10.1056/NEJMoa1613512

Bradshaw, D., Vasylyeva, T.I., Davis, C., et al. 2020. Transmission of hepatitis C virus in HIV-positive and PrEP-using MSM in England. J. Viral Hepat. 27, 721–730.

Brown, R.S., Buti, M., Rodrigues, L., et al. 2020. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. J. Hepatol. 72, 441–449.

Carrat, F., Fontaine, H., Dorival, C., et al., French ANRS CO22 Hepather cohort, 2019. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet Lond. Engl. 393, 1453–1464.

Castéra, L., Sebastiani, G., Le Bail, B., de Lédinghen, V., Couzigou, P., Alberti, A., 2010. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J. Hepatol. 52, 191–198.

Castéra, L., Vergniol, J., Foucher, J., et al. 2005. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 128, 343–350.

Chappell et al., Safety, tolerability and outcomes of sofosbuvir/velpatasvir in treatment of chronic hepatitis C virus during pregnancy: interim results from the STORC Study. AASLD 2023; #LB5018

Chhatwal, J., Samur, S., Kues, B., et al. 2017. Optimal timing of hepatitis C treatment for patients on the liver transplant waiting list. Hepatology 65, 777.

Cortesi, P.A., Belli, L.S., Facchetti, R., et al., the European Liver and Intestine Transplant Association (ELITA), 2018. The optimal timing of hepatitis C therapy in liver transplant-eligible patients: Cost-effectiveness analysis of new opportunities. J. Viral Hepat. 25, 791–801.

Cunningham, E.B., Wheeler, A., Hajarizadeh, B., et al. 2022. Interventions to enhance testing, linkage to care, and treatment initiation for hepatitis C virus infection: a systematic review and meta-analysis. Lancet Gastroenterol. Hepatol. 7, 426–445.

Curry, M.P., O'Leary, J.G., Bzowej, N., et al., ASTRAL-4 Investigators, 2015. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N. Engl. J. Med. 373, 2618–2628.

de Franchis, R., Bosch, J., Garcia-Tsao, G., Reiberger, T., Ripoll, C., Baveno VII Faculty, 2022. Baveno VII - Renewing consensus in portal hypertension. J. Hepatol. 76, 959–974.

Degasperi, E., Spinetti, A., Lombardi, A., et al., NAVIGATORE-Lombardia and Veneto Study Groups, 2019. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. J. Hepatol. 71, 1106–1115. https://doi.org/10.1016/j.jhep.2019.07.020

Degenhardt, L., Peacock, A., Colledge, S., et al., 2017. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob. Health 5, e1192–e1207.

Deng, S., Zhong, W., Chen, W., Wang, Z., 2023. Hepatitis C viral load and mother-to-child transmission: A systematic review and meta-analysis. J. Gastroenterol. Hepatol. 38, 177–186.

Deterding, K., Höner Zu Siederdissen, C., Port, K., et al., 2015. Improvement of liver function parameters in advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies. Aliment. Pharmacol. Ther. 42, 889–901.

Dietz, J., Di Maio, V.C., de Salazar, et al. HCV Virology Italian Resistance Network (VIRONET-C) collaborators, Spanish GEHEP-004 Collaborators, Members of the German HCV resistance study group, 2021. Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy. J. Hepatol. 74, 801–810.

Dietz J, Graf C, Berg CP et al. Rare HCV subtypes and retreatment outcomes in a cohort of European DAA-experienced patients, JHEP Reports 2024; S2589-5559(24)00076-4

European AIDS Clinical Society. EACS Guidelines 2024. URL: https://www.eacsociety.org/guidelines/eacs-guidelines/ (accessed 12.03.24).

El-Sherif, O., Jiang, Z.G., Tapper, E.B., et al., 2018. Baseline Factors Associated With Improvements in Decompensated Cirrhosis After Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection. Gastroenterology 154, 2111-2121.e8.

Esposto, G., Santini, P., Galasso, L., et al., 2024. Shear-wave elastography to predict hepatocellular carcinoma after hepatitis C virus

eradication: A systematic review and meta-analysis. World J. Gastroenterol. 30, 1450–1460.

European Association for the Study of the Liver. 2020. EASL recommendations on treatment of hepatitis C: Final update of the series. J. Hepatol. 2020; 73:1170–1218.

Fattovich, G., Giustina, G., Degos, F., et al., 1997. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 112, 463–472.

Feld, J.J., Jacobson, I.M., Hézode, C., et al., ASTRAL-1 Investigators, 2015. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N. Engl. J. Med. 373, 2599–2607.

Fierer, D.S., Wyles, D.L., 2020. Re-treatment of Hepatitis C Infection After Multiple Failures of Direct-Acting Antiviral Therapy. Open Forum Infect. Dis. 7.

Foster, G.R., Afdhal, N., Roberts, et al., 2015. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N. Engl. J. Med. 373, 2608–2617.

Freeman, A.J., Dore, G.J., Law, M.G., et al., 2001. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatol. Baltim. Md 34, 809–816.

Frías, M., Rivero-Juárez, A., Téllez, F., et al., 2019. Evaluation of hepatitis C viral RNA persistence in HIV-infected patients with long-term sustained virological response by droplet digital PCR. Sci. Rep. 9, 12507.

AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. URL: https://www.hcvguidelines.org/ (accessed 12.04.2024)

Gottwein, J.M., Pham, L.V., Mikkelsen, L.S., et al., 2018. Efficacy of NS5A Inhibitors Against Hepatitis C Virus Genotypes 1-7 and Escape Variants. Gastroenterology 154, 1435–1448.

Gower, E., Estes, C., Blach, S., Razavi-Shearer, K., Razavi, H., 2014. Global epidemiology and genotype distribution of the hepatitis C virus infection. J. Hepatol. 61, S45-57. https://doi.org/10.1016/j.jhep.2014.07.027

Graf, C., D'Ambrosio, R., Degasperi, E., et al., 2024. Real-world effectiveness of voxilaprevir/velpatasvir/sofosbuvir in patients following DAA failure. JHEP Rep. Innov. Hepatol. 6, 100994.

Grebely, J., Page, K., Sacks-Davis, R., et al., InC3 Study Group, 2014. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatol. Baltim. Md 59, 109–120.

Hajarizadeh, B., Grady, B., Page, K., et al., 2015. Patterns of Hepatitis C Virus RNA Levels during Acute Infection: The InC3 Study. PLOS ONE 10, e0122232.

Philip Spradling (2024): Hepatitis C. In: CDC Yellow Book 2024. URL: https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/hepatitis-c (accessed 4.1.24).

Indolfi, G., Easterbrook, P., Dusheiko, G., et al., 2019. Hepatitis C virus infection in children and adolescents. Lancet Gastroenterol. Hepatol. 4, 477–487.

Ingiliz, P., Martin, T.C., Rodger, A., et al., 2017. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J. Hepatol. 66, 282–287.

Jacobson, I.M., Lawitz, E., Kwo, P.Y., et al., 2017. Safety and Efficacy of Elbasvir/Grazoprevir in Patients With Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis. Gastroenterology 152, 1372-1382.e2.

Jin, F., Prestage, G.P., Matthews, G., et al., 2010. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV-negative and HIV-positive men in Sydney, Australia. Sex. Transm. Infect. 86, 25–28.

Jonas, M., Romero, R., Sokal, E.M., et al., 2019. Safety and efficacy of sofosbuvir/velpatasvir in pediatric patients 6 to <18 years old with chronic hepatitis C infection. Hepatology (Suppl) 2019, 465A

Jonas, M.M., Squires, R.H., Rhee, S.M., et al., 2020. Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Adolescents With Chronic Hepatitis C Virus: Part 1 of the DORA Study. Hepatol. Baltim. Md 71, 456–462.

Kushner, T., Djerboua, M., Biondi, M.J., Feld, J.J., Terrault, N., Flemming, J.A., 2022. Influence of hepatitis C viral parameters on pregnancy complications and risk of mother-to-child transmission. J. Hepatol. 77, 1256–1264.

Kwo, P.Y., Poordad, F., Asatryan, A., et al., 2017. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J. Hepatol. 67, 263–271.

Lauer, G.M., Walker, B.D., 2001. Hepatitis C virus infection. N. Engl. J. Med. 345, 41–52.

Liang, T.J., Ward, J.W., 2018. Hepatitis C in Injection-Drug Users - A Hidden Danger of the Opioid Epidemic. N. Engl. J. Med. 378, 1169–1171.

Llaneras, J., Riveiro-Barciela, M., Lens, S., et al., 2019. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. J. Hepatol. 71, 666–672.

Lu, M., Wu, K.-H., Li, J., et al., 2019. Adjuvant ribavirin and longer direct-acting antiviral treatment duration improve sustained virological response among hepatitis C patients at risk of treatment failure. J. Viral Hepat. 26, 1210–1217.

Mandorfer, M., Kozbial, K., Schwabl, P., et al., 2016. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J. Hepatol. 65, 692–699.

Martin, M.T., Patel, S., Kulik, L., Chan, C., 2021. Glecaprevir/pibrentasvir + sofosbuvir + ribavirin offers high cure rate for hepatitis C virus retreatment in real-world settings. J. Hepatol. 75, 251–254.

Martinello, M., Hajarizadeh, B., Grebely, J., Dore, G.J., Matthews, G.V., 2018. Management of acute HCV infection in the era of direct-acting antiviral therapy. Nat. Rev. Gastroenterol. Hepatol. 15, 412–424.

Messina, J.P., Humphreys, I., Flaxman, A., et al., 2015. Global distribution and prevalence of hepatitis C virus genotypes. Hepatol. Baltim. Md 61, 77–87.

Micallef, J.M., Kaldor, J.M., Dore, G.J., 2006. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J. Viral Hepat. 13, 34–41.

Morris, M.D., Shiboski, S., Bruneau, J., et al., International Collaboration of Incident HIV and HCV in Injecting Cohorts (InC3), 2017. Geographic Differences in Temporal Incidence Trends of Hepatitis C Virus Infection Among People Who Inject Drugs: The InC3 Collaboration. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 64, 860–869.

Murray, K.F., Balistreri, W.F., Bansal, S., et al., 2018. Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. Hepatol. Baltim. Md 68, 2158–2166.

Nahon, P., Bourcier, V., Layese, R., Aet al., ANRS CO12 CirVir Group, 2017. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology 152, 142-156.e2.

Netski, D.M., Mosbruger, T., Depla, E., et al., 2005. Humoral Immune Response in Acute Hepatitis C Virus Infection. Clin. Infect. Dis. 41, 667–675.

Newsum, A.M., Matser, A., Schinkel, J., et al., MSM Observational Study of Acute Infection with hepatitis C (MOSAIC) study group, 2021. Incidence of HCV Reinfection Among HIV-Positive MSM and Its Association With Sexual Risk Behavior: A Longitudinal Analysis. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 73, 460–467.

Ohto, H., Terazawa, S., Sasaki, N., et al., 1994. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. N. Engl. J. Med. 330, 744–750.

Pawlotsky, J.-M., Negro, F., Aghemo, A., et al., 2020. EASL recommendations on treatment of hepatitis C: Final update of the series. J. Hepatol. 73, 1170–1218.

Petruzziello, A., Marigliano, S., Loquercio, G., Cozzolino, A., Cacciapuoti, C., 2016. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J. Gastroenterol. 22, 7824–7840.

Polaris Observatory HCV Collaborators, 2022. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. Lancet Gastroenterol. Hepatol. 7, 396–415.

Polaris Observatory HCV Collaborators, 2017. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol. Hepatol. 2, 161–176.

Powdrill, M.H., Bernatchez, J.A., Götte, M., 2010. Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase NS5B. Viruses 2, 2169–2195.

Rauch, A., Kutalik, Z., Descombes, P., et al., 2010. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 138, 1338–1345, 1345.e1–7.

Samur, S., Kues, B., Ayer, T.,et al., 2018. Cost Effectiveness of Pre- vs Post-Liver Transplant Hepatitis C Treatment With Direct-Acting Antivirals. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 16, 115-122.e10.

Sarrazin, C., Isakov, V., Svarovskaia, E.S., et al., 2017. Late Relapse Versus Hepatitis C Virus Reinfection in Patients With Sustained Virologic Response After Sofosbuvir-Based Therapies. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 64, 44–52.

Schwarz, K.B., Rosenthal, P., Murray, K.F., et al., 2020. Ledipasvir-Sofosbuvir for 12 Weeks in Children 3 to <6 Years Old With Chronic Hepatitis C. Hepatol. Baltim. Md 71, 422–

Semmler, G., Alonso López, S., Pons, M., et al., cACLD-SVR Study Group, 2024. Post-treatment LSM rather than change during treatment predicts decompensation in patients with cACLD after HCV cure. J. Hepatol. S0168-8278(24)00198-3.

Shin, E.-C., Sung, P.S., Park, S.-H., 2016. Immune responses and immunopathology in acute and chronic viral hepatitis. Nat. Rev. Immunol. 16, 509–523.

Sulkowski M. S., Gardiner D. F., Rodriguez-Torres M., et al., 2014. Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. N. Engl. J. Med. 370, 211–221.

Terrault, N.A., Dodge, J.L., Murphy, E.L., et al., 2013. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: the HCV partners study. Hepatol. Baltim. Md 57, 881–889.

Terrault, N.A., Levy, M.T., Cheung, K.W., Jourdain, G., 2021. Viral hepatitis and pregnancy.Nat. Rev. Gastroenterol. Hepatol. 18, 117–130.

Thein, H.-H., Yi, Q., Dore, G.J., Krahn, M.D., 2008. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatol. Baltim. Md 48, 418–431.

Thomas, D.L., Thio, C.L., Martin, M.P., et al., 2009. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461, 798–801.

Trickey, A., Fraser, H., Lim, A.G., et al., 2019. The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. Lancet Gastroenterol. Hepatol. 4, 435–444.

van der Meer, A.J., Veldt, B.J., Feld, J.J., et al., 2012. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 308, 2584–2593.

Vermehren, J., Serfert, Y., Cornberg, M., et al., 2020. Sofosbuvir, velpatasvir, and voxilaprevir for patients with failure of previous direct-acting antiviral therapy for chronic hepatitis C: Results from the German Hepatitis C-Registry (DHC-R). Z. Gastroenterol. 58, 841–846.

Villanueva, A., 2019. Hepatocellular Carcinoma. N. Engl. J. Med. 380, 1450–1462.

Vogel, M., Deterding, K., Wiegand, J., et al., German Hepatitis Group, Hep-Net, 2009. Initial presentation of acute hepatitis C virus (HCV) infection among HIV-negative and HIV-positive individuals-experience from 2 large German networks on the study of acute HCV infection. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 49, 317–319; author reply 319.

Wei, L., Lim, S.G., Xie, Q., et al., 2019. Sofosbuvir-velpatasvir for treatment of chronic hepatitis C virus infection in Asia: a single-arm, open-label, phase 3 trial. Lancet Gastroenterol. Hepatol. 4, 127–134.

Wei, L., Wang, G., Alami, N.N., et al., 2020. Glecaprevir–pibrentasvir to treat chronic hepatitis C virus infection in Asia: two multicentre, phase 3 studies—a randomised, double-blind study (VOYAGE-1) and an open-label, single-arm study (VOYAGE-2). Lancet Gastroenterol. Hepatol. 5, 839–849.

Wyles, D., Brău, N., Kottilil, S., et al., ASTRAL-5 Investigators, 2017. Sofosbuvir and Velpatasvir for the Treatment of Hepatitis C Virus in Patients Coinfected With Human Immunodeficiency Virus Type 1: An Open-Label, Phase 3 Study. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 65, 6–12.

Yeung, C.-Y., Lee, H.-C., Chan, W.-T., Jiang, C.-B., Chang, S.-W., Chuang, C.-K., 2014. Vertical transmission of hepatitis C virus: Current knowledge and perspectives. World J. Hepatol. 6, 643–651.

Zeng, H., Li, L., Hou, Z., Zhang, Y., Tang, Z., Liu, S., 2020. Direct-acting Antiviral in the Treatment of Chronic Hepatitis C: Bonuses and Challenges. Int. J. Med. Sci. 17, 892–902.

Zeuzem, S., Foster, G.R., Wang, S., et al., 2018. Glecaprevir–Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. N. Engl. J. Med. 378, 354–369.

Zhang, Y., Chen, L.-M., He, M., 2017. Hepatitis C Virus in mainland China with an emphasis on genotype and subtype distribution. Virol. J. 14, 41.

Zhang, Y.-Q., Guo, J.-S., 2015. Antiviral therapies for hepatitis B virus-related hepatocellular carcinoma. World J. Gastroenterol. 21, 3860–3866.

Zignego, A.L., Craxì, A., 2008. Extrahepatic manifestations of hepatitis C virus infection. Clin. Liver Dis. 12, 611–636.

4. Hepatitis D – diagnosis and treatment

Lisa Sandmann, Heiner Wedemeyer, Markus Cornberg

Introduction

The hepatitis delta virus (HDV) is a defective RNA virus which requires the hepatitis B virus (HBV) surface antigen (HBsAg) for generation of infectious virus particles and transmission, while the full extent of the HBV helper function is unexplored (Rizzetto 1983, Taylor 2012). Hence, HDV occurs only in HBsAg positive individuals either as acute coinfection or as superinfection in patients with chronic HBV (Wedemeyer 2010b) (Figure 1). Several studies have shown that chronic HDV infection leads to more severe liver disease than chronic HBV monoinfection, with an accelerated course of fibrosis progression, an increased risk of hepatocellular carcinoma and early decompensation in the setting of established cirrhosis (Beguelin 2017b, Hughes 2011, Manesis 2013). Currently, two treatment options are available and recommended by guidelines (EASL 2023, Sandmann 2023a). The entry-inhibitor bulevirtide has been approved by EMA. Results from phase 2 and 3 studies were published (Wedemeyer 2023a, Wedemeyer 2023c) and confirmed in real-world cohort analyses (Degasperi 2022a, Dietz-Fricke 2023) In the phase 3 study, on-treatment rates of combined response were 45% and 55% at 48 or 96 weeks of treatment, respectively (Wedemeyer 2024, Wedemeyer 2023a). Currently, treatment is recommended indefinitely for as long as the patient is benefitting (EMA 2024a). This is in contrast to treatment with pegylated interferon alfa (PEG-IFN) in which a defined treatment duration of 48 weeks is recommended (EASL 2023, Sandmann 2023a). About one quarter of patients showed prolonged virological off-treatment response but long-term HDV RNA relapses may occur (Heidrich 2014). HBsAg clearance should be the preferred endpoint of interferon-based therapies of HDV, but this is rarely achieved. Yet, suppression of HDV RNA in the presence of HBsAg has been associated with improved clinical outcomes (Farci 2004, Wranke 2017, Yurdaydin 2018a). Additional treatment options are currently in clinical development.

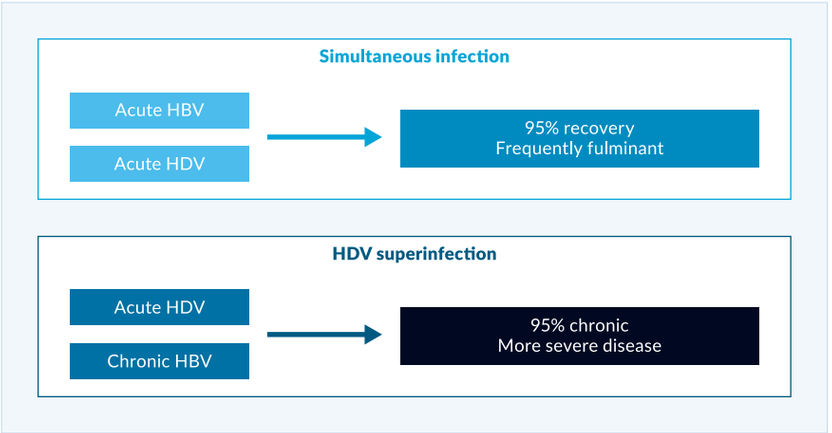

Figure 1. Courses of hepatitis delta

Virology of HDV

The hepatitis D virion is approximately 36 nm in size, containing HDV RNA and delta antigen. HDV RNA is single-stranded, highly base-paired, circular and by far the smallest known genome of any animal virus, containing close to 1700 nucleotides (Sureau 2016, Taylor 2012). It is coated with the envelope protein derived from the pre-S and S antigens of HBV. Other enveloped viruses including HCV and VSV can also propagate HDV infection, both *in vitro* as well in humanized mice (Perez-Vargas 2019). Still, it is currently unclear if viruses distinct from HBV induce dissemination of HDV also in patients. The HDV RNA has six open reading frames (ORFs), three on the genomic and three on the antigenomic strand. One ORF codes for the hepatitis delta antigen (HDAg), while the other ORFs do not appear to be actively transcribed. Two HDAgs exist: the small HDAg (24 kD) is 155 amino acids long and the large HDAg (27 kD) is 214 amino acids long. A single nucleotide change (A-G) in the small HDAg sequence leads to the synthesis of the large HDAg. The small HDAg accelerates genome synthesis, while the large HDAg that inhibits HDV RNA synthesis is necessary for virion morphogenesis (Taylor 2012). Replication of HDV RNA occurs through a 'double rolling circle' model in which the genomic strand is replicated by a host RNA polymerase to yield a multimeric linear structure that is then autocatalytically cleaved to linear monomers and ligated into the circular HDV RNA viral progeny (Sureau 2016). Recent work showed that the host RNA polymerase II-is coactivated by S-HDAg using a histone mimicry strategy (Abeywickrama-Samarakoon 2020).

Genetic analysis has revealed the presence of at least eight HDV genotypes (Le Gal 2017) (Figure 2). Genotype 1 is the most frequently seen and is distributed throughout the world, especially in Europe, the Middle East, North America and North Africa. Genotype 2 is seen in East Asia and the Yakutia region of Russia, and genotype 3 is present exclusively in the northern part of South America, especially in the Amazon basin. Genotype 4 is seen in Taiwan and Japan, while genotypes 5-8 are found in Africa (Deny 2006). HDV genotype 1 is associated with both severe and mild disease whereas genotype 2 causes a milder disease over a long-term course (Su 2006). HDV genotype 5 may also take a milder course and a better response to PEG-IFN treatment compared to genotype 1 (Spaan 2020).

HDV quasispecies evolution declines over time during HDV infection even though a continuous adaptation of HDV occurs indicating ongoing immune pressure in chronic HDV (Homs 2016).

HBV genotypes may also contribute to distinct clinical courses of HDV. There is no evidence that specific HDV genotypes may infect patients with one specific HBV genotype exclusively. However, data indicate that distinct HDV mutations may facilitate association of certain HDV genotypes with different HBV genotypes (Kay 2014). The global distribution of HBV and HDV genotypes is shown in Table 1.

Table 1. HBV and HDV genotypes

Region	HDV genotype	HBV genotype
Europe	1	D/A
Brazil	1/3	F/A/D
China, Taiwan, Japan	1/2/4	B/C
Turkey, Iran, Pakistan, India	1	D
Western Pacific	1/2	B/C/D
Africa	1, 5–8	D/A/E

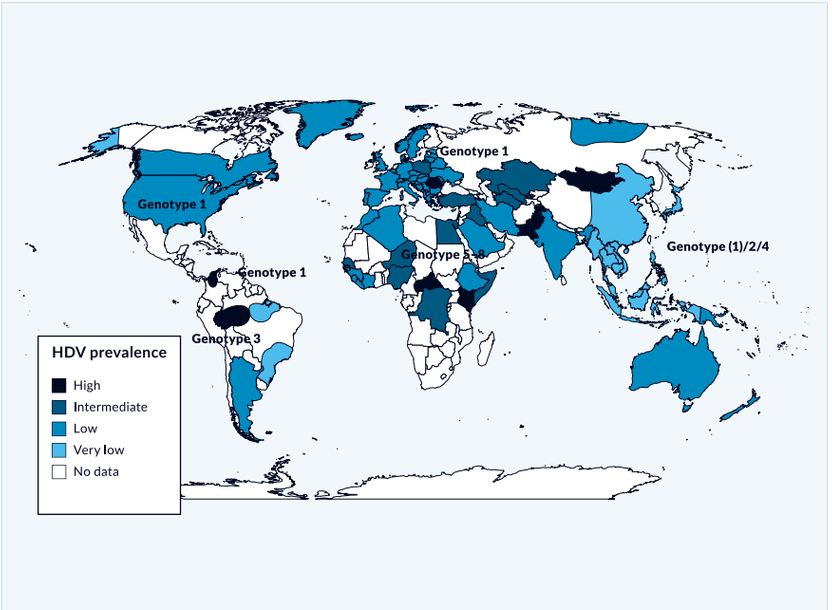

Figure 2. HDV prevalence

Epidemiology of HDV

Being linked to HBV, HDV is spread in the same way as HBV, mainly through parenteral exposure (Niro 1999). Worldwide, 217 to 316 million people are chronically infected with HBV (Polaris Observatory 2023) and 9–19 million of those are estimated to be anti-HDV positive (Stockdale 2020). However, conflicting data on the prevalence of HDV exists (Wedemeyer 2020) which might be partially due to different testing strategies that are currently present. Risk-based testing is recommended by the AASLD guideline (Terrault 2018) while anti-HDV testing for all HBsAg positive samples is recommended by EASL (EASL 2023). In high-income countries, high anti-HDV prevalence is found in people who inject drugs (PWID) who are HBsAg positive, both in Europe (Erhardt 2010, Gaeta 2000, Heidrich 2009) and North America (Kucirka 2010). Historically, HDV was endemic in Southern Europe. Several studies performed in the 1980s and 1990s showed a prevalence of anti-HDV of more than 20% among HBsAg positive individuals. As a result of the implementation of HBV vaccination programs, the incidence of HDV infections significantly decreased in Southern Europe in the 1990s (Degertekin 2008, Gaeta 2000). Countries with a particularly high prevalence of HDV are Mongolia with up to one third of chronic hepatitis cases being caused by HDV (Tsatsralt-Od 2005), Romania (Gheorghe 2015), some Central Asian countries like Uzbekistan (Khodjaeva 2019) and Pakistan (Abbas 2012), northwestern states of Brazil (Braga 2014, Kay 2014), distinct regions in Africa (Andernach 2014), and some Polynesian islands (Han 2014) (Figure 2). Of note, prevalence rates of HBV and HDV are not linked - for example, HDV infections have been considered to be rare in most parts of mainland China despite very high frequencies of HBV. However, some studies revealed an HDV prevalence of up to 6.5%, suggesting that HDV may be more frequent in China than previously thought (Liao 2014). In Taiwan, a country with a well-established national HBV vaccination program, the epidemiology of HDV changed over the last 20 years with PWID and HIV positive persons being particular risk groups and representing a main reservoir for HDV infection (Hung 2014, Lee 2015, Lin 2015). Thus, even though HDV is a major problem in distinct regions and specific cohorts, HDV is overall a rare disease and has therefore been granted orphan designation both by the FDA and by the European Commission.

One problem is that many HBsAg positive patients are not tested for HDV. The HDV testing rate was low in four hospitals in London where people with HDV frequently had severe disease and patients were of very diverse ethnicity (El Bouzidi 2015). In the United States Veterans Affairs medical system, only 8.5% of more than 25,000 HBsAg positive patients were tested for HDV. Of those, 3.4% had evidence for HDV and HDV was associated with a 2.9-fold higher HCC incidence and a higher risk of all-cause mortality (Kushner 2015). Recent studies evaluated the effects of reflex testing in HBsAg positive individuals (Palom 2022). In doing so, the absolute number of HDV diagnoses quintrupled compared to the era without reflex testing. A current modelling analysis from the Polaris Observatory recommends double reflex testing (anti-HDV testing for all HBsAg positive individuals followed by HDV RNA testing in anti-HDV positive samples) for the correct estimation of the worldwide HDV prevalence (Razavi 2023).

Pathogenesis of HDV

Knowledge about the pathogenesis of HDV infection is limited. Clinical observations have provided examples of mostly an immune-mediated process in HDV (Grabowski 2010). However, patterns suggesting a cytopathic viral disease have occasionally been observed. A typical example of this were outbreaks of severe hepatitis in the northern part of South America (Nakano 2001). These mostly fulminant hepatitis cases were induced by genotype 3 HDV. In HDV, liver histology is not different from a patient with HBV or HCV with accompanying necroinflammatory lesions. Importantly, HDV viremia is not directly associated with the stage of liver disease in HDV genotype 1 infection (Zachou 2010) while in HDV genotype 3 infection

higher viral loads were observed in patients with cirrhosis (Braga 2014). In both humanized chimeric mice as well as mice expressing the human HBV receptor (sodium taurocholate co-transporting polypeptide (NTCP)) HDV infection provoked a marked and broad induction of interferon stimulated genes and cytokines which was more pronounced than in HBV monoinfection (Giersch 2015, He 2015) which may directly contribute to the more severe inflammation in patients with HDV. Another study showed that modification of three amino acids in mouse NTCP (H84R, T86K, and S87N) rendered mice susceptible to HDV (He 2016). In this respect it is important to note that distinct polymorphisms in the IL28B gene may be associated with HBsAg persistence also in HDV coinfected patients (Karatayli 2015).

Cellular immune responses against the HDV have been described (Hoblos 2023, Huang 2004, Nisini 1997) suggesting that the quantity and quality of T cell responses may be associated with some control of the infection. HDV-specific IFN gamma and IL-2 responses are more frequent in patients with low HDV viraemia (Grabowski 2011). However, HDV-specific T cell responses are very weak and exhausted in chronic infection. *In vitro,* the third signal cytokine IL-12 was able to restore the function of HDV-specific CD4+ and CD8+ T cells (Schirdewahn 2017). In addition to immune exhaustion, T cell failure may also be caused by T cell escape variants (Karimzadeh 2018, Karimzadeh 2019, Kefalakes 2019). However, T cell responses in the liver may also lead to immune pathogenesis. One study investigated innate and adaptive immune responses localized in the liver and showed that also liver-resident CD8+ T cells, and in particular antigen-nonspecific T cells, contribute to liver disease pathogenesis (Kefalakes 2021). NK cells from patients with HDV have recently been investigated in more detail (Lunemann 2014). Overall, NK cell frequencies increased but the cells were less activated and functionally impaired. HDV infection also did not alter NK cell differentiation, and the activity of liver disease reflected alterations in NK cell surface receptor expression. NK cell frequency may also be associated with early virological response to PEG-IFN therapy although NK cells are severely functionally impaired during antiviral therapy (Lunemann 2015). Finally, mucosa-associated invariant T (MAIT) cells, which are innate-like T cells highly enriched in the human liver, are activated, functionally impaired and severely depleted in patients with chronic hepatitis D (Dias 2019). This loss of MAIT cells was associated with severity of liver disease. Collectively, this information suggests that HDV is mainly an immune-mediated disease, at least in HDV genotype 1 infection. Ideally, antiviral therapies should therefore also aim to enhance anti-HDV immunity to confer long-term control of the infection.

Coinfections with multiple hepatitis viruses are associated with diverse patterns of reciprocal inhibition of viral replication (Raimondo 2006, Wedemeyer 2010a). HDV has frequently been shown to suppress HBV replication (Calle Serrano 2012). Between 70% and 90% of HDV patients are HBeAg negative with low levels of HBV DNA. Humanized HBsAg positive mice that become superinfected with HDV also show a decrease in HBV replication (Lutgehetmann 2012). A molecular explanation for the suppression of HBV replication by HDV has been suggested via the HDV proteins p24 and p27 repressing HBV enhancers (Williams 2009). In addition, induction of a type-I interferon response by HDV may contribute to HBV repression. This hypothesis is supported by the induction of interferon stimulated genes in HBV cells which were superinfected with HDV which led to a decrease of HBV replication markers (Alfaiate 2016). Viral dominance may change over time and about half of the hepatitis delta patients showed significant HBV replication in one study (Schaper 2010).

HDV may also play a direct role in the development of hepatocellular carcinoma by altering DNA methylation events (Benegiamo 2013). Recent systematic reviews and meta-analyses noted a significantly higher risk of HCC development in HDV compared to HBV monoinfection (Alfaiate 2020, Kamal 2021). If this higher risk is due to earlier development of liver cirrhosis or a consequence of direct oncogenic effects of HDV is a matter of debate.

Clinical course of HDV

Acute HBV/HDV coinfection

Acute HBV/HDV coinfection in adults leads to recovery in more than 90% of cases but frequently causes severe acute hepatitis with a high risk for developing a fulminant course (Rizzetto 2009). In contrast, HDV is cleared spontaneously only in a minority of patients with HDV superinfection of chronic HBsAg carriers (Figure 1). The observation that the histopathology of simultaneous HBV and HDV infection is more severe than in infection with HBV alone has also been documented in experiments with chimpanzees (Dienes 1990). Several outbreaks of very severe courses of acute HDV have been described in different regions of the world (Casey 1996, Flodgren 2000, Tsatsralt-Od 2006). Fortunately, acute HDV has become infrequent over the last two decades in high-income countries due to the introduction of vaccination programs.

Chronic HDV infection

Several early studies showed that chronic HDV leads to more severe liver disease compared to chronic HBV monoinfection, with an accelerated

course of fibrosis progression, and early decompensation in the presence of cirrhosis (Asselah 2023, Wranke 2023, Wranke 2024). Long- term follow-up data from Italy, Spain, Greece and Germany confirmed the particularly severe course of HDV (Buti 2011, Calle Serrano 2014, Manesis 2013, Niro 2010, Romeo 2009). Characteristics of patients with HDV genotype 3 infection were reported in more detail confirming the severity of liver disease also for this specific HDV genotype (Braga 2014). HDV infection has been associated with a particular high risk of developing liver cirrhosis in people who are living with HIV (Calle Serrano 2012, Fernandez-Montero 2014). In one cross-sectional study from Spain, 66% of people coinfected with HIV/HBV/HCV/HDV presented with liver cirrhosis compared to only 6% of people coinfected with only HBV/HCV/HIV (Castellares 2008) and this translated to higher rates of liver decompensation and death (Fernandez-Montero 2014). Similarly, HDV was associated with poorer survival in HIV positive people in Taiwan (Lee 2015, Sheng 2007) and in the Swiss HIV cohort study (Beguelin 2017b). The Swiss study showed a prevalence of HDV of 15.4% and showed a 2.3- fold increased risk of overall death for those coinfected with HIV/HDV. Furthermore, a six-fold increased risk of HCC was calculated for HIV/HBV/HDV triple infected patients (Kamal 2021). Recent data from Sweden showed that HDV infection was associated with a 3.8-fold higher risk for liver related outcomes (Kamal 2020).

An easy-to-apply clinical score, the baseline-event anticipation (BEA) score, has been suggested to predict the risk of developing liver-related morbidity and mortality (Calle Serrano 2014). Factors associated with a poor long-term outcome included age above 40, male sex, low platelet counts, high bilirubin and INR values and southeast Mediterranean origin. The BEA score was validated in two independent European cohorts. However, the cohort size was limited (n=77 and 62, respectively), so the use of the score has not yet become widespread.

Diagnosis of HDV

Current EASL guidelines recommend that everyone who is HBsAg positive should be tested for anti-HDV antibodies at least once (Figure 3). Testing should be repeated whenever clinically indicated, e.g. in case of elevated liver enzymes or decompensation of chronic liver disease (EASL 2023, Sandmann 2023a).

In case of positive anti-HDV, HDV RNA testing should be performed with a standardized and sensitive nucleic acid test. It is important to note that the sensitivity of available HDV RNA assays varies (Le Gal 2016) and also the extraction method has an influence on the viral load quantification (Bremer 2019). This has to be taken into account when comparing results from different laboratories (Sandmann 2024a, Wedemeyer 2023b). In case of detectable HDV RNA subsequent evaluation of grading and staging of liver disease, surveillance for hepatocellular carcinoma and consideration of antiviral treatment is indicated (EASL 2023, Sandmann 2023a). So far, there is no consistent evidence that HDV RNA levels are strongly correlated with histological markers of liver disease (Zachou 2010) even though high HDV RNA levels may be predictive of developing cirrhosis and HCC in the long term (Romeo 2014). HDV genotyping may help to stratify patients, e.g. identify patients with a higher or lower risk of developing end-stage liver disease (Su 2006). In high-income countries, almost all patients are infected with HDV genotype 1, thus genotyping may be considered mainly in immigrants or populations with mixed genotype prevalence. However, genotyping is no prerequisite for antiviral treatment and can be omitted based on current treatment guidelines (Sandmann 2023a). As HDV occurs only in the context of HBV coinfection, a work-up of HBV infection including HBV DNA quantification and HBeAg/anti-HBe determination is warranted. Between 10% and 20% of HDV patients are HBeAg positive. Of note, HBV DNA can be suppressed even in HBeAg positive hepatitis (Heidrich 2012) suggesting that the inhibitory effect of HDV on HBV is independent from the phase of HBV infection. The long-term clinical outcome of anti-HDV positive patients did not differ between HBeAg positive and HBeAg negative individuals in one study from Germany (Heidrich 2012). Most HDV patients in Europe are infected with HBV genotype D but infection with genotype A can also occur (Soriano 2011). Because of the similar risk profiles of the patients, tests for HIV and HCV are also mandatory.

Quantitative HBsAg levels may be helpful for therapeutic management in certain situations (Sandmann 2023a). During treatment with PEG-IFN, a strong HBsAg decline may be a reason to extend the treatment duration from 48 to 96 weeks. During bulevirtide (BLV) monotherapy no effect on HBsAg has been observed so far. Therefore, quantitative determination is not mandatory during BLV treatment. Staging of liver disease is of particular importance in HDV as treatment options are still limited. Various non-invasive serum markers have been developed to predict liver fibrosis and cirrhosis in HCV, HBV and MASLD. However, scores such as APRI, FIB-4 or AST/ALT ratio have to be used with caution in HDV infection (Da 2020, Lutterkort 2017, Sandmann 2024b, Takyar 2017). Novel scores specifically developed for HDV have been proposed. One score is based on serum cholinesterase, gamma glutamyl transferase, albumin and age and has been validated in European patients (Lutterkort 2017). Transient elastography has been shown to be useful to exclude liver cirrhosis (<15 kPa) and advanced fibrosis (<10 kPa) in HDV patients (Sandmann 2024b).

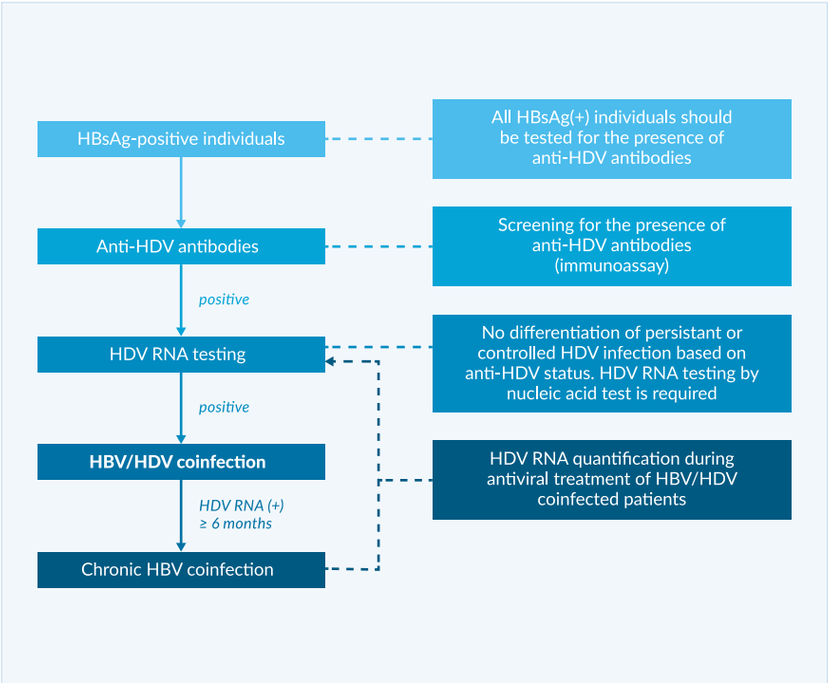

Figure 3. Diagnostic algorithm in HBsAg positive individuals

Treatment of HDV

With bulevirtide (BLV) and pegylated interferon alfa (PEG-IFN) two treatment options are currently available. Antiviral efficacy against HDV has been demonstrated in randomized trials for both compounds. Therefore, treatment options should be evaluated in all patients with chronic HDV infection and detectable HDV RNA. Patients with high levels of liver inflammation advanced liver fibrosis or liver cirrhosis should be prioritized for antiviral therapy (Sandmann 2023a). Due to the rarity of the disease, treatment in a hepatology center is recommended. This is especially true for patients with advanced liver disease as liver transplantation should also be considered for these patients (Sandmann 2023a). In general, BLV and PEG-IFN show different treatment modalities, side effect profile and response rates. For the choice of treatment, advantages and disadvantages of available treatment options should be weighed up and discussed with the patient (Table 2 and Table 3). A summary of treatment options is depicted in figure 4.

Table 2. Advantage and disadvantages of bulevirtide and pegylated interferon treatment (adapted from (8))

	Advantages	Disadvantages
Bulevirtide	• Approval by the European Medicines Agency (EMA 2024a) • Good tolerability (Lampertico 2022, Wedemeyer 2023a, Wedemeyer 2023c) • Approximately 50% virologic and biochemical response after 48 weeks of therapy (Lampertico 2022, Wedemeyer 2023a, Wedemeyer 2023c) • Use in advanced liver disease appears to be safe (Dietz-Fricke 2023)	• Long-term data not yet available due to new availability • Effect on clinical endpoints not yet investigated • No effect on HBsAg (Lampertico 2022, Wedemeyer 2023a, Wedemeyer 2023c) • Duration of therapy not defined (currently continuous therapy) (EMA 2024a) • Daily subcutaneous administration (EMA 2024a)
Pegylated interferon alfa	• Limited treatment duration (Wedemeyer 2011, Wedemeyer 2019b) • Long-term data available and effect on clinical endpoints have been studied (Farci 2004, Wranke 2020, Wranke 2017) • Weekly administration (EMA 2024b) • Substance with much experience in clinical use (Sandmann 2023b) • HBsAg loss rare but possible (Wedemeyer 2019b)	• Approximately 25% virologic response 24 weeks after end of therapy (Heidrich 2014, Sandmann 2023b) • Subcutaneous administration (EMA 2024b) • Side effect profile • Dose adjustments required for thrombocytopenia or not recommended (EMA 2024b) • Contraindicated in autoimmune diseases (EMA 2024b) • Contraindicated in decompensated liver cirrhosis (EMA 2024b) • Restricted approval indication* (EMA 2024b)
Pegylated interferon alfa plus bulevirtide	• Synergistic effect possible (Zhang 2022) • HBsAg loss possible (Wedemeyer 2019a) • Limited treatment duration possible (Lampertico 2022, Wedemeyer 2019a)	• No additional effect of combination with bulevirtide 2 mg compared to interferon monotherapy (Asselah 2024) • Treatment regimen and combination strategy unclear (De Ledinghen 2022, de Lédinghen 2022, Fontaine 2022, Lampertico 2022, Wedemeyer 2019a)

* PEG-IFN-2a is indicated for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease, evidence of viral replication, elevated alanine aminotransferase (ALT) levels, and histologically verified liver inflammation and/or fibrosis (EMA 2024b).

Table 3. Virological and biochemical response rates from major clinical studies investigating PEG-IFN or BLV (adapted from (Sandmann 2023a)).

Study	Cohorts	**Combined response** (≥2 log HDV RNA decline or negativity + ALT normalization) **at EOT**	**Virological response** (≥2 log HDV RNA decline or negativity) **at EOT**	**HDV RNA negativity at EOT**	**Biochemical response** (ALT normalization) **at EOT**	**HDV RNA negativity at FU24**
MYR202 N=118 (Wedemeyer 2023c)	a) 2mg BLV plus TDF 24W (n=28) b) 5mg BLV plus TDF 24W (n=32) c) 10mg plus TDF 24W (n=30) d) TDF 24W (n=28)	a) 21% b) 28% c) 37% d) 0%	a) 54% b) 50% c) 77% d) 4%	a) 4% b) 6% c) 3% d) 0%	a) 43% b) 50% c) 40% d) 7%	a) 4% b) 3% c) 0% d) 0%
MYR301, n=150 (Wedemeyer 2023a)	a) No therapy 48W1 (n=51) b) 2mg BLV 48W1 (n=49) c) 10mg BLV 48W1 (n=50) All groups with or without TDF	a) 2% b) 45% c) 48%	a) 4% b) 71% c) 76%	a) 0% b) 12% c) 20%	a) 12% b) 51% c) 56%	n.a.
HIDIT-I, n=90 (Wedemeyer 2011)	a) PEG-IFN plus ADF 48W (31) b) PEG-IFN 48W (n=29) c) ADV 48W (n=30)	n.a.	a) 26%[2] b) 31%[2] c) 0%2	a) 23% b) 24% c) 0%	a) 32% b) 28% c) 7%	a) 26% b) 31% c) 0%
HIDIT-II, n=120 (Wedemeyer 2019b)	a) PEG-IFN plus TDF 96W (n=59) b) PEG-IFN 96W (n=61)	n.a.	n.a.	a) 48% b) 33%	a) 44% b) 38%	a) 31% b) 23%

[1] total treatment duration of 96 (a) or 144 (b and c) weeks, primary endpoint analyses after 48 weeks of treatment. 2 from baseline to week 72

ADF, adefovir; BLV, bulevirtide; EOT, end of treatment; FU24, follow-up 24 weeks (24 weeks after end of treatment); PEG-IFN, pegylated interferon alfa; TDF, tenofovir; W, weeks

Bulevirtide

Bulevirtide is the first drug for the treatment of chronic HDV infection that received approval by the European Medicines Agency (EMA 2024a). BLV is approved for the treatment of patients with chronic HDV infection, detectable HDV RNA and compensated liver disease (EMA 2024a). Treatment is administered subcutaneously once daily at a dose of 2 mg with or without concomitant nucleos(t)ide analog (NA) treatment. Currently, the optimal treatment duration is not known and treatment should be administered as long as there is a benefit for the patient.

BLV blocks the entry of HBV and HDV into hepatocytes by binding to and blocking NTCP, a bile salt transporter of the liver (Li 2016). Analyses of biopsy data from clinical trials have shown that BLV leads to a reduction in necroinflammation (Wedemeyer 2023c) and a reduction in HDV-infected hepatocytes, which correlates with a reduction in intrahepatic HDV RNA (Allweiss 2024). Due to the mechanism of action, patients treated with BLV show elevated bile acid levels, which has not been shown to be of clinical relevance (i.e. patients do not experience pruritus) (Wedemeyer 2023a).

BLV was approved on the basis of two phase 2 studies in which either BLV in combination with tenofovir (MYR202) or BLV monotherapy (MYR203) was carried out. The duration of therapy was 24 and 48 weeks, respectively. BLV therapy resulted in a decrease in HDV RNA, which, however, was reversible after the end of therapy. Recently, results of the ongoing phase 3 study, MYR301 have been published (Wedemeyer 2023a). The primary endpoint, combined response (HDV RNA decline or undetectability and ALT normalization) after 48 weeks of treatment, was significantly more frequent in patients receiving BLV 2 mg compared to patients without BLV treatment (45% vs. 2%, $p<0.001$). After 48 weeks of treatment, 12% of patients receiving BLV 2 mg showed HDV RNA undetectability and 51% of patients had normalized their ALT values (Table 3) (Wedemeyer 2023a). BLV treatment was overall well tolerated and no treatment interruptions due to side effects were registered. Furthermore, health related quality of life measured by Hepatitis Quality of Life Questionnaire improved significantly for patients receiving treatment (Buti 2022).

Results of the interim analysis after 96 weeks of treatment were recently published. With ongoing treatment duration, virological, biochemical and combined response rates further increased (Wedemeyer 2024) . Due to the conditional approval in 2020, case reports and case series from Europe have been published that show the use of bulevirtide in clinical practice. Treatment response rates were overall comparable to the ones from clinical trials. In July 2023, BLV received full approval by EMA.

Importantly, the proportion of patients with cirrhosis, even portal hypertension, was high in these real-world cohorts, emphasizing that

bulevirtide can be safely used in (compensated) advanced cirrhosis (Degasperi 2022b, Dietz-Fricke 2023, Herta 2022, Jachs 2022, Zollner 2022). As of 4/2024, BLV is not approved in patients with decompensated liver disease. However, in the German real-world cohort, a total of 5 patient with decompensated liver cirrhosis (Child-Pugh B n=4, Child-Pugh C: n=1) were treated with BLV. ALT levels decreased and platelet counts increased in 4 patients and one patient with refractory ascites experienced transient improvement. One patient developed decompensation (ascites) during therapy, BLV was safely continued, and the cause of decompensation was attributed to another precipitating cause (Dietz-Fricke 2023). This is of particular importance as discontinuation of BLV therapy can lead to a rebound in HDV RNA and in patients with decompensated liver function there is concern that the rebound in HDV RNA could lead to a further deterioration of liver function. Therefore, if possible, treatment with BLV should be continued if decompensation occurs during therapy, especially if the HDV RNA is suppressed by the therapy.

In general, the treatment duration of BLV therapy is still unclear. Current guidelines recommend to continue treatment for as long as there is a benefit for the patient (EASL 2023). The phase 3 study (MYR301) is investigating the course after discontinuation of bulevirtide after a previous treatment duration of 96 to 144 weeks (Wedemeyer 2023a). These results are not yet available and must be awaited in order to assess whether a maintained response can be achieved after discontinuation of bulevirtide therapy for more than 96 weeks. Current real-world data show a rebound in HDV RNA after stopping bulevirtide, even after a treatment duration of more than 48 weeks (Jachs 2022). Re-treatment with BLV was successful in all cases and no resistances were detected (Jachs 2023). Nevertheless, some patients remained HDV RNA suppressed after treatment cessation even without achieving HBsAg loss (Anolli 2023, Jachs 2023). However, so far there are no stopping rules and due to the above-mentioned risk of deteriorating liver function, BLV should not be stopped in patients with decompensated liver disease. Maintained virological control has so far been shown in particular with the combination therapy PEG-IFN plus bulevirtide and HBsAg loss (Lampertico 2022).

The addition of PEG-IFN to bulevirtide therapy may in principle increase response rates, as the combination therapy may have synergistic effects. It has been shown *in vitro,* that interferon treatment inhibits cell-to-cell spread of HDV (Zhang 2022) thereby reducing the number of HDV-infected hepatocytes. The combination of PEG-IFN and BLV has been and is being investigated in clinical trials (Bogomolov 2016, Lampertico 2022). Data from the phase 2 study MYR204 has recently been published. The combination of PEG-IFN and BLV 2 mg showed similar off-treatment results compared to PEG-IFN monotherapy while the combination of PEG-IFN and BLV 10 mg achieved the highest rate of HDV RNA undetectability at 48 weeks after end of treatment (Asselah 2024). Data from the MYR203 study has only been presented as a congress paper (Wedemeyer 2019a) and further information is summarized in a review (Lampertico 2022). In addition, real-world data on the use of PEG-IFN plus BLV have been presented at congresses (De Ledinghen 2022, de Lédinghen 2022, Fontaine 2022) and published in small case series (Jachs 2022). With the limitation of heterogeneous treatment regimens, the overall data confirm the virological response rates and safety of PEG-IFN/BLV therapy reported in clinical trials (Lampertico 2022). Preliminary data from the French early access cohort show comparable data to BLV monotherapy in terms of combined response (HDV RNA decline ≥ 2 log plus ALT normalization) after 2 years of PEG-IFN/BLV therapy (De Ledinghen 2022). In an Austrian case series, combination therapy with PEG-IFN was initiated in patients who plateaued HDV RNA HDV RNA after 24-48 weeks of BLV therapy, regardless of initial response classification (Jachs 2022). It is currently unclear which patients will benefit from combination therapy. In addition, timing and duration of combination therapy are not known. It is unclear whether combination therapy should be given from the start or whether it should be started during the course of BLV monotherapy after certain criteria have been met. However, based on many years of experience with PEG-IFN therapy and the first real-world data, combination therapy with BLV plus PEG-IFN may be an option for experienced physicians treating hepatitis D in individual cases (EASL 2023, Sandmann 2023a).

Pegylated interferon alfa

Pegylated interferon alfa-2a (PEG-IFN) has antiviral activity against HDV, however, it is only approved for the treatment of hepatitis B (EMA 2024b). The specific mechanism of action of interferon alfa on HDV is still not fully understood. One effect of PEG-IFN treatment is the activation of the JAK-STAT pathway, which leads to transcription of interferon-stimulated genes, resulting in an "antiviral state." Importantly, in HDV infection, interferon alfa also suppresses cell division-mediated HDV spread by destabilizing HDV RNA during cell division (Zhang 2022). Interferon alfa therapy (standard or PEG-IFN) achieves up to 47% HDV RNA suppression, with the highest response rates documented in smaller cohort studies (Farci 1994, Sandmann 2023b). In the two large prospective randomized controlled HIDIT trials, the response rate in the PEG-IFN monotherapy groups was 23-33% at the end of treatment. At 24 weeks after end of treatment, 23-31% of patients had undetectable HDV RNA (Wedemeyer 2011, Wedemeyer 2019b) (Table 3). However, during long-term follow-up, late HDV RNA relapses

were detected in 55% of the patients from the HIDIT-I study (Heidrich 2014, Wranke 2020). Therefore, unlike in hepatitis C, the term "sustained virlogical response" (SVR) should not be used and long-term follow-up is needed even after antiviral treatment has ended. Based on these studies, the long-term effects on clinical endpoints after PEG-IFN based treatment have been investigated, providing a solid data base for therapy with PEG-IFN.

Current treatment guidelines recommend a treatment duration of 48 weeks (EASL 2023, Sandmann 2023a). During treatment, regularly blood tests are warranted as a decrease in leukocytes and platelets is a common side-effect and dose adjustments might be necessary. Interferon treatment can induce autoimmune thyreopathy (Andrade 2011). Therefore, also TSH should be monitored before and during therapy.

Extension of treatment duration to 96 weeks was investigated in the HIDIT-II study (Wedemeyer 2019b). Longer treatment duration did not significantly increase the number of patients with maintained treatment response. Therefore, an extension of therapy beyond 48 weeks is not generally recommended. However, if a decrease in HBsAg levels is observed during treatment, continuation of treatment beyond 48 weeks may be reasonable as the goal of HBsAg loss may be achieved in some patients (Heller 2014, Hercun 2021). HBsAg loss defines functional cure of the underlying HBV infection and is associated with improved long-term clinical outcome (Cornberg 2020, Wranke 2017).

Predictors of response or nonresponse to PEG-IFN have only been studied retrospectively. Based on data from the HIDIT-I trial (Wedemeyer 2011) HDV RNA and HBsAg were analyzed as predictors of treatment response to PEG-IFN (with or without adefovir). Patients with ≥ 2 log HDV RNA decrease at treatment week 24 were at low risk for nonresponse at the end of therapy and negative HDV RNA at treatment week 24 or 48 proved to be an important prerequisite for treatment response 24 weeks after end of therapy. The best parameter for predicting nonresponse at the end of therapy was an HDV RNA decline < 1 log combined with no decline of HBsAg at treatment week 24 (positive predictive value of 83%) (Keskin 2015). Post-hoc analyses also exist for the HIDIT-II study (Wedemeyer 2019b). Here, low levels of hepatitis B core related antigen (HBcrAg) before treatment initiation and at week 24 of therapy were associated with treatment response 24 weeks after the end of therapy (Sandmann 2022). However, the data are not yet robust enough to define clear stopping rules for PEG-IFN-based therapies. It is important to be aware that that PEG-IFN-related side effects (flu-like symptoms, myelosuppression, psychiatric effects) limit PEG IFN-based treatment in some patient groups, and the therapy is contraindicated in advanced liver disease and decompensated liver cirrhosis. Nevertheless, synergistic effects of PEG-IFN with other drugs under development are conceivable because of its particular mechanism of action.

Nucleoside and nucleotide analogues

Nucleoside and nucleotide analogues (NA) used for the treatment of HBV infection have no direct antiviral effects against HDV as HDV uses host polymerases for replication. Several studies have shown the lack of efficacy of NA against HDV (Famciclovir (Yurdaydin 2002), lamivudine (Niro 2005), entecavir (Kabacam 2012) and adefovir (Wedemeyer 2011)). However, data from HIV/HBV/HDV-coinfected patients from Spain and Switzerland showed a decline of HDV RNA during treatment with tenofovir (TDF) (Beguelin 2017a, Soriano 2014). In the Spanish cohort, HDV RNA suppression to undetectable levels occurred in 10/19 patients after a median use of TDF of 58 months (Soriano 2014). It is interesting to note that HDV RNA declines were not associated with HBsAg declines In the SWISS HIV cohort, TDF-containing ART was associated with relevant HDV RNA declines in 29% of patients and 14% had undetectable HDV RNA after 5 years (Beguelin 2017a). One hypothesis is that TDF may induce interferon lambda (Murata 2020) which has been shown to exert also direct antiviral effects against HDV (Giersch 2017). However, TDF in combination PEG-IFN showed no additional effect compared with PEG-IFN alone in the treatment of HBV/HDV coinfected patients (Wedemeyer 2019b). Another hypothesis is the improvement of host immunity that has been compromised by HIV through the effective treatment of antiretroviral therapy, which includes TDF.

Additionally, retrospective studies investigated the clinical course of patients receiving NA treatment. In these studies, outcomes were worse with NA alone compared to PEG-IFN treatment. However, selection bias should be considered here since NA monotherapy was usually used in patients with contraindication against PEG-IFN, e.g. decompensated liver disease (Kamal 2020, Wranke 2017).

To what extend liver disease progression due to hepatitis B viremia can be reduced by suppression of HBV DNA in HDV coinfected patients is elusive. Still, it can be assumed that the therapeutic principles that have been established in HBV monoinfection can also be applied in coinfection with HDV (EASL 2023). Therefore, in daily practice, the same treatment indications apply to HBV viremia in chronic HDV infection as to HBV monoinfection (EASL 2017). Importantly, patients with liver cirrhosis and detectable HBV DNA should receive NA treatment with entecavir or tenofovir (EASL 2023, Sandmann 2023a).

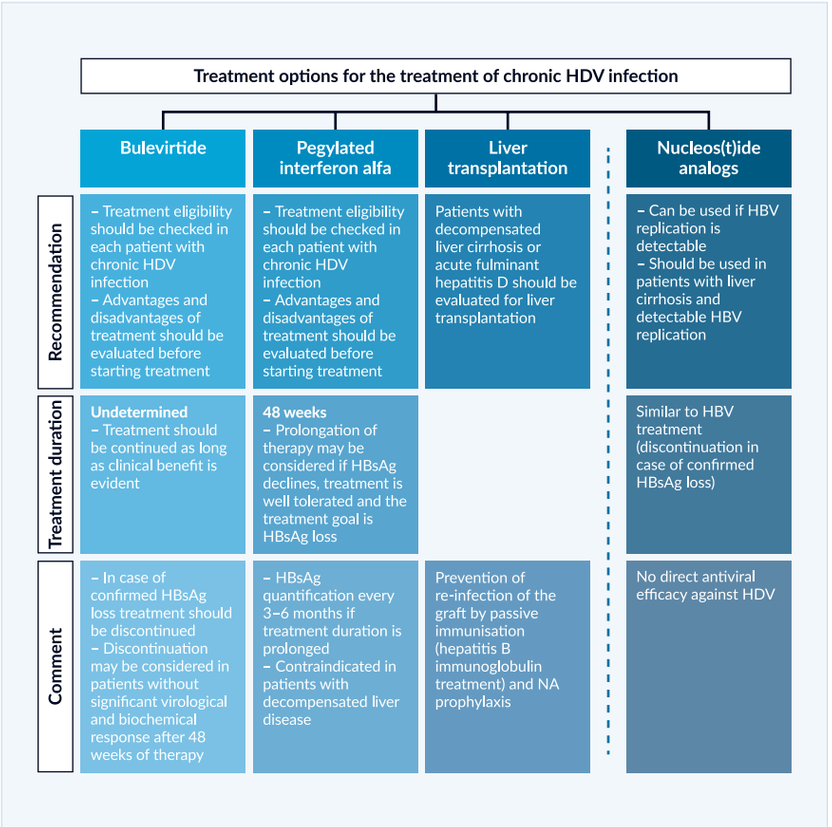

Figure 4. Treatment options for the treatment of chronic HDV infection (EASL 2017, 2023, Sandmann 2023a)

New drugs against HDV in clinical development

The prenylation of the large delta antigen is essential for virus particle formation. The prenylation inhibitor lonafarnib (LNF) showed a dose-dependent reduction of HDV RNA levels of up to 2 log IU/mL after 28 days of therapy (Yurdaydin 2018b). Importantly, HDV RNA declines were associated with LNF serum concentrations. While there was no evidence for viral resistance, higher doses of LFN caused nausea and diarrhea in most patients. Therefore, boostering with ritonavir was introduced in later clinical trials (Eiger 2023a). The phase 3 study is currently investigating the combination of LNF plus ritonavir (LFN/r) with or without PEG-IFN in chronic HDV patients receiving NA maintenance therapy. After 48 weeks of treatment, LNF/r and LFN/r plus PEG-IFN achieved the primary endpoint of virological and biochemical response in 12.6% and 24.2% of patients, respectively. Moreover, the combination arm showed statistically significant histological improvement (Etzion 2023a). Recently, follow-up 72-week data presented at the EASL 2023 meeting revealed that the combination still showed consistent endpoint response and that the treatment was well tolerated in both arms.

Nucleic acid polymers are being developed to treat patients with HDV (Bazinet 2017). Rep 2139-Ca is believed to block the release of subviral HBsAg particles from hepatocytes. The compound was injected once weekly and induced a marked decline of HBsAg in some but not all patients with HDV treated in a center in Moldova. Of note, all patients treated (n=12) showed an HDV RNA decline after 15 weeks of monotherapy when PEG-IFN was added. Responses were maintained in seven patients one year after completing treatment. A transient ALT increase was observed in patients with low HBsAg levels after REP 2139 monotherapy when PEG-IFN was introduced. In addition, several case reports from a Compassionate Use program have been presented at meetings confirming responses (HDV RNA decline and also HBsAg loss in some patients) observed in the trial from Moldavia (Stern 2023). Future studies will need to determine the efficacy and safety of REP 2139 in a larger group of patients with HDV infection.

Interferon lambda was also explored in patients with HDV infection, both as a monotherapy or in combination with LNF (Etzion 2023b, Sandmann 2021). *In vitro* and in humanized mice, an antiviral effect comparable to interferon alpha has been observed (Giersch 2017). The potential advantage of interferon lambda is the lower frequency of systemic side effects as compared to interferon alfa. However, the further development was recently stopped due to ALT flares in some patients that resulted in liver decompensation (Eiger 2023b).

Last but not least, monoclonal antibodies against HBsAg with neutralizing activity, as well as RNA interfering drugs (ASO, siRNA), have entered clinical evaluation. However, additional research is needed to validate their use in larger trials and real-world clinical settings (Sandmann 2021).

Liver transplantation for HDV

Liver transplantation remains the ultimate treatment option for many patients with chronic hepatitis D with end-stage liver disease. If prophylaxis by passive immunization with anti-HBs antibodies (hepatitis B immunoglobulins, HBIG) and administration of NA prophylaxis is applied, HBV/HDV reinfection can be prevented in all individuals (Rosenau 2007) leading to an excellent long-term outcome after transplantation. HDV RNA levels rapidly decline during the first days after transplantation (Mederacke 2012) but HDVAg may persist in the transplanted liver for several years

(Mederacke 2012, Smedile 1998). The possibility of reactivation of latent HDV infection by HBV superinfection has also been confirmed experimentally in a mouse model with transplanted human hepatocytes (Giersch 2014). Mice infected with HDV lacking HBV could be rescued by HBV superinfection after 2-6 weeks leading to a productive coinfection. Long-term prophylaxis to prevent HBV reinfection is therefore generally recommended in patients transplanted for HDV as reinfection may lead to HDV reactivation for which treatment options are very limited. Still, two recent reports challenge the current practice of dual prophylaxis as only 2 out of 34 and 1 out of 17 patients had HBV/HDV recurrence when administration of HBV immunoglobulins was stopped after transplantation (Cholongitas 2016, Ossami Saidy 2021). Furthermore, HDV recurrence was not observed after HBIG discontinuation in 64 cases that were separately reported from different groups (Caccamo 2017, Fernandez 2015, Lenci 2023, Manini 2018, Ocal 2015). However, due to the small risk of HBV/HBV recurrence and the present limited treatment options, HBIG discontinuation is not recommended by current guidelines (EASL 2023, Sandmann 2023a). Since evidence on HBIG discontinuation after one to two years after liver transplantation is accumulating, there is the need to address the safety of this approach as part of future clinical trials.

Summary and outlook

Chronic infection with the hepatitis D virus (HDV) is rare, but represents a severe form of chronic liver disease. Immunopathogenesis plays an essential role in the control or progression of the infection. As treatment options are available with bulevirtide and pegylated interferon alfa, early identification of infected patients is important. Therefore, all HBsAg-positive patients should be tested for HDV and risk groups, i.e. intravenous drug use, migration from countries with high HDV prevalence, should be tested repeatedly. Antiviral treatment should be evaluated in all individuals with chronic HDV infection, with priority given to patients with high inflammatory activity and advanced fibrosis and cirrhosis. For treatment decision, the advantages and disadvantages of current treatment options should be weighed against each other. Treatment with PEG-IFN is finite, may result in HBsAg loss in some patients, but is associated with side effects and cannot be used in the presence of advanced liver disease or autoimmune disease. Bulevirtide is well tolerated, leads to HDV RNA suppression and ALT normalization in a large proportion of patients, but the duration of treatment is not yet defined. Liver transplantation is a remaining option when antiviral treatment is no longer possible or in the setting of hepatic decompensation or hepatocellular carcinoma. Further promising therapy concepts are currently being developed with the aim of achieving HDV cure. These ongoing developments hold the promise of providing more effective and comprehensive care for individuals affected by HDV in the near future.

References

Abbas Z. 2012. Hepatitis d in pakistan. J Coll Physicians Surg Pak. 22(9):547-548.

Abeywickrama-Samarakoon N, Cortay JC, Sureau C, Muller S, Alfaiate D, Guerrieri F et al. 2020. Hepatitis delta virus histone mimicry drives the recruitment of chromatin remodelers for viral rna replication. Nat Commun. 11(1):419.

Alfaiate D, Clément S, Gomes D, Goossens N, Negro F. 2020. Chronic hepatitis d and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. Journal of Hepatology. 73(3):533-539.

Alfaiate D, Lucifora J, Abeywickrama-Samarakoon N, Michelet M, Testoni B, Cortay JC et al. 2016. Hdv rna replication is associated with hbv repression and interferon-stimulated genes induction in super-infected hepatocytes. Antiviral Res. 136:19-31.

Allweiss L, Volmari A, Suri V, Wallin JJ, Flaherty JF, Manuilov D et al. 2024. Blocking viral entry with bulevirtide reduces the number of hdv-infected hepatocytes in human liver biopsies. J Hepatol.

Andernach IE, Leiss LV, Tarnagda ZS, Tahita MC, Otegbayo JA, Forbi JC et al. 2014. Characterization of hepatitis delta virus in sub-saharan africa. J Clin Microbiol. 52(5):1629-1636.

Andrade LJ, D'Oliveira A, Jr., Silva CA, Nunes P, Franca LS, Malta AM et al. 2011. A meta-analysis of patients with chronic hepatitis c treated with interferon-alpha to determine the risk of autoimmune thyroiditis. Acta Gastroenterol Latinoam. 41(2):104-110.

Anolli MP, Degasperi E, Allweiss L, Sangiovanni A, Maggioni M, Scholtes C et al. 2023. A 3-year course of bulevirtide monotherapy may cure hdv infection in cirrhotics. J Hepatol.

Asselah T, Chulanov V, Lampertico P, Wedemeyer H, Streinu-Cercel A, Pantea V et al. 2024. Bulevirtide combined with pegylated interferon for chronic hepatitis d. N Engl J Med. 391(2):133-143.

Asselah T, Rizzetto M. 2023. Hepatitis d virus infection. N Engl J Med. 389(1):58-70.

Bazinet M, Pântea V, Cebotarescu V, Cojuhari L, Jimbei P, Albrecht J et al. 2017. Safety and efficacy of rep 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis b virus and hepatitis d virus co-infection (rep 301 and rep 301-ltf): A non-randomised, open-label, phase 2 trial. The Lancet Gastroenterology & Hepatology. 2(12):877-889.

Beguelin C, Friolet N, Moradpour D, Sahli R, Suter-Riniker F, Luthi A et al. 2017a. Impact of tenofovir on hepatitis delta virus replication in the swiss human immunodeficiency virus cohort study. Clin Infect Dis. 64(9):1275-1278.

Beguelin C, Moradpour D, Sahli R, Suter-Riniker F, Luthi A, Cavassini M et al. 2017b. Hepatitis delta-associated mortality in hiv/hbv-coinfected patients. J Hepatol. 66(2):297-303.

Benegiamo G, Vinciguerra M, Guarnieri V, Niro GA, Andriulli A, Pazienza V. 2013. Hepatitis delta virus induces specific DNA methylation processes in huh-7 liver cancer cells. FEBS Lett. 587(9):1424-1428.

Bogomolov P, Alexandrov A, Voronkova N, Macievich M, Kokina K, Petrachenkova M et al. 2016. Treatment of chronic hepatitis d with the entry inhibitor myrcludex b: First results of a phase ib/iia study. J Hepatol. 65(3):490-498.

Braga WS, de Oliveira CM, de Araujo JR, Castilho Mda C, Rocha JM, Gimaque JB et al. 2014. Chronic hdv/hbv co-infection: Predictors of disease stage---a case series of hdv-3 patients. J Hepatol. 61(6):1205-1211.

Bremer B, Anastasiou OE, Ciesek S, Wedemeyer H. 2019. Automated nucleic acid isolation methods for hdv viral load quantification can lead to viral load underestimation. Antivir Ther. 24(2):117-123.

Buti M, Homs M, Rodriguez-Frias F, Funalleras G, Jardi R, Sauleda S et al. 2011. Clinical outcome of acute and chronic hepatitis delta over time: A long-term follow-up study. J Viral Hepat. 18(6):434-442.

Buti M, Wedemeyer H, Aleman S, Chulanov V, Viacheslav M, Sagalova O et al. 2022. Treatment with bulevirtide improves patient-reported outcomes in patients with chronic hepatitis delta: An exploratory analysis of a phase 3 trial at 48 weeks. Journal of Hepatology. 77:S103.

Caccamo L. 2017. Long-term nucleos(t)ide analog(s) monoprophylaxis in delta coinfected liver transplant recipients. Transpl Infect Dis. 19(1).

Calle Serrano B, Grosshennig A, Homs M, Heidrich B, Erhardt A, Deterding K et al. 2014. Development and evaluation of a baseline-event-anticipation score for hepatitis delta. J Viral Hepat. 21(11):e154-163.

Calle Serrano B, Manns MP, Wedemeyer H. 2012. Hepatitis delta and hiv infection. Semin Liver Dis. 32(2):120-129.

Casey JL, Niro GA, Engle RE, Vega A, Gomez H, McCarthy M et al. 1996. Hepatitis b virus (hbv)/hepatitis d virus (hdv) coinfection in outbreaks of acute hepatitis in the peruvian amazon basin: The roles of hdv genotype iii and hbv genotype f. J Infect Dis. 174(5):920-926.

Castellares C, Barreiro P, Martin-Carbonero L, Labarga P, Vispo ME, Casado R et al. 2008. Liver cirrhosis in hiv-infected patients: Prevalence, aetiology and clinical outcome. J Viral Hepat. 15(3):165-172.

Cholongitas E, Goulis I, Antoniadis N, Fouzas I, Imvrios G, Giakoustidis D et al. 2016. Nucleos(t)ide analog(s) prophylaxis after hepatitis b immunoglobulin withdrawal against hepatitis b and d recurrence after liver transplantation. Transpl Infect Dis. 18(5):667-673.

Cornberg M, Lok AS, Terrault NA, Zoulim F, Faculty E-AHTEC. 2020. Guidance for design and endpoints of clinical trials in chronic hepatitis b - report from the 2019 easl-aasld hbv treatment endpoints conference(double dagger). J Hepatol. 72(3):539-557.

Da BL, Surana P, Takyar V, Kleiner DE, Heller T, Koh C. 2020. Vibration-controlled transient elastography for the detection of cirrhosis in chronic hepatitis d infection. J Viral Hepat. 27(4):428-436.

De Ledinghen V, Hermabessière P, Metivier S, Bardou Jacquet E, Hilleret M-N, Loustaud Ratti V et al. 2022. Bulevirtide, with or without peg- interferon, in hdv infected patients in a real-life setting. Two-year results from the french multicenter early access program. Hepatology. 76:S26-S28.

de Lédinghen V, Metivier S, Bardou-Jacquet E, Hilleret M-N, Loustaud-Ratti V, Ganne-Carrié N et al. 2022. Treatment with bulevirtide in patients with chronic hbv/hdv co-infection. Safety and efficacy at month 18 in real-world settings. Journal of Hepatology. 77:S840-S840.

Degasperi E, Anolli MP, Sara C, Renteria U, Sambarino D, Borghi M et al. 2022a. Bulevirtide monotherapy for 48 weeks in hdv patients with compensated cirrhosis and clinically significant portal hypertension. Journal of Hepatology. 77:S868-S868.

Degasperi E, Anolli MP, Uceda Renteria SC, Sambarino D, Borghi M, Perbellini R et al. 2022b. Bulevirtide monotherapy for 48 weeks in patients with hdv-related compensated cirrhosis and clinically significant portal hypertension. J Hepatol. 77(6):1525-1531.

Degertekin H, Yalcin K, Yakut M, Yurdaydin C. 2008. Seropositivity for delta hepatitis in patients with chronic hepatitis b and liver cirrhosis in turkey: A meta-analysis. Liver Int. 28(4):494-498.

Deny P. 2006. Hepatitis delta virus genetic variability: From genotypes i, ii, iii to eight major clades? Curr Top Microbiol Immunol. 307:151-171.

Dias J, Hengst J, Parrot T, Leeansyah E, Lunemann S, Malone DFG et al. 2019. Chronic hepatitis delta virus infection leads to functional impairment and severe loss of mait cells. J Hepatol. 71(2):301-312.

Dienes HP, Purcell RH, Popper H, Ponzetto A. 1990. The significance of infections with two types of viral hepatitis demonstrated by histologic features in chimpanzees. J Hepatol. 10(1):77-84.

Dietz-Fricke C, Tacke F, Zollner C, Demir M, Schmidt HH, Schramm C et al. 2023. Treating hepatitis d with bulevirtide - real-world experience from 114 patients. JHEP Rep. 5(4):100686.

EASL (European Association for the Study of the Liver). 2017. Easl 2017 clinical practice guidelines on the management of hepatitis b virus infection. J Hepatol. 67(2):370-398.

EASL (European Association for the Study of the Liver). 2023. Easl clinical practice guidelines on hepatitis delta virus. J Hepatol. 79(2):433-460.

Eiger 2023a. [accessed August 24, 2023]. https://clinicaltrials.gov/study/NCT03719313.

Eiger 2023b. [accessed accessed August 24, 2023]. https://ir.eigerbio.com/news-releases/news-release-details/eiger-discontinue-phase-3-limt-2-trial-peginterferon-lambda.

El Bouzidi K, Elamin W, Kranzer K, Irish DN, Ferns B, Kennedy P et al. 2015. Hepatitis delta virus testing, epidemiology and management: A multicentre cross-sectional study of patients in london. J Clin Virol. 66:33-37.

EMA (European Medicines Agency). Product information hepcludex. 2024a. [accessed 2024]. https://www.ema.europa.eu/en/documents/product-information/hepcludex-epar-product-information_de.pdf.

EMA (European Medicines Agency). Product information pegasys. 2024b. [accessed 2024]. https://www.ema.europa.eu/en/documents/product-information/pegasys-epar-product-information_de.pdf.

Erhardt A, Hoernke M, Heinzel-Pleines U, Sagir A, Gobel T, Haussinger D. 2010. Retrospective analysis of chronic hepatitis d in a west german university clinic over two decades: Migratory pattern, prevalence and clinical outcome. Z Gastroenterol. 48(8):813-817.

Etzion O, Hamid S, Asselah T, et al. 2023a. Gs-012 - week 48 results of the phase 3 d-livr study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of lonafarnib-boosted with ritonavir with or without peginterferon alfa in patients with chronic hepatitis delta. Journal of Hepatology. 78(S10).

Etzion O, Hamid S, Lurie Y, Gane EJ, Yardeni D, Duehren S et al. 2023b. Treatment of chronic hepatitis d with peginterferon lambda-the phase 2 limt-1 clinical trial. Hepatology. 77(6):2093-2103.

Farci P, Mandas A, Coiana A, Lai ME, Desmet V, Van Eyken P et al. 1994. Treatment of chronic hepatitis d with interferon alfa-2a. N Engl J Med. 330(2):88-94.

Farci P, Roskams T, Chessa L, Peddis G, Mazzoleni AP, Scioscia R et al. 2004. Long-term benefit of interferon alpha therapy of chronic hepatitis d: Regression of advanced hepatic fibrosis. Gastroenterology. 126(7):1740-1749.

Fernandez-Montero JV, Vispo E, Barreiro P, Sierra-Enguita R, de Mendoza C, Labarga P et al. 2014. Hepatitis delta is a major determinant of liver decompensation events and death in hiv-infected patients. Clin Infect Dis. 58(11):1549-1553.

Fernandez I, Loinaz C, Hernandez O, Abradelo M, Manrique A, Calvo J et al. 2015. Tenofovir/entecavir monotherapy after hepatitis b immunoglobulin withdrawal is safe and effective in the prevention of hepatitis b in liver transplant recipients. Transpl Infect Dis. 17(5):695-701.

Flodgren E, Bengtsson S, Knutsson M, Strebkova EA, Kidd AH, Alexeyev OA et al. 2000. Recent high incidence of fulminant hepatitis in samara, russia: Molecular analysis of prevailing hepatitis b and d virus strains. J Clin Microbiol. 38(9):3311-3316.

Fontaine H, Fougerou-Leurent C, Gordien E, Scholtes C, Metivier S, de Lédinghen V et al. 2022. Real life study of bulevirtide in chronic hepatitis delta: Preliminary results of the anrs hd ep01 buledelta prospective cohort. Journal of Hepatology. 77:S72-S72.

Gaeta GB, Stroffolini T, Chiaramonte M, Ascione T, Stornaiuolo G, Lobello S et al. 2000. Chronic hepatitis d: A vanishing disease? An italian multicenter study. Hepatology. 32(4 Pt 1):824-827.

Gheorghe L, Csiki IE, Iacob S, Gheorghe C, Trifan A, Grigorescu M et al. 2015. Hepatitis delta virus infection in romania: Prevalence and risk factors. J Gastrointestin Liver Dis. 24(4):413-421.

Giersch K, Allweiss L, Volz T, Helbig M, Bierwolf J, Lohse AW et al. 2015. Hepatitis delta co-infection in humanized mice leads to pronounced induction of innate immune responses in comparison to hbv mono-infection. J Hepatol. 63(2):346-353.

Giersch K, Helbig M, Volz T, Allweiss L, Mancke LV, Lohse AW et al. 2014. Persistent hepatitis d virus mono-infection in humanized mice is efficiently converted by hepatitis b virus to a productive co-infection. J Hepatol. 60(3):538-544.

Giersch K, Homs M, Volz T, Helbig M, Allweiss L, Lohse AW et al. 2017. Both interferon alpha and lambda can reduce all intrahepatic hdv infection markers in hbv/hdv infected humanized mice. Sci Rep. 7(1):3757.

Grabowski J, Wedemeyer H. 2010. Hepatitis delta: Immunopathogenesis and clinical challenges. Dig Dis. 28(1):133-138.

Grabowski J, Yurdaydin C, Zachou K, Buggisch P, Hofmann WP, Jaroszewicz J et al. 2011. Hepatitis d virus-specific cytokine responses in patients with chronic hepatitis delta before and during interferon alfa-treatment. Liver Int. 31(9):1395-1405.

Han M, Littlejohn M, Yuen L, Edwards R, Devi U, Bowden S et al. 2014. Molecular epidemiology of hepatitis delta virus in the western pacific region. J Clin Virol. 61(1):34-39.

He W, Cao Z, Mao F, Ren B, Li Y, Li D et al. 2016. Modification of three amino acids in sodium taurocholate cotransporting polypeptide renders mice susceptible to infection with hepatitis d virus in vivo. J Virol. 90(19):8866-8874.

He W, Ren B, Mao F, Jing Z, Li Y, Liu Y et al. 2015. Hepatitis d virus infection of mice expressing human sodium taurocholate co-transporting polypeptide. PLoS Pathog. 11(4):e1004840.

Heidrich B, Deterding K, Tillmann HL, Raupach R, Manns MP, Wedemeyer H. 2009. Virological and clinical characteristics of delta hepatitis in central europe. J Viral Hepat. 16(12):883-894.

Heidrich B, Serrano BC, Idilman R, Kabacam G, Bremer B, Raupach R et al. 2012. Hbeag-positive hepatitis delta: Virological patterns and clinical long-term outcome. Liver Int. 32(9):1415-1425.

Heidrich B, Yurdaydin C, Kabacam G, Ratsch BA, Zachou K, Bremer B et al. 2014. Late hdv rna relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology. 60(1):87-97.

Heller T, Rotman Y, Koh C, Clark S, Haynes-Williams V, Chang R et al. 2014. Long-term therapy of chronic delta hepatitis with peginterferon alfa. Aliment Pharmacol Ther. 40(1):93-104.

Hercun J, Kim GE, Da BL, Rotman Y, Kleiner DE, Chang R et al. 2021. Durable virological response and functional cure of chronic hepatitis d after long-term peginterferon therapy. Aliment Pharmacol Ther. 54(2):176-182.

Herta T, Hahn M, Maier M, Fischer J, Niemeyer J, Honemann M et al. 2022. Efficacy and safety of bulevirtide plus tenofovir disoproxil fumarate in real-world patients with chronic hepatitis b and d co-infection. Pathogens. 11(5).

Hoblos R, Kefalakes H. 2023. Immunology of hepatitis d virus infection: General concepts and present evidence. Liver Int. 43 Suppl 1:47-59.

Homs M, Rodriguez-Frias F, Gregori J, Ruiz A, Reimundo P, Casillas R et al. 2016. Evidence of an exponential decay pattern of the hepatitis delta virus evolution rate and fluctuations in quasispecies complexity in long-term studies of chronic delta infection. PLoS One. 11(6):e0158557.

*Huang YH, Tao MH, Hu CP, Syu WJ, Wu JC. 2004. Identification of novel hla-a*0201-restricted cd8+ t-cell epitopes on hepatitis delta virus. J Gen Virol. 85(Pt 10):3089-3098.*

Hughes SA, Wedemeyer H, Harrison PM. 2011. Hepatitis delta virus. Lancet. 378(9785):73-85.

Hung CC, Wu SM, Lin PH, Sheng WH, Yang ZY, Sun HY et al. 2014. Increasing incidence of recent hepatitis d virus infection in hiv-infected patients in an area hyperendemic for hepatitis b virus infection. Clin Infect Dis. 58(11):1625-1633.

Jachs M, Panzer M, Hartl L, Schwarz M, Balcar L, Camp JV et al. 2023. Long-term follow-up of patients discontinuing bulevirtide treatment upon long-term hdv-rna suppression. JHEP Rep. 5(8):100751.

Jachs M, Schwarz C, Panzer M, Binter T, Aberle SW, Hartl L et al. 2022. Response-guided long-term treatment of chronic hepatitis d patients with bulevirtide-results of a "real world" study. Aliment Pharmacol Ther. 56(1):144-154.

Kabacam G, Onder FO, Yakut M, Seven G, Karatayli SC, Karatayli E et al. 2012. Entecavir treatment of chronic hepatitis d. Clin Infect Dis. 55(5):645-650.

Kamal H, Fornes R, Simin J, Stal P, Duberg AS, Brusselaers N et al. 2021. Risk of hepatocellular carcinoma in hepatitis b and d virus co-infected patients: A systematic review and meta-analysis of longitudinal studies. J Viral Hepat. 28(10):1431-1442.

Kamal H, Westman G, Falconer K, Duberg AS, Weiland O, Haverinen S et al. 2020. Long-term study of hepatitis delta virus infection at secondary care centers: The impact of viremia on liver-related outcomes. Hepatology. 72(4):1177-1190.

Karatayli SC, Bozdayi M, Karatayli E, Ozturk T, Husseini AA, Albayrak R et al. 2015. Interleukin-28 gene polymorphisms may contribute to hbsag persistence and the development of hbeag-negative chronic hepatitis b. Liver Int. 35(3):846-853.

*Karimzadeh H, Kiraithe MM, Kosinska AD, Glaser M, Fiedler M, Oberhardt V et al. 2018. Amino acid substitutions within hla-b*27-restricted t cell epitopes prevent recognition by hepatitis delta virus-specific cd8(+) t cells. J Virol. 92(13).*

Karimzadeh H, Kiraithe MM, Oberhardt V, Salimi Alizei E, Bockmann J, Schulze Zur Wiesch J et al. 2019. Mutations in hepatitis d virus allow it to escape detection by cd8(+) t cells and evolve at the population level. Gastroenterology. 156(6):1820-1833.

Kay A, Melo da Silva E, Pedreira H, Negreiros S, Lobato C, Braga W et al. 2014. Hbv/hdv co-infection in the western brazilian amazonia: An intriguing mutation among hdv genotype 3 carriers. J Viral Hepat. 21(12):921-924.

Kefalakes H, Horgan XJ, Jung MK, Amanakis G, Kapuria D, Bolte FJ et al. 2021. Liver-resident bystander cd8(+) t cells contribute to liver disease pathogenesis in chronic hepatitis d virus infection. Gastroenterology. 161(5):1567-1583 e1569.

Kefalakes H, Koh C, Sidney J, Amanakis G, Sette A, Heller T et al. 2019. Hepatitis d virus-specific cd8(+) t cells have a memory-like phenotype associated with viral immune escape in patients with chronic hepatitis d virus infection. Gastroenterology. 156(6):1805-1819 e1809.

Keskin O, Wedemeyer H, Tuzun A, Zachou K, Deda X, Dalekos GN et al. 2015. Association between level of hepatitis d virus rna at week 24 of pegylated interferon therapy and outcome. Clin Gastroenterol Hepatol. 13(13):2342-2349 e2341-2342.

Khodjaeva M, Ibadullaeva N, Khikmatullaeva A, Joldasova E, Ismoilov U, Colombo M et al. 2019. The medical impact of hepatitis d virus infection in uzbekistan. Liver Int. 39(11):2077-2081.

Kucirka LM, Farzadegan H, Feld JJ, Mehta SH, Winters M, Glenn JS et al. 2010. Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. J Infect Dis. 202(6):845-852.

Kushner T, Serper M, Kaplan DE. 2015. Delta hepatitis within the veterans affairs medical system in the united states: Prevalence, risk factors, and outcomes. J Hepatol. 63(3):586-592.

Lampertico P, Roulot D, Wedemeyer H. 2022. Bulevirtide with or without pegifnalpha for patients with compensated chronic hepatitis delta: From clinical trials to real-world studies. J Hepatol. 77(5):1422-1430.

Le Gal F, Brichler S, Drugan T, Alloui C, Roulot D, Pawlotsky J-M et al. 2017. Genetic diversity and worldwide distribution of the deltavirus genus: A study of 2,152 clinical strains. Hepatology (Baltimore, Md). 66(6):1826-1841.

Le Gal F, Brichler S, Sahli R, Chevret S, Gordien E. 2016. First international external quality assessment for hepatitis delta virus rna quantification in plasma. Hepatology. 64(5):1483-1494.

Lee CY, Tsai HC, Lee SS, Wu KS, Sy CL, Chen JK et al. 2015. Higher rate of hepatitis events in patients with human immunodeficiency virus, hepatitis b, and hepatitis d genotype ii infection: A cohort study in a medical center in southern taiwan. J Microbiol Immunol Infect. 48(1):20-27.

Lenci I, Tariciotti L, Angelico R, Milana M, Signorello A, Manzia TM et al. 2023. Successful clinical and virological outcomes of liver transplantation for hdv/hbv-related disease after long-term discontinuation of hepatitis b immunoglobulins. Clin Transplant. 37(6):e14971.

Li W, Urban S. 2016. Entry of hepatitis b and hepatitis d virus into hepatocytes: Basic insights and clinical implications. J Hepatol. 64(1 Suppl):S32-S40.

Liao B, Zhang F, Lin S, He H, Liu Y, Zhang J et al. 2014. Epidemiological, clinical and histological characteristics of hbv/hdv co-infection: A retrospective cross-sectional study in guangdong, china. PLoS One. 9(12):e115888.

Lin HH, Lee SS, Yu ML, Chang TT, Su CW, Hu BS et al. 2015. Changing hepatitis d virus epidemiology in a hepatitis b virus endemic area

with a national vaccination program. Hepatology. 61(6):1870-1879.

Lunemann S, Malone DF, Grabowski J, Port K, Beziat V, Bremer B et al. 2015. Effects of hdv infection and pegylated interferon alpha treatment on the natural killer cell compartment in chronically infected individuals. Gut. 64(3):469-482.

Lunemann S, Malone DF, Hengst J, Port K, Grabowski J, Deterding K et al. 2014. Compromised function of natural killer cells in acute and chronic viral hepatitis. J Infect Dis. 209(9):1362-1373.

Lutgehetmann M, Mancke LV, Volz T, Helbig M, Allweiss L, Bornscheuer T et al. 2012. Humanized chimeric upa mouse model for the study of hepatitis b and d virus interactions and preclinical drug evaluation. Hepatology. 55(3):685-694.

Lutterkort GL, Wranke A, Yurdaydin C, Budde E, Westphal M, Lichtinghagen R et al. 2017. Non-invasive fibrosis score for hepatitis delta. Liver Int. 37(2):196-204.

Manesis EK, Vourli G, Dalekos G, Vasiliadis T, Manolaki N, Hounta A et al. 2013. Prevalence and clinical course of hepatitis delta infection in greece: A 13-year prospective study. J Hepatol. 59(5):949-956.

Manini MA, Whitehouse G, Bruce M, Passerini M, Lim TY, Carey I et al. 2018. Entecavir or tenofovir monotherapy prevents hbv recurrence in liver transplant recipients: A 5-year follow-up study after hepatitis b immunoglobulin withdrawal. Dig Liver Dis. 50(9):944-953.

Mederacke I, Filmann N, Yurdaydin C, Bremer B, Puls F, Zacher BJ et al. 2012. Rapid early hdv rna decline in the peripheral blood but prolonged intrahepatic hepatitis delta antigen persistence after liver transplantation. J Hepatol. 56(1):115-122.

Murata K, Tsukuda S, Suizu F, Kimura A, Sugiyama M, Watashi K et al. 2020. Immunomodulatory mechanism of acyclic nucleoside phosphates in treatment of hepatitis b virus infection. Hepatology. 71(5):1533-1545.

Nakano T, Shapiro CN, Hadler SC, Casey JL, Mizokami M, Orito E et al. 2001. Characterization of hepatitis d virus genotype iii among yucpa indians in venezuela. J Gen Virol. 82(Pt 9):2183-2189.

Niro GA, Casey JL, Gravinese E, Garrubba M, Conoscitore P, Sagnelli E et al. 1999. Intrafamilial transmission of hepatitis delta virus: Molecular evidence. J Hepatol. 30(4):564-569.

Niro GA, Ciancio A, Tillman HL, Lagget M, Olivero A, Perri F et al. 2005. Lamivudine therapy in chronic delta hepatitis: A multicentre randomized-controlled pilot study. Aliment Pharmacol Ther. 22(3):227-232.

Niro GA, Smedile A, Ippolito AM, Ciancio A, Fontana R, Olivero A et al. 2010. Outcome of chronic delta hepatitis in italy: A long-term cohort study. J Hepatol. 53(5):834-840.

Nisini R, Paroli M, Accapezzato D, Bonino F, Rosina F, Santantonio T et al. 1997. Human cd4+ t-cell response to hepatitis delta virus: Identification of multiple epitopes and characterization of t-helper cytokine profiles. J Virol. 71(3):2241-2251.

Ocal S, Korkmaz M, Harmanci O, Ensaroglu F, Akdur A, Selcuk H et al. 2015. Hepatitis b- and hepatitis d-virus-related liver transplant: Single-center data. Exp Clin Transplant. 13 Suppl 1:133-138.

Ossami Saidy RR, Sud I, Eurich F, Aydin M, Postel MP, Dobrindt EM et al. 2021. Discontinuation of passive immunization is safe after liver transplantation for combined hbv/hdv infection. Viruses. 13(5).

Palom A, Rando-Segura A, Vico J, Pacin B, Vargas E, Barreira-Diaz A et al. 2022. Implementation of anti-hdv reflex testing among hbsag-positive individuals increases testing for hepatitis d. JHEP Rep. 4(10):100547.

Perez-Vargas J, Amirache F, Boson B, Mialon C, Freitas N, Sureau C et al. 2019. Enveloped viruses distinct from hbv induce dissemination of hepatitis d virus in vivo. Nat Commun. 10(1):2098.

Polaris Observatory C. 2023. Global prevalence, cascade of care, and prophylaxis coverage of hepatitis b in 2022: A modelling study. Lancet Gastroenterol Hepatol. 8(10):879-907.

Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, Saitta C et al. 2006. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis b virus/hepatitis c virus-coinfected patients. Hepatology. 43(1):100-107.

Razavi HA, Buti M, Terrault NA, Zeuzem S, Yurdaydin C, Tanaka J et al. 2023. Hepatitis d double reflex testing of all hepatitis b carriers in low-hbv- and high-hbv/hdv-prevalence countries. J Hepatol. 79(2):576-580.

Rizzetto M. 1983. The delta agent. Hepatology. 3(5):729-737.

Rizzetto M. 2009. Hepatitis d: Thirty years after. J Hepatol. 50(5):1043-1050.

Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R et al. 2009. A 28-year study of the course of hepatitis delta infection: A risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology. 136(5):1629-1638.

Romeo R, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. 2014. High serum levels of hdv rna are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. PLoS One. 9(3):e92062.

Rosenau J, Kreutz T, Kujawa M, Bahr MJ, Rifai K, Hooman N et al. 2007. Hbsag level at time of liver transplantation determines hbsag decrease and anti-hbs increase and affects hbv DNA decrease during early immunoglobulin administration. J Hepatol. 46(4):635-644.

Sandmann L, Berg T, Deterding K, Fischer N, Hinrichsen H, Petersen J et al. 2023a. Antiviral therapy of chronic hepatitis d virus infection - addendum to the s3 guideline "prophylaxis, diagnosis and therapy of hepatitis b virus infection" of the german society for gastroenterology, digestive and metabolic diseases (dgvs). Z Gastroenterol. 61(12):e715-e732.

Sandmann L, Bremer B, Deterding K, Port K, Gey B, Fruchtel C et al. 2024a. Letter to the editor: The who hdv rna international standard does not reflect variability of real-world samples. Hepatology.

Sandmann L, Cornberg M. 2021. Experimental drugs for the treatment of hepatitis d. Journal of experimental pharmacology. 13:461-468.

Sandmann L, Degasperi E, Port K, Aleman S, Wallin JJ, Manuilov D et al. 2024b. Liver stiffness measurement as a noninvasive method for the diagnosis of liver cirrhosis in patients with chronic hepatitis d virus infection. Aliment Pharmacol Ther.

Sandmann L, Wedemeyer H. 2023b. Interferon-based treatment of chronic hepatitis d. Liver Int. 43 Suppl 1:69-79.

Sandmann L, Yurdaydin C, Deterding K, Heidrich B, Hardtke S, Lehmann P et al. 2022. Hbcrag levels are associated with virological response to treatment with interferon in patients with hepatitis delta. Hepatol Commun. 6(3):480-495.

Schaper M, Rodriguez-Frias F, Jardi R, Tabernero D, Homs M, Ruiz G et al. 2010. Quantitative longitudinal evaluations of hepatitis delta virus rna and hepatitis b virus DNA shows a dynamic, complex replicative profile in chronic hepatitis b and d. J Hepatol. 52(5):658-664.

Schirdewahn T, Grabowski J, Owusu Sekyere S, Bremer B, Wranke A, Lunemann S et al. 2017. The third signal cytokine interleukin 12 rather than immune checkpoint inhibitors contributes to the functional restoration of hepatitis d virus-specific t cells. J Infect Dis. 215(1):139-149.

Sheng WH, Hung CC, Kao JH, Chang SY, Chen MY, Hsieh SM et al. 2007. Impact of hepatitis d virus infection on the long-term outcomes of patients with hepatitis b virus and hiv coinfection in the era of highly active antiretroviral therapy: A matched cohort study. Clin Infect Dis. 44(7):988-995.

Smedile A, Casey JL, Cote PJ, Durazzo M, Lavezzo B, Purcell RH et al. 1998. Hepatitis d viremia following orthotopic liver transplantation involves a typical hdv virion with a hepatitis b surface antigen envelope. Hepatology. 27(6):1723-1729.

Soriano V, Grint D, d'Arminio Monforte A, Horban A, Leen C, Poveda E et al. 2011. Hepatitis delta in hiv-infected individuals in europe. AIDS. 25(16):1987-1992.

Soriano V, Vispo E, Sierra-Enguita R, Mendoza C, Fernandez-Montero JV, Labarga P et al. 2014. Efficacy of prolonged tenofovir therapy on hepatitis delta in hiv-infected patients. AIDS. 28(16):2389-2394.

Spaan M, Carey I, Bruce M, Shang D, Horner M, Dusheiko G et al. 2020. Hepatitis delta genotype 5 is associated with favourable disease outcome and better response to treatment compared to genotype 1. J Hepatol. 72(6):1097-1104.

Stern C, de Freitas C, Bazinet M, Mackiewicz V, Brichler S, Gordien E et al. 2023. Safety and efficacy of rep 2139-mg in association with tdf in chronic hepatitis delta patients with decompensated cirrhosis. Journal of Hepatology. 78(S1):1160.

Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C et al. 2020. The global prevalence of hepatitis d virus infection: Systematic review and meta-analysis. J Hepatol. 73(3):523-532.

Su CW, Huang YH, Huo TI, Shih HH, Sheen IJ, Chen SW et al. 2006. Genotypes and viremia of hepatitis b and d viruses are associated with outcomes of chronic hepatitis d patients. Gastroenterology. 130(6):1625-1635.

Sureau C, Negro F. 2016. The hepatitis delta virus: Replication and pathogenesis. J Hepatol. 64(1 Suppl):S102-S116.

Takyar V, Surana P, Kleiner DE, Wilkins K, Hoofnagle JH, Liang TJ et al. 2017. Noninvasive markers for staging fibrosis in chronic delta hepatitis. Aliment Pharmacol Ther. 45(1):127-138.

Taylor JM. 2012. Virology of hepatitis d virus. Semin Liver Dis. 32(3):195-200.

Terrault NA, Lok ASF, McMahon BJ, Chang K-M, Hwang JP, Jonas MM et al. 2018. Update on prevention, diagnosis, and treatment of chronic hepatitis b: Aasld 2018 hepatitis b guidance. Hepatology 67(4):1560-1599.

Tsatsralt-Od B, Takahashi M, Endo K, Buyankhuu O, Baatarkhuu O, Nishizawa T et al. 2006. Infection with hepatitis a, b, c, and delta viruses among patients with acute hepatitis in mongolia. J Med Virol. 78(5):542-550.

Tsatsralt-Od B, Takahashi M, Nishizawa T, Endo K, Inoue J, Okamoto H. 2005. High prevalence of dual or triple infection of hepatitis b, c, and delta viruses among patients with chronic liver disease in mongolia. J Med Virol. 77(4):491-499.

Wedemeyer H. 2010a. Re-emerging interest in hepatitis delta: New insights into the dynamic interplay between hbv and hdv. J Hepatol. 52(5):627-629.

Wedemeyer H. 2020. The burden of hepatitis d - defogging the epidemiological horizon. J Hepatol. 73(3):493-495.

Wedemeyer H, Aleman S, Brunetto M, Blank A, Andreone P, Bogomolov P et al. 2024. Bulevirtide monotherapy in patients with chronic hdv: Efficacy and safety results through week 96 from a phase iii randomized trial. J Hepatol. 81(4):621-629.

Wedemeyer H, Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P et al. 2023a. A phase 3, randomized trial of bulevirtide in chronic hepatitis d. N Engl J Med. 389(1):22-32.

Wedemeyer H, Leus M, Battersby TR, Glenn J, Gordien E, Kamili S et al. 2023b. Hdv rna assays: Performance characteristics, clinical utility, and challenges. Hepatology.

Wedemeyer H, Manns MP. 2010b. Epidemiology, pathogenesis and management of hepatitis d: Update and challenges ahead. Nature reviews Gastroenterology & hepatology. 7(1):31-40.

Wedemeyer H, Schoneweis K, Bogomolov P, Blank A, Voronkova N, Stepanova T et al. 2023c. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis b virus and hepatitis d virus coinfection (myr202): A multicentre, randomised, parallel-group, open-label, phase 2 trial. Lancet Infect Dis. 23(1):117-129.

Wedemeyer H, Schöneweis K, Bogomolov PO, Voronkova N, Chulanov V, Stepanova T et al. 2019a. Gs-13-final results of a multicenter, open-label phase 2 clinical trial (myr203) to assess safety and efficacy of myrcludex b in cwith peg-interferon alpha 2a in patients with chronic hbv/hdv co-infection. Journal of Hepatology. 70(1):e81.

Wedemeyer H, Yurdaydin C, Dalekos GN, Erhardt A, Cakaloglu Y, Degertekin H et al. 2011. Peginterferon plus adefovir versus either drug alone for hepatitis delta. N Engl J Med. 364(4):322-331.

Wedemeyer H, Yurdaydin C, Hardtke S, Caruntu FA, Curescu MG, Yalcin K et al. 2019b. Peginterferon alfa-2a plus tenofovir disoproxil fumarate for hepatitis d (hidit-ii): A randomised, placebo controlled, phase 2 trial. Lancet Infect Dis. 19(3):275-286.

Williams V, Brichler S, Radjef N, Lebon P, Goffard A, Hober D et al. 2009. Hepatitis delta virus proteins repress hepatitis b virus enhancers and activate the alpha/beta interferon-inducible mxa gene. J Gen Virol. 90(Pt 11):2759-2767.

Wranke A, Hardtke S, Heidrich B, Dalekos G, Yalcin K, Tabak F et al. 2020. Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta. J Viral Hepat. 27(12):1359-1368.

Wranke A, Heidrich B, Deterding K, Hupa-Breier KL, Kirschner J, Bremer B et al. 2023. Clinical long-term outcome of hepatitis d compared to hepatitis b monoinfection. Hepatol Int. 17(6):1359-1367.

Wranke A, Lobato C, Ceausu E, Dalekos GN, Rizzetto M, Turcanu A et al. 2024. Long-term outcome of hepatitis delta in different regions world-wide: Results of the hepatitis delta international network. Liver Int. 44(9):2442-2457.

Wranke A, Serrano BC, Heidrich B, Kirschner J, Bremer B, Lehmann P et al. 2017. Antiviral treatment and liver-related complications in hepatitis delta. Hepatology. 65(2):414-425.

Yurdaydin C, Bozkaya H, Gurel S, Tillmann HL, Aslan N, Okcu-Heper A et al. 2002. Famciclovir treatment of chronic delta hepatitis. J Hepatol. 37(2):266-271.

Yurdaydin C, Keskin O, Kalkan C, Karakaya F, Caliskan A, Kabacam G et al. 2018a. Interferon treatment duration in patients with chronic delta hepatitis and its effect on the natural course of the disease. J Infect Dis. 217(8):1184-1192.

Yurdaydin C, Keskin O, Kalkan C, Karakaya F, Caliskan A, Karatayli E et al. 2018b. Optimizing lonafarnib treatment for the management of chronic delta hepatitis: The lowr hdv-1 study. Hepatology. 67(4):1224-1236.

Zachou K, Yurdaydin C, Drebber U, Dalekos GN, Erhardt A, Cakaloglu Y et al. 2010. Quantitative hbsag and hdv-rna levels in chronic delta hepatitis. Liver Int. 30(3):430-437.

Zhang Z, Ni Y, Lempp FA, Walter L, Mutz P, Bartenschlager R et al. 2022. Hepatitis d virus-induced interferon response and administered interferons control cell division-mediated virus spread. J Hepatol. 77(4):957-966.

Zollner C, Hofmann J, Lutz K, Tacke F, Demir M. 2022. Real-life experiences with bulevirtide for the treatment of hepatitis delta-48 weeks data from a german centre. Liver Int. 42(11):2403-2407.

5. Hepatitis E

Sven Pischke, Katja Dinkelborg, Patrick Behrendt

Epidemiology

Hepatitis E is an inflammatory liver disease caused by infection with the hepatitis E virus (HEV): It has been described to be endemic in many tropical countries with reduced sanitary conditions in the 1980ies. For more than two decades, it was considered to be a travel-associated, acute, self-limiting liver disease that only causes fulminant hepatic failure in specific, high-risk groups (Pischke 2013b). More recently, HEV infection was estimated to cause approximately 56, 000 deaths each year worldwide (WHO 2014). Within the last two decades sporadic cases of HEV infections have emerged also in industrialised countries, mostly caused by HEV genotype 3, which are mostly caused by zoonotic transmission (Wedemeyer 2012, Pischke 2013).

Today we know that HEV infections occur worldwide but the genotypes are distributed differently (Figure 1). HEV is classified into the family of Hepeviridae and belongs to the subfamily of Orthohepevirinae which includes four species. Until recently, infections to humans have only been described from the species A with 8 genotypes. Recently, transmission of rat-HEV (Orthohepevirinae C) from rodents to humans have also been described (Rivero-Juarez 2022).

The vast majority of cases of hepatitis E worldwide is caused by HEV genotype 1 and 2 infections transmitted by the fecal-oral route. These are causative for outbreaks and are transmitted by contaminated drinking water. For examplean outbreak in south sudan with a case-fatality ratio of 5.5% occurred in the spring of 2023 (WHO 2023) In contrast, genotypes 3 and 4 are mostly transmitted zoonotically in industrialised countries (figure 1). Both direct contact with HEV-infected domestic animals and foodborne transmission are possible routes of transmission (Wedemeyer 2012). Commercial food products such as pig meat may be contaminated with HEV as shown in studies from the Netherlands, France and Germany (Colson 2010, Melenhorst 2007, Wenzel 2011). Meat should be cooked at above 70°C to prevent foodborne HEV infections (Emerson 2005). In the last few years, an increasing frequency of diagnosed cases of HEV infections has been reported from various industrialised countries (Wedemeyer 2012). The presence of HEV RNA in urban sewage samples from Spain, the US and France has been shown, suggesting that HEV may be more prevalent in industrialised countries than previously assumed (Clemente-Casares

2003). In each of these three countries it was possible to discover HEV contamination in sewage samples in a notably high frequency. These findings may partially explain the huge gap between seroprevalence rates and the rather low numbers of diagnosed and reported cases of acute hepatitis E in western countries. The mismatch between high seroprevalence rates and the low number of symptomatic cases has also been investigated in a recent study from Egypt. 919 anti-HEV seronegative individuals from rural Egypt were followed and, interestingly, 3.7% (n=34) of these individuals seroconverted to anti-HEV within 11 months of follow up (Stoszek 2006). However, none of these 34 individuals suffered from symptomatic hepatitis E. This finding corresponds with data from a recently published large vaccine study performed in China where very few of the patients in the placebo group who seroconverted during a follow-up period developed symptomatic acute hepatitis E (Zhu 2010). Overall, these data suggest that far less than 5% of all contacts with HEV lead to symptomatic hepatitis E (Wedemeyer 2011).

Genotypes 5-8 occur in animals (wild boars, camels), but play only a minor role in humans, with only a few published cases. For example an HEV genotype 7 infection transmitted by camel meat leading to chronic hepatitis E in a liver transplant recipient has been demonstrated (Lee 2015). Although this is surely of limited relevance in European countries and the USA, it highlights a novel mode of transmission in Arabian countries. In these Islamic countries, HEV genotype 3 and 4 infections originating from pigs certainly play a minor role.

Furthermore the variant "rat-HEV" (HEV-C) has attracted increased attention in recent years, as cases of human infections caused by this variant have been diagnosed in Hong Kong, Spain and France (Rivero-Juarez 2022). This HEV variant differs genetically from the other versions to such an extent, that the conventional commercial HEV PCR tests do not detect it and specially designed primers are needed. This especially poses a threat to being underdiagnosed in the clinic and in the case of severe hepatitis of an unknown cause, HEV-C infection should be considered.

Reference sequences have been published to facilitate communication between researchers and enable improved classification of HEV strains (Smith 2016).

Figure 1. Worldwide distribution of the four main HEV genotypes

Patient-to-patient transmission of HEV is very rare but has been described from a large outbreak in Northern Uganda (Teshale 2011) and from hematology wards in Europe (Mansuy 2009). Bloodborne transmission of HEV was suggested in the late nineties (Fainboim 1999). Subsequent studies from Hong Kong, Japan, Great Britain and France confirmed blood transfusions as a possible source of HEV transmission (Wedemeyer 2012). A large study from Germany investigating 1019 blood donors determined that 0.35% seroconverted within 1 year (Juhl 2013). A study from the Netherlands revealed that 13 out of 40, 176 blood donors were HEV-viremic (Slot 2013). These data correspond to one HEV positive blood donation per day in the Netherlands. A large study from England investigating 225, 000 blood products confirmed blood transfusions as a possible source for HEV transmission, in that 0.035% of blood products were viremic for HEV (Hewitt 2014). Post-transfusion infections were associated with viral load in the blood product and absence of HEV antibodies. A study from the Netherlands estimated a duration of 68 day of viraemia within apparently healthy blood donors with subclinical HEV infections (Hogema 2015). These observations led to many countries now routinely testing blood donations for HEV RNA to exclude bloodborne transmission of this virus. HEV transmission by solid organ transplantation is possible but rare (Schlosser 2011).

In summary, there are many different sources of infection for HEV transmission (Figure 2).

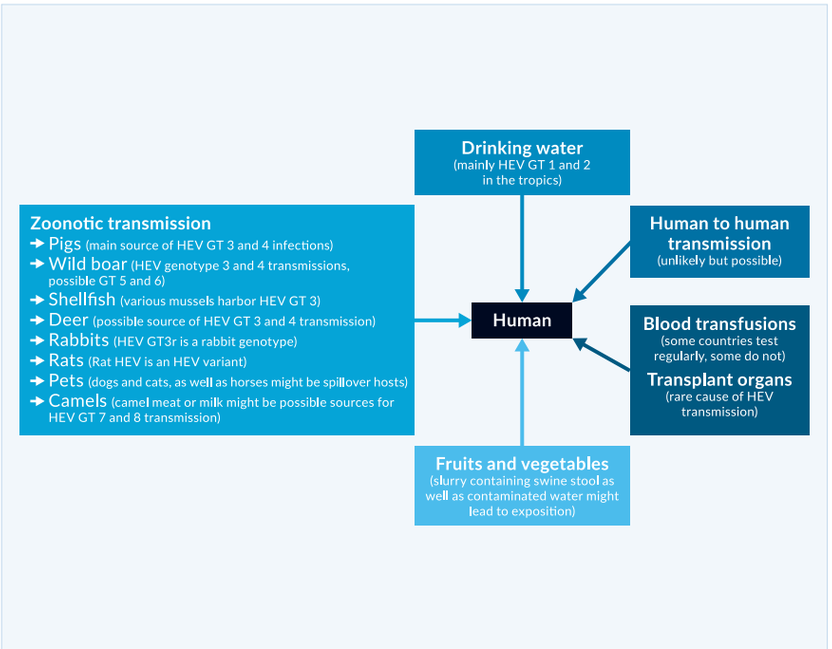

Figure 2. Possible sources of HEV infection

Diagnostic

In immunocompetent patients the diagnosis of hepatitis E usually relies on the detection of HEV-specific antibodies. While IgG antibodies indicate acute and past HEV infections, IgM antibodies can only be found in patients with recent infections (Wedemeyer 2012). There are different commercial assays available for detection of HEV-specific antibodies. Comparison of six of these assays reveals a wide variation of diagnostic sensitivities and specificities as well as interassay disagreements (Drobeniuc 2010). Thus, some of the remarkable discrepancies in HEV seroprevalence rates reported in different studies may be explained by varying sensitivities of the respective assays.

HEV-specific IgG antibodies can be detected in patients with previous contact with HEV. They do not differentiate between ongoing HEV infection and past contact with the virus. To prove current infection the detection of HEV RNA by PCR has been established. Numerous assays using different primers have been developed (Meng 1999, Zhao 2007). Furthermore, few quantitative PCR assays have been described (Ahn 2006, Enouf 2006). Recently a novel WHO-approved RNA standard assay has been developed (Baylis 2011).

In immunocompromised individuals, diagnosis of HEV infection may only be based on the detection of HEV RNA as seroassays lack sensitivity especially in the early phase of infection (Pischke 2010b). HEV RNA can not only be detected in serum samples but also in stool (Wedemeyer 2012), and thus infectivity of HEV infected persons can be determined by investigating stool for HEV RNA. Furthermore HEV could be detected in urine (Geng 2015), but the clinical relevance of this observation still needs to be determined. An HEV antigen assay for detection of HEV has been described (Gupta 2013) but the clinical value of this test still needs to be verified.

Acute hepatitis E in immunocompetent individuals

In the vast majority of cases, contact with HEV takes an asymptomatic course (Stoszek 2006, Wedemeyer 2012, Wedemeyer 2013), especially if the contact happens during childhood (Buti 2008). Immunocompetent individuals should be able to clear the virus spontaneously. In symptomatic cases the incubation period of HEV infections ranges from three to eight weeks with a mean of 40 days (Wedemeyer 2012). The peak of HEV viraemia can be detected in the early phase of infection while the peak of ALT elevation usually occurs around 6 weeks after infection (Wedemeyer 2012).

Initial symptoms in acute hepatitis E are typically unspecific and can include flu-like myalgia, arthralgia, weakness and vomiting. In some patients jaundice, itching, uncoloured stool and darkened urine occur accompanied by elevation of liver transaminases, bilirubin, alkaline phosphatase and gamma-glutamyltransferase.

HEV infection can lead to more severe acute liver disease in pregnant women or patients with underlying chronic liver diseases progressing to fulminant hepatic failure in individual cases (Wedemeyer 2012). Possible explanations for the more severe course in pregnant women are hormonal and immunological changes during pregnancy, they are also associated with the genotype 1 (Navaneethan 2008). Recently, an association between reduced expression of the progesterone receptor and fatal outcome of hepatitis E in pregnant women has been reported (Bose 2011).

Single cases of prolonged courses of HEV infection in immunocompetent individuals with up to two years of viraemia have been described from France (Mallet 2010), Spain (Gonzalez Tallon 2011) and China (Liu 2011). However, no case of HEV-associated liver cirrhosis or development of hepatocellular carcinoma has been reported in immunocompetent individuals. Prolonged HEV viraemia may indicate a previously undiagnosed disturbance of the immune system in otherwise healthy individuals (Höner zu Siederdissen 2014).

Acute and chronic HEV infections in organ transplant recipients

Chronic courses of HEV infection have been described in European liver or kidney transplant recipients since 2008 (Gerolami 2008, Haagsma 2009, Kamar 2008, Pischke 2010b, Behrendt 2014). 14 cases of hepatitis E were initially reported in kidney- and liver-transplanted patients from southwest France (Kamar 2008). Eight of them developed a chronic course leading to persistently elevated ALT levels and significant inflammatory activity and fibrosis in liver biopsies after a follow-up of more than 12 months (range 10 to 18). Subsequently, additional cases of chronic HEV infections have been reported in transplant patients by several groups (Wedemeyer 2012), clearly demonstrating that chronic hepatitis E can be associated with progressive liver disease in patients after organ transplantation (Kamar 2011c).

A study from Germany examined 226 liver-transplanted patients and 129 patients with chronic liver disease to evaluate the frequency of chronic HEV infections in liver transplant recipients in a low endemic country (Pischke 2010b). All patients were tested for HEV RNA and anti-HEV IgG. Two cases of chronic HEV infections in liver transplanted patients were identified. One of them developed significant liver fibrosis (ISHAK F3) within less than 2 years. Both patients were infected with HEV genotype 3. The possibility of reverse zoonotic transmission was experimentally confirmed by infecting pigs with a patient's blood. HEV RNA was detectable in various organs of the pigs including muscle. Thus, these findings further support the recommendations that eating uncooked meat should be avoided by organ transplant recipients as this may represent a source for acquiring HEV infection.

Retrospective data on hepatitis E in transplant recipients were summarised from 17 centres. Overall, 85 cases of HEV infection were described, 56 (66%) of whom developed chronic hepatitis E. Of note, chronicity was associated with the use of tacrolimus and with low platelet count (Kamar 2011c). However it has to be considered that the vast majority of patients had been recruited by one centre and experiences from other regions and transplant centres need to be reported.

Chronic courses of HEV infection have also been reported in heart transplant recipients (de Man 2011, Pischke 2012b). A study from Germany investigating heart transplant recipients and non-transplant cardiac patients revealed that the seroprevalence of HEV-specific antibodies is increased 5-fold in these patient groups in comparison to healthy controls (Pischke 2012b). It has been assumed that medical procedures, especially blood products, could explain this difference in seroprevalence rates.

Chronic HEV infections have also been described in lung transplant recipients from the Netherlands (Rizebos-Brilman 2013) and Germany (Pischke 2014).

Overall, all recipients of solid organ transplant with elevated liver enzymes should be tested for HEV RNA unless other obvious reasons already explain the hepatitis. In immunosuppressed patients, testing for HEV RNA should be applied as antibody testing may lack sensitivity. Distinct immunosuppressive drugs may indirectly or directly effect HEV replication, which needs to be considered in the management of organ transplant recipients (Behrendt 2014).

In contrast to solid organ transplant recipients, studies from Germany (Koenecke 2012) and France (Abravanel 2012) did not observe any case of chronicity in stem cell transplant recipients, leading to the assumption that this phenomenon is rare in this patient population. However, a large study from the Netherlands, investigating 328 stem cell transplant recipients, identified 8 cases (2.4%) of chronic HEV viraemia. Four of these patients died after development of hepatitis, while the other four patients cleared HEV infection after a median period of 6.3 months. These data demonstrate that chronic HEV infections in stem cell transplant recipients are indeed relevant (Versluis 2013).

Hepatitis E in patients with HIV infection or other immunological deficiencies

Chronic hepatitis E was described for the first time in a patient with underlying HIV infection in 2009 (Dalton 2009). This patient had a CD4 T cell count of less than 200 cells and high HIV RNA levels (>100, 000 copies/mL). However, subsequent studies from Spain (n=93) (Madejon 2009), Germany (n=123) (Pischke 2010a) and England (n=138) (Keane 2012) could not identify cases of chronic hepatitis E in HIV-infected individuals. HEV RNA was detected for more than 10 months in only one out of 184 HIV positive individuals in France (Kaba 2010). This patient had particularly low CD4 counts (<50 cells/mm) while two additional patients with higher CD4 levels were able to clear HEV spontaneously. Thus, persistent HEV infection is rarely observed in HIV-infected patients. Recently, it has been demonstrated that HEV may persist in HIV infected patients despite improvement of their immune system (Kuniholm 2015).

In addition to HIV infected patients, chronic HEV infections in patients with different underlying conditions of immunosuppression including lupus erythematodes, granulomatosis, retroperitoneal fibrosis or CD4 deficiency have been reported (Grewal 2013, Höner zu Siederdissen 2014). In contrast to these diseases, there was no case of chronic HEV infection within a German cohort of 73 patients with common variable immunodeficiency

(CVID). It has been hypothesised, that eventually regular immunoglobulin infusions in these patients may have protected them from infection (Pischke 2012a).

Extrahepatic manifestations of hepatitis E

There is some evidence that HEV infections are associated with extrahepatic manifestations, particularly neurological, immunological and renal diesases. Neurological symptoms associated with acute or chronic HEV infection have been described in single cases in the past few few years (Kamar 2011b). More recently, HEV infections were linked with neuralgic amyotrophy (van Eijk 2014), Guillain-Barré syndrome (Van den Berg 2014) and common inflammatory demyelinisating polyneuropathy (Pischke 2024). The underlying mechanisms and the clinical relevance of these associations require further investigation.

It still needs to be determined if extrahepatic manifestations are caused by direct effects of the virus or by indirect, immunological mechanisms. A possible link between HEV and cryoglobulinemia has recently been suggested (Pischke 2014, Kamar 2012).

Recently a pathophysiological link between HEV infections and glomerulonephritis has been suggested by demonstrating an association between production of HEV ORF2 protein and the development of glomerulonephritis in a kidney transplant recipient (Leblond 2024).

Therapy and prevention

Treatment options for chronic hepatitis E include reduction of immunosuppression, administration of pegylated interferon α or use of ribavirin. The first step in the treatment of chronic HEV infection should be to evaluate if it is possible to reduce the immunosuppressive medication (Wedemeyer 2012). Reduction of immunosupression in 16 solid organ transplant recipients with chronic hepatitis E led to clearance of HEV in 4 cases (25%) (Kamar 2011a). A second possible treatment option is the use of PEG-IFN α (Haagsma 2010, Kamar 2010a). Treatment durations varied between 3 and 12 months. Overall, 4 out 5 patients were successfully treated with sustained clearance of HEV RNA. However, the use of interferon can be associated with significant side effects and may cause rejection in organ transplant recipients. Interferon α is therefore not recommended in heart or kidney transplant recipients. Another therapeutic option for HEV infections is the off-label use of Ribavirin. The antiviral efficacy of ribavirin monotherapy has been evaluated by two French groups (Kamar 2010b, Mallet 2010). A sustained virological response was observed in 2/2 and 4/6 treated patients, respectively. Ribavirin has also been used in a non-transplanted patient with severe acute hepatitis E who showed rapid improvement of symptoms and liver function tests during treatment (Gerolami 2011).

A study from France demonstrated the safe use of ribavirin in non transplant individuals with acute HEV genotype 3 infections (Peron 2015). Furthermore the use of ribavirin has been demonstrated in one single case with severe HEV genotype 1 infection (Pischke 2013a). Starting and stopping rules for the treatment of HEV with ribavirin still need to be defined. In contrast to immunocompetent individuals, in solid organ transplant recipients with chronic HEV infection ribavirin remains a frequently used therapeutic option. A multicentric French study confirmed that treatment of chronic HEV infections in transplant recipients with ribavirin is safe and efficient (Kamar 2014). However, ribavirin treatment failures have been described in single patients (Pischke 2012b, Pischke 2013a) that may be linked to selection of a distinct HEV polymerase variant with increased replication fitness (Debing 2014).

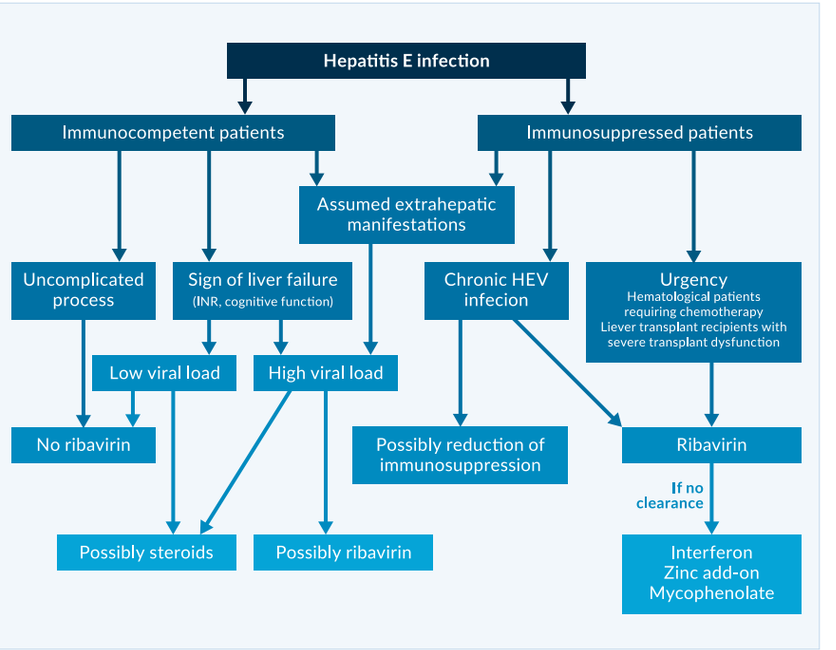

Figure 3. Treatment algorythm

Sofosbuvir, as a novel antiviral approach, failed to achieve HEV RNA elimination in a pilot study of 9 patients (Cornberg 2020). Recently, distinct resistance mutations in the RNA dependent RNA polymerase were identified in this patient cohort (Gömer 2023). The therapeutic effect

of a combinational therapy of Sofosbuvir and Ribavirin has yet to be investigated in bigger cohorts.

In addition to the treatment of acute or chronic HEV infection, the possibility of preventing a relevant infection in the event of HEV exposure through vaccination is also of great importance.

A vaccine developed by GSK and the Walter Reed Army Institute that was successfully tested in a phase 2 study (Shrestha 2007) has not been further developed. A group from China reported data from a very large successful phase 3 vaccine trial (Zhu 2010). This trial included almost 110, 000 individuals who received either a recombinant HEV vaccine ("Hecolin") or placebo. The vaccine efficacy after three doses was 100%. This vaccine was approved in China in early 2012 and in Pakistan in 2020. It is currently not known if and when this vaccine will become available elsewhere. Moreover, the efficacy of this vaccine needs to be evaluated in special risks groups such as patients with end-stage liver disease or immunosuppressed individuals. It is also unknown if HEV 239 also protects from HEV genotype 3 infection (Wedemeyer 2011). However, it was demonstrated that either the vaccine or naturally acquired, post-infectious antibodies are able to prevent symptomatic hepatitis E, but not asymptomatic infection (Zhang 2013). Furthermore, it was shown that this vaccine could be safely used in pregnant women (Wu 2012). In contrast to this study, a recent double-blind placebo-controlled trial from Bangladesh showed containing 5011 pregnant women vaccinated prior to pregnancy showed a significantly increased risk of the group of women receiving HEV vaccine for miscarriage (Binte-Aziz 2024).

Furthermore a follow-up study of the initial Hecolin vaccine trial demonstrated a 10-year efficacy above 80% (Huang 2024).

The use of this vaccine in developing countries needs to be discussed and investigated. Eventually this vaccine may help to prevent the morbidity and mortality caused by hepatitis E.

Conclusions and recommendations

In general, HEV infection has a self-limiting course associated with the clinical picture of acute hepatitis in immunocompetent populations. Special populations like pregnant women may be more likely to develop hepatic failure. In patients with immunosuppression of different aetiologies, chronic cases have been reported.

In organ transplant recipients, the diagnosis of HEV infection should not be based on serological assays alone as these assays may lack sensitivity. Detection of HEV RNA by PCR in serum or stool represents the gold standard for diagnosis of HEV infection.

The prevalence of chronic HEV infection in solid organ transplant recipients depends on the general prevalence in the population and is low in most industrialised countries. However, chronic hepatitis E occurs and needs to be considered in the differential diagnosis of graft hepatitis, as persistent HEV infection can be associated with progressive graft hepatitis and the development of liver cirrhosis. Currently, all reported cases of chronic HEV infections in transplant recipients have been due to HEV genotype 3 or 4. It is not known if chronic hepatitis E can also be caused by the genotypes 1 or 2.

Organ transplant recipients and other immunocompromised individuals should be made aware of this risk and avoid eating uncooked meats.

First results indicate that ribavirin treatment of chronic hepatitis E (3 to 5 months duration) is effective to achieve sustained virological response in immunocompromised persons. In contrast, in immunocompetent individuals with acute HEV infection this treatment is only required in few cases to avoid liver failure.

Due to the side effects of the current available antiviral therapies as well as the many cases of relapse after therapy, novel treatment options for chronic HEV infections need to be investigated. Additionally, an optimisation of the evaluation of therapeutic response might be possible by investigating HEV antigen in urine.

A widely available and efficacious vaccine would prove important to lower the overall burden HEV infections cause on the health system.

The relevance of extrahepatic manifestations associated with acute or chronic HEV infection needs further exploration, especially the association between positive anti-HEV serostatus and autoimmune hepatitis, cryoglobulinaemia or neurological symptoms.

Key Messages

- HEV is the most prevalent causative agent of acute viral hepatitis worldwide
- Most infections are asymptomatic and self-resolving, pregnant women and people with underlying liver disease are at risk of fulminant hepatitis
- Immunosuppressed individuals, especially organ transplant recipients, are at risk of chronic infection, leading to liver fibrosis and cirrhosis
- In organ transplant recipients with unclear elevation of liver enzymes, HEV infection should be ruled out by PCR testing

References

Abravanel F, Mansuy JM, Huynh A, Kamar N, Alric L, Peron JM, et al. Low risk of hepatitis E virus reactivation after haematopoietic stem cell transplantation. J Clin Virol. 2012;152-5.

Ahn JM, Rayamajhi N, Gyun Kang S, Sang Yoo H. Comparison of real-time reverse transcriptase-polymerase chain reaction and nested or commercial reverse transcriptase-polymerase chain reaction for the detection of hepatitis E virus particle in human serum. Diagn Microbiol Infect Dis 2006;56:269-74.

Baylis S, Hanschmann KM, Blümel J, Nübling CM; HEV Collaborative Study Group. Standardisation of hepatitis E virus (HEV) nucleic acid amplification technique-based assays: an initial study to evaluate a panel of HEV strains and investigate laboratory performance. J Clin Microbiol. 2011;1234-9.

Behrendt P, Steinmann E, Manns MP, Wedemeyer H. The impact of hepatitis E in the liver transplant setting. J. Hepatol. 2014;61:1418-1429.

Binte Aziz A,, Dudman S, Halle Julin CH, et al. Receipt of hepatitis E vaccine and fetal loss in rural Bangladesh: further analysis of a double-blind, cluster-randomised, controlled trial. Lancet Global Health 2024 Aug;12(8):e1300-e1311

Bose PD, Das BC, Kumar A, Gondal R, Kumar D, Kar P. High viral load and deregulation of the progesterone receptor signaling pathway: Association with Hepatitis E-related poor pregnancy outcome. J Hepatol 2011;54:1107-13.

Buti M, Plans P, Dominguez A, et al. Prevalence of hepatitis E virus infection in children in the northeast of Spain. Clin Vaccine Immunol 2008;15:732-4.

Caron M, Enouf V, Than SC, Dellamonica L, Buisson Y, Nicand E. Identification of genotype 1 hepatitis E virus in samples from swine in Cambodia. J Clin Microbiol. 2006;3440-2.

CDC, Investigation of hepatitis E outbreak among refugees - Upper Nile, South Sudan, 2012-2013. MMWR Morb Mortal Wkly Rep. 2013;26:581-6.

Clemente-Casares P, Pina S, Buti M, et al. Hepatitis E virus epidemiology in industrialised countries. Emerg Infect Dis 2003;9:448-54.

Colson P, Borentain P, Queyriaux B, et al. Pig liver sausage as a source of hepatitis E virus transmission to humans. J Infect Dis 2010;202:825-34.

Cornberg M, Pischke S, Müller T, et al. Sofosbuvir monotherapy fails to achieve HEV RNA elimination in patients with chronic hepatitis E - The HepNet SofE pilot study. J Hepatol. 2020 Sep;73(3):696-699.

Dalton HR, Bendall RP, Keane FE, Tedder RS, Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. N Engl J Med 2009;361:1025-7.

Debing Y, Gisa A, Dallmeier K, et al. Ribavirin treatment failure in chronic hepatitis E is associated with an enhanced fitness polymerase variant. Gastroenterology 2014;147:1008-1011.

de Man RA, Pas SD, Osterhaus AD, Balk AH, Van der Eijk A. Diagnosis and clinical consequences of hepatitis E virus infection in orthotopic heart transplant recipients. Hepatology 2011; AASLD annual meeting.

Drobeniuc J, Meng J, Reuter G, et al. Serologic assays specific to immunoglobulin M antibodies against hepatitis E virus: pangenotypic evaluation of performances. Clin Infect Dis 2010;51:e24-7.

Emerson SU, Arankalle VA, Purcell RH. Thermal stability of hepatitis E virus. J Infect Dis 2005;192:930-3.

Enouf V, Dos Reis G, Guthmann JP, et al. Validation of single real-time TaqMan PCR assay for the detection and quantitation of four major genotypes of hepatitis E virus in clinical specimens. J Med Virol 2006;78:1076-82.

Fainboim H, Gonzalez J, Fassio E, et al. Prevalence of hepatitis viruses in an anti-human immunodeficiency virus positive population from Argentina. A multicentre study. J Viral Hepat 1999;6:53-7.

Geng Y, Wang C, Zhao C, et al. Serological Prevalence of Hepatitis E Virus in Domestic Animals and Diversity of Genotype 4 Hepatitis E Virus in China. Vector Borne Zoonotic Dis 2009.

Geng Y, Zhao C, Huang W, et al. Detection and assessment of infectivity of hepatitis E virus in urine. J Hepatol 2016; 64(1):37-43

Gerolami R, Borentain P, Raissouni F, Motte A, Solas C, Colson P. Treatment of severe acute hepatitis E by ribavirin. J Clin Virol 2011;52:60-2.

Gerolami R, Moal V, Colson P. Chronic hepatitis E with cirrhosis in a kidney-transplant recipient. N Engl J Med 2008;358:859-60.

Gonzalez Tallon AI, Moreira Vicente V, Mateos Lindemann ML, Achecar Justo LM. [Chronic hepatitis E in an immunocompetent patient.]. Gastroenterol Hepatol 2011.

Gömer A, Klöhn M, Jagst M, Nocke M, Pischke S, Horvatits T, Schulze Zur Wiesch J, Müller T, Hardtke S, Cornberg M, Wedemeyer H, Behrendt P, Steinmann E, Todt D. Emergence of resistance-associated variants during sofosbuvir treatment in chronically infected hepatitis E patients. Hepatology. 2023 Jun 20.

Grewal P, Kamili S, Motamed D. Chronic hepatitis E in an immunocompetent patient: A case report. Hepatology 2014;59:347-8.

Gupta E, Pandey P, Sharma MK, et al. Role of Hepatitis E virus antigen in confirming active viral replication in patients with acute viral hepatitis Einfection. J. Clin. Virology 2013;58; 374-377.

Haagsma E, Riezebos-Brilman A, Van den Berg AP, Porte RJ, Niesters HG. Treatment of chronic hepatitis E in liver transplant recipients with pegylated interferon alpha-2b. Liver Transpl 2010. [epub ahead of print]

Haagsma EB, Niesters HG, van den Berg AP, et al. Prevalence of hepatitis E virus infection in liver transplant recipients. Liver Transpl 2009;15:1225-8.

Hakze-van der Honing RW, van Coillie E, Antonis AF, van der Poel WH. First Isolation of Hepatitis E Virus Genotype 4 in Europe through Swine Surveillance in the Netherlands and Belgium. PLoS One 2011;6:e22673.

Helsen N, Debing Y, Paeshuyse J, et al. Stem cell derived hepatocytes: a novel model for hepatitis E virus replication. J Hepatol 2015, pii: S0168-8278(15)00771-0, epub ahead of print

Hewitt PE, Ijaz S, Braisford SR, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 2014;1766-1773.

Höner zu Siederdissen C, Pischke S, Schlue J, et al. Chronic HEV infection beyond transplantation or HIV infection. Hepatology 2014;60; 1112-1113.

Hogema BM, Molier M, Sjerps M, et al. Incidence and duration of hepatitis E virus infections in Dutch blood donors. Transfusion 2015, epub ahead of print.

Huang S, ZhangX, Su Y, et al. Long-term efficacy of a recombinant hepatitis E vaccine in adults: 10-year results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2024; Mar 2;403(10429):813-823.

Juhl D, Baylis SA, Blumel J, Gorg S, Hennig H. Seroprevalence and incidence of hepatitis E virus infection in German blood donors. Transfusion 2013; 54: 49-56.

Kaba M, Richet H, Ravaux I, et al. Hepatitis E virus infection in patients infected with the human immunodeficiency virus. J Med Virol 2010;83:1704-16.

Kamar N, Abravanel F, Selves J, et al. Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. Transplantation 2011a;89:353-60.

Kamar N, Bendall RP, Peron JM, et al. Hepatitis E virus and neurologic disorders. Emerg Infect Dis 2011b;17:173-9.

Kamar N, Garrouste C, Haagsma EB, et al. Factors associated with chronic hepatitis in patients with hepatitis e virus infection who have received solid organ transplants. Gastroenterology 2011c;140:1481-9.

Kamar N, Izopet J, Cintas P, et al. Hepatitis e virus-induced neurological symptoms in a kidney-transplant patient with chronic hepatitis. Am J Transplant 2011d;10:1321-4.

Kamar N, Rostaing L, Abravanel F, et al. Pegylated Interferon-alpha for Treating Chronic Hepatitis E Virus Infection after Liver Transplantation. Clin Infect Dis 2010a.

Kamar N, Rostaing L, Abravanel F, et al. Ribavirin Therapy Inhibits Viral Replication on Patients With Chronic Hepatitis E Virus Infection. Gastroenterology 2010b.

Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med 2008;358:811-7.

Kamar N, Izopet J, Tripon S, et al. Ribavirin for chronic hepatitis E virus infection in transplant recipients. N. Engl. J. Med. 2014; 370, 1111-1120

Kamar N, Weclawiak H, Guilbeau-Frugier C, et al.. Hepatittis E Virus and the kidney in Solid-Organ transplant patients. Transplantation 2012;6: 617-623.

Keane F, Gompels M, Bendall R, et al. Hepatitis E virus coinfection in patients with HIV infection. HIV Med 2012 Jan;13(1):83-88.

Koenecke C, Pischke S, Heim A, Raggub L, Bremer B, Raupach R, et al. Chronic hepatitis E in hematopoietic stem cell transplant patients in a low-endemic country? Transpl Infect Dis. 2012:103-6.

Kuniholm MH, OngE, Hogema BM, et al. Acute and Chronic Hepatitis E Virus Infection in HIV-infected United States Women. Hepatology 2015. Epub ahead of print

Leblond AL, Helmchen B, Ankavay M, et al. HEV ORF2 protein-antibody complex deposits are associated with glomerulonephritis in hepatitis E with reduced immune status. Nat Commun. 2024 Oct 14;15(1):8849

Lee GH, Tan BH, Teo EC, et al. Chronic Infection With Camelid Hepatitis E Virus in a Liver-transplant Recipient Who Regularly Consumes Camel Meat and Milk. Gastroenterology 2015 epub ahead of print.

Liu L, Liu Y. Analysis of acute to chronic hepatitis E: 6-10 year follow-up. Hepatogastroenterology 2011;58:324-5.

Madejon A, Vispo E, Bottecchia M, Sanchez-Carrillo M, Garcia-Samaniego J, Soriano V. Lack of hepatitis E virus infection in HIV patients with advanced immunodeficiency or idiopathic liver enzyme elevations. J Viral Hepat 2009.

Mallet V, Louvet A, Chakvetadze C, et al. Ribavirin Treatment for Chronic Hepatitis E: a Case-Series. Hepatology 2010;52:919A-1020A.

Melenhorst WB, Gu YL, Jaspers WJ, Verhage AH. Locally acquired hepatitis E in the Netherlands: associated with the consumption of raw pig meat? Scand J Infect Dis 2007;39:454-6.

Meng J, Cong M, Dai X, et al. Primary structure of open reading frame 2 and 3 of the hepatitis E virus isolated from Morocco. J Med Virol 1999;57:126-33.

Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. Liver Int 2008;28:1190-9.

Peron JM, Abravanel F, Guillaume M, et al.Liver International 2015, epub ahead of print

Pischke S, Heim A, Bremer B, et al. Hepatitis E: An Emerging Infectious Disease in Germany? Z Gastroenterol 2011a;49:1255-1257.

Pischke S, Hardtke S, Bode U, et al. Ribavirin treatment of acute and chronic hepatitis E: a single center experience. Liver International 2013a;33:722-6.

Pischke S, Geer M, Hardtke S, et al. Course and treatment of chronic hepatitis E virus infection in lung transplant recipients. Transpl. Inf. Dis. 2014;16, 333-339

Pischke S, Gisa A, Suneetha PV, et al. Increased HEV seroprevalence in patients with autoimmune hepatitis. PLOS One 2014, e85330.

Pischke S, Ho H, Urbanek F, et al. Hepatitis E in HIV positive patients in a low-endemic country. J Viral Hepat 2010a;17:598-9.

Pischke S, Horn-Wichmann R, Ernst, D, et al. Absence of chronic hepatitis E in a German cohort of common variable immunodeficiency patients. Infectious Disease Reports 20120;volume 4:e28.

Pischke S, Kjasimov A, Skripuletz T, et al. Serological indication of chronic inflammatory demyelinating polyneuropathy as an extrahepatic manifestation of hepatitis E virus infection. Scientific reports 2024 Aug 20;14(1):19244.

Pischke S, Stiefel P, Franz B, Bremer B, Suneetha PV, Heim A, et al. Chronic hepatitis e in heart transplant recipients. Am J Transplant. 2012b:3128-33.

Pischke S, Suneetha PV, Baechlein C, et al. Hepatitis E virus infection as a cause of graft hepatitis in liver transplant recipients. Liver Transpl 2010b;16:74-82.

Pischke S, Voigtlaender T, Koenecke C, et al. Chronic hepatitis E in immunosuppressed patients beyond liver- and kidney transpantation. Journal of Hepatology 2011b;54, S1:495.

Pischke S, Wedemeyer H. Hepatitis E Virus Infection: multiple faces of an underestimated problem. J. Hepoatol. 2013b;58: 1045-6.

Rein DB, Stevens G, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus. Hepatology 2011;55:988-97.

Rizebos-Brilman A, Puchhammer-Stockl E, Van der Weide HY, et al. Chronic hepatitis E infection in lung transplant recipients. J Heart Lung Transplant 2013;32:341-6.

Rivero-Juarez A, Frias M, Perez AB, Pineda JA, et al. Orthohepevirus C infection as an emerging cause of acute hepatitis in Spain: First report in Europe. J Hepatol. 2022 Aug;77(2):326-331.

Schlosser B, Stein A, Neuhaus R, et al. Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in

the recipient. J Hepatol 2011.

Shrestha MP, Scott RM, Joshi DM, et al. Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med 2007;356:895-903.

Slot E, Hogema BM, Rizebos-Brillman A, Kok TM, Molier M, Zaaijer HL. Silent hepatitis E virus infection in Dutch blood donors, 2011 to 2012. Euro Surveill. 2013;18 pii: 20550.

Smith DB, Simmonds P, Izopet J, et al. J Gen Virol 2016, epub ahead of print

Stoszek SK, Engle RE, Abdel-Hamid M, et al. Hepatitis E antibody seroconversion without disease in highly endemic rural Egyptian communities. Trans R Soc Trop Med Hyg 2006;100:89-94.

Teshale EH, Grytdal SP, Howard C, et al. Evidence of person-to-person transmission of hepatitis E virus during a large outbreak in Northern Uganda. Clin Infect Dis 2011;50:1006-10.

Van den Berg B, Annemick A, Van den Eijk A, et al. Guillain-Barré syndrome associated with preceding hepatitis E virus infection. Neurology 2013;82, 491-497.

Van Eijk JJ, Madden RG, van der Eijk AA, et al. Neuralgic amyotrophy and hepatitis E virus infection. Neurology 2014;82, 498-503.

Versluis J, Pas SD, Agteresch HJ, et al. Hepatitis E virus: an underestimated opportunistic pathogen in recipients of allogeneic hematopoietic stem cell transplantation. Blood 2013;122:1079-86.

Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis e virus infection. Gastroenterology 2012;1388-1397.

Wedemeyer H, Pischke S. Hepatitis: Hepatitis E vaccination-is HEV 239 the breakthrough? Nat Rev Gastroenterol Hepatol 2011;8:8-10.

Wedemeyer, H, Rybczynska J, Pischke S, Krawczynski K. Immunopathogenesis of hepatitis E virus infection. Semin. Liver Dis. 2013;33: 71-78.

Wenzel JJ, Preiss J, Schemmerer M, Huber B, Plentz A, Jilg W. Detection of hepatitis E virus (HEV) from porcine livers in Southeastern Germany and high sequence homology to human HEV isolates. J Clin Virol 2011.

WHO, Hepatitis E Factsheet No 280, Updated June 2014, http://www.who.int/mediacentre/factsheets/fs280/en [Accessed 20 January 2015]

WHO, Acute hepatitis E – South Sudan, updated 5 May 2023, https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON466 [accessed 12 October 2023]

WuT, Zhu FC, Huang SJ, et al. Safety of the hepatitis E vaccine for pregnant women: A preliminary analysis. Hepatology 2012;55: 2038.

Zhang J, Zhang XF, Zhou C, et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. Clin Microbiol Infect 2013; epub ahead of print.

Zhao ZY, Ruan B, Shao H, Chen ZJ, Liu SL. Detection of hepatitis E virus RNA in sera of patients with hepatitis E by polymerase chain reaction. Hepatobiliary Pancreat Dis Int 2007;6:38-42.

Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010;376:895-902.

6. Viral hepatitis and HIV coinfection

6.1 Management of HBV/HIV coinfection

Stefan Mauss, Kathrin van Bremen

Abstract

HBV/HIV-coinfection represents the most frequent viral coinfection in people living with HIV (PLWH). About 2.7 million (7.4%) PLWH are thought to be HBV-coinfected. Due to the mutual interference of HBV and HIV-coinfection, fibrosis progression, liver cirrhosis, risk of development of hepatocellular carcinoma and overall liver-disease related death is increased. Therefore, every PLWH with chronic HBV-coinfection needs an HBV-active drug as part of their antiretroviral treatment (ART) with the overall goal of HBV-DNA suppression. Functional cure with loss of HBs-Ag is a rare but possible event particularly after initiation of antiretroviral therapy as part of an immune reconstitution phenomenon.

Introduction

The prevalence and transmission routes of HBV coinfection in the HIV+ population vary substantially by geographic region (Alter 2006, Konopnicki 2005). Globally, 7, 4% of the 37 Mio PLWH are estimated to be coinfected with HBV (WHO 2021). In the United States and Europe, the majority of HIV positive men who have sex with men (MSM) have evidence of past HBV infection, and 5–10% show persistence of HBs- antigen, with or without replicative hepatitis B as defined by the presence of HBV DNA (Konopnicki 2005). Overall, rates of HBV/HIV coinfection are slightly lower among intravenous drug users compared to MSM and much lower among people infected through heterosexual contact (Núñez 2005).

In endemic regions of Africa and Asia, the majority of HBV infections are transmitted vertically at birth or before the age of 5 through close contact within households, medical procedures and traditional scarification (Modi 2007). The prevalence among youth in most Asian countries has substantially decreased since the introduction of vaccination on nationwide scales (Shepard 2006). In Europe, vaccination of children and members of

risk groups is promoted and reimbursed by health care systems in most countries.

The natural history of hepatitis B is altered by simultaneous infection with HIV. Immune control of HBV is negatively affected leading to a reduction of HBs-antigen seroconversion. If HBV persists, the HBV DNA levels are generally higher in HIV positive patients not on antiretroviral therapy (Bodsworth 1989, Bodsworth 1991, Hadler 1991). In addition, with progression of cellular immune deficiency, reactivation of HBV replication despite previous HBs-antigen seroconversion may occur (Soriano 2005). However, after immune recovery due to antiretroviral therapy, HBe-antigen and HBs-antigen seroconversion occur in a higher proportion of patients compared to HBV monoinfected patients (up to 18%) treated for chronic hepatitis B (Schmutz 2006, Piroth 2010, Kosi 2012, van Bremen 2020).

In untreated HIV infection, faster progression to liver cirrhosis is reported for HBV/HIV-coinfected patients (Puoti 2006). Moreover, hepatocellular carcinoma may develop at an earlier age and is more aggressive in this population (Puoti 2004, Brau 2007). Moreover, persisting HBV-DNA >200 IU/L presents a risk factor in PLWH (Kim 2021). Start of HBV suppressive treatment with tenofovir at early age (<46 years) was found to be associated with a lower HCC incidence (Wandeler 2021).Being HBV-coinfected results in increased mortality for HIV positiveindividuals, even after the introduction of effective antiretroviral therapy (ART), as demonstrated by an analysis of the EuroSIDA Study, which shows a 3.6-fold higher risk of liver-related deaths among HBsAg positive patients compared to HBsAg negative individuals (Konopnicki 2005, Nikolopoulos 2009 (Figure 1). In the UK Collaborative HIV cohort a 10-fold increased risk of liver-related mortality was seen among HBV/HIV- coinfected compared to HIV-monoinfected individuals, particularly among individuals with low CD4+ cell counts (Thornton 2017). Therefore, early treatment and screening for complications of liver disease in HBV/HIV-coinfected patients especially for HCC remains crucial.

The beneficial impact of treatment of HBV in HBV/HIV coinfection was first demonstrated by data from a large cohort showing a reduction in mortality with lamivudine treatment compared to untreated patients (Puoti 2007). This result is even more remarkable because lamivudine is the least effective HBV polymerase inhibitor due to the rapid development of drug resistance. In general, because of its limited long-term efficacy, lamivudine monotherapy cannot be considered as appropriate therapy for either mono HBV infection or HBV/HIV coinfection (Matthews 2011).

In addition, two large cohort studies (EuroSIDA and MACS) plus data from HBV monoinfection studies showing a reduction in morbidity and mortality established the need to treat chronic hepatitis B in HBV/HIV-coinfected patients as early as possible.

Treatment of chronic hepatitis B in HBV/HIV-coinfected patients on antiretroviral therapy

As antiretroviral therapy is recommended for all HIV patients independent of CD4-count to reduce HIV-associated morbidity and mortality and to prevent HIV transmission, all HBV/HIV-coinfected patients are considered eligible for antiretroviral therapy by current guidelines (e. g. EACS 2022). A TDF/TAF-containing regimen is now recommended in all HBV/HIV-coinfected patients. The previous complicated recommendations for how to treat chronic hepatitis B in patients without antiretroviral therapy are obsolete. As antiretroviral drugs that are also active against HBV can usually be used, interferon- based treatment of HBV is not indicated. Data in the literature for HIV-coinfected patients on interferon therapy for HBV infection are limited and not very encouraging (Núñez 2003). In addition, treatment studies intensifying TDF therapy with pegylated interferon for one year showed no increase in HBV seroconversion rates (Boyd 2016).

In general, tenofovir based therapy is the standard of care for HBV in HIV-coinfected patients, because of its strong HBV polymerase activity and antiretroviral efficacy. Tenofovir has been a stable and effective therapy in the vast majority of treated HBV/HIV-coinfected patients (van Bömmel 2004, Mathews 2009, Martin-Carbonero 2011, Thibaut 2011). Its antiviral efficacy is not impaired in HBV/HIV-coinfected compared to HBV-monoinfected patients (Plaza 2013). No conclusive pattern of resistance mutations has been identified in studies or cohorts (Snow-Lampart 2011). These data are still valid in 2023. In theory, resistance may occur in patients on long-term therapy, as with any other antivirals. Because of that, when choosing an HBV polymerase inhibitor, complete suppression of HBV DNA is important to avoid the development of HBV drug resistance.

In HBV treatment naïve patients, a combination of tenofovir (either TAF or TDF) plus lamivudine/emtricitabine to treat both infections is usually recommended. Even for patients who harbour lamivudine-, telbivudine- or adefovir-resistant HBV due to previous therapies this strategy proves to work very well. As adefovir and telbivudine are no longer available and obsolete to use HBV-relevant resistance against these antivirals will no longer be relevant.

Initiating ART including tenofovir resulted in higher rates of HBe antigen loss and seroconversion as expected from HBV-monoinfected patients (Schmutz 2006, Piroth 2010, Kosi 2012, van Bremen 2020). This may be due to the additional effect of immune reconstitution in HBV/HIV coinfected patients improving immunological control of HBV replication.

For patients with advanced liver fibrosis or liver cirrhosis a maximally

active continuous HBV polymerase inhibitor therapy is important to avoid further fibrosis progression and hepatic decompensation and to reduce the risk of developing hepatocellular carcinoma. Tenofovir plus lamivudine/emtricitabine is the treatment of choice. If the results are not fully suppressive, adding entecavir should be considered (Ratcliffe 2011). A reduction in the incidence of hepatocellular carcinoma has been shown for patients on HBV polymerase inhibitors compared to untreated patients, strengthening the antiproliferative effects of suppressive antiviral therapy (Hosaka 2012).

Liver ultrasound or an alternative imaging procedure is indicated at least every six months in patients with liver cirrhosis irrespective of HBV-DNA suppression as well as in non-cirrhotic patients with risk factors (family history of HCC, Asian/Africans patients, HDV-coinfection, age>45 years) for early detection of hepatocellular carcinoma. In patients with advanced cirrhosis, esophagogastroscopy should be performed as screening for oesophageal varices. For patients with hepatic decompensation and full treatment options for HBV and who have stable HIV infection, liver transplantation should be considered as posttransplant life expectancy seems to be the same as for HBV-monoinfected patients (Coffin 2007, Tateo 2009). Patients with hepatocellular carcinoma may also be considered liver transplant candidates, PLWH showed similar rates concerning recurrence and disease free survival vs. patients without HIV-infection. (Eman 2019).

The acquisition of adefovir resistance mutations from the past as well as multiple lamivudine resistance mutations may impair the activity of tenofovir (Fung 2005, Lada 2012, van Bömmel 2010), although even in these situations tenofovir retains sufficient activity against HBV (Berg 2010, Patterson 2011, Petersen 2012).

In lamivudine-resistant HBV the antiviral efficacy of entecavir in HIV-coinfected patients is reduced, as it is in HBV monoinfection (Shermann 2008). Because of this and the property of tenofovir as a fully active antiretroviral, tenofovir-disoproxilfumarate or tenofovir-alafenamide is the preferred choice in treatment-naïve HBV/ HIV coinfected patients who will use ART. The use of entecavir as an add-on to tenofovir or other drugs in the case of not fully suppressive antiviral HBV therapy has not yet been studied in HBV/HIV coinfection. This decision should be made on a case-by-case basis.

Based on history of antiretroviral therapy, combination HBV therapy of tenofovir plus lamivudine/emtricitabine was expected to be superior to tenofovir monotherapy, in particular in patients with highly replicative HBV infection. However, this hypothesis has not as yet been supported by studies (Schmutz 2006, Mathews 2008, Mathews 2009, Price 2013). However, there are data showing better viral suppression for entecavir and tenofovir-DF compared to entecavir monotherapy in highly replicative patients with HBV-monoinfection, but no such a study is available for a comparison with tenofovir monotherapy (Lok 2012).

In the case of HIV resistance to tenofovir, it is usually important to continue using tenofovir for HBV activity when switching to other antiretrovirals. Discontinuation of the HBV polymerase inhibitor without maintaining the antiviral pressure on HBV can lead to necroinflammatory flares that can result in acute liver decompensation, particularly in patients with liver cirrhosis. Therefore, life-long treatment with HBV-active drugs are recommended.

Nowadays, two-drug regimens (2DR) without TDF have become more frequent. 2DR are not recommended in HBV/HIV-coinfected patients as HBV suppression needs to be maintained at any time to prevent further related morbidity and mortality.

In 2015, tenofovir alafenamide (TAF) was approved as antiretroviral therapy in Europe and the US. TAF is a new formulation of tenofovir with lower plasma exposure of the active drug tenofovir compared to tenofovir disoproxil fumarate (TDF). TAF may offer advantages concerning long term toxicities involving bone and kidney over TDF (Agarwal 2015, Sax 2015). TAF can substitute TDF as HBV therapy in HBV/HIV-coinfected patients (Gallant 2016). The ALLIANCE study has shown a higher rate of maximal HBV-DNA suppression on TAF- vs. TDF-based therapy (B/F/TAF 63.0% vs. DTG+F/TDF 43.4%) in PLWH with recent ART-initiation at week 48. However, no breakthroughs or treatment failures were observed under TDF therapy compared to TAF. Interestingly, rate of HBsAg-loss was higher when using TAF-based therapy (12.6% vs. 5.8%) (Avihingsanon 2022Clinical consequences of these preliminary findings seem limited.

The potentially nephrotoxic effect of TDF is a concern. Although nephrotoxicity is rarely observed in HIV negative patients treated with TDF monotherapy (Heathcote 2011, Mauss 2011), renal impairment has been more frequently reported in HIV positive patients using TDF as a component in ART and may be associated in particular with the combined use of TDF and ritonavir-boosted HIV protease inhibitors (Mauss 2005, Fux 2007, Goicoecha 2008, Mocroft 2010). In addition, the approved cytochrome P450 3A inhibitor cobicistat can also increase creatinine levels. Regular monitoring of renal function in HBV/HIV-coinfected patients including estimated glomerular filtration rate (eGFR) and assessment of proteinuria is necessary. In the case of a reduced eGFR, TDF should be substituted by TAF or should be dosed at a reduced frequency according to the label. In the case of significant proteinuria, TDF should also be replaced by TAF. Alternatively in specific situations in the case of tenofovir associated nephrotoxicity tenofovir can also be replaced by entecavir.

Conclusion

For HBV/HIV coinfected patients, antiretroviral therapy is indicated to treat both infections simultaneously. Therefore, HBV treatment of choice is tenofovir-based therapy. Due to rapid development of resistance when HBV is not fully suppressed HBV monotherapy with either lamivudine or emtricitabine should not be considered. A combination of tenofovir plus lamivudine or emtricitabine as a primary combination therapy has theoretical advantages over tenofovir alone, but studies supporting this concept have not been published to date. However, as tenofovir is combined with emtricitabine or lamivudine in most antiretroviral regimen this seems to be a more theoretical argument and not reflected by reality.

In general, treatment of HBV as a viral disease follows the same rules as HIV therapy, aiming at full suppression of the replication of the virus to avoid the development of resistance. Successful viral suppression of hepatitis B results in inhibition of necroinflammatory activity, reversion of fibrosis, and most importantly a decrease in the incidence of hepatic decompensation and hepatocellular carcinoma.

Key messages

- HBV/HIV-coinfection leads to increased liver and overall mortality rates
- Screening of HBV-coinfection in every PLWH is guideline recommended
- Vaccinate PLWH without HBV-seroprotection
- TDF/TAF-containing ART is recommend in every PLWH with HBV-coinfection
- HCC-screening recommended every 6 months in cirrhotic patients and non-cirrhotic patients with risk factors
- Functional cure with HBsAg loss rare but possible event

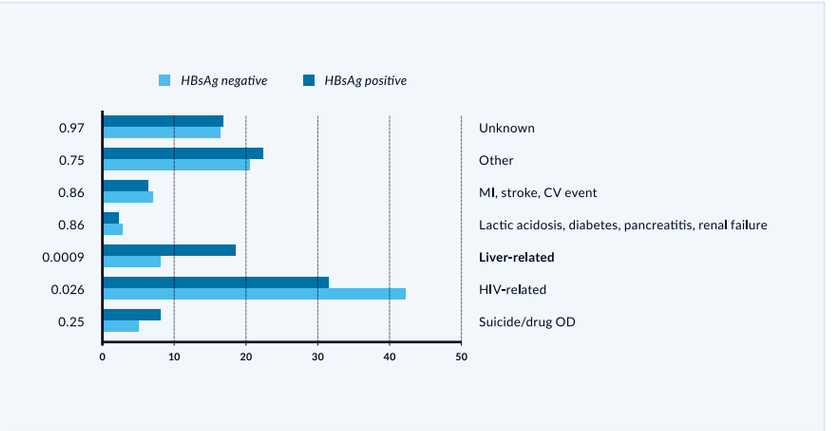

Figure 1. Association of HBV/HIV coinfection and mortality (Konopnicki 2005). More than one cause of death allowed per patient; p-values from chi-squared tests.

References

Alter M. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol 2006; 44:6-9.

Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol. 2015;62(3):533-40.

Avihingsanon A, Lu H, Leong CL, et al. Week 48 of a phase 3 randomised controlled trial of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) vs dolutegravir + emtricitabine/ tenofovir disoproxil fumarate (DTG+F/TDF) as initial treatment in HIV/HBV-coinfected adults (ALLIANCE). AIDS 2022, July 29-August 2, Montreal. Abstract OALBX0105

Berg T, Marcellin P, Zoulim F, et al. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. Gastroenterology 2010;139:1207-17.

Bodsworth N, Donovan B, Nightingale BN. The effect of concurrent human immunodeficiency virus infection on chronic hepatitis B: a study of 150 homosexual men. J Infect Dis 1989;160:577-82.

Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. J Infect Dis 1991;163:1138-40.

Boyd A, Piroth L, Maylin S, et al. Intensification with pegylated interferon during treatment with tenofovir in HIV-hepatitis B virus co-infected patients. J Viral Hepat. 2016;23(12):1017-1026.

Brau N, Fox R, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: A US-Canadian multicenter study. J Hepatol 2007;47:527-37.

Chan HL, Heathcote EJ, Marcellin P, et al. Treatment of Hepatitis B e Antigen-Positive Chronic Hepatitis with Telbivudine or Adefovir: A Randomised Trial. Ann Intern Med 2007;147:2-11.

Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. Am J Transplant 2010;10:1268-75.

Crowell TA, Gebo KA, Balagopal A, et al. Impact of hepatitis coinfection on hospitalisation rates and causes in a multicenter cohort of persons living with HIV. J Acquir Immune Defic Syndr. 2014;65(4):429-37.

EACS guidelines 2022 Version 11.1. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

Eman P, Chacon E, Gupta M et al. Long term outcomes of patients transplanted for hepatocellular carcinoma with human immunodeficiency virus infection. HPB (Oxford). 2019 (8):1009-1016

Fung SK, Andreone P, Han SH, et al. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. J Hepatol 2005;43:937-43.

Fux CA, Simcock M, Wolbers M, et al. Swiss HIV Cohort Study. Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. Antivir Ther 2007;12:1165-73.

Gallant J, Brunetta J, Crofoot G, et al. Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide in HIV-1/Hepatitis B-Coinfected Adults. J Acquir Immune Defic Syndr. 2016;73(3):294-298.

Goicoechea M, Liu S, Best B, et al. California Collaborative Treatment Group 578 Team. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. J Infect Dis 2008;197:102-8.

Hadler SC, Judson FN, O'Malley PM, et al. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. J Infect Dis 1991;163:454-9.

Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011;140:132-43.

Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2012.

Kim N, Newcomb C, Carbonari C et al. Risk of HCC With Hepatitis B Viraemia Among HIV/HBV-Coinfected Persons in North America. Hepatology 2021; 74(3):1190-1202

Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS 2005;19:593-601.

Kosi L, Reiberger T, Payer BA, et al. Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. J Viral Hepat. 2012,19(11):801-10.

Lada O, Gervais A, Branger M, et al. Quasispecies analysis and in vitro susceptibility of HBV strains isolated from HIV-HBV-coinfected patients with delayed response to tenofovir. Antivir Ther. 2012;17(1):61-70.

Lampertico P, Viganò M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with Lamivudine: a 3-year study of 145 Lamivudine-resistant hepatitis B patients. Gastroenterology 2007;133:1445-51.

Lin K, Karwowska S, Lam E, Limoli K, Evans TG, Avila C. Telbivudine exhibits no inhibitory activity against HIV-1 clinical isolates in vitro.

Antimicrob Agents Chemother 2010;54:2670-3.

Lok AS, Trinh H, Carosi G, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. Gastroenterology. 2012;143(3):619-28.

Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J, et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. AIDS 2011;25:73-9.

Matthews GV, Avihingsanon A, Lewin SR, et al. A randomised trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand. Hepatology 2008;48:1062-9.

Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. AIDS 2009;23:1707-15.

Matthews GV, Manzini P, Hu Z, et al. Impact of lamivudine on HIV and hepatitis B virus-related outcomes in HIV/hepatitis B virus individuals in a randomised clinical trial of antiretroviral therapy in southern Africa. AIDS 2011;25:1727-35.

Mauss S, Berger F, Schmutz G. Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. AIDS 2005;19:93-5.

Mauss S, Berger F, Filmann N, et al. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. J Hepatol 2011;55:1235-40.

Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV positive patients. AIDS. 2010;24(11):1667-78.

Modi A, Feld J. Viral hepatitis and HIV in Africa. AIDS Rev 2007;9:25-39.

Núñez M, Puoti M, Camino N, Soriano V. Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. Clin Infect Dis 2003;37:1678-85.

Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis 2009;48:1763-71.

Núñez M, Soriano V. Management of patients co-infected with hepatitis B virus and HIV. Lancet Infect Dis 2005;5:374-82.

Patterson SJ, George J, Strasser SI, et al. Tenofovir disoproxil fumarate rescue therapy following failure of both lamivudine and adefovir dipivoxil in chronic hepatitis B. Gut. 2011;60:247-54.

Petersen J, Ratziu V, Buti M, et al. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: An international multicenter cohort study. J Hepatol 2012;56(3):520-6.

Piroth L, Pol S, Lacombe K, Miailhes P, et al. Management and treatment of chronic hepatitis B virus infection in HIV positive and negative patients: the EPIB 2008 study. J Hepatol 2010;53:1006-12.

Plaza Z, Aguilera A, Mena A, et al. Influence of HIV infection on response to tenofovir in patients with chronic hepatitis B. AIDS.2013;27(14):2219-24.

Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PLoS One. 2013;8(7):e68152.

Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. AIDS 2004;18:2285-93.

Puoti M, Cozzi-Lepri A, Arici C, et al. Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV positive individuals: results from an inter-cohort analysis. Antivir Ther 2006;11:567-74.

Puoti M, Torti C, Bruno R. Natural history of chronic hepatitis B in co-infected patients. J Hepatol 2006;44:65-70.

Ratcliffe L, Beadsworth MB, Pennell A, Phillips M, Vilar FJ. Managing hepatitis B/HIV co-infected: adding entecavir to truvada (tenofovir disoproxil/emtricitabine) experienced patients. AIDS 2011;25:1051-6.

Rosenthal E, Roussillon C, Salmon-Céron D, et al. Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: the Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalité 2010 survey. HIV Med. 2014. doi: 10.1111/hiv.12204.

Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15.

Schmutz G, Nelson M, Lutz T, et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. AIDS 2006;20:1951-4.

Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. Epidemiol, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology 2008;48:99-108.

Snow-Lampart A, Chappell B, Curtis M, et al. No resistance to tenofovir disoproxil fumarate detected after up to 144 weeks of therapy in patients monoinfected with chronic hepatitis B virus. Hepatology 2011;53:763-73.

Soriano V, Puoti M, Bonacini M. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel. AIDS 2005;19:221-240.

Soriano V, Mocroft A, Peters L, et al. Predictors of hepatitis B virus genotype and viraemia in HIV-infected patients with chronic hepatitis B in Europe. J Antimicrob Chemother 2010;65:548-55.

Tateo M, Roque-Afonso AM, Antonini TM, et al. Long-term follow-up of liver transplanted HIV/hepatitis B virus coinfected patients: perfect control of hepatitis B virus replication and absence of mitochondrial toxicity. AIDS 2009;23:1069-76.

Thibault V, Stitou H, Desire N, Valantin MA, Tubiana R, Katlama C. Six-year follow-up of hepatitis B surface antigen concentrations in tenofovir disoproxil fumarate treated HIV-HBV-coinfected patients. Antivir Ther 2011;16:199-205.

Thornton A; Jose S, Bhagani S et al. Hepatitis V, hepatitis C, and mortality among HIV positive individuals.AIDS 2017 (18):2525-2532.

Van Bömmel F, Wünsche T, Mauss S, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology 2004;40:1421-5.

Van Bömmel F, de Man RA, Wedemeyer H, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology 2010;51:73-80.

Van Bremen K, Hoffmann C, Mauss S et al.Obstacles to HBV functional cure: Late presentation and ist impact on HBV seroconversio in HIV/HBV coinfection. Liver Int. 2020; 12:2978-2981.

Wandeler G, Mauron E, Atkinson A et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: Relevance for screening strategies. J Hepatol. 2019. 71(2):274-280

World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. https://www.who.int/publications/i/item/9789240027077.

6. Viral hepatitis and HIV coinfection

6.2 Hepatitis C virus and HIV coinfection

Stefan Mauss, Jürgen Kurt Rockstroh, Christoph Boesecke

Short history of HCV/HIV-coinfection

In the beginning of the HIV epidemic co-infection with the hepatitis C virus (HCV) was usually caused by contaminated blood products or blood in particular in patients with hemophilia or intravenous drug use (Darby 1997, Nelson 2011). As there were at best limited treatment options for HIV most patients died due to AIDS. With the substantial improvement of efficacy of antiretroviral therapy chronic hepatitis C gained increasing clinical importance. Liver related death due to decompensated liver cirrhosis and hepatocellular carcinoma became one of the most frequent causes of death in Western cohorts of HIV patients (Rosenthal 2003, Klein 2016). Immunodeficiency due to HIV co-infection promotes fibrosis progression and the development of hepatocellular carcinomas (Eyster 1993, Rockstroh 1996, Darby 1997, Puoti 2000, Puoti 2000, Giordano 2004, Pineda 2007, Danta 2008). In addition, immunodeficiency decreased the efficacy of interferon-based therapy of HCV leading to an accumulation of HCV/HIV-coinfected patients in clinical cohorts with a history of often multiple unsuccessful interferon-based therapies and advanced liver fibrosis.

On the other hand, due to HIV and HCV testing of blood products, the approval of genetically produced clotting factors, the transmission of these viruses by medical procedures or blood products was drastically reduced. In addition, the broad acceptance of opioid maintenance therapies and safer use as harm reduction in people with intravenous drug use also had a marked effect on the incidence of HIV and HCV. However, in particular in Russia and some of the countries formerly belonging to the Soviet republic, such as Belarus, Ukraine and Georgia the incidence of HIV and HCV infections increased in the last twenty years mainly through exposure to intravenous drug use, sexual contacts and unsafe procedures associated with blood contacts (Nelson 2011, Platt 2016). In Asia, coinfection rates of up to 85% have been reported among Chinese plasma donors whereas in countries with predominantly heterosexual HIV transmission like Thailand, coinfection rates are around 10% (Qian 2006). In Sub-Saharan

Africa, where the primary route of transmission of HIV is sexual, HCV coinfection rates have so far been reported to be low.

In Western countries after the start of the next millennium an epidemic in men having sex with men (MSM) turned HCV into a sexually transmitted disease (Gotz 2005, Danta 2007, Vogel 2009, Jin 2010, Vogel 2010, CDC 2011, Matthews 2011, Schmidt 2011, Boesecke 2015). The main risk factors for transmission are traumatic sex practices associated with bleeding such as fisting or sharing sex toys and sex parties using recreational drugs (chemsex) – often intravenously (slamsex) (Van de Laar 2009, Schmidt 2011, Jin 2017, Mata-Marin 2022). This still ongoing epidemic was first observed in Europe and the US soon becoming a worldwide phenomenon. In the HIV population HCV as a sexually transmitted disease in MSM passed HCV transmitted by intravenous drug use in incidence in Western cohorts (Danta 2011, Peters 2014).

In the initial period (pegylated) interferon plus ribavirin was the only available therapy and efficacy remained far from optimal in chronic hepatitis C (Berenguer 2009). In contrast, when administered in recently acquired hepatitis C the efficacy of interferon and ribavirin was much higher. Despite the lack of a formal approval of interferon-based therapies for acute hepatitis C, early treatment was recommended by guidelines to improve treatment outcomes.

The introduction of direct acting antivirals changed the treatment paradigm radically. A brief transition period with boceprevir and telaprevir in combination with pegylated interferon and ribavirin increased antiviral efficacy, but at the expense of even more toxicities.

Finally, in 2014 the broad introduction of interferon-free antiviral combination therapy with excellent tolerance and efficacy lead to the demise of interferon-based therapies. The main concern remaining was their high costs. In some regions of the world the production of generic substances or special pricing negotiations helped to overcome this challenge (Hill 2014, Hézode 2017).

In patent protected markets due to the pricing politics only combination therapies under exclusive control of a single manufacturer survived. However, in generic markets other highly effective combination therapies may be available.

Specifics of the clinical course of hepatitis C in HIV coinfected patients

The natural course of chronic hepatitis C is characterised by a negative effect of HIV induced cellular immunosuppression on the progression of liver fibrosis compared to HCV monoinfected individuals (Eyster 1993, Rockstroh 1996, Soto 1997, Benhamou 2001, Puoti 2004, Danta 2008). This effect was shown to be partially reversible by immune-restoration due to highly active antiretroviral therapy (Qurishi 2003). A negative impact of antiretroviral therapy on the development of liver fibrosis due to liver toxicity could not be demonstrated (Rockstroh 1998, Sulkowski 2000, Rockstroh 2005, Jones 2011).

In cohort data an increased incidence of hepatocellular carcinoma compared to HCV monoinfected individuals was reported. In addition, the progression of hepatocellular carcinoma is thought to be more aggressive (Giordano 2004, Salmon-Ceron 2009, Bourcier 2012, Klein 2016).

A negative impact of HCV infection on the clinical course of HIV infection was not observed in several cohort studies (Sulkowski 2002, Peters 2009). However, a decreased CD4+ cell count was reported in patients with HCV/HIV-coinfection, which may have been due to lymphopenia in patients with splenomegaly (Greub 2000).

Vertical transmission of HCV is a further concern. HCV is detected after birth in 4 to 8% of infants born to HCV positive mothers (Bevilacqua 2009). HCV/HIV coinfection increases the risk for transmission of both viruses and high levels of HCV viraemia in the mother increases the risk of perinatal HCV transmission (Zanetti 1995). However, the risk of HCV transmission is reduced to less than 1% in mothers with HCV/HIV coinfection receiving antiretroviral therapy (ART) and undergoing caesarean section.

Treatment of hepatitis C in patients with HIV coinfection

In general, treatment of HCV in patients with HIV coinfection follows the rules of patients with HCV monoinfection. Efficacy of HCV therapy is comparable to HCV monoinfected patients which is a marked change compared to the interferon era (Molina 2015, Rockstroh 2015, Wyles 2015, Ingiliz 2016, Rockstroh 2018, Buggisch 2018). In contrast to interferon-based therapy, cellular immunosuppression has little influence on treatment efficacy with direct acting antivirals (Opravil 2008, Berenguer 2018). No specific recommendations concerning dosing or duration of HCV therapy exist for HCV/HIV-coinfected patients.

However due to the presence of concomitant antiretroviral therapies and a higher number of comedications in HIV coinfected patients the assessment of drug-drug interactions is important before initiation of HCV therapy.

Aspects to be considered before the start of therapy

As a general rule, the simultaneous administration of cobicistat or ritonavir in combination with a HCV protease inhibitor, i.e. glecaprevir, grazoprevir or voxilaprevir should be avoided due to an increase in drug levels of the latter.

The second rule concerning drug-drug interactions is to avoid any other strong inducers of the cytochrome P 450 3A enzyme family or inducers of p-glycoprotein. Antiretroviral drugs such as efavirenz, nevirapine or rifampicin, rifabutin, rifapentine, carbamazepine and phenytoin should also be avoided (Kaur 2015, Kempker 2019). This may lead to prioritising one treatment over the other in the case of concurrent tuberculosis. In patients without liver cirrhosis completion of tuberculostatic therapy may be preferred before initiating HCV therapy.

The third rule is to avoid the potentially fatal interaction of sofosbuvir with antiarrhytmics. In particular amiodarone should be avoided taking into account the very long half-life of the drug of more than 3 months (Back 2015, Boglione 2019).

For specific information on drug-drug interactions consultation of the website https://www.hep-druginteractions.org/ is highly recommended.

Another important aspect is that HCV protease inhibitors such as glecaprevir, voxilaprevir or grazoprevir are not recommended in patients with decompensated liver cirrhosis due to marked increases in drug levels (summary of product characteristics EMEA). This may cause a problem in case of antiviral failure in patients with decompensated liver cirrhosis as voxilaprevir is contraindicated. In this situation the patient should be registered with a transplant centre as treatment may be completed after liver transplantation.

Treatment of HCV in HIV coinfection

In most countries pangenotypic regimen such as sofosbuvir/velpatasvir (12 weeks) or glecaprevir/pibrentasvir (8 weeks) are the current standard therapy for treatment-naïve HCV patients. Ribavirin may be added to sofosbuvir/velpatasvir in case of liver cirrhosis. As re-treated patients from the interferon era are disappearing, prolonging therapy of glecaprevir/pibrentasvir to 12 weeks in genotype 3 patients is of little relevance. With these regimens tolerance is very good and efficacy of >98% in non-cirrhotic patients is achieved *(see Chapter 3.4)*.

In case of treatment failure sofosbuvir/velpatasvir/voxilaprevir is the treatment of choice with an efficacy of 95% SVR12 (Bourlière 2019). In case of re-infection standard treatments can be used.

Treating patients with failure to sofosbuvir/velpatasvir/voxilaprevir is more complex and requires adherence assessments and resistance testing leading to individual treatment decisions in specialised care centres (Dietz 2021).

In countries with a generic environment sofosbuvir/daclatasvir for 12 weeks is an alternative treatment option except for genotype 2 patients (Rockstroh 2017). Alternatively, sofosbuvir/ravidasvir for 12/24 weeks is another option in particular in Asia as this drug combination was developed with financial support from Thailand and Malaysia (Andrieux-Meyer 2021).

Treatment of recently acquired HCV in HIV

In the past, interferon-based regimens were more efficacious when used in the acute phase of HCV infection, but given the SVR rate of >90% with most DAA regimens in chronic HCV this advantage is no longer important. Nevertheless, some trials assessed the option of shortening treatment with direct acting antivirals in patients with recently acquired hepatitis C with mixed results (Naggie 2017, Rockstroh 2017, Matthews 2021, Martinello 2023). As a consequence, no shortened treatment duration is recommended for patients with acute or recently acquired hepatitis C.

Treatment is recommended in PLWH without a decrease of 2 log of HCV RNA at 4 weeks compared with initial HCV RNA due to the very low probability of spontaneous clearance and in persons with persistent serum HCV RNA 12 weeks after diagnosis of recently acquired HCV (Vogel 2009, NEAT 2011, Thomson 2011, Monin 2023). HCV treatment immediately after diagnosis may be considered in PLWH with ongoing risk behavior to reduce onward transmission. However, counseling strategies to change the risk behavior are also an essential part of the prevention measures (Braun 2021).

Data assessing the effect of early HCV therapy on the incidence of recently acquired hepatitis C in HIV-infected patient populations are conflicting and in 2020-2022 were over-shadowed by lockdown efforts and social distancing due to the COVID-19 pandemic (Smit 2021, Chromy 2022, Kusejko 2022, Popping 2022). However, at least some cohort studies are suggesting a regional effect of DAA therapy on the incidence of acute HCV infection in particular in MSM communities. Nevertheless, reinfection in successfully treated patients is not infrequent and remains a challenge (Berenguer 2019, Ingiliz 2020). Chemsex is an addiction with all the associated psychological aspects and is not easy to modify (Künzler-Heule 2021).

Management of liver cirrhosis and liver transplantation in people with HCV/HIV coinfection

In general, compared to HCV monoinfection, individuals with HCV/HIV coinfection develop more rapid HCV-related hepatic injuries such as liver fibrosis and cirrhosis. Additionally, HCV/HIV coinfection is associated with an increased rate of hepatocellular carcinoma (HCC). Typically, HCC occurs in coinfection at an earlier age and the course is more aggressive, with a shorter survival compared to HCV mono-infection (Giordano 2004, Salmon-Ceron 2009, Bourcier 2012, Klein 2016). An ultrasound of the liver should be performed every six months for HCC surveillance in patients with F3/F4 fibrosis, according to EACS guidelines (EACS 2022). Alternative imaging procedures (MRI, CT) should be considered in case of low-quality ultrasound results. It is important to note that HCC screening and monitoring of decompensation is upheld in patients with cirrhosis even after HCV cure has been achieved as improvement in liver stiffness may occur but not complete reversal (Berenguer 2024).

As upper gastrointestinal bleeding is another important complication, the presence of oesophageal varices using upper-gastrointestinal endoscopy should be monitored in patients with liver cirrhosis every year. Liver transplantation should be considered in patients with decompensated liver cirrhosis. Clinical experience is encouraging in patients with well-controlled HIV infection (Mindikoglu 2008, Baccarini 2011, Anadol 2012). To fulfil the selection criteria for a liver transplant in individuals with HCV/HIV coinfection, the CD4+ T cell count has to be at least 100 cells/µl. Additionally, the patient has to have either undetectable HIV viraemia (<50 copies/mL) or at least rational treatment options to control HIV infection successfully after liver transplantation. Further contraindications for transplantation are opportunistic diseases, ongoing alcohol or drug use, large multilocular HCC or HCC metastasis in other organs, a second malignant disease, advanced cardiopulmonary disease or older age with an elevated perioperative mortality risk (EACS 2022).

The possibility to eradicate HCV in virtually all patients posttransplant due to the high efficacy of DAA regimen will positively affect transplant survival. On the other hand, the need for liver transplantation due to chronic HCV will be substantially reduced over the years to come in countries with large scale access to DAAs.

References

Anadol E, Beckebaum S, Radecke K, et al. Orthotopic liver transplantation in human-immunodeficiency-virus-positive patients in Germany. AIDS Res Treat. 2012;2012:197501.

Andrieux-Meyer I, Tan SS, Thanprasertsuk S et.al. Efficacy and safety of ravidasvir plus sofosbuvir in patients with chronic hepatitis C infection without cirrhosis or with compensated cirrhosis (STORM-C-1): interim analysis of a two-stage, open-label, multicentre, single arm, phase 2/3 trial. Lancet Gastroenterol Hepatol. 2021;6(6):448-458.

Baccarani U, Adani GL, Bragantini F, et al. Long-term outcomes of orthotopic liver transplantation in human immunodeficiency virus-infected patients and comparison with human immunodeficiency virus negative cases. Transplant Proc. 2011;43:1119-22.

Back DJ, Burger DM. Interaction between amiodarone and sofosbuvir-based treatment for hepatitis C virus infection: potential mechanisms and lessons to be learned. Gastroenterology 2015; 149(6):1315-7.

Benhamou Y, Demartinio V, Boche T, et al. Factors effecting liver fibrosis in human immunodeficiency virus and hepatitis C virus coinfected patients. Impact of protease inhibitor therapy. Hepatology 2001;34:283-7.

Berenguer J, González-García J, López-Aldeguer J, et al. Pegylated interferon α-2a plus ribavirin versus pegylated interferon α-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. J Antimicrob Chemother. 2009;63:1256-63.

Berenguer J, von Wichmann MA, Quereda C, et al. Effect of accompanying antiretroviral drugs on virological response to pegylated interferon and ribavirin in patients co-infected with HIV and hepatitis C virus. J Antimicrob Chemother. 2011;66:2843-9.

Berenguer J, Gil-Martin Á, Jarrin I, et al. All-oral direct-acting antiviral therapy against hepatitis C virus (HCV) in human immunodeficiency virus/HCV-coinfected subjects in real-world practice: Madrid coinfection registry findings. Hepatology 2018 Jul;68(1):32-47.

Berenguer J, Gil-Martin Á, Jarrin I, et al. Reinfection by hepatitis C virus following effective all-oral direct-acting antiviral drug therapy in HIV/hepatitis C virus coinfected individuals. AIDS. 2019;33(4):685-689.

Berenguer J, Aldámiz-Echevarría T, Hontañón V, et al. Clinical outcomes and prognostic factors after HCV clearance with DAA in HIV/HCV-coinfected patients with advanced fibrosis/cirrhosis. J.Hepatology. 2024 Mar 7.

Bevilacqua E, Fabris A, Floreano P, Pembrey L, Newell ML, Tovo PA, Amoroso A; EPHN collaborators. Genetic factors in mother-to-child transmission of HCV infection. Virology 2009;390:64-70.

Boglione L, De Nicolò A, Di Perri G, D'Avolio A. Flecainide plasma level modifications during ledipasvir/sofosbuvir coadministration in two patients affected by chronic hepatitis C. Antivir Ther. 2019;24(7):553-555.

Boerekamps A, Newsum AM, Smit C, et al. High Treatment Uptake in Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients After Unrestricted Access to Direct-Acting Antivirals in the Netherlands. Clin Infect Dis. 2018;17;66(9):1352-1359.

Boesecke C, Rockstroh JK. Treatment of acute hepatitis C infection in HIV-infected patients. Curr Opin HIV AIDS. 2011;6:278-84.

Boesecke C, Grint D, Soriano V, et al. Hepatitis C seroconversions in HIV infection across Europe: which regions and patient groups are affected? Liver Int. 2015;35(11):2384-91.

Bourlière M, Gordon SC, Flamm SL et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med. 2017;376(22):2134-2146.

Braun DL, Hampel B, Ledergerber B, et al. A Treatment-as-Prevention Trial to Eliminate Hepatitis C Among Men Who Have Sex With Men Living With Human Immunodeficiency Virus (HIV) in the Swiss HIV Cohort Study. Clin Infect Dis. 2021;73(7):e2194-e2202.

Bourcier V, Winnock M, Ait Ahmed A et al. ANRS CO13 Hepavih study group; ANRS CO12 Cirvir study group. Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection. A prospective study (ANRS CO13 Hepavih and CO12 Cirvir). Clin Res Hepatol Gastroenterol. 2012;36(3):214-21.

Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med. 2017;376(22):2134-2146.

Buggisch P, Vermehren J, Mauss S, et al. Real-world effectiveness of 8-week treatment with ledipasvir/sofosbuvir in chronic hepatitis C. J Hepatol. 2018;68(4):663-671.

Centers for Disease Control and Prevention (CDC). Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men – New York City, 2005-2010. MMWR Morb Mortal Wkly Rep. 2011;60:945-50.

Chromy D, Bauer DJM, Simbrunner B, et al. The "Viennese epidemic" of acute HCV in the era of direct-acting antivirals. J Viral Hepat 2022;29(5):385–94.

Danta M, Semmo N, Fabris P, et al. Impact of HIV on host-virus interactions during early hepatitis C virus infection. J Infect Dis. 2008;197:1558-66.

Danta M, Brown D, Bhagani S, et al. and Acute HCV (HAAC) group. Recent epidemic of acute hepatitis C virus in HIV positive men who have sex with men linked to high-risk sexual behaviours. AIDS. 2007;21:983-91.

Darby SC, Ewart DW, Giangrande PL, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. Lancet 1997;350:1425-1431.

Dietz J, Di Maio VC, de Salazar A, et al. Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy. J Hepatol. 2021;74(4):801-810.

European AIDS Clinical Society. EACS Guidelines. Version 11.1. http://eacsociety.org/guidelines/eacs-guidelines/

Eyster ME, Diamondstone LS, Lien JM et al. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immune deficiency virus – a multicenter hemophiliac cohort study. J Acquir Immune Def Syndr 1993;6:602-610.

Giordano TP, Kramer JR, Souchek J, Richardson P, El-Serag HB. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. Arch Intern Med. 2004;164:2349-54.

Gotz HM, van Doormun G, Niesters HG, et al. A cluster with acute hepatitis C virus infection among men who have sex with men – results from contact tracing and public health implications. AIDS 2005;19:969-974.

Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection. Lancet 2003; 356: 1800-1805.

Hézode C. Pan-genotypic treatment regimens for hepatitis C virus: Advantages and disadvantages in high- and low-income regions.J Viral

Hepat. 2017;24(2):92-101.

Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programmes in developing countries. Clin Infect Dis. 2014;58(7):928-36.

Ingiliz P, Christensen S, Kimhofer T, et al. Sofosbuvir and Ledipasvir for 8 Weeks for the Treatment of Chronic Hepatitis C Virus (HCV) Infection in HCV-Monoinfected and HIV-HCV-Coinfected Individuals: Results From the German Hepatitis C Cohort (GECCO-01). Clin Infect Dis. 2016;63(10):1320-1324.

Ingiliz P, Wehmeyer MH, Boesecke C, et al. Reinfection With the Hepatitis C Virus in Men Who Have Sex With Men After Successful Treatment With Direct-acting Antivirals in Germany: Current Incidence Rates, Compared With Rates During the Interferon Era. Clin Infect Dis. 2020;71:1248–54.

Jin F, Prestage GP, Matthews GV, Zablotska I, Rawstorne P, Kippax SC, Kaldor J, Grulich AE. Prevalence, incidence and risk factors for hepatitis C in homosexual men: Data from two cohorts of HIV negative and HIV positive men in Sydney, Australia. Sex Transm Infect. 2010;86:25-8.

Jin F, Matthews GV, Grulich AE. Sexual transmission of hepatitis C virus among gay and bisexual men: a systematic review. Sex Health. 2017;14(1):28-41.

Jones M, Núñez M. HIV and hepatitis C co-infection: the role of HAART in HIV/hepatitis C virus management. Curr Opin HIV AIDS. 2011:6(6):546-52.

Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med 2003;163:2187-2195.

Kaur K, Gandhi MA, Slish J. Drug-Drug Interactions Among Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Medications. Infect Dis Ther. 2015;4(2):159–172.

Kempker RR, Alghamdi WA, Al-Shaer MH, Burch G, Peloquin CA. A Pharmacology Perspective on Simultaneous Tuberculosis and Hepatitis C Treatment. Antimicrob Agents Chemother. 2019; 63(12):e01215-19.

Klein MB, Rockstroh JK, Wittkop L. Effect of coinfection with hepatitis C virus on survival of individuals with HIV-1 infection. Curr Opin HIV AIDS. 2016;11(5):521-526.

Künzler-Heule P, Fierz K, Schmidt AJ, Rasi M, Bogdanovic J, Kocher A, et al. Response to a sexual risk reduction intervention provided in combination with hepatitis C treatment by HCV/HIV co-infected men who have sex with men: a reflexive thematic analysis. BMC Infect Dis;21(1).

Kusejko K, Salazar-Vizcaya L, Shah C, et al. Sustained Effect on Hepatitis C Elimination Among Men Who Have Sex With Men in the Swiss HIV Cohort Study: A Systematic Re-Screening for Hepatitis C RNA Two Years Following a Nation-Wide Elimination Program. Clin Infect Dis 2022;75(10):1723–31.

Martinello M, Bhagany S, Shaw D et al. TARGET3D: Glecaprevir-Pibrentasvir for four weeks in people with recent HCV infection. 30th Conference on Retroviruses and Opportunistic Infections , Seattle; abstract 194.

Mata-Marín JA, de Pablos-Leal AA, Mauss S, et al. Risk factors for HCV transmission in HIV positive men who have sex with men in México. PLoS One. 2022;17(7):e0269977.

Matthews GV, Pham ST, Hellard M, et al. Patterns and characteristics of hepatitis C transmission clusters among HIV positive and HIV negative individuals in the Australian trial in acute hepatitis C. Clin Infect Dis. 2011;52:803-11.

Matthews GV, Bhagani S, Van der Valk M, et al. Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection. J Hepatol. 2021;75(4):829-839.

Mindikoglu AL, Regev A, Magder LS. Impact of human immunodeficiency virus on survival after liver transplantation: analysis of United Network for Organ Sharing database. Transplantation 2008;85:359-68.

Molina JM, Orkin C, Iser DM, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. Lancet. 2015 ;385(9973):1098-106.

Monin MB, Ingiliz P, Lutz T et al. Low Spontaneous Clearance Rates of Recently Acquired Hepatitis C Virus in Human Immunodeficiency Virus-Positive Men Who Have Sex With Men PROBE-C Study. Clin Infect Dis. 2023;76(3):e607-e612.

Naggie S, Marks KM, Hughes M, et al. Sofosbuvir Plus Ribavirin Without Interferon for Treatment of Acute Hepatitis C Virus Infection in HIV-1-Infected Individuals: SWIFT-C. Clin Infect Dis. 2017;64(8):1035-1042.

NEAT, The European AIDS Treatment Network. Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. AIDS. 2011;25:399-409.

Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378:571-83.

Nunez M, Miralles C, Berdun MA, et al. Role of weight-based ribavirin dosing and extended duration of therapy in chronic hepatitis C in HIV-infected patients: The PRESCO trial. AIDS Res Hum Retrovir 2007;23:972-982.

Opravil M, Sasadeusz J, Cooper DA, et al. Effect of baseline CD4 cell count on the efficacy and safety of peg-interferon-α 2a (40 kd) + ribavirin in patients with HIV-HCV coinfection. J Acquir Immune Def Syndr 2008;47:36-49.

Peters L, Mocroft A, Soriano V, et al. Hepatitis C virus coinfection does not influence the CD4 cell recovery in HIV-1-infected patients with maximum virologic suppression. J Acquir Immune Defic Syndr. 2009;50:457-63.

Peters L, Mocroft A, Lundgren J, et al. HIV and hepatitis C co-infection in Europe, Israel and Argentina: a EuroSIDA perspective. BMC Infect Dis. 2014;14(Suppl 6):S13.

Pineda JA, García-García JA, Aguilar-Guisado M, et al. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology. 2007;46:622-30.

Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):797-808.

Popping S, Cuypers L, Claassen MAA, et al. Persistent Transmission of HCV among Men Who Have Sex with Men despite Widespread Screening and Treatment with Direct-Acting Antivirals. Viruses 2022;14(9).

Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. J Infect Dis. 2001;183:134-7.

Qian HZ, Vermund SH, Kaslow RA, et al. Co-infection with HIV and hepatitis C virus in former plasma/blood donors: challenge for patient care in rural China. AIDS 2006;20:1429-1435.

Qurishi N, Kreuzberg C, Lüchters G et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C coinfection. Lancet 2003;362:1708-1713.

Rockstroh JK, Spengler U, Sudhop T, et al. Immunosuppression may lead to progression of hepatitis C virus associated liver disease in hemophiliacs coinfected with HIV. Am J Gastroenterol 1996;91:2563-2568.

Rockstroh JK, Theisen A, Kaiser R, et al. Antiretroviral triple therapy decreases the HIV viral load and does not alter hepatitis C virus serum levels in HCV/HIV-coinfected hemophiliacs. AIDS 1998;12:829-830.

Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly antiretroviral therapy. J Infect Dis 2005;192:992-1002.

Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV, 2015;8:e319–e327.

Rockstroh JK, Ingiliz P, Petersen J, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, in real-world patients with HIV-HCV coinfection and advanced liver disease. Antivir Ther. 2017;22(3):225-236.

Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2017;2(5):347-353.

Rockstroh JK, Lacombe K, Viani RM et al. Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Co-infected with Hepatitis C Virus and Human Immunodeficiency Virus-1: the EXPEDITION-2 Study. Clin Infect Dis. 2018 67(7):1010-1017.

Rosenthal E, Poirée M, Pradier C, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). AIDS. 2003;17(12):1803-9.

Salmon-Ceron D, Rosenthal E, Lewden C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: The French national Mortalité 2005 study. J Hepatol. 2009;50(4):736-45.

Schmidt AJ, Rockstroh JK, Vogel M, et al. Trouble with bleeding: risk factors for acute hepatitis C among HIV positive gay men from Germany – a case-control study. PLoS One 2011;6:e17781.

SeyedAlinaghi S, Jam S, Mehrkhani F, et al. Hepatitis-C and hepatitis-B co-infections in patients with human immunodeficiency virus in Tehran, Iran. Acta Med Iran 2011; 49:252-7.

Smit C, Boyd A, Rijnders BJA, et al. HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study. Lancet HIV 2021;8(2):e96–105.

Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997;26: 1-5.

Stenkvist J, Nyström J, Falconer K, et al. Occasional spontaneous clearance of chronic hepatitis C virus in HIV-infected individuals. J Hepatol. 2014 Oct;61(4):957-61.

Sulkowski NS, Thomas DL, Chaisson RE, Moore D. Hepatotoxicity associated with antiretroviral in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000 283:74-80.

Thomson E, Fleming VM, Main J, et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut. 2011;60:837-45.

Van de Laar T, Pybus O, Bruisten S et al. Evidence of a large, international network of HCV transmission in HIV positive men who have sex with men. Gastroenterology. 2009;136(5):1609-17.

Vogel M, Deterding K, Wiegand J, Grüner NH, Baumgarten A, Jung MC, et al. Hep-Net. Initial presentation of acute hepatitis C virus (HCV) infection among HIV negative and HIV positive individuals-experience from 2 large German networks on the study of acute HCV infection. Clin Infect Dis. 2009;49:317-9.

Weinbaum CM, Sabin KM, Santibanez SS. Hepatitis B, hepatitis C, and HIV in correctional populations: a review of epidemiology and prevention. AIDS 2005; 19 Suppl 3: S41-46.

Wyles DL, Ruane DJ, Sulkowski MS, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. 2015;373(8):714-25.

Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. Lombard study group on vertical HCV transmission. Lancet 1995;345:289-291.

7. Prophylaxis and vaccination against viral hepatitis

Heiner Wedemeyer, Lea Marie Bartsch

Abstract

Despite vaccines or effective anti-viral treatment strategies, hepatotropic viruses are still a global problem. In order to prevent fulminant liver failure or chronic liver disease leading to liver cirrhosis and hepatocellular carcinoma, the prophylaxis and vaccination against hepatotropic viruses is fundamental. Effective vaccines against the hepatitis A and B virus are available world-wide. The hepatitis B virus vaccine was the first one being able to prevent cancer development. Nevertheless, chronic hepatitis B virus infections are still a world-wide burden and functional cure can only be achieved in a minority of chronically infected patients. Thus, further research is a necessity to overcome the viral and immunology challenges to improve our treatment strategies. Due to extremely effective direct-antiviral therapy, the hepatitis C virus can be cured in the majority of the patients. Unfortunately, the vaccine development is hampered by the genetic diversity of the virus, escape mutations and the complex immune responses towards the infection. Knowledge about hepatitis E virus is evolving fast. A vaccine is available in some countries. Fulminant liver failure and chronic course of infection in immune-compromised patients are the main challenges. Thus, collectively, prevention of infection with hepatotropic viruses persist as the best option to prevent liver diseases.

Introduction

Understanding of the biology and modes of transmission of hepatitis viruses has significantly improved over the last decades. Even so, prophylactic vaccines are only available for hepatics A (HAV) and B (HBV). Although an enormous amount of basic and clinical research has been performed in trying to develop a vaccine against hepatitis C (HCV), it is unlikely that either a prophylactic or therapeutic HCV vaccine will be available soon. A phase 3 vaccine trial against hepatitis E (HEV) in China resulted in the vaccine being licensed there; it is currently unknown whether or when this vaccine will become available broadly across the globe. Prophylaxis of HCV, HDV (for patients) and HEV infection therefore

involves avoiding the routes of exposure to the respective hepatitis viruses discussed in detail in *Chapters 1–4*.

Prophylaxis of infections with hepatitis viruses

Hepatitis A and E

HAV and HEV are usually transmitted by oral ingestion of contaminated food or water. Acute HEV infection is often asymptomatic in immunocompetent individuals. Nevertheless, some people can develop fulminant liver failure and the risk factors are not yet fully understood. Immune compromised people for example after organ transplantation can progress to chronic HEV infection leading to advanced liver fibrosis (EASL 2018). Thus, caution is warranted when individuals from low endemic areas such as Western Europe and the US travel to countries with a high prevalence of HAV and HEV. Several outbreaks of HEV infection have occurred in different regions of the world and were associated with significant morbidity and mortality, e.g., the recent outbreaks of HEV in refugee camps in Africa.

In addition, HEV (but not HAV) can also be a zoonosis. Consumption of offal and wild boar is associated with a risk for HEV infection. HEV has frequently been detected in the pork and occupational exposure has frequently been identified as a risk factor for being anti-HEV positive (Pischke 2014). Importantly, zoonotic HEV is usually caused by HEV genotype 3 while HEV genotype 1 can be found in travel associated HEV (Wedemeyer 2012, Kamar 2017). *In vitro* experiments have shown that HEV is heat sensitive (> 70°C; > 2 min), but it remains unclear whether heat can be used to sterilise food preparation (Johne 2016). The avoidance of the consumption of certain food is the best prevention strategy especially for people who are immune compromised or at risk for a fulminant acute infection to prevent HEV infection (EASL 2018).

HAV (Hettman 2016) and HEV can also be transmitted by blood transfusion as confirmed in a large study from England screening more than 200.000 blood products (Hewitt 2014). Of note, up to 12% of pooled plasma products can contain HEV RNA in Europe. The overall relevance of HEV transmission by blood products is discussed in more detail in Chapter 4. Distinct genetic polymorphisms may be associated with the risk of becoming infected with HAV (Zhang 2012) and HEV (Wedemeyer 2012). To prevent HEV infection and the complications of chronic liver disease of a very vulnerable cohort, a policy statement of the EASL of 2019 recommends a selective screening of blood products for HEV RNA for immune compromise patients e.g. patients who received an organ transplantation.

However, even if HEV RNA screening is performed by HEV RNA testing, this is usually performed in pooled samples resulting in a remaining risk for HEV transmission if high volume plasma products are transfused (Cordes 2022). Thus, the risk of transfusion-transmitted hepatitis E in these patients may not be sufficiently controlled by mini-pool HEV RNA screening. Single donor screening should therefore be considered to improve the safety of blood products.

Sexual transmission of HEV is poorly studied. Some studies highlight a sexual transmission in men who have sex with men (Montella 1994, Payne 2013). HEV can be detected in ejaculate of chronically infected men (Horvatits 2021). The use of condoms could be an effective strategy to prevent infection (EASL 2019).

HEV is excreted in the stool and thereby extremely infectious. In many patients, HEV is also detectable in urine (Stahl 2023). Though, the relevance on the transmission is not fully understood yet (Geng 2016).

Hepatitis B and D

HBV and HDV were frequently transmitted by blood transfusion before HBsAg testing of blood products was introduced in the 1970s. Since then, vertical transmission and sexual exposure have become the most frequent routes of HBV infection. Medical procedures still represent a potential source for HBV and thus strict and careful application of standard hygienic precautions for all medical interventions are mandatory, and not only in endemic areas.

Immune compromised individuals are particularly susceptible to HBV infection as HBV is characterised by very high infectivity. Moreover, immunosuppressed patients are at risk for reactivation of occult HBV after serological recovery from HBV. Treatments with high doses of steroids and rituximab have especially been identified as major risk factors for HBV reactivation. The FDA and all scientific associations highlight attention to the potential risk for fatal HBV reactivations in patients receiving B cell depleting therapies (EASL 2017). However, also other immunosuppressive drugs may lead to increased HBV replication. Thus, immune compromised individuals would benefit most from effective HBV prevention. All patients receiving immune modulating agents should be screened for HBsAg and anti-HBc. The need for pre-emptive antiviral differs according to the HBV serostatus (anti-HBs positive or negative, HBsAg positive or negative) and the level of immunomodulation induced by the respective drug (Perillo 2015). The reactivation in HBsAg positive patients differs depending on the therapy and it is up to 75% after bone marrow transplantation. Among the complications of HBV reactivation, fulminant courses with liver failure and

death are the most severe (Cornberg 2021).

To prevent infection after a positive test of a family member or sexual partner, the patients need to be tested for their immune status against HBV. Immediate active vaccination is recommended for contacts who are anti-HBc negative. HBsAg positive individuals should use condoms during sexual intercourse if it is not known whether the partner has been vaccinated. Non-immune individuals who have experienced an injury and were exposed to HBsAg positive fluids should undergo passive immunisation with anti-HBs as soon as possible, preferentially within 2–12 hours (Cornberg 2021).

Infant HBV infections develop to a chronic stage in 90% of the cases. Thus, it is tremendously important to prevent perinatal infection and HBV infection during early childhood. To prevent vertical infection during pregnancy, an HBV screening should be performed in the first trimester. Women with high HBV viraemia of 200.000 IU/mL or more, should receive antiviral therapy with a potent HBV polymerase inhibitor during their pregnancy (EASL 2017, Pan 2025, Li 2018). Randomised trials showed that both tenofovir (Pan 2016) and telbivudine (Han 2011, Wu 2015) can reduce the risk for vertical HBV transmission when antiviral treatment is started during the third trimester of pregnancy. Tenofovir and telbivudine have been classified as category B drugs by the FDA and can therefore be given during pregnancy. HBV positive pregnant women should continue their anti-viral medication, but it might be necessary to exchange the medication to tenofovir or telbivudine (EASL 2017). A caesarean section is not recommended for women with low viral load or under anti-viral therapy but could be beneficial to prevent transmission if the viral load exceeds 200 000 IU/mL (Cornberg 2021, Pan 2013). Recent guidelines also recommend that breat-feeding can be continued if antiviral therapy is administered (EASL 2025, in press).

Hepatitis C

An important factor in preventing HCV infection is screening the population to prevent further transmission. HCV infection can be asymptomatic for a long period of time so that many people are not aware of their infection. Screening should be performed regarding local epidemiology and risk factors of the individuals (Cooke 2019, EASL guidelines 2020). The treatment of HCV positive patients is one important strategy to prevent onward infection ("treatment as prevention"), this is particularly important for individuals with risk factors of infection (EASL 2020). Several studies confirmed the efficacy and safety of direct acting antivirals also in patients with acute ore recent HCV infection (Deterding 2017, Cornberg 2025).

Less than 1% of individuals who are exposed to HCV by an injury with contaminated needles develop an acute HCV infection. For example, in the early 2000s 166 occupational HCV exposures have been reported over a period of 6 years at Hannover Medical School and for none of the cases a seroconversion has been observed during a 6 year follow-up. A systematic literature review identified 22 studies including a total of 6956 injuries with HCV contaminated needles. Only 52 individuals (0.75%) became infected. The risk of acute HCV was lower in Europe at 0.42% compared to eastern Asia at 1.5% (Kubitschke 2007). Thus, the risk of acquiring HCV infection after a needle-stick injury is lower than frequently reported. Global differences in HCV seroconversion rates may suggest that genetic factors provide some level of natural protection. Indeed, distinct polymorphisms have been identified that are associated either with protection from HCV or with a higher likelihood of recovering spontaneously from acute HCV (Schaefer 2011). Factors associated with a higher risk of HCV transmission are likely to be HCV viraemia in the index patient, the amount of transmitted fluid and the duration between contamination of the respective needle and injury. Suggested follow-up procedures after needle stick episode include:

- Testing for HCV RNA immediately and an ALT testing.
- If possible, HCV RNA quantification in the serum of index patient.
- There is no need for prophylactic treatment with IFN and ribavirin or direct acting antivirals.
- HCV RNA testing should be performed after 2 and 4 weeks; if the results are negative, HCV RNA testing should be repeated at weeks 6 and 8.
- After 12 and 24 weeks, anti-HCV and ALT levels should be determined; if the results are out of range or positive, HCV RNA testing should be performed.

On the other hand, individuals who consume intravenous drugs have a high risk of HCV infection if they share their equipment e.g. syringes, needles etc. (Simmons 2016, Hahn 2002). Long term strategies should be implemented to avoid HCV transmission by reducing frequency of injections, using new sterile needles (e.g. in needle syringe service programmes), avoiding re-use of materials, disposing materials safely, opioid substitution programmes, medical support and counseling of possible re-infection (Tsui 2014, Hagan 2011, Platt 2017, Grady 2013).

Sexual transmission has clearly been identified as a risk for HCV, as about 10–20% of patients with acute HCV report this as having been a potential risk factor (Deterding 2009). However, there is also evidence that the risk of acquiring HCV sexually is extremely low in individuals in stable partnerships who avoid injuries: Cohort studies including more than 500 HCV positive patients followed over periods of more than four years could not identify any cases of confirmed HCV transmission. The risk for HCV

transmission has recently been estimated to be about 1 per 190,000 sexual contacts in monogamous relationships (Terrault 2013). Having multiple sexual partners increases the risk of HCV infection (Tohme 2010). There was no association between specific sexual practices and HCV infection in monogamous heterosexual couples. Thus, current guidelines do not recommend the use of condoms in monogamous heterosexual relationships (EASL 2020). Risk of sexual transmission of HCV is increased in men who have sex with men. Several outbreaks of acute HCV have been described in this population (Boesecke 2012, Bradshaw 2013). Transmission of HCV was associated with more sexual partners, increased levels of high-risk sexual behavior (in particular fisting) and were more likely to have shared drugs via a nasal or anal route than controls (Newson 2020). The CDC recommends certain prevention strategies (CDC 1998). In long-term monogamous relationship regular testing should be performed but the sexual behavior does not need to be altered. In other settings use of latex condoms plus reduction of injuries and bleeding is highly effective to avoid HCV transmission. Besides to "treatment as prevention", education to increase the awareness of risk factors is extremely important.

Due to the low HCV prevalence in most European countries and a relatively low vertical transmission rate of 1–6%, general screening of pregnant women for anti-HCV is not recommended. The German guidelines only recommend screening for individuals with a high risk of HCV infection. The U.S. Preventive Services Task Force and CDC recommends universal HCV screening of all adults, including all pregnant women (CDC 2018). Interestingly, vertical transmission may be higher for girls than for boys (European Paediatric Hepatitis C Virus Network 2005). Transmission rates are higher in HIV positive women, so these women should be tested for HCV. Other factors possibly associated with high transmission rates are the level of HCV viraemia, maternal intravenous drug use, and the specific HLA types of the children. Immunoregulatory changes during pregnancy reduce the pressure by cytotoxic T cells which may select viruses with optimised replication fitness and thereby facilitate vertical transmission (Honegger 2013, Coss 2020). Cesarean sections are not recommended for HCV RNA positive mothers as there is no clear evidence that these reduce transmission rates. It is not clear yet whether direct-acting antivirals (DAAs) against HCV can reduce transmission rates of HCV when given during the last trimester of pregnancy. HCV therapy should be considered in all HCV positive women who want to become pregnant (EASL 2020). Children of HCV positive mothers should be tested for HCV RNA after one month as maternal anti-HCV antibodies can be detected for several months after birth. Mothers with chronic HCV can breastfeed their children if they are HIV negative, do not have any breast injuries and do not use intravenous drugs (European Paediatric Hepatitis C Virus Network 2001, EASL 2020). This clinical recommendation is supported by experimental data showing inactivation of HCV by human breast milk in a dose dependent manner. Of note this effect is specific to human breast milk and the mechanism is destruction of the lipid envelope but not of viral RNA or capsids (Pfaender 2013).

Vaccination against HAV

The first active HAV vaccine was licensed in 1995 and currently there are multiple inactivated and live-attenuated vaccines available (Martin 2006).

The currently available inactive vaccines are manufactured from cell culture adapted HAV, grown either in human fibroblasts or diploid cells (Nothdurft 2008). Two doses of the vaccine are recommended. The second dose should be given between 6 and 18 months after the first dose. All vaccines are highly immunogenic and all vaccinated healthy persons develop protective anti-HAV antibodies. Similar vaccine responses are obtained in both children and adults and no relevant regional differences in response to HAV vaccination have been observed. The weakest vaccine responses have been described for young children receiving a 0, 1 and 2 month schedule (Hammitt 2008). Of note, maternal anti-HAV positive children vaccinated at age 6 months have lower vaccine responses and are less likely to maintain HAV antibodies through age 10 years (Spradling 2016). Patients with chronic liver disease do respond to vaccination but may display lower anti-HAV titres (Keeffe 1998). HAV vaccination in HIV positive people is more effective if HIV replication is already suppressed by antiretroviral therapy and patients have higher CD4+ T-cell counts (Tseng 2013).

A combined vaccine against HAV and HBV is available that needs to be administered three times, on a 0, 1, and 6 months schedule. More than 80% of healthy individuals have detectable HAV antibodies by day 21 applying an accelerated vaccine schedule of 0, 7 and 21 days using the combined HAV/HBV vaccine, and all study subjects were immune against HAV by 2 months (Kallinowski 2003). HAV vaccines are very well tolerated, and no serious adverse events have been linked with the administration of HAV vaccines (Nothdurft 2008). The vaccine can safely be given together with other vaccines or immunoglobulins without compromising the development of protective antibodies. Vaccination is recommended for non-immune individuals who plan to travel to endemic countries, medical health professionals, men who have sex with men, people in contact with patients with HAV, and individuals with chronic liver diseases. Some studies have suggested that patients with chronic HCV have a higher risk of developing fulminant HAV (Vento 1998), although this finding has not been confirmed by other investigators (Deterding 2006). The recommendation to vaccinate all patients with HCV against HAV has recently been challenged. A meta-analysis including

studies on mortality from HAV in people with HCV revealed a number-needed-to-vaccinate to prevent one death of more than 800,000 (Rowe 2012), thus questioning the use of routine HAV vaccination in HCV positive people. The implementation of childhood vaccination programmes has led to significant and impressive declines of HAV infections in several countries, justifying further efforts aiming at controlling the spread of HAV in endemic countries (Hendrickx 2008). It is important to highlight that most studies have confirmed that HAV vaccination is cost-effective (Rein 2008, Hollinger 2007). Several long-term follow-up studies after complete HAV vaccinations have been published in recent years (Stuurman 2016). Anti-HAV titres usually decline during the first year after vaccination but remain detectable in almost all individuals for at least 10–15 years after vaccination (Van Herck 2011) which also has been confirmed by systematic reviews (Ott 2012). Based on these studies it was estimated that protective anti-HAV antibodies should persist for ≥30 years after successful vaccination (Hammitt 2008, Bovier 2010, Spradling 2016).

A single dose administration of an inactivated HAV vaccine can induce protective antibody levels which can persist for more than 10 years (Ott 2012). Argentina, Brazil and Russia, as countries with a high incidence of hepatitis A infection in children causing liver failure and being the leading cause of liver transplantation, implemented a single dose vaccine programme. In these countries a single dose vaccine seems to be an effective method to reduce liver failure, but effectiveness of this approach needs to be closely monitored which would be cost saving and increase overall vaccine coverage (Brito 2020, Mikhailov 2020, Vizzotti 2014).

Live-attenuated hepatitis A vaccines are approved in China, India and a few other countries (Fangcheng 2012). Studies showing the efficacy and longevity of these vaccines were only performed in China and demonstrated a 93% effectiveness to prevent HAV infection and IgG antibodies in 72-88 % of the participants 15 years after the single dose vaccine (Irving 2012, Zhao 2000).

Vaccination against HBV

The HBV vaccine was the first vaccine able to reduce the incidence of cancer. In Taiwan, a significant decline in cases of childhood hepatocellular carcinoma (HCC) has been observed since the implementation of programmes to vaccinate all infants against HBV (Chang 1997). This landmark study impressively highlighted the usefulness of universal vaccination against HBV in endemic countries. The findings were confirmed in various additional studies and a reduced incidence of HCC not only in infants but also in young adults has been shown in a 30 year follow-up of a randomised neonatal vaccination study (Qu 2014). Controversial discussions are ongoing regarding to what extent universal vaccination against HBV may be cost-effective in low-endemic places such as the UK, the Netherlands or Scandinavia (Zuckerman 2007). In 1992 the World Health Organization recommended general vaccination against HBV. It should be possible to eradicate HBV by worldwide implementation of this recommendation, because humans are the only epidemiologically relevant host for HBV. The first plasma-derived HBV vaccine was approved by FDA in 1981. Recombinant vaccines consisting of HBsAg produced in yeast became available in 1986. In the US, two recombinant vaccines have been licensed (Recombivax and Engerix-B) while additional vaccines are used in other countries. The vaccines are administered three times, on a 0, 1, and 6 month timetable. The third-generation vaccines Heplisav-B and PreHevbrio/PreHevbri have been approved by FDA and EMA and show higher vaccine efficacy, especially in subgroups that respond sub-optimally to conventional hepatitis B vaccines.

Who should be vaccinated? This list is based on the German Guidelines for Hepatitis B and can be considered as a recommendation for most countries (Cornberg 2021).

- HBV high-risk persons working in health care settings including trainees, students, cleaning personnel;
- Personnel in psychiatric facilities or comparable welfare institutions for cerebrally damaged or disturbed patients; other people who are at risk because of blood contact with people who are possibly infected depending on the risk evaluation, e.g., persons giving first aid professionally or voluntarily, employees of ambulance services, police officers, social workers, and prison staff who have contact with drug addicts;
- People with chronic kidney disease, dialysis patients, patients with frequent blood or blood component transfusions (e.g., haemophiliacs), patients prior to extensive surgery (e.g., before operations using heart-lung machine. The urgency of the operation and the patient's wish for vaccination protection are of primary importance);
- People with chronic liver disease including chronic diseases with liver involvement as well as HIV positive people without HBV markers;
- People at risk of contact with HBsAg carriers in the family or shared housing, sexual partners of HBsAg carriers;
- Patients in psychiatric facilities or residents of comparable welfare institutions for cerebrally damaged or disturbed persons as well as persons in sheltered workshops;
- Special high-risk groups, e.g., men who have sex with men, people who inject drugs (PWID), sex workers, prisoners serving extended sentences;

- People at risk of being in contact with HBsAg carriers in facilities (kindergarten, children's homes, nursing homes, school classes, day care groups);
- People travelling to regions with high HBV prevalence for an extended period of time or with expected close contact with the local population;
- People who have been injured by possibly contaminated items, e.g., needle puncture (see post-exposition prophylaxis);
- Infants of HBsAg positive mothers or of mothers with unknown HBsAg status (independent of weight at birth) (see post-exposition prophylaxis);
- Routine testing for previous contact with HBV is not necessary before vaccination unless the person belongs to a risk group and may have acquired immunity against HBV before. Pre-vaccine testing is usually not cost-effective in populations with an anti-HBc prevalence below 20%. Vaccination of HBsAg positive individuals can be performed without any danger – however, it is ineffective.

Efficacy of vaccination against HBV

A response to HBV vaccination is determined by the development of anti-HBs antibodies, detectable in 90–95% of individuals one month after a complete vaccination schedule (Coates 2001). Responses are lower in elderly people and much weaker in immunocompromised persons such as organ transplant recipients, patients receiving haemodialysis and HIV positive individuals who have low CD4 counts. In case of vaccine nonresponse, another three courses of vaccine should be administered, and the dose of the vaccine should be increased. Other possibilities to increase the immunogenicity of HBV vaccines include intradermal application and co-administration of adjuvants and cytokines (Cornberg 2021). The response to vaccination should be monitored in high-risk individuals such as medical health professionals and immunocompromised persons. Some guidelines also recommend testing elderly persons after vaccinations as vaccine response does decline more rapidly in the elderly (Wolters 2003).

Post-exposure prophylaxis

People who are not immune who have been in contact with HBV contaminated materials (e.g., needles) or who have had recent sex with an HBV positive person should undergo active-passive immunisation (active immunisation plus HBV immunoglobulin) as soon as possible – preferentially within the first 48 hours of exposure to HBV. Individuals previously vaccinated but who have an anti-HBs titre of <10 IU/L should also be vaccinated both active and passive. No action is required if an anti-HBs titre of 100 IU/L is documented; active vaccination alone is sufficient for persons with intermediate anti-HBs titres between 10 and 100 IU/L (Cornberg 2021).

Safety of HBV vaccines

Several hundred million individuals have been vaccinated against HBV. The vaccine is very well tolerated. Injection site reactions in the first 1 to 3 days and mild general reactions are common, although they are usually not long lasting. Whether there is a causal relationship between the vaccination and the seldom observed neurological disorders occurring around the time of vaccination is not clear. In the majority of these case reports the concomitant events most likely occurred coincidentally and are independent and not causally related. That HBV vaccination causes and induces acute episodes of multiple sclerosis or other demyelinating diseases have been repeatedly discussed 10 to 15 years ago (Geier 2001, Hernan 2004, Girard 2005). However, there is no scientific proof of such a relationship. Numerous studies have not been able to find a causal relationship between the postulated disease and the vaccination (Sadovnick 2000, Monteyne 2000, Ascherio 2001, Confavreux 2001, Schattner 2005).

Long-term immunogenicity of HBV vaccination

Numerous studies have been published in recent years investigating the long-term efficacy of HBV vaccination. After 10 to 30 years, between one third and two thirds of vaccinated individuals have completely lost antiHBs antibodies and only a minority maintain titres of >100 IU/L. However, in low/intermediate endemic countries such as Italy, this loss in protective humoral immunity did not lead to many cases of acute or even chronic HBV infection (Zanetti 2005). To what extent memory T cell responses contribute to a relative protection against HBV in the absence of anti-HBs remains to be determined. Nevertheless, in high-endemic countries such as Gambia, a significant proportion of vaccinated infants still seroconvert to antiHBc indicating active HBV infection (18%) and some children even develop chronic HBV (van der Sande 2007). A very high efficacy of a single booster vaccine after 15 to 30 years has been shown in several studies (e.g. Su 2013, Bruce 2016) suggesting that immune memory is maintained in the majority of initial vaccine responders. However, protective titres are frequently lost

again a few years after booster vaccination. Overall, these data indicate that no regular HBV booster doses are recommended in vaccine responders. Still, booster vaccinations should be considered in persons at risk including medical health professionals.

Prevention of vertical HBV transmission

Infants of HBsAg positive mothers should receive an active and passive immunisation within 12 hours of birth. Thereby, vertical HBV transmission rate can be reduced from 95% to 5% (Ranger-Rogez 2004). If active/passive immunisation can be performed, there is no need to recommend cesarean section (Wong 2014). Mothers of vaccinated infants can breastfeed even if antiviral medications against HBV are being taken by the mother (EASL 2025 HBV Clinical Practice Guidelines).

New HBV vaccines

Although available vaccines are already very effective, new vaccine strategies have been shown to improve the vaccine response of elderly people or individuals with a low antibody reaction towards the available mono-antigenic vaccines. A detailed summary of currently available and recently approved vaccines against HBV is given in the current version of the EASL HBV Clinical Practice Guidelines (EASL 2025, in press).

Vaccination against HCV

Despite the vastly improved anti-viral treatment strategies against HCV, there are no prophylactic or therapeutic vaccines against HCV available at the moment. HCV elimination will be very unlikely with HCV treatments alone (Razavi 2025) – thus an effective and safe HCV vaccination is highly warranted to prevent HCV spreading in high-risk groups.

Vaccine development is hampered by the genetic diversity of the virus, escape mutations and the complex immune responses towards the infection. The host-virus interaction including cellular and humoral immunity determines the outcome of infection. HCV leads to a chronic course of infection in the majority of individuals, although 25-40% of infected individuals can clear the infection spontaneously (Mosley 2008). Spontaneous viral clearance is much higher after re-infection with HCV (Sacks-Davis 2013). HCV specific T cell responses play an important role in the natural course of HCV infection. The adaptive T cell response is mediated by both CD4+ helper T cells and CD8+ killer T cells. As CD8+ T cells have effector functions and destroy the target cells, CD4+ T cells are important to establish a long-lasting T cell memory pool and contribute to the longevity of the humoral immune response (Laidlaw 2016, Zhang 2019). Several studies have consistently found an association between a strong, multispecific and maintained HCV specific CD4+ and CD8+ T cell response and the resolution of acute HCV infection (Rehermann 2013). While CD4+ T cells seem to be present for several years after recovery, there is conflicting data whether HCV specific CD8+ T cell responses persist or decline over time (Wiegand 2007). Studies in chimpanzees have demonstrated that CD4+ and CD8+ specific T cells are mandatory for spontaneous viral clearance, as the absence of one of the subpopulations lead to persistent infection (Grakoui 2003, Shoukry 2003).

However, several studies have observed durable HCV specific T cells in HCV negative individuals who were exposed to HCV by occupational exposure or as household members of HCV positive partners, but who never became HCV RNA positive. A 10-year longitudinal study involving 72 healthcare workers demonstrated that about half of the individuals developed HCV specific T cell responses, detectable most frequently four weeks after exposure (Heller 2013). These observations suggest that HCV specific T cells may be induced upon subclinical exposure and may contribute to protection against clinically apparent HCV infection. However, it could be possible that repeated subinfectious exposure to HCV may not protect from HCV but rather increase susceptibility by expansion of regulatory T cells which suppress effector T cell responses in case of an infection (Park 2013). Virus specific T cells are usually detected at a lower frequency during chronic HCV infection and have an impaired functionality in comparison virus specific T cells during acute HCV infection. Different mechanisms contribute to the impaired T cell effector function, including higher frequencies of regulatory T cells, altered dendritic cell activity, upregulation of inhibitory molecules such as PD-1, CTLA-4 or 2B4 on T cells and escape mutations. In addition, HCV peptides can directly or indirectly contribute to altered functions of different immune cells (Rehermann 2013, Owusu Sekyere 2015).

The contribution of the humoral immune response to spontaneous clearance of HCV infection has not yet been clearly clarified. Higher levels of neutralising antibodies early during the infection are associated with viral clearance (Pestka 2007). These early neutralising antibodies detect a narrow epitope variety against the original virus without covering escape mutations (Walker 2019, Gu 2018). Broadly neutralisation antibodies develop with a delay in chronic HCV infection which might contribute to ineffective or delayed viral clearance (Dowd 2009, Law 2008). Although, cross-reactive neutralising antibodies are detectable in chronic infection they are not potent to clear the virus but are associated with less severe

liver fibrosis (Swann 2016). The understanding of development of broadly neutralising antibodies against HCV has improved in recent years e.g. by studying antibodies from HCV elite neutralisers (Weber 2022). This opens the idea of creating *de novo* highly potent neutralising antibodies which may also be generated *in vivo* as an alternative vaccination strategy.

A large HCV vaccine trial based on recombinant viruses expressing HCV proteins has been conducted in 548 individuals at risk for HCV infection with the aim to prevent chronicity of HDV infection by induction of HCV-specific T cell responses (Page 2021). This trial was negative regarding the primary endpoint, which was defined as HCV viraemia for 6 months. Still, peak viraemia was significantly lower in vaccinated individuals in whom HCV-specific T cell responses were detected in more than three quarter of vaccinated persons. Future vaccine development against HCV may be accelerated with controllend human infection models which are currently being explored in different settings (Liang 2021, Barnes 2023, Feld 2023).

Vaccination against HEV

A phase 2 vaccine trial performed in Nepal with 2000 soldiers showed a 95% efficacy for an HEV recombinant protein (Shrestha 2007). However, the development of this vaccine was stopped. In September 2010, data from a very large phase 3 trial were reported involving about 110,000 individuals in China (Zhu 2010). The vaccine efficacy of HEV-239 was 100% after three doses to prevent cases of symptomatic acute HEV. Further observation confirmed the ability of the vaccine to prevent clinical hepatitis. However, the induction of HEV antibodies does not induce sterilising immunity and thus does not completely protect from HEV infection. Still, vaccination largely reduces infection rates with a RR of 0.15 during further follow-up of the Chinese vaccine trial (Huang 2014). Similarly, naturally acquired immunity against HEV does not provide complete protection (Huang 2014). A 10 year follow-up of the phase 3 vaccine study was published in 2024 confirming long-lasting protection from symptomatic hepatitis E infections (Huang 2024). It remains to be formally determined if the HEV genotype 1-derived vaccine also prevents against zoonotic HEV genotype 3, while the vaccine was effective in China against HEV genotype 4. HEV-specific T cell immunity has been shown to be cross-HEV genotype-specific in patients with acute HEV (Gisa 2016). One can therefore assume that the vaccine should induce pan-genotypic immunity. Still, preclinical studies in pig models with other vaccine candidates suggested that cross-genotype induced complete protection from infection may be difficult to achieve (Dähnert 2024). Moreover, vaccine efficacy in special risk groups such patients with end-stage liver disease, immunocompromised individuals or elderly persons are unknown. Finally, the duration of protection needs to be determined as antibody titres have been shown to decline after vaccination (Shrestha 2007, Zhu 2010). To what extent cellular immunity against HEV is important in the context of HEV vaccination is also unknown but HEV specific T cell response has been associated with the control of chronic (Suneetha 2012) and acute (Gisa 2016, Brown 2016) HEV infection. It is currently unknown if and when the vaccine HEV-239 will become available in other countries. Until then, preventive hygienic measures remain the only option to avoid HEV infection. There are currently many efforts from the Word Health Organization to reach the "emergency prequalification" for the vaccine in order to prevent outbreaks in high-risk areas such as refugees camps.

Recently, broadly neutralising antibodies have been identified conferring protection against HEV infection *in vitro* against different HEV genotypes and also against enveloped virions. The antibodies also prevented durable HEV infection in a chimeric mouse model. The clinical development of these antibodies could be an option both to treat chronic HEV infection as well as a strategy to protect individuals at risk for acute severe infection by passive immunisation (Ssebyatika 2025). HEV-induce acute-on-chronic liver failure is an emerging threat considering the increasing prevalence of liver cirrhosis due to metabolic dysfunction-associated steatotic liver disease in regions with very frequent HEV exposures.

Outlook

Hepatitis A virus: Effective vaccine strategies are available. Though, current vaccines require a three-dose regimen which is rather unpractical in most parts of the world with highest incidences. Current efforts are on the way to investigate the efficiency and the longevity of a one dose regimen, which would reduce cost and could dramatically increase vaccine acceptance and availability. Furthermore, a greater understanding of the routes of infection may lead to improved prevention campaigns.

Hepatitis B virus: Although the vaccination is very effective for most individuals, around 5 % of all vaccinees do not develop a measurable humoral response to current vaccines. The development of novel vaccines with different antigens and adjuvants offers the opportunity to improve the protection of a very vulnerable cohort. More data on requirements for booster vaccinations are needed both for individuals after infant or childhood vaccination as well as for persons who have been vaccinated as adults.

Hepatitis C virus: The complex immune response and viral strategies to evade the immune system e.g. by viral mutations, impedes the development of a vaccine. First promising preclinical and clinical trials were performed.

Novel vaccine strategies are currently in pre-clinical development. Until vaccines become available, access to antiviral treatment both for chronically as well as recently infected individuals is critical to prevent further spreading of the virus.

Hepatitis E virus: As the virus can be detected urine and in blood, a better understanding of spreading of the virus within families and close contact persons is needed. Correlates of protection are also not well understood as well as duration of immune responses after exposure and infection or vaccination. As the solitary vaccine with phase 3 data is available in China and few other countries only, additional efforts are needed to develop vaccines against HEV. The development of neutralising antibodies would be valuable that could be used in a passive vaccination strategy for high-risk groups such as immunocompromised individuals. The protection of active or passive vaccination strategies across against different HEV genotypes will be another challenge.

References

Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med. 2001;344:327-32.

Barnes E, Cooke GS, Lauer GM, Chung RT. Implementation of a controlled human infection model for evaluation of HCV vaccine candidates. Hepatology. 2023;77:1757-1772.

Boesecke C, Rockstroh JK. Acute hepatitis C in patients with HIV. Semin Liver Dis. 2012;32:130-7.

Bovier PA, Bock J, Ebengo TF, et al. Predicted 30-Year Protection After Vaccination With an Aluminum-Free Virosomal Hepatitis A Vaccine. J Med Virol. 2010;82:1629-34.

Bradshaw D, Matthews G, Danta M. Sexually transmitted hepatitis C infection: the new epidemic in MSM? Curr Opin Infect Dis. 2013;26:66-72.

Brito WI, Souto FJD. Universal hepatitis A vaccination in Brazil: analysis of vaccination coverage and incidence five years after program implementation. Vacinação universal contra hepatite A no Brasil: análise da cobertura vacinal e da incidência cinco anos após a implantação do programa. Rev Bras Epidemiol. 2020;23:e200073.

Brown A, Halliday JS, Swadling L, et al. Characterization of the Specificity, Functionality, and Durability of Host T-Cell Responses Against the Full-Length Hepatitis E Virus. Hepatology. 2016;64:1934-1950.

Bruce MG, Bruden D, Hurlburt D, et al. Antibody Levels and Protection After Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose. J Infect Dis. 2016;214:16-22.

Centers for Disease Control and Prevention (CDC). National Notifiable Diseases Surveillance System (NNDSS). Hepatitis C, Perinatal Infection: 2018 Case Definition. (Hepatitis C, Perinatal Infection 2018 Case Definition | CDC)

Centers for Disease Control (CDC). Investigation of hepatitis E outbreak among refugees – South Sudan 2012-2013. MMWR Morb Mortal Wkly Rep. 2013;62:581-6.

Centers for Disease Control. Recommendations for the prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep. 1998;47(RR-19):1-39.

Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med. 1997;336:1855-9.

Coates T, Wilson R, Patrick G, Andre F, Watson V. Hepatitis B vaccines: assessment of the seroprotective efficacy of two recombinant DNA vaccines. Clin Ther 2001;23:392-403.

Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. N Engl J Med 2001;344:319-26.

Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2019;4:135-184.

Cordes AK, Goudeva L, Lütgehetmann M, et al. Risk of transfusion-transmitted hepatitis E virus infection from pool-tested platelets and plasma. J Hepatol. 2022;76:46-52.

Cornberg M, Wedemeyer H. Early treatment of acute or recently acquired hepatitis C: An important tool on the path to HCV elimination! Hepatology. 2025;81:771-773.

Cornberg M, Sandmann L, Protzer U, et al. S3-Leitlinie der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) zur Prophylaxe, Diagnostik und Therapie der Hepatitis-B-Virusinfektion – (AWMF-Register-Nr. 021-11). Z Gastroenterol. 2021;59:691-776.

Coss SL, Torres-Cornejo A, Prasad MR, et al. CD4+ T cell restoration and control of hepatitis C virus replication after childbirth. J Clin Invest. 2020;130:748-753.

Dähnert L, Aliabadi E, Fast C, et al. Immunisation of pigs with recombinant HEV vaccines does not protect from infection with HEV genotype 3. One Health. 2024;18:100674.

Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis. 2017;17:215-222.

Deterding K, Wiegand J, Gruner N, et al. The German Hep-Net acute hepatitis C cohort: impact of viral and host factors on the initial presentation of acute hepatitis C virus infection. Z Gastroenterol. 2009;47:531-40.

Deterding K, Tegtmeyer B, Cornberg M, et al. Hepatitis A virus infection suppresses hepatitis C virus replication and may lead to clearance of HCV. J Hepatol. 2006;45:770-8.

Dowd KA, Netski DM, Wang XH, Cox AL, Ray SC. Selection pressure from neutralizing antibodies drives sequence evolution during acute infection with hepatitis C virus. Gastroenterology. 2009;136:2377-2386.

European Association For The Study Of The Liver. EASL 2025 Clinical Practice Guidelines Hepatitis B. J Hepatol. 2025;in press.

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020;73:1170-1218.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol. 2018;68:1256-1271.

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-398.

European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66:153-194.

European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167-185.

European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. BJOG. 2001;108:371-7.

European Paediatric Hepatitis C Virus Network. A significant sex – but not elective cesarean section – effect on mother-to-child transmission of hepatitis C virus infection. J Infect Dis. 2005;192:1872-9.

FDA Pregnancy Exposure Registries. Science and Research. (https://www.fda.gov/Science-Research/ science-and-research-special-topics/ womens-health-research)

Feld JJ, Bruneau J, Dore GJ, et al. Controlled Human Infection Model for Hepatitis C Virus Vaccine Development: Trial Design Considerations. Clin Infect Dis. 2023;77:S262-S269.

Geier MR, Geier DA. Immunologic reactions and hepatitis B vaccine. Ann Intern Med. 2001;134:1155.

Fangcheng Z, Xuanyi W, Mingding C, et al. Era of vaccination heralds a decline in incidence of hepatitis A in high-risk groups in China. Hepat Mon. 2012;12:100-105.

Geng Y, Zhao C, Huang W, et al. Detection and assessment of infectivity of hepatitis E virus in urine. J Hepatol. 2016;64:37-43.

Girard M. Autoimmune hazards of hepatitis B vaccine. Autoimmun Rev. 2005;4:96-100.

Gisa A, Suneetha PV, Behrendt P, et al. Cross-genotype-specific T-cell responses in acute hepatitis E virus (HEV) infection.J Viral Hepat. 2016;23:305-15.

Gu J, Hardy J, Boo I, et al. Escape of Hepatitis C Virus from Epitope I Neutralization Increases Sensitivity of Other Neutralization Epitopes. J Virol. 2018;92:e02066-17.

Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clin Infect Dis. 2013;57:S105-10.

Grakoui A, Shoukry NH, Woollard DJ, et al. HCV persistence and immune evasion in the absence of memory T cell help. Science. 2003;302:659-662.

Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. J Infect Dis. 2011;204:74-83.

Hahn JA, Page-Shafer K, Lum PJ, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. J Infect Dis. 2002;186:1558-1564.

Hammitt LL, Bulkow L, Hennessy TW, et al. Persistence of antibody to hepatitis A virus 10 years after vaccination among children and adults. J Infect Dis. 2008;198:1776-82.

Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011;55:1215-21.

Heller T, Werner JM, Rahman F, et al. Occupational exposure to hepatitis C virus: early T-cell responses in the absence of seroconversion in a longitudinal cohort study. J Infect Dis. 2013;208:1020-5.

Hendrickx G, Van Herck K, Vorsters A, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat. 2008;15 Suppl 2:1-15.

Hernan MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology. 2004;63:838-42. (Abstract)

Hettmann A, Juhász G, Dencs Á, et al. Phylogenetic analysis of a transfusion-transmitted hepatitis A outbreak. Virus Genes. 2017;53:15-20.

Hewitt PE, Ijaz S, Braisford SR, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet. 2014;384:1766-1773.

Hollinger FB, Bell B, Levy-Bruhl D, Shouval D, Wiersma S, Van Damme P. Hepatitis A and B vaccination and public health. J Viral Hepat. 2007;14 Suppl 1:1-5. (Abstract)

Honegger JR, Kim S, Price AA, et al. Loss of immune escape mutations during persistent HCV infection in pregnancy enhances replication of vertically transmitted viruses. Nat Med. 2013;19:1529-33.

Horvatits T, Wißmann JE, Johne R, et al. Hepatitis E virus persists in the ejaculate of chronically infected men. J Hepatol. 2021;75:55-63.

Huang S, Zhang X, Su Y, et al. Long-term efficacy of a recombinant hepatitis E vaccine in adults: 10-year results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403:813-823.

Huang SJ, Liu XH, Zhang J, Ng MH. Protective immunity against HEV. Curr Opin Virol. 2014;5:1-6.

Irving GJ, Holden J, Yang R, Pope, D. Hepatitis A immunisation in persons not previously exposed to hepatitis A. Cochrane Database Syst

Rev. 2012;2012:Cd009051.

Johne R, Trojnar E, Filter M, Hofmann J. Thermal Stability of Hepatitis E Virus as Estimated by a Cell Culture Method. Appl Environ Microbiol. 2016;82:4225-31.

Kallinowski B, Jilg W, Buchholz L, Stremmel W, Engler S. Immunogenicity of an accelerated vaccination regime with a combined hepatitis a/b vaccine in patients with chronic hepatitis C. Z Gastroenterol 2003;41:983-90. (Abstract)

Kamar N, Izopet J, Pavio N, et al. Hepatitis E virus infection. Nat Rev Dis Primers. 2017;3:17086.

Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. Hepatology. 1998;27:881-6.

Kubitschke A, Bader C, Tillmann HL, Manns MP, Kuhn S, Wedemeyer H. Verletzungen mit Hepatitis-C-Virus-kontaminierten Nadeln: Wie hoch ist das Risiko einer Serokonversion bei medizinischem Personal wirklich? [Injuries from needles contaminated with hepatitis C virus: how high is the risk of seroconversion for medical personnel really?]. Internist (Berl). 2007;48:1165-1172. (Abstract)

Laidlaw BJ, Craft JE, Kaech SM. The multifaceted role of CD4(+) T cells in CD8(+) T cell memory. Nat Rev Immunol. 2016;16:102-111.

Law M, Maruyama T, Lewis J, et al. Broadly neutralizing antibodies protect against hepatitis C virus quasispecies challenge. Nat Med. 2008;14:25-27.

Li W, Jia L, Zhao X, et al. Efficacy and safety of tenofovir in preventing mother-to-infant transmission of hepatitis B virus: A meta-analysis based on 6 studies from China and 3 studies from other countries. BMC Gastroenterol. 2018;18:121.

Liang TJ, Feld JJ, Cox AL, Rice CM. Controlled Human Infection Model - Fast Track to HCV Vaccine?. N Engl J Med. 2021;385:1235-1240.

Martin A, Lemon SM. Hepatitis A virus: from discovery to vaccines. Hepatology. 2006;43:S164-S172.

Mikhailov MI, Lopatukhina MA, Asadi Mobarhan FA, et al. Universal Single-Dose Vaccination against Hepatitis A in Children in a Region of High Endemicity. Vaccines (Basel). 2020;8:780.

Montella F, Rezza G, Di Sora F, Pezzotti P, Recchia O. Association between hepatitis E virus and HIV infection in homosexual men. Lancet. 1994;344:1433

Monteyne P, Andre FE. Is there a causal link between hepatitis B vaccination and multiple sclerosis? Vaccine. 2000;18:1994-2001. (Abstract)

Mosley JW, Operskalski EA, Tobler LH, et al. The course of hepatitis C viraemia in transfusion recipients prior to availability of antiviral therapy. J Viral Hepat. 2008;15:120-128.

Newsum AM, Matser A, Schinkel J, et al. Incidence of HCV reinfection among HIV-positive MSM and its association with sexual risk behavior: a longitudinal analysis. Clin Infect Dis. 2021;73:460-467.

Nothdurft HD. Hepatitis A vaccines. Expert Rev Vaccines. 2008;7:535-545. (Abstract)

Ott JJ, Irving G, WIersma ST. Long-term protective effects of hepatitis A vaccines: A systematic review. Vaccine. 2012;31:3-11.

Ott JJ, Wiersma ST. Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations. Int J Infect Dis. 2013;17:e939-44.

Owusu Sekyere S, Suneetha PV, Kraft AR, et al. A heterogeneous hierarchy of co-regulatory receptors regulates exhaustion of HCV-specific CD8 T cells in patients with chronic hepatitis C. J Hepatol. 2015;62:31-40.

Page K, Melia MT, Veenhuis RT, et al. Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection. N Engl J Med. 2021;384:541-549.

Pan CQ, Dai E, Mo Z, et al. Tenofovir and Hepatitis B Virus Transmission During Pregnancy: A Randomized Clinical Trial. JAMA. 2025;333:390-399.

Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med. 2016;374:2324-34.

Pan CQ, Zou HB, Chen Y et al. Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis b surface antigen-positive women to their infants. Clin Gastroenterol Hepatol. 2013;11:1349–1355.

Park SH, Veerapu NS, Shin EC, et al. Subinfectious hepatitis C virus exposures suppress T cell responses against subsequent acute infection. Nat Med. 2013;19:1638-42.

Payne BA, Medhi M, Ijaz S, et al. Hepatitis E virus seroprevalence among men who have sex with men, United Kingdom. Emerg Infect Dis. 2013;19:333-335.

Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:221-244.e3.

Pestka JM, Zeisel MB, Blaser E, et al. Rapid induction of virus-neutralizing antibodies and viral clearance in a single-source outbreak of hepatitis C. Proc Natl Acad Sci U S A. 2007;104:6025-30. (Abstract)

Pfaender S, Heyden J, Friesland M, et al. Inactivation of hepatitis C virus infectivity by human breast milk. J Infect Dis. 2013;208:1943-52.

Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database Syst Rev. 2017;9:CD012021.

Qu C, Chen T, Fan C, et al. Efficacy of Neonatal HBV Vaccination on Liver Cancer and Other Liver Diseases over 30-Year Follow-up of the Qidong Hepatitis B Intervention Study: A Cluster Randomized Controlled Trial. PLoS Med. 2014;11:e1001774.

Ranger-Rogez S, Denis F. Hepatitis B mother-to-child transmission. Expert Rev Anti Infect Ther. 2004;2:133-45. (Abstract)

Razavi HA, Waked I, Qureshi H, et al. Number of people treated for hepatitis C virus infection in 2014-2023 and applicable lessons for new HBV and HDV therapies. J Hepatol. 2025. Epub ahead of print.

Rehermann B. Pathogenesis of chronic viral hepatitis: different roles of T cells and NK cells. Nat Med. 2013;19:859-68.

Rein DB, Weinbaum CM. The cost-effectiveness of using hepatitis A/B combined vaccine versus hepatitis B vaccine alone for high-risk heterosexuals. Vaccine. 2008;26:5331-3. (Abstract)

Rowe IA, Parker R, Armstrong MJ, Houlihan DD, Mutimer DJ. Hepatitis A virus vaccination in persons with hepatitis C virus infection: consequences of quality measure implementation. Hepatology. 2012;56:501-6.

Sacks-Davis R, Aitken CK, Higgs P, et al. High rates of hepatitis C virus reinfection and spontaneous clearance of reinfection in people who inject drugs: a prospective cohort study. PLoS One. 2013;8:e80216.

Sadovnick AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. Lancet. 2000;355:549-50. (Abstract)

Sayed IM, Verhoye L, Cocquerel L, et al. Study of hepatitis E virus infection of genotype 1 and 3 in mice with humanised liver. Gut. 2017;66:920-929.

Schaefer EA, Chung RT. The impact of human gene polymorphisms on HCV infection and disease outcome. Sem Liver Dis. 2011;31:374-86.

Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. Vaccine. 2005;23:3876-86. (Abstract)

Shoukry NH, Grakoui A, Houghton M, et al. Memory CD8+ T cells are required for protection from persistent hepatitis C virus infection. J Exp Med. 2003;197:1645-1655.

Shrestha MP, Scott RM, Joshi DM, et al. Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med. 2007;356:895-903.

Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016;62:683-94.

Spradling PR, Bulkow LR, Negus SE, Homan C, Bruce MG, McMahon BJ. Persistence of seropositivity among persons vaccinated for hepatitis A during infancy by maternal antibody status: 15-year follow-up. Hepatology. 2016;63:703-11.

Ssebyatika G, Dinkelborg K, Ströh LJ, et al. Broadly neutralizing antibodies isolated from HEV convalescents confer protective effects in human liver-chimeric mice. Nat Commun. 2025;16:1995.

Stahl Y, Kabar I, Heinzow H, et al. Enhanced monitoring and detection of recent genotype 3 hepatitis E virus infection through urine antigen testing. Emerg Microbes Infect. 2023;12:2251598.

Stuurman AL, Marano C, Bunge EM, De Moerlooze L, Shouval D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines - A systematic review. Hum Vaccin Immunother. 2017;13:724-736.

Su FH, Chu FY, Bai CH, et al. Efficacy of hepatitis B vaccine boosters among neonatally vaccinated university freshmen in Taiwan. J Hepatol. 2013;58:684-9.

Suneetha PV, Pischke S, Schlaphoff V, et al. Hepatitis E virus (HEV)-specific T-cell responses are associated with control of HEV infection. Hepatology. 2012;55:695-708.

Swann RE, Cowton VM, Robinson MW, et al. Broad Anti-Hepatitis C Virus (HCV) Antibody Responses Are Associated with Improved Clinical Disease Parameters in Chronic HCV Infection. J Virol. 2016;90:4530-4543.

Terrault NA, Dodge JL, Murphy EL, et al. Sexual transmission of HCV among monogamous heterosexual couples: The HCV partners study. Hepatology. 2013;57:881-9.

Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? Hepatology. 2010;52:1497-505.

Tseng YT, Chang SY, Liu WC, et al. Comparative effectiveness of two doses versus three doses of hepatitis A vaccine in human immunodeficiency virus-infected and -uninfected men who have sex with men. Hepatology. 2013;57:1734-41.

Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. JAMA Intern Med. 2014;174:1974-81.

van der Sande MA, Waight PA, Mendy M, et al. Long-term protection against HBV chronic carriage of Gambian adolescents vaccinated in infancy and immune response in HBV booster trial in adolescence. PLoS One. 2007;2:e753. (Abstract)

Van Herck K, Jacquet JM, Van Damme P. Antibody Persistence and Immune Memory in Healthy Adults Following Vaccination With a TwoDose Inactivated Hepatitis A Vaccine: Long-Term Follow-Up at 15 Years. J Med Virol. 2011;83:1885-91. (Abstract)

Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med. 1998;338:286-90. (Abstract)

Vizzotti C, González J, Gentile A, et al. Impact of the single-dose immunization strategy against hepatitis A in Argentina. Pediatr Infect Dis J. 2014;33:84-88.

Walker MR, Leung P, Eltahla AA, et al. Clearance of hepatitis C virus is associated with early and potent but narrowly-directed, Envelope-specific antibodies. Sci Rep. 2019;9:13300.

Weber T, Potthoff J, Bizu S, et al. Analysis of antibodies from HCV elite neutralizers identifies genetic determinants of broad neutralization. Immunity. 2022;55:341-354.e7.

Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis E virus infection. Gastroenterology. 2012;142:1388-1397.e1.

Wiegand J, Cornberg M, Aslan N, et al. Fate and function of hepatitis-C-virus-specific T-cells during peginterferon-alpha 2b therapy for acute hepatitis C. Antivir Ther. 2007;12:303-16. (Abstract)

Wolters B, Junge U, Dziuba S, Roggendorf M. Immunogenicity of combined hepatitis A and B vaccine in elderly persons. Vaccine. 2003;21:3623-28. (Abstract)

Wong F, Pai R, Van Schalkwyk J, Yoshida EM. Hepatitis B in pregnancy: a concise review of neonatal vertical transmission and antiviral prophylaxis. Ann Hepatol. 2014;13:187-95.

Wu Q, Huang H, Sun X, et al. Telbivudine Prevents Vertical Transmission of Hepatitis B Virus from Women High Viral Loads: A Prospective Long-term Study. Clin Gastroenterol Hepatol. 2015;13:1170-6.

Zanetti AR, Mariano A, Romano L, et al. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. Lancet. 2005;366:1379-84. (Abstract)

Zhang J, Liu W, Wen B, et al. Circulating CXCR3+ Tfh cells positively correlate with neutralizing antibody responses in HCV-infected patients. Sci Rep. 2019;9:10090.

Zhang L, Yesupriya A, Hu DJ, et al. Variants in ABCB1, TGFB1, and XRCC1 genes and susceptibility to viral hepatitis A infection in Mexican Americans. Hepatology. 2012;55:1008-18.

Zhao YL, Meng ZD, Xu ZY, et al. H2 strain attenuated live hepatitis A vaccines:protective efficacy in a hepatitis A outbreak. World J Gastroenterol. 2000;6:829-832.

Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, doubleblind placebo-controlled, phase 3 trial. Lancet. 2010;376:895-902. (Abstract)

Zuckerman J, van Hattum J, Cafferkey M, et al. Should hepatitis B vaccination be introduced into childhood immunisation programmes in northern Europe? Lancet Infect Dis. 2007;7:410-19. (Abstract)

8. Grading and staging of liver diseases

Michael Praktiknjo, Juliana Gödiker

Liver disease encompasses a spectrum of disorders, with cirrhosis and portal hypertension representing critical and advanced stages that necessitate precise grading and staging for effective clinical management. Cirrhosis, characterised by the progressive replacement of healthy liver tissue with scar tissue, fundamentally alters liver architecture and function, often leading to severe complications. Among these complications, portal hypertension—the increased pressure within the portal venous system—stands out as a major driver of morbidity and mortality. Accurate assessment of the severity and progression of liver disease is crucial for prognosis, therapeutic decision-making, and evaluation of treatment efficacy.

The current Baveno VII consensus promotes the use of non-invasive methods to assess clinically significant portal hypertension (CSPH), aiming to identify at-risk patients and reduce the need for unnecessary endoscopic screenings (de Franchis 2022). Additionally, spleen stiffness measurement (SSM) is gaining traction as a new elastography technique. Both elastography and cross-sectional imaging techniques now offer comparable predictive accuracy, and their effectiveness is enhanced when these non-invasive tests are used sequentially.

Nevertheless, the use of interventional transjugular procedures plays an increasingly relevant role in in the diagnosis of acute and chronic liver diseases. Measurement of the hepatic venous pressure gradient (HVPG) has become a relevant tool in clinical hepato y as it is considered the gold standard for sinusoidal portal hypertension (PH) diagnosis in patients with compensated advanced chronic liver disease (cACLD; compensated cirrhosis) according to the current Baveno VII consensus (de Franchis 2022). In addition, as HVPG measurement can be combined with transjugular liver biopsy (TJLB), the combination of these two procedures enables correlation of hemodynamic data with the underlying histopatho ical changes, providing a more comprehensive understanding of the pathophysio ical mechanisms of the underlying liver disease. More recently, endoscopic ultrasound (EUS-)guided approaches to obtaining liver biopsies and measurements of portal pressure gradient (EUS-PPG) gain attention as an emerging technique, overcoming most of the shortcomings of aforementioned HVPG measurements (Laleman 2023).

Clinical stages of liver cirrhosis

The progression of liver cirrhosis can be classified into different clinical stages. From compensated liver cirrhosis various events can lead to acute decompensation (AD) being defined by the sudden onset of ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infections, or any combination of these conditions. At this stage, patients are highly susceptible to bacterial infections due to complex cirrhosis-associated immune dysfunction severely affecting the overall prognosis (Trebicka 2020). The initial occurrence of AD indicates a shift from compensated to decompensated cirrhosis. For decompensated cirrhosis the prognosis worsens significantly compared to compensated stages with a median survival of only about two years (D'Amico 2018). Modern concepts also include non-acute decompensation (NAD) defined as non-acute occurrence of grade 2 ascites and/or grade 1–2 HE manageable in the outpatient clinic, which have a better prognosis than AD (Schulz 2025, Tonon 2024). Decompensated cirrhosis is further identified by repeated episodes of AD, finally leading to acute-on-chronic liver failure (ACLF) (European Association for the Study of the Liver 2018, Moreau 2013).

Acute-on-chronic liver failure (ACLF) is a severe complication of liver cirrhosis and can occur in all of the disease stages of liver cirrhosis. ACLF is marked by a high short-term mortality (D'Amico 2018, Trebicka 2020). A bacterial infection, active consumption of alcohol and surgeries are only some factors that can trigger the development of an ACLF. However, in a significant number of patients the trigger cannot be identified (Trebicka 2021). For the definition of ACLF two criteria have to be fulfilled: presence of decompensated liver cirrhosis (in this case presence of ascites, bacterial infection, gastro-oesophageal bleeding or hepatic encephalopathy) and development of at least one organ failure (Table 1). The ACLF can be further divided into different grades: ACLF grade 1 (presence of renal failure alone or other organ failure in combination with renal dysfunction or hepatic encephalopathy), ACLF grade 2 (presence of two organ failures) and ACLF grade 3 (presence of at least three organ failures) (Arroyo 2020, European Association for the Study of the Liver 2023; Moreau 2013) (Table 2).

Table 1. Organ failure score in acute-on-chronic liver failure

Organ System	1 Point	2 Point	3 Points
Liver (bilirubin, mg/dL)	Bilirubin <6 mg/dL	Bilirubin 6.0–11.9 mg/dL	Bilirubin ≥12 mg/dL
Kidney (creatinine, mg/dL)	Creatinine <1.5 mg/dL or 1.5–1.9 mg/dL	Creatinine 2.0–3.4 mg/dL	Creatinine ≥3.5 mg/dL or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation (INR)	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation (MAP, mm Hg)	MAP ≥70 mm Hg	MAP <70 mm Hg	Vasopressor requirement
Respiration (PaO_2/FiO_2 or SpO_2/FiO_2)	PaO_2/FiO_2 >300 or SpO_2/FiO_2 >357	PaO_2/FiO_2 201–300 or SpO_2/FiO_2 357–512	PaO_2/FiO_2 ≤200 or SpO_2/FiO_2 ≤214

Table 2. Grades of acute-on-chronic liver failure

Patient Group	Prevalence (% of patients)	28-Day Mortality (%)	Assigned Grade
Absence of OF	68.3	4.4	Absence of ACLF
Single, nonkidney OF without KD or BD	9.9	6.3	Absence of ACLF
Single KF	6.7	18.6	ACLF-1a
Single, nonkidney OF with KD or BD	4.2	27.8	ACLF-1b
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3

Baveno VII stages of liver cirrhosis including portal hypertension

The international Baveno VII consensus brought about numerous innovations in the management of portal hypertension. The focus was on the non-invasive diagnosis of clinically significant portal hypertension defining five stages in advanced chronic liver disease:

Stage 1: Compensated liver cirrhosis without clinically significant portal hypertension

Stage 2: Compensated liver cirrhosis with clinically significant portal hypertension

Stage 3: First decompensation of liver cirrhosis

Stage 4: Further decompensation of liver cirrhosis

Stage 5: Recompensated liver cirrhosis

Definition of first decompensation and further decompensation (Baveno VII)

Compensated liver cirrhosis is progressing to decompensation at the time of first presence of one of the following complications: overt ascites, overt hepatic encephalopathy and variceal bleeding. At this time point it remains controversial whether minimal manifestation of the mentioned complication already define the development of hepatic decompensation. Of note, other complications such as onset of acute-on-chronic-liver-failure, development of hepatocellular carcinoma, superimposed liver injury, onset of infection and presence of jaundice do currently not define the progress to decompensated liver cirrhosis according to the Baveno consensus. The mortality increases significantly with onset of hepatic decompensation (de Franchis 2022).

Decompensated liver cirrhosis is divided into two stages: first decompensation and further decompensation. First decompensation is defined as first presence of overt ascites, overt hepatic encephalopathy or variceal bleeding. The prognosis worsens again with onset of further decompensation. Further decompensation is defined as either development of an additional second decompensating event or jaundice or the development of recurrent variceal bleeding, recurrent ascites, recurrent hepatic encephalopathy, spontaneous bacterial peritonitis or hepato-renal syndrome. Of note, in patients with variceal bleeding development of ascites, encephalopathy or jaundice at the time point of the bleeding is not considered as further decompensation. But development of either of these events after the bleeding defines the stage of further decompensation(de Franchis 2022).

Definition of recompensation

Despite the presence of a decompensating event in the past an improvement of liver disease is possible defined as the stage of recompensated liver disease. All of the following criteria have to be fulfilled: sufficient treatment of the primary aetio y of cirrhosis (e. g. alcohol abstinence, viral elimination of hepatitis c virus), for at least 12 months resolution of ascites (and no medication with diuretics), encephalopathy (no medication with lactulose and rifaximin) and absence of variceal bleeding and stable liver synthesis function (albumin, bilirubin, INR)(de Franchis 2022).

Clinical scores to determine the severity of liver cirrhosis

Several score systems are proposed to determine the severity of liver cirrhosis. The Child-Turcotte-Pugh score is one of the most commonly used scores in clinical practice and assigns the patient into one of three stages (A, B and C). It includes markers of liver synthesis function (albumin, INR), detoxification function (bilirubin, hepatic encepahalopathy) and portal hypertension (ascites).

Another commonly used score is the MELD (model for end stage liver disease). It is suggested to be more objective since it does not include subjective markers such as ascites and HE but only laboratory markers (bilirubin, creatinine,INR) (Durand 2005). The MELD score was developed to predict the mortality in patients with portal hypertension and implantation of a TIPS and application was expanded in all patients with liver cirrhosis (Kamath 2001).

Invasive tests

Liver biopsy

The term compensated advanced chronic liver disease (cACLD) has been defined by LSM to classify the progressive disease of severe fibrosis and cirrhosis in the Baveno VII criteria irrespective of histo ical features (de Franchis 2022). Although non-invasive testing and elastography are gradually taking over as mentioned below, liver biopsy remains a basic skill and necessity of the hepato ist's diagnostic armamentarium to confirm diagnosis, assess stage and grade of the underlying chronic liver disease and to perform additional molecular analysis (Laleman 2023). The performance of a liver biopsy is the reference standard to assess the grade of liver fibrosis (European Association for the Study of the Liver 2021). Nevertheless, liver biopsy is also not always accurate as the quality of the specimen can differ and its interpretation can be quite complex requiring expertise in liver patho y. As with all invasive procedures complications such as bleeding especially in patients with impaired coagulation may occur (Davison 2020, Neuberger 2020). To improve the quality of pertcutaneous liver biopsy it is recommended to gain a sample length >15 mm with more than 10 portal tracts by a 16G needle and the assessment of a sample should be performed by an experienced patho ist (Neuberger 2020).

The liver biopsy is classified with the ISHAK score into seven categories (ranging from zero to six) according to the level of fibrosis in the sample. In the category 0 no evidence of fibrosis is present whereas in category 6 cirrhosis is probable or even diagnosed (Knodell 1981) (Table 3).

Table 3. ISHAK fibrosis stages

ISHAK Score	Fibrosis stage description
0	No fibrosis
1	Expansion of some portal areas, no septa
2	Expansion of most portal areas, rare septa
3	Portal fibrosis with occasional bridging septa
4	Portal fibrosis with frequent bridging septa
5	Incomplete cirrhosis (numerous septa but no true regenerative nodules)
6	Established cirrhosis with regenerative nodules

The most common methods to perform a liver biopsy are a percutaneous or transjugular. The transjugular route should be preferred, if possible, in patients with a relevant coagulopathy (INR≥ 1.5) as the risk of bleeding is lower since the liver capsule is usually intact. Also, in patients with ascites a percutaneous biopsy is associated with a higher risk of bleeding and therefore a transjugular approach is better suited. Another advantage is the possibility of measurement the hepatic venous pressure gradient (HVPG) in the same procedure. However, the sample size is smaller and often more fragmented than in a percutaneous liver biopsy since a 18G or 19G needle is the standard needle in transjugular liver biopsy (Neuberger 2020).

In recent years, endoscopic ultrasound-guided liver biopsy EUS-LB has regained interest and has emerged as a well-tolerated, effective, and safe alternative to traditional liver tissue sampling (Laleman 2023). There are several benefits to EUS-LB in comparison to traditional approaches such as a lower perceived apprehension for the patient (given the use of sedation, lower post-procedural discomfort and shorter recovery), and the ability to target widely separated areas and even perform bilobar tissue sampling minimising as such sampling error and capturing inhomogeneous disease activity. Significant complications, bleeding and/or subcapsular hematoma, requiring emergency visit or hospitalisation occur about 1% of patients, similar to percutaneous approach (Baran 2021). Real-life data of percutaneous LBs showed that only 19% of cores are adequate, 56% suboptimal and 24% inadequate (Fryer 2013). A systematic review on EUS-LB, including 1326 patients showed a diagnostic yield of over 95% with an overall pooled mean tissue specimen length of 45.3 + 4.6mm containing 15.8 + 1.5 complete portal tracts (Pineda 2016). Currently, a 19G needle is favoured, and preferably the Franseen type (Laleman 2023).

Similarly to the transjugular approach, EUS-LB can be combined with direct EUS-guided portal pressure gradient (EUS-PPG) measurement as mentioned below. Therefore, endohepato y is not only conceptually and technically innovative but also highly practical for everyday use. It allows for a "one-stop clinic" approach, where patients can receive comprehensive endoscopic diagnostic and therapeutic procedures in a single outpatient visit.

Hepatic Venous Pressure Gradient (HVPG)

The gold standard to determine the presence of CSPH is the invasive performance of a hepatic venous pressure gradient (HVPG) measurement. This is an interventional technique that uses a transjugular venous access to place a catheter in a hepatic vein. The free hepatic venous pressure is then measured followed by measurement of the wedged hepatic venous pressure, which is created by inflating a balloon in the hepatic vein. The wedged hepatic venous pressure approximates the hepatic sinusoidal pressure and thus the portal venous pressure. The gradient between free and wedged hepatic venous pressure defines the HVPG. Clinically significant portal hypertension (CSPH) is defined as an HVPG ≥ 10 mmHg for most etio ies, especially viral- and alcohol-related cirrhosis (Table 4). CSPH defines a condition of high-risk for clinical portal hypertension related acute decompensation of compensated cirrhosis. At HVPG ≥ 10 mmHg patients are at risk of developing gastro-oesophageal varices, which then would indicate medical primary prophylaxis (de Franchis 2022, Villanueva 2019).

Table 4. Risk categories according to Hepatic Venous Pressure Gradient (HVPG)

HVPG	Risk category
<5 mmHg	normal
5–9 mmHg	portal hypertension
≥10 mmHg	clinical significant portal hypertension
>12 mmHg	high-risk for development of varices
>16 mmHg	high-risk variceal bleedings

Endoscopic Ultrasound-guided Portal Pressure Gradient (EUS-PPG)

The gold standard for indirect measurement of portal vein pressure (HVPG) methodo ical limitations. It provides only an indirect measurement of portal pressure, relying on wedged hepatic vein pressure to reflect "free"

sinusoidal perfusion and complete hepatic vein occlusion, thus unable to detect pre-sinusoidal and pre-hepatic portal hypertension. In clinical practice, this means HVPG measurement may underestimates the degree of portal hypertension in conditions like Primary Biliary Cholangitis (PBC) (Navasa 1987), Porto-Sinusoidal Vascular Disease (PSVD, previously Idiopathic Non-Cirrhotic Portal Hypertension) (De Gottardi 2019), or metabolic-associated fatty liver disease (MASLD) (Baffy 2022), as recently demonstrated for MASLD as one of the most common causes of chronic liver disease (Bassegoda 2022). By directly measuring portal and hepatic venous pressures, EUS-PPG avoids the risk of underestimated values in aforementioned clinical scenarios such as PBC, PSVD, and MASLD. For the large group of patients with liver cirrhosis (and sinusoidal portal hypertension), EUS-PPG can be used for personalised therapy management. In contrast to HVPG, EUS-PPG directly measures hepatic vein and portal pressures by transgastric puncture of these vessels under EUS guidance using a 25-G FNA needle.

While some authors describe that PPG values under sedation may be underestimated compared to awake measurements (Benmassaoud 2022, Reverter 2014), others showed that PPG values under Propofol sedation during EUS-PPG were even slightly higher compared to HVPG measurements without sedation (Martinez-Moreno 2024), suggesting inconclusive data on sedation's influence. Moreover, data on correlation of EUS-PPG with clinical outcome are still scarce.

Non-invasive tests

Liver stiffness measurement

Non-invasive strategies to determine PH are crucial to stratify patient care and to plan their clinical management. Since healthcare resources are limited, HVPG measurement, as a complex and invasive procedure, is only available in specialised centres and contains a periprocedural risk of bleeding and organ injury. Non-invasive tests (NIT) for CSPH are needed to guide patients' management from a clinicians point-of-view, being useful in ruling out CSPH and therewith avoiding unnecessary examinations. On the other hand, they can rule in CSPH and can identify patients requiring further examinations or referral to a hepato ist (Brol 2023).

Liver fibrosis is the main mechanistic driver of portal hypertension. Portal hypertension is further aggravated by splanchnic blood flow and congestion. For a long time, histo ical analysis of liver biopsy was the most common tool to quantify liver fibrosis in patients with chronic liver disease, while HVPG was the gold standard for the diagnosis of CSPH. However, liver fibrosis and portal hypertension are both reflected in an increase in stiffness of the liver tissue due to congestion and fibrosis itself (Brol 2023).

Over the past few decades, non-invasive liver stiffness measurement (LSM) using transient elastography (TE) has emerged as a more widely spread method, nearly replacing liver biopsy for grading fibrosis in selected etio ies such as viral hepatitis and alcohol-related liver disease. Research has shown that TE correlates well with hepatic venous pressure gradient (HVPG), making it a useful tool for assessing high or low probability of the presence of clinically significant portal hypertension (CSPH). Today, TE is becoming more accessible and more frequently used to evaluate liver stiffness. However, LSM is not only determined by liver fibrosis but can be affected by different factors. As such recent food intake, cardiac congestion and hepatic inflammation can all increase LSM values, which needs to be taken into account when interpreting such LSM (Friedrich-Rust 2008). Successful measurements are validated using the following criteria: 1) number of valid shots ≥ 10; 2) ratio of valid shots to the total number of shots ≥ 60%; and 3) interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median liver stiffness measurement (LSM) value (IQR/LSM ≤30%) (Ferraioli 2015).

Rule of five of liver stiffness measurement and platelet count

Both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) recommend a threshold of >25 kPa, regardless of platelet count, to define high probability for the presence of CSPH in patients with virus-, alcohol-related and non-obese MASH-related etio y of liver disease. According to the Baveno VII consensus, when liver stiffness measurement values are between 15 and 25 kPa, platelet count should be considered for confirming high likelihood for the presence of CSPH in chronic liver disease.

CSPH is not likely present in patients with a liver stiffness measurement ≤15 kPa and a platelet count ≥150 x 10^9/L. Moreover, in the cACLD patients with liver stiffness measurement between 20–25 kPa, 15–20 kPa respectively and a platelet count ≤150 x 10^9/L, ≤110 x 10^9/L, respectively the probability for CSPH is increased (60 % risk). Further validation for use of the model in the aetio y of MASH is needed (Baveno VII) (Figure 1).

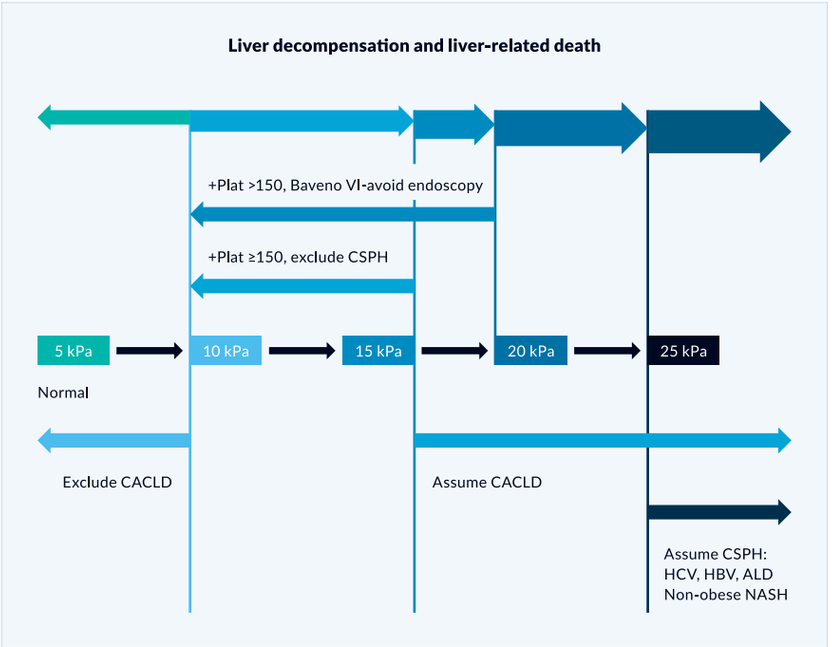

Figure 1. Algorithm for the noninvasive determination of cACLD and CSPH; from: Baveno VII – de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959-974

Shear wave elastography (SWE), like transient elastography (TE), is used as an alternative technique to assess liver fibrosis. However, the comparability of studies is often challenged by the use of different manufacturers and varying elastography techniques, such as two-dimensional SWE (2D-SWE) or point SWE, depending on the device used. SWE is popular because it can be performed frequently and easily with standard ultrasound machines (Brol 2023).

One significant advantage of SWE over TE is its ability to be performed independently of the presence of ascites. Several earlier studies indicated that SWE was more effective in diagnosing clinically significant portal hypertension (CSPH) in patients with ascites and does not seem inferior to TE (Elkrief 2015, Leung 2013). However, the cut-off values for diagnosing CSPH depend on the specific ultrasound device used and may vary based on the underlying disease etio y.

More recent developments use LSM as a biomarker, that can be incorporated into predictive algorithms alongside other biomarkers. For example, the M10LS20 algorithm incorporates MELD and LSM identifying high-risk of death in patients with MELD >10 points and LSM > 20kPa (Trebicka 2022).

Spleen stiffness measurement

During portal hypertension (PH), the pressure in the splenic vein increases. This congestion of blood in the spleen causes it to enlarge, making spleen stiffness a reliable indicator for clinically significant portal hypertension (CSPH). In healthy adults, the average spleen stiffness measurement (SSM) is around 18 kPa, but it significantly increases in patients with CSPH (Kani 2022).

A meta-analysis of nine studies found that SSM measured by ultrasound-based elastography demonstrated a strong correlation with hepatic venous pressure gradient (HVPG), effectively detecting clinically significant portal hypertension (CSPH) (Song 2018). According to the new Baveno VII consensus statement, spleen stiffness (SSM) can be used to rule out (SSM <21 kPa) and rule in (>50kPa) CSPH. Moreover, for patients, who cannot take non-selective beta-blockers (due to contraindications or intolerance) and who would typically require an endoscopy based on the Baveno VI criteria (LSM by TE ≥20 kPa or platelet count ≤150 x 10^9/L), an SSM ≤40 kPa by TE can be used to identify those with a low risk of high-risk varices, allowing endoscopy to be avoided (Dajti 2023). The main advantage of including SSM in the diagnostic of CSPH is the reduction of the diagnostic grey zone. This leads to further reduction in unnecessary endoscopy to rule out varices. Hemato ical disorders, such as acute myeloid leukaemia and bone marrow fibrosis, have been identified as factors that can increase spleen stiffness.

Blood-based tests

Noninvasive assessment of CSPH using laboratory tests is convenient as it eliminates the need for technical expertise or specific devices. This convenience has led to numerous efforts to develop predictive algorithms for CSPH.

FIB-4 score

The Fibrosis-4 index (FIB-4) is a serum-based noninvasive score used to predict liver fibrosis, based on age, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, and platelet count. Initially developed for predicting liver fibrosis in patients coinfected with HIV and HCV, its predictive value has been validated for liver fibrosis of various other etio ies. The advantages of the score are the broad availability, good accuracy for advanced liver fibrosis and rather low costs (European Association for the Study of the Liver 2021). Recent retrospective studies have shown that

FIB-4 can be used with adjusted thresholds to predict clinically significant portal hypertension (CSPH). However, for the use in primary care not many validation studies were performed yet and misclassification is possible (European Association for the Study of the Liver 2021, Ginès 2022). The Fib-4 score is best used to exclude the presence of fibrosis than to diagnose the presence of fibrosis. However, especially in patients older than 65 years false positive results are common. Additionally, a significant number of patients have a FIB-4 score within a transitional range with no clear recommendation being defined (EASL guideline noninvasive tests 2021). A FIB-4 value below 1.30 is considered as low risk for advanced fibrosis; a value over 2.67 is considered as high risk for advanced fibrosis; and FIB-4 values between 1.30 and 2.67 are considered as intermediate risk of advanced fibrosis. (European Association for the Study of the Liver 2021)

MAFLD fibrosis score

To calculate the NAFLD fibrosis score (MFS) (former NAFLD fibrosis score) age, BMI, diabetes, aminotransferases, platelets and albumin were taken into consideration (European Association for the Study of the Liver 2021). In patients with diabetes and obesity the performance of NFS seems to be impaired. Therefore, in these patients the FIB-4 score might be preferred (European Association for the Study of the Liver 2021). Similar to the FIB-4 score the MFS can show false positive results in patients older than 65 years.

However, in MASH the performance of a liver biopsy remains the standard procedure to determine the diagnosis as all noninvasive tests are not reaching an acceptable level of accuracy(European Association for the Study of the Liver 2021).

Conclusion

The grading and staging of liver diseases are crucial for assessing disease severity, guiding treatment decisions, and predicting patient outcomes. Cirrhosis and portal hypertension represent advanced stages of liver disease, with clinically significant portal hypertension (CSPH) being a major determinant of morbidity and mortality.

Non-invasive methods such as liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) have largely replaced liver biopsy for fibrosis staging, aligning with the Baveno VII recommendations. Blood-based tests like FIB-4 and the MAFLD fibrosis score offer additional tools for fibrosis assessment, though their predictive accuracy varies by patient demographics and disease etio y.

Despite advancements in non-invasive diagnostics, hepatic venous pressure gradient (HVPG) measurement remains the gold standard for CSPH assessment, particularly for conditions like viral and alcohol-related cirrhosis. EUS-guided techniques, including endoscopic ultrasound-guided liver biopsy (EUS-LB) and endoscopic ultrasound-guided portal pressure gradient (EUS-PPG) measurement, are gaining attention as less invasive alternatives that directly measure portal pressures and allow for more precise, comprehensive tissue sampling. These EUS-guided approaches overcome technical limitations of HVPG by providing more accurate portal pressure measurements, especially in conditions with pre-sinusoidal or pre-hepatic portal hypertension, and offer the benefit of real-time tissue acquisition under ultrasound guidance. However, its predictive value on clinical outcomes have to be determined before broad clinical use can be recommended.

Clinical classification systems, including the NAD, AD, ACLF classification or the Baveno VII staging as well as scoring systems such as Child-Pugh and MELD, provide structured frameworks for evaluating liver disease progression. The concept of recompensated cirrhosis highlights the potential for disease improvement with targeted treatment strategies.

Moving forward, a multimodal approach combining non-invasive tests, laboratory biomarkers, imaging techniques, and EUS-guided methods will be essential for optimising liver disease management while minimising procedural risks for patients. Further validation and standardisation of these non-invasive and EUS-guided methods will be key to their broader clinical implementation.

References

Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. N Engl J Med. 2020;382(22):2137-2145.

Baffy G, Bosch J. Overlooked subclinical portal hypertension in non-cirrhotic NAFLD: Is it real and how to measure it?. J Hepatol. 2022;76(2):458-463.

Baran B, Kale S, Patil P, et al. Endoscopic ultrasound-guided parenchymal liver biopsy: a systematic review and meta-analysis. Surg Endosc. 2021;35(10):5546-5557.

Bassegoda O, Olivas P, Turco L, et al. Decompensation in Advanced Nonalcoholic Fatty Liver Disease May Occur at Lower Hepatic Venous Pressure Gradient Levels Than in Patients With Viral Disease. Clin Gastroenterol Hepatol. 2022;20(10):2276-2286.e6.

Benmassaoud A, Chen YI. Sedation during EUS-guided portal pressure gradient measurement: the elephant in the room. Gastrointest Endosc. 2022;96(4):690-691.

Brol MJ, Gödiker J, Uschner FE, Praktiknjo M, Trebicka J. Non-invasive Assessment of Clinically Significant Portal Hypertension. Current Hepatology Reports, 22(3), 206–215.

Dajti E, Ravaioli F, Zykus R, et al. Accuracy of spleen stiffness measurement for the diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease: a systematic review and individual patient data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(9):816-828.

D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. J Hepatol. 2018;68(3):563-576.

Davison BA, Harrison SA, Cotter G, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol. 2020;73(6):1322-1332.

de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension [published correction appears in J Hepatol. 2022 Jul;77(1):271. doi: 10.1016/j.jhep.2022.03.024.]. J Hepatol. 2022;76(4):959-974.

De Gottardi A, Rautou PE, Schouten J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet

Gastroenterol Hepatol. 2019;4(5):399-411.

Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol. 2005;42 Suppl(1):S100-S107.

Elkrief L, Rautou PE, Ronot M, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology. 2015;275(2):589-598.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406-460.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. J Hepatol. 2023;79(2):461-491.

European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75(3):659-689.

Ferraioli G, Filice C, Castera L, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. Ultrasound Med Biol. 2015;41(5):1161-1179.

Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology. 2008;134(4):960-974.

Fryer E, Wang LM, Verrill C, Fleming K. How often do our liver core biopsies reach current definitions of adequacy?. J Clin Pathol. 2013;66(12):1087-1089.

Ginès P, Castera L, Lammert F, et al. Population screening for liver fibrosis: Toward early diagnosis and intervention for chronic liver diseases. Hepatology. 2022;75(1):219-228.

Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464-470.

Kani HT, Keklikkıran Ç, Ergenç İ, Yılmaz Y. Evaluation of spleen stiffness in healthy population: A vibration-controlled transient elastography study. Journal of Health Sciences and Medicine. 2022;5(2), Article 2.

Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 1981;1(5):431-435.

Laleman W, Mertens J, Vanderschueren E, Praktiknjo M, Trebicka J. Advances in Endohepatology. Am J Gastroenterol. 2023;118(10):1756-1767.

Leung VY, Shen J, Wong VW, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. Radiology. 2013;269(3):910-918.

Martinez-Moreno B, Martínez Martínez J, Herrera I, et al. Correlation of endoscopic ultrasound-guided portal pressure gradient measurements with hepatic venous pressure gradient: a prospective study. Endoscopy. 2025;57(1):62-67.

Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426-1437.e14379.

Navasa M, Parés A, Bruguera M, Caballería J, Bosch J, Rodés J. Portal hypertension in primary biliary cirrhosis. Relationship with histological features. J Hepatol. 1987;5(3):292-298.

Neuberger J, Patel J, Caldwell H, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut. 2020;69(8):1382-1403.

Pineda JJ, Diehl DL, Miao CL, et al. EUS-guided liver biopsy provides diagnostic samples comparable with those via the percutaneous or transjugular route. Gastrointest Endosc. 2016;83(2):360-365.

Reverter E, Blasi A, Abraldes JG, et al. Impact of deep sedation on the accuracy of hepatic and portal venous pressure measurements in patients with cirrhosis. Liver Int. 2014;34(1):16-25.

Schulz MS, Angeli P, Trebicka J. Acute and non-acute decompensation of liver cirrhosis (47/130). Liver Int. 2025;45(3):e15861.

Tonon M, D'Ambrosio R, Calvino V, et al. A new clinical and prognostic characterization of the patterns of decompensation of cirrhosis. J Hepatol. 2024;80(4):603-609.

Trebicka J, Fernandez J, Papp M, et al. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. J Hepatol. 2021;74(5):1097-1108.

Trebicka J, Fernandez J, Papp M, et al. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol. 2020;73(4):842-854.

Trebicka J, Gu W, de Ledinghen V, et al. Two-dimensional shear wave elastography predicts survival in advanced chronic liver disease. Gut. 2022;71(2):402-414.

Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2019 Jun 22;393(10190):2492.

9. MASLD / MASH

Andreas Geier, Elke Roeb

Summary

Metabolic dysfunction-associated steatotic liver disease (MASLD) formerly known as non-alcoholic fatty liver disease (NAFLD) is viewed as a serious health concern in industrial countries. MASLD pathogenesis and its detailed progression to fibrosis and chronic liver disease is still unclear. Many studies have shown that MASLD/NAFLD may be associated with increased insulin resistance (IR). IR, obesity, low adiponectin, (postprandial) dyslipidaemia, and hyperglycaemia represent the main factors leading to MASLD and accelerate the course and progression of this disease. MASLD can affect people of all ages and appears to vary in different ethnic groups. Environmental and lifestyle factors such as reduced physical activity and high-fat diets are well-studied factors in the development of IR-associated comorbidities and MASLD. Recent studies have made advances in the area of genetic risk factors and immune responses in metabolic dysfunction-associated steatohepatitis (MASH) pathogenesis. Changing lifestyle in form of weight loss, dietary changes and physical activity is an important therapeutic measure. Drug therapy is based on the associated diseases (dyslipidaemia, obesity, diabetes) and the stage of liver fibrosis – in the current absence of specific (EMA-, FDA-) approved MASLD drugs. In case of severe obesity, bariatric surgery might be performed to treat MASLD and MASH. In case of severe MASH-complications liver transplantation might be an option. Targeted interventions in the numerous mechanisms involved in the progression of MASH are intended in particular to prevent the development and progression of liver fibrosis. Follow-up and surveillance of MASH patients is recommended according to their individual risk.

The new nomenclature for fatty liver disease used in this chapter is based on an international consensus from the hepatological societies AASLD (USA) and EASL (Europe), which the German DGVS has also explicitly endorsed. [Rinella 2023] The new definition requires the presence of at least one cardiometabolic risk factor in addition to hepatic steatosis. The term metabolic dysfunction-associated steatotic liver disease (MASLD) was defined as a replacement term for NAFLD and metabolic dysfunction-associated steatohepatitis (MASH) as a replacement term for NASH. The acronym MetALD was chosen to designate a separate group of patients with MASLD who consume 140-350 g/week in women and 210-420 g/week in men. The proposed nomenclature allows for flexible refinement as new

insights into the underlying pathophysiology and risk factors of hepatic steatosis are gained. An analysis by the European LITMUS consortium showed that 98% of the existing registry cohort of patients with NAFLD would fulfil the new criteria for MASLD.(Hardy, Wonders et al. 2020, Rinella, Lazarus et al. 2023) In the North American NHANES cohort and the national Swedish registry, there is even a 99% match between the diagnoses of MASLD and NAFLD.(Hagström, Vessby et al. 2023, Lee, Dodge et al. 2023) In places where NASH was used as a histological diagnosis, this is indicated by the use of both terms (MASH/NASH).

Introduction

According to the current guidelines of the DGVS (German Society for Gastroenterology, Digestive and Metabolic Diseases)(Roeb, Canbay et al. 2022), EASL (European Association for the Study of the Liver 2016) (2016) AASLD (American Association for the Study of Liver Diseases 2018) (Chalasani, Younossi et al. 2018), APASL (Asian Pacific Association for the Study of the Liver, HCC Guideline, 2017)(Kim, Lee et al. 2017), and the World Gastroenterology Organisation (2012)(LaBrecque, Abbas et al. 2014) non-alcoholic fatty liver disease (NAFLD) includes the fatty liver diseases NAFL (Non-alcoholic fatty liver), NASH (Non-alcoholic steatohepatitis), NASH fibrosis and NASH cirrhosis. Other nomenclatures (e.g. metabolically associated fatty liver disease or metabolic dysfunction-associated fatty liver disease / MASLD) have been proposed to strengthen the relevance of metabolic disorders in this context .(Roeb 2021)

The progression of MASH is associated with liver cell stress, consecutive inflammation and fibrosis, with potential development of liver cirrhosis, portal hypertension and end-stage liver disease. MASH is also a relevant risk factor for the occurrence of hepatocellular carcinoma (HCC). The pathogenesis and natural course of MASLD are increasingly better understood, even if the heterogeneity of the patients and the multifactorial triggers make it difficult to estimate the individual prognosis. End-stage MASH-associated liver disease is expected to represent the highest proportion of patients listed for liver transplantation in the future. Although genetic factors have also been identified, the disease is thought to be primarily a consequence of hyperalimentation and the hepatic manifestation of the metabolic syndrome.(Loomba, Friedman et al. 2021) The clinical symptoms of non-cirrhotic MASLD are usually non-specific. (Geier, Rinella et al. 2021) With a global prevalence of approximately 25%, MASLD is now the leading cause of chronic liver disease worldwide and a growing public health challenge. A further increase in MASLD in the sense of the obesity epidemic, especially among adolescents and younger patients, is to be expected. Changes in lifestyle and demographic changes are causing an increase in MASLD prevalence. Doctors and patient organisations have to deal with this collectively and individually.(Roeb, Canbay et al. 2022) In 2023, a new category was introduced alongside pure metabolic dysfunction-associated steatotic liver disease, called metabolic and alcohol-related/associated liver disease (MetALD). This category describes people with metabolic dysfunction-associated steatotic liver disease who consume larger amounts of alcohol per week (140-350 g/week and 210-420 g/week for women and men respectively). (Rinella, Lazarus et al. 2023)

Prevalence

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a major disease burden in the last decades. The estimated overall global prevalence of MASLD in the general population diagnosed by imaging is about 25%-30% with an expected significant increase in the next years.(Younossi, Koenig et al. 2016, Estes, Anstee et al. 2018, Younossi, Golabi et al. 2023) Newest data report a global MASLD prevalence of 30% and increasing in adults, and 7, 4% in children/adolescents which requires urgent and comprehensive strategies on local, regional, and global levels. (Paik, Henry et al. 2023)

The incidence of MASLD ranges globally between 28 and 52 per 1000 person years.(Younossi, Henry et al. 2018, Paik, Henry et al. 2023) In absolute numbers, it is estimated that 64 million subjects are affected by MASLD in the United States and 52 million in Europe.(Younossi, Koenig et al. 2016) Following a steady increase over the past decades, MASLD represents in the meantime the second most common indication for liver transplantation in the north American UNOS network.(Younossi, Stepanova et al. 2021) On the European transplant waiting list by far less end-stage patients with MASLD appear in the ELTR registry.(Haldar, Kern et al. 2019)

Global estimates of MASLD prevalence vary among the different continents and range from 32% in the Middle East and 31% in South America to 23% in Europe, 24% in the United States and 27% in Asia.(Younossi, Koenig et al. 2016, Younossi, Henry et al. 2018) The steady increase over the past decades can be monitored globally. According to recent modelling, the number of MASLD patients in Germany has been estimated to be 18.4 million with more than 3 million affected by MASH. The number of MASH patients with advanced fibrosis may be as high as 600.000 and is expected to more than double until 2030.(Estes, Anstee et al. 2018) Projections suggest that the number of NASH cases in the United States will increase by 82.6% from 11.61 million (2020) to 19.53 million (2039).(Younossi, Paik et al. 2023)

In a population based study with data from 2007-2012, the prevalence of

FIB-4 >2.67 was 1.1% in the general population which is in rough accordance with these numbers.(Huber, Schulz et al. 2022) Given an estimated current number of 200.000 MASH patients with cirrhosis in Germany, it appears remarkable that MASLD/MASH represented only 13% of the indications on German liver transplantation waiting lists in 2015.(Tacke, Kroy et al. 2016) One reason for this discrepancy may be the frequently absent diagnosis in clinical reality. It has been suggested that MASH accounts for more than 50% of cases of cryptogenic cirrhosis.(Ratziu, Giral et al. 2000)

Among all subjects with MASLD, the relative proportion of MASH as the inflammatory and progressive disease entity ranges from 10% to 20%. The absolute prevalence of MASH in Western countries is approximately 2-6%.(Younossi, Koenig et al. 2016, Younossi, Henry et al. 2018) Due to a preselection of patients at risk, the prevalence of MASH/NASH in liver biopsies of NAFLD/MASLD patients is around 60-70% (Younossi, Koenig et al. 2016).

Demographics and risk factors

MASLD is more prevalent in males than in females and its prevalence increases with age.(Roeb, Canbay et al. 2022, Le, Le et al. 2023) There is a clear association with metabolic comorbidities. In German MASLD cohorts, more than 30-60% of MASLD patients have type 2 diabetes, 37-84% show hyperlipidaemia, and 52-67% have arterial hypertension.(Labenz, Huber et al. 2018, Alsenbesy, Rau et al. 2019, Hofmann, Buggisch et al. 2020, Geier, Rau et al. 2023) All comorbidities were more prevalent in high risk as compared to low risk patients (FIB-4 <1.3) including arterial hypertension (85% vs. 42%), hypercholesterolaemia (39% vs. 16%), and type 2 diabetes mellitus (69% vs. 26%).(Geier, Rau et al. 2023)

Increased BMI, particularly visceral obesity and presence of the metabolic syndrome are established risk factors for the presence of MASLD. The prevalence of MASLD has been continuously rising over the past decades along the global increase in BMI and obesity, which affects more than 650 million subjects worldwide.(Younossi, Loomba et al. 2018) Based on ultrasound data, the prevalence of MASLD increases proportionally to BMI from 25% with normal BMI up to >90% in subjects with obesity (BMI >30kg/m2).(Bedogni, Miglioli et al. 2007) The prevalence of type 2 diabetes has increased in parallel to the increasing prevalence of obesity with more than 400 million affected subjects worldwide.(Younossi 2019) MASLD affects 60-70% of patients with type 2 diabetes and the presence of diabetes represents a significant risk factor for fibrosis progression and cirrhosis development.(Younossi, Koenig et al. 2016, Younossi, Anstee et al. 2018) Based on the steady increase in diabetes over the past, projections for the year 2030 estimate an increase by around 50% in MASH and even a more than doubling in MASH patients with end-stage liver disease.(Estes, Anstee et al. 2018) The expected increase in end-stage disease is at least partly explained by the aging of western populations. Prevalence and advanced stages of the disease are both increasing with patient age, which in turn is associated with more frequent metabolic comorbidities.(Younossi 2019, Roeb, Canbay et al. 2022)

MASLD represents a multifactorial disease caused by environmental, genetic, and epigenetic factors. The inheritable component accounts for 20-40% of the NAFLD phenotype.(Zimmer and Lammert 2011) The prevalence of MASLD differs with ethnicity and is highest in subjects with Hispanic descent.(Williams, Stengel et al. 2011, Rich, Oji et al. 2018) Several single nucleotide polymorphisms have been associated with an increased prevalence of MASLD. The most relevant has been located in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene in the first genome-wide association study.(Romeo, Kozlitina et al. 2008) Indeed, the PNPLA3 risk G allele frequency worldwide is highest in populations of Mesoamerica.

However, around 20% of patients with MASLD have normal body weight and were therefore formely referred to as lean NAFLD (BMI <25kg/m² or <23kg/m² in Asians).(Ye, Zou et al. 2020, Young, Tariq et al. 2020) Lean NAFLD patients have a different disease phenotype with less inflammatory activity, increased odds for genetic contribution such as PNPLA3 risk allele polymorphism and probably a better prognosis.(Ye, Zou et al. 2020, Young, Tariq et al. 2020) In non-obese MASLD the PNPLA3 risk allele frequency exceeds the prevalence of obese MASLD patients with almost 80% carrying at least one risk allele.(Krawczyk, Liebe et al. 2020) In the new internationally agreed nomenclature, the term lean NAFLD no longer appears and is largely identical to the new definition of MASLD patients (Rinella, Lazarus et al. 2023).

Pathogenesis

Hepatic steatosis (fatty liver cells) is characterised by storage of fat in more than 5% of hepatocytes. Steatohepatitis is present when inflammation and liver cell damage can be detected in addition to hepatic steatosis. (Loomba, Friedman et al. 2021) Although diet-related and alcoholic causes of steatosis and steatohepatitis are the most common, the differential diagnostic spectrum of possible causes of obesity-associated liver damage is broad. These causes should be determined in any case and considered for the final interpretation of the liver damage.

Both, alcoholic (ASH) and non-alcoholic steatohepatitis (MASH/NASH)

are characterised by fatty degeneration and lobular inflammation with ballooning of liver cells, resulting in mesh wire fibrosis (progressive if the inflammation persists).(Kleiner, Brunt et al. 2005) In general, a reliable differential diagnosis of ASH vs. MASH/NASH cannot be made solely on the basis of histological criteria. The differences between ALD and MASLD worked out are of a gradual nature and therefore not sufficiently reliable for the typing of the individual case (cave: lifestyle modification before the liver biopsy). Fatty degeneration and the formation of glycogen hole cores are often more pronounced in MASH/NASH, while inflammatory activity and the detection of Mallory Denk Bodies (MDB) and satellitosis (granulocytic demarcation of a hepatocyte with MDB) might be observed more frequently in ASH.(Morita, Ueno et al. 2005)

Most patients with MASLD have central obesity and other components of a metabolic syndrome. However, MASLD can also develop in patients of normal weight (formerly lean NAFLD, approx. 20% of cases, BMI = 18.5-24.9 kg/m2). It is assumed that these patients may have less inflammatory activity and therefore have a better prognosis.(Ye, Zou et al. 2020) Due to the frequent association with the metabolic syndrome, a consensus panel suggested that NAFLD could be called metabolic-associated fatty liver disease (MASLD).(Eslam, Sanyal et al. 2020) This designation, however, excludes some entities. On the one hand, the lean NAFLD in the absence of metabolic comorbidities is blurred; on the other hand, the congenital metabolic diseases (e.g. mitochondriopathies, glycogenoses) represent independent pathogenetic and therapeutic entities.(George, Gish et al. 2021) The new nomenclature means that all fatty liver diseases, including ALD, monogenetic and cryptogenic liver damage and drug-induced liver injury, are now summarised under the term steatotic liver disease, SLD (Rinella, Lazarus et al. 2023).

Figure 1 depicts the positive and negative factors for the development of MASLD. The diagnosis of MASH represents a precancerous condition/lesion, so that it can lead to the development of hepatocellular carcinoma (HCC) and more rarely intrahepatic cholangiocarcinoma (iCCA; ratio: 5-7 HCC/ 1 iCCA). As detailed below, tumour surveillance should be performed according to current liver cancer guidelines (Loomba, Lim et al. 2020).

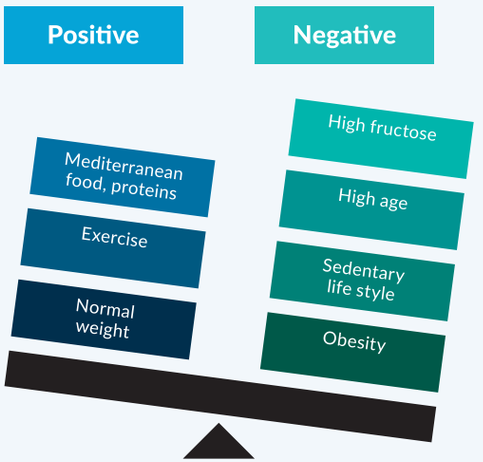

Figure 1. Risk factors (negative) and protective factors (positive) for the development of MASLD.

The decisive factor for the prognosis of MASLD patients is the stage of fibrosis. A meta-analysis from five studies involving 1495 biopsy-proven MASLD/NAFLD patients and a follow-up of 17, 452 patient-years showed that compared to MASLD patients without fibrosis (F0), those with fibrosis were at increased risk for both, total and also liver-specific mortality, which increased continuously with the fibrosis stage. With regard to liver-specific mortality, an exponential increase in risk was recorded.(Dulai, Singh et al. 2017) The greatest risk for liver-specific but also overall morbidity and mortality from MASLD was found for advanced fibrosis (F3) and liver cirrhosis (F4). The following event rates existed in an average observation period of 5.5 years: 8% all-cause mortality, 8% liver transplantation, 19% first-time hepatic decompensation, 9% HCC, 3% vascular events and 7% non-hepatic malignancies. The 10-year transplant-free survival was 94% for F3 and 45.5% for F4. Higher cumulative incidences of vascular events (7% vs. 2%) and non-hepatic malignancies (14% vs. 6%) were found in F3. In patients with liver cirrhosis, on the other hand, the frequency of hepatic decompensation and HCC development was increased: 44% (F4) vs. 6% (F3) and 17% (F4) vs. 2.3% (F3).(Vilar-Gomez, Calzadilla-Bertot et al. 2018) These data suggest that cardiovascular and non-hepatic morbidity and mortality are already dominant in non-cirrhotic MASLD patients, while the complications of advanced liver disease determine further prognosis in established liver cirrhosis.

Xiao et al. conducted a meta-analysis of over 13, 000 subjects to determine

the best method for assessing fibrosis in MASLD. Comparing APRI, FIB-4, BARD score, NAFLD fibrosis score (NFS), transient hepatic elastography, shear wave elastography (SWE) and magnetic resonance elastography (MRE), MRE and SWE showed the highest diagnostic accuracy for the fibrosis stage. Among the four non-invasive simple indices, NFS and FIB-4 were at best for detecting advanced fibrosis.(Xiao, Zhu et al. 2017) According to current meta-analyses, complex biomarker panels and elastography can identify MASLD-related fibrosis with moderate accuracy in obese subjects, but these methods are not yet well validated (Ooi, Mgaieth et al. 2018).

Human genetic factors

Genetic factors play a considerable role in the development of hepatic fat accumulation. In 2008, two GWAS studies linked the rs738409 polymorphism (I148M) of PNPLA3 (see above) with hepatic fat content and alanine aminotransferase (ALT) levels.(Romeo, Kozlitina et al. 2008, Yuan, Waterworth et al. 2008) Further studies suggest that the I148M variant is an important risk factor for the development of MASH fibrosis, cirrhosis and hepatocellular carcinoma.(Dubuquoy, Burnol et al. 2013) The I148M PNPLA3 variant favours hepatic carcinogenesis not only in steatohepatitis but also in other liver diseases. Further GWAS studies have uncovered robust and reproducible associations in other genes including transmembrane 6 superfamily member 2 (TM6SF2), membrane bound O-acyltransferase domain-containing 7 (MBOAT7) and more recently in the 17-beta hydroxysteroid dehydrogenase 13 (HSD17B13) genes.(Trépo and Valenti 2020) Phenome-wide association studies (PheWAS) for disease endpoints revealed that PNPLA3 is also associated to other forms of liver injury and support the hypothesis that therapeutic inhibition of PNPLA3 could treat liver diseases.(Diogo, Tian et al. 2018) At this time, the use genetic SNPs as biomarkers for risk assessment are not recommended in clinical routine since the odds ratio of these variants to predict clinical endpoints is too low to justify their use.(Roeb, Canbay et al. 2022) However, combined models may be used in the future. Combined effects of PNPLA3, TM6SF2 and MBOAT7 have been detected on liver damage in MASLD as transaminase levels are proportionally increasing with increasing number of risk alleles present (Krawczyk, Rau et al. 2017).

Microbiome

Several studies indicate that the intestinal microbiome is involved in both the development and progression of MASLD.(Boursier, Mueller et al. 2016) NASH patients are characterised, for example, by a different composition of the gut microbiome with higher faecal levels of short-chain fatty acids (SCFAs) and an increased frequency of SCFAs-producing bacteria. These changes are associated with immunological features of MASLD progression. (Rau, Rehman et al. 2018) However, no specific microbiota composition for MASLD can currently be determined. Therefore, stool diagnostics are currently not suitable for screening or diagnosing MASLD.

Fetal development is influenced not only by genetics, but also by the interaction of parental and environmental conditions before conception and during pregnancy. Collectively, these factors could lead to fetal programming of adulthood diseases, including MASLD. Programming of MASLD can be influenced by maternal factors such as obesity/overweight, nutritional status, health status, changes in the microbiome and epigenetic changes, vitamin supplements, use of medications during pregnancy, and exposure to environmental pollutants. Paternal factors such as nutritional status, exercise, and alcohol consumption may also play important roles in programming for MASLD (Galvan-Martinez, Bosquez-Mendoza et al. 2023).

Natural history

So far, histological MASH/NASH has been considered the progressive form of MASLD; meanwhile it has been repeatedly shown that simple steatosis or in analogy to the new nomenclature MASL (metabolic dysfunction associated steatotic liver) can also be progressive.(Sanyal, Harrison et al. 2019) In a meta-analysis of 11 studies with paired biopsies, fibrosis progression by one stage was 14.3 years for NAFL and 7.1 years for MASH/NASH.(Singh, Allen et al. 2015) In another large study (n=646), the mean time to the development of end-stage liver cirrhosis was examined in biopsy-confirmed MASLD and an observation period of 20 years. Time to cirrhosis was for F0; F1; F2; F3 and F4 each at 33.4; 34.1; 22.7; 11.8 and 5.6 years. As outlined, the decisive factor for MASLD prognosis is the underlying stage of fibrosis.(Dulai, Singh et al. 2017) The greatest risk for liver-specific but also overall morbidity and mortality in NAFLD is the presence of advanced fibrosis (F3) and liver cirrhosis (F4). Cardiovascular and non-hepatic morbidity and mortality are the main factors in non-cirrhotic MASLD patients (Long, Zhang et al. 2021), while the complications of advanced liver disease determine the further prognosis in patients

with manifest liver cirrhosis. The latter particularly includes the risk of HCC development. Depending on the region and study population, the prevalence is between 0.8% and 34%.(Younossi 2019) The major challenge is that in MASLD, HCC can also develop in non-cirrhotic livers (up to 20-50% of cases in some series).(Kanwal, Kramer et al. 2018) Following epidemiology, MASLD is increasingly becoming an indication for LTX (see below).

Depending on the fibrosis stage, patients with MASLD have increased liver-related and all-cause mortality compared to healthy controls. Cardiovascular causes of death come first. In a retrospective analysis of 619 NAFLD patients over the period 1975-2005 and a median follow-up of 12.6 years, cardiovascular disease was the most common cause of death (38%), followed by non-hepatic cancer (19%) and complications of liver cirrhosis (8%).(Angulo, Kleiner et al. 2015) Similar data come from two prospective studies from Sweden with a follow-up up to 33 years: cardiovascular causes of death 43% and 48%, non-hepatic tumours 23% and 22%, and liver-related mortality 9% and 10%.(Ekstedt, Hagström et al. 2015, Nasr, Ignatova et al. 2018) A meta-analysis with 6, 263 patients showed that MASLD is associated with the occurrence of extrahepatic tumours such as colorectal adenomas (OR 1.74).(Shen, Lipka et al. 2014) In a study with 25, 497 participants and an observation period of 7.5 years, patients with MASLD showed an increased incidence of colorectal carcinoma in men and breast carcinoma in women in addition to the known risk of HCC, especially in advanced fibrosis. (Kim, Lee et al. 2017, Yang, Teng et al. 2023) Surveillance of these patients is therefore warranted.

Screening

Liver fibrosis is the only liver lesion independently associated with long-term overall mortality, liver transplantation, and liver-related events in MASLD.(Angulo, Kleiner et al. 2015, Dulai, Singh et al. 2017) Aim of the screening process is therefore to identify patients with progressive fibrosis who are at risk to develop complications over time. Several non-invasive tests (NIT) are available for the evaluation of liver fibrosis in MASLD, essentially blood-based tests and elastography devices including Fibroscan (vibration controlled transient elastometry, VCTE).(Loomba and Adams 2020) Investigating a larger region of interest compared to the volume of a liver biopsy, elastometry procedures offer obvious advantages and have a good accuracy for the diagnosis of advanced F3-4 fibrosis. In a recent individual patient data meta-analysis AUROCs of individual VCTE, Fibrosis-4 Index (FIB-4) and NAFLD Fibrosis Score (NFS) for advanced fibrosis were 0.85, 0.76 and 0.73.(Mózes, Lee et al. 2022) Both, blood-based tests and elastography can identify the subset of MASLD patients who have an impaired liver-related prognosis and who therefore require an intensive management of their liver disease.

According to current guidelines, screening is recommended in the established populations with an increased risk for fatty liver disease but should be performed in the unselected general population.(2016, Chalasani, Younossi et al. 2018, Roeb, Canbay et al. 2022) As outlined above, these populations at risk are subjects with obesity, metabolic syndrome or metabolic disease such as type 2 diabetes, hypertension, hyperlipidaemia. In current real world settings, the initial diagnosis of MASLD is typically achieved through suggestive laboratory results and ultrasound findings mostly in patients with obesity and/or metabolic risk.(Roeb, Canbay et al. 2022) Principal aim of the initial workup of patients with MASLD is the identification of patients at risk for advanced fibrosis and in turn related clinical events over time. Even more important is the exclusion of advanced disease in low-risk patients who will not be considered for further costly and time-consuming workup. Based on clinical risk factors for disease progression such as age, presence of diabetes and/or laboratory findings, various algorithms have been established for initial MASLD risk assessment (NAFLD Fibrosis Score (NFS) and fibrosis-4 index (FIB-4)) and are recommended in current guidelines.(2016, Chalasani, Younossi et al. 2018, Roeb, Canbay et al. 2022) Thresholds for the different risk categories mentioned in table 1 are as follows: FIB-4 score (<1.3, ≥1.3-<2.67, ≥2.67 for low, indeterminate and high risk), NAFLD fibrosis score (NFS) (<-1.455, -1.455-0.676, >0.676 for low, indeterminate and high risk). For patients with intermediate or high risk in primary testing (≤8.0 kPa, >8.0-<10.0 kPa, ≥10.0 kPa for low, indeterminate and high risk), elastography is recommended in a second step to guide the decision for liver biopsy to confirm advanced hepatic fibrosis. Again, patients with low risk of advanced disease will not be considered for further workup. Primary goal of the proposed algorithms is to narrow down the large number of patients with putative MASLD (mostly suggestive ultrasound findings) in primary care (estimated 25-30%) to a limited number of patients at risk for secondary and tertiary care (estimated 3-5%).(Dietrich, Rau et al. 2021) In contrast to fibrosis assessment, no NIT has so far achieved enough accuracy and validation for the non-invasive diagnosis of MASH.

Diagnosis

MASLD has been defined as a liver disease with more than 5% steatotic hepatocytes in the absence of a relevant alcohol consumption and secondary causes of hepatic lipid accumulation. Since only approximately 10% of Western populations are completely abstinent from alcohol, thresholds

of a daily alcohol ingestion of 10-20 g in females and 20-30 g in males (different thresholds in the international guidelines) have been defined to differentiate "MASLD " from metALD and ALD.(Roeb, Canbay et al. 2022) r(Rinella, Lazarus et al. 2023)

The initial diagnosis of MASLD is most frequently made by routine ultrasound based on typical finding of a "bright" or "hyperechogenic" liver parenchyma. Of note, the sensitivity of ultrasound is only sufficient to reliably detect hepatic steatosis of 30% or more.(Saadeh, Younossi et al. 2002) Hepatic steatosis can be semi-quantitatively graded into four grades (0-3). Integrated into the FibroScan® device, controlled attenuation parameter (CAP) has been developed as a more sensitive non-invasive method for detection and quantification of hepatic steatosis. CAP detects the attenuation of the ultrasound which correlates with the hepatic fat content and is given in dB/m (reference value for absent steatosis <250 dB/m). The AUROC for the detection of nay hepatic steatosis is 0.82.(Karlas, Petroff et al. 2017) The most obvious advantage of CAP over ultrasound is the high sensitivity with a lower treshold of 5% for fat detection. At least as sensitive as CAP is the magnetic resonance (MR) based fat quantification which represents the gold standard. MR Proton density fat fraction (PDFF) has emerged to be a promising tool in precise fat quantification with a lower detection limit of 5%.(Loomba 2018) However, this method is not widely available at present and mostly used for clinical research in academic centres.

The diagnosis of MASH/NASH is restricted to histopathological workup as this disorder is characterised by the simultaneous presence of steatosis, hepatocyte damage, lobular inflammation and fibrosis with centrilobular (zone 3) pattern of injury. The term "fatty liver hepatitis" as a surrogate of "steatohepatitis" first appeared in 1962 in the German literature to describe fatty liver with necroinflammation.(Geier, Tiniakos et al. 2021) Subsequently, Jurgen Ludwig from the Mayo Clinic, Rochester, MN, USA coined the term "non-alcoholic steatohepatitis" in 1980 as a "hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis".(Ludwig, Viggiano et al. 1980) The NASH Clinical Research Network (NASH CRN) established and validated the NASH CRN score as the first globally accepted, scoring system that addressed the full spectrum of MASLD lesions and proposed the summative NAFLD activity score (NAS) to semi-quantify disease activity in clinical trials.(Kleiner, Brunt et al. 2005) The NAS (range 0-8) is calculated by summing-up semi-quantitative scores for three of the most important histological features of NAFLD: steatosis (0-3), lobular inflammation (0-2), and hepatocellular ballooning (0-2). Kleiner and colleagues observed that NAS >5 correlated with MASH/NASH diagnosis whereas biopsies with NAS scores of <3 correlated with "not MASH/NASH."(Kleiner, Brunt et al. 2005) However, MASLD displays a continuous spectrum of hepatocytic, inflammatory and fibrous lesions and therefore, the binary categorisation of MASLD into MASH/NASH and "not MASH/NASH" is artificial in a continuous disease process.(Bedossa 2013) In 2012, Bedossa and colleagues developed a simple algorithm to standardise the histological diagnosis of MASH/NASH and reduce inter-observer variability. This diagnostic algorithm was informed by scores for steatosis (S0-S3), activity grade (A0-A4 by adding scores for ballooning (0-2) and lobular inflammation (0-2)) and fibrosis stage (F0-F4).(Bedossa, Poitou et al. 2012) Validated by pathologists from the Fatty Liver Inhibition of Progression (FLIP) consortium, the SAF scoring system (Steatosis, Activity, Fibrosis) includes the same categories as NAS for the semi-quantitation of liver injury but the diagnostic FLIP algorithm requires the simultaneous presence of steatosis, ballooning and lobular inflammation for MASH/NASH diagnosis.(Bedossa and Consortium 2014)

The available elastrography devices calibrated on the different fibrosis stages allow of fully non-invasive stratification of MASLD that is well adapted to decision-making in clinical practice. However, the sensitivity and specificity for early fibrosis stages is modest and a high rate of false positive results limit the positive predictive value of these methods.

Recently, the LiverRisk score was prospectively developed from an international cohort from six countries of individuals in the general population without known liver disease who underwent assessment of liver fibrosis by transient elastography. The score includes age, gender and six standard laboratory variables. The overall AUC of the score for predicting 10-year liver-related mortality was 0-90 (0-88-0-91) compared to 0.84 (0-82-0-86) for the FIB-4 consisting of liver age and three laboratory values. (Serra-Burriel, Juanola et al. 2023)

Histopathology as the gold-standard of fibrosis staging is still used whenever exact fibrosis staging is needed, particularly in clinical trials.

Table 1. Calculation of non-invasive fibrosis scores

NFS	-1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio – 0.013 x platelet (x10^9/L) – 0.66 x albumin (g/dL)
FIB-4	$\frac{\text{Age (years) x AST (U/L)}}{\text{Platelet counts (10}^9\text{/L) x } \sqrt{\text{ALT(U/L)}}}$

Notice

Ultrasound (US) should be used as primary imaging in patients with suspected MASLD can be used, but does not allow a differentiation between simple steatosis and MASH (steatohepatitis).

Magnetic resonance-based methods (MR-PDFF, MR-S) can be performed to quantify fat in the liver, but are not suitable for comprehensive diagnostics due to cost and availability.

Computed tomography (CT) should not be used in the primary diagnosis of MASLD.

Non-invasive fibrosis scores such as FIB-4 or the NAFLD Fibrosis Score (NFS) are used for risk assessment for the primary evaluation of high-risk patients in whom fatty liver has been detected or who have elevated liver values (GOT, GPT and/or γGT). Suitable as well are ultrasound-based elastography methods.

A liver biopsy should only be performed if fibrosis needs to be reliably detected or ruled out (e.g. in the context of studies) or to rule out/prove other liver diseases.

FIB-4 = [age (years) × AST (U/L)] / [Platelets (10^9/L) × (ALT (U/L)$^{1/2}$]

Therapy

a) Diet, physical exercise and lifestyle recommendations

A decrease in body weight is accompanied by regression of steatosis in overweight or obese MASLD patients.(2016) The decrease in steatosis and ALT/GPT is proportional to weight loss; there is a clear relationship between degree of weight loss and effect.(Parry and Hodson 2020) It is irrelevant how the weight loss is achieved. The evaluation of paired liver biopsies from MASH patients before and after weight reduction shows that a weight reduction of at least 10% must be achieved in order to achieve regression of fibrosis and complete resolution of MASH/NASH.(Vilar-Gomez, Martinez-Perez et al. 2015) Systematic reviews and guidelines also come to this conclusion. Less weight loss primarily leads to an improvement in steatosis and transaminases. In normal-weight MASLD patients, a controlled study showed 50% remission of steatosis if a weight reduction of 3-5% was achieved.

A combination of hypocaloric nutrition and exercise is recommended based on existing evidence. A 16-week lifestyle intervention with hypocaloric nutrition and aerobic exercise resulted in significant reductions in weight and portal hypertension in overweight or obese patients with liver cirrhosis; a weight reduction of at least 10% was associated with a 23% reduction in hepatic venous pressure gradient (HVPG).(Berzigotti, Albillos et al. 2017) No long-term results from studies on lifestyle intervention are available to date on the question of regression of existing MASH cirrhosis or prevention of disease progression including the development of HCC.

Overall, a weight reduction of at least 10% is extremely effective in the treatment of MASH (90% cure rate), but in clinical practice a goal that has only been achieved by 10% of patients. Concepts such as web-based training, text messaging or increased motivation through donations for charitable purposes are new approaches to solving this dilemma.

Exercise should be done to reduce fatty liver and increase the anti-inflammatory effect of weight loss. An improvement in the necro-inflammatory process has not yet been proven. Determinations of liver fat using 1H-MRS show that aerobic exercise without changing body weight resulted in a decrease in hepatic fat content. Meta-analyses show that aerobic training and/or isometric training in MASLD patients even improved transaminases and hepatic fat content independently of weight loss.(Hashida, Kawaguchi et al. 2017) Both training concepts are apparently equally effective. Aerobic or isometric training can reduce hepatic fat content and insulin resistance. It therefore seems plausible to recommend such training to normal-weight MASLD patients in order to improve steatosis and insulin sensitivity. A meta-analysis came to an end, that both forms of training are equally effective with regard to hepatological endpoints, but that isometric training is less stressful for people with poor cardiorespiratory fitness.(Hashida, Kawaguchi et al. 2017)

According to the WHO exercise guidelines of November 25th, 2020, published at https://www.who.int/publications/i/item/9789240015128, patients with MASLD and a BMI >20 and <25kg/m2 should exercise at least 150 to 300 minutes per week engage in moderate-intensity aerobic physical activity or at least 75 to 150 minutes of vigorous-intensity aerobic physical activity. Alternatively, an equivalent combination of moderate- and vigorous-intensity activity during the week can also be considered.

The rationale for weight reduction is an improvement in comorbidity risks, in transaminases and in liver histology (necroinflammation). Mediterranean diet (ME) can improve steatosis and insulin sensitivity. The results of seven interventional and four observational studies suggest that ME has beneficial effects on body weight and insulin sensitivity and hepatic steatosis.(Roeb, Canbay et al. 2022) However, the available data

on the preventive effectiveness of ME with regard to the occurrence of MASLD is less clear. Data from the Framingham study show a reduced risk of developing MASLD in people with high adherence to ME; here, a high-quality diet such as ME was effective, especially in the presence of genetic risk factors.(Suárez, Boqué et al. 2017)

Overweight or obese MASLD patients should be advised on a hypocaloric diet in accordance with the guidelines for the treatment of obesity (AWMF Guideline Adiposity Prevention and Therapy 050-001).(Garvey, Mechanick et al. 2016) The caloric target is 1200 kcal/d for women and 1400-1500 kcal/d for men, corresponding to a reduction of -500 to -1000 kcal/d. The combination of hypocaloric nutrition with aerobic or isometric training acts synergistically and increases the effectiveness in improving steatosis and necroinflammatory activity.(Vilar-Gomez, Martinez-Perez et al. 2015) When energy balance was altered to the same extent by either a hypocaloric diet alone or a combination of less restrictive nutrition and exercise, participants in a systematic study each achieved the same weight loss (-10%) and the same improvement in transaminases, liver fat, and insulin sensitivity. Both interventions are also effective on their own if the other variable – weight or physical activity – is held constant.

The study situation shows no advantage for a specific composition of the macro nutrients fat or carbohydrates of a hypocaloric diet with regard to weight reduction or improvement of transaminases or histological changes in MASLD. This also applies to the use of formula diets, so-called very low energy diets (VLED), as a meal replacement.(Deibert, Lazaro et al. 2019) Using a VLED (800 kcal/d), more than 80% of a Munich cohort achieved a weight loss of at least 10% in 52 weeks, accompanied by significant improvements in transaminases, Fatty Liver Index and NAFLD Fibrosis Score.(Hohenester, Christiansen et al. 2018) A high-protein diet may be beneficial. In obese patients with T2DM, an isocaloric high-protein diet led to an improvement in steatosis, insulin sensitivity, and BMI after 6 weeks. (Markova, Pivovarova et al. 2017)

The rapidly increasing obesity prevalence in recent decades has been associated with the increasing consumption of fructose and fructose-containing corn syrup in processed foods and beverages.(Stricker, Rudloff et al. 2021) However, meta-analyses did not show that fructose consumption as part of a normocaloric diet promotes the development or progression of MASLD. In a double-blind study in obese subjects, excess caloric intake, but not fructose versus isocaloric amounts of glucose, was associated with increases in hepatic fat content and transaminases.(Johnston, Stephenson et al. 2013)

Compared to metabolically healthy people, also people of normal weight who are metabolically ill have a more than three-fold increased risk of mortality or cardiovascular events. A controlled study of normal-weight (BMI 22.7 kg/m2) MASLD patients in Hong Kong showed that a hypocaloric diet with a weight reduction of 3-5% led to remission of MASLD in 50% (measured by determining hepatic fat content using 1H-MRS). (Wong, Wong et al. 2018)

b) Alcohol and coffee, stimulants

Retrospective studies that show a beneficial effect of moderate alcohol consumption on health must be evaluated critically, since they only examined associations and not causalities. In addition, prospective data from animal experiments clearly showed a negative influence of alcohol on, for example, diet-induced fatty liver. This observation could also be made in MASLD patients who showed accelerated fibrosis progression due to alcohol consumption.(Ajmera, Terrault et al. 2017) Finally, a retrospective study showed that patients with MASH cirrhosis who consume alcohol, even in small amounts, had a significantly higher risk of developing HCC.(Ascha, Hanouneh et al. 2010) Alcohol consumption is a significant risk factor for the development of liver cirrhosis, and social alcohol consumption should be avoided completely, especially in advanced stages of the disease. Absolute abstinence is recommended here. Due to the relevant and significant damaging mechanisms of alcohol in metabolic dysfunction associated fatty liver disease, the new nomenclature provides for a separate group for these patients, the metALD.(Rinella, Lazarus et al. 2023)

Systematic reviews and meta-analyses suggest that drinking coffee reduces disease progression and HCC risk. Higher doses of coffee resulted in a higher risk reduction. The protective agents from coffee and the molecular mechanisms of HCC prevention have so far remained unclear. Positive effects related to coffee consumption can be derived from epidemiological studies.(Poole, Kennedy et al. 2017) A protective effect of coffee consumption was shown here in relation to the risk of suffering from MASLD and also in relation to the fibrosis stage, although there are no controlled studies on the subject. In a pooled meta-analysis with a total of 11 studies, people who drank coffee had a relative risk of 0.77 (95% CI 0.60-0.98) of suffering from MASLD. In addition, there was a significantly reduced risk of advanced liver fibrosis compared to patients who did not drink coffee (RR 0.68). (Hayat, Siddiqui et al. 2021)

Figure 2 summarises the diet, physical exercise and lifestyle recommendations in case of MASLD diagnosis.

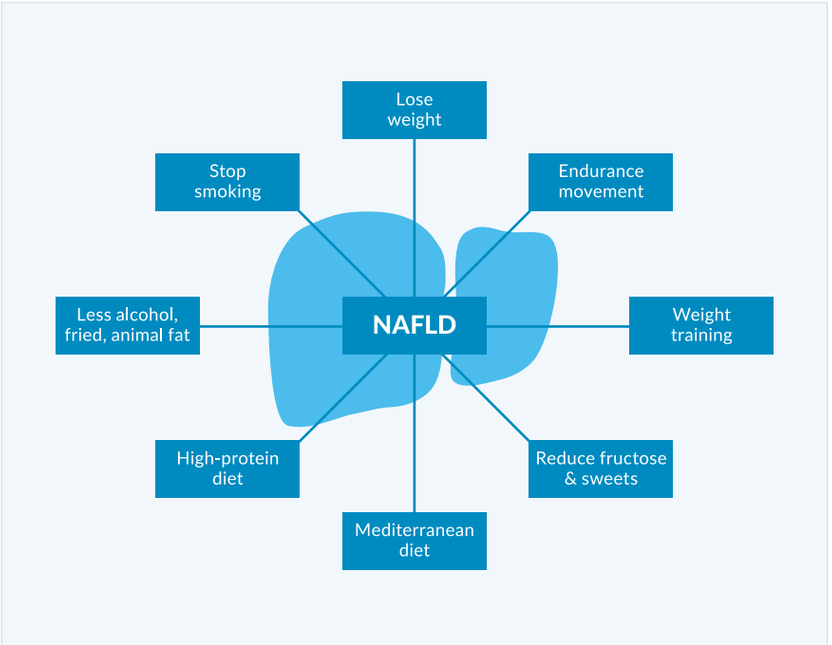

Figure 2. Recommendations for life style changes, cornerstone of medical recommendations. All recommendations are discussed intensively within the text.

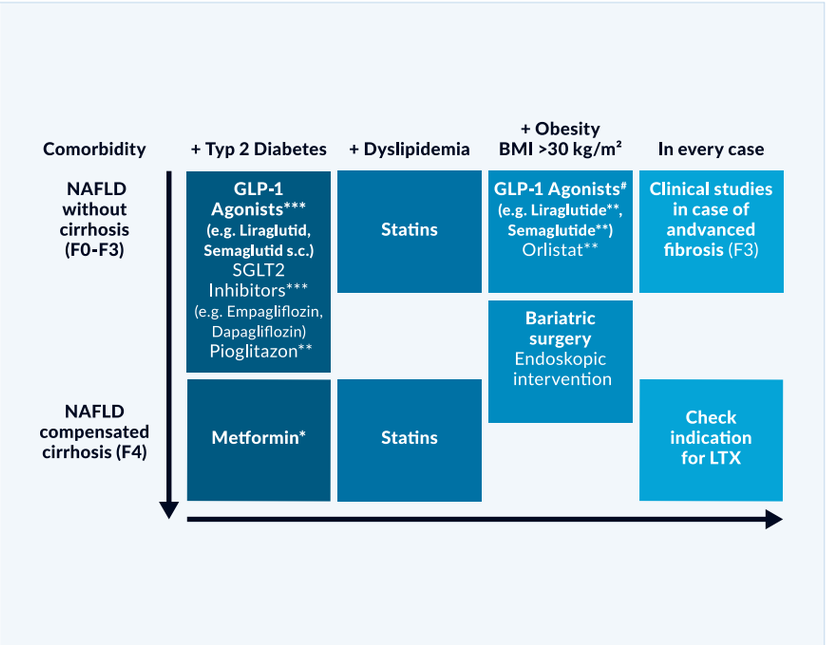

Figure 3. Recommendations to treat MASLD with regard of the fibrosis stage and accompanying comorbidities. *in case of GFR >30ml/min; **currently not reimbursable in statutory health insurance; ***approved in combination with metformin; #approval for liraglutide and semaglutide so far. Modified with regard to (Roeb, Canbay et al. 2022).

c) Pharmacological treatment

At the time this text was written, there was no medication approved for the MASLD indication.(Rau and Geier 2021) The general use of drugs such as ursodeoxycholic acid, pioglitazone, metformin, silymarin or pentoxifylline as well as dietary supplements such as vitamin E or omega-3 fatty acids should not take place based on the current data for the treatment of NAFLD. (Roeb, Canbay et al. 2022)

However, this does not imply that no pharmacological therapy would be available at all. The therapy of MASLD is currently based on the comorbidities where several drugs are approved with additional benefit an MASLD. Figure 3 gives an overview of these available drug therapies based on the fibrosis stage according to (Roeb, Canbay et al. 2022).

Due to the beneficial effects on MASH, non-cirrhotic MASLD patients with type 2 diabetes should be given (metformin plus) glucagon-like peptide 1 (GLP-1) agonists, e.g. liraglutide or semaglutide can be used. The use of sodium glucose dependent transporter 2 (SGLT2) inhibitors, e.g. drugs such as empagliflozin and dapagliflozin or the thiazolidinedione pioglitazone may be considered in these patients. Patients with MASH-associated cirrhosis and type 2 diabetes with compensated Child A cirrhosis and normal renal function may receive metformin.

GLP-1 agonists and SGLT2 inhibitors are only approved in combination with metformin (or as monotherapy in the case of metformin intolerance). The German guideline for type 2 diabetes from 2020 provides for a combination therapy of metformin + SGLT2 inhibitors or GLP-1 agonists for type 2 diabetes with risk factors; without risk factors even metformin monotherapy:

https://www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/dm-2aufl-konsultation.pdf. In the current European recommendations, metformin is only listed as the drug of first choice for T2DM therapy if there are no cardiovascular complications.(Cosentino, Grant et al. 2020) A placebo-controlled study with 52 MASH/NASH patients, in which 33% had T2DM, showed more frequent resolution of MASH/NASH and less frequent

progression of fibrosis after one year of liraglutide therapy.(Armstrong, Gaunt et al. 2016) Therapy with semaglutide for MASH and MASH fibrosis in stages F1-F3 was also associated with more frequent resolution of MASH/NASH, but without significant improvement in fibrosis. However, the daily injections tested in this phase 2 study correspond to a higher dosage than is currently approved in Germany for the treatment of T2DM (in combination with metformin). In addition, GLP-1 analogues showed positive effects in cardiovascular endpoint studies and have comparatively few contraindications. Therapy with sodium glucose dependent transporter 2 (SGLT2) inhibitors showed a significant improvement in liver fat content in patients with MASLD and T2D in proof-of-concept (phase 2a) studies. Data from randomised controlled studies on the effect of SGLT2 inhibitors on liver histology (phase 2b) are currently not available. SGLT2 inhibitors also show positive effects in cardiovascular and renal endpoint studies. The side effects mainly concern urogenital infection, dehydration and the masking of the symptoms and findings of diabetic ketoacidosis.

Furthermore, there are a number of older studies on the use of pioglitazone in patients with MASH who have either impaired glucose tolerance or T2DM. In an 18-month placebo-controlled study using a hypocaloric diet in patients with MASH and prediabetes or T2DM, followed by 18 months of open-label follow-up, therapy with pioglitazone showed greater reductions in liver fat content, more frequent resolution of MASH/NASH and also a greater improvement in fibrosis.(Cusi, Orsak et al. 2016) However, pioglitazone is contraindicated, particularly in heart failure (NYHA I-IV) and bladder carcinoma. Caution is also advised in those with an increased risk of bone fractures and higher degrees of obesity, since pioglitazone promotes weight gain. These safety concerns explain the overall lower strength of recommendation for pioglitazone.

There is currently insufficient experience with the possible use of GLP1 agonists, SGLT2 inhibitors or pioglitazone in patients with MASH-associated liver cirrhosis. SGLT2 inhibitors should be reduced in dose at GFR <60 mL/min and discontinued at <45 mL/min.

Other antidiabetics such as metformin, dipeptidyl peptidase IV inhibitors or insulin have so far not shown any specific advantages with regard to the therapy of MASLD . However, large retrospective studies have reported that there is a reduced risk of developing HCC in MASLD patients taking metformin. Also in patients with MASH-associated compensated liver cirrhosis Child A, taking metformin for diabetic treatment is associated with a reduced risk of hepatic decompensation and HCC. Thus, metformin can be used as the basis of T2D treatment even in compensated liver cirrhosis (up to a dose of 2 g/d with normal renal function).(Vilar-Gomez, Calzadilla-Bertot et al. 2021) Metformin is contraindicated at GFR below 30 mL/min. However, there are no prospective controlled studies on the use of metformin in liver cirrhosis.

A placebo-controlled study of patients with MASH and T2DM showed that vitamin E (800 IU/day) resulted in a greater reduction in liver fat content and more frequent MASH/NASH reduction without improvement in fibrosis.(Bril, Biernacki et al. 2019) The risk of increased mortality and morbidity with supplementation with vitamin E (see above) limits its use, particularly in patients with diabetes mellitus.

If a lipid metabolism disorder is present in MASLD patients, this should be treated effectively. In view of the overall beneficial effects, statins can also be used in MASLD patients with compensated liver cirrhosis.

The drug orlistat, which is approved for the treatment of obesity, also showed positive effects on the course of MASH. Such data (beneficial influence on MASLD) are not available for other approved weight reduction medicinal products.

d) Novel pharmacological approaches

Given the epidemic increase, regulatory agencies have defined an unmet medical need and implemented initiatives to expedite the development of drugs for MASH treatment (US Food and Drug Administration. Noncirrhotic Non-Alcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. https://wwwfdagov/media/119044/download. December 2018).

Taking the prognostic value of the fibrosis stage into account, the FDA encourages sponsors to focus future drug development on the area of greatest need and potential effect on health, which is the stage of non-cirrhotic MASH with liver fibrosis (US Food and Drug Administration. Noncirrhotic Non-Alcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. https://wwwfdagov/media/119044/download. December 2018).

New drugs for MASH treatment in clinical phase 2 and 3 development act on different pathophysiological processes such as metabolism/steatosis, inflammation or fibrosis. However, monotherapy with these drugs led to a histological resolution of MASH/NASH at the maximum of 32% of patients compared to a 10-15% response in placebo.(Dufour, Caussy et al. 2020) Therefore, the future in MASH therapy will putatively be a combination therapy of two different drug classes with complementary effects. Current drug classes for MASH treatment include agonists of nuclear receptors such as FXR agonists (including FGF19), PPAR agonists, thyroid hormone receptor-ß agonists as well as analogues of enterohepatic hormones such as GLP-1, FGF21(Loomba, Sanyal et al. 2023) or SGLT2 inhibitors.(Rau and Geier 2021) Therapeutic targets for MASH are summarised in figure 4.

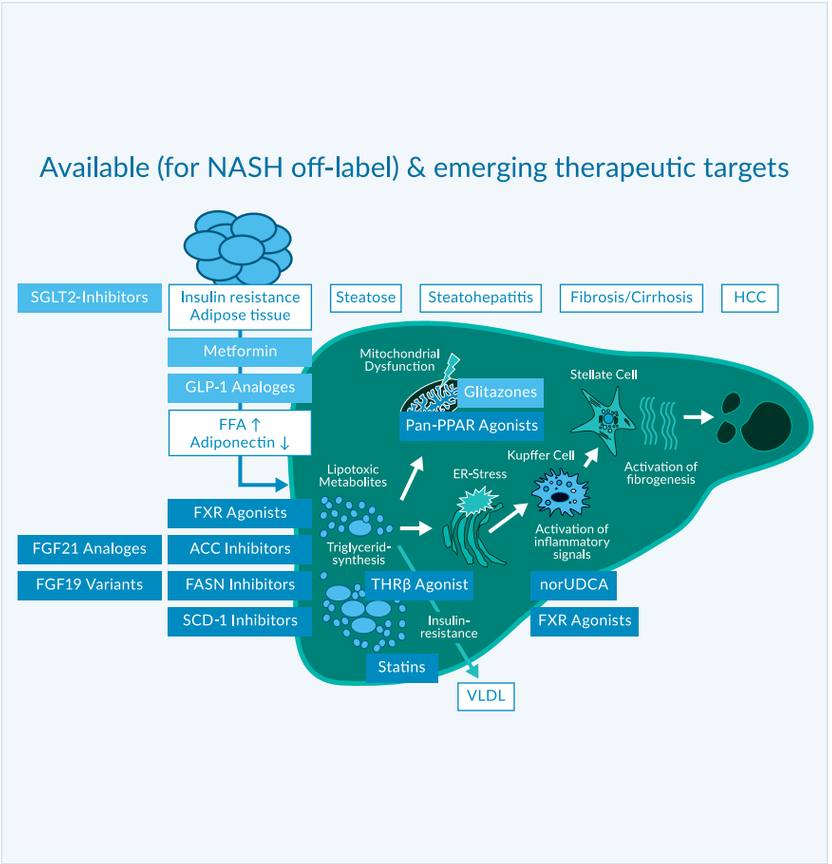

Figure 4. Emerging therapeutic targets and substances which are already available (off label use in case of MASLD) adapted from [85].

Obeticholic acid (OCA*) as agonist of the bile acid receptor farnesoid X receptor (FXR) is currently investigated in two phase 3 studies in MASH patients. Interim analysis after 18 months of the ongoing phase 3 study for MASH patients with F2-F3 fibrosis or F1 fibrosis with at least one accompanying comorbidity (REGENERATE) showed an improvement in fibrosis in both treatment groups compared to placebo (18 and 23% with OCA 10/25mg vs. 12% placebo), but without amelioration of the particular histological features of MASH/NASH.(Younossi, Ratziu et al. 2019, Sanyal, Ratziu et al. 2023) However, OCA treatment has some limitations, as a dose-dependent pruritus occurred in all studies, e.g. in 51% of patients in the high-dose group of OCA 25mg in the REGENERATE trial. Furthermore, a change in lipid parameters with increase of LDL-cholesterol and decrease of HDL-cholesterol can be observed during OCA treatment and requires a lipid-lowering therapy with statins in half of the patients in the OCA group.

** OCA has been withdrawn and is no longer developed.*

Tropifexor is another potent oral FXR agonist, which is structurally not related to bile acids. Anti-inflammatory and anti-steatotic effects were observed in an adaptive phase 2a/b trial (FLIGHT-FXR). Decreases from baseline in ALT and hepatic fat fraction measured by MRI-PDFF were sustained from week 12 up to week 48.(Sanyal, Lopez et al. 2023) Interestingly, pruritus was also observed for compound despite its non-steroidal nature.

Cilofexor is another non-steroidal FXR agonist with dose-dependent, anti-steatotic effect in MRI-PDFF in a phase 2 study. Pruritus was also observed in the high dose treatment arm.(Patel, Harrison et al. 2020)

Nor-Ursodeoxycholic acid (norUDCA), a synthetic bile acid characterised by anti-inflammatory properties without relevant FXR agonistic effects, is currently investigated in a phase 2b study (EudraCT 2018-003443-31).

Aldafermin (NGM282) is a nontumourigenic variant of the FXR target gene fibroblast growth factor FGF19 inhibits *de novo* lipogenesis, improves insulin sensitivity, corrects mitochondrial dysfunction, and reduces hepatic inflammation and fibrosis. In a phase 2a study over 12 weeks Aldafermin treatment led more often to a 5% or more reduction of hepatic fat fraction (MRI-PDFF) compared to placebo (74% for NGM282 3mg, 79% for NGM282 6mg and 7% for placebo).(Harrison, Neff et al. 2021) However, in phase 2b, no significant dose response on improvement in liver fibrosis with no worsening of MASH/NASH has been detected (19% in the placebo group, 31% 0.3 mg aldafermin, 15% 1.0 mg and 30% 3.0 mg; p=0.12).(Harrison, Abdelmalek et al. 2022) The most common adverse events were gastrointestinal (e.g. diarrhoea, nausea, frequent bowel movements and abdominal pain).

Efruxifermin (EFX) is a long-acting fibroblast growth factor FGF21 analogue based on a human IgG1 Fc-fusion protein with beneficial effect on glucose- and lipid metabolism. It mimics the balanced potency of endogenous FGF21 over the three FGF receptors 1c, 2c and 3c. In the phase 2a BALANCED study all Efruxifermin dose groups (28mg, 50mg, 70mg) met the primary endpoint with absolute changes in hepatic fat fraction of –12.3% from baseline compared to 0.3% in the placebo group.(Harrison, Ruane et al. 2021) Consistent with reduced hepatic fat fraction, 78% of Efruxifermin-treated patients in this study were NAS responders (≥2 points without worsening of fibrosis) and 48% had MASH/NASH resolution without worsening of fibrosis. Beneficial effects on cholesterol and glucose metabolism have been confirmed. In the recently published phase 2b HARMONY study, both 50mg and 28mg doses of Efruxifermin led to at least a one stage improvement in liver fibrosis with no worsening of MASH/NASH by week 24 (41% and 39%, respectively) compared to 20% for placebo (Press Release Akero December 8, 2022). Based on these data, Efruxifermin has received a Breakthrough Therapy Designation from the FDA.

As outlined above, Glucagon-like peptide-1 (GLP-1) analogues are

established drugs in diabetes and obesity therapy with beneficial metabolic effects particularly on glucose metabolism. Semaglutide, a new generation GLP-1 agonist, has been investigated in a phase 2b trial for MASH patients (NCT02970942). In this study involving 230 patients with MASH/NASH F2-3 fibrosis, the primary endpoint of MASH/NASH resolution was achieved by a significantly greater proportion of patients with doses of 0.1, 0.2 and 0.4 mg in 40%, 35% and 58%, respectively, versus placebo (17%).(Newsome, Buchholtz et al. 2021) Although there was a reduction in the proportion of patients with fibrosis progression, no significant improvement in fibrosis has been observed due to a very high rate of fibrosis resolution in the placebo group. A phase 3 study is now further investigating the long-term effects of Semaglutide in MASH patients (currently ongoing).

Resmetirom (MGL-3196) is a highly selective thyroid hormone receptor ß (THRß) agonist. THRß agonists target dyslipidaemia but have also been shown to reduce hepatic steatosis, improving insulin sensitivity, promoting liver regeneration and reducing apoptosis in preclinical studies. In a phase 2 study Resmetirom has significantly reduced liver fat content after 12 weeks of treatment by MRI-PDFF (-32% for Resmetirom vs -10% in placebo). (Harrison, Bashir et al. 2019)

In the phase 2 MAESTRO trial, 955 MASH F2-F3 patients were analysed in the interim analysis that showed a significant effect of both doses of Resmetirom 80mg and 100mg on fibrosis improvement by at least one stage without worsening of MASH/NASH (24% and 26%, respectively) as compared to placebo (14%; p<0.0001) after 52 weeks of treatment.(Harrison, Taub et al. 2023) (Madrigal Pharmaceuticals, Press Release December 19, 2022). Similarly, a significant improvement in MASH/NASH without worsening of fibrosis has been detected (26% and 30% for Resmetirom 80/100mg compared to 10% in placebo; p<0.0001). A decrease in LDL cholesterol could be observed as secondary endpoint. Resmetirom was generally well tolerated with mild, transient diarrhoea and nausea as the most common gastrointestinal adverse events. Results of the recently published phase 3 study show that Resmetirom was safe and well tolerated in adults with NASH, which favours further clinical development.(Harrison, Taub et al. 2023).

VK2809 is another THRß agonist in clinical development (Phase 2b VOYAGE study ongoing).

PPAR (peroxisome proliferator-activated receptor) agonists exert beneficial effects in glucose as well as lipid metabolism and are therefore an interesting drug class for NASH treatment. As outlined above for Pioglitazone, PPAR agonists have traditionally been used for the treatment of patients with metabolic syndrome to lower serum triglyceride and glucose levels. Lanifibranor (IVA337) is a pan-PPAR agonist with activation of three different receptor isoforms α, δ and ɣ. In a phase 2b NATIVE study involving 247 NASH patients with F1-F3 fibrosis, Lanifibranor has met the primary endpoint with a reduction of the steatosis activity fibrosis score (SAF) by at least 2 points in SAF-A with no worsening of fibrosis (1200mg versus placebo, 55% vs. 33%, P=0.007; 800mg versus placebo, 48% vs. 33%, P=0.07).(Francque, Bedossa et al. 2021) As a key secondary endpoint, improvement in fibrosis of at least one stage without worsening of MASH/NASH also favoured both Lanifibranor doses over placebo (48% and 34%, respectively, vs. 29%). As expected for this pan-PPAR agonist, lipid, inflammatory and fibrosis biomarkers were improved in the Lanifibranor groups. Lanifibranor showed an overall favourable tolerability profile. However, it is worth to note that weight gain occurred more frequently with Lanifibranor than with placebo. These findings support further assessment of Lanifibranor in the ongoing phase 3 trial (NATIV3). Elafibranor (GFT505), a dual PPAR α/δ agonist, did not demonstrate a statistically significant effect on the primary endpoint of MASH/NASH resolution without worsening of fibrosis in the respective phase 3 study (RESOLVE-IT), which has been terminated early.

Aramchol is a liver-targeted steroyl-CoA desaturase (SCD-1) inhibitor. SCD-1 represents a key enzyme in hepatic lipogenesis that converts saturated fatty acids into monounsaturated fatty acids. In a 52-week phase 2b study (ARREST), Aramchol showed liver fat reduction, biochemical improvement, MASH/NASH resolution and fibrosis reduction in a dose dependent manner.(Ratziu, de Guevara et al. 2021) Aramchol is currently being evaluated in an ongoing phase 3 programme ARMOR clinical trial (open-label phase followed by a randomised, double-blinded and placebo-controlled phase). As announced in a recent press release, histological improvement in fibrosis by at least one stage was demonstrated in 39% of subjects in the open-label part (Galmed Pharmaceuticals, Press Release January 4 2023).

TVB-2640 represents a novel, first-in-class, fatty acid synthase (FASN) inhibitor which has recently been tested in a phase 2 study in MASH patients over 12 weeks.(Loomba, Mohseni et al. 2021) Following the same approach as Aramchol to target a key enzyme hepatic lipogenesis, a dose-dependent reduction of liver fat fraction (-9.6% and -28.1% at 25mg and 50mg respectively) has been observed with MRI-PDFF together with favourable metabolic effects in serum.

Given the complex pathogenesis of MASH, it is intuitive that multiple mechanistic pathways could be targeted to achieve an optimal treatment response. Several treatment combinations are currently tested in MASH. Most combination therapies include an FXR agonist as therapeutic backbone. In a phase 2 study (ATLAS trial) the safety and efficacy of monotherapy and dual combination regimens of Cilofexor 30mg, Firsocostat 20mg and Selonsertib 18mg in patients with advanced MASH

fibrosis and cirrhosis (F3-F4) were evaluated. The monotherapy arm with Selonsertib was discontinued shortly after the negative results of Selonsertib monotherapy. In the ATLAS trial a ≥1-stage improvement in fibrosis without worsening of MASH/NASH after 48 weeks of treatment was numerically higher in the combination therapy group (Cilofexor and Firsocostat) compared with placebo (21% vs 11%, p=0.17), respectively. The primary endpoint was not met probably due to a small sample size.(Loomba, Noureddin et al. 2021) Subsequently, the two active compounds from this trial (Cilofexor 30-100mg, Firsocostat 20mg) have been combined with Semaglutide 0.24-2.4mg in a phase 2 study in F2-3 MASH patients over 24 weeks.(Alkhouri, Herring et al. 2022) Despite similar reductions in body weight like in Semaglutide alone, combination regimens resulted in greater improvements in hepatic steatosis as assessed by MRI-PDFF (−9.8 to −11.0% vs. −8.0%).(Loomba, Noureddin et al. 2021) Side effects in combination were similar to the single compounds. Other trials are currently testing the combination of Tropifexor with the SGLT1/2 Inhibitor Licogliflozin or with the Leukotriene A4 hydrolase inhibitor LYS006.

At this point, approval of first drugs for the indication treatment of MASH cannot be predicted but it appears unlikely that a drug will become available before 2024.

e) Modification of the intestinal microbiome

In a randomised study, the supplementation of a combination of pro- and prebiotics showed a change in the microbiome, but no effect on liver fat content or liver stiffness as a surrogate for liver fibrosis.(Scorletti, Afolabi et al. 2020) In lean MASLD patients (n=50), synbiotics showed a benefit in terms of improving non-invasive surrogates of fatty liver and fibrosis over 28 weeks.(Mofidi, Poustchi et al. 2017) Data on the transfer of microbiota are not available.

A recent work investigated the role of the gut-liver axis in MASLD hepatocarcinogenesis. The study suggests that the gut microbiota in MASLD -HCC is characterised by a distinct microbiome or metabolomic profile and can modulate the peripheral immune response (Behary, Amorim et al. 2021).

f) Bariatric Surgery

An increasing number of studies are investigating endoscopic and laparoscopic methods of bariatric surgery for the treatment of MASLD /MASH. Bariatric surgery improves the serological, imaging, and histological markers of MASLD.(Schmid, Arians et al. 2022, Verrastro, Panunzi et al. 2023) In obesity and MASLD, sleeve gastrectomy, Roux-Y gastric bypass and single-anastomosis gastric bypass can be recommended or performed as metabolic surgical procedures. The adjustable gastric band should not be used in obesity and MASLD due to inferior efficacy. (Roeb, Canbay et al. 2022) Because of the risk of progressive liver failure, the severity of MASLD should be critically considered when an indication for malabsorptive procedures (e.g. biliopancreatic diversion, distal gastric bypass and single anastomosis bypass with a biliopancreatic loop longer than 200 cm) is made. If liver cirrhosis is present, sleeve gastrectomy should preferably be used. Endoscopic procedures can also be used in MASLD and obesity if conservative therapy fails and if bariatric surgery is rejected or contraindicated. Here, the endoscopic intragastric balloon application or the endoscopic gastric sleeve (ESG) may still come into question.(Roeb, Canbay et al. 2022) At the end, it is important to point out that surgical methods represent an ultimate approach after failure of conservative treatment strategy and is reserved to patients with morbid obesity (BMI >40 kg/m2 or BMI >35kg/m2 with serious concomitant disease).

g) Liver transplantation for MASH

Liver transplantation is the final option for patients with end-stage liver disease due to NASH cirrhosis with decompensation or complications of portal hypertension. Due to the increase in the prevalence of MASH, this disease entity is the second most frequent reason for liver transplantation listing in the North-American UNOS network.(Younossi, Stepanova et al. 2021) In the US, it is currently the second most common LTX indication, with an increase of 167% over the period 2003-2014; in Germany the trend is constantly increasing.(Rademacher, Aehling et al. 2021) However, MASH as underlying disease for liver transplantation is also increasing but not exceeding 10% of cases in the European ELTR registry so far. (Haldar, Kern et al. 2019) MASH can recur after liver transplantation, since this does not cure the metabolic defect that causes MASH. Postoperative outcomes may even worsen in the future with an increasing proportion of steatotic (and therefore marginal) donor organs. Furthermore, it can be emphasised that preexisting MASH-related comorbidity like nephropathy and cardiovascular disease in organ recipients with MASH cirrhosis may further limit the long-term outcomes after transplantation.(Canbay, Sowa et al. 2016) Unfavourable metabolic effects of calcineurin inhibitors further impact on this dilemma.

Follow-up of MASLD and MASH patients

Patients with MASH should undergo clinical follow-up and ultrasound surveillance according to their individual risk.(Roeb, Canbay et al. 2022) The intervals of clinical follow-up are based on the progression risk and are therefore stratified by presence of MASH, fibrosis stage and comorbidities. While patients with bland steatosis can be followed on a more liberal basis in 2 to 3 years intervals, those with advanced fibrosis, particularly cirrhosis, should undergo follow-up with tumour surveillance every 6 months. (bouzas 2016, Roeb, Canbay et al. 2022) Although hepatocellular carcinoma may occur even in MASH patients without cirrhosis, the relative incidence of such an event does probably not justify to screen non-cirrhotic MASH patients for HCC on a regular basis.(Kanwal, Kramer et al. 2018, Roeb, Canbay et al. 2022) The HCC incidence in MASH patients without liver cirrhosis is given as 0.02% per year and increases to 1.5% per year in the presence of liver cirrhosis.(Kanwal, Kramer et al. 2018) An elevated FIB-4 score predicts liver cancer development and may be used for risk stratification in MASH patients.(Loosen, Kostev et al. 2022) Follow-up examinations using non-invasive laboratory based tests or elastography allow to monitor for fibrosis progression. Patients with cirrhosis should be screened for gastro-oesophageal varices according to current practice guidelines.(bouzas 2016, Roeb, Canbay et al. 2022) Current evidence does not support to routinely repeat liver biopsy in patients with MASLD or MASH (Chalasani, Younossi et al. 2018).

References

(2016). "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease." Diabetologia 59(6): 1121-1140.

(2016). "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease." J Hepatol 64(6): 1388-1402.

Ajmera, V. H., N. A. Terrault and S. A. Harrison (2017). "Is moderate alcohol use in nonalcoholic fatty liver disease good or bad? A critical review." Hepatology 65(6): 2090-2099.

Alkhouri, N., R. Herring, H. Kabler, Z. Kayali, T. Hassanein, A. Kohli, R. S. Huss, Y. Zhu, A. N. Billin, L. H. Damgaard, K. Buchholtz, M. S. Kjær, C. Balendran, R. P. Myers, R. Loomba and M. Noureddin (2022). "Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial." J Hepatol 77(3): 607-618.

Alsenbesy, M., M. Rau, J. Weiss, O. Götze and A. Geier (2019). "A 2-step fast-track elastometry service for advanced workup of nonalcoholic fatty liver disease (NAFLD) patients - single-center real-world experience of outpatient clinical practice." Z Gastroenterol 57(10): 1209-1217.

Angulo, P., D. E. Kleiner, S. Dam-Larsen, L. A. Adams, E. S. Bjornsson, P. Charatcharoenwitthaya, P. R. Mills, J. C. Keach, H. D. Lafferty, A. Stahler, S. Haflidadottir and F. Bendtsen (2015). "Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease." Gastroenterology 149(2): 389-397.e310.

Armstrong, M. J., P. Gaunt, G. P. Aithal, D. Barton, D. Hull, R. Parker, J. M. Hazlehurst, K. Guo, G. Abouda, M. A. Aldersley, D. Stocken, S. C. Gough, J. W. Tomlinson, R. M. Brown, S. G. Hübscher and P. N. Newsome (2016). "Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study." Lancet 387(10019): 679-690.

Ascha, M. S., I. A. Hanouneh, R. Lopez, T. A. Tamimi, A. F. Feldstein and N. N. Zein (2010). "The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis." Hepatology 51(6): 1972-1978.

Bedogni, G., L. Miglioli, F. Masutti, A. Castiglione, L. S. Crocè, C. Tiribelli and S. Bellentani (2007). "Incidence and natural course of fatty liver in the general population: the Dionysos study." Hepatology 46(5): 1387-1391.

Bedossa, P. (2013). "Current histological classification of NAFLD: strength and limitations." Hepatol Int 7 Suppl 2: 765-770.

Bedossa, P. and F. P. Consortium (2014). "Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease." Hepatology 60(2): 565-575.

Bedossa, P., C. Poitou, N. Veyrie, J. L. Bouillot, A. Basdevant, V. Paradis, J. Tordjman and K. Clement (2012). "Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients." Hepatology 56(5): 1751-1759.

Behary, J., N. Amorim, X. T. Jiang, A. Raposo, L. Gong, E. McGovern, R. Ibrahim, F. Chu, C. Stephens, H. Jebeili, V. Fragomeli, Y. C. Koay, M. Jackson, J. O'Sullivan, M. Weltman, G. McCaughan, E. El-Omar and A. Zekry (2021). "Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma." Nat Commun 12(1): 187.

Berzigotti, A., A. Albillos, C. Villanueva, J. Genescá, A. Ardevol, S. Augustín, J. L. Calleja, R. Bañares, J. C. García-Pagán, F. Mesonero and J. Bosch (2017). "Effects of an intensive lifestyle intervention programme on portal hypertension in patients with cirrhosis and obesity: The SportDiet study." Hepatology 65(4): 1293-1305.

Boursier, J., O. Mueller, M. Barret, M. Machado, L. Fizanne, F. Araujo-Perez, C. D. Guy, P. C. Seed, J. F. Rawls, L. A. David, G. Hunault, F. Oberti, P. Calès and A. M. Diehl (2016). "The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota." Hepatology 63(3): 764-775.

bouzas (2016). "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease." J Hepatol 64(6): 1388-1402.

Bril, F., D. M. Biernacki, S. Kalavalapalli, R. Lomonaco, S. K. Subbarayan, J. Lai, F. Tio, A. Suman, B. K. Orsak, J. Hecht and K. Cusi (2019). "Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomised Controlled Trial." Diabetes Care 42(8): 1481-1488.

Canbay, A., J. P. Sowa, W. K. Syn and J. Treckmann (2016). "NASH Cirrhosis - the New Burden in Liver Transplantation: How Should It Be Managed?" Visc Med 32(4): 234-238.

Chalasani, N., Z. Younossi, J. E. Lavine, M. Charlton, K. Cusi, M. Rinella, S. A. Harrison, E. M. Brunt and A. J. Sanyal (2018). "The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases." Hepatology 67(1): 328-357.

Cosentino, F., P. J. Grant, V. Aboyans, C. J. Bailey, A. Ceriello, V. Delgado, M. Federici, G. Filippatos, D. E. Grobbee, T. B. Hansen, H. V. Huikuri, I. Johansson, P. Jüni, M. Lettino, N. Marx, L. G. Mellbin, C. J. Östgren, B. Rocca, M. Roffi, N. Sattar, P. M. Seferović, M. Sousa-Uva, P. Valensi and D. C. Wheeler (2020). "2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD." Eur Heart J 41(2): 255-323.

Cusi, K., B. Orsak, F. Bril, R. Lomonaco, J. Hecht, C. Ortiz-Lopez, F. Tio, J. Hardies, C. Darland, N. Musi, A. Webb and P. Portillo-Sanchez (2016). "Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomised Trial." Ann Intern Med 165(5): 305-315.

Deibert, P., A. Lazaro, D. Schaffner, A. Berg, D. Koenig, W. Kreisel, M. W. Baumstark, D. Steinmann, M. Buechert and T. Lange (2019). "Comprehensive lifestyle intervention vs soy protein-based meal regimen in non-alcoholic steatohepatitis." World J Gastroenterol 25(9): 1116-1131.

Dietrich, C. G., M. Rau and A. Geier (2021). "Screening for nonalcoholic fatty liver disease-when, who and how?" World J Gastroenterol 27(35): 5803-5821.

Diogo, D., C. Tian, C. S. Franklin, M. Alanne-Kinnunen, M. March, C. C. A. Spencer, C. Vangjeli, M. E. Weale, H. Mattsson, E. Kilpeläinen, P. M. A. Sleiman, D. F. Reilly, J. McElwee, J. C. Maranville, A. K. Chatterjee, A. Bhandari, K. H. Nguyen, K. Estrada, M. P. Reeve, J. Hutz, N. Bing, S. John, D. G. MacArthur, V. Salomaa, S. Ripatti, H. Hakonarson, M. J. Daly, A. Palotie, D. A. Hinds, P. Donnelly, C. S. Fox, A. G. Day-Williams, R. M. Plenge and H. Runz (2018). "Phenome-wide association studies across large population cohorts support drug target validation." Nat Commun 9(1): 4285.

Dubuquoy, C., A. F. Burnol and M. Moldes (2013). "PNPLA3, a genetic marker of progressive liver disease, still hiding its metabolic function?" Clin Res Hepatol Gastroenterol 37(1): 30-35.

Dufour, J. F., C. Caussy and R. Loomba (2020). "Combination therapy for non-alcoholic steatohepatitis: rationale, opportunities and challenges." Gut 69(10): 1877-1884.

Dulai, P. S., S. Singh, J. Patel, M. Soni, L. J. Prokop, Z. Younossi, G. Sebastiani, M. Ekstedt, H. Hagstrom, P. Nasr, P. Stal, V. W. Wong, S. Kechagias, R. Hultcrantz and R. Loomba (2017). "Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis." Hepatology 65(5): 1557-1565.

Ekstedt, M., H. Hagström, P. Nasr, M. Fredrikson, P. Stål, S. Kechagias and R. Hultcrantz (2015). "Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up." Hepatology 61(5): 1547-1554.

Eslam, M., A. J. Sanyal, J. George and P. International Consensus (2020). "MASLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease." Gastroenterology 158(7): 1999-2014 e1991.

Estes, C., Q. M. Anstee, M. T. Arias-Loste, H. Bantel, S. Bellentani, J. Caballeria, M. Colombo, A. Craxi, J. Crespo, C. P. Day, Y. Eguchi, A. Geier, L. A. Kondili, D. C. Kroy, J. V. Lazarus, R. Loomba, M. P. Manns, G. Marchesini, A. Nakajima, F. Negro, S. Petta, V. Ratziu, M. Romero-Gomez, A. Sanyal, J. M. Schattenberg, F. Tacke, J. Tanaka, C. Trautwein, L. Wei, S. Zeuzem and H. Razavi (2018). "Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030." J Hepatol 69(4): 896-904.

Francque, S. M., P. Bedossa, V. Ratziu, Q. M. Anstee, E. Bugianesi, A. J. Sanyal, R. Loomba, S. A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J. M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M. P. Richard, J. L. Abitbol, P. Broqua, J. L. Junien and M. F. Abdelmalek (2021). "A Randomised, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH." N Engl J Med 385(17): 1547-1558.

Galvan-Martinez, D. H., V. M. Bosquez-Mendoza, Y. Ruiz-Noa, L. D. R. Ibarra-Reynoso, G. Barbosa-Sabanero and M. L. Lazo-de-la-Vega-Monroy (2023). "Nutritional, pharmacological, and environmental programming of NAFLD in early life." Am J Physiol Gastrointest Liver Physiol 324(2): G99-g114.

Garvey, W. T., J. I. Mechanick, E. M. Brett, A. J. Garber, D. L. Hurley, A. M. Jastreboff, K. Nadolsky, R. Pessah-Pollack and R. Plodkowski (2016). "AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY." Endocr Pract 22 Suppl 3: 1-203.

Geier, A., M. Rau, A. Pathil-Warth, M. von der Ohe, J. Schattenberg, N. Dikopoulos, K. Stein, Y. Serfert, T. Berg, P. Buggisch, M. Demir, E. Roeb, B. Wiebner, H. Wedemeyer, S. Zeuzem and W. P. Hofmann (2023). "Clinical characteristics of patients with non-alcoholic fatty liver disease (NAFLD) in Germany - First data from the German NAFLD-Registry." Z Gastroenterol 61(1): 60-70.

Geier, A., M. E. Rinella, M. M. Balp, S. J. McKenna, C. A. Brass, R. Przybysz, J. Cai, A. Knight, M. Gavaghan, T. Howe, D. Rosen and V. Ratziu (2021). "Real-World Burden of Nonalcoholic Steatohepatitis." Clin Gastroenterol Hepatol 19(5): 1020-1029.e1027.

Geier, A., D. Tiniakos, H. Denk and M. Trauner (2021). "From the origin of NASH to the future of metabolic fatty liver disease." Gut 70(8): 1570-1579.

George, J., R. G. Gish and A. Geier (2021). "MASLD and Cardiovascular Events: What Does the Evidence Show?" Clin Gastroenterol

Hepatol 19(10): 2025-2028.

Hagström, H., J. Vessby, M. Ekstedt and Y. Shang (2023). "99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical." J Hepatol.

Haldar, D., B. Kern, J. Hodson, M. J. Armstrong, R. Adam, G. Berlakovich, J. Fritz, B. Feurstein, W. Popp, V. Karam, P. Muiesan, J. O'Grady, N. Jamieson, S. J. Wigmore, J. Pirenne, S. A. Malek-Hosseini, E. Hidalgo, Y. Tokat, A. Paul, J. Pratschke, M. Bartels, P. Trunecka, U. Settmacher, M. Pinzani, C. Duvoux, P. N. Newsome and S. Schneeberger (2019). "Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study." J Hepatol 71(2): 313-322.

Hardy, T., K. Wonders, R. Younes, G. P. Aithal, R. Aller, M. Allison, P. Bedossa, F. Betsou, J. Boursier, M. J. Brosnan, A. Burt, J. Cobbold, H. Cortez-Pinto, C. P. Day, J. F. Dufour, M. Ekstedt, S. Francque, S. Harrison, L. Miele, P. Nasr, G. Papatheodoridis, S. Petta, D. Tiniakos, R. Torstenson, L. Valenti, A. G. Holleboom, H. Yki-Jarvinen, A. Geier, M. Romero-Gomez, V. Ratziu, E. Bugianesi, J. M. Schattenberg and Q. M. Anstee (2020). "The European NAFLD Registry: A real-world longitudinal cohort study of nonalcoholic fatty liver disease." Contemp Clin Trials 98: 106175.

Harrison, S. A., M. F. Abdelmalek, G. Neff, N. Gunn, C. D. Guy, N. Alkhouri, M. R. Bashir, B. Freilich, A. Kohli, A. Khazanchi, M. Y. Sheikh, M. Leibowitz, M. E. Rinella, M. S. Siddiqui, M. Kipnes, S. E. Moussa, Z. H. Younes, M. Bansal, S. J. Baum, B. Borg, P. J. Ruane, P. J. Thuluvath, M. Gottwald, M. Khan, C. Chen, L. Melchor-Khan, W. Chang, A. M. DePaoli, L. Ling and H. D. Lieu (2022). "Aldafermin in patients with non-alcoholic steatohepatitis (ALPINE 2/3): a randomised, double-blind, placebo-controlled, phase 2b trial." Lancet Gastroenterol Hepatol 7(7): 603-616.

Harrison, S. A., M. R. Bashir, C. D. Guy, R. Zhou, C. A. Moylan, J. P. Frias, N. Alkhouri, M. B. Bansal, S. Baum, B. A. Neuschwander-Tetri, R. Taub and S. E. Moussa (2019). "Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial." Lancet 394(10213): 2012-2024.

Harrison, S. A., G. Neff, C. D. Guy, M. R. Bashir, A. H. Paredes, J. P. Frias, Z. Younes, J. F. Trotter, N. T. Gunn, S. E. Moussa, A. Kohli, K. Nelson, M. Gottwald, W. C. G. Chang, A. Z. Yan, A. M. DePaoli, L. Ling and H. D. Lieu (2021). "Efficacy and Safety of Aldafermin, an Engineered FGF19 Analog, in a Randomized, Double-Blind, Placebo-Controlled Trial of Patients With Nonalcoholic Steatohepatitis." Gastroenterology 160(1): 219-231.e211.

Harrison, S. A., P. J. Ruane, B. L. Freilich, G. Neff, R. Patil, C. A. Behling, C. Hu, E. Fong, B. de Temple, E. J. Tillman, T. P. Rolph, A. Cheng and K. Yale (2021). "Efruxifermin in non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial." Nat Med 27(7): 1262-1271.

Harrison, S. A., R. Taub, G. W. Neff, K. J. Lucas, D. Labriola, S. E. Moussa, N. Alkhouri and M. R. Bashir (2023). "Resmetirom for nonalcoholic fatty liver disease: a randomised, double-blind, placebo-controlled phase 3 trial." Nat Med.

Hashida, R., T. Kawaguchi, M. Bekki, M. Omoto, H. Matsuse, T. Nago, Y. Takano, T. Ueno, H. Koga, J. George, N. Shiba and T. Torimura (2017). "Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review." J Hepatol 66(1): 142-152.

Hayat, U., A. A. Siddiqui, H. Okut, S. Afroz, S. Tasleem and A. Haris (2021). "The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies." Ann Hepatol 20: 100254.

Hofmann, W. P., P. Buggisch, L. Schubert, N. Dikopoulos, J. Schwenzer, M. Muche, G. Felten, R. Heyne, P. Ingiliz, A. Schmidt, K. Stein, H. Wedemeyer, T. Berg, J. Wiegand, F. Lammert, S. Zeuzem and J. M. Schattenberg (2020). "The Fatty Liver Assessment in Germany (FLAG) cohort study identifies large heterogeneity in NAFLD care." JHEP Rep 2(6): 100168.

Hohenester, S., S. Christiansen, J. Nagel, R. Wimmer, R. Artmann, G. Denk, M. Bischoff, G. Bischoff and C. Rust (2018). "Lifestyle intervention for morbid obesity: effects on liver steatosis, inflammation, and fibrosis." Am J Physiol Gastrointest Liver Physiol 315(3): G329-g338.

Huber, Y., A. Schulz, I. Schmidtmann, M. Beutel, N. Pfeiffer, T. Münzel, P. R. Galle, P. S. Wild, K. J. Lackner and J. M. Schattenberg (2022). "Prevalence and Risk Factors of Advanced Liver Fibrosis in a Population-Based Study in Germany." Hepatol Commun 6(6): 1457-1466.

Johnston, R. D., M. C. Stephenson, H. Crossland, S. M. Cordon, E. Palcidi, E. F. Cox, M. A. Taylor, G. P. Aithal and I. A. Macdonald (2013). "No difference between high-fructose and high-glucose diets on liver triacylglycerol or biochemistry in healthy overweight men." Gastroenterology 145(5): 1016-1025.e1012.

Kanwal, F., J. R. Kramer, S. Mapakshi, Y. Natarajan, M. Chayanupatkul, P. A. Richardson, L. Li, R. Desiderio, A. P. Thrift, S. M. Asch, J. Chu and H. B. El-Serag (2018). "Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease." Gastroenterology 155(6): 1828-1837.e1822.

Karlas, T., D. Petroff, M. Sasso, J. G. Fan, Y. Q. Mi, V. de Lédinghen, M. Kumar, M. Lupsor-Platon, K. H. Han, A. C. Cardoso, G. Ferraioli, W. K. Chan, V. W. Wong, R. P. Myers, K. Chayama, M. Friedrich-Rust, M. Beaugrand, F. Shen, J. B. Hiriart, S. K. Sarin, R. Badea, K. S. Jung, P. Marcellin, C. Filice, S. Mahadeva, G. L. Wong, P. Crotty, K. Masaki, J. Bojunga, P. Bedossa, V. Keim and J. Wiegand (2017). "Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis." J Hepatol 66(5): 1022-1030.

Kim, G. A., H. C. Lee, J. Choe, M. J. Kim, M. J. Lee, H. S. Chang, I. Y. Bae, H. K. Kim, J. An, J. H. Shim, K. M. Kim and Y. S. Lim (2017). "Association between non-alcoholic fatty liver disease and cancer incidence rate." J Hepatol.

Kleiner, D. E., E. M. Brunt, M. Van Natta, C. Behling, M. J. Contos, O. W. Cummings, L. D. Ferrell, Y. C. Liu, M. S. Torbenson, A. Unalp-Arida, M. Yeh, A. J. McCullough, A. J. Sanyal and N. Nonalcoholic Steatohepatitis Clinical Research (2005). "Design and validation of a histological scoring system for nonalcoholic fatty liver disease." Hepatology 41(6): 1313-1321.

Krawczyk, M., R. Liebe and F. Lammert (2020). "Toward Genetic Prediction of Nonalcoholic Fatty Liver Disease Trajectories: PNPLA3 and Beyond." Gastroenterology 158(7): 1865-1880.e1861.

Krawczyk, M., M. Rau, J. M. Schattenberg, H. Bantel, A. Pathil, M. Demir, J. Kluwe, T. Boettler, F. Lammert and A. Geier (2017). "Combined effects of the PNPLA3 rs738409, TM6SF2 rs58542926, and MBOAT7 rs641738 variants on NAFLD severity: a multicenter biopsy-based study." J Lipid Res 58(1): 247-255.

Labenz, C., Y. Huber, E. Kalliga, M. Nagel, C. Ruckes, B. K. Straub, P. R. Galle, M. A. Wörns, Q. M. Anstee, D. Schuppan and J. M. Schattenberg (2018). "Predictors of advanced fibrosis in non-cirrhotic non-alcoholic fatty liver disease in Germany." Aliment Pharmacol Ther 48(10): 1109-1116.

LaBrecque, D. R., Z. Abbas, F. Anania, P. Ferenci, A. G. Khan, K. L. Goh, S. S. Hamid, V. Isakov, M. Lizarzabal, M. M. Peñaranda, J. F. Ramos, S. Sarin, D. Stimac, A. B. Thomson, M. Umar, J. Krabshuis and A. LeMair (2014). "World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis." J Clin Gastroenterol 48(6): 467-473.

Le, M. H., D. M. Le, T. C. Baez, Y. Wu, T. Ito, E. Y. Lee, K. Lee, C. D. Stave, L. Henry, S. D. Barnett, R. Cheung and M. H. Nguyen (2023). "Global incidence of non-alcoholic fatty liver disease: A systematic review and meta-analysis of 63 studies and 1,201,807 persons." J Hepatol 79(2): 287-295.

Lee, B. P., J. L. Dodge and N. A. Terrault (2023). "National prevalence estimates for steatotic liver disease and Sub-Classifications using consensus nomenclature." Hepatology.

Long, M. T., X. Zhang, H. Xu, C. T. Liu, K. E. Corey, R. T. Chung, R. Loomba and E. J. Benjamin (2021). "Hepatic Fibrosis Associates With Multiple Cardiometabolic Disease Risk Factors: The Framingham Heart Study." Hepatology 73(2): 548-559.

Loomba, R. (2018). "Role of imaging-based biomarkers in NAFLD: Recent advances in clinical application and future research directions." J Hepatol 68(2): 296-304.

Loomba, R. and L. A. Adams (2020). "Advances in non-invasive assessment of hepatic fibrosis." Gut 69(7): 1343-1352.

Loomba, R., S. L. Friedman and G. I. Shulman (2021). "Mechanisms and disease consequences of nonalcoholic fatty liver disease." Cell 184(10): 2537-2564.

Loomba, R., J. K. Lim, H. Patton and H. B. El-Serag (2020). "AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review." Gastroenterology 158(6): 1822-1830.

Loomba, R., R. Mohseni, K. J. Lucas, J. A. Gutierrez, R. G. Perry, J. F. Trotter, R. S. Rahimi, S. A. Harrison, V. Ajmera, J. D. Wayne, M. O'Farrell, W. McCulloch, K. Grimmer, M. Rinella, V. Wai-Sun Wong, V. Ratziu, G. J. Gores, B. A. Neuschwander-Tetri and G. Kemble (2021). "TVB-2640 (FASN Inhibitor) for the Treatment of Nonalcoholic Steatohepatitis: FASCINATE-1, a Randomised, Placebo-Controlled Phase 2a Trial." Gastroenterology 161(5): 1475-1486.

Loomba, R., M. Noureddin, K. V. Kowdley, A. Kohli, A. Sheikh, G. Neff, B. R. Bhandari, N. Gunn, S. H. Caldwell, Z. Goodman, I. Wapinski, M. Resnick, A. H. Beck, D. Ding, C. Jia, J. C. Chuang, R. S. Huss, C. Chung, G. M. Subramanian, R. P. Myers, K. Patel, B. B. Borg, R. Ghalib, H. Kabler, J. Poulos, Z. Younes, M. Elkhashab, T. Hassanein, R. Iyer, P. Ruane, M. L. Shiffman, S. Strasser, V. W. Wong and N. Alkhouri (2021). "Combination Therapies Including Cilofexor and Firsocostat for Bridging Fibrosis and Cirrhosis Attributable to NASH." Hepatology 73(2): 625-643.

Loomba, R., A. J. Sanyal, K. V. Kowdley, D. L. Bhatt, N. Alkhouri, J. P. Frias, P. Bedossa, S. A. Harrison, D. Lazas, R. Barish, M. D. Gottwald, S. Feng, G. D. Agollah, C. L. Hartsfield, H. Mansbach, M. Margalit and M. F. Abdelmalek (2023). "Randomised, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH." N Engl J Med 389(11): 998-1008.

Loosen, S. H., K. Kostev, V. Keitel, F. Tacke, C. Roderburg and T. Luedde (2022). "An elevated FIB-4 score predicts liver cancer development: A longitudinal analysis from 29,999 patients with NAFLD." J Hepatol 76(1): 247-248.

Ludwig, J., T. R. Viggiano, D. B. McGill and B. J. Oh (1980). "Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease." Mayo Clin Proc 55(7): 434-438.

Markova, M., O. Pivovarova, S. Hornemann, S. Sucher, T. Frahnow, K. Wegner, J. Machann, K. J. Petzke, J. Hierholzer, R. Lichtinghagen, C. Herder, M. Carstensen-Kirberg, M. Roden, N. Rudovich, S. Klaus, R. Thomann, R. Schneeweiss, S. Rohn and A. F. Pfeiffer (2017). "Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes." Gastroenterology 152(3): 571-585.e578.

Mofidi, F., H. Poustchi, Z. Yari, B. Nourinayyer, S. Merat, M. Sharafkhah, R. Malekzadeh and A. Hekmatdoost (2017). "Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial." Br J Nutr 117(5): 662-668.

Morita, Y., T. Ueno, N. Sasaki, K. Kuhara, S. Yoshioka, Y. Tateishi, E. Nagata, M. Kage and M. Sata (2005). "Comparison of liver histology between patients with non-alcoholic steatohepatitis and patients with alcoholic steatohepatitis in Japan." Alcohol Clin Exp Res 29(12 Suppl): 277S-281S.

Mózes, F. E., J. A. Lee, E. A. Selvaraj, A. N. A. Jayaswal, M. Trauner, J. Boursier, C. Fournier, K. Staufer, R. E. Stauber, E. Bugianesi, R. Younes, S. Gaia, M. Lupsor-Platon, S. Petta, T. Shima, T. Okanoue, S. Mahadeva, W. K. Chan, P. J. Eddowes, G. M. Hirschfield, P. N. Newsome, V. W. Wong, V. de Ledinghen, J. Fan, F. Shen, J. F. Cobbold, Y. Sumida, A. Okajima, J. M. Schattenberg, C. Labenz, W. Kim, M. S. Lee, J. Wiegand, T. Karlas, Y. Yılmaz, G. P. Aithal, N. Palaniyappan, C. Cassinotto, S. Aggarwal, H. Garg, G. J. Ooi, A. Nakajima, M. Yoneda, M. Ziol, N. Barget, A. Geier, T. Tuthill, M. J. Brosnan, Q. M. Anstee, S. Neubauer, S. A. Harrison, P. M. Bossuyt and M. Pavlides (2022). "Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis." Gut 71(5): 1006-1019.

Nasr, P., S. Ignatova, S. Kechagias and M. Ekstedt (2018). "Natural history of nonalcoholic fatty liver disease: A prospective follow-up study with serial biopsies." Hepatol Commun 2(2): 199-210.

Newsome, P. N., K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A. J. Sanyal, A. S. Sejling, S. A. Harrison and N. N. Investigators (2021). "A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis." N Engl J Med 384(12): 1113-1124.

Ooi, G. J., S. Mgaieth, G. D. Eslick, P. R. Burton, W. W. Kemp, S. K. Roberts and W. A. Brown (2018). "Systematic review and meta-analysis: non-invasive detection of non-alcoholic fatty liver disease related fibrosis in the obese." Obes Rev 19(2): 281-294.

Paik, J. M., L. Henry, Y. Younossi, J. Ong, S. Alqahtani and Z. M. Younossi (2023). "The burden of nonalcoholic fatty liver disease (NAFLD) is rapidly growing in every region of the world from 1990 to 2019." Hepatol Commun 7(10).

Parry, S. A. and L. Hodson (2020). "Managing NAFLD in Type 2 Diabetes: The Effect of Lifestyle Interventions, a Narrative Review." Adv Ther 37(4): 1381-1406.

Patel, K., S. A. Harrison, M. Elkhashab, J. F. Trotter, R. Herring, S. E. Rojter, Z. Kayali, V. W. Wong, S. Greenbloom, S. Jayakumar, M. L. Shiffman, B. Freilich, E. J. Lawitz, E. J. Gane, E. Harting, J. Xu, A. N. Billin, C. Chung, C. S. Djedjos, G. M. Subramanian, R. P. Myers, M. S. Middleton, M. Rinella and M. Noureddin (2020). "Cilofexor, a Nonsteroidal FXR Agonist, in Patients With Noncirrhotic NASH: A Phase 2 Randomised Controlled Trial." Hepatology 72(1): 58-71.

Poole, R., O. J. Kennedy, P. Roderick, J. A. Fallowfield, P. C. Hayes and J. Parkes (2017). "Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes." Bmj 359: j5024.

Rademacher, S., N. F. Aehling, R. Sucher, T. Berg and D. Seehofer (2021). "Current State and Future Possibilities in Liver Transplantation." Surg Technol Int 39: 128-134.

Ratziu, V., L. de Guevara, R. Safadi, F. Poordad, F. Fuster, J. Flores-Figueroa, M. Arrese, A. L. Fracanzani, D. Ben Bashat, K. Lackner, T. Gorfine, S. Kadosh, R. Oren, M. Halperin, L. Hayardeny, R. Loomba, S. Friedman and A. J. Sanyal (2021). "Aramchol in patients with nonalcoholic steatohepatitis: a randomised, double-blind, placebo-controlled phase 2b trial." Nat Med 27(10): 1825-1835.

Ratziu, V., P. Giral, F. Charlotte, E. Bruckert, V. Thibault, I. Theodorou, L. Khalil, G. Turpin, P. Opolon and T. Poynard (2000). "Liver fibrosis in overweight patients." Gastroenterology 118(6): 1117-1123.

Rau, M. and A. Geier (2021). "An update on drug development for the treatment of nonalcoholic fatty liver disease - from ongoing clinical trials to future therapy." Expert Rev Clin Pharmacol 14(3): 333-340.

Rau, M., A. Rehman, M. Dittrich, A. K. Groen, H. M. Hermanns, F. Seyfried, N. Beyersdorf, T. Dandekar, P. Rosenstiel and A. Geier (2018). "Fecal SCFAs and SCFA-producing bacteria in gut microbiome of human NAFLD as a putative link to systemic T-cell activation and advanced disease." United European Gastroenterol J 6(10): 1496-1507.

Rich, N. E., S. Oji, A. R. Mufti, J. D. Browning, N. D. Parikh, M. Odewole, H. Mayo and A. G. Singal (2018). "Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis." Clin Gastroenterol Hepatol 16(2): 198-210.e192.

Rinella, M. E., J. V. Lazarus, V. Ratziu, S. M. Francque, A. J. Sanyal, F. Kanwal, D. Romero, M. F. Abdelmalek, Q. M. Anstee, J. P. Arab, M. Arrese, R. Bataller, U. Beuers, J. Boursier, E. Bugianesi, C. D. Byrne, G. E. Castro Narro, A. Chowdhury, H. Cortez-Pinto, D. R. Cryer, K. Cusi, M. El-Kassas, S. Klein, W. Eskridge, J. Fan, S. Gawrieh, C. D. Guy, S. A. Harrison, S. U. Kim, B. G. Koot, M. Korenjak, K. V. Kowdley, F. Lacaille, R. Loomba, R. Mitchell-Thain, T. R. Morgan, E. E. Powell, M. Roden, M. Romero-Gómez, M. Silva, S. P. Singh, S. C. Sookoian, C. W. Spearman, D. Tiniakos, L. Valenti, M. B. Vos, V. W. Wong, S. Xanthakos, Y. Yilmaz, Z. Younossi, A. Hobbs, M. Villota-Rivas and P. N. Newsome (2023). "A multisociety Delphi consensus statement on new fatty liver disease nomenclature." J Hepatol.

Roeb, E. (2021). "Excess Body Weight and Metabolic (Dysfunction)-Associated Fatty Liver Disease (MASLD)." Visceral Medicine.

Roeb, E., A. Canbay, H. Bantel, J. Bojunga, J. de Laffolie, M. Demir, U. W. Denzer, A. Geier, W. P. Hofmann, C. Hudert, T. Karlas, M. Krawczyk, T. Longerich, T. Luedde, M. Roden, J. Schattenberg, M. Sterneck, A. Tannapfel, P. Lorenz and F. Tacke (2022). "[Not Available]." Z Gastroenterol 60(9): 1346-1421.

Roeb, E., A. Canbay, H. Bantel, J. Bojunga, J. de Laffolie, M. Demir, U. W. Denzer, A. Geier, W. P. Hofmann, C. Hudert, T. Karlas, M. Krawczyk, T. Longerich, T. Luedde, M. Roden, J. Schattenberg, M. Sterneck, A. Tannapfel, P. Lorenz, F. Tacke and Collaborators (2022). Z Gastroenterol 60(9): 1346-1421.

Romeo, S., J. Kozlitina, C. Xing, A. Pertsemlidis, D. Cox, L. A. Pennacchio, E. Boerwinkle, J. C. Cohen and H. H. Hobbs (2008). "Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease." Nat Genet 40(12): 1461-1465.

Saadeh, S., Z. M. Younossi, E. M. Remer, T. Gramlich, J. P. Ong, M. Hurley, K. D. Mullen, J. N. Cooper and M. J. Sheridan (2002). "The utility of radiological imaging in nonalcoholic fatty liver disease." Gastroenterology 123(3): 745-750.

Sanyal, A. J., S. A. Harrison, V. Ratziu, M. F. Abdelmalek, A. M. Diehl, S. Caldwell, M. L. Shiffman, R. Aguilar Schall, C. Jia, B. McColgan, C. S. Djedjos, J. G. McHutchison, G. M. Subramanian, R. P. Myers, Z. Younossi, A. J. Muir, N. H. Afdhal, J. Bosch and Z. Goodman (2019). "The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials." Hepatology 70(6): 1913-1927.

Sanyal, A. J., P. Lopez, E. J. Lawitz, K. J. Lucas, J. Loeffler, W. Kim, G. B. B. Goh, J. F. Huang, C. Serra, P. Andreone, Y. C. Chen, S. H. Hsia, V. Ratziu, D. Aizenberg, H. Tobita, A. M. Sheikh, J. M. Vierling, Y. J. Kim, H. Hyogo, D. Tai, Z. Goodman, F. Schaefer, I. R. I. Carbarns, S. Lamle, M. Martic, N. V. Naoumov and C. A. Brass (2023). "Tropifexor for nonalcoholic steatohepatitis: an adaptive, randomised, placebo-controlled phase 2a/b trial." Nat Med 29(2): 392-400.

Sanyal, A. J., V. Ratziu, R. Loomba, Q. M. Anstee, K. V. Kowdley, M. E. Rinella, M. Y. Sheikh, J. F. Trotter, W. Knapple, E. J. Lawitz, M. F. Abdelmalek, P. N. Newsome, J. Boursier, P. Mathurin, J. F. Dufour, M. M. Berrey, S. J. Shiff, S. Sawhney, T. Capozza, R. Leyva, S. A. Harrison and Z. M. Younossi (2023). "Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis." J Hepatol 79(5): 1110-1120.

Schmid, A., M. Arians, T. Karrasch, J. Pons-Kühnemann, A. Schäffler, M. Roderfeld and E. Roeb (2022). "Improvement of Type 2 Diabetes Mellitus and Attenuation of NAFLD Are Associated with the Success of Obesity Therapy." J Clin Med 11(7).

Scorletti, E., P. R. Afolabi, E. A. Miles, D. E. Smith, A. Almehmadi, A. Alshathry, C. E. Childs, S. Del Fabbro, J. Bilson, H. E. Moyses, G. F. Clough, J. K. Sethi, J. Patel, M. Wright, D. J. Breen, C. Peebles, A. Darekar, R. Aspinall, A. J. Fowell, J. K. Dowman, V. Nobili, G. Targher, N. M. Delzenne, L. B. Bindels, P. C. Calder and C. D. Byrne (2020). "Synbiotics Alter Fecal Microbiomes, But Not Liver Fat or Fibrosis, in a Randomised Trial of Patients With Nonalcoholic Fatty Liver Disease." Gastroenterology 158(6): 1597-1610.e1597.

Serra-Burriel, M., A. Juanola, F. Serra-Burriel, M. Thiele, I. Graupera, E. Pose, G. Pera, I. Grgurevic, L. Caballeria, S. Piano, L. van Kleef, M. Reichert, D. Roulot, J. M. Pericàs, J. M. Schattenberg, E. A. Tsochatztis, I. N. Guha, M. Garcia-Retortillo, R. Hernández, J. Hoyo, M. Fuentes, C. Expósito, A. Martínez, P. Such, A. Madir, S. Detlefsen, M. Tonon, A. Martini, A. T. Ma, J. Pich, E. Bonfill, M. Juan, A. Soria, M. Carol, J. Gratacós-Ginès, R. M. Morillas, P. Toran, J. M. Navarrete, A. Torrejón, C. Fournier, A. Llorca, A. Arslanow, H. J. de Koning, F. Cucchietti, M. Manns, P. N. Newsome, R. Hernáez, A. Allen, P. Angeli, R. J. de Knegt, T. H. Karlsen, P. Galle, V. W. Wong, N. Fabrellas, L. Castera, A. Krag, F. Lammert, P. S. Kamath and P. Ginès (2023). "Development, validation, and prognostic evaluation of a risk score for long-term liver-related outcomes in the general population: a multicohort study." Lancet 402(10406): 988-996.

Shen, H., S. Lipka, A. Kumar and P. Mustacchia (2014). "Association between nonalcoholic fatty liver disease and colorectal adenoma: a systemic review and meta-analysis." J Gastrointest Oncol 5(6): 440-446.

Singh, S., A. M. Allen, Z. Wang, L. J. Prokop, M. H. Murad and R. Loomba (2015). "Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies." Clin Gastroenterol Hepatol 13(4): 643-654.e641-649; quiz e639-640.

Stricker, S., S. Rudloff, A. Geier, A. Steveling, E. Roeb and K. P. Zimmer (2021). "Fructose Consumption-Free Sugars and Their Health Effects." Dtsch Arztebl Int 118(5): 71-78.

Suárez, M., N. Boqué, J. M. Del Bas, J. Mayneris-Perxachs, L. Arola and A. Caimari (2017). "Mediterranean Diet and Multi-Ingredient-Based Interventions for the Management of Non-Alcoholic Fatty Liver Disease." Nutrients 9(10).

Tacke, F., D. C. Kroy, A. P. Barreiros and U. P. Neumann (2016). "Liver transplantation in Germany." Liver Transpl 22(8): 1136-1142.

Trépo, E. and L. Valenti (2020). "Update on NAFLD genetics: From new variants to the clinic." J Hepatol 72(6): 1196-1209.

Verrastro, O., S. Panunzi, L. Castagneto-Gissey, A. De Gaetano, E. Lembo, E. Capristo, C. Guidone, G. Angelini, F. Pennestrì, L. Sessa, F. M. Vecchio, L. Riccardi, M. A. Zocco, I. Boskoski, J. R. Casella-Mariolo, P. Marini, M. Pompili, G. Casella, E. Fiori, F. Rubino, S. R. Bornstein, M. Raffaelli and G. Mingrone (2023). "Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial." Lancet 401(10390): 1786-1797.

Vilar-Gomez, E., L. Calzadilla-Bertot, V. Wai-Sun Wong, M. Castellanos, R. Aller-de la Fuente, M. Metwally, M. Eslam, L. Gonzalez-Fabian, M. Alvarez-Quiñones Sanz, A. F. Conde-Martin, B. De Boer, D. McLeod, A. W. Hung Chan, N. Chalasani, J. George, L. A. Adams and M. Romero-Gomez (2018). "Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study." Gastroenterology 155(2): 443-457.e417.

Vilar-Gomez, E., L. Calzadilla-Bertot, V. W. Wong, M. Castellanos, R. Aller-de la Fuente, M. Eslam, G. L. Wong, J. George, M. Romero-Gomez and L. A. Adams (2021). "Type 2 Diabetes and Metformin Use Associate With Outcomes of Patients With Nonalcoholic Steatohepatitis-Related, Child-Pugh A Cirrhosis." Clin Gastroenterol Hepatol 19(1): 136-145.e136.

Vilar-Gomez, E., Y. Martinez-Perez, L. Calzadilla-Bertot, A. Torres-Gonzalez, B. Gra-Oramas, L. Gonzalez-Fabian, S. L. Friedman, M. Diago and M. Romero-Gomez (2015). "Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis." Gastroenterology 149(2): 367-378.e365; quiz e314-365.

Williams, C. D., J. Stengel, M. I. Asike, D. M. Torres, J. Shaw, M. Contreras, C. L. Landt and S. A. Harrison (2011). "Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilising ultrasound and liver biopsy: a prospective study." Gastroenterology 140(1): 124-131.

Wong, V. W., G. L. Wong, R. S. Chan, S. S. Shu, B. H. Cheung, L. S. Li, A. M. Chim, C. K. Chan, J. K. Leung, W. C. Chu, J. Woo and H. L. Chan (2018). "Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease." J Hepatol 69(6): 1349-1356.

Xiao, G., S. Zhu, X. Xiao, L. Yan, J. Yang and G. Wu (2017). "Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis." Hepatology 66(5): 1486-1501.

Yang, Y., Y. Teng, J. Shi, J. Xu, J. Bao, X. Zhang and Q. Wang (2023). "Association of nonalcoholic fatty liver disease with colorectal adenomatous polyps and non-adenomatous polyps: a cross-sectional study." Eur J Gastroenterol Hepatol 35(12): 1389-1393.

Ye, Q., B. Zou, Y. H. Yeo, J. Li, D. Q. Huang, Y. Wu, H. Yang, C. Liu, L. Y. Kam, X. X. E. Tan, N. Chien, S. Trinh, L. Henry, C. D. Stave, T. Hosaka, R. C. Cheung and M. H. Nguyen (2020). "Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis." Lancet Gastroenterol Hepatol 5(8): 739-752.

Young, S., R. Tariq, J. Provenza, S. K. Satapathy, K. Faisal, A. Choudhry, S. L. Friedman and A. K. Singal (2020). "Prevalence and Profile of Nonalcoholic Fatty Liver Disease in Lean Adults: Systematic Review and Meta-Analysis." Hepatol Commun 4(7): 953-972.

Younossi, Z., Q. M. Anstee, M. Marietti, T. Hardy, L. Henry, M. Eslam, J. George and E. Bugianesi (2018). "Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention." Nat Rev Gastroenterol Hepatol 15(1): 11-20.

Younossi, Z., P. Golabi, J. Paik, A. Henry, C. Van Dongen and L. Henry (2023). "The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review." Hepatology.

Younossi, Z. M. (2019). "Non-alcoholic fatty liver disease - A global public health perspective." J Hepatol 70(3): 531-544.

Younossi, Z. M., L. Henry, H. Bush and A. Mishra (2018). "Clinical and Economic Burden of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis." Clin Liver Dis 22(1): 1-10.

Younossi, Z. M., A. B. Koenig, D. Abdelatif, Y. Fazel, L. Henry and M. Wymer (2016). "Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes." Hepatology 64(1): 73-84.

Younossi, Z. M., R. Loomba, Q. M. Anstee, M. E. Rinella, E. Bugianesi, G. Marchesini, B. A. Neuschwander-Tetri, L. Serfaty, F. Negro, S. H. Caldwell, V. Ratziu, K. E. Corey, S. L. Friedman, M. F. Abdelmalek, S. A. Harrison, A. J. Sanyal, J. E. Lavine, P. Mathurin, M. R. Charlton, Z. D. Goodman, N. P. Chalasani, K. V. Kowdley, J. George and K. Lindor (2018). "Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis." Hepatology 68(1): 349-360.

Younossi, Z. M., J. M. Paik, L. Henry, J. Yang, G. Fernandes, M. Stepanova and F. Nader (2023). "The Growing Economic and Clinical Burden of Nonalcoholic Steatohepatitis (NASH) in the United States." J Clin Exp Hepatol 13(3): 454-467.

Younossi, Z. M., V. Ratziu, R. Loomba, M. Rinella, Q. M. Anstee, Z. Goodman, P. Bedossa, A. Geier, S. Beckebaum, P. N. Newsome, D. Sheridan, M. Y. Sheikh, J. Trotter, W. Knapple, E. Lawitz, M. F. Abdelmalek, K. V. Kowdley, A. J. Montano-Loza, J. Boursier, P. Mathurin, E. Bugianesi, G. Mazzella, A. Olveira, H. Cortez-Pinto, I. Graupera, D. Orr, L. L. Gluud, J. F. Dufour, D. Shapiro, J. Campagna, L. Zaru, L. MacConell, R. Shringarpure, S. Harrison and A. J. Sanyal (2019). "Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial." Lancet 394(10215): 2184-2196.

Younossi, Z. M., M. Stepanova, J. Ong, G. Trimble, S. AlQahtani, I. Younossi, A. Ahmed, A. Racila and L. Henry (2021). "Nonalcoholic Steatohepatitis Is the Most Rapidly Increasing Indication for Liver Transplantation in the United States." Clin Gastroenterol Hepatol 19(3): 580-589.e585.

Yuan, X., D. Waterworth, J. R. Perry, N. Lim, K. Song, J. C. Chambers, W. Zhang, P. Vollenweider, H. Stirnadel, T. Johnson, S. Bergmann, N. D. Beckmann, Y. Li, L. Ferrucci, D. Melzer, D. Hernandez, A. Singleton, J. Scott, P. Elliott, G. Waeber, L. Cardon, T. M. Frayling, J. S. Kooner and V. Mooser (2008). "Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes." Am J Hum Genet 83(4): 520-528.

Zimmer, V. and F. Lammert (2011). "Genetics and epigenetics in the fibrogenic evolution of chronic liver diseases." Best Pract Res Clin Gastroenterol 25(2): 269-280.

.

10. Genetic liver diseases

10.1 Haemochromatosis

Claus Niederau

Abstract

Hereditary haemochromatosis may be classified into five subtypes. The most frequent type 1 is an autosomal recessive trait affecting the HFE gene on chromosome 6. The homozygous C282Y mutation accounts for more than 90% of phenotypes in Caucasian populations and leads to an increase in intestinal iron absorption with a long-term risk of iron overload and organ damage including liver cirrhosis and diabetes mellitus. Early diagnosis in a non-cirrhotic stage and iron removal by phlebotomies are associated with a normal life expectancy.

This review will focus on type 1 HFE haemochromatosis. Other genetic types affect hemojuvelin, hepcidin, transferrin receptor 2, ferroportin 1, and bone morphogenetic protein 6.

Secondary haemochromatosis is usually caused by multiple blood transfusions in haemolytic anaemias such as thalassaemia, sickle cell anaemia, and myelodysplasia. Here, iron may accumulate faster than in genetic haemochromatosis leading to cardiomyopathy and liver cirrhosis. Therapy in secondary haemochromatosis consists of iron chelators because phlebotomies cannot be done due to anaemia.

Definition and classification of iron overload diseases

Hereditary haemochromatosis may be classified into five subtypes (Table 1). Type 1 is the well-known form of iron overload due to an autosomal recessive genetic metabolic malfunction; the homozygous C282Y mutation of the HFE gene on chromosome 6 accounts for more than 90% of clinical phenotypes in populations of Caucasian origin (Feder 1996). This mutation leads to an inadequately high intestinal iron absorption that after decades may cause iron overload and damage to various organs (Figure 1). Types 2a and 2b of genetic haemochromatosis are juvenile forms of iron overload that lead to a severe outcome prior to age 30, with cardiomyopathy and hypogonadism.

The corresponding mutations are located in the hemojuvelin and hepcidin genes, respectively (Roetto 1999). Type 3 has mainly been described in Italian families and refers to a mutation in the transferrin receptor 2 gene (Girelli 2002). Clinical consequences of type 3 haemochromatosis are similar to type 1. Types 2 and 3 are autosomal recessive traits. The mutations of the autosomal dominant type 4 haemochromatosis are located in the gene coding for the basolateral iron transporter ferroportin 1 (Njajou 2001). In contrast to the other types, iron is accumulated in type 4 mainly in macrophages; ferritin values are markedly elevated although transferrin saturation is only slightly higher. Mutations in the gene of the bone morphogenetic protein 6 (BMP6) can also lead to a clinically often mild hepatic iron overload and may be defined as type 5 (Andriopoulos 2009, Meynard 2009, Daher 206). Neonatal haemochromatosis is characterised by severe fatal liver disease due to iron overload. Gestational alloimmune liver disease (GALD) has been established as the cause of fetal liver injury in the majority of cases with neonatal haemochromatosis (Feldman 2013). Probably, neonatal haemochromatosis is not a genetic disease (Feldman 2013, Kelly 2001, Hardy 1990). Further, non-classified rare iron overload syndromes include iron overload in Bantu Africans (Senba 1989) and iron overload in acaeruloplasminaemia (Doyle 2015).

Secondary haemochromatosis is usually caused by multiple blood transfusions in hemolytic anaemias such as thalassaemia, sickle cell anaemia and myelodysplasia syndrome. Iron first accumulates in RES macrophages and is later transferred to parenchymal cells. With frequent blood transfusions, iron may accumulate faster than with genetic haemochromatosis; iron overload often leads to severe cardiomyopathy and liver cirrhosis, limiting effective prognosis. Therapy consists of iron chelators because phlebotomies cannot be done due to the underlying anaemia. This review will focus on type 1 HFE haemochromatosis, the most prevalent genetic form in Germany. Most consequences of iron overload are similar, whatever the cause. Thus, the pathophysiology of tissue and organ damage by iron excess is discussed in detail only for HFE haemochromatosis.

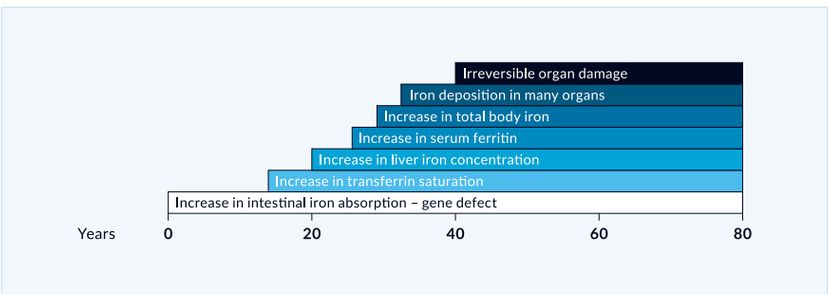

Figure 1. Scheme of natural history of type 1 genetic haemochromatosis (HFE)

Table 1. Classification of haemochromatosis

I) Genetic haemochromatosis				
Types	**Gene defect on**	**Affected gene**	**Inheritance**	**High prevalence**
Type 2a	Chromosome 1	Hemojuvelin	Autosomal recessive	Juvenile form
Type 2b	Chromosome 19	Hepcidin	Autosomal recessive	Juvenile form
Type 3	Chromosome 7	Transferrin receptor 2	Autosomal recessive	Italy
Type 4	Chromosome 2	Ferroportin 1	Autosomal dominant	Italy
Type 5	Chromosome 6	BMP6	Autosomal dominant	Panethnic?
Others	Unknown	Unknown	Unknown	Of non-Caucasian origin
II) Neonatal haemochromatosis, in most cases caused by non-genetic gestational alloimmune liver disease (GALD)				
III) Secondary haemochromatosis				
a) Chronic anaemias (thalassaemia, sickle cell disease, MDS, other rare hemolytic anaemias) b) Multiple blood transfusions in general c) Long-term oral intake of high amounts of iron (diet-related or intravenous)				
IV) Dysmetabolic Iron Overload Syndrome (DIOS) usually associated with metabolic syndrome and fatty liver disease				
V) Further, non-classified iron overload syndromes				
a) iron overload in Bantu Africans b) iron overload in aceruloplasminaemia				

Type 1 HFE haemochromatosis

History

The association between liver cirrhosis, pigment deposits in the liver, and diabetes mellitus was recognised over a century ago (Trosseau 1865, Troisier 1871, Hanot and Schachmann 1886). The term haemochromatosis was first introduced in the 19th century (Recklinghausen 1889) but was not generally accepted until used as the title of a classic monograph (Sheldon 1935). The controversy over whether haemochromatosis was merely a form of alcoholic liver cirrhosis (MacDonald 1960) or a genetic error of iron metabolism (Sheldon 1935, Crosby 1966) lasted almost a century until the association between special HLA haplotypes and haemochromatosis which recognised the genetic nature of the disease was described (Simon 1975). The mode of inheritance was identified as an autosomal recessive disorder (Simon 1977). Finally, the major mutation on the HFE gene associated with clinical manifestations was identified (Feder 1996).

Epidemiology

Type 1 haemochromatosis is probably the most prevalent genetic metabolic error in Caucasian populations (Adams 2005). The prevalence of C282Y homozygotes is approximately 0.5% in central Europe and in the Caucasian population of North America; the prevalence of C282Y and H63D heterozygotes approaches 40% in similar populations (Adams 2005). Phenotypic expression also depends on several non-genetic factors such the amount of dietary iron and blood loss (Figure 2). For example, due to menses, females develop clinical consequences of iron overload 5–8 times less frequently and 10–20 years later than males. It is now widely accepted that not all C282Y homozygous men will develop the full clinical manifestation of haemochromatosis. It also remains unclear how many men will show clinical disease during their lifetime and what factors determine that phenotype.

As mentioned previously, the homozygous C282Y mutation accounts for more than 90% of the clinical phenotype in Caucasian populations (Feder 1996, Adams 2005) (Table 2). A point mutation at H63D is also frequently identified in the HFE gene as well as other less frequent mutations. None of these gene alterations or polymorphisms, found in up to 40% of Caucasians, correlates with the phenotype. A subject with a C282Y variation on one allele and a H63D variation on the other is called a "compound heterozygote" (Table 2). Only a small percentage of such compound heterozygotes are at risk for clinical consequences of iron overload (Gallego 2015). A recent meta-analysis showed a positive association between compound heterozygosity for C282Y/H63D and the risk of NAFLD and HCC, but not liver cirrhosis (Ye et al. 2016). Patients who are compound heterozygous for C282Y/H63D or homozygous for H63D with confirmed iron overload should be investigated for other causes of iron overload and may be treated with phlebotomy on an individual basis (EASL 2022); the benefit of phlebotomy is however largely unclear in the latter patients. C282Y and H63D heterozygotes are at no risk of iron overload (Table 2). In non-Caucasian populations other genes may be involved in causing iron overload.

Aetiology and pathogenesis

Intestinal iron absorption and iron losses are finely balanced under physiological conditions. Approximately 10% of the total daily intake of iron (10–20 mg) is absorbed by the small intestine (1–2 mg). However, subjects with the homozygous C282Y mutation may absorb up to 20% of iron intake; i.e., up to 2–4 mg/day. Thus, homozygotes have an excessive iron intake of approximately 1 mg/day. It may therefore take several decades until iron stores approach 10 g, above which organ damage is considered to start. Many patients at the clinical end stage of haemochromatosis, including liver cirrhosis and diabetes mellitus, have total body iron stores of 20–30 g. Intestinal iron absorption is downregulated when iron stores increase in these patients, as it is in patients with genetic haemochromatosis. This downregulation, however, occurs on an increased level when compared to subjects without the HFE gene mutation. Correspondingly, intestinal iron absorption is massively increased in patients with haemochromatosis when iron stores have been depleted by phlebotomy. It is important to continue phlebotomies after iron depletion in order to prevent reaccumulation (see Table 4). These regulatory processes however do not explain how HFE gene mutations cause the increase in intestinal iron absorption since the HFE gene product is neither an iron transporter nor an iron reductase or oxidase. However, carriers and regulators of cellular iron uptake and release been identified (Pietrangelo 2002, Fleming 2002, Townsend 2002, Fletcher 2002).

Some of these carriers also interact with the HFE gene product in the regulation of intestinal iron absorption (Pietrangelo 2002, Fleming 2002, Townsend 2002, Fletcher 2002) and the Nramp2 protein is the luminal iron carrier. Luminal iron reductase has also been identified as the Dcytb protein (duodenal cytochrome B) (Pietrangelo 2002, Fleming 2002, Townsend 2002, Fletcher 2002). The basolateral iron transporter ferroportin 1 (also named Ireg1 or MTP1) has also been identified (Donovan 2000, Abboud 2000) as well as the basolateral iron oxidase haephestin (Vulpe 1999). Mutations in some of these proteins are responsible for the rarer types 2–4 of genetic haemochromatosis, although none of these genes is altered in type 1 haemochromatosis. Two other proteins have been shown to act as important iron regulating proteins, transferrin receptor 2 and hepcidin (Pietrangelo 2002, Fletcher 2002, Fleming 2005). Mutations in the transferrin receptor 2 gene may lead to the rare type 3 haemochromatosis, and mutations in the ferroportin 1 gene to type 4 haemochromatosis. More recent studies also indicate that hepcidin may be the most important regulator of iron metabolism, involved in iron deficiency and overload. Hepcidin has been shown to downregulate the basolateral iron carrier ferroportin. It has also been demonstrated that hepcidin itself is upregulated by HFE. Thus, an HFE mutation may reduce the upregulation of hepcidin that then does not downregulate ferroportin; the corresponding increase in ferroportin expression finally causes the increase in intestinal iron uptake (DeDomenico 2007). The BMP-SMAD pathway in addition plays an important role in regulating hepcidin to control systemic iron homeostasis (Feldmann 2013). There may be further interactions between HFE, transferrin receptor 2, Nramp2, Dcytb, ferroportin, haephestin, BMP6, and hepcidin.

The penetrance of genetic HFE haemochromatosis depends on various

non-genetic factors and genetic co-factors such as HCP1, GNPAT, PCSK7, TM6SF2, PNPLA3 and MBOAT7 (Niederau 2018) (Figure 2).

The Dysmetabolic Iron Overload Syndrome (DIOS) is usually associated with the metabolic syndrome and fatty liver disease; it is further characterised by an increase in serum ferritin with normal/slightly elevated transferrin saturation and only slightly elevated liver iron (Datz 2017, Deugnier 2017, Fernandez 2022). The increase in liver iron may accelerate fibrosis in patients with DIOS. The pathogenetic mechanisms linking metabolic abnormalities, insulin resistance, and fatty liver disease to iron accumulation are still ill defined. There is as yet no evidence that iron removal by phlebotomies has a benefit for the patient with DIOS.

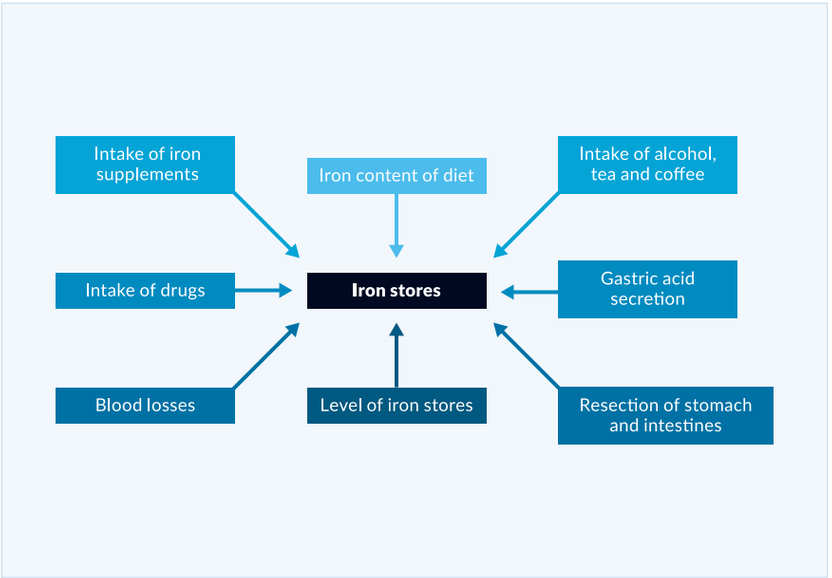

Figure 2. Non-genetic factors and genetic co-factors that may influence iron absorption

Table 2. Genotype/phenotype correlation in haemochromatosis

Mutations/ polymorphisms	Prevalence in Caucasian populations	Risk of advanced clinical phenotype
C282Y/C282Y	85–95%	low if ferritin is <1000 ng/mL
H63D/C282Y	3–8%	very low
C282Y/wild type	-	none
H63D/wild type	-	none
Others	1 %	unknown

Diagnosis

Laboratory tests. Any increase in serum iron should start with the exclusion of haemochromatosis so as not to overlook early disease. Normal serum iron, however, does not exclude haemochromatosis, and increased serum iron often occurs in the absence of haemochromatosis. Serum iron values are highly variable and should not be used either for diagnosis or for screening of haemochromatosis. The determination of transferrin saturation is a better indicator of iron overload than serum iron. The increase in transferrin saturation usually precedes the ferritin increase (Figure 1). Transferrin saturation is more sensitive and specific for detection of haemochromatosis when compared to serum ferritin. For screening, a threshold of 50% for transferrin saturation in men and 45% for women may be optimal under fasting conditions (EASL 2022). Ferritin on the other hand is a good indicator of largely increased iron stores and reliably indicates iron deficiency. It has less value for early detection of haemochromatosis.

In HFE haemochromatosis a slightly increased serum ferritin (300–500 ng/mL) is usually accompanied by transferrin saturations exceeding 80–90%. Unfortunately, serum ferritin is often increased also in the presence of infections and malignancies (regularly without a major increase in transferrin saturation), and thus has a low specificity for indicating haemochromatosis (Niederau 1998). Ferritin increases not due to genetic haemochromatosis are usually associated with normal or only slightly elevated transferrin saturation. Therefore, transferrin saturation should be measured in order to correctly interpret ferritin increases.

Liver biopsy, determination of liver iron concentration, and fibrosis assessment. Although simultaneous increases of both serum ferritin and transferrin saturation strongly indicate a risk for haemochromatosis, diagnosis needs to be confirmed by genetic testing or by liver biopsy with a determination of iron content in the liver. Hepatic iron concentration also increases with time in subjects with an HFE gene mutation. In order to obtain the "hepatic iron index", divide the liver iron concentrations by the patient's age. (Summers 1990). The semi-quantitative estimation of liver iron stores by the Berlin blue colour is less sensitive and specific than the chemical quantification of liver iron concentration. In case of a homozygous C282Y gene test, liver biopsy is not required for the diagnosis of genetic haemochromatosis (Figure 3).

There may, however, be other reasons to perform a liver biopsy in iron overload: (1) subjects with biochemical or clinical evidence of iron overload in the absence of the homozygous C282Y mutation should have a liver biopsy to substantiate iron overload and to look for hepatic comorbidities; (2) in C282Y homozygotes the risk for liver fibrosis and cirrhosis only increases at ferritin values >1000 ng/mL (Loreal 1992); in those patients liver biopsy may

be useful because the presence of liver cirrhosis (and probably also of severe fibrosis) markedly increases subsequent risks of hepatocellular carcinoma (HCC) and thus warrants HCC surveillance. Patients with evident cirrhosis and those with a stiffness <6, 4 kPa do not need a liver biopsy (EASL 2022) (Figure 3). All patients with iron overload should have a non-invasive assessment of liver fibrose e.g. by elastography or FIB4 test (EASL 2022).

Deferoxamine testing and ferrokinetic measurements. Determination of urinary excretion of iron after administration of deferoxamine allows some estimation of total body iron stores. The deferoxamine test, however, often only shows pathological results when serum ferritin and transferrin saturation are markedly increased and does not allow diagnosis of early disease. Ferrokinetic measurements today are only done for scientific research or in difficult diagnostic situations.

Computed tomography (CT), magnetic resonance imaging (MRI), and biomagnetometry. CT density measurements of the liver allow a semi-quantitative estimation of iron concentration in the liver. This method however is associated with radiation and therefore not allowed in many countries where alternative methods are available. MRI, on the other hand, allows a reliable measurement of liver iron content, provided that special software is used and the equipment is calibrated for such measurement. In clinical practice most MRI do not fulfil these criteria. The recent EASL guidelines nevertheless state that iron overload should be assessed by MRI and not by liver biopsy any longer (EASL 2022). This recommendation may be difficult to observe in situations where no specific MRI is available and in situations where the costs for such MRI are not reimbursed by the health insurances.

Biomagnetometry allows the most accurate non-invasive measurement of liver iron concentration. However, this equipment is expensive and only allows measurement of iron concentration. Consequently, biomagnetometry is done only at a few centres worldwide and is primarily used for scientific studies and not in daily clinical practice. With the availability of reliable and inexpensive genetic testing, CT, MRI, and biomagnetometry are usually not needed for diagnosis of most patients with HFE haemochromatosis.

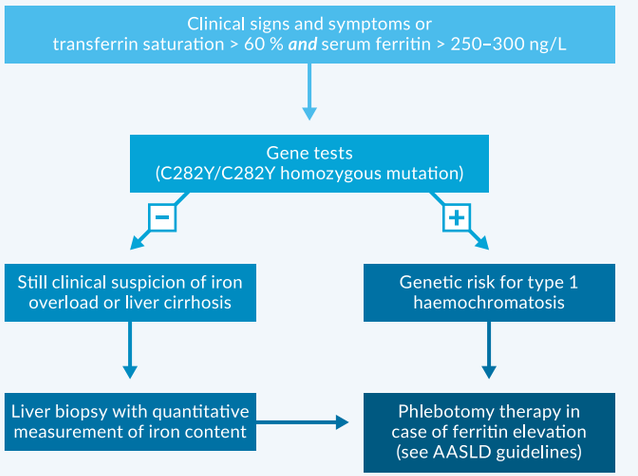

Figure 3. Diagnosis and treatment algorithm for type 1 haemochromatosis

Genetic tests. As outlined previously, in Caucasian populations the homozygous C282Y mutation accounts for more than 90% of patients with the clinical phenotype of type 1 HFE haemochromatosis (Adams 2005, Erhardt 1999). Approximately 5% of patients with the clinical phenotype are C282Y/H63D compound heterozygotes; the prevalence of C282Y or H63D heterozygosity in patients with the clinical phenotype of haemochromatosis is considerably lower than in the general population. Thus, a subject who is heterozygous for C282Y or H63D *per se* has no risk of iron overload. In subjects homozygous for C282Y, both serum ferritin and transferrin saturation are frequently increased; however, only male subjects have an increased risk for liver disease when compared to subjects without HFE gene alterations in a recent large screening study (Adams 2005). It is unknown how many C282Y homozygotes will later develop clinical signs and symptoms due to iron overload. It is increasingly evident that only a minority of C282Y homozygotes progress to end stage iron overload with liver cirrhosis and diabetes mellitus. In subjects who are not C282Y homozygotes but have laboratory, histological or clinical evidence of iron overload, further genes may be analysed for mutations such as hemojuvelin, transferrin receptor 2, ferroportin 1 BMP6, and hepcidin.

Early diagnosis and screening

The prevalence of C282Y homozygotes is 0.5% in Caucasians (Adams 2005, Erhardt 1999). Clinical manifestations however are variable and depend on non-genetic factors such as dietary iron intake and blood loss. Until 1980, most patients with haemochromatosis were detected with late irreversible complications such as liver cirrhosis and diabetes mellitus. With a better understanding of the disease, the broad use of ferritin and transferrin saturation measurements and the availability of a reliable genetic test, diagnostic efforts have concentrated on the detection of early disease before liver cirrhosis and diabetes mellitus. Several studies have shown that iron removal by phlebotomy is associated with normal life expectancy in patients diagnosed early (Niederau 1985, Niederau 1996, Fargion 1992) (Figure 4). Several other studies have focused on screening procedures in order to diagnose more subjects with early disease (Edwards 1988). These studies include populations with special risks, family members, as well as the general population (Table 3) (Niederau 2002). It has been shown that an increasing number of patients are now diagnosed early and that this trend increases survival (Figure 5).

A large number of studies have shown that screening is useful for detection of asymptomatic C282Y homozygotes by using transferrin saturation and serum ferritin as well a genetic test for the C282Y mutation (Edwards 1988, Phatak 1998, Niederau 1998). A broad screening of the general population however is as yet not recommended by WHO and CDC mainly because it is unknown how many of the asymptomatic C282Y homozygotes will later develop clinical disease (see US Preventive Services Task Force 2007). The largest screening study analysed HFE gene mutations in almost 100, 000 subjects in North America. In Caucasians, C282Y homozygosity was found in 0.44%, a value similar to many previous studies in other populations with a similar background. Asian or Black people in contrast almost never have an HFE gene mutation (Adams 2005). Among the Caucasian C282Y homozygotes only males had a significant increase in liver disease when compared to subjects without an HFE gene variation (Adams 2005). Only further prospective follow-up studies will determine how many asymptomatic C282Y homozygotes will develop clinical consequences of iron overload.

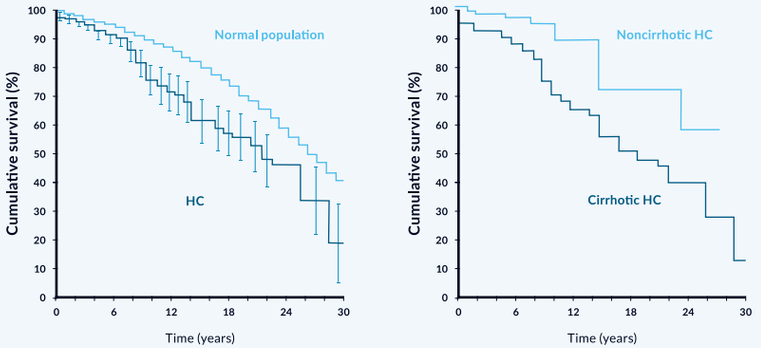

Figure 4. Survival of 251 patients with genetic haemochromatosis (with and without cirrhosis) in comparison with a matched general population. Modified from (Niederau 1996)

Table 3. Methods for early diagnosis of haemochromatosis

1. Screening in the general population not recommended
Screening of HFE gene alterations is not recommended in the general population because it remains unknown how many of the C282Y homozygotes will develop clinical manifestations. Such screening would be meaningful only in Caucasian populations.
2. Family screening
Genetic testing can reliably determine who, among the first-degree relatives of a haemochromatotic patient, is a heterozygote or homozygote. Heterozygotes are healthy and do not need follow-up. C282Y homozygotes should be followed and treated by phlebotomy if ferritin increases >300 ng/mL in men and >200 ng/mL in women.
3. Haemochromatosis should be excluded in patients with
newly diagnosed diabetes mellitus chronic liver disease of unknown aetiology elevation of iron, transferrin saturation or serum ferritin cardiomyopathy of unknown aetiology arthropathy of unknown aetiology loss of potency/libido and amenorrhea of unknown aetiology
4. Every liver biopsy needs to be checked for iron deposits

It is also unknown at which ferritin values phlebotomy treatment should be initiated in asymptomatic C282Y homozygotes (Table 4). The values recommended by the AASLD are based more on the judgment of experts than on solid data. The only solid data show that the risk for liver fibrosis and cirrhosis increases above the threshold of 1000 ng/mL for serum

ferritin (Loreal 1996). The value of screening family members is obvious when a first-degree relative has clinical haemochromatosis. Such family screening is easy to do with the genetic test. Heterozygous family members are not at risk for haemochromatosis unless they have other risk factors.

The clinical phenotype of haemochromatosis is seen in 1–2% of patients with newly diagnosed diabetes mellitus and in 3–15% of patients with liver cirrhosis (Niederau 1999). These latter patients should be screened for iron overload although such screening obviously does not aim at a very early diagnosis. Nevertheless, cirrhotic and diabetic patients with haemochromatosis can benefit significantly from phlebotomy therapy. Little is known about the prevalence of haemochromatosis in patients with arthropathy or cardiomyopathy of unclear aetiology. Several smaller studies indicate that arthropathy may be a rather early clinical sign of iron overload, whereas cardiomyopathy usually occurs in late stage iron overload.

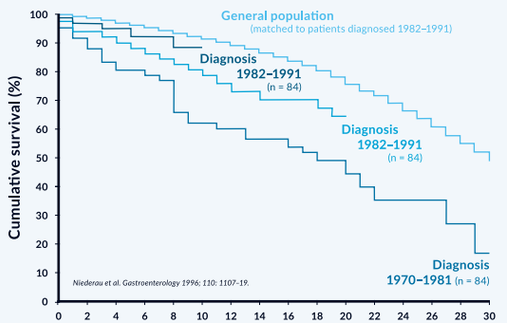

Figure 5. Cumulative survival in 251 patients with genetic haemochromatosis according to the time of diagnosis. Modified from Niederau 1996

Table 4. Iron overload therapy

1. Phlebotomy
a) In symptomatic genetic haemochromatosis
Aims: complete iron depletion in 12-24 months; Treatment: 1-2 phlebotomies of 500 mL each week until serum ferritin is in the range of 50-100 ng/mL; Long-term therapy with 4-8 phlebotomies per year to keep ferritin between 50-100 ng/mL and thus prevent reaccumulation of iron
b) In asymptomatic C282Y homozygotes therapy should be initiated above these ferritin values:
Subjects <18 years >200 ng/mL Men >300 ng/mL Women (not pregnant) >200 ng/mL Women (pregnant) >500 ng/mL
2. Therapy with iron chelators in secondary haemochromatosis and anaemia
Aims: removal of iron overload by increase of iron excretion in faeces and urine In case of further blood transfusions at high frequency at stabilisation of iron balance and reduction of further iron accumulation Treatment: until recently, 25-50 mg deferoxamine/kg as sc infusion for 10-12 h daily; today, deferoxamine is largely replaced by the oral chelator deferasirox – 20 mg/kg deferasirox once daily to prevent iron accumulation up to 800 mL erythrocytes concentrates/month Long-term treatment necessary Normalisation of ferritin and liver iron concentration often not possible
3. Diet
Recommended: avoidance of food with very high iron content (e.g., liver) and iron-supplemented food; A further strict iron-depleted diet very difficult to adhere to and not recommended A single phlebotomy of 500 mL blood as effective for iron removal as a very rigid iron-restricted diet for a full year

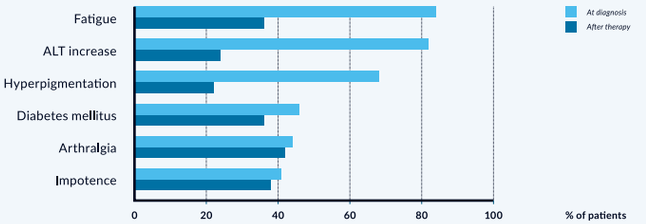

Figure 6. Signs and symptoms in 185 patients with genetic haemochromatosis prior to and after iron removal. Modified from Niederau 1996

Complications of iron overload

Liver cirrhosis, diabetes mellitus and increased skin pigmentation are the classical trio of genetic haemochromatosis. Cardiomyopathy, cardiac arrhythmias and impotence are also typical complications of advanced iron overload. Arthropathy in contrast may be an early sign of haemochromatosis, which may help with diagnosis in the precirrhotic stage (Niederau 1996).

Liver disease. The liver is the organ that is affected by genetic iron overload most early and heavily. At early stages excess iron stores are mainly found in periportal parenchymal cells as ferritin and hemosiderin. When iron excess further increases, there is development of perilobular fibrosis and iron stores are also found in bile ducts and Kupffer cells. Septal fibrosis eventually progresses towards complete cirrhosis. The stage of fibrosis is closely associated with the degree of excess of iron. In many affected symptomatic patients with type 1 haemochromatosis there are some signs of liver disease at the time of diagnosis (Niederau 1985, Niederau 1996). Many nonspecific symptoms such as abdominal discomfort and fatigue may also be due to liver involvement. In asymptomatic patients diagnosed by a screening procedure, signs of liver disease are infrequent. Complications due to cirrhosis such as ascites, jaundice and portal hypertension are seen only rarely and only in cases of advanced severe iron overload (Niederau 1985, Niederau 1996). The risk for liver cirrhosis increases at ferritin values >1000 ng/mL (Loreal 1996). Similar to insulin-dependent diabetes, liver cirrhosis cannot be reversed by removal of iron (Niederau 1996). However, less advanced stages like hepatic fibrosis and abnormalities in liver enzymes and function respond well to iron removal (Niederau 1996) (Figure 5). Survival is significantly reduced in the presence of liver cirrhosis whereas patients diagnosed in the precirrhotic stage have a normal life expectancy when treated by phlebotomy (Niederau 1996) (Figure 4).

Association of haemochromatosis with other liver diseases. Some studies indicate that C282Y heterozygosity may aggravate the progression of concomitant liver diseases such as porphyria cutanea tarda, chronic hepatitis C, alcoholic hepatitis and non-alcoholic steatohepatitis (NASH). In these latter patients one might find slightly elevated liver iron concentrations and serum ferritin levels when they are C282Y heterozygotes (for review see Erhardt 2003). Most studies however have shown that these associations are of only minor importance in the clinical course of the disease. Phlebotomy has so far only been proven meaningful in porphyria cutanea tarda because it can ameliorate the cutaneous manifestations.

Liver carcinoma. Liver carcinoma develops in approximately 30% of patients with haemochromatosis and cirrhosis independent of iron depletion (Niederau 1996). The interval between complete iron depletion and reported diagnosis of liver cancer is approximately nine years in large cohorts in German patients (Niederau 1985, Niederau 1996). The risk of liver cancer is increased 100–200-fold in patients with haemochromatosis when compared to the general population (Figure 6). Among liver cancers there are hepatocellular carcinoma (HCC) as well as cholangiocellular carcinoma. Most liver cancers develop in patients with cirrhosis. Thus, cancer screening by ultrasound and potentially also by AFP (twice a year) is only recommended for patients with cirrhotis or severe fibrosis (EASL 2022). Patients who develop liver cancer usually have the largest amount of iron accumulation among various subgroups (Niederau 1996, Niederau 1999).

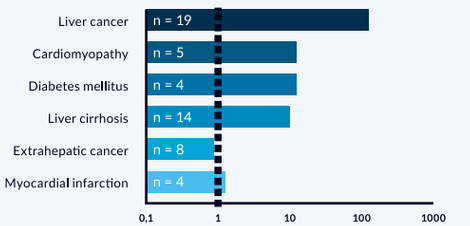

Figure 7. Relative mortality risk of 251 patients with genetic haemochromatosis in comparison to the general population. Modified from Niederau 1996

Diabetes mellitus. The prevalence of diabetes in hereditary haemochromatosis ranges from 20–50% (Niederau 1996, Adams 1991). The prevalence and stage of diabetes is related to the degree of iron deposition in the pancreas. Patients with diabetes have a twofold higher mobilisable iron content than non-diabetics (Yaouanq 1995). Investigations into the prevalence of unrecognised genetic haemochromatosis in diabetic patients show some variation in Europe vs. elsewhere; i.e., screening revealed a prevalence of 5–8 per 1000 unrecognised cases in Europe (Singh 1992) and 9.6 per 1000 in Australia (Phelps 1989). Diabetes mellitus and impaired glucose tolerance are frequent features in several chronic liver diseases (Creutzfeldt 1970, Blei 1982). This author's study (Niederau 1984) showed hyperinsulinaemia and hence insulin resistance without impaired glucose tolerance in noncirrhotic haemochromatosis. The increase in circulating insulin concentrations is likely to be due to a decrease in diminished hepatic extraction of insulin. With the progression of iron overload and destruction of beta cells, insulin secretion becomes impaired (Dymock 1972, Bierens de Haan 1973). In end-stage haemochromatosis, insulin deficiency is associated with severe reduction in the mass of beta cells (Rahier 1987). Insulin resistance observed in early iron overload may be partially reversible after phlebotomy therapy

(Niederau 1985, Niederau 1996) whereas insulin-dependent diabetes is irreversible (Niederau 1996). Survival is significantly reduced in patients with diabetes mellitus at diagnosis compared to patients without diabetes (Niederau 1996). Survival of non-diabetic patients is virtually identical to that of a matched normal population.

Heart disease. Cardiomyopathy and cardiac arrhythmias are specific complications of haemochromatosis caused by iron deposition in the heart (Buja and Roberts 1971, Short 1981). Clinical or electrocardiographic signs of heart disease can be found in 20–35% of patients with HFE haemochromatosis (Niederau 1985). Arrhythmias usually respond well to iron removal (Short 1981, Niederau 1996). In type 1 haemochromatosis cardiomyopathy is rare and usually associated with advanced iron overload and an older patient population. However, particularly in young patients who present with cardiac disease due to haemochromatosis, cardiomyopathy is a frequent cause of death (Finch 1966, Short 1981). It has also become clear that young patients with severe cardiomyopathy may be affected by juvenile type 2 haemochromatosis; these patients may show severe iron overload, hypogonadism, cardiomyopathy, liver cirrhosis, and amenorrhea by ages 15–24. The type 2-associated cardiomyopathy is often irreversible despite initiation of phlebotomy or chelation therapy and may require an immediate transplant of the heart and potentially of the liver as well (von Herbay 1996, Jensen 1993).

Arthropathy. Joint changes in genetic haemochromatosis may occur in two different ways (Schuhmacher 1964, Dymock 1970, Niederau 1985, Niederau 1996). The most prevalent changes are seen in the metacarpophalangeal joints II and III, in the form of cystic and sclerotic changes, cartilage damage and a narrowing of the intraarticular space. Sometimes other joints of the hands and the feet are affected. Large joints, i.e., of the knees and hips, may be affected in the form of chondrocalcinosis. The pathogenesis of joint changes in haemochromatosis remains unclear. Arthropathy is one of the few complications not associated with the degree of iron overload. It has been speculated that iron may inhibit pyrophosphatase and may thereby lead to a crystallisation of calcium pyrophosphates. Alternatively, iron may have direct toxic effects on the joints. Arthropathy may be an early sign of haemochromatosis and may help to make the diagnosis at a precirrhotic stage (Niederau 1996). Haemochromatosis should therefore been considered in all patients with an arthropathy of unknown aetiology.

Endocrine abnormalities. In contrast to the early onset of arthropathic changes, endocrine abnormalities are a late consequence of iron overload. Sexual impotence and loss of libido may occur in up to 40% of male patients (Niederau 1985). The endocrine abnormalities in haemochromatosis are mainly, if not exclusively, due to pituitary failure. This is in contrast to alcoholic cirrhosis where testicular failure is predominant (Kley 1985a, Kley 1985b). In contrast to alcoholic cirrhosis, where oestrogen levels are usually increased, oestrogen levels were found decreased in haemochromatosis (Kley 1985a). Most endocrine changes are late and irreversible complications of genetic haemochromatosis and do not respond well to phlebotomy treatment (Niederau 1996). Iron overload only infrequently affects other endocrine organs such as the thyroid and adrenal glands. Severe hypogonadism with amenorrhea in young women and impotence in young men is today thought to be due to type 2 haemochromatosis.

Skin. Increased skin pigmentation is mainly seen in areas exposed to sunlight. A large part of the darkening of pigmentation is thought to be due to an increase in melanin and not due to iron excess itself. The increase in skin pigmentation is reversible on iron removal (i.e., phlebotomy).

Other potential complications. Iron overload has been speculated to aggravate atherosclerosis; however, the evidence for that is rather weak (for review see Niederau 2000). There have also been reports that extrahepatic malignancies may be increased in HFE haemochromatosis (Amman 1980, Fracanzani 2001) while other studies have not found extrahepatic associations (Bain 1984, Niederau 1996, Elmberg 2003). It is not clear whether HFE gene mutations are involved in the pathogenesis of porphyria cutanea tarda since the prevalence of both risk factors vary greatly in different parts of the world; associations between HFE gene mutations and porphyria have often been described in southern Europe but not in northern Europe (Toll 2006).

Polymorphisms beyond C282Y homozygocity. Recent studies have suggested that the C282Y and H63D polymorphisms in the HFE gene are associated with a selection advantage. This selection may also explain the high frequency of up to 40% of these polymorphisms seen in Celtic populations (Adams 2005). These polymorphisms are almost exclusively found in people with Celtic decent. A French study recently showed that these polymorphisms are seen in 27% of the French general population (Hermine 2015). Interestingly, 80% of French winners of WM, EM and Olympic sport events had one of these polymorphisms (Hermine 2015).

Along this line, a recent Swiss study showed that C282Y homozygotes are several centimeters taller than the reference population (Cippa 2013), although these homozygotes are usually considered not to be healthy. Indeed the greater height and physical fitness of the Celts have already been mentioned by Julius Caesar in his work „De Bello Gallico“ (Caesar 50 a.c.).

Thus, subjects with heterozygous HFE polymorphisms are usually “very healthy” people without a major risk for iron overload and associated organ damage. Only in the presence of other hepatotoxic factors such as hepatitis C or fatty liver disease HFE heterozygotes may have an increased risk to develop liver fibrosis (Erhardt 2003).

Therapy

Phlebotomy treatment. Phlebotomy treatment is the standard of care for removing iron in genetic haemochromatosis. One phlebotomy session removes approximately 250 mg iron from the body. Since patients with the classical clinical phenotype may have an excess of 10–30 g iron, it may take 12–24 months to remove the iron overload when phlebotomies of 500 mL blood are done weekly (Table 4). Phlebotomy treatment is generally well tolerated and hemoglobin usually does not drop below 12 g/dL. Several studies have shown that liver iron is completely removed at such low ferritin values; thus the effect of therapy can be checked by ferritin measurements and a control liver biopsy is not necessary. After complete removal of excess iron the intervals of phlebotomies may be increased to once every 2–3 months; serum ferritin should be kept in the lower normal range, between 50–100 ng/mL. Phlebotomy should not be interrupted for longer intervals; there is a risk of reaccumulation of iron due to the genetic autosomal recessive metabolic malfunction.

Erythrocytapheresis. Three prospective, randomised studies have compared the advantages and disadvantages of erythrocytapheresis compared to phlebotomy in patients with hereditary HFE haemochromatosis (Rombout-Sestrienkova 2012, Sundic 2013, Rombout-Sestrienkova 2016). Erythrocytapheresis can theoretically remove up to three times more red blood cells per single procedure when compared with regular phlebotomy and thus may have a clinical and economic benefit.

In one of these studies serum ferritin levels initially declined more rapidly in the apheresis group; however, time to normalisation of the ferritin level was equal in both groups (Sundic 2013). The cumulative costs for materials and technician times until achievement of the desired ferritin levels were three-fold higher in the apheresis group (Sundic 2013).

In the other study, after adjustments for initial serum ferritin and body weight, the number of therapeutic procedures was lower for erythrocytapheresis when compared with regular phlebotomy (0.43; 95% CI, 0.35–0.52; p <0.001) (Rombout-Sestrienkova 2012). Cost analysis however showed no significant difference in treatment costs between the two procedures (Rombout-Sestrienkova 2012).

The third study evaluated the effectiveness of erythrocytapheresis over phlebotomy for maintenance therapy in patients with HFE haemochromatosis (Rombout-Sestrienkova 2016). The two treatment-arms, randomised, crossover clinical trial involved 46 patients who were treated for one year with either erythrocytapheresis or phlebotomy to keep the ferritin level < 50 ng/mL. After one year, patients were switched to the other treatment modality. The mean number of treatment procedures per treatment year was significantly higher using phlebotomy versus erythrocytapheresis (3.3 vs. 1.9; p<0, 01). There was no significant difference between arms in overall health assessed by SF-36 and EQ-5D, respectively. The mean costs of one treatment year however were 235 € for phlebotomy versus 511 € for erythrocytapheresis.

In summary, regular phlebotomy remains the gold standard for removing excess iron in hereditary haemochromatosis type 1. It has few side-effects and is more cost-effective than erythrocytapheresis.

Monitoring of phlebotomy treatment. Phlebotomy treatment is usually monitored by repetitive measurements of serum ferritin. According to ESAL and AASLD guidelines, phlebotomies should be done at frequent intervals until serum ferritin is reduced to low normal values of about 50–100 ng/mL (Bacon 2011, EASL 2010). Thereafter, the interval of phlebotomies can be prolonged to assure that serum ferritin remains at 50–100 ng/mL. It is known that the liver and other organs do not contain excess iron when ferritin is in that range. On the other hand, it is also know that transferrin saturation may still be increased up to 70% at such ferritin levels in C282Y homozygotes. Recent studies have shown that serum concentrations of Non-Tranferrin-Bound Iron (NTBI) and Labile Plasma-Iron (LPI) may increase sharply beyond a tranferrin saturation of 70–80% (Cabantchik 2014). Such increases in NTBI and LPI may be associated with oxidative stress and risks for cell damage (Hershko 1978, Le Lan 2005, Pootrakul 2004, Hod 2011, Brissot 2012, Cabantchik 2014). Therefore, there is a current debate whether transferrin saturation should be used for monitoring long-term phlebotomy and transferrin saturation should aim to be kept below 50% (Cabantchik 2014, de Swart 2015). This would mean that a considerable number of patients would be at the risk to become iron deficient – which should be avoided according to EASL and AASLD guidelines (Bacon 2011, EASL 2010). It is also known that the usual ferritin monitoring assures a normal life expectancy in patients diagnosed without liver cirrhosis (Niederau 1985, Niederau 1996). Thus, as yet the monitoring of phlebotony treatment should be based on serum ferritin which should kept at 50–100 ng/mL (Bacon 2011, EASL 2010).

Iron removal by chelators. Deferoxamine therapy for genetic haemochromatosis is not recommended because phlebotomy is more effective with less side effects and lower cost. A phase 2/3 study proved the safety and effectiveness of the new oral iron chelator deferasirox in genetic HFE haemochromatosis (Phatak 2010). However, deferasirox is only currently approved for secondary haemochromatosis.

Diet. A diet low in iron is not recommended for patients with genetic haemochromatosis. One phlebotomy of 500 mL blood removes approximately 250 mg iron. A difficult-to-follow iron-restricted diet for a complete year would have the effect of a single phlebotomy. It is therefore recommended that patients simply do not eat excessive amounts of food

with very high iron content (such as liver) and that they do not eat food to which iron has been added (Table 4). The recent EASL guidelines recommend to avoid supplemental vitamin C and to limit red meat and alcohol intake; cirrhotic patients should abstain from alcohol consumption (EASL 2022).

Use of proton pump inhibitors. A double-blind randomised placebo-controlled trial has shown that the use of proton pump inhibtors (PPI) significantly lowered the need for phlebotomies in the maintenance phase in patients with HFE haemochromatosis (Vanclooster 2017). This effect is probably mediated by diminishing the intestinal absorption of non-heme iron due to an increase in gastric pH. As stated by the recent EASL guideline (EASL 2022) PPI may have side effects and have not been studied in the induction phase of iron removal. Thus, PPI should be considered only as a supportive treatment in specific cases and not as a first- or second-line therapeutic tool (EASL 2022),

Liver transplantation. Advanced liver cirrhosis and carcinoma may be indications for a liver transplant in haemochromatosis (Kowdley 1995, Brandhagen 2000). The prognosis of patients who have a liver transplant for haemochromatosis is markedly worse than that for patients with other liver diseases; a considerable number of patients with haemochromatosis die after transplant from infectious complications or heart failure (Brandhagen 2000). Liver transplantation does not heal the original genetic defect.

Hepcidin administration. In HFE haemochromatosis hepcidin deficiency leads to increased intestinal absorption of dietary iron and subsequent to iron overload (Nemeth 2004). Thus, administration of hepcidin might be beneficial in this situation. However, hepcidin preparations turned out to have difficult pharmacokinetic characteristics which have recently been overcome by synthesis of the hepcidin mimetic rusfertide. Rusfertide has recently demonstrated control of iron in an animal model of hereditary haemochromatosis (Taranath 2022). In human HFE haemochromatosis rusfertide reduced transferrin saturation and serum iron with corresponding significant reduction in the number of phlebotomies in patients who had been on a stable phlebotomy regimen of 0.25 to 1 phlebotomy per month for at least 6 months (Kowdley 2021). Under the administration of rusfertide the liver iron concentration maintained at pre-study levels with minimal use of phlebotomies. Rusfertide was well tolerated by the patients (Kowdley 2021). These data suggest that rusfertide might be used as an alternative treatment for selected patients with HFE haemochromatosis in the future.

Prognosis

Untreated haemochromatosis often has a bad prognosis in the presence of liver cirrhosis and diabetes mellitus. The prognosis is markedly worse in patients with cirrhosis than in those without cirrhosis at diagnosis (Figure 3); the same is true for diabetes mellitus. It is generally accepted that phlebotomy therapy improves the prognosis. Patients diagnosed and treated in the early non-cirrhotic stage have a normal life expectancy (Figure 3) (Niederau 1985, Niederau 1996). Thus, early diagnosis markedly improves the prognosis (Figure 4). Iron removal by phlebotomy also improves the outcome in patients with liver cirrhosis. The prognosis of liver cirrhosis due to haemochromatosis is markedly better than those with other types of cirrhosis (Powell 1971). Hepatomegaly and elevation of aminotransferases often regress after iron removal (Niederau 1985, Niederau 1996) (Figure 5). Insulin-dependent diabetes mellitus and hypogonadism are irreversible complications despite complete iron removal (Niederau 1996) (Figure 5). Earlier changes in glucose and insulin metabolism, however, may be ameliorated after iron removal. For unknown reasons arthropathy does not respond well to phlebotomy treatment although it may be an early sign of iron overload (Figure 5). The AASLD consensus guidelines recommend to start phlebotomy treatment at ferritin values >300 ng/mL in men and >200 ng/mL in women. The risk for liver fibrosis and cirrhosis is increased only at ferritin levels >1000 ng/mL. Further studies need to determine whether asymptomatic C282Y homozygotes with ferritin values between 300 and 1000 ng/mL need to be treated or whether one might wait and monitor ferritin at that stage.

Juvenile hereditary haemochromatosis

Two genes have been associated with juvenile haemochromatosis: 90% of cases are associated with mutations in hemojuvelin (HJV) (locus name HFE2A, which encodes HJV), while 10% of cases are associated with HAMP (locus name HFE2B, which encodes hepcidin). Despite the nomenclature of HFE2A and HFE2B, juvenile haemochromatosis is not associated with HFE mutations. In order to avoid confusion most physicians use the terms type 2A (hemojuvelin mutations) and type 2B (HAMP mutations). Mutations in hemojuvelin are associated with low levels of hepcidin in urine suggesting that hemojuvelin regulates hepcidin. Hepcidin is the key regulator of intestinal iron absorption and iron release from macrophages. Hepcidin facilitates ferroportin internalisation and degradation. Hepcidin mutations may thereby lead to an increase in ferroportin and thus iron uptake from the intestine. Juvenile haemochromatosis is very rare. A clustering of HJV

mutations can be seen in Italy and Greece although few families account for this phenomenon. Mutations in HJV represent the majority of worldwide cases of juvenile haemochromatosis.

Only a small number of patients have been identified with HAMP-related juvenile haemochromatosis. Juvenile haemochromatosis is characterised by an onset of severe iron overload in the first to third decades of life. Clinical features include hypogonadism, cardiomyopathy, and liver cirrhosis (Diamond 1989, Vaiopoulos 2003). The main cause of death is cardiomyopathy (De Gobbi 2002, Filali 2004). In contrast to HFE type 1 haemochromatosis, both sexes are equally affected. Mortality can be reduced in juvenile haemochromatosis when it is diagnosed early and treated properly. Phlebotomy is the standard therapy in juvenile haemochromatosis as well and is treated similarly to HFE haemochromatosis (Tavill 2001). In patients with juvenile haemochromatosis and anaemia or severe cardiac failure, administration of chelators such as deferoxamine have been tried to reduce mortality; some case reports suggest that this might improve left ventricular ejection fraction (Kelly 1998).

Transferrin receptor 2 (TFR2)-related type 3 haemochromatosis

TFR2-related haemochromatosis is defined as type 3 and is also known as HFE3; however, the term HFE3 should not be used because the HFE gene is not affected in type 3 haemochromatosis. TFR2-related haemochromatosis is inherited in an autosomal recessive manner. TFR2 is a type II 801-amino acid transmembrane glycoprotein expressed in hepatocytes and at lower levels in Kupffer cells (Zhang 2004). A finely regulated interaction between TFR2, TFR1 and HFE is now thought to affect the hepcidin pathway, and, consequently, iron homeostasis (Fleming 2005). Patients with homozygous TFR2 mutations have increased intestinal iron absorption that leads to iron overload. Hepcidin concentrations in urine are low in TFR2 haemochromatosis (Nemeth 2005). TFR2-related haemochromatosis is very rare with only about 20 patients reported worldwide (Mattman 2002). Age of onset in TFR2-related type 3 haemochromatosis is earlier than in HFE-associated type 1 (Piperno 2004, Girelli 2002, Hattori 2003). Progression is, however, slower than in juvenile type 2 (De Gobbi 2002, Roetto 2001, Girelli 2002). The phenotype is similar to type 1. Many patients present with fatigue, arthralgia, abdominal pain, decreased libido, or with biochemical signs of iron overload (Roetto 2001, Girelli 2002, Hattori 2003). Complications of type 3 haemochromatosis include cirrhosis, hypogonadism, and arthropathy. Cardiomyopathy and diabetes mellitus appear to be rather rare. Hepatocellular carcinoma has not been observed in the small number of cases diagnosed. Most individuals with type 3 haemochromatosis have an Italian or Japanese genetic background. Some of the Japanese males have had liver cirrhosis at diagnosis (Hattori 2003). Similar to type 1 haemochromatosis, the penetration of type 3 haemochromatosis is also considerably less than 100% (Roetto 2001). Standard therapy is iron removal by weekly phlebotomy similar to the management of type 1 disease. Individuals with increased ferritin should be treated similar to those with HFE haemochromatosis.

Type 4 haemochromatosis – Ferroportin Disease

Ferroportin-associated iron overload (also called Ferroportin Disease) was first recognised by Pietrangelo (1999) who described an Italian family with an autosomal dominant non-HFE haemochromatosis. Many family members had iron overload resulting in liver fibrosis, diabetes, impotence, and cardiac arrhythmias. In addition to autosomal dominant inheritance, features distinguishing this from HFE haemochromatosis included early iron accumulation in reticuloendothelial cells and a marked increase in ferritin earlier than what is seen in transferrin saturation (Pietrangelo 1999, Rivard 2003, Montosi 2001, Wallace 2004, Fleming 2001). Several patients showed a reduced tolerance to phlebotomy and became anemic despite elevated ferritin (Pietrangelo 1999, Jouanolle 2003).

In 2001, this form of non-HFE haemochromatosis was linked to mutations of ferroportin (Montosi 2001) that had just been identified as the basolateral iron transporter (Abboud 2000, Donovan 2000). Since that time, numerous mutations in the gene have been implicated in patients from diverse ethnic origins with previously unexplained haemochromatosis. Iron overload disease due to ferroportin mutations has been defined as type 4 haemochromatosis or Ferroportin Disease (for review see Pietrangelo 2004 and 2017). The iron export is tightly regulated because both iron deficiency and iron excess are harmful. The main regulator of this mechanism is the peptide hepcidin which binds to ferroportin, induces its internalisation and degradation, thereby reducing iron efflux (Nemeth 2004). Increase in iron absorption may be caused either by hepcidin deficiency or its ineffective interaction with ferroportin. All recent studies have shown that hepcidin deficiency appears to be the common characteristic of most types of genetic haemochromatosis (mutations in HFE, transferrin receptor 2, hemojuvelin, or hepcidin itself). The remaining cases of genetic iron overload are due to heterozygous mutations in the hepcidin target, ferroportin. Because of the mild clinical penetrance of the genetic defect there were doubts about the rationale for iron removal therapy. However, a more recent study shows that there may be clinically relevant iron overload with organ damage and liver

cancer in patients carrying the A77D mutation of ferroportin (Corradini 2007). Treatment schemes are similar to those described for other types of genetic haemochromatosis.

Loss-of-function of one ferroportin 1 allele results in haemochromatosis type 4a with a normal intestinal iron export but a diminished iron export from tissue macrophages leading to progressive iron accumulation in liver, spleen and bone marrow macrophages and in an inappropriately low iron delivery to circulating transferrin (Gozzelino 2016). Thus in the presence of high serum ferritin, transferrin saturation is relatively low in this type of genetic iron overload. The diminished iron delivery may also result in reduced erythropoiesis and anaemia. Liver iron deposition is primarily seen in macrophages (Wallace 2013).

The rare gain-of-function mutations of ferroportin can lead to haemochromatosis type 4b by reducing the inhibitory activity of hepcidin leading to an increase in intestinal iron absorption and to a release of iron from macrophages. Transferrin saturation is high (Callebau 2014). Liver iron deposition is primarily seen in hepatocytes (Kasvosv 2013).

Secondary haemochromatosis

Pathophysiology

Most forms of secondary haemochromatosis are due to hemolytic anaemia associated with polytransfusions such as thalassaemia, sickle cell disease, and myelodysplastic syndromes (MDS). Most of these patients need blood transfusions on a regular basis for survival. However, in the long run, multiple blood transfusions often lead to iron overload if patients are not treated with iron chelators. In general, iron overload due to blood transfusions is similar to genetic haemochromatosis; however, secondary iron overload develops much faster than the genetic forms (McLaren 1983), sometimes as soon as after 10–12 blood transfusions (Porter 2001). Subsequently secondary iron overload can result in more rapid organ damage when compared with genetic haemochromatosis. Secondary iron overload can obviously not be treated by phlebotomy because a marked anaemia is the clinical marker of the disease. Secondary iron overload often limits the prognosis of patients with thalassaemia; life expectancy deteriorates with increasing iron concentrations in the liver (Telfer 2000). Therapy with iron chelator may reduce the transfusional iron burden if the frequency of transfusion is not too high. The development of HFE versus secondary haemochromatosis not only differs in terms of the speed of iron accumulation but also in the type of organ damage; in secondary haemochromatosis cardiomyopathy is often the complication that limits the prognosis (Liu 1994). It is interesting that heart disease is also very frequent in juvenile genetic haemochromatosis where there is also rapid iron accumulation. In general, serum ferritin values closely reflect liver iron concentration and may be used as an indication for timing of therapy as well as to check the effects of iron chelation.

For many years, deferoxamine was the only iron chelator available in most countries but in some countries deferiprone is also approved for patients who do not tolerate deferoxamine (Hoffbrandt 2003). The clinical use of deferiprone is limited due to side effects such as agranulocytosis and neutropenia (Refaie 1995). Long-term data prove that deferoxamine can reduce iron overload and its organ complications (Olivieri 1994, Cohen 1981). Deferoxamine, however, needs to be given daily subcutaneously or by IV infusion for several hours. Thus, patients with thalassaemia often report that deferoxamine treatment is worse than thalassaemia itself (Goldbeck 2000). Therefore, adherence problems often limit the beneficial effects of this iron chelator (Cohen 1989).

Without iron chelation, children with thalassaemia often develop a severe cardiomyopathy prior to age 15 (Cohen 1987). After that age, liver cirrhosis is also a significant complication in secondary iron overload due to thalassaemia (Zurlo 1992). Iron chelation should start early to prevent complications of iron overload. By the ages of 3–5, liver iron concentration may reach values associated with a significant risk for liver fibrosis in severe thalassaemia (Angelucci 1995). Children younger than 5 should therefore be cautiously treated with chelators if they have received transfusions for more than a year (Olivieri 1997). Deferoxamine can reduce the incidence and ameliorate the course of iron-associated cardiomyopathy (Olivieri 1994, Brittenham 1994, Miskin 2003).

Deferasirox is an oral iron chelator with high selectivity for iron III (Nick 2003). Deferasirox binds iron in a 2:1 proportion with a high affinity and increases the biliary iron excretion (Nick 2003). This chelator is able to reduce iron overload in hepatocytes and cardiomyocytes (Nick 2003, Hershko 2001). Due to its half-life of 11–18 hours it needs to be taken only once daily (Nisbet-Brown 2003). Deferasirox exerted a similar iron chelation when compared with deferoxamine in patients with thalassaemia; the effect of 40 mg/kg deferoxamine was similar to that of 20 mg/kg deferasirox (Piga 2006). Both in adults and children 20–30 mg/kg/day deferasirox significantly reduced liver iron concentration and serum ferritin (Cappellini 2006). Magnetic resonance imaging showed that 10–30 mg/kg/day deferasirox may also reduce iron concentration in the heart within one year of maintenance therapy. Deferasirox may cause minor increases in serum creatinine as well as gastrointestinal discomfort and skin exanthema which are usually self-limiting. Considering the compliance problems with deferoxamine, deferasirox has a better cost-effectiveness ratio (Vichinsky

2005). Deferasirox is defined as standard therapy both in the guidelines of the National Comprehensive Cancer Network (NCCN) (USA) and in the international guidelines on MDS (Greenberg 2006, Gattermann 2005).

Use of blood from patients with HFE haemochromatosis (type 1) for blood donation

For some decades it has been debated whether blood phlebotomised from patients with HFE haemochromatosis may be used for blood transfusions (Nouel 1991, Barton 1999, Conry-Cantilena 2001, De Buck 2012, Leitmann 2013). In many countries blood from haemochromatosis patients is still not used for blood transfusion because of several arguments and precautions:

For a long time such blood has not been accepted by many blood banks because there was a hypothesis that such blood may be associated with increased risk for the recipient. Indeed, excess iron may increase the risk for bacterial and viral infections (Walker 2000, Khan 2007, Drakesmith 2008). In particular there were some hints that siderophilic bacteria including Vibrio sp., Salmonella sp. and Yersinia sp. grow particularly well in iron-overloaded blood (Nouel 1991, Cauchie 1987, Boelaert 1987, Piroth 1997). There have also been reports that Yersinia enterocolitica is responsible for posttransfusion sepsis and death (Leclercq 2005). *In vitro* there is a significantly decreased antibacterial activity against S. typhimurium LT2 and a better survival of Vibrio vulnificus in blood from iron-overloaded HFE patients when compared with healthy subjects (Jolivet-Gougeon 2007, Jolivet-Gougeon 2008, Bullen 1991).

In contrast, such risks were not present in blood from iron-depleted patients with HFE haemochromatosis (Jolivet-Gougeon 2008, Bullen 1991). A further study showed that the presence of anti-Yersinia antibodies was similar in the blood of uncomplicated HFE haemochromatosis patients when compared to blood from control donors (Jolivet-Gougeon 2007). Based on screening tests for antibodies to hepatitis B core antigen, syphilis, human immunodeficiency virus, hepatitis C virus, hepatitis B surface antigen, and human T-lymphotropic virus, no statistically significant difference could be found for HFE donors versus regular donors (Leitman 2003, Sanchez 2001).

It has in addition been argued that the blood donation by haemochromatosis patients is not voluntary because they benefit from the donation (Conry-Cantilena 2001, De Gonzalez 2007, Pennings 2005). Also phlebotomies from haemochromatosis patients does not require a financial compensation and may thus provide a financial advantage for the physician (Leitman 2013). The latter argument needs to be discussed considering that management of haemochromatosis patients as well as the use of their blood vary between industrialised countries (Butzeck 2011, Leitman 2013). In any case, it has been proposed that all phlebotomies should be free to haemochromatosis patients in order to eliminate any financial incentives and the non-voluntary character of the donation (Leitman 2013).

In general, blood banks need to observe rigorously that their criteria for haemochromatosis patients are also applicable to other donors. In a cohort of 130 subjects with HFE polymorphisms referred to a blood centre for management, 76% met all eligibility criteria for allogeneic blood donation and 55% had previously been blood donors before being made aware of their HFE diagnosis (Leitmann 2003). In the latter study, HFE donors were documented to more regularly observing their donation appointments than non-HFE donors, and they were less likely to have low screening hemoglobin of < 12.5 g/dL (Leitman 2003).

Since 2001, many European and U.S. transfusion services have changed their policy for the management of blood drawn from haemochromatosis patients (Courtois 2001, Radojska 2011, Buring 2002, Guidelines for the Blood Transfusion Services in the United Kingdom 2005, Ministrial Order of the Government of France 2009, FDA guidance for variances for blood collection from individuals with hereditary haemochromatosis 2001). For the USA, the FDA (Food and Drug Administration) issued a guidance in 2001 to allow blood banks to submit variances to federal code to accept blood from HFE patient for blood transfusion (Center for Biologics Evaluation and Research 2013). This guidance contains several criteria (Leitman 2013):

- The donor meets all other general allogeneic donor criteria.
- Phlebotomy is provided free of charge to all HFE patients in that blood centre.
- Incentives for HFE donors are considered untruthful in responding to standardised health history screening questions.
- A medical prescription for phlebotomy therapy including frequency and hemoglobin threshold is provided by the donor's physician.
- A short physical examination is performed at each visit if the patient donates more often than every 8 weeks.

In the 12 years following the publication of this guidance, 163 blood banks in 43 US states have submitted variances and implemented polices for collection of blood from HFE donors (Leitman 2013). HFE donors have been shown to have a considerable satisfaction from knowing that their blood is being used to save lives rather than being discarded (Center for Biologics Evaluation and Research 2013).

It is estimated that routine referral of HFE subjects to blood centres for phlebotomy care could supplement the U.S. blood supply by an additional 1.3

million RBC units per year, possibly help to avoid periodic blood shortages, avoid wastage of safe units, and decrease the costs of care (Leitman 2013).

People with C282Y/H63D and H63D/H63D genotypes and slightly elevated ferritin levels are often referred to the blood centre for phlebotomy treatment (Leitman 2013). These subjects in general do not have organ damage due to iron overload and do need an aggressive phlebotomy therapy like the C282Y homozygotes. In blood centres with active recruitment of HFE patients, blood donations from HFE patients may contribute to 10 – 40% of available blood (Leitman 2013).

Nevertheless, there is still no consensus about the acceptance of haemochromatosis patients as blood donors (Leitman 2013, de Buck 2012). Most recent studies however share the following policy when dealing with a potential acceptance of haemochromatosis patients as blood donors (De Buck 2012, Sackett 1996):

In general, all criteria applicable to any other donor need to be rigorously observed also for HFE patients. Blood from HFE patients should only be used for transfusion when patients have already been iron-depleted and do not have major organ complications. There are no incentives or financial advantages for the HFE patients and their physicians for the use of phlebotomised blood for donation.

Key messages and future directions

- Measurement of transferrin saturation and serum ferritin is the first and most important step in the diagnosis of genetic haemochromatosis. High serum ferritin with normal transferrin saturation is usually not associated with genetic haemochromatosis (except for the rare ferroportin type 4b disease).
- Individuals with signs of iron overload, females with transferrin saturation >45% and serum ferritin > 200µg/L and males with transferrin saturation >50% and ferritin >300µg/L, or otherwise unexplained high transferrin saturation should be tested for the C282Y variation in the HFE gene. The search for other HFE gene variations is less important.
- The homozygous C282Y mutation accounts for <90% of phenotypes in Caucasians and leads to an increase in intestinal iron absorption with a risk of iron overload and organ damage including liver cirrhosis and diabetes mellitus.
- Early diagnosis in a non-cirrhotic stage and subsequent iron removal by phlebotomies are associated with a normal life expectancy. All future efforts should aim at such early diagnosis.
- All patients with haemochromatosis should be assessed for liver fibrosis. In patients with ferritin <1000 µg/L and no signs of liver disease, the risk of fibrosis is very low. Elastography can rule out advanced fibrosis. Liver biopsy is only necessary when fibrosis stage remains unclear; liver iron concentration should rather be assessed by MRI and not by biopsy.
- Patients with cirrhosis or severe fibrosis have a risk for development of HCC and should be offered adequate HCC surveillance.
- Young individuals with evidence of haemochromatosis (amenorrhea, hypogonadism, cardiomyopathy) should be tested for rare haemochromatosis gene variants. Patients with evidence of significant, unexplained iron overload should be referred to an iron disorder specialist to look for further rare genetic defects associated with haemochromatosis (e.g. HFE, HAMP, HJV, TFR2, TF, CP, BMP6, SCL40A1).
- Secondary haemochromatosis is usually caused by multiple blood transfusions in haemolytic anaemias such as thalassaemia, sickle cell anaemia, and myelodysplasia. Here, iron may accumulate faster than in genetic haemochromatosis with risks for cardiomyopathy and liver cirrhosis. Therapy consists of iron chelators because phlebotomies cannot be done due to underlying anaemia.

References

Abboud S, Haile DJ. A novel mammalian iron-regulated protein involved in intracellular iron metabolism. J Biol Chem 2000;275:19906-12.

Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary haemochromatosis. Gastroenterology 1991;101:368-72.

Adams PC, Reboussin DM, Barton JC, et al. Haemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med 2005; 352:1769-78.

Andriopoulos B Jr, Corradini E, Xia Y, et al. BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. Nat Genet 2009;41:482-7.

Angelucci E, Baronciani D, Lucarelli G, et al. Needle liver biopsy in thalassaemia: analyses of diagnostic accuracy and safety in 1184 consecutive biopsies. Br J Haematol 1995;89:757-61.

Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS. Diagnosis and management of haemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:328-43.

Bain C, Bradbear R, Siskind V, et al. Cohort study of the risk of malignancy in haemochromatosis and other nonalcoholic liver diseases. Hepatology 1984;4:A1020.

Barton JC, Grindon AJ, Barton NH, Bertoli LF. Haemochromatosis probands as blood donors. Transfusion 1999;39:578-85.

Biasiotto G, Belloli S, Ruggeri G, et al. Identification of new mutations of the HFE, hepcidin, and transferrin receptor 2 genes by denaturing HPLC analysis of individuals with biochemical indications of iron overload. Clin Chem 2003;49:1981-8.

Bierens deHaan B, Scherrer JR, Stauffacher W, et al. Iron excess, early glucose intolerance, and impaired insulin secretion in idiopathic haemochromatosis. Eur J Clin Invest 1973;3:179-87.

Blei AT, Robbins DC, Drobny E, et al. Insulin resistance and insulin receptors in hepatic cirrhosis. Gastroenterology 1982;83:1313-8.

Boelaert JR, van Landuyt HW, Valcke YJ, et al. The role of iron overload in Yersinia enterocolitica and Yersinia pseudotuberculosis bacteraemia in hemodialysis patients. J Infect Dis 1987;156:384-7.

Brandhagen DJ, Alvarez W, Therneau TM, et al. Iron overload in cirrhosis-HFE genotypes and outcome after liver transplantation. Hepatology 2000;31:456-60.

Brissot P, Ropert M, Le Lan C, Loreal O. Non-transferrin bound iron: a key role in iron overload and iron toxicity. Biochim Biophys Acta 2012;1820:403-10.

Brittenham GM, Griffith PM, Nienhuis AW, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassaemia major. N Engl J Med 1994;331:567-73.

de Buck E, Pauwels NS, Dieltjens T, et al. Is blood of uncomplicated haemochromatosis patients safe and effective for blood transfusion? A

systematic review J Hepatol 2012; 57: 1126-34.

Buja L, Roberts W. C Iron in the heart. Am J Med 1971;51:209-21.

Buring ML. Haemochromatosis: red cross blood service policy. Med J Aust 2002;176:564.

Bullen JJ, Spalding PB, Ward CG, Gutteridge JMC. Haemochromatosis, iron, and septicaemia caused by Vibrio vulnificus. Arch Intern Med 1991;151:1606-9.

Butzeck B, Rialland J, Brissot P, Porto G, Courtois F. Management, costs of phlebotomies and use of removed blood in haemochromatosis varies throughout Europe. Am J Hematol 2011;86:E81.

Cabantchik ZI. Labile iron in cells and body fluids: physiology, pathology, and pharmacology. Frontiers Pharmacol 2014;5:1-11.

Callebaut I, Joubrel R, Pissard S, et al. Comprehensive functional annotationof 18 missense mutations found in suspected haemochromatosis type 4 patients. Human Mol Genet 2014; 23:4479-90.

Caesar J. Commentarii de Bello Gallico, Book II, Chapter 30. 50 a.c. www.thelatinlibrary.com/caesar/gall1.shtml

Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassaemia. Blood 2006;107:3455-62.

Cauchie P, Vincken W, Peeters O, Charels K. Haemochromatosis and Yersinia enterocolitica septicaemia. Dig Dis Sci 1987;32:1438.

Center for Biologics Evaluation and Research. Guidance for industry: variances for blood collection from individuals with hereditary haemochromatosis. Available from: http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm076719.htm. Accessed May 13, 2013.

Cippà PE, Krayenbuehl P. Increased height in HFE haemochromatosis. N Engl J Med 2013;369:785-6.

Conry-Cantilena C. Phlebotomy, blood donation, and hereditary haemochromatosis.Transfus Med Rev 2001;15:136-43.

Courtois F, Danic B. Genetic haemochromatosis and blood donation. Ann Med Interne 2001;152:452-54.

Cohen A, Martin M, Schwartz E. Response to long-term deferoxamine therapy in thalassaemia. J Pediatr 1981;99:689-94.

Cohen AR, Mizanin J, Schwartz E. Rapid removal of excessive iron with daily, high-dose intravenous chelation therapy. J Pediatr 1989;115:151-5.

Cohen A. Management of iron overload in the paediatric patient. Hematol Oncol Clin North Am 1987;1:521-44.

Corradini E, Ferrara F, Pollicino T, et al. Disease progression and liver cancer in the ferroportin disease. Gut 2007;56:1030-2.

Creutzfeldt W, Frerichs H, Sickinger K. Liver diseases and diabetes mellitus. Prog Liver Dis 1970;3:371-407.

Crosby WH. Hereditary haemochromatosis. In: Ingelfinger FJ (ed) Controversy in internal medicine. Saunders, Philadelphia, 1966:261-70.

Daher R, Kannengiesser C, Houamel D, et al. Heterozygous Mutations in BMP6 pro-peptide lead to inappropriate hepcidin synthesis and moderate iron overload in humans. Gastroenterology 2016;150:672-83.

Datz C, Müller E, Aigner E. Iron overload and non-alcoholic fatty liver disease. Minerva Endocrinol 2017;42:173-83.

De Domenico I, Diane M, Ward DM, et al. Hepcidin regulation: ironing out the details. J Clin Invest 2007;117:1755-8.

De Gobbi M, Pasquero P, Brunello F, et al. Juvenile haemochromatosis associated with B-thalassaemia treated by phlebotomy and recombinant human erythropoietin. Haematologica 2000;85:865-7.

De Gonzalez GL. Hereditary haemochromatosis and blood donation. ISBT Sci Ser 2007;2:12-8.

Deugnier Y, Bardou-Jacquet É, Lainé F. Dysmetabolic iron overload syndrome (DIOS). Presse Med 2017;46: e306-11.

Diamond T, Stiel D, Posen S. Osteoporosis in haemochromatosis: iron excess, gonadal deficiency, or other factors? Ann Intern Med 1989;110:430-6.

Donovan A, Brownlie A, Zhou Y, et al. Positional cloning of zebrafish ferroportin1 identifies a conserved vertebrate iron exporter. Nature 2000;403:778-81.

Doyle A, Rusli F, Bhathal P. Aceruloplasminaemia: a rare but important cause of iron overload. BMJ Case Repn2015: bcr2014207541.

Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol 2008;6:541–52.

Dymock W, Hamilton EBD, Laws JW, et al. Arthropathy of haemochromatosis: clinical and radiological analysis of 73 patients with iron overload. Ann Rheum Dis 1970;29:469-76.

Dymock W, Cassar J, Pyke DA, et al. Observations on the pathogenesis, complications, and treatment of diabetes in 115 cases of haemochromatosis. Am J Med 1972;52:203-10.

EASL. EASL clinical practice guidelines for HFE haemochromatosis. J Hepatol 2010; 53:3-22.

European Association for the Study of the Liver. EASL Clinical practice guidelines on haemochromatosis. J Hepatol 2022;77:479-502

Edwards CQ, Griffen LM, Goldgar D, et al. Prevalence of haemochromatosis among 11,065 presumably healthy blood donors. N Engl J Med 1988;318:1355-62.

Elmberg M, Hultcrantz R, Ekbom A, et al. Cancer risk in patients with hereditary haemochromatosis and in their first-degree relatives. Gastroenterology 2003;125:1733-41.

Erhardt A, Niederau C, Osman Y, et al. Demonstration of HFE polymorphism in German patients with hereditary haemochromatosis. Dtsch Med Wochenschr 1999;124:1448-52.

Erhardt A, Maschner-Olberg A, Mellenthin C, et al. HFE mutations and chronic hepatitis C: H63D and C282Y heterozygosity are independent risk factors for liver fibrosis and cirrhosis. J Hepatol 2003;38:335-42.

Fargion S, Mandelli C, Piperno A, et al. Survival and prognostic factors in 212 Italian patients with genetic haemochromatosis. Hepatology 1992;15:655-9.

Feder JN, Gnirke A, Thomas W, et al. A novel MCH class I-like gene is mutated in patients with hereditary haemochromatosis. Nature Genetics 1996;13:399-407.

Feldman AG, Whitington PF. Neonatal haemochromatosis. J Clin Exp Hepatol 2013;3:313-20.

Fernandez M, Lokan J, Leung C, Grigg A. A critical evaluation of the role of iron overload in fatty liver disease. J Gastroenterol Hepatol 2022;37:1873-83.

Filali M, Le Jeunne C, Durand E, et al. Juvenile haemochromatosis HJV-related revealed by cardiogenic shock. Blood Cells Mol Dis 2004;33:120-4.

Finch SC, Finch CA. Idiopathic haemochromatosis, an iron storage disease. Medicine 1966;34:381-430.

Fleming RE, Sly WS. Ferroportin mutation in autosomal dominant haemochromatosis: loss of function, gain in understanding. J Clin Invest 2001;108:521-2.

Fleming RE, Sly WS. Mechanisms of iron accumulation in hereditary haemochromatosis. Ann Rev Physiol 2002;4:663-80.

Fletcher LM, Halliday JW. Haemochromatosis: Understanding the mechanism of disease and implications for diagnosis and patient management following the recent cloning of novel genes involved in iron metabolism. J Intern Med 2002;251:181-92.

Gallego CJ, Burt A, Sundaresan AS, et al. Penetrance of haemochromatosis in HFE genotypes resulting in p.Cys282Tyr and p.[Cys282Tyr];[His63Asp] in the eMERGE network. Am J Hum Genet 2015;97:512-20.

Gattermann N. Consensus statement on iron overload in myelodysplastic syndromes. Hematol Oncol Clin N Am 2005;19:S18-S25.

Girelli D, Bozzini C, Roetto A. Clinical and pathological finding in haemochromatosis type 3 due to a novel mutation in transferrin receptor 2 gene. Gastroenterology 2002;122:1295-1302.

Goldbeck L, Baving A, Kohne E. Psychosocial aspects of beta-thalassaemia: distress, coping and adherence. Klin Pädiatr 2000;212:254-9.

Gozzelino R, Arosio P. Iron homeostasis in health and disease. Intern J Mol Sci 2016;17:130.

Greenberg PL, Baer MR, Bennett JM, et al. Myelodysplastic syndromesclinical practice guidelines in oncology. J Natl Compr Canc Netw 2006;4:58-77.

Guidelines for the Blood Transfusion Services in the United Kingdom. seventh ed. London: TSO (The Stationary Office); 2005.

Hanot V, Schachmann M. Sur la cirrhose pigmentaire dans le diabe`te. sucré. Arch Physiol Norm Pathol 1886;7:50-72.

Hardy L, Hansen JL, Kushner JP, Knisely AS. Neonatal haemochromatosis. Genetic analysis of transferrin-receptor, H-apoferritin, and L-apoferritin loci and of the human leukocyte antigen class I region. Am J Pathol 1990;137:149-53.

Hattori A, Wakusawa S, Hayashi H, et al. AVAQ 594-597 deletion of the TfR2 gene in a Japanese family with haemochromatosis. Hepatol Res 2003;26:154-6.

Herbay von A, Niederau C, Pelichowska M, et al. Kardiomyopathie als Todesursache bei genetischer Hämochromatose. Z Gastroenterol 1996;34:178-82.

Hermine O, Dine G, Genty V, et al. Eighty percent of French sport winners in Olympic, World and Europeans competitions have mutations in the haemochromatosis HFE gene. Biochimie 2015;119:1-5.

Hershko C, Graham G, Bates GW, Rachmilewitz EA. Non-specific serum iron in thalassaemia: an abnormal serum iron fraction of potential toxicity. Br J Haematol 1978;40:255-63.

Hershko C, Konijn AM, Nick HP, et al. ICL670A: a new syntheticoral chelator: evaluation in hypertransfused rats with selective radio iron probes of hepatocellular and reticuloendothelial iron stores and in ironloadedrat heart cells in culture. Blood 2001 ;97:1115-22.

Hider RC, Silva AM, Podinovskaia M, Ma Y. Monitoring the efficiency of iron chelation therapy: the potential of nontransferrin-bound iron. Ann N Y Acad Sci 2010;1202:94-9.

Hod EA, Brittenham GM, Billote GB, et al. Transfusion of human volunteers with older, stored red blood cells produces extravascular hemolysis and circulating non-transferrin bound iron. Blood. 2011;118:6675-82.

Jensen PD, Bagger JP, Jensen FT, et al. Heart transplantation in a case of juvenile hereditary haemochromatosis followed up by MRI and endomyocardial biopsies. Eur J Haematol 1993;51:199-205.

Jolivet-Gougeon A, Loreal O, Ingels A, et al. Serum transferrin saturation increase is associated with decrease of antibacterial activity of serum in patients with HFE-related genetic haemochromatosis. Am J Gastroenterol 2008;103:2502–2508.

Jolivet-Gougeon A, Ingels A, Danic B, et al. No increased seroprevalence of anti-Yersinia antibodies in patients with type 1 (C282Y/C282Y) haemochromatosis. Scand J Gastroenterol 2007;42: 1388–9.

Jouanolle AM, Douabin-Gicquel V, Halimi C, et al. Novel mutation in ferroportin 1 gene is associated with autosomal dominant iron overload. J Hepatol 2003;39:286-9.

Kasvosve I. Effect of ferroportin polymorphism on iron homeostasis and infection. Clinica Chimica Acta 2013;416:20-25.

Kelly AL, Lunt PW, Rodrigues F, et al. Classification and genetic features of neonatal haemochromatosis: a study of 27 affected pedigrees and molecular analysis of genes implicated in iron metabolism. J Med Genet 2001;38:599-610.

Khan FA, Fisher MA, Khakoo RA. Association of haemochromatosis with infectious diseases: expanding spectrum. Int J Infect Dis 2007;11:482-7.

Kelly AL, Rhodes DA, Roland JM, et al. Hereditary juvenile haemochromatosis: a genetically heterogeneous life-threatening iron-storage disease. QJM 1998;91:607-18.

Kley HK, Stremmel W, Niederau C, et al. Androgen and oestrogen response to adrenal and gonadal stimulation in idiopathic haemochromatosis: evidence for decreased oestrogen formation Hepatology 1985a:251-6.

Kley HK, Niederau C, Stremmel W, et al. Conversion of androgens to oestrogens in idiopathic haemochromatosis: comparison with alcoholic cirrhosis. J Clin Endocrinol Metabol 1985b;61:1-6.

Kowdley K, Hassanein T, Kaur S, et al. Primary liver cancer and survival in patients undergoing liver transplantation for haemochromatosis. Liver Transpl Surg 1995;1:237-41.

Kowdley KV, Modi NB, Valone F, et al. Rusfertide (PTG-300), a hepcidin mimetic, maintains liver iron concentration in the absence of phlebotomies in patients with hereditary haemochromatosis. Blood 2021:13:S943.

Leclercq A, Martin L, Vergnes ML, et al. Fatal Yersinia enterocolitica biotype 4 serovar O:3 sepsis after red blood cell transfusion. Transfusion 2005;45:814–8.

Leitman SF. Haemochromatosis: the new blood donor. Transfusion Med 2013; 645-50.

Leitman S, Browning J, Yau Y, et al. Haemochromatosisc subjects as allogeneic blood donors: a prospective study. Transfusion 2003;43:1538-44.

Le Lan C, Loreal O, Cohen T, et al. Redox active plasma iron in C282Y/C282Y haemochromatosis. Blood 2005;105:4527-31.

Liu P, Olivieri N. Iron overload cardiomyopathies: new insights into an old disease. Cardiovasc Drugs Ther 1994;8:101-10.

Loreal O, Deugnier Y, Moirand R. Liver fibrosis in genetic haemochromatosis. Respective roles of iron and non-iron related factors in 127 homozygous patients. J Hepatol 1992;16:122-7.

MacDonald RA, Mallory GK. Haemochromatosis and hemosiderosis. Study in 211 autopsied cases. Arch Intern Med 1960;105:686-700.

Mattman A, Huntsman D, Lockitch G, et al. Transferrin receptor 2. (TfR2) and HFE mutational analysis in non-C282Y iron overload: identification of a novel TfR2 mutation. Blood 2002;100:1075-7.

McLaren GD, Muir WA, Kellermeyer RW. In overload disorders: natural history, pathogenesis, diagnosis, and therapy. Crit Rev Clin Lab Sci 1983;19:205-66.

Meynard D, Kautz L, Darnaud V, et al. Lack of the bone morphogenetic protein BMP6 induces massive iron overload Nat Genet 2009;41:478-81.

Ministrial Order of the Government of France. Arrêté du 12 janvier 2009 fixants les critères de selection des donneurs de sang 2009.

Miskin H, Yaniv I, Berant M, et al. Reversal of cardiac complications in thalassaemia major by long-term intermittent daily intensive iron chelation. Eur J Haematol 2003;70:398-403.

Montosi G, Donovan A, Totaro A, et al. Autosomal-dominant haemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene. J Clin Invest 2001;108:619-3.

Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalisation. Science 2004;306:2090-3.

Nemeth E, Roetto A, Garozzo G, et al. Hepcidin is decreased in TFR2-Haemochromatosis. Blood 2005;105:1803-6.

Newman B. Haemochromatosis blood donor programmes: marginal for the red blood cell supply but potentially good for patient care. Transfusion 2004;44:1535-7.

Nick H, Acklin P, Lattmann R, et al. Development of tridentate iron chelators: from desferrithiocin to ICL670. Curr Med Chem 2003;10:1065-76.

Niederau C, Berger M, Stremmel W, et al. Hyperinsulinaemia in non-cirrhotic haemo-chromatosis: impaired hepatic insulin degradation? Diabetologia 1084; 26:441-4.

Niederau C, Fischer R, Sonnenberg A, et al. Survival and causes of death in cirrhotic and noncirrhotic patients with primary haemochromatosis. New Engl J Med 1985;313:1256-62.

Niederau C, Fischer R, Pürschel A, et al. Long-term survival in patients with hereditary haemochromatosis. Gastroenterology 1996;110:1107-19.

Niederau C, Niederau CM, Littauer A, et al. Screening for iron overload and iron deficiency. Ann Int Med 1998;128:337-45.

Niederau C. Diabetes mellitus bei Hämochromatose. Z Gastroenterol 1999;37:22-32.

Niederau C. Hepatische Eisenüberladung. Gastro-News 2018;5:46-53.

Niederau C. Iron overload and atherosclerosis. Hepatology 2000;32:672-4.

Nisbet-Brown E, Olivieri F, Giardina PJ, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet 2003;361:1597-602.

Njajou OT, Vaessen N, Joosse M, et al. A mutation in SLC11A3 is associated with autosomal dominant haemochromatosis. Nat Genet 2001;28:213-4.

Nouel O, Voisin PM, Vaucel J, Dartois-Hoguin M, Le BM. Yersinia enterocolitica septicaemia associated with idiopathic haemochromatosis and deferoxamine therapy. A case. Presse Med 1991;20:1494-6.

Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassaemia. Blood 1997;89:739-61.

Olivieri NF, Nathan DG, Macmillan JH, et al. Survival in medically treated patients with homozygous beta-thalassaemia. N Engl J Med 1994;331:574-8.

Pennings G. Demanding pure motives for donation: the moral acceptability of blood donations by haemochromatosis patients. J Med Ethics 2005;31:69-72.

Phatak PD, Sham RL, Raubertas RF, et al. Prevalence of hereditary haemochromatosis in 16,031 primary care patients. Ann Intern Med 1998;129:954-61.

Phatak P, Brissot P, Wurster M, et al. A phase 1/2, dose-escalation trial of deferasirox for the treatment of iron overload in HFE-related hereditary haemochromatosis. Hepatology 2010;52:1671-779.

Phelps G, Chapman I, Hall P, et al. Prevalence of genetic haemochromatosis among diabetic patients. Lancet 1989;2:233-4.

Pietrangelo A, Montosi G, Totaro A. Hereditary haemochromatosis in adults without pathogenic mutations in the haemochromatosis gene. N Engl J Med 1999;341:725-32.

Pietrangelo A. Physiology of iron transport and the haemochromatosis gene. Am J Physiol Gastrointest Liver Physiol 2000;282:G403-14.

Pietrangelo A. Hereditary haemochromatosis -a new look at an old disease. N Engl J Med 2004;350:2383-97.

Pietrangelo A. The ferroportin disease. Blood Cells Mol Dis 2004;32:131-8.

Pietrangelo A. Ferroportin disease: pathogenesis, diagnosis and treatment. Haematologica 2017;102:1972-84.

Piga A, Galanello R, Forni GL, et al. Randomised phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassaemia patients with transfusional iron overload. Haematologica 2006;91:873-80.

Piga A, Longo F, Duca L, et al. High nontransferrin bound iron levels and heart disease in thalassaemia major. Am J Hematol 2009;84:29-33.

Piperno A, Roetto A, Mariani R, et al. Homozygosity for transferrin receptor-2 Y250X mutation induces early iron overload. Haematologica 2004; 89:359-60.

Piroth L, Meyer P, Bielefeld P, Besancenot JF. Yersinia bacteraemia and iron overload. Rev Med Interne 1997;18:932-8.

Pootrakul P, Breuer W, Sametband M, et al. Labile plasma iron (LPI) as an indicator of chelatable plasma redox activity in iron overloaded beta-thalassaemia/HbE patients treated with an oral chelator. Blood 2004;104:1504-10.

Porter JB Practical management of iron overload. Br J Haematol 2001;115:239-52.

Powell LW, Mortimer R, Harris OD. Cirrhosis of the liver: A comparative study of the four major aetiological groups. Med J Aust 1971;58:1941-50.

Radojska S, Hengeoz O, Gathof B. Hereditary haemochromatosis patients/ carriers as blood donors – a single center experience. Transfus Med Hemother 2011;38:32.

Rahier J, Loozen S, Goebbels RM, et al. The haemochromatosis human pancreas: a quantitative immunochemical and ultrastructural study. Diabetologia 1987;30:5-12.

Recklinghausen von FD. Über Hämochromatose. Berl Klin Wochenschr 1898;26:925.

Rivard SR, Lanzara C, Grimard D, et al. Autosomal dominant reticuloendothelial iron overload (HFE type 4) due to a new missense mutation in the FERROPORTIN 1 gene (SLC11A3) in a large French-Canadian family. Haematologica 2003;88:824-6.

Rombout-Sestrienkova E, Nieman FH, et al. Erythrocytapheresis versus phlebotomy in the initial treatment of HFE haemochromatosis patients: results from a randomised trial. Transfusion 2012;52:470-7.

Rombout-Sestrienkova E, Winkens B, et al. Erythrocytapheresis versus phlebotomy in the maintenance treatment of HFE haemochromatosis patients: results from a randomised crossover trial. Transfusion. 2016;56:261-70.

Roetto A, Totaro A, Cazzola M, et al. Juvenile haemochromatosis locus maps to chromosome 1q. Am J Hum Genet 1999;64:1388-93.

Roetto A, Totaro A, Piperno A, et al. New mutations inactivating transferrin receptor 2 in haemochromatosis type 3. Blood 2001;97:2555-60.

Sackett DL, Rosenberg MC, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71-2.

Sanchez AM, Schreiber GB, Bethel J, et al. Prevalence, donation practices, and risk assessment of blood donors with haemochromatosis. J Am Med Assoc 2001;286:1475-81.

Schuhmacher HR. Haemochromatosis and arthritis. Arthr Rheum 1964;7:41-50.

Senba M, Nakamura T, Itakura H. Relationships among iron accumulation, cirrhosis, and hepatitis B virus infection in Bantu siderosis. Ann Soc Belg Med Trop 1989;69:77-8.

Sheldon JH. Haemochromatosis. Oxford University Press, 1935, London.

Short EM, Winkle RA, Billingham ME. Myocardial involvment in idiopathic haemochromatosis. Am J Med 1979;70:1275-9.

Singh BM, Grunewald RA, Press M, et al. Prevalence of haemochromatosis amongst patients with diabetes mellitus. Diabet Med 1992;9:730-1.

Simon M, Pawlotsky Y, Bourel M, et al. Hemochromatose idiopathique. Maladie associee a l'antigen HLA-A3? Nouv Press Med 1075;4:1432.

Simon M, Bourel M, Genetet B. Idiopathic haemochromatosis: demonstration of recessive transmission and early detection by family HLA typing. N Engl J Med 1977;297:1017-21.

Summers KM, Halliday JW, Powell LW. Identification of homozygous haemochromatosis subjects by measurement of hepatic iron index. Hepatology 1990;12:20-5.

Sundic T, Hervig T, Hannisdal S, et al. Erythrocytapheresis compared with whole blood phlebotomy for the treatment of hereditary haemochromatosis. Blood Transfus 2014;12:S84-9.

Swart de L, Hendriks JC, van der Vorm LN, et al. Second International Round Robin for the quantification of serum Non-Transferrin-Bound Iron and Labile Plasma Iron in patients with iron-overload disorders. Haematologica 2015:133983.

Taranath RP, Dion C, Bhandari A, Liu DY. Rusfertide analog-PN23114 as a hepcidin mimetic provides efficacy benefits in conjunction with phlebotomy in mouse model for hereditary haemochromatosis. Blood 2022;14: S5345.

Tavill AS. Diagnosis and management of haemochromatosis. Hepatology 2001;33:1321-8.

Telfer PT, Prestcott E, Holden S, et al. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. Br J Haematol 2000;110:971-7.

Toll A, Celis R, Ozalla MD, et al. The prevalence of HFE C282Y gene mutation is increased in Spanish patients with porphyria cutanea tarda without hepatitis C virus infection. J Eur Acad Dermatol Venereol 2006;20:1201-6.

Troisier M. Diabete sucre. Bull Soc Anatom (Paris) 1871;16:231-5.

Trosseau A. Glucosurie: Diabete sucre. Bull Soc Anatom (Paris) 1865;2:663.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER). Guidance for industry Variances for Blood Collection from Individuals with Hereditary Haemochromatosis 2001. Available from: http://www.fda.gov/cber/guidelines.htm.

U.S. Preventive Services Task Force. Screening for Haemochromatosis: Recommendation Statement. Am Fam Phys 2007;75:11-21.

Vaiopoulos G, Papanikolaou G, Politou M, et al. Arthropathy in juvenile haemochromatosis. Arthritis Rheum 2003;48:227-30.

Vanclooster A, van Deursen C, Jaspers R, Cassiman D, Koek G. Proton pump inhibitors decrease phlebotomy need in HFE haemochromatosis: double-blind randomised placebo-controlled trial. Gastroenterology 2017;153:678-80.

Vichinsky E, Fischer R, Pakbaz Z, et al. Satisfaction and convenience of chelation therapy in patients with sickle cell disease (SCD): comparison between deferasirox (Exjade®, ICL670) and deferoxamine (DFO). Blood 2005;106:A2334.

Vulpe CD, Kuo YM, Murphy TL, et al. Hephaestin, a ceruloplasmin homologue implicated in intestinal iron transport, is defective in the sla mouse. Nat Genet 1999;21:195-9.

Wallace DF, Clark RM, Harley HA, et al. Autosomal dominant iron overload due to a novel mutation of ferroportin1 associated with parenchymal iron loading and cirrhosis. J Hepatol 2004;40:710-3.

Wallace DF, Subramaniam VN. Non-HFE haemochromatosis. World J Gastroenterol 2007;13:4690-8

Walker EM, Walker SM. Review: Effects of iron overload on the immune system. Ann Clin Lab Sci 2000;30:354-65.

Yaouanq JM. Diabetes and haemochromatosis: current concepts, management and prevention. Diabete et Metabolisme. (Paris) 1995;21:319-29.

Ye Q, Qian BX, Yin WL, Wang FM, Han T. Association between the HFE C282Y, H63D polymorphisms and the risks of non-alcoholic fatty liver disease, liver cirrhosis and hepatocellular carcinoma: An updated systematic review and meta-analysis of 5,758 cases and 14,741 controls. PLoS One 2016;11:e0163423.

Zhang AS, Xiong S, Tsukamoto H, et al. Localisation of iron metabolism-related mRNAs in rat liver indicate that HFE is expressed predominantly in hepatocytes. Blood 2004;103:1509-14.

Zurlo MG, De Stefano P, Borgna-Pignatti C, et al. Survival and causes of death in thalassaemia major. Lancet 1989;2:27-30.

10. Genetic liver diseases

10.2 Wilson disease

Uta Merle

Abstract

Wilson disease is an autosomal-recessively inherited metabolic disease of the liver. Copper overload leads to organ damage of the liver and other organs. Patients present with either predominant hepatic or predominant neuropsychiatric symptoms, but clinical presentation can vary widely. Manifestation of disease is typically between the ages 5 and 35, but can be also at younger and older ages. In order to diagnose Wilson disease at an early stage and introduce therapy, knowledge of the symptoms and diagnostic criteria is important. Copper overload in Wilson disease patients is treated with either chelating medications (D-penicillamine or trientine) or zinc salts. After introduction of lifelong therapy Wilson disease typically has a favourable disease course and further development of organ-damage can be prevented, especially with respect to liver-damage.

Introduction

Wilson disease is a rare autosomal-recessive disorder of copper metabolism with a prevalence of ~ 1:30, 000. It is not just a disease of children and young adults, but may present at any age. Wilson disease is characterised by hepatic and/or neuropsychiatric symptoms. Clinical presentation can vary widely, but the key features of Wilson disease are liver disease and cirrhosis, neuropsychiatric disturbances and Kayser–Fleischer rings in Desçemet's membrane of the cornea. Without treatment Wilson disease is assumed to be progressive and fatal. Therefore, knowledge of the symptoms, diagnostic criteria and treatment options is important.

Aetiology and pathogenesis

Approximately 50% of dietary copper (~ 0.8 – 2 mg/d) is absorbed in the upper small intestine. After uptake by hepatocytes biliary excretion is the main pathway for elimination of excess copper. In Wilson disease export of copper into bile is impaired leading to a pathological copper accumulation primarily within the liver and subsequently in the brain (particularly in basal ganglia) and other tissues (e.g. kidneys and cornea). Wilson disease is caused by mutations of the Wilson disease gene ATP7B coding for a copper-transporting, transmembrane P-type ATPase primarily expressed in the liver (Bull 1993, Tanzi 1993). About 750 polymorphisms of the ATP7B gene have been described with several of them of to date unknown clinical significance (Czlonkowska 2018). Most Wilson disease patients are compound heterozygotes, possessing alleles with different mutations in both parental genes. The mutation variability has in general no relevant impact on phenotypic expression in individual Wilson disease patients (Ferenci 2019).

In addition to reduced biliary copper excretion impaired ATP7B function leads to a disturbed incorporation of copper into ceruloplasmin. Failure to incorporate copper during ceruloplasmin biosynthesis results in the secretion of an apoprotein that is devoid of enzymatic activity and rapidly degraded. The resulting decrease in serum ceruloplasmin concentration is a diagnostic hallmark of Wilson disease. Because ceruloplasmin accounts for most of serum copper, total serum copper is most often reduced in Wilson disease.

Clinical presentation

Although the biochemical defect that leads to the copper accumulation in Wilson disease is already present at birth, manifestation of Wilson disease is typically between 5 to 35 years of age. Of note, Wilson disease is increasingly diagnosed in children who are less than 5 years-old. Clinical findings may be nonspecific in children who are less than 2 years-old (Wiernicka 2017, Wilson 2000). Although the majority of patients manifest disease-related symptoms until the age of 35, evaluation for Wilson disease should also be carried out in older individuals as manifestation even at higher ages is possible (Ferenci 2007).

Hepatic presentation

Most paediatric patients with Wilson disease present with hepatic disease, whereas adults present with hepatic disease with or without concurrent neuropsychiatric disease. Liver disease associated with Wilson disease can be highly variable. Therefore, Wilson disease is often misdiagnosed, and the average time from symptom onset to diagnostic treatment is long, about 12 months (Merle 2007).

All forms of clinical presentations occur, including clinically asymptomatic states with only biochemical abnormalities, chronic hepatitis, steatosis, splenomegaly, hepatomegaly, and compensated or decompensated liver cirrhosis (Table 1) (EASL Wilson Didease guideline 2012, Schilsky 2022). The features of hepatitis can be similar to other causes of hepatitis, such as chronic viral hepatitis, chronic autoimmune hepatitis, chronic steatohepatitis, or drug-related hepatitis. In some patients transient episodes of hemolysis presenting as intermittent jaundice can occur.

Acute liver failure

About 5% of patients present with a fulminant hepatic failure, typically associated with hemolysis. They have a poor prognosis without liver transplantation. Typically, in these patients cirrhosis is present, although it is the first manifestation of the disease. Diagnosis of Wilson disease presenting as fulminant hepatic failure can be challenging. In these typically young and predominantly female patients coagulopathy, hyperbilirubinaemia, Coombs negative hemolytic anaemia (due to massive release of copper from dying hepatocytes), and elevated serum and urinary copper concentrations as well as often the combination of those are characteristic features. Despite massive hepatic necrosis, which is responsible for the deleterious clinical course especially in the presence of hepatic encephalopathy, serum aminotransferases are usually less than 10 times normal and, thus, much lower than the values commonly recorded in fulminant hepatitis of other etiologies. Renal insufficiency is frequently present but in general reversible. It is a result of tubular injury from copper and of the multi-organ failure that can occur during acute liver failure.

Neuropsychiatric presentation

Neurological symptoms usually develop later than hepatic symptoms, most often in the twenties (Table 1). The initial symptoms may be very subtle, such as changes in behavior, deterioration in practical performances, speech and writing problems with micrographia. Other common findings are tremor, lack of motoric coordination, drooling, dysarthria, dystonia, and spasticity.

Psychiatric abnormalities in Wilson disease patients are more common than generally acknowledged. Approximately 50 to 70% of patients have psychiatric symptoms at the beginning or at later stages of their illness, with or without hepatic or neurological findings (Akil 1991, Mura 2017). These psychiatric symptoms include depression, bipolar disorder, neurotic behaviors, personality changes, anxiety, labile mood, and even frank psychosis (Table 1). Many of the individuals with neuropsychiatric symptoms may have concomitant liver disease that is frequently asymptomatic.

Kayser-Fleischer rings represent the corneal deposition of copper within the Descemet's membrane and have a golden-brown appearance. They are present in nearly all patients with neurological symptoms. About 50% of Wilson disease patients with liver disease lack Kayser-Fleischer rings. In addition, in early stages of the disease and in asymptomatic siblings they are commonly absent.

Other manifestations

In addition to the common hepatic and neuropsychiatric presentations signs and symptoms of Wilson disease may arise as a result of the dysfunction of any organ in which excess copper is deposited. Clinical manifestations may include abnormalities of the kidney (aminoaciduria and nephrolithiasis), the endocrine system (hypoparathyreodism, infertility, secondary amenorrhea, and repeated miscarriages), the heart (cardiac arrhythmias and cardiomyopathy), and the skeleton (premature osteoporosis and arthritis) (Table 1).

Table 1. Clinical symptoms in Wilson disease patients

Manifestation	Clinical symptom
Hepatic	Asymptomatic hepatomegaly
	Isolated splenomegaly
	Acute hepatitis of variable severity
	Chronic hepatitis
	Hepatic steatosis
	Liver cirrhosis, compensated or decompensated
	Acute-on-chronic liver failure
	Acute liver failure, typically with Coombs negative hemolysis, high bilirubin level and high bilirubin:ALP level
Neurological	Dysarthria
	Movement disorders (tremor, involuntary movements)
	Akinetic-rigid syndrome similar to Parkinson's disease
	Gait abnormality, Ataxia
	Dystonia
	Chorea, Athetosis
	Drooling, oropharyngeal dystonia, transfer dysphagia
	Dysautonomia
	Seizures
	Sleep disorder, insomnia
Psychiatric	Depression
	Bipolar spectrum disorder
	Neurotic behaviors
	Personality and behavioral changes
	Psychosis
	Subtle cognitive dysfunction
Eye	Kayser-Fleischer rings, Sunflower cataract

Diagnostic findings

Diagnosis is usually established on the basis of clinical findings and laboratory abnormalities. Based on Sternlieb's criteria diagnosis is straightforward if two or more of the following symptoms are present: Kayser-Fleischer rings, typical neurologic symptoms, low serum ceruloplasmin levels (< 20 mg/dL), and increased hepatic copper content (> 250 µg/g dry weight). Diagnosis is far more complex in patients presenting with liver disease as – compared to patients with primary neurological presentation – diagnostic markers are in ~20% of Wilson disease patients with primary hepatic presentation in the normal range, and by that misleading. In most patients a combination of various parameters is

necessary to firmly establish the diagnosis as no one single finding is adequate for diagnosis of Wilson disease. Not a single test is *per se* specific and, thus, a range of tests has to be applied (Table 2). A diagnostic score based on all available tests was proposed by the Working Party at the 8th International Meeting on Wilson's disease, Leipzig 2001 – commonly named "Leipzig-Score" (Ferenci 2003) (Table 3). The Wilson's disease scoring system provides a good diagnostic accuracy and was re-evaluated also for children with liver disease (Nicastro 2010).

Table 2. Biochemical tests for diagnosis of Wilson disease (adapted to EASL Wilson disease guideline 2012)

Test	Typical finding	False "negative"	False "positive"
Serum ceruloplasmin	Decreased by 50% of lower normal value	"Inflammation, measurement by immunologic assay, pregnancy, contraceptive/ oestrogen therapy"	"Malabsorbtion, protein-losing nephropathy, aceruloplasminaemia, heterozygous carriers, acquired copper deficiency"
24-hour urinary copper	>1.6 µmol/24h	Incorrect/incomplete collection, kidney failure	Hepatocellular necrosis, cholestasis, sample contamination, heterozygous carriers
Serum "free" copper	>1.6 µmol/L	Normal if ceruloplasmin overestimated by immunological assay	
To date not in clinical routine: Relative exchangeable copper (REC)	>18.5%	Not reported	Not reported
Hepatic copper content	>250µg/g dry weight >4 µmol/d dry weight	Sampling error, especially in patients with active liver disease and in patients with regenerative nodules	Cholestatic syndromes
Kayser-Fleischer rings	Present in examination by slit lamp	Absent in up to 50% of Wilson disease patients with hepatic presentation, absent in most asymptomatic siblings	Chronic cholestatic disorders like primary biliary cholestasis

Table 3. Diagnostic criteria for Wilson disease – Leipzig-Score

Kayser-Fleischer ring (slit lamp examination)	
present	2
absent	0
Neurological symptoms and/or typical signs in cMRI	
severe	2
mild	1
absent	0
Serum ceruloplasmin	
Normal (>0.2g/L)	0
0.1-0.2g/L	1
<0.1g/L	2
Coombs negative hemolytic anaemia	
present	1
absent	0
Total liver copper content	
>250µg/g dry weight	2
>50 ≤250µg/g dry weight	1
normal (<50µg/g dry weight)	-1
If no copper-quantification available: positive rhodanine-staining	1
24h-urinary copper excretion	
normal	0
1-2x ULN (upper limit of normal)	1
>2x ULN	2
Normal, but positive D-penicillamine provocation test	2
ATP7B mutation analysis	
present on both chromosomes	4
Present on one chromosome	1
none	0
Total score	**Evaluation**
4 or more	Diagnosis established
3	Diagnosis possible, more tests needed
2 or less	Diagnosis very unlikely

Kayser-Fleischer rings

Kayser-Fleischer rings are found in most neurological Wilson disease patients and in ~ 50% of hepatic patients (Medici 2006, Merle 2007). Although sometimes they can be visible by eye, slit lamp examination is necessary to confirm the presence or absence of Kayser-Fleischer rings.

They are not pathognomonic for Wilson disease, and can also be found in cholestatic liver disease such as primary biliary cirrhosis or intrahepatic cholestasis associated with prolonged parenteral nutrition.

Serum ceruloplasmin

Serum ceruloplasmin is typically decreased below 20 mg/dL in patients with Wilson disease. However, serum ceruloplasmin concentration has its limitations as about 20 to 30% of Wilson disease patients with hepatic symptoms have serum ceruloplasmin levels in the normal range (Steindl 1997). Diagnostic accuracy of serum ceruloplasmin depends on the selected cutoff values (Mak 2008). Serum ceruloplasmin concentrations below 20, 14, and 10 mg/dL showed positive predictive values of 48.3%,

100%, and 100%, respectively, and negative predictive values of 98.7%, 97.1%, and 91.9%. In line with this finding, in the Leipzig score (Ferenci 2003), the informative cutoff is 10 mg/dL. In some Wilson disease patients hormonal and other stimuli can increase the levels of the acute-phase-reactant ceruloplasmin above the lower limit of normal. For example, ceruloplasmin may be elevated in inflammatory stages, during pregnancy, and in response to exogenous administration of oestrogens. Conversely, a reduced serum ceruloplasmin concentration can be seen in about 20% of ATP7B-heterozygotes, in hypoproteinaemia due to renal or enteric protein loss, in severe end-stage liver disease of any aetiology, and in the rare condition of aceruloplasminaemia. Decreased serum ceruloplasmin is in addition reported in patients with non-alcoholic fatty liver disease (NAFLD). In a recent study in NAFLD patients (without diabetes mellitus) a decreased ceruloplasmin ratio (ceruloplasmin value divided by the lower limit of normal) was associated with a more severe histological activity, a diagnosis of Non-alcoholic steatohepatitis, and hepatic iron deposition among patients with NAFLD (Wang 2022).

Total serum copper and relative exchangeable serum copper

In contrast to what would seem intuitive for a disorder of copper overload, total serum copper is often reduced (<70 µg/dL) in Wilson disease due to the lowered level of serum ceruloplasmin. However, serum copper levels vary and can be elevated in the setting of fulminant Wilson disease. The copper that is not part of ceruloplasmin is known as the serum non-ceruloplasmin bound copper concentration and is elevated above 10 µg/dL in most untreated patients. The non-ceruloplasmin bound "free" copper concentration can be calculated using the estimation that approximately 0.3 µg of copper are associated per mg ceruloplasmin:

Serum copper (µg/dL) – 3 x serum ceruloplasmin (mg/dL) = non-ceruloplasmin bound copper (µg/dL)

Recently, the direct exchangeable copper assay has been suggested as a robust and feasible diagnostic tool for Wilson disease. Exchangeable copper corresponds to the labile fraction of copper complexed to albumin and other peptides but not complexed within ceruloplasmin. This exchangeable copper fraction is easily exchanged in the presence of high–copper-affinity chelating agents such as EDTA and can be measured afterwards – and has been proposed as a method for estimating bioavailable non-ceruloplasmin bound copper in the circulation. For diagnostic purposes, the ratio of exchangeable copper to total serum copper, called the "relative exchangeable copper" (REC), with the cutoff set at 18.5%, distinguishes patients with Wilson disease from simple heterozygotes and normal individuals and also from adults and children with various chronic liver diseases (El Balkhi 2011, Guillaud 2018, Poujois 2017, Trocello 2014).

Urinary copper excretion

Urinary copper excretion is commonly increased in patients with Wilson disease and reflects the amount of non-ceruloplasmin copper in the circulation. While a daily urinary copper excretion of 40 µg (0.6 µmol) is the upper limit of normal the conventional level taken as diagnostic of Wilson disease is 100 µg (1.6 µmol). However, urinary copper excretion can also be increased in any disease with extensive hepatocellular necrosis, cirrhosis with cholestasis, and nephrotic syndrome.

Urinary copper excretion after provocation with D-penicillamine may be a utilised as an adjunctive diagnostic test to establish the diagnosis of Wilson disease, but has only been standardised in children (Martins da Costa 1992). Commonly 500 mg of D-penicillamine are administered to untreated patients orally at time zero and 12 h later during a 24-h urine collection and an increase of urinary copper excretion to >1600 µg / 24 hours is considered as diagnostic for Wilson disease.

Liver biopsy

Liver biopsy with determination of hepatic copper content remains the gold standard for diagnosing Wilson disease. Normal hepatic copper content is less than 40 µg/g dry weight and that of Wilson disease patients typically exceeds 250 µg/g dry weight. Lowering the threshold value to 75 µg/g was increases test sensitivity with still acceptable specificity (Ferenci 2005). Another large Chinese study proposed 209 µg/g dry weight as optimal threshold value (with a sensitivity of 99% and specificity of 96% (Yang 2015).

A slightly elevated hepatic copper content can also be associated with cholestatic liver diseases, such as progressive familiar intrahepatic cholestasis type 3 (PFIC 3), primary biliary cirrhosis and primary sclerosing cholangitis (Anheim 2010, Shneider 2011, Sood 2015).

The major problem with hepatic parenchymal copper concentration is that in later stages of Wilson disease the distribution of copper within the liver is often not homogenous. Thus, the concentration can be underestimated due to sampling error. As the accuracy of measurement is improved with adequate specimen size, at least 1-2 cm of biopsy core length should be submitted for copper dry weight analysis (Liggi 2013).

Regarding to liver histology, there is no one single feature pathognomonic for the diagnosis of Wilson disease. Intracellular fat accumulations, hepatitis-like features, Mallory bodies, focal necrosis, fibrosis, and cirrhosis can often be found. The pathology can be similar to an ethanol-induced steatohepatitis, while other patients may show histological signs resembling autoimmune hepatitis. Although histological findings are often not helpful for the diagnosis of Wilson disease, the exclusion of other etiologies by liver biopsy may be equally important. The presence of copper staining in histological sections by rhodanine or by other means can provide supportive evidence for Wilson disease. However, especially in early stages of Wilson disease a negative histochemical staining for copper does not rule out increased hepatic copper content and should not be considered sufficient for the exclusion of Wilson disease. Indeed, hepatic copper concentration can be particularly high under this condition.

Genetic studies

De novo diagnosis by molecular studies remains difficult due to the large number of disease-specific mutations scattered across the coding region ATP7B. Depending on the population tested specific mutations can be prevalent and can facilitate the otherwise cumbersome diagnostic mutation analysis (Ferenci 2006); in northern Europeans, the H1069Q mutation accounts for 60-70% of the disease alleles (Caca 2001, Ferenci 2019, Firneisz 2002, Margarit 2005) and in Asians the A778L mutation occurs in 30% of affected individuals.

Genetic analyses are useful in patients with uncertain diagnosis. In such patients sequencing the ATP7B gene can confirm Wilson disease if two ATP7B mutations are found. Genetic diagnosis of Wilson disease should always be corroborated with clinical and biochemical findings. The absence of two pathogenic mutations does not exclude a diagnosis of Wilson disease.

Other diagnostic tests

By ultrasound imaging signs of liver steatosis or cirrhosis as well as hepato- and splenomegaly can help establishing the diagnosis of Wilson disease.

Magnetic resonance imaging (MRI) of the brain may show increased density on T2 weighed images in the region of the basal ganglia and other regions as well as cortical atrophy. MRI changes are most often seen in Wilson disease patients with neurological manifestation, but may also be found in Wilson disease patients without neurological symptoms or completely asymptomatic patients.

As bone density is frequently decreased in Wilson disease patients performing an osteodensitometry is recommended.

Family screening

Screening should be performed in every first-degree relative of any Wilson disease patient. The probability of finding a homozygote is in siblings 25% and in parents or children 0.5%. There is no one single biochemical test that accurately discriminates between homozygous patients and heterozygote carriers. Kayser-Fleischer rings may be absent at early stages of the disease. Determination of Ceruloplasmin levels and 24-hour urinary copper excretion can be misleading because heterozygotes can have borderline pathological values. The serum ceruloplasmin concentration as a screening tool has poor diagnostic strength due to an inadequate predictive value as a single test. Thus, individuals without Kayser-Fleischer rings who have subnormal ceruloplasmin and abnormal liver functions should undergo a liver biopsy for quantitative copper determination. In first-degree relatives of a patient with two detected mutations, targeted mutational analysis is straightforward as family screening of first-degree relatives. Mutation analysis for screening the family of an index patient with known mutations is by that a very reliable tool. If mutations are not known in the index patient, haplotype analysis may be used (Houwen 1993).

Prognosis

Early diagnosis, correct treatment and compliance with anti-copper treatment are crucial for good prognosis in Wilson disease. This is reflected in studied analysing long-term prognosis: in patients diagnosed early and treated correctly and with good compliance long-term survival in Wilson patients seems to be very similar as for the general population (Bruha 2011). However, Wilson disease patients with liver cirrhosis or primarily neurologic patients diagnosed late or with insufficient treatment compliance show higher mortality compared to healthy controls (Beinhardt 2014, Czlonkowska 2005).

If therapy is started in pre-symptomatic patients, development of symptoms is only rarely seen and prognosis is very good (Walshe 1988). Symptomatic patients in general stabilise or improve on adequate long-term treatment. This is especially true for hepatic symptoms, while neurologic symptoms can persist and sometimes even worsen despite treatment.

Treatment

Medical treatment

Once the diagnosis of Wilson disease is established, lifelong medical treatment is recommended because copper accumulation is progressive and ultimately fatal without specific therapy.

As drug treatment, copper chelating agents and zinc salts are used. Under treatment most Wilson disease patients improve their liver function within 6 to 12 months of treatment. Under sufficient therapy asymptomatic patients (e.g. diagnosed by family screening) should stay asymptomatic. Therapy should be taken lifelong. Discontinuation of medical therapy (e.g. due to incompliance) typically leads to progression of liver disease or of neurological symptoms in 1 to 12 months following treatment discontinuation.

D-penicillamine and trientine are chelating agents that remove copper by enhancing its urinary excretion. Therefore, chelators require adequate renal function to be effective. The mode of action of zinc therapy differs from chelators as zinc inhibits the intestinal uptake of copper by inducing enterocyte metallothionein. Ingested copper is bound to metallothionein in enterocytes and lost via feces due to enterocyte shedding.

In addition to medical de-coppering therapy patients with Wilson disease should avoid intake of

foods and water containing high concentrations of copper.

According to the EASL and the AASLD guidelines on Wilson disease, initial treatment for symptomatic patients should include a chelating agent (EASL Wilson disease guideline 2012, Schilsky 2022). Although the larger body of published evidence exists for penicillamine, trientine seems to have a more favourable safety profile, especially in patients with neurological symptoms. Treatment of pre-symptomatic patients and lifelong maintenance therapy of successfully treated symptomatic patients can be accomplished with zinc salts or chelating agents in a reduced dosage. Nevertheless, definitive recommendations are difficult as randomised head-to-head studies are missing.

D-penicillamine

D-penicillamine was introduced 1956 as the first oral treatment for Wilson disease. Besides its action as a copper chelator it may be able to induce hepatic metallothionein synthesis which is capable of sequestering copper in a non-toxic form within cells (Scheinberg 1987). There is a large body of published evidence that D-penicillamine can effectively ameliorate hepatic and neurological symptoms. In addition, it can prevent the onset of disease in asymptomatic patients detected by family screening.

The usual dosage of D-penicillamine for initial treatment is 900 – 1, 800 mg/day divided in 2 to 4 dosages. For maintenance treatment a reduced dose of 600 – 900 mg/day is recommended. Because absorption can be impaired if taken with a meal D-penicillamine should be taken 1h before or 2h after a meal.

The disadvantage of D-penicillamine is its serious toxicity with a side-effects rate of 25 – 30%. These adverse events can be divided in short- and long-term adverse effects. In the first 1 to 3 weeks after starting D-penicillamine therapy hypersensitivity reactions like rash, fever, neutropenia, thrombocytopenia, proteinuria, and lymphadenopathy can occur. These early side effects may be managed by stopping D-penicillamine treatment and using an alternative drug. An early serious side-effect is neurological worsening that is seen especially in patients with a neurological presentation or at least pre-existing neurological symptoms (Litwin 2015). Neurological worsening recovers only in about half of the patients. Immunologically induced long-term effects require immediate cessation of D-penicillamine treatment. They include systemic lupus erythematodes, immune complex nephritis, Goodpasture syndrome, arthritis, and bone marrow depression with leucopenia and thrombocytopenia. Long-term effects that are dose-dependent and due to interference with collagen and elastin formation include skin lesions like cutis laxa and elastosis perforans serpingiosa.

Triethylentetramine / Trientine

Trientine (Triethylentetramine) is a chelating drug that was introduced in 1969 as an alternative to D-penicillamine. Trientine exists as two different salts: Triethylentetramine/trientine dihydrochloride (TETA-2HCl) and Triethylentetramine/trientine tetrahydrochloride (TETA-4HCl). Both salt formulations are stable and can be stored at room temperature.

Trientine is effective by promoting renal copper excretion like D-penicillamine does but seems to have fewer side-effects. In addition, accumulated clinical experience suggests that adverse effects due to D-penicillamine resolve when trientine is substituted for D-penicillamine and do not recur. Especially the initial neurological worsening is thought to be less frequent than under D-penicillamine treatment – although head-to-head comparison was never performed. Reported side effects are few and include iron deficiency anaemia. Rarely seen side-effects are colitis and pancytopenia.

Trientine is an effective treatment and is indicated especially in patients who are intolerant to D-penicillamine. As trientine formulations are typically more cost-expensive than D-penicillamine, notion should be given to decision taken by national health authorities concerning reimbursement.

Dose is referred to mg of trientine-base. Adult dose for trientine-2HCl is 800 to 1600 mg/day (4–8 capsules á 200mg trientine-base) and for trientine-4HCl is 450 to 975 mg/day (3 to 6½ tablets á 150mg trientine-base). Because absorption can be impaired by parallel intake of food trientine should be administered 1 h before or 2 h after meals, in two or three divided doses. As for D-penicillamine, for maintenance therapy trientine-dose can be reduced to a lower dosage than necessary in the initial phase.

When switching from one trientine-salt formulation to the other the higher bioavailability of trientine-4HCl than trientine-2HCl should be taken into account (Weiss 2021). Approximately 0.6mg of trientine base (of 4HCl formulation) equates to 1mg of trientine-base (of the 2HCl formulation). Subsequently, dosage is titrated according to clinical response and urinary copper excretion.

Zinc salts

Zinc salts were first used as treatment for Wilson disease in the early 1960s. In contrast to chelating agents zinc blocks copper absorption in the gastrointestinal tract by inducing metallothionein synthesis in enterocytes. Copper is bound to metallothionein with a high affinity and subsequently is lost when enterocytes shed during normal cell turnover. The dose of elemental zinc is 150 mg per day, given in three doses. Effectiveness of treatment is dependent on the strict administration separately from meals, because food and even milk can interfere with zinc absorption. A major advantage of zinc therapy is its safety with no serious side-effects reported (Brewer 1997, Hoogenraad 1987). The frequently occurring zinc-related dyspepsia can sometimes be overcome by changing the zinc formulation (to acetate, sulphate, or gluconate), but sometimes may cause the need for a change to another treatment.

Treatment failures under zinc-therapy can occur. Therefore, patients under zinc therapy should be followed regularly.

Tetrathiomolybdate

Tetrathiomolybdate is another chelating agent which complexes protein-bound copper. When taken together with meals, it complexes copper in the food and prevents its absorption. Taken separately from foods, tetrathiomolybdate is absorbed and complexes copper with albumin rendering it unavailable for cellular uptake. Tetrathiomolybdate as the more stable bis-choline salt of the drug is in late stages of drug development – but is not yet commercially available. Data from phase II suggested that tetrathiomolybdate caused an effective reduction in non-ceruloplasmin bound copper and an improvement in clinical neurological symptoms. It appears to be useful for the initial treatment of neurological patients. However, tetrathiomolybdate has not yet been released by the authorities for general clinical use and trials continue to determine if more chronic use may be effective and tolerated.

Treatment has to be monitored to ensure its efficacy and the compliance with treatment, and to identify adverse events. Patients should be monitored at least twice a year. Especially shortly after starting treatment a frequent monitoring is recommended. To confirm the clinical and biochemical improvement liver function tests and neurological assessment should be performed.

Monitoring of treatment

For routine monitoring, serum copper and ceruloplasmin, liver enzymes and international normalised ratio, functional parameters, complete blood count and urine analysis as well as physical and neurological examinations should be performed regularly, at least twice annually (EASL Wilson disease guideline 2012). More frequent monitoring is required in the initial phase after diagnosis and initiation of treatment, if symptoms worsen and if nonadherence to treatment is suspected.

Adequacy of chelating treatment can best be assessed by measuring 24-h urinary copper excretion. The 24-hour urinary copper excretion on medication and after 2 days of cessation of therapy should be measured at least yearly (EASL Wilson disease guideline 2012). An adequate long-term treatment can be postulated if the 24-h urinary copper excretion (measured after two days of treatment cessation) is below 100 µg/d (1.6 µmol/d). Urinary copper excretion upon initiation of treatment is often 1000–2000µg/24 h (16-32 µmol/L) (for D-penicillamine) and >1000 µg/24 h (8 µmol/L) (for trientine) and decreases over time on treatment. With chronic (maintenance) treatment, urinary copper excretion should be for D-penicillamine and trientine approximately 150–500 µg/24 h (3–8 µmol/24 h) (Pfeiffenberger 2019).

For monitoring zinc-therapy collection of 24-h urine under zinc treatment is recommended. Efficiency of zinc treatment can be supposed if 24-h urinary copper excretion is below 100 µg/d (1.6 µmol/d), while compliance with zinc therapy and adequate absorption of zinc is reflected in a 24-h urinary zinc excretion of more than 2 mg/d.

In addition, the efficiency of therapy can be estimated from the non-ceruloplasmin bound copper concentration in serum that should be below 10 µg/dL (<1.6 µmol/L).

Liver transplantation

Liver transplantation corrects the underlying metabolic defect and by that cures the disease. However, the great shortage of donor organs and the need for immunosuppression posttransplantation render liver transplantation only an option in fulminant Wilson disease or in patients especially with decompensated liver disease unresponsive to medical therapy. The outcome of liver transplantation is excellent with one-year survival rates of 80% to 90%. Neurological symptoms can improve after liver transplantation (Weiss 2013), but the outcome of patients with neurological symptoms is inferior to patients without. Thus, the indication for liver transplantation in patients with neurological symptoms should be evaluated carefully.

Key messages

- Wilson disease should be considered in any individual with liver abnormalities or neuropsychiatric symptoms of uncertain cause. Although the disease typically manifests between 5 to 35 years, age alone should not be the basis for excluding Wilson disease.
- Recognition and diagnosis of Wilson disease at an early stage has an impact on prognosis.
- Diagnostic gold standard is hepatic copper content (measured in dry weight). In untreated patients, normal hepatic copper content excludes a diagnosis of Wilson disease with high certainty.
- Genetic diagnosis of Wilson disease should always be corroborated with clinical and biochemical findings. The absence of two pathogenic mutations does not exclude a diagnosis of Wilson disease.
- Initial treatment for symptomatic patients with Wilson disease should include a chelating agent (D-penicillamine or trientine).
- Treatment is lifelong and should not be discontinued, unless liver transplantation is performed.
- Patients should adhere to medical therapy and to a diet avoiding foods and water with high concentrations of copper.
- Routine monitoring should be performed regularly, at least twice annually.

Future directions

For approximately ten years, there has been a rapid improvement in the efficiency of procedures of genetic analysis. As a consequence of improvements and greater availability of genetic testing, a relevant part of patients with and also without suspicion of Wilson disease will receive a test report stating that an ATP7B-variant of unknown significance has been detected. As medical therapy of Wilson disease is recommended also in asymptomatic patients, it will be of even increasing relevance to classify ATP7B variants for their clinical effects thoroughly. This is especially important, as Wilson disease is among a limited number of inherited diseases for which symptoms can be prevented if the affected individuals can be identified and intervened early.

With respect to future therapies currently two gene therapy studies are ongoing in Wilson disease patients. Both constructs (UX701 from Ultragenyx Pharmaceutical and VTX-801 from Vivet Therapeutics) are based on adeno-associated viral vectors and contain a shortened form of the ATP7B gene, which is otherwise too large to package in an adeno-associated viral vector.

Both studies use single intravenous application of the investigational drug. Patients with Wilson disease and clinicians are eagerly awaiting the results of these ongoing clinical gene therapy trials. The ongoing trials will demonstrate if the correction of copper metabolism is only temporary or long term at the point that anti-copper medications can be stopped, offering a real life-changing solution to patients.

References

Akil M, Schwartz JA, Dutchak D, Yuzbasiyan-Gurkan V, and Brewer GJ. The psychiatric presentations of Wilson's disease, J Neuropsychiatry Clin Neurosci. 1991;3:377-382.

Anheim M, Chamouard P, Rudolf G, et al. Unexpected combination of inherited chorea-acanthocytosis with MDR3 (ABCB4) defect mimicking Wilson's disease, Clin Genet. 2010;78:294-295.

Beinhardt S, Leiss W, Stattermayer AF, et al. Long-term outcomes of patients with Wilson disease in a large Austrian cohort, Clin Gastroenterol Hepatol. 2014;12:683-689.

Brewer GJ, Johnson V, and Kaplan J. Treatment of Wilson's disease with zinc: XIV. Studies of the effect of zinc on lymphocyte function, J Lab Clin Med. 1997;129:649-652.

Bruha R, Marecek Z, Pospisilova L, et al. Long-term follow-up of Wilson disease: natural history, treatment, mutations analysis and phenotypic correlation, Liver Int. 2011;31:83-91.

Bull PC, Thomas GR, Rommens JM, Forbes JR, and Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene, Nat Genet. 1993;5:327-337.

Caca K, Ferenci P, Kuhn HJ, et al. High prevalence of the H1069Q mutation in East German patients with Wilson disease: rapid detection of mutations by limited sequencing and phenotype-genotype analysis, J Hepatol. 2001;35:575-581.

Czlonkowska A, Litwin T, Dusek P, et al. Wilson disease, Nat Rev Dis Primers. 2018;4:21.

Czlonkowska A, Tarnacka B, Litwin T, Gajda J, and Rodo M. Wilson's disease-cause of mortality in 164 patients during 1992-2003 observation period, J Neurol. 2005;252:698-703.

El Balkhi S, Trocello JM, Poupon J, et al. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis, Clin Chim Acta. 2011;412:2254-2260.

European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease, J Hepatol. 2012;56:671-685.

Ferenci P. Regional distribution of mutations of the ATP7B gene in patients with Wilson disease: impact on genetic testing, Hum Genet. 2006;120:151-159.

Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease, Liver Int. 2003;23:139-142.

Ferenci P, Czlonkowska A, Merle U, et al. Late-onset Wilson's disease, Gastroenterology. 2007;132:1294-1298.

Ferenci P, Steindl-Munda P, Vogel W, et al. Diagnostic value of quantitative hepatic copper determination in patients with Wilson's Disease, Clin Gastroenterol Hepatol. 2005;3:811-818.

Ferenci P, Stremmel W, Czlonkowska A, et al. Age and Sex but Not ATP7B Genotype Effectively Influence the Clinical Phenotype of Wilson Disease, Hepatology. 2019;69:1464-1476.

Firneisz G, Lakatos PL, Szalay F, et al. Common mutations of ATP7B in Wilson disease patients from Hungary, Am J Med Genet. 2002;108:23-28.

Guillaud O, Brunet AS, Mallet I, et al. Relative exchangeable copper: A valuable tool for the diagnosis of Wilson disease, Liver Int. 2018;38:350-357.

Hoogenraad TU, Van Hattum J, and Van den Hamer CJ. Management of Wilson's disease with zinc sulphate. Experience in a series of 27 patients, J Neurol Sci. 1987;77:137-146.

Houwen RH, Roberts EA, Thomas GR, and Cox DW. DNA markers for the diagnosis of Wilson disease, J Hepatol. 1993;17:269-276.

Liggi M, Mais C, Demurtas M, et al. Uneven distribution of hepatic copper concentration and diagnostic value of double-sample biopsy in Wilson's disease, Scand J Gastroenterol. 2013;48:1452-1458.

Litwin T, Dziezyc K, Karlinski M, et al. Early neurological worsening in patients with Wilson's disease, J Neurol Sci. 2015;355:162-167.

Mak CM, Lam CW, and Tam S. Diagnostic accuracy of serum ceruloplasmin in Wilson disease: determination of sensitivity and specificity by ROC curve analysis among ATP7B-genotyped subjects, Clin Chem. 2008;54:1356-1362.

Margarit E, Bach V, Gomez D, et al. Mutation analysis of Wilson disease in the Spanish population -- identification of a prevalent substitution and eight novel mutations in the ATP7B gene, Clin Genet. 2005;68:61-68.

Martins da Costa C, Baldwin D, Portmann B, et al. Value of urinary copper excretion after penicillamine challenge in the diagnosis of Wilson's disease, Hepatology. 1992;15:609-615.

Medici V, Trevisan CP, D'Inca R, et al. Diagnosis and management of Wilson's disease: results of a single centre experience, J Clin Gastroenterol. 2006;40:936-941.

Merle U, Schaefer M, Ferenci P, and Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study, Gut. 2007;56:115-120.

Mura G, Zimbrean PC, Demelia L, and Carta MG. Psychiatric comorbidity in Wilson's disease, Int Rev Psychiatry. 2017;29:445-462.

Nicastro E, Ranucci G, Vajro P, Vegnente A, and Iorio R. Re-evaluation of the diagnostic criteria for Wilson disease in children with mild liver disease, Hepatology. 2010;52:1948-1956.

Pfeiffenberger J, Lohse CM, Gotthardt D, et al. Long-term evaluation of urinary copper excretion and non-caeruloplasmin associated copper in Wilson disease patients under medical treatment, J Inherit Metab Dis. 2019;42:371-380.

Poujois A, Trocello JM, Djebrani-Oussedik N, et al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease, Eur J Neurol. 2017;24:154-160.

Scheinberg IH, Sternlieb I, Schilsky M, and Stockert RJ. Penicillamine may detoxify copper in Wilson's disease, Lancet. 1987;2:95.

Schilsky ML, Roberts EA, Bronstein JM, et al. A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 practice guidance on Wilson disease from the American Association for the Study of Liver Diseases, Hepatology. 2022.

Shneider BL. ABCB4 Disease Presenting with Cirrhosis and Copper Overload-Potential Confusion with Wilson Disease, J Clin Exp Hepatol. 2011;1:115-117.

Sood V, Rawat D, Khanna R, and Alam S. Cholestatic liver disease masquerading as Wilson disease, Indian J Gastroenterol. 2015;34:174-177.

Steindl P, Ferenci P, Dienes HP, et al. Wilson's disease in patients presenting with liver disease: a diagnostic challenge, Gastroenterology. 1997;113:212-218.

Tanzi RE, Petrukhin K, Chernov I, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene, Nat Genet. 1993;5:344-350.

Trocello JM, El Balkhi S, Woimant F, et al. Relative exchangeable copper: a promising tool for family screening in Wilson disease, Mov Disord. 2014;29:558-562.

Walshe JM. Diagnosis and treatment of presymptomatic Wilson's disease, Lancet. 1988;2:435-437.

Wang Q, Zhou D, Wang M, et al. A Novel Non-Invasive Approach Based on Serum Ceruloplasmin for Identifying Non-Alcoholic Steatohepatitis Patients in the Non-Diabetic Population, Front Med (Lausanne). 2022;9:900794.

Weiss KH, Schafer M, Gotthardt DN, et al. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease, Clin Transplant. 2013;27:914-922.

Weiss KH, Thompson C, Dogterom P, et al. Comparison of the Pharmacokinetic Profiles of Trientine Tetrahydrochloride and Trientine Dihydrochloride in Healthy Subjects, Eur J Drug Metab Pharmacokinet. 2021;46:665-675.

Wiernicka A, Dadalski M, Janczyk W, et al. Early Onset of Wilson Disease: Diagnostic Challenges, J Pediatr Gastroenterol Nutr. 2017;65:555-560.

Wilson DC, Phillips MJ, Cox DW, and Roberts EA. Severe hepatic Wilson's disease in preschool-aged children, J Pediatr. 2000;137:719-722.

Yang X, Tang XP, Zhang YH, et al. Prospective evaluation of the diagnostic accuracy of hepatic copper content, as determined using the entire core of a liver biopsy sample, Hepatology. 2015;62:1731-1741.

10. Genetic liver diseases

10.3 Cholestatic syndroms

Verena Keitel

This chapter will be published shortly.

10. Genetic liver diseases

10.4 Alpha-1 antitrypsin deficiency

Michelle Walkenhaus, Pavel Strnad

Abstract

Alpha-1 antitrypsin (AAT) deficiency (AATD) is caused by a mutation in the SERPINA1 gene, which encodes the protease inhibitor alpha1 antitrypsin. This leads to AAT retention in the hepatocytes. As a result, a proteotoxic stress reaction occurs in the liver and predisposes to liver fibrosis/cirrhosis (gain-of-function). Less AAT reaches the lungs, which can lead to pulmonary emphysema or COPD (loss-of-function). The homozygous Pi*ZZ genotype causes severe AATD and may result in paediatric and adult liver diseases. The heterozygous Pi*MZ genotype is a risk factor for the development of lung and liver diseases. The progression of lung disease can be slowed down by AAT substitution therapy and a phase II clinical study suggests a therapeutic benefit of AAT silencing via siRNA for AATD-related liver disease. This chapter summarises the pathomechanisms, diagnostic approach, clinical consequences as well as recommendations for clinical management of the subjects with AATD.

Background

Alpha-1 antitrypsin deficiency (AATD) is a common inherited disorder that is potentially life-threatening due to the associated lung and liver damage (Greene 2016). In the ICD-10 nomenclature, it is reflected by an unspecific code E88.0 and because of that, Orphanet nomenclature of rare diseases (ORPHA) code 60 represents a more specific way to identify this condition. Alternatively, ICD modifications such as E88.0A code that is used in some European countries or the upcoming ICD-11 system offer a better assignment (Picker 2023). AATD arises due to mutations in the SERPINA-1 gene, located on chromosome 14. It encodes the protein alpha-1 antitrypsin (AAT), a protease inhibitor that is mainly produced in hepatocytes. After being secreted from the hepatocytes into the bloodstream, AAT inhibits a variety of proteases such as neutrophil elastase or proteinase 3 thereby preventing an undesired tissue digestion (Greene 2016). The liver produces up to 34 mg of AAT per kilogram of body weight per day. It results in

serum levels of 0.9 to 1.75 mg per millilitre in healthy individuals. AAT is a stress-inducible protein and consequently, this level can be doubled during infections. In individuals with AATD, AAT production/secretion is impaired. This fact results in diminished serum AAT levels and a less pronounced increase during infections (Strnad 2020).

Most individuals have two wild type alleles of the SERPINA-1 gene, labeled as Pi*MM genotype. More than 100 AAT variants have been described and they are subdivided into groups based on the migration of the resulting protein in the electric field. The wild type allele Pi*M indicates a medium velocity, while Pi*F, Pi*S and Pi*Z refer to fast, slow and very slow movement, respectively (Wedzicha 2017). The most clinically relevant variants are Pi*Z (glutamate-to-lysine substitution at position 342) and Pi*S (glutamate-to-valine substitution at position 264) (Ferrarotti 2014). Depending on the amount of affected alleles, they cause the genotypes Pi*MZ/Pi*ZZ (heterozygous/ homozygous Pi*Z mutation) and Pi*MS/ SS (heterozygous Pi*S mutation/ homozygous Pi*S mutation), while a combined presence of Pi*Z and Pi*S variant is termed Pi*SZ (Ferrarotti 2014, Strnad 2020).

Given the AATD pathomechanism described above, measurement of the AAT serum level is the first step in the detection of this condition. When decreased levels are seen, a genetic analysis and/or protein phenotyping is usually performed. While a cut-off of <50mg/dL can be used to identify individuals with severe AATD genotypes, there is no level reliably identifying subjects with mild genotypes such as Pi*MZ although a level of 110mg/dL has been advocated by some researchers (Ferrarotti 2012, Miravitlles 2017). The genotyping can be performed via a cheek swab or a blood draw with DNA isolation. A routine diagnosis typically consists of a PCR for Pi*Z/Pi*S or a multiplex-PCR that distinguishes ~20 most common variants. If this approach does not yield a definitive diagnosis or the detected genotype does not match with serum AAT levels, a sequencing is typically performed (Strange 2006, Strnad 2020). As an alternative to genotyping, AAT phenotyping takes advantage of different migration in the electric field described above and because of that provides an assignment to subclasses rather than a final genetic diagnosis (Bornhorst 2013). The major advantage of that approach is that it is often faster than the definitive genetic diagnosis.

While the liver and lung affection are the major AATD-associated conditions, the underlying mechanism differs. In the former case, the abnormal AAT that cannot be released into the bloodstream, polymerises and causes a toxic “gain-of-function” injury (Clark 2018, Schneider 2020). The hepatocellular retention of the heavily glycosylated AAT leads to an emergence of PAS-D positive globules that are the histological hallmark of this condition. In contrast, the lung suffers from the "loss-of-function" phenotype caused by the lower amount of AAT in the systemic circulation and consequently the lung. This results in an impaired inhibition of the target proteases and an increased degradation of the alveolar septa. This leads to panlobular emphysema and chronic obstructive pulmonary disease (COPD) that are the prevailing AATD-specific cause of death (Greene 2016, Janciauskiene 2018, Janciauskiene 2011). Notably, additional events such as inflammatory reaction caused by the polymerised AAT might also contribute to the lung damage but their exact contribution remains to be clarified.

The different mechanistic cause of lung and liver affection becomes important when counseling subjects with the rare, so called "null mutations" (Pi*Q0), i.e. mutations that do not display any serum AAT. Because of the lack of the AAT, the affected individuals are highly predisposed to lung damage while their liver-related risks differ, depending on whether or not they produce any hepatic AAT (Ferrarotti 2014).

Besides being an anti-protease, AAT is also an important immunomodulatory protein and consequently, AATD subjects are susceptible to immunologic disorders such as antineutrophil cytoplasmic antibody (ANCA)– associated vasculitis or panniculitis, a disorder characterised by subcutaneous inflammation. Accordingly, current guideline suggests that individuals with the latter two conditions, COPD, liver disease of unknown origin, asthma not responsive to the treatment, bronchiectasis as well as first-degree relatives of AAT subjects should be tested for this condition. Given that AATD can be both liver disease-causing and –modifying, we advocate for AATD testing in all subjects where the result might be of clinical relevance.

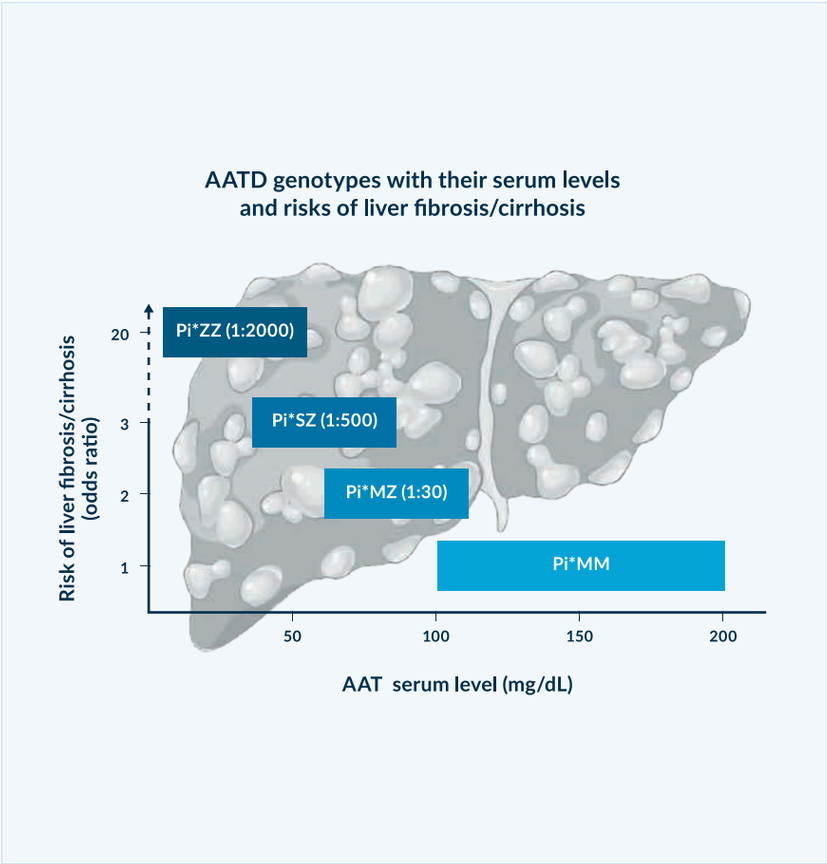

Figure 1. Characteristic AATD genotypes, their prevalence, AAT serum levels and corresponding risk of adult liver fibrosis/cirrhosis.

Pi*ZZ

The genotype Pi*ZZ is responsible for >95% of severe AATD cases and occurs at a frequency of 1:2000 in subjects of European ancestry (Blanco 2017). Patients with the corresponding homozygous Z mutation, have a markedly decreased serum AAT level (mostly <50 mg/dL AAT serum level) and a marked susceptibility to liver and lung damage (Hamesch 2019, Strnad 2020, Teckman 2013).

Adult liver

Pi*Z mutation does not affect the production of AAT protein in the hepatocytes but leads to protein misfolding and an 85% reduction in secreted AAT. As a result, the protein is retained in the endoplasmic reticulum (ER) (Lomas 1992, Teckman 2017). About 70% of it can be degraded while the rest forms polymers. The degradation occurs with the help of autophagy and ER-associated degradation (ERAD) (Teckman 2000, Christianson 2008). ERAD is responsible for removal of smaller species which autophagy can degrade even larger aggregates. These can be visualised as purple inclusion bodies in the periodic Acid-Schiff staining and are resistant to diastase treatment (PAS-D stain) that is used to digest glycogen. Immunohistochemistry using anti-Pi*Z antibodies is even more sensitive but is rarely used in the clinical routine (Strnad 2013). On the other hand, AAT aggregates are rather indistinct in the hematoxylin and eosin staining. The misfolding and polymerisation of the AAT leads to a proteotoxic "gain-of-function" stress, which promotes the development of liver fibrosis/cirrhosis (Clark 2018, Schneider 2020). Accordingly, Pi*ZZ subjects display higher liver transaminases (AST, ALT) as well as GGT values (Fromme 2022b). However, elevated AST/ALT levels are seen only in 10-15% of Pi*ZZ subjects and repeatedly elevated levels should therefore trigger thorough evaluation to exclude potential co-morbidities.

Despite the often normal liver enzyme levels, Pi*ZZ patients show a 20-fold higher risk of developing liver fibrosis/liver cirrhosis compared to the normal population and the life-long risk of cirrhosis of about 10%. These data are supported by several independent sources. Among them, the United Kingdom Biobank (UKB), a population-based cohort of ~500, 000 individuals who all received AATD genotyping, assessed the presence of advanced liver fibrosis based on ICD codes documented during inpatient visits (Fromme 2022a). The EASL AATD consortium collected almost 600 Pi*ZZ subjects, who were examined by transient elastography-based liver stiffness measurement (LSM) as well as other non-invasive liver fibrosis surrogates such as AST-to-platelet ratio (APRI) or Fib-4 index (Schneider 2020, Hamesch 2019). Another study compared the need for liver transplantation and came to similar conclusions. (Adam 2012, Fromme 2022a). Finally, a cohort from North America subjected 94 Pi*ZZ individuals to a liver biopsy and found that 35% of them had significant liver fibrosis defined as a fibrosis grade of at least 2 on a 0-4 scale (Clark 2018). This study as well as a report from the EASL AATD consortium demonstrated the usefulness of non-invasive fibrosis parameters (particularly LSM) to reflect the histological amount of liver fibrosis. Similar to other etiologies, LSM was particularly useful to recognise advanced fibrosis while its performance in intermediate fibrosis stages was less impressive (Clark 2018). Clark et al also revealed that increased fibrosis stage associates with higher amount of AAT inclusions. However, further studies are needed whether inclusion load really increases during fibrosis progression or whether subjects with increased AAT accumulation are more susceptible to

the fibrosis development.

In contrast to data on liver fibrosis, there are only limited data on susceptibility to liver tumours (Fromme 2022a, Hamesch 2019, Schneider 2020). The UKB analyses showed an odds ratio of > 40, while another study reported a ~20x increased risk (Hiller 2022). However, it remains unclear whether tumours develop only at advanced fibrosis stage, as seen in most liver disease etiologies or can also arise earlier. Because of that, we advocate for regular liver tumour screening in Pi*ZZ subjects with at least an intermediate liver fibrosis stage (Fromme 2022a).

Given the above described risks, a hepatological assessment of Pi*ZZ subjects is warranted. For an initial evaluation, we recommend a combination of liver enzyme levels and LSM. A LSM≥7.1 kPa suggests a fibrosis of grade 2 or higher, while LSM≥10 kPa points towards an advanced liver fibrosis. Ideally, LSM values are in accordance with at least one widely available non-invasive liver fibrosis surrogate such as APRI or Fib-4. In discrepant cases, magnetic resonance elastography can be used as an additional methods although the data on its usefulness in AATD are highly limited (Kim 2016). While liver biopsy is not needed to establish the diagnosis, it might be useful in case of recurrently elevated liver enzymes to assess co-morbidities or to clarify the extent of fibrosis in unclear cases. In addition to the LSM, transient elastography can be used to quantify steatosis of the liver via assessment of controlled attenuation parameters (CAP). Notably, Pi*ZZ individuals display increased CAP values (Hamesch 2019).

A longitudinal examination of Pi*ZZ subjects should be based on results of the initial evaluation. Given their markedly increased risks, we advocate for measurement of the inexpensive liver enzymes once or twice a year. However shorter intervals might be needed in subjects with increased values or advanced fibrosis. We recommend an ultrasound of the liver once a year to exclude tumours, at least in subjects with intermediate fibrosis and twice a year in individuals with advanced liver fibrosis. If the baseline transient elastography and the liver values are unremarkable, a further transient elastography can occur in about 3 years. Patients with decompensated liver cirrhosis should be considered for liver transplantation and the evaluation should include a careful examination of the lung status.

Paediatric liver

While adult AATD-associated liver disease (AATD-LD) typically manifests in/after 40 years of age, Pi*ZZ genotype also causes paediatric liver damage that often manifests in form of neonatal cholestasis (Ruiz 2019). It is characterised by prolonged cholestatic jaundice that is accompanied by increased serum enzyme levels. It can lead to failure to thrive and hepatosplenomegaly and progress to liver failure with ascites and coagulopathy (Feldman 2013).

The highest level of evidence about paediatric AAT-LD stems from the Swedish Newborn Screening programme, which screened a cohort of 200, 000 newborns and identified 120 Pi*ZZs (Mostafavi 2019, Sveger 1976, Sveger 1995). 12% of them displayed prolonged jaundice (Sveger 1976). Over half of the children with the Pi*ZZ genotype showed abnormal liver enzymes and these values often normalised in the next months/years (Sveger 1995). Less than 3% of the Pi*ZZ newborns developed an end-stage liver disease. At the age of 18 years, only 12% of the Pi*ZZ subjects had elevated liver enzyme levels (Ruiz 2019, Fromme 2019, Sveger 1995). The programme also systematically evaluated the psychological burden of the disease and layed out both advantages of disadvantages of neonatal screening for AATD.

While some Pi*ZZ infants/children develop typical symptoms of decompensated liver cirrhosis, such as a distended abdomen or gastrointestinal (GI) bleeding from oesophageal varices, many remain asymptomatic even in case of portal hypertension and are discovered through checkups or biochemical screenings. These included altered liver enzymes, thrombocytopenia or splenomegaly. Some have a history of prolonged jaundice as a newborn, while others are first noticed in screening procedures later on. In general, children with symptoms of chronic liver disease, hepatosplenomegaly, unexplained jaundice or abnormal liver enzymes should be tested for AATD. Similar to adults, liver biopsy is not needed to diagnose the disease but might be useful in unclear cases (Feldman 2013).

Similar to adults, a management of paediatric AATD-LD is based on the rate of liver affection. Given that the course of the disease can be very variable and rapid decompensations have been described in those with advanced liver fibrosis, a careful monitoring by a paediatric liver transplantation centre is recommended. Those with signs of portal hypertension and failure to thrive should be considered for liver transplantation. Since cholestatic liver disease impairs the absorption of fat-soluble vitamins, an evaluation of vitamin deficiencies and their supplementation might be needed. Further liver damage from alcohol or a steatosis should be avoided and a healthy lifestyle promoted (Feldman 2013).

Although no specific treatment of paediatric AATD-LD exists, ursodeoxycholic acid (UDCA) is frequently administered, although the data are based only on one open-label trial. In the latter, 42 Pi*ZZ children with the Pi*ZZ genotype were assessed over the course of several years. They all received UDCA and were clinically and biochemically examined at least once a year. UDCA improved liver test results in some, but no benefit was seen in those with pre-existing severe liver damage (Lykavieris 2008).

Given the marked liver- and lung-related risks associated with the Pi*ZZ genotype, a systematic transitional programme for adolescents is warranted. The topics should include the awareness about disease, the promotion of healthy lifestyle, avoidance of smoking, dust exposition or excessive alcohol consumption. In addition, the importance of regular lung and liver monitoring as well as the usefulness of vaccinations should be addressed.

Lung

In contrast to liver injury, proteolytic lung damage is caused by a "loss-of-function" mechanism. The strongly reduced AAT levels in the blood result in an insufficient inhibition of the proteases, particularly neutrophil elastase (Janciauskiene 2011). This leads to increased degradation of the alveolar septa, an elevated mucin production and secretion as well as activation of several proinflammatory downstream targets (Strnad 2020). In addition to that, AAT is a potent anti-inflammatory agent and its lack promotes neutrophil chemotaxis, degranulation and apoptosis (Strnad 2020). To make things worse, the polymerised, misfolded AAT also constitutes a proinflammatory agent and a potent neutrophil chemoattractant (Mahadeva 2005). Smoking oxidises and thereby inactivates AAT, but also induces its polymerisation (Alam 2011). Collectively, the effects lead to panlobular emphysema or chronic obstructive pulmonary disease (COPD) that often becomes symptomatic in fourth or fifths decade and develops particularly rapidly, especially in smokers. The lung damage is the most common specific cause of death in Pi*ZZ patients (Tanash 2017). Therefore, smoking Pi*ZZ subjects should be offered a counselling to help them with smoking cessation. Notably, early intervention reduced the frequency of smoking and mortality (Piitulainen 2002).

The monitoring of Pi*ZZ subjects with lung disease involves spirometry assessing the mean forced expiratory volume in 1 second (FEV1) a measurement of diffusing capacity of the lung for carbon monoxide (DLCO), a 6-minute walk test and a quality-of-life questionnaire (Miravitlles 2017). The frequency of check-ups depends on the degree of impairment. At the beginning, a biannual testing is appropriate, while a once-a-year evaluation is often sufficient later on. COPD guidelines can be used as a guide (Strnad 2020). Notably, neither FEV1 nor DLCO reflect the full lung phenotype and lung density assessment via computed tomography has been advocated as a better tool, however, long-term studies analysing its predictive value are lacking (McElvaney 2017).

The treatment of Pi*ZZ-associated lung disease follows the recommendations for COPD. Additionally, the loss of lung density can be slowed down by weekly intravenous administration of purified human AAT (Greene 2016, Strnad 2020). Notably, AAT augmentation does not seem to affect COPD exacerbations nor FEV1 (McElvaney 2017, Chapman 2015). AAT augmentation infusion is recommended for non-smoking patients with severe AATD with diminished FEV1, frequent exacerbation or a rapid decline in lung function. However, AAT augmentation is not reimbursed in all countries and is not recommended for subjects with mild AATD such as Pi*MZ nor for patients without airflow obstruction (Sandhaus 2016, Miravitlles 2017).

In addition to the above described measures, the management of PI*ZZ patients should include a prevention and aggressive treatment of respiratory infections. For the former, regular vaccinations against influenza, SARS-CoV2 and pneumococci are recommended (Miravitlles 2017). The subjects with chronic respiratory failure benefit from long-term oxygen therapy. Lung transplantation, surgical lung volume reduction and endobronchial valve placement might be helpful in patients with advanced emphysema, although the latter two are controversial and require a careful selection (Miravitlles 2017).

Others

AATD constitutes a systemic disease and in addition to lung and liver, it may also affect other organs. In particular, about 1% of Pi*ZZ subjects develop a neutrophilic panniculitis (Blanco 2016), a painful inflammation of the subcutaneous fat tissue characterised by nodular or ulcerating skin lesions. Some patients also report a discharge of a yellow exudate (Franciosi 2022). The upper and lower extremities are most commonly affected, but the back, abdomen or face can also be involved. The disease can occur gradually or intermittently in episodes. It predominantly affects women and the typical age at first presentation is 36 years (Franciosiz 2015, Elsensohn 2015). The first-line treatment is dapsone, whereas AAT augmentation therapy is used in refractory cases. Because of the option for a specific treatment, it is important to identify AATD as the underlying cause, especially since panniculitis associated with AATD is often resistant to treatment with glucocorticoids (Franciosi 2022).

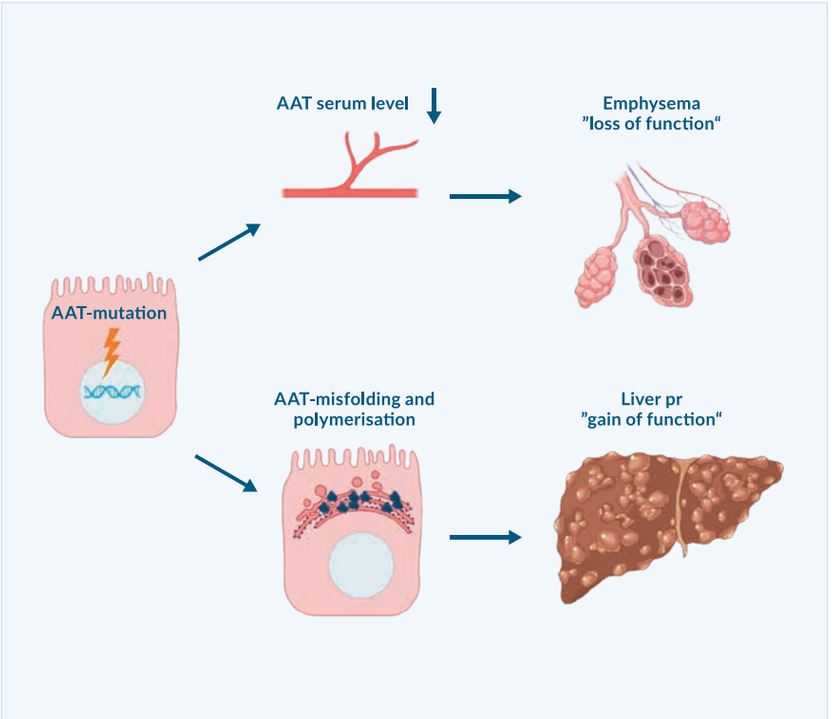

Figure 2. Pathophysiology of liver and lung damage in alpha-1 antitrypsin deficiency. Alpha-1 antitrypsin (AAT) mutation causes AAT accumulation and a consecutive proteotoxic „gain-of-function" stress in the liver. The impaired AAT secretion leads to a „loss-of-function" lung injury due to a reduced inhibition of proteases.

Pi*MZ

The heterozygous genotype Pi*MZ is found in about 1:30 Caucasians. These individuals have normal to slightly decreased serum AAT levels (typically 70-100 mg/dL). Many of them are discovered during family screening of Pi*ZZ relatives.

Liver

In this genotype, the presence of a Z mutation is partially compensated by the remaining wild-type allele. This means, that more AAT is transported into the bloodstream and less misfolded AAT remains in the ER. This results in less polymerisation seen in the liver biopsies. For example, in a large study, only 40 % of Pi*MZ patients harbored AAT inclusion bodies in the PAS-D staining, while immunohistochemistry detected AAT polymers in 63 % of them (Fu 2017, Schneider 2020). In line with that, in a population-based UKB cohort, individuals with Pi*MZ showed only a slightly increased odds ratio of 1.7 for liver fibrosis/ liver cirrhosis as well as liver mortality and no increased risk for liver cancer (Fromme 2022a, Hamesch 2019, Schneider 2020). Therefore, Pi*MZ genotype is considered a risk factor rather than a disease-causing agent and a second hit is typically needed to develop a disease (Schneider 2020). For example, the genetically determined 1.7-fold risk of liver-related mortality is amplified by established factors such as obesity, diabetes mellitus, male gender and age ≥ 50 years (Schneider 2020). Among them, obesity is well-known to increase the profibrogenic effects of several other genetic variants (Williams 2014, Stender 2017), while diabetes was suggested to promote proteotoxic cell stress, oxidative stress and lipolysis (Lebeaupin 2018, Petersen 2018). Several studies have shown that the Pi*MZ genotype increases susceptibility to liver fibrosis in metabolic disorders such as ALD/NAFLD. The odds ratio for NAFLD-related cirrhosis in subjects with Pi*MZ genotype was 2-7 times higher than in non-carriers and similar magnitude was reported for ALD (Strnad 2019, Abul-Husn 2018, Cacciottolo 2014). In contrast, the interaction between Pi*MZ genotype and viral hepatitis or haemochromatosis remains to be conclusively clarified (Guldiken 2019, Regev 2006, Kuscuoglu 2021), while the worsening impact on cystic fibrosis-related liver disease is unequivocal (Strnad 2020) and confers an odds ratio of ~5 (Ruiz 2023). Notably, cystic fibrosis constitutes a cholestatic disease and the detrimental impact of Pi*MZ phenotype on proper bile secretion is also supported by their predisposition to gallstone formation (Ferkingstad 2018).

In line with the above described considerations, liver enzyme levels are typically within normal range in Pi*MZ subjects although the mean ALT values in the UKB cohorts were significantly elevated compared to non-carriers (Fromme 2022a). It is worthwhile to note that up to 10% of liver transplant candidates carry a Pi*MZ genotype and that Pi*MZ subjects with liver cirrhosis decompensate faster than non-carriers (Ruiz 2023). Therefore, a liver check-up should be offered to Pi*MZ subjects with established risk factors and/or elevated liver enzymes, while there are no sufficient data to recommend a systematic hepatologic management of asymptomatic Pi*MZ individuals.

Lung

Similar to liver disease, the Pi*MZ genotype alone does not constitute a dramatic risk factor for the development of lung disease. In fact, population studies did not identify an elevated predisposition on a population level (Strnad 2020), while several reports demonstrated an increased susceptibility in presence of additional risk factors or a permissive genetic

background (Molloy 2014).

For example, the COPDGene study investigated the lung function of current and ex-smokers with at least 10 pack-years using a cross-sectional observational cohort. It was established that Pi*MZ patients have significantly lower FEV1 values and more radiological emphysema than non-carriers. Notably, the phenotype was shown across all races (Foreman 2017).

Other studies showed that the significant difference between Pi*MZ and Pi*MM subjects is not observed in never smokers and particularly pronounced in continuous smokers. The odds ratio was the highest by forever-smokers at 10.65 (Molloy 2014). These data should be used to discourage Pi*MZ subjects from smoking and to include them in corresponding preventative programmes. While not every Pi*MZ person needs regular pulmonological examinations, these should be considered in those with additional risk factors such as smoking or pre-existing COPD or asthma.

Rare associations

Milder genotypes such as the Pi*MZ do not seem to *per se* trigger a development of liver disease in children, but can contribute to such a disease in presence of additional risk factors such as cystic fibrosis (Ruiz 2019). However, partly due to their abundance, several disorders were shown to be associated with Pi*MZ genotype (Strnad 2020).

For example, Pi*MZ subjects are susceptible to gallstone formation with an odds ratio of 1.3 for both Pi*ZZ and the Pi*MZ genotype (Ferkingstad 2018). Pi*MZ individuals also harbor a 2.9times elevated risk of ANCA-associated vasculitis (Merkel 2017) with a clear data for both myeloperoxidase-reactive ANCA with perinuclear staining (p-ANCA) and proteinase 3-reactive ANCA with cytoplasmic staining (c-ANCA) subtypes. This overrepresentation was detected not only in individuals with a Pi*Z mutation, but also in those with a Pi*S mutation. The pathomechanism seems to be a loss-of-function of AAT leading to an imbalanced protease activity (Rahmattulla 2016).

Less common genotypes

While >100 genotypes have been described (Strnad 2020), Pi*MZ and Pi*ZZ are the clinically by far most relevant ones. Additionally, Pi*SZ genotype is also relatively common (ca. 1:500-1:1000 in Caucasians) and displays intermediate AAT serum levels (ca. 40-80 mg/dL) (Fromme 2022a). Susceptibility to lung and liver diseases is moderately increased, but seems to be closer to Pi*MZ than Pi*ZZ subjects (Blanco 2017, Fromme 2022a). For example, Pi*SZ individuals have a 3-fold higher risk of liver fibrosis or cirrhosis, but a 7-fold higher risk of liver cancer (Fromme 2022a). Therefore, regular ultrasound examinations should be performed when advanced liver fibrosis is present. The risk factors that promote the development of liver fibrosis seem to be the same (i.e. male gender, ≥ 50 years, metabolic syndrome) as reported above for Pi*MZ subjects (Fromme 2022a). Along the same line, Pi*SZs should be discouraged from smoking. While non-smoking Pi*SZ individuals with lung disease are offered augmentation therapy in some countries, but not in others (Cazzola 2020).

The genotype Pi*SS has a comparable prevalence as Pi*SZ but does not seem to be a relevant risk factor for the development of lung and liver diseases (Fromme 2022a). Paediatric liver diseases do not typically develop in the less severe genotypes such as Pi*SZ and Pi*SS, but these genotypes may play a role in the presence of other risk factors (Ruiz 2019). In the even less frequent genotypes, the risk of lung disease seems to be indirectly proportional to the serum AAT level, while the liver related risk also depends on the underlying biology as described above for the Pi*Qo variants (Strnad 2020).

Therapeutic approaches for AATD-related liver disease

The current treatment options in AATD are limited to lung/liver transplantation and the augmentation therapy. Liver transplantation is associated with a good prognosis in carefully selected patients (Carey 2013, Clark 2017) and since the majority of human AAT is produced in the liver, results in a normalisation of serum AAT levels. While this fact should protect from progression of lung disease, the current data supporting this consideration are limited (Carey 2013). Similarly, AATD candidates with sever lung damage were demonstrated to benefit from lung transplantation (Tanash 2011), although they might have a faster FEV1 decline than COPD patients without AATD (Banga 2014). Although experimental data suggest a beneficial impact of AAT augmentation after lung transplantation (Iskender 2016), lung-transplanted AATD subjects are not regularly augmented.

In line with the pathomechanism of AATD-associated lung disease described above, lung-directed candidates focus on AAT supplementation or on inhibition of its target protein. With regard to the former, an inhaled AAT was demonstrated to be safe in a phase 2 clinical trial (Stolk 2019) and its efficacy is currently studied in a phase 3 trial. While the current augmentation therapy relies on purified human protein, inhibrix-101

constitutes a recombinant AAT form with a longer half-life that is studied in early phase clinical trials (Kuhn 2023). Alvelestat is an oral inhibitor of neutrophil elastase and in a phase 2 trial, its administration at higher dose was associated with decreased neutrophil elastase activity (Stockley 2023).

On the other hand, liver-targeted treatments aim to decrease the production of the misfolded protein or improve its secretion from the liver. The former strategy relies primarily on hepatocyte-targeted small interfering RNAs (siRNAs) fazirsiran or belcesiran. In a phase 2 open-label study, fazirsiran reduced hepatic AAT accumulation as well as the levels of Z-AAT in serum by 85% and this reduction was associated with improved liver enzyme levels as well as decreased liver fibrosis (Strnad 2020). While fazirsiran (also labeled as TAK-999) is currently tested in a placebo-controlled phase 3 trial, belcesiran is currently in a phase 2 trials and no efficacy data for AATD subjects exist. Several other strategies aiming to reduce hepatic AAT production such as CRISPR/Cas approach, gene or RNA editing are at a pre-clinical or early clinical level (Ruiz 2023, Strnad 2023). As a complementary approach, the so called folding correctors aim to promote AAT folding and the consecutive secretion from the liver. In an ideal case, this would improve both lung and liver disease, however, the candidates tested up to date led to only minor increases in serum AAT levels and in part also displayed si gnificant adverse effects (Ruiz 2023). Despite that, AATD constitutes an important model disease promoting the development of several modern therapies, mainly in the area of genetic medicine.

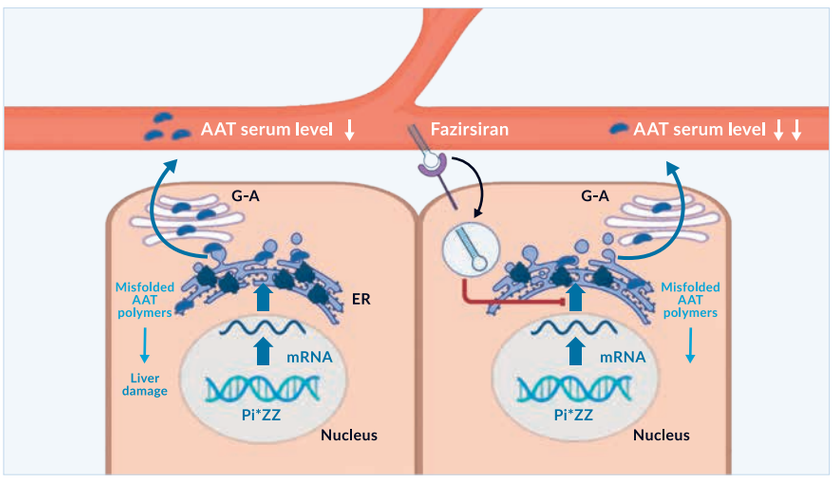

Figure 3. Biological effect of alpha-1 antitrypsin (AAT) mutation and the mode of action of fazirsiran, a small interfering RNA blocking AAT production

Key messages

- Alpha1-antitrypsin (AAT) is a protease inhibitor primarily produced in hepatocytes.
- Mutations in the SERPINA1-gene, encoding AAT, impair AAT production or secretion and result in alpha-1 antitrypsin deficiency (AATD).
- AATD predisposes to liver diseases caused by a proteotoxic "gain-of-function" and lung emphysema/chronic obstructive pulmonary disease caused by a "loss-of-function".
- Over 100 different SERPINA1 mutations are known. The hetero- and homozygous Pi*Z variants (Pi*MZ/Pi*ZZ) constitute the most clinically relevant genotypes.
- Pi*ZZ is the predominant cause of severe AATD.
- Pi*ZZ patients can display prolonged jaundice as newborns or progressive liver fibrosis as adults.
- Pi*MZ patients typically require a second hit such as cystic fibrosis or non-alcoholic/alcoholic liver disease to develop significant liver fibrosis.
- In Pi*ZZ patients, weekly intravenous AAT substitution slows down the progression of lung disease.
- No specific treatment for AATD-associated liver disease exists, but AAT silencing with small interfering RNA showed promising results in a phase II clinical trial.

Future directions

In recent years, our knowledge about AATD-associated liver disease has expanded substantially. Despite this, a large number of people remain undiagnosed and their liver disease is misclassified. Many are recognised only at a stage of decompensated liver cirrhosis that is associated with a very poor prognosis and liver transplantation constitutes the only option. An proactive testing for AATD is needed to allow an early diagnosis. The latter should promote an adjustment of life-style, avoidance of risk factors and a family counseling. Patients with significant lung involvement should be offered an augmentation treatment as well as participation in promising clinical trials. Longitudinal studies are needed to better understand disease development as well as risk of liver cancer.

References

Abul-Husn NS, Cheng X, Li AH, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. N Engl J Med. 2018;378: 1096-106.

Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57: 675-88.

Alam H, Sehgal L, Kundu ST, Dalal SN, and Vaidya MM. Novel function of keratins 5 and 14 in proliferation and differentiation of stratified epithelial cells. Mol Biol Cell. 2011;22: 4068-78.

Banga A, Gildea T, Rajeswaran J, Rokadia H, Blackstone EH, and Stoller JK. The natural history of lung function after lung transplantation for α(1)-antitrypsin deficiency. Am J Respir Crit Care Med, 2014;190: 274-81.

*Blanco I, Bueno P, Diego I, et al. Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. Int J Chron Obstruct Pulmon Dis. 2017;12: 561-69.*

Blanco I, Lipsker D, Lara B, and Janciauskiene S. Neutrophilic panniculitis associated with alpha-1-antitrypsin deficiency: an update. Br J Dermatol. 2016;174: 753-62.

Bornhorst JA, Greene DN, Ashwood ER, and Grenache DG. α1-Antitrypsin phenotypes and associated serum protein concentrations in a large clinical population. Chest. 2013;143: 1000-08.

*Cacciottolo TM, Gelson WT, Maguire G, Davies SE, and Griffiths WJ. Pi*Z heterozygous alpha-1 antitrypsin states accelerate parenchymal but not biliary cirrhosis. Eur J Gastroenterol Hepatol. 2014;26: 412-7.*

Carey EJ, Iyer VN, Nelson DR, Nguyen JH, and Krowka MJ. Outcomes for recipients of liver transplantation for alpha-1-antitrypsin deficiency–related cirrhosis. Liver Transpl. 2013;19: 1370-6.

Cazzola M, Stolz D, Rogliani P, and Matera MG. α(1)-Antitrypsin deficiency and chronic respiratory disorders. Eur Respir Rev.2020;29.

Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386: 360-8.

Christianson JC, Shaler TA, Tyler RE, and Kopito RR. OS-9 and GRP94 deliver mutant alpha1-antitrypsin to the Hrd1-SEL1L ubiquitin ligase complex for ERAD. Nat Cell Biol. 2008;10: 272-82.

Clark VC. Liver transplantation in alpha-1 antitrypsin deficiency. Clin Liver Dis. 2017;21: 355-65.

Clark VC, Marek G, Liu C, et al. Clinical and histologic features of adults with alpha-1 antitrypsin deficiency in a non-cirrhotic cohort. J Hepatol. 2018;69: 1357-64.

Elsensohn AN, Curtis JA, Secrest AM, et al. Alpha-1-antitrypsin deficiency panniculitis presenting with severe anasarca, pulmonary embolus and hypogammaglobulinaemia. Br J Dermatol. 2015;173: 289-91.

Feldman A, and Sokol RJ. Alpha-1-antitrypsin deficiency: an important cause of paediatric liver disease. Lung Health Prof Mag. 2013;4: 8-11.

Ferkingstad E, Oddsson A, Gretarsdottir S, et al. Genome-wide association meta-analysis yields 20 loci associated with gallstone disease. Nat Commun. 2018;9: 5101.

Ferrarotti I, Carroll TP, Ottaviani S, et al. Identification and characterisation of eight novel SERPINA1 Null mutations. Orphanet Journal of Rare Diseases. 2014;9: 172.

Ferrarotti I, Thun GA, Zorzetto M, et al. Serum levels and genotype distribution of α1-antitrypsin in the general population. Thorax. 2012;67: 669-74.

Foreman MG, Wilson C, DeMeo DL, et al. Alpha-1 Antitrypsin PiMZ genotype Is associated with chronic obstructive pulmonary disease in two racial groups. Ann Am Thorac Soc. 2017;14: 1280-87.

Franciosi AN, Ralph J, O'Farrell NJ, et al. Alpha-1 antitrypsin deficiency-associated panniculitis. J Am Acad Dermatol. 2022;87: 825-32.

Franciosi AN, McCarthy C, Carroll TP, and McElvaney NG. Unusual acute sequelae of α1-antitrypsin deficiency: a myriad of symptoms with one common cure. Chest. 2015;148: e136-e38.

Fromme M, Oliverius M, and Strnad P. DEFI-ALFA: The French key to the alpha1 mystery?. Liver Int. 2019;39: 1019-21.

Fromme M, Schneider CV, Pereira V, et al. Hepatobiliary phenotypes of adults with alpha-1 antitrypsin deficiency. Gut. 2022a;71: 415-23.

Fromme M, Schneider CV, Trautwein C, Brunetti-Pierri N, and Strnad P. Alpha-1 antitrypsin deficiency: A re-surfacing adult liver disorder. J Hepatol. 2022b;76: 946-58.

Fu DA, and Campbell-Thompson M. Immunohistochemistry staining for human alpha-1 antitrypsin. Methods Mol Biol. 2017;1639: 139-43.

Greene CM, Marciniak SJ, Teckman J, et al. α1-Antitrypsin deficiency. Nat Rev Dis Primers. 2016;2: 16051.

*Guldiken N, Hamesch K, Schuller SM, et al. Mild iron overload as seen in individuals homozygous for the alpha-1 antitrypsin Pi*Z variant does not promote liver fibrogenesis in HFE knockout mice. Cells. 2019;8.*

*Hamesch K, Mandorfer M, Pereira VM, et al. Liver fibrosis and metabolic alterations in adults with alpha-1-antitrypsin deficiency caused by the Pi*ZZ mutation. Gastroenterology. 2019;157: 705-19.e18.*

Hiller AM, Ekström M, Piitulainen E, Lindberg A, Rönmark E, and Tanash H. Cancer risk in severe alpha-1-antitrypsin deficiency. Eur Respir J. 2022;60.

Iskender I, Sakamoto J, Nakajima D, et al. Human α1-antitrypsin improves early posttransplant lung function: Pre-clinical studies in a pig lung transplant model. J Heart Lung Transplant. 2016;35: 913-21.

Janciauskiene S, Wrenger S, Immenschuh S, et al. The multifaceted effects of alpha1-antitrypsin on neutrophil functions. Frontiers in Pharmacology. 2018;9.

Janciauskiene SM, Bals R, Koczulla R, Vogelmeier C, Köhnlein T, and Welte T. The discovery of α1-antitrypsin and its role in health and disease. Respir Med. 2011;105: 1129-39.

Kim RG, Nguyen P, Bettencourt R, et al. Magnetic resonance elastography identifies fibrosis in adults with alpha-1 antitrypsin deficiency liver disease: a prospective study. Aliment Pharmacol Ther. 2016;44: 287-99.

Kuhn BT, Veale A, Farah H, et al. Recombinant human alpha-1 antitrypsin (AAT) protein INBRX-101 demonstrates potential to achieve lung penetration and normal functional serum AAT levels in patients with AAT deficiency. American Journal of Respiratory and Critical Care Medicine. 2023;207: A4492.

Kuscuoglu D, Bewersdorf L, Wenzel K, et al. Dual proteotoxic stress accelerates liver injury via activation of p62-Nrf2. J Pathol. 2021;254: 80-91.

Lebeaupin C, Vallée D, Hazari Y, Hetz C, Chevet E, and Bailly-Maitre B. Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease. J Hepatol. 2018;69: 927-47.

Lomas DA, Evans DL, Finch JT, and Carrell RW. The mechanism of Z alpha 1-antitrypsin accumulation in the liver. Nature. 1992;357: 605-7.

Lykavieris P, Ducot B, Lachaux A, et al. Liver disease associated with ZZ alpha1-antitrypsin deficiency and ursodeoxycholic acid therapy in children. J Pediatr Gastroenterol Nutr. 2008;47: 623-9.

Mahadeva R, Atkinson C, Li Z, et al. Polymers of Z alpha1-antitrypsin co-localise with neutrophils in emphysematous alveoli and are chemotactic in vivo. Am J Pathol. 2005;166: 377-86.

McElvaney NG, Burdon J, Holmes M, et al. Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). Lancet Respir Med. 2017;5: 51-60.

Merkel PA, Xie G, Monach PA, et al. Identification of functional and expression polymorphisms associated with risk for antineutrophil cytoplasmic autoantibody-associated vasculitis. Arthritis Rheumatol. 2017;69: 1054-66.

Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α(1)-antitrypsin deficiency. Eur Respir J. 2017;50.

Molloy K, Hersh CP, Morris VB, et al. Clarification of the risk of chronic obstructive pulmonary disease in α1-antitrypsin deficiency PiMZ heterozygotes. Am J Respir Crit Care Med. 2014;189: 419-27.

Mostafavi B, Piitulainen E, and Tanash HA. Survival in the Swedish cohort with alpha-1-antitrypsin deficiency, up to the age of 43-45 years. Int J Chron Obstruct Pulmon Dis. 2019;14: 525-30.

Petersen MC, and Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018;98: 2133-223.

Piitulainen E, and Sveger T. Respiratory symptoms and lung function in young adults with severe alpha(1)-antitrypsin deficiency (PiZZ). Thorax. 2002;57: 705-8.

Picker N, Hagiwara M, Baumann S, et all. Liver disease epidemiology and burden in patients with alterations in plasma protein metabolism: German retrospective insurance claims analysis. World J Hepatol. 2023;15(10): 1127-1139

Rahmattulla C, Mooyaart AL, van Hooven D, et al. Genetic variants in ANCA-associated vasculitis: a meta-analysis. Ann Rheum Dis. 2016;75: 1687-92.

Regev A, Guaqueta C, Molina EG, et al. Does the heterozygous state of alpha-1 antitrypsin deficiency have a role in chronic liver diseases? Interim results of a large case-control study. J Pediatr Gastroenterol Nutr. 2006;43 Suppl 1: S30-5.

Ruiz M, Lacaille F, Berthiller J, et al. Liver disease related to alpha1-antitrypsin deficiency in French children: The DEFI-ALPHA cohort. Liver Int. 2019;39: 1136-46.

Ruiz M, Lacaille F, Schrader C, et al. Paediatric and adult liver disease in alpha-1 antitrypsin deficiency. Semin Liver Dis. 2023;43: 258-66.

Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. Chronic Obstr Pulm Dis. 2016;3: 668-82.

*Schneider CV, Hamesch K, Gross A, et al. Liver phenotypes of European adults heterozygous or homozygous for Pi*Z variant of AAT (Pi*MZ vs Pi*ZZ genotype) and noncarriers. Gastroenterology. 2020;159: 534-48.e11.*

Stender S, Kozlitina J, Nordestgaard BG, Tybjærg-Hansen A, Hobbs HH, and Cohen JC. Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci. Nat Genet. 2017;49: 842-47.

Stolk J, Tov N, Chapman KR, et al. Efficacy and safety of inhaled α1-antitrypsin in patients with severe α1-antitrypsin deficiency and frequent exacerbations of COPD. Eur Respir J. 2019;54.

Stockley RA, Titlestad I, Tanash H, et al. Alvelestat, an oral neutrophil elastase inhibitor in alpha-1 antitrypsin deficiency (AATD): result of a phase II trial. American Journal of Respiratory and Critical Care Medicine. 2023;207: A4493.

Strange C, Moseley MA, Jones Y, Schwarz L, Xie L, and Brantly ML. Genetic testing of minors for alpha1-antitrypsin deficiency. Arch Pediatr Adolesc Med. 2006;160: 531-4.

*Strnad P, Buch S, Hamesch K, et al. Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis. Gut. 2019;68: 1099-107.*

Strnad P, McElvaney NG, and Lomas DA. Alpha(1)-Antitrypsin Deficiency. N Engl J Med. 2020;382: 1443-55.

Strnad P, Nuraldeen R, Guldiken N, et al. Broad spectrum of hepatocyte inclusions in humans, animals, and experimental models. Compr Physiol. 2013;3: 1393-436.

Strnad P, and San Martin J. RNAi therapeutics for diseases involving protein aggregation: fazirsiran for alpha-1 antitrypsin deficiency-associated liver disease. Expert Opin Investig Drugs. 2023;32: 571-81.

Sveger T. Liver disease in alpha1-antitrypsin deficiency detected by screening of 200,000 infants. N Engl J Med. 1976;294: 1316-21.

Sveger T, and Eriksson S. The liver in adolescents with alpha 1-antitrypsin deficiency. Hepatology. 1995;22: 514-7.

Tanash HA, Ekström M, Rönmark E, Lindberg A, and Piitulainen E. Survival in individuals with severe alpha 1-antitrypsin deficiency (PiZZ) in comparison to a general population with known smoking habits. Eur Respir J. 2017;50.

Tanash HA, Riise GC, Hansson L, Nilsson PM, and Piitulainen E. Survival benefit of lung transplantation in individuals with severe α1-anti-trypsin deficiency (PiZZ) and emphysema. J Heart Lung Transplant. 2011;30: 1342-7.

Teckman JH. Liver disease in alpha-1 antitrypsin deficiency: current understanding and future therapy. Copd. 2013;10 Suppl 1: 35-43.

Teckman JH, and Blomenkamp KS. Pathophysiology of alpha-1 antitrypsin deficiency liver disease. Methods Mol Biol. 2017;1639: 1-8.

Teckman JH, and Perlmutter DH. Retention of mutant alpha(1)-antitrypsin Z in endoplasmic reticulum is associated with an autophagic response. Am J Physiol Gastrointest Liver Physiol. 2000;279: G961-74.

Wedzicha JAEC-C, Miravitlles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;49.

Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet. 2014;384: 1953-97.

11. AIH

Christian P. Strassburg

(This chapter corresponds to the tenth edition from 2020.)

Autoimmune hepatitis (AIH)

Autoimmune hepatitis (AIH) is a chronic inflammatory disease, in which a loss of tolerance against hepatic tissue is presumed. Autoimmune hepatitis (AIH) was first described as a form of chronic hepatitis in young women showing jaundice, elevated gamma globulins and amenorrhoea, which eventually led to liver cirrhosis (Waldenström 1950). A beneficial effect of steroids was described in the reported patient cohort and thus the groundwork was laid for the first chronic liver disease found to be curable by drug therapy. AIH was later recognised in combination with other extrahepatic autoimmune syndromes, and the presence of antinuclear antibodies (ANA) led to the term lupoid hepatitis (Mackay 1956). Systematic evaluations of the cellular and molecular immunopathology, of the clinical symptoms and of laboratory features has subsequently led to the establishment of autoimmune hepatitis as a clinical entity on its own, which is serologically heterogeneous, treated by an immunosuppressive therapeutic strategy (Strassburg 2000). An established (Alvarez 1999a) and recently simplified (Hennes 2008b) revised scoring system allows for a reproducible and standardised approach to diagnosing AIH in a scientific context but has limitations in everyday diagnostic applications. The use and interpretation of seroimmunological and molecular biological tests permits a precise discrimination of autoimmune hepatitis from other etiologies of chronic hepatitis, in particular from chronic viral infection as the most common cause of chronic hepatitis worldwide (Strassburg 2002). Today, AIH is a treatable chronic liver disease in the majority of cases. Much of the same initial treatment strategies of immunosuppression still represent the standard of care. The largest challenge regarding treatment is the timely establishment of the correct diagnosis.

Definition and diagnosis of autoimmune hepatitis

In 1992, an international panel met in Brighton, UK, to establish diagnostic criteria for AIH because it was recognised that several features

including histological changes and clinical presentation are also prevalent in other chronic liver disorders (Johnson 1993). In this and in a revised report the group noted that there is no single test for the diagnosis of AIH. In contrast, a set of diagnostic criteria was suggested in the form of a scoring system designed to classify patients as having probable or definite AIH (Table 1). According to this approach the diagnosis relies on a combination of indicative features of AIH and the exclusion of other causes of chronic liver diseases. AIH predominantly affects women of any age, and is characterised by a marked elevation of serum globulins, in particular gamma globulins, and circulating autoantibodies. It should be noted that AIH regularly affects individuals older than 40 but should be considered in all age groups (Strassburg 2006). The clinical appearance ranges from an absence of symptoms to a severe or fulminant presentation (Stravitz 2011) and responds to immunosuppressive treatment in most cases. An association with extrahepatic autoimmune diseases such as rheumatoid arthritis, autoimmune thyroiditis, ulcerative colitis and diabetes mellitus and a family history of autoimmune or allergic disorders has been reported (Strassburg 1995).

Autoantibodies are one of the distinguishing features of AIH. The discovery of autoantibodies directed against different cellular targets including endoplasmatic reticulum membrane proteins, nuclear antigens and cytosolic antigens has led to a suggested subclassification of AIH based upon the presence of three specific autoantibody profiles. According to this approach, AIH type 1 is characterised by the presence of antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA) directed predominantly against smooth muscle actin. AIH type 2 is characterised by anti-liver/kidney microsomal autoantibodies (LKM-1) directed against cytochrome P450 CYP2D6 (Manns 1989, Manns 1991) (Figure 1) and with lower frequency against UDP-glucuronosyltransferases (UGT) (Strassburg 1996). AIH type 3 (Manns 1987, Stechemesser 1993) is characterised by autoantibodies against a soluble liver antigen (SLA/LP) identified as UGA suppressor serine tRNA-protein complex (Gelpi 1992, Wies 2000, Volkmann 2001, Volkmann 2010). However, this serological heterogeneity does not influence the decision of whom to treat or of what strategy to employ.

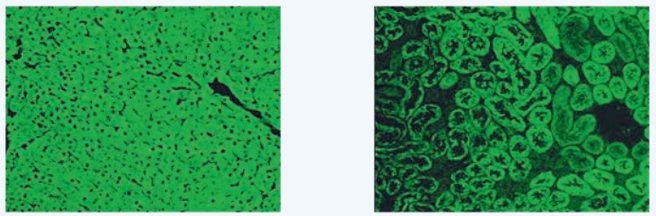

Figure 1. Indirect immunofluorescence showing LKM-1 autoantibodies on rat kidney and liver cryostat sections. Serum of a patient with autoimmune hepatitis type 2. A) Using rat hepatic cryostat sections a homogeneous cellular immunofluorescence staining is visualised excluding the hepatocellular nuclei (LKM-1). B) Typical indirect immunofluorescence pattern of LKM-1 autoantibodies detecting the proximal (cortical) renal tubules but excluding the distal tubules located in the renal medulla, which corresponds to the tissue expression pattern of the autoantigen CYP2D6

Although the histological appearance of AIH is characteristic, there is no specific histological feature that can be used to prove the diagnosis (Dienes 1989). Percutaneous liver biopsy is recommended initially for grading and staging (EASL 2015), as well as for therapeutic monitoring when this is considered necessary for therapeutic planning. Histological features usually include periportal hepatitis with lymphocytic infiltrates, plasma cells, and piecemeal necrosis. With advancing disease, bridging necrosis, panlobular and multilobular necrosis may occur and ultimately lead to cirrhosis. A lobular hepatitis can be present, but is only indicative of AIH in the absence of copper deposits or biliary inflammation. However, biliary involvement does not rule out AIH. The presence of granulomas and iron deposits argue against AIH.

Viral hepatitis should be excluded by the use of reliable, commercially available tests. Hepatitis E is frequently found in AIH patients and should be considered (van Gerven 2016). The exclusion of other hepatotropic viruses such as cytomegalovirus, Epstein-Barr and herpes may only be required in cases suspicious of such infections or if the diagnosis of AIH based on the above-mentioned criteria remains inconclusive.

The probability of AIH usually decreases whenever signs of bile duct involvement are present, such as elevation of alkaline phosphatase, histological signs of cholangiopathy and detection of AMA. If one or more components of the scoring system are not evaluated, only a probable diagnosis can be made (Table 1).

Epidemiology and clinical presentation

Based on limited epidemiological data, the prevalence is estimated to range between 20 to 50 cases per million among the Caucasian population in Western Europe and North America (Jepsen 2015). The prevalence of AIH is similar to that of systemic lupus erythematosus, primary biliary cholangitis and myasthenia gravis, which also have an autoimmune aetiology (Nishioka 1997, Nishioka 1998). Among the Caucasian population in North American and Western European, AIH accounts for up to 20% of cases with chronic hepatitis (Cancado 2000). However, chronic viral hepatitis remains the major cause of chronic hepatitis in most Western societies.

Autoimmune hepatitis is part of the syndrome of chronic hepatitis, which is characterised by sustained hepatocellular inflammation for at least six months and an elevation of ALT and AST of 1.5 times the upper limit of normal. In about 49% of AIH patients an acute onset of AIH is observed and rare cases of fulminant AIH have been reported. In most cases, however, the clinical presentation is not spectacular and is characterised by fatigue, right upper quadrant pain, jaundice and occasionally also by palmar erythema and spider naevi. In later stages, the consequences of portal hypertension dominate, including ascites, bleeding oesophageal varices and encephalopathy. A specific feature of AIH is the association of extrahepatic immune-mediated syndromes including autoimmune thyroiditis, vitiligo, alopecia, nail dystrophy, ulcerative colitis, rheumatoid arthritis, and also diabetes mellitus and glomerulonephritis.

Table 1. International criteria for the diagnosis of AIH (Alvarez 1999)

Parameter	Score
Gender	
Female	+ 2
Male	0
Serum biochemistry	
Ratio of elevation of serum alkaline phosphatase to aminotransferase	
>3.0	– 2
1.5–3	0
<1.5	+ 2
Total serum globulin, γ-globulin or IgG (x upper limit of normal)	
>2.0	+ 3
1.5–2.0	+ 2
1.0–1.5	+ 1
<1.0	0
Autoantibodies (titres by immunfluorescence on rodent tissues)	
Adults	
ANA, SMA or LKM-1	
>1:80	+ 3
1:80	+ 2
1:40	+ 1
<1:40	0
Antimitochondrial antibody	
Positive	– 4
Negative	0
Hepatitis viral markers	+ 3
Negative	– 3
Positive	
History of drug use	
Yes	– 4
No	+ 1
Alcohol (average consumption)	
<25 gm/day	+ 2
>60 gm/day	- 2
Genetic factors: HLA-DR3 or -DR4	+ 1
Other autoimmune diseases	+ 2
Response to therapy	
Complete	+ 2
Relapse	+ 3
Liver histology	
Interface hepatitis	+ 3
Predominant lymphoplasmacytic infiltrate	+ 1
Rosetting of liver cells	+ 1
None of the above	– 5
Biliary changes	– 3
Other changes	– 3
Seropositivity for other defined autoantibodies	+ 2

Interpretation of aggregate scores: definite AIH – greater than 15 before treatment and greater than 17 after treatment; probable AIH – 10 to 15 before treatment and 12 to 17 after treatment

Natural history and prognosis

Data describing the natural history of AIH are scarce. The last placebo-controlled immunosuppressive treatment trial containing an untreated arm was published in 1980 (Kirk 1980). The value of these studies is limited considering that these patients were only screened for then available epidemiological risk factors for viral hepatitis and were not characterised by standardised diagnostic criteria and available virological tests. Nevertheless, these studies reveal that untreated AIH had a very poor prognosis and 5- and 10-year survival rates of 50% and 10% were reported. They furthermore demonstrated that immunosuppressive treatment significantly improved survival.

Up to 30% of adult patients had histological features of cirrhosis at diagnosis. In 17% of patients with periportal hepatitis, cirrhosis developed within five years, but cirrhosis develops in 82% when bridging necrosis or necrosis of multiple lobules is present. The frequency of remission (86%) and treatment failure (14%) are comparable in patients with and without cirrhosis at presentation. Importantly, the presence of cirrhosis does not influence 10-year survival and those patients require a similarly aggressive treatment strategy (Geall 1968, Soloway 1972).

Almost half of the children with AIH already have cirrhosis at the time of diagnosis. Long-term follow-up revealed that few children can completely stop all treatment and about 70% of children receive long-term treatment (Homberg 1987, Gregorio 1997). Most of these patients relapse when treatment is discontinued, or if the dose of the immunosuppressive drug is reduced. About 15% of patients develop chronic liver failure and are transplanted before the age of 18 years.

In elderly patients, a more severe initial histological grade has been reported (Strassburg 2006). The risk of hepatocellular carcinoma varies considerably between the different diseases PBC, PSC and AIH. Particular PSC is regularly complicated by cholangiocarcinoma, gall bladder carcinoma and rarely hepatocellular carcinoma (Zenousi 2014). In contrast, occurrence of HCC in patients with AIH is a rare event and develops only in long-standing cirrhosis.

Who requires treatment?

Autoimmune hepatitis (AIH) is a remarkably treatable chronic liver disease (Manns 2001, Czaja 2010). Untreated, the prognosis of active AIH is dismal, with 5- and 10-year survival rates between 50 and 10% and a well-recognised therapeutic effect exemplified by the last placebo-controlled treatment trials (Soloway 1972, Kirk 1980). For these reasons the indication for treatment is given in any patient who has an established AIH diagnosis, elevations of aminotransferase activities (ALT, AST), an elevation of serum IgG and histological evidence of interface hepatitis or necroinflammatory activity. This has been discussed in the newest version of the AASLD (Manns 2010a) and the EASL (EASL 2015) AIH guidelines. An initial liver biopsy is recommended for confirmation of the diagnosis and for grading and staging. Biopsies are also helpful for observation of aminotransferase activities in serum reflecting inflammatory activity in the liver, which is not always closely correlated.

Who does not require treatment?

Very few patients with an established AIH diagnosis should not be treated. Rare cases, in which the initiation of standard therapy should be weighed against potential side effects, are contraindications with steroids or azathioprine, or for certain other immunosuppressants (see below). In decompensated liver cirrhosis of patients on the waiting list for liver transplantation and in individuals with complete cirrhosis and absent inflammatory activity treatment does not appear beneficial (Manns 2010a, EASL 2015).

Standard treatment strategy

Independent of the clinically- or immunoserologically-defined type of AIH, standard treatment is implemented with predniso(lo)ne alone or in combination with azathioprine. Both strategies are as effective (Manns 2001, Manns 2010a). The basic premise is based upon the findings of studies of almost three decades ago that indicated the effectiveness of steroids in AIH. Since that time, no single multicentre randomised treatment trial in AIH patients has been performed. Advances of alternative treatments are based on small cohorts and on the need to develop strategies for difficult-to-treat patients. The use of prednisone or its metabolite prednisolone, which is used more frequently in Europe, is effective since chronic liver disease does not seem to have an effect on the synthesis of prednisolone from prednisone. The exact differentiation between viral infection and autoimmune hepatitis is important. Treatment of replicative viral hepatitis with corticosteroids must be prevented as well as administration of interferon in AIH, which can lead to dramatic disease exacerbation.

Standard induction treatment and suggested follow-up examinations are summarised in Table 2. Please note the differences in preferred regimen in Europe and the US, which are delineated in the AASLD AIH Guideline

(Manns 2010a). Therapy is usually administered over the course of two years. The decision between monotherapy and combination therapy is guided principally by side effects. Long-term steroid therapy leads to cushingoid side effects. Cosmetic side effects decrease patient compliance considerably (Table 3). Serious complications such as steroid diabetes, osteopenia, aseptic bone necrosis, psychiatric symptoms, hypertension and cataract formation also have to be anticipated in long-term treatment. Side effects are found in 44% of patients after 12 months and in 80% of patients after 24 months of treatment. However, predniso(lo)ne monotherapy is possible in pregnant patients. Azathioprine, on the other hand, leads to a decreased dose of prednisone. It bears a theoretical risk of teratogenicity. In addition, abdominal discomfort, nausea, cholestatic hepatitis, rash and leukopenia can be encountered. These side effects are seen in 10% of patients receiving a dose of 50 mg per day. From a general point of view, a postmenopausal woman with osteoporosis, hypertension and elevated blood glucose would be a candidate for combination therapy. In young women, pregnant women or patients with haematological abnormalities, prednisone monotherapy may be the treatment of choice.

Table 2. Treatment regimen and follow-up examinations of autoimmune hepatitis regardless of autoantibody type

	Monotherapy			Combination therapy		
Prednis(ol)-one	60 mg reduction by 10 mg/week to maintenance of 20 mg/wk reduction by 5 mg to 10 mg find lowest dose in 2.5 mg decrements			30–60 mg reduction as in monotherapy		
Azathioprine	n.a. (maintenance with azathioprine: monotherapy: 2 mg/kg body weight)			1 mg/kg of body weight (Europe) 50 mg (US)		
Examination	Before therapy	During therapy before remission q 4 weeks	Remission on therapy q 3–6 months	Cessation of therapy q 3 weeks (x 4)	Remission post-therapy q 3–6 months	Evaluation of relapse
Physical	+		+	+	+	+
Liver biopsy	+		(+/-)			+
Blood count	+	+	+	+	+	
Aminotrans-ferases	+	+	+	+	+	+
Gamma glutamyl-transferase	+	+	+			
Gamma-globulin	+	+	+	+	+	+
Bilirubin	+	+	+	+	+	+
Coagulation studies	+	+	+	+	+	
Autoanti-bodies	+	+/-				+
Thyroid function tests	+	+/-				+

Table 3. Side effects

Prednis(ol)one	Azathioprine
acne moon-shaped face striae rubra dorsal hump obesity weight gain diabetes mellitus cataracts hypertension	nausea vomiting abdominal discomforts hepatotoxicity rash leukocytopenia teratogenicity (?) oncogenicity (?)

One of the most important variables for treatment success is adherence. The administration of treatment is essential since most cases of relapse are the result of erratic changes of medication and/or dose. Dose reduction is aimed at finding the individually appropriate maintenance dose. Since histology lags 3 to 6 months behind the normalisation of serum parameters, therapy has to be continued beyond the normalisation of aminotransferase levels. Usually, maintenance doses of predniso(lo)ne range between 10 and 2.5 mg. After 12 to 24 months of therapy predniso(lo)ne can be tapered over the course of 4 to 6 weeks to test whether a sustained remission has been achieved. Tapering regimens aiming at withdrawal should be attempted with great caution and only after obtaining a liver biopsy that demonstrates a complete resolution of inflammatory activity. Relapse of AIH and risk of progression to fibrosis is almost universal when immunosuppression is tapered in the presence of residual histological inflammation. Withdrawal should be attempted with caution to prevent recurrence and subsequent fibrosis progression and should be discussed with the patient and closely monitored.

Outcomes of standard therapy can be classified into four categories: remission, relapse, treatment failure and stabilisation.

Remission is a complete normalisation of all inflammatory parameters including histology. The achievement of aminotransferase activities within two-fold of the upper limit of normal is not recommended as treatment goal, rather, normalisation should be aimed at. Remission is ideally the goal of all treatment regimens and ensures the best prognosis. Remission can be achieved in 65 to 75% of patients after 24 months of treatment. Remission can be sustained with azathioprine monotherapy of 2 mg/kg bodyweight (Johnson 1995). This prevents cushingoid side effects. However, side effects such as arthralgia (53%), myalgia (14%), lymphopenia (57%) and myelosuppression (6%) have been observed. Complete remission is not achieved in about 20% of patients and these patients continue to carry a risk of progressive liver injury.

Relapse is characterised by an increase in aminotransferase levels and the reccurrence of clinical symptoms either while on treatment, following tapering of steroid doses to determine the minimally required dose, or, after a complete withdrawal of therapy. Relapse happens in 50% of patients within six months of treatment withdrawal and in 80% after three years. Relapse is associated with progression to cirrhosis in 38% and liver failure in 14%. Relapse requires reinitiation of standard therapy, consideration of dosing as well as diagnosis, and perhaps a long-term maintenance dose with predniso(lo)ne or azathioprine monotherapy.

Treatment failure characterises a progression of clinical, serological and histological parameters during standard therapy. This is seen in about 10% of patients. In these cases the diagnosis of AIH has to be carefully reconsidered to exclude other etiologies of chronic hepatitis. In these patients experimental regimens can be administered or liver transplantation will become necessary.

Stabilisation is the achievement of a partial remission. Since 90% of patients reach remission within three years, the benefit of standard therapy has to be reevaluated in this subgroup of patients. Ultimately, liver transplantation provides a definitive treatment option.

Treatment of elderly patients

The presentation of acute hepatitis, clinical symptoms of jaundice, abdominal pain and malaise have a high likelihood of attracting medical attention and subsequently leading to the diagnosis of AIH (Nikias 1994). More subtle courses of AIH may not lead to clinically relevant signs and may develop unnoticed other than via routine work-up for other problems or via screening programmes. The question of disease onset in terms of initiation of immune-mediated liver disease versus the clinical consequences that become noticeable after an unknown period of disease progression is not easily resolved. Thus, “late onset” AIH may simply just reflect a less severe course of the disease with slower progression to cirrhosis. While LKM positive patients display a tendency towards an earlier presentation, both acute and subtle (earlier and late presentation) variants appear to exist in ANA positive AIH. In practice, the diagnostic dilemma is that AIH is still perceived by many as a disease of younger individuals and that therefore this differential diagnosis is less frequently considered in elderly patients with cryptogenic hepatitis or cirrhosis. Another relevant question resulting from these considerations is the issue of treatment. Standard therapy in AIH consists of steroids alone or a combination with azathioprine. In maintenance therapy azathioprine monotherapy can also be administered but induction with azathioprine alone is not effective. From a general standpoint most internists will use caution when administering steroids to elderly patients, especially in women in whom osteopenia or diabetes may be present.

Recommendations for the treatment of AIH suggest that side effects be weighed against the potential benefit of therapy, and that not all patients with AIH are good candidates for steroid treatment (Manns 2001). Controversy exists surrounding the benefit of therapy in this group of elderly patients. One cohort reported on 12 patients aged over 65 out of a total of 54 AIH patients. Cirrhosis developed after follow-up in 26% irrespective of age although the histological grade of AIH activity was more severe in the elderly group. Although 42% of the patients over 65 did not receive therapy, deaths were only reported in the younger group (Newton 1997). Another cohort of 20 patients aged over 65, reported a longer time to

diagnosis (8.5 vs. 3.5 months) with patients presenting mainly with jaundice and acute onset AIH but that they showed a comparable response rate to immunosuppression to that of younger patients (Schramm 2001). The authors also noted that the prevalence of the HLA A1-B8 allotype was less frequent in older patients suggesting a role for immunogenetics.

This point was further elaborated by a report analysing 47 patients with ANA positive AIH aged 60 years and older, as well as 31 patients aged 30 years and younger in whom DR4+/DR3– prevalence was 47% (older) versus 13% (younger) patients (Czaja 2006). Steroid responsiveness was better in the older patients, in line with previous findings in the same cohort (Czaja 1993). Cirrhosis and extrahepatic immune-mediated syndromes including thyroid and rheumatologic disease (47% vs. 26%) were more prevalent in older AIH patients. However, although more treatment failures were observed in the younger patients (24% vs 5%), the rates of remission, sustained remission and relapse were similar. Interestingly, an assessment of age-stratified prevalence showed an increase after the age of 40 from 15% to over 20%.

From all this data, AIH in elderly patients appears to be characterised by a distinct clinical feature, a distinct immunogenetic profile, favourable response rates and higher rates of cirrhosis present at diagnosis, all of which contribute to the heterogeneity of AIH. A UK cohort of 164 AIH patients included 43 individuals aged 60 years (Al-Chalabi 2006). The different age groups showed no significant differences regarding serum biochemistry, autoantibody titres, time to establishment of diagnosis, and mode of presentation. The authors provided a substratification of patients below and above 40 years of age and reported that older patients had a higher median histological stage and a comparable median grade but that younger patients had more median relapse episodes and a higher median stage at follow-up biopsy. The most distinguishing clinical sign was a higher prevalence of ascites in the older group. However, rates of complete, partial and failed response were similar, and the median number of relapses was higher in younger patients, which nevertheless did not lead to differences in liver-related deaths in either group (12% vs. 15%). In comparison to the study of ANA positive AIH patients from the US (Czaja 2006), the differing findings regarding HLA association are noteworthy. In the UK study there was no differential distribution of HLA DR3 and DR4 and this questions the suggested hypothesis of a primary influence of immunogenetics on the observed clinical distinctions. The reasons for the clinical differences of AIH in older and younger patients are unclear. They may include differences in hepatic blood flow and alterations involving the regulation of cellular immunity during ageing (Talor 1991, Prelog 2006). In summary, these data suggest that AIH in elderly patients should be considered and treated (Strassburg 2006).

Alternative treatments

When standard treatment fails or drug intolerance occurs, alternative therapies such as cyclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil, rapamycin, UDCA, and budesonide can be considered (Table 4). The efficacy of most of these options has not yet been definitively decided and is only reported in small case studies.

Budesonide

Budesonide is a synthetic steroid with high first-pass metabolism in the liver, in principle with limited systemic side effects compared to conventional steroids. In comparison to prednisone the absolute bioavailability of budesonide is less than 6-fold lower (Thalen 1979) but it has an almost 90% first-pass metabolism in the liver, a higher affinity to the glucocorticoid receptor, acts as an anti-inflammatory and immunosuppressive drug and leads to inactive metabolites (6-OH-budesonide, 16-OH-prednisolone). In a pilot study treating 13 AIH patients with budesonide over a period of 9 months the drug was well-tolerated and aminotransferase levels were normalised (Danielson 1994). However, in a second study budesonide therapy was associated with a low frequency of remission and high occurrence of side effects (Czaja 2000) in 10 patients who had previously been treated with azathioprine and steroids and had not reached a satisfactory remission. This study concluded that budesonide was not a good treatment option in those patients. A third study reported that remission was induced with budesonide combination therapy in 12 previously untreated patients (Wiegand 2005). The authors performed kinetic analyses and reported that the area under the curve (AUC) of budesonide was increased in those with high inflammatory activity and cirrhosis. This finding plausibly demonstrates that in patients with portosystemic shunts in portal hypertension the effect of high hepatic first-pass metabolism that would limit typical steroid side effects is reduced.

Table 4. Alternative drugs in autoimmune hepatitis

Compound	Advantage	Disadvantage
Budesonide	High first pass effect Immunosuppressive action Inactive metabolites	Cirrhosis (portosystemic shunts) and side effects
Cyclosporine	Satisfactory experience Potent immunosuppressant Transplant immunosuppressant	Renal toxicity
Tacrolimus	Potent immunosuppressant Transplant immunosuppressant	Renal toxicity
Mycophenolic acid	Favourable toxicity profile Transplant immunosuppressant	Disappointing effectiveness
Cyclophosphamide	Effective	Continuous therapy Hematological side effects

The main advantage of budesonide for the future treatment of autoimmune hepatitis would therefore be to replace prednisone in long-term maintenance therapy and induction therapy to reduce steroid side effects. To this end the first multicentre placebo-controlled randomised AIH treatment trial in 3 decades was performed with a total of 207 non-cirrhotic patients from 30 centres in nine European countries and Israel (Manns 2010b). In this trial 40 mg prednisone (reduction regimen) and azathioprine was compared to 3 mg budesonide (TID initially, reduced to BID) in combination with azathioprine. The data shows that budesonide in combination with azathioprine is efficient in inducing stable remission, is superior in comparison to a standard prednisone tapering regimen beginning with 40 mg per day and leads to a substantially superior profile of steroid-specific side effects. From these data, budesonide has emerged as an alternative first line treatment strategy for non-cirrhotic patients with AIH (Manns 2010b, EASL 2015). Budesonide is licensed for the use in AIH in many countries. Effective treatment of children with budesonide has been reported (Woynarowski 2013).

Deflazacort

This alternative corticosteroid has also been studied for immunosuppression in AIH because of its feature of fewer side effects than conventional glucocorticoids. In a pilot study 15 patients with AIH type 1 were treated with deflazacort, who had been previously treated with prednisone with or without azathioprine until they reached a biochemical remission. Remission was sustained for two years of follow-up. However, the long-term role of second-generation corticosteroids to sustain remission in AIH patients with reduced treatment-related side effects requires further controlled studies (Rebollo Bernardez 1999).

Cyclosporine A

Cyclosporine A (CyA) is a lipophylic cyclic peptide of 11 residues produced by Tolypocladium inflatum that acts on calcium-dependent signaling and inhibits T cell function via the interleukin 2 gene (Strassburg 2008). Out of the alternative AIH drugs considerable experience has been reported with CyA. CyA was successfully used for AIH treatment and was well tolerated (Alvarez 1999b, Debray 1999). The principal difficulty in advocating widespread use of CyA as first line therapy relates to its toxicity profile, particularly with long-term use (increased risk of hypertension, renal insufficiency, hyperlipidaemia, hirsutism, infection, and malignancy) (Alvarez 1999b, Debray 1999, Fernandez 1999, Heneghan 2002).

Tacrolimus

Tacrolimus is a macrolide lactone compound with immunosuppressive qualities exceeding those of CyA. The mechanism of action is similar to that of CyA but it binds to a different immunophilin (Strassburg 2008). The application of tacrolimus in 21 patients treated for one year led to an improvement of aminotransferase and bilirubin levels with a minor increase in serum BUN and creatinine levels (Van Thiel 1995). In a second study with 11 steroid-refractory patients, improvement of inflammation was also observed (Aqel 2004). A recent study demonstrated the effectiveness of tacrolimus in difficult to treat patients (Than 2016). However, although tacrolimus represents a promising immunosuppressive candidate drug, larger randomised trials are required to assess its role in the therapy of AIH.

Mycophenolic acid

Mycophenolate is a noncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the rate-limiting enzymatic step in *de novo* purine synthesis and is widely used in solid organ transplantation. Mycophenolate has a selective action on lymphocyte activation, with marked reduction of both T and B lymphocyte proliferation. In a pilot study, seven patients with AIH type 1 who either did not tolerate azathioprine or did not respond to standard therapy with a complete normalisation of aminotransferase levels, were treated with mycophenolate in addition to

steroids. Normalisation of aminotransferase levels was achieved in five out of seven patients within three months. These preliminary data suggested that mycophenolate may represent a promising treatment strategy for AIH (Richardson 2000). However, in a retrospective study, there was no statistically significant benefit for mycophenolate treatment in 37 patients with AIH and azathioprine failure or intolerance who were treated with mycophenolate (Hennes 2008a). Less than 50% reached remission and in the azathioprine non-responders failure was 75%. Mycophenolate has been demonstrated to be most effective as a second line therapy in patients found to be intolerant to azathioprine. There is some evidence that mycophenolate can be used as first line therapy (Zachou 2016). There is limited data available on the use of mTOR inhibitors such as everolimus in AIH (Ytting 2015).

Cyclophosphamide

The induction of remission with 1–1.5 mg per kg per day of cyclophosphamide in combination with steroids has been reported. However, the dependency of continued application of cyclophosphamide with its potentially severe haematological side effects renders it a highly experimental treatment option (Kanzler 1996).

Anti-TNF α antibodies

There is some emerging evidence that anti-TNF antibodies are capable of inducing remission in AIH patients in whom standard or alternative therapeutic options have been exhausted (Efe 2010, Umekita 2011, Weiler-Norman 2013). However, the development of AIH has also been observed under treatment with anti-TNF antibodies (Ramos-Casals 2008). Future studies will have to define the role of this therapeutic option in difficult-to-treat cases of AIH.

Ursodeoxycholic acid

Ursodeoxycholic acid is a hydrophilic bile acid with putative immunomodulatory capabilities. It is presumed to alter HLA class I antigen expression on cellular surfaces and to suppress immunoglobulin production. Uncontrolled trials have shown a reduction in histological abnormalities, clinical and biochemical improvement but not a reduction of fibrosis in four patients with AIH type 1 (Calmus 1990, Nakamura 1998, Czaja 1999). However, its role in AIH therapy or in combination with immunosuppressive therapy is still unclear.

Other alternative treatment strategies include methotrexate, anti-TNF α antibodies, and rituximab, but there is currently insufficient data on any of these.

Overlap syndromes and treatment

Overlap syndrome describes a disease condition that is not completely defined (Strassburg 2006). A valid definition is difficult (Boberg 2011). It is characterised by the coexistence of clinical, biochemical or serological features of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and depending on the definition, also viral hepatitis C (HCV) (Ben-Ari 1993, Colombato 1994, Duclos-Vallee 1995, Chazouilleres 1998, Angulo 2001, Rust 2008). In adult patients an overlap of PBC and AIH is most frequently encountered although it is unclear whether this is true co-existence of both diseases or an immunoserological overlap characterised by the presence of antinuclear (ANA) as well as antimitochondrial (AMA) antibodies (Poupon 2006, Gossard 2007, Silveira 2007, Al-Chalabi 2008). In many AMA negative patients with a cholestatic liver enzyme profile ANA are present. This has been termed autoimmune cholangiopathy or AMA negative PBC (Michieletti 1994).

Apart from coexisting, autoimmune liver diseases can also develop into each other, i.e., the sequential manifestation of PBC and autoimmune hepatitis. The true coexistence of AIH and PSC has only been conclusively shown in paediatric patients (Gregorio 2001). It can be hypothesised whether a general predisposition toward liver autoimmunity exists which has a cholestatic, a hepatitic and a bile duct facet, which may be variable depending upon unknown host factors. The diagnosis of an overlap syndrome relies on the biochemical profile (either cholestatic with elevated alkaline phosphatase, gamma glutamyltransferase and bilirubin, or hepatitic with elevated aspartate aminotransferase and alanine aminotransferase levels in addition to elevated gamma globulins), the histology showing portal inflammation with or without the involvement of bile ducts, and the autoantibody profile showing AMA or autoantibodies associated primarily with AIH such as liver-kidney microsomal antibodies (LKM), soluble liver antigen antibodies (SLA/LP) or ANA. In cholestatic cases cholangiography detects sclerosing cholangitis. In an overlap syndrome the classical appearance of the individual disease component is mixed with features of another autoimmune liver disease. Immunoglobulins are usually elevated in all autoimmune liver diseases.

Regarding a therapeutic strategy, the leading disease component is

treated. In an overlap syndrome presenting as hepatitis, immunosuppression with prednisone (or combination therapy with azathioprine) is initiated. In cholestatic disease ursodeoxycholic acid is administered. Both treatments can be combined when biochemistry and histology suggest a relevant additional disease component (Chazouilleres 1998). Validated therapeutic guidelines for overlap syndromes are not available. It is important to realise that treatment failure in AIH may be related to an incorrect diagnosis or an overlap syndrome of autoimmune liver diseases (Potthoff 2007). Several studies show that treatment of the AIH component of overlap syndromes is important to avoid progression to cirrhosis (Chazouilleres 2006, Gossard 2007, Silveira 2007, Al-Chalabi 2008).

Liver transplantation

In approximately 10% of AIH patients liver transplantation remains the only life-saving option (Strassburg 2004). The indication for liver transplantation in AIH is similar to that in other chronic liver diseases and includes clinical deterioration, development of cirrhosis, bleeding oesophageal varices and coagulation abnormalities despite adequate immunosuppressive therapy (Neuberger 1984, Sanchez-Urdazpal 1991, Ahmed 1997, Prados 1998, Tillmann 1999, Vogel 2004). There is no single indicator or predictor for the necessity of liver transplantation. Candidates for liver transplant are usually patients who do not reach remission within four years of continuous therapy. Indicators of a high mortality associated with liver failure are histological evidence of multilobular necrosis and progressive hyperbilirubinaemia. In Europe, 4% of liver transplants are for AIH (Strassburg 2009). The long-term results of liver transplantation for AIH are excellent. The five-year survival is up to 92% (Sanchez-Urdazpal 1991, Prados 1998, Ratziu 1999) and well within the range of other indications for liver transplantation. The European liver transplant database indicates 76% survival in five years and 66% survival after 10 years (1647 liver transplantations between 1988 and 2007). When these numbers are considered it is necessary to realise that patients undergoing liver transplantation usually fail standard therapy and may therefore have a reduced life expectancy after liver transplant compared to those who achieve stable complete remission on drug therapy.

Recurrence and *de novo* AIH after liver transplantation

The potential of AIH to recur after liver transplantation is beyond serious debate (Schreuder 2009). The first case of recurrent AIH after liver transplant was reported in 1984 (Neuberger 1984) and was based upon serum biochemistry, biopsy findings and steroid reduction. Studies published over the years indicate that the rate of recurrence of AIH ranges between 10–35%, and that the risk of AIH recurrence is perhaps as high as 68% after five years of follow-up (Wright 1992, Devlin 1995, Götz 1999, Milkiewicz 1999, Manns 2000, Vogel 2004). It is important to consider the criteria upon which the diagnosis of recurrent AIH is based. When transaminitis is chosen as a practical selection parameter many patients with mild histological evidence of recurrent AIH may be missed. It is therefore suggested that all patients with suspected recurrence of autoimmune hepatitis receive a liver biopsy, biochemical analyses of aminotransferases as well as a determination of immunoglobulins and autoantibody titres (Vogel 2004). Significant risk factors for the recurrence of AIH have not yet been identified although it appears that the presence of fulminant hepatic failure before transplantation protects against the development of recurrent disease. Risk factors under discussion include steroid withdrawal, tacrolimus versus cyclosporine, HLA mismatch, HLA type, and LKM-1 autoantibodies. An attractive risk factor for the development of recurrent AIH is the presence of specific HLA antigens that may predispose toward a more severe immunoreactivity. In two studies recurrence of AIH appeared to occur more frequently in HLA DR3 positive patients receiving HLA DR3 negative grafts. However, this association was not confirmed in all studies. There have not been conclusive data to support the hypothesis that a specific immunosuppressive regimen represents a risk factor for the development of recurrent AIH (Gautam 2006). However, data indicate that patients transplanted for AIH require continued steroids in 64% versus 17% of patients receiving liver transplants for other conditions (Milkiewicz 1999).

Based on these results and other studies it would appear that maintenance of steroid medication in AIH patients is indicated to prevent not only cellular rejection but also graft-threatening recurrence of AIH (Vogel 2004). Steroid withdrawal should therefore be performed only with great caution. The recurrence of AIH is an important factor for the probability of graft loss. Apart from HCV and primary sclerosing cholangitis a recent report found AIH recurrence to represent the third most common reason for graft loss (Rowe 2008). Transplanted patients therefore require a close follow-up and possibly an immunosuppressive regimen including steroids, although this is controversial and not backed by prospective studies (Campsen 2008).

In addition to AIH recurrence the development of *de novo* autoimmune hepatitis after liver transplantation has been reported (Kerkar 1998, Jones 1999a, Salcedo 2002). The pathophysiology of this is also elusive. From a treatment point of view *de novo* autoimmune hepatitis, which appears to occur mostly in patients transplanted with PBC but may just be the serendipitous occurrence of AIH, is responsive to steroid treatment (Salcedo 2002).

References

Ahmed M, Mutimer D, Hathaway M, Hubscher S, McMaster P, Elias E. Liver transplantation for autoimmune hepatitis: a 12-year experience. Transplant Proc 1997;29:496.

Al-Chalabi T, Boccato S, Portmann BC, McFarlane IG, Heneghan MA. Autoimmune hepatitis (AIH) in the elderly: a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. J Hepatol 2006;45(4):575-83.

Al-Chalabi T, Portmann BC, Bernal W, McFarlane IG, Heneghan MA. Autoimmune hepatitis overlap syndromes: an evaluation of treatment response, long-term outcome and survival. Aliment Pharmacol Ther 2008;28(2):209-20.

Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatology 1999;31:929-38.

Alvarez F, Ciocca M, Canero-Velasco C, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. J Hepatol 1999;30:222-7.

Angulo P, El-Amin O, Carpenter HA, Lindor KD. Development of autoimmune hepatitis in the setting of long-standing primary biliary cirrhosis. Am J Gastroenterol 2001;96(10):3021-7.

Aqel BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid refractory autoimmune hepatitis. J Clin Gastroenterol 2004;38(9):805-9.

Ben-Ari Z, Dhillon AP, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. Hepatology 1993;18(1):10-5.

Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011;54(2):374-85.

Calmus Y, Gane P, Rouger P, Poupon R. Hepatic expression of class I and class II major histocompatibility complex molecules in primary biliary cirrhosis: effect of ursodeoxycholic acid. Hepatology 1990;11(1):12-5.

Campsen J, Zimmerman MA, Trotter JF, et al. Liver transplantation for autoimmune hepatitis and the success of aggressive corticosteroid withdrawal. Liver Transpl 2008;14(9):1281-6.

Cancado ELR, Porta G. Autoimmune hepatitis in South America. Dordrecht, Boston, London, Kluwer Academic Publishers, 2000.

Chazouilleres O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, Poupon R. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28(2):296-301.

Chazouilleres O, Wendum D, Serfaty L, Rosmorduc O, Poupon R. Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. J Hepatol 2006;44(2):400-6.

Colombato LA, Alvarez F, Cote J, Huet PM. Autoimmune cholangiopathy: the result of consecutive primary biliary cirrhosis and autoimmune hepatitis? Gastroenterology 1994;107(6):1839-43.

Czaja AJ, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. Hepatology 1999;30(6):1381-6.

Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Significance of HLA DR4 in type 1 autoimmune hepatitis. Gastroenterology 1993;105:1502-7.

Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. Hepatology 2006;43(3):532-8.

Czaja AJ, Lindor KD. Failure of budesonide in a pilot study of treatment-dependent autoimmune hepatitis. Gastroenterology 2000;119(5):1312-6.

Czaja AJ, Manns MP. Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. Gastroenterology 2010;139(1):58- 72 e4.

Danielson A, Prytz H. Oral budesonide for treatment of autoimmune chronic hepatitis. Aliment Pharmacol Ther 1994;8:585-90.

Debray D, Maggiore G, Giradet JP, Mallet E, Bernard O. Efficacy of cyclosporin A in children with type 2 autoimmune hepatits. J Pediatr 1999;135:111-4.

Devlin J, Donaldson P, Portman B, et al. Recurrence of autoimmune hepatitis following liver transplantation. Liver Transpl Surg 1995;1:162-5.

Dienes HP, Popper H, Manns M, Baumann W, Thoenes W, Meyer zum Büschenfelde K-H. Histologic features in autoimmune hepatitis. Z Gastroenterol 1989;27:327-30.

Duclos-Vallee JC, Hadengue A, Ganne-Carrie N, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. Corticoresistance and effective treatment by cyclosporine A. Dig Dis Sci 1995;40(5):1069-73.

EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51(2):237-67. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63(4):971-1004.

Efe C, Purnak T, Ozaslan E. Anti TNF-alpha therapy can be a novel treatment option in patients with autoimmune hepatitis. Aliment Pharmacol Ther 2010;32(1):115; author reply 6-7.

Fernandez NF, Redeker AG, Vierling JM, Villamil FG, Fong T-L. Cyclosporine therapy in patients with steroid resistant autoimmune hepatitis. Am J Gastroenterol 1999;94:241-8.

Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. Liver Transpl 2006;12(12):1813-24.

Geall MG, Schoenfield LJ, Summerskill WHJ. Classification and treatment of chronic active liver disease. Gastroenterology 1968;55:724-9.

Gelpi C SE, Rodriguez-Sanchez JL. Autoantibodies against a serine tRNA-protein complex implicated in cotranslational selenocysteine insertion. Proc Natl Acad Sci U S A 1992;89(20):9739-43.

Gossard AA, Lindor KD. Development of autoimmune hepatitis in primary biliary cirrhosis. Liver Int 2007;27(8):1086-90.

Götz G, Neuhaus R, Bechstein WO, et al. Recurrence of autoimmune hepatitis after liver transplantation. Transplant Proc 1999;31:430-1.

Gregorio GV, Portman B, Reid F, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology 1997;25:541-7.

Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001;33(3):544-53.

Heneghan MA, McFarlane IG. Current and novel immunosuppressive therapy for autoimmune hepatitis. Hepatology 2002;35(1):7-13.

Hennes EM, Oo YH, Schramm C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? Am J Gastroenterol. 2008;103(12):3063-70.

Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48(1):169-76.

Jepsen P, Gronbaek L, Vilstrup H. Worldwide Incidence of Autoimmune Liver Disease. Dig Dis. 2015;33 Suppl 2:2-12.

Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med. 1995;333(15):958-63.

Johnson PJ, McFarlane IG. Meeting report: International autoimmune hepatitis group. Hepatology 1993;18:998-1005.

Jones DE, James OF, Portmann B, Burt AD, Williams R, Hudson M. Development of autoimmune hepatitis following liver transplantation for primary biliary cirrhosis. Hepatology 1999;30(1):53-7.

Kanzler S, Gerken G, Dienes HP, Meyer zum Büschenfelde K-H, Lohse AW. Cyclophosphamide as alternative immunosuppressive therapy for autoimmune hepatitis - report of three cases. Z Gastroenterol 1996;35:571-8.

Kerkar N, Hadzic N, Davies ET, et al. De-novo autoimmune hepatitis after liver transplantation. Lancet 1998;351(9100):409-13.

Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. Gut 1980;21:7893.

Mackay IR, Taft LI, Cowling DC. Lupoid hepatitis. Lancet 1956;2:1323-6.

Manns M, Gerken G, Kyriatsoulis A, Staritz M, Meyer zum Büschenfelde KH. Characterisation of a new subgroup of autoimmune chronic active hepatitis by autoantibodies against a soluble liver antigen. Lancet 1987;1(8528):292-4.

Manns MP, Bahr MJ. Recurrent autoimmune hepatitis after liver transplantation - when non-self becomes self. Hepatology 2000;32(4):868-70.

Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010;51(6):2193-213.

Manns MP, Griffin KJ, Sullivan KF, Johnson EF. LKM-1 autoantibodies recognize a short linear sequence in P450IID6, a cytochrome P-450 monooxygenase. J Clin Invest 1991;88:1370-8.

Manns MP, Johnson EF, Griffin KJ, Tan EM, Sullivan KF. Major antigen of liver kidney microsomal antibodies in idiopathic autoimmune hepatitis is cytochrome P450db1. J Clin Invest 1989;83:1066-72.

Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges. Gastroenterology 2001;120(6):1502-17.

Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010;139(4):1198-206.

Michieletti P, Wanless IR, Katz A, et al. Antimitochondrial antibody negative primary biliary cirrhosis: a distinct syndrome of autoimmune cholangitis. Gut 1994;35(2):260-5.

Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. Transplantation 1999;68(2):253-6.

Nakamura K, Yoneda M, Yokohama S, et al. Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis [see comments]. J Gastroenterol Hepatol 1998;13(5):490-5.

Neuberger J, Portmann B, Calne R, Williams R. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. Transplantation 1984;37(4):363-5.

Newton JL, Burt AD, Park JB, Mathew J, Bassendine MF, James OF. Autoimmune hepatitis in older patients. Age Ageing 1997;26(6):441-4.

Nikias GA, Batts KP, Czaja AJ. The nature and prognostic implications of autoimmune hepatitis with acute presentation. J Hepatol. 1994;21:866-71.

Nishioka M, Morshed SA, Kono K, et al. Frequency and significance of antibodies to P450IID6 protein in Japanese patients with chronic hepatiis C. J Hepatol 1997;26:992-1000.

Nishioka M, Morshed SA, McFarlane IG. Geographical variation in the frequency and characteristics of autoimmune liver diseases. Amsterdam: Elsevier; 1998.

Potthoff A, Deterding K, Trautwein C, et al. Steroid treatment for severe acute cryptogenic hepatitis. Z Gastroenterol 2007;45(1):15-9.

Poupon R, Chazouilleres O, Corpechot C, Chrétien Y. Development of autoimmune hepatitis in patients with typical primary biliary cirrhosis. Hepatology. 2006;44(1):85-90.

Prados E, Cuervas-Mons V, De La Mata M, et al. Outcome of autoimmune hepatitis after liver transplantation. Transplantation 1998;66:1645-50.

Prelog M. Aging of the immune system: a risk factor for autoimmunity? Autoimmun Rev 2006;5(2):136-9.

Ramos-Casals M, Brito-Zeron P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol 2008;22(5):847-61.

Ratziu V, Samuel D, Sebagh M, et al. Long-term follow-up after liver transplantation for autoimmune hepatitis: evidence of recurrence of primary disease. J Hepatol 1999;30(1):131-41.

Rebollo Bernardez J, Cifuentes Mimoso C, Pinar Moreno A, et al. Deflazacort for long-term maintenance of remission in type I autoimmune hepatitis. Rev Esp Enferm Dig 1999;91(9):630-8.

Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. J Hepatol 2000;33(3):371-5.

Rowe IA, Webb K, Gunson BK, Mehta N, Haque S, Neuberger J. The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. Transpl Int 2008;21(5):459-65.

Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. World J Gastroenterol 2008;14(21):3368-73.

Salcedo M, Vaquero J, Banares R, et al. Response to steroids in de novo autoimmune hepatitis after liver transplantation. Hepatology 2002;35(2):349-56.

Sanchez-Urdazpal L, Czaja AJ, Van Holk B. Prognostic features and role of liver transplantation in severe corticoid-treated autoimmune chronic active hepatitis. Hepatology 1991;15:215-21.

Schramm C, Kanzler S, zum Büschenfelde KH, Galle PR, Lohse AW. Autoimmune hepatitis in the elderly. Am J Gastroenterol

2001;96(5):1587-91.

Schreuder TC, Hubscher SG, Neuberger J. Autoimmune liver diseases and recurrence after orthotopic liver transplantation: what have we learned so far? Transpl Int 2009;22(2):144-52.

Silveira MG, Talwalkar JA, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary biliary cirrhosis: long-term outcomes. Am J Gastroenterol 2007;102(6):1244-50.

Soloway RD, Summerskill WH, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology 1972;63(5):820-33.

Stechemesser E, Klein R, Berg PA. Characterization and clinical relevance of liver-pancreas antibodies in autoimmune hepatitis. Hepatology 1993;18:1-9.

Strassburg CP, Bahr MJ, Becker T, Klempnauer J, Manns MP. Progress in immunosuppression. Chirurg 2008;79(2):149-56.

Strassburg CP, Becker T, Klempnauer J, Manns MP. Liver transplantation: deciding between need and donor allocation. Internist (Berl) 2004;45(11):1233-45.

Strassburg CP, Manns MP. Liver transplantation: indications and results. Internist (Berl) 2009.

Strassburg CP, Manns MP. Primary biliary liver cirrhosis and overlap syndrome. Diagnosis and therapy. Internist (Berl) 2004;45(1):16-26. Strassburg CP, Manns MP. Autoantibodies and autoantigens in autoimmune hepatitis. Semin Liver Dis 2002;22(4):339-52.

Strassburg CP, Manns MP. Autoimmune hepatitis in the elderly: what is the difference? J Hepatol 2006;45(4):480-2. Strassburg CP, Manns MP. Autoimmune hepatitis versus viral hepatitis C. Liver 1995;15:225-32.

Strassburg CP, Obermayer-Straub P, Alex B, et al. Autoantibodies against glucuronosyltransferases differ between viral hepatitis and autoimmune hepatitis. Gastroenterology 1996;111(6):1576-86.

Strassburg CP, Obermayer-Straub P, Manns MP. Autoimmunity in liver diseases. Clin Rev Allergy Immunol 2000;18(2):127-39. Strassburg CP. Autoimmune liver diseases and their overlap syndromes. Praxis (Bern 1994) 2006;95:1363-81.

Stravitz RT, Lefkowitch JH, Fontana RJ, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011;53(2):517-26.

Talor E, Rose NR. Hypothesis: the aging paradox and autoimmune disease. Autoimmunity 1991;8(3):245-9.

Thalen A, Brattsand R. Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. Arzneimittelforschung 1979;29(11):1687-90.

Than NN, Wiegard C, Weiler-Normann C, et al. Long-term follow-up of patients with difficult to treat type 1 autoimmune hepatitis on Tacrolimus therapy. Scand J Gastroenterol. 2016;51(3):329-36.

Tillmann HL, Jackel E, Manns MP. Liver transplantation in autoimmune liver disease-selection of patients. Hepatogastroenterology 1999;46(30):3053-9.

Umekita K, Miyauchi S, Ueno S, et al. Improvement of rheumatoid arthritis and autoimmune hepatitis in a patient treated with the tumour necrosis factor inhibitor, etanercept. Intern Med 2011;50(11):1245-9.

Van Gerven NM, van der Eijk AA, Pas SD, et al. Seroprevalence of Hepatitis E Virus in Autoimmune Hepatitis Patients in the Netherlands. J Gastrointestin Liver Dis. 2016;25(1):9-13.

Van Thiel DH, Wright H, Carroll P, et al. Tacrolimus: A potential new treatment for autoimmune chronic active hepatitis: results of an open- label preliminary trial. Am J Gastroenterol 1995;90:771-6.

Vogel A, Heinrich E, Bahr MJ, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant 2004;18(1):62-9.

Volkmann M, Luithle D, Zentgraf H, et al. SLA/LP/tRNP((Ser)Sec) antigen in autoimmune hepatitis: identification of the native protein in human hepatic cell extract. J Autoimmun 2010;34(1):59-65.

Volkmann M, Martin L, Baurle A, et al. Soluble liver antigen: isolation of a 35-kd recombinant protein (SLA-p35) specifically recognizing sera from patients with autoimmune hepatitis. Hepatology 2001;33(3):591-6.

Waldenström J. Leber, Blutproteine und Nahrungseiweisse. Dtsch Gesellsch Verd Stoffw 1950;15:113-9.

Weiler-Normann C, Schramm C, Quaas A, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. J Hepatol. 2013;58(3):529-34.

Wiegand J, Schuler A, Kanzler S, et al. Budesonide in previously untreated autoimmune hepatitis. Liver Int 2005;25(5):927-34.

Wies I, Brunner S, Henninger J, et al. Identification of target antigen for SLA/LP autoantibodies in autoimmune hepatitis [see comments]. Lancet 2000;355(9214):1510-5.

Woynarowski M, Nemeth A, Baruch Y, et al. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. The Journal of paediatrics 2013;163(5):1347-53.e1.

Wright HL, Bou-Abboud CF, Hassanenstein T, et al. Disease recurrence and rejection following liver transplantation for autoimmune chronic active liver disease. Transplantation 1992;53:136-9.

Ytting H, Larsen FS. Everolimus treatment for patients with autoimmune hepatitis and poor response to standard therapy and drug alternatives in use. Scand J Gastroenterol. 2015;50(8):1025-31.

Zachou K, Gatselis NK, Arvaniti P, et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. Aliment Pharmacol Ther. 2016;43(10):1035-47.

Zenouzi R, Weismuller TJ, Hubener P, et al. Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association 2014;12(10):1733-8.

12. Primary sclerosing cholangitis

Tobias J. Weismüller

Introduction

Primary sclerosing cholangitis (PSC) is a chronic progressive autoimmune cholestatic liver disease characterised by fibrotic strictures of the intra- and/or extrahepatic bile ducts. This causes the pathognomonic image of pearl cord-like bile duct dilatations in the cholangiogram. In a relevant number of patients, but not in all, biliary liver fibrosis and eventually cirrhosis occur as the disease progresses (Karlsen 2017, Weismuller 2017).

The disease is typically diagnosed in young patients (median age at diagnosis: approximately 40 years) and about 2/3 of patients are male. The epidemiology of PSC varies significantly between different geographic regions with highest incidences seen in Northern Europe and North America (Trivedi 2022). Incidence of PSC appears to be increasing according to epidemiological studies from the Netherlands and Sweden (Boonstra 2013, Lindkvist 2010) and is in these areas approximately 1/100000/year while the prevalence ranges around 10 / 100 000. There is a clear association with inflammatory bowel disease (IBD). In Northern Europe and North America, the prevalence of IBD in patients with PSC is 60–80%, with ulcerative colitis (CU) as the dominating subtype in more than 80% (Tsaitas, Semertzidou, and Sinakos 2014).

Diagnosis of PSC

PSC should be suspected in individuals with clinical and/or biochemical markers of cholestasis, especially when IBD is present; a detailed cholangiogram showing the characteristic biliary tract changes confirms the diagnosis, when secondary causes of sclerosing cholangitis and other biliary diseases have been excluded (Figure 1).

Symptoms at initial diagnosis of PSC include nonspecific general symptoms such as fatigue, lassitude, right upper abdominal pain, or weight loss, as well as clinical signs of cholestasis such as jaundice and pruritus, which can be accompanied by fever and chills in case of acute bacterial cholangitis. However, more than one third of patients are asymptomatic at initial diagnosis and are only incidentally diagnosed with elevated

cholestasis parameters during routine laboratory checks. In particular, alkaline phosphatase (AP) is elevated three- to tenfold in 90% of patients, whereas aminotransferases are not or only minimally elevated. Serum bilirubin can be seen as a marker of late-stage disease, which increases when the fibrotic inflammation of the biliary tract leads to high grade strictures or to severe ductopenia ("pruning"). Autoantibodies do not play a role to confirm the diagnosis of PSC itself but to rule out variant syndromes or other autoimmune or cholestatic liver diseases. Physical examination at initial diagnosis rarely shows hepatomegaly or splenomegaly (Broome 1996, Tischendorf 2007) but results in normal findings in most patients. Abdominal ultrasound also frequently shows normal findings in early PSC, but sometimes liver parenchymal changes, cholestasis, or hilar lymphadenopathy can already be apparent.

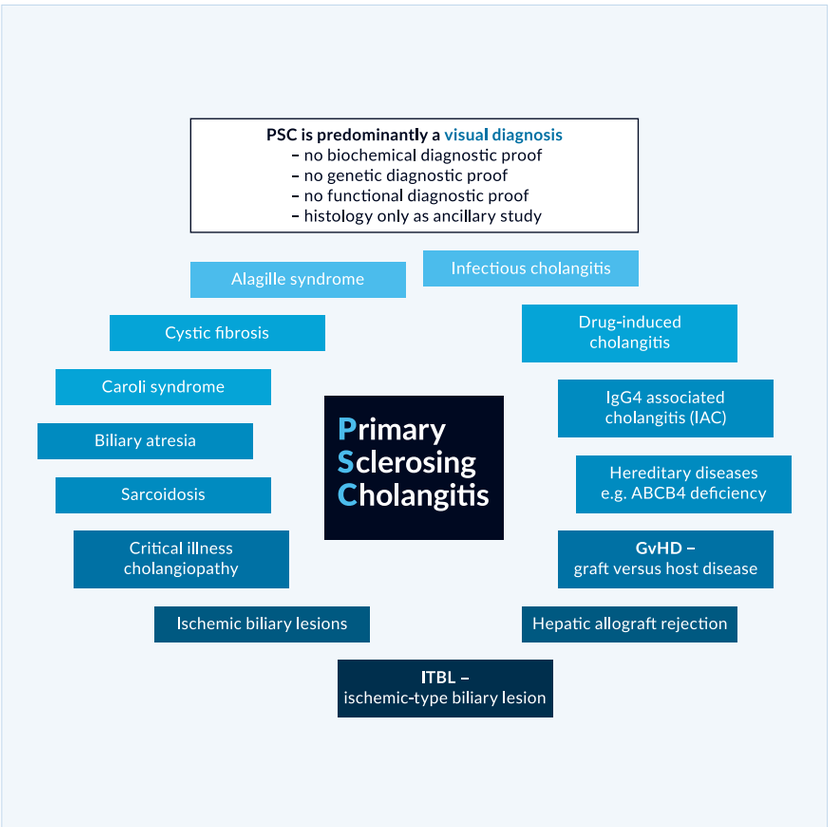

Figure 1. Differential diagnosis of PSC: Diseases of the liver and those affecting the liver, which can lead to features of sclerosing cholangitis. The differential diagnostic considerations in visually apparent sclerosing cholangitis cover a diverse array of conditions apart from PSC.

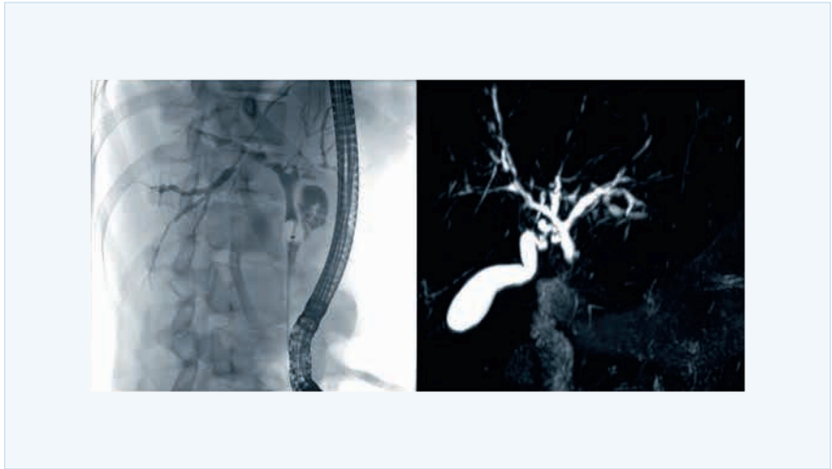

Figure 2. Cholangiogram in PSC: ERC (left image) or MRI / MRCP (right image).

According to current guidelines (European Association for the Study of the Liver 2022, Bowlus 2023) detailed imaging of the extra- and intrahepatic bile ducts by magnetic resonance cholangiography (MRC) is the crucial step in the diagnosis of PSC. The cholangiogram shows the characteristic bile duct changes with multifocal segmental strictures and consecutive dilatations of the intra- and/or extrahepatic bile ducts (Figure 2). Due to the much higher risk potential (especially iatrogenic pancreatitis and cholangitis) endoscopic retrograde cholangiography (ERC) is limited to cases when a therapeutic or diagnostic biliary intervention is indicated. Furthermore, MRI offers the advantage of imaging the hepatic parenchyma and visualising dilated bile duct segments proximal to complete stenoses.

Only in patients in early stages or in rare cases when image quality is limited by metallic implants or ascites, diagnostic ERC can be performed after weighing the risks and the expected therapeutic consequences.

Liver biopsy should be performed when high-quality MRI with MRCP is normal but elevated serum markers of cholestasis, especially in patients with IBD, raise the suspicion of small-duct PSC. Typical histopathological findings include "onion-skin"-like periductal fibrosis, fibroobliterative cholangitis, ductular reaction or ductopenia, periductal and sometimes also portal inflammation. Liver biopsy can also be considered in patients with markedly elevated transaminases, high IgG levels, and positive autoantibodies to corroborate the diagnosis of the variant syndrome of PSC with features of autoimmune hepatitis (AIH) (Boberg 2011).

Figure 3 summarises the diagnostic algorithm, when PSC is suspected.

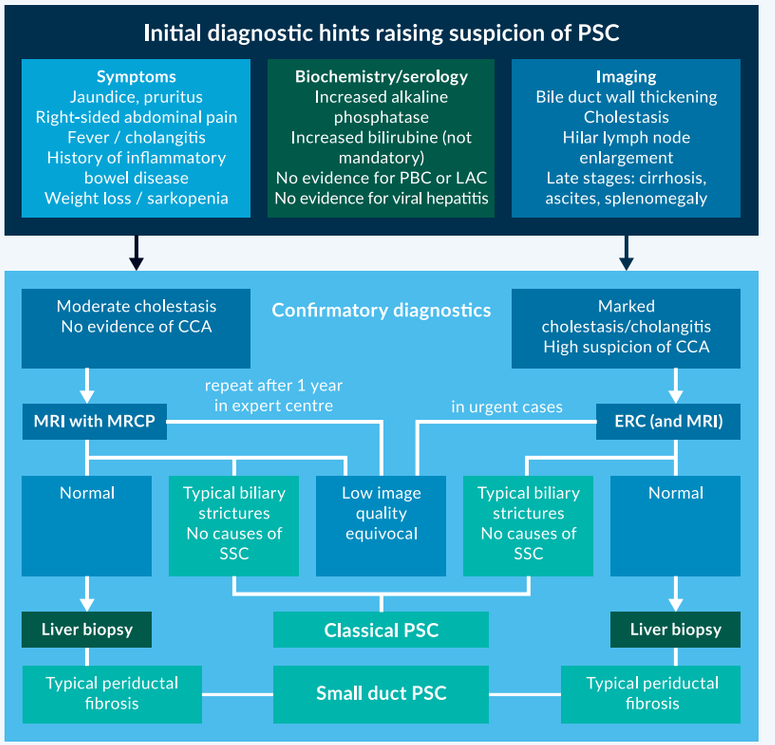

Figure 3. Diagnostic algorithm for PSC.
Abbreviations: PSC: Primary Sclerosing Cholangitis, PBC: Primary Biliary Cholangitis, IAC: IgG4 associated cholangitis, CCA: Cholangiocarcinoma, MRI: Magnetic Resonance Imaging, MRCP: Magnetic Resonance Cholangiopancreaticography, ERC: Endoscopic Retrograde Cholangiography

Variant Syndromes and secondary causes of sclerosing cholangitis

Small-duct PSC (sdPSC) is a variant subtype which is diagnosed in about 4% of all PSC patients, when typical biochemical and histological features of PSC are present while a high-quality cholangiogram shows normal bile ducts (Kaplan 2007, Weismuller 2017, Bjornsson 2008). Other cholangiopathies such as PBC, ABCB4 deficiency, sarcoidosis, eosinophilic or IgG4-associated cholangitis must be excluded serologically and/or histologically. As compared with classical "large-duct" PSC this variant has a more benign disease course with only a minority of patients developing large-duct involvement and with a much lower risk of progression to end-stage liver disease or to cholangiocarcinoma.

PSC with features of AIH or so-called **PSC-AIH-Overlap** is another variant subtype that can be assumed when patients with a diagnosis of PSC show biochemical, serological, and/or histological features that overlap with those of AIH before or at the time of diagnosis of PSC, or later during the disease. Whether this is an independent syndrome or merely the coexistence of two separate diseases is still controversial. Applying the revised IAIHG scoring system 6–9% of PSC patients meet the diagnostic criteria of at least probable AIH (Boberg 2011, Weismuller 2017) and in paediatric PSC the frequency of features of AIH is even higher than 30% (Deneau 2017). According to the European Association for the Study of the Liver (EASL) clinical practice guidelines (European Association for the Study of the Liver 2022) a liver biopsy should be considered in PSC patients with alanine aminotransferase (ALT) levels five times the upper limit of normal (>5x ULN) and/or serum IgG levels > 1.5x ULN. If histology shows moderate to severe interface hepatitis in a patient with established PSC the co-existence or overlap with AIH can be diagnosed. Although there is not much systematic evidence regarding the course of the PSC-AIH-variant and its treatment options, management of the AIH component is based on the recommendations for the management of classical AIH.

IgG4-associated cholangitis (IAC) is the biliary phenotype of IgG4 related diseases (IgG4-RD), a systemic disease characterised by involvement of different organs, especially exocrine glands like pancreas but also retroperitoneum and bile ducts. The diagnosis of IgG4-RD is based on serology with markedly elevated IgG4-levels (>4 times) and on histology, imaging, other organ involvement and response to therapy (HISORt criteria). The biliary phenotype impressively resembles that of PSC, both in cholangiography and in clinical presentation (Lohr 2022). Since IAC in contrast to PSC responds well to corticosteroids it is crucial to check IgG4 serum levels in every patient with a first diagnosis of PSC and to exclude involvement of other organs.

IAC must be distinguished from another subtype of PSC in which borderline elevated serum levels of IgG4 can be detected without the HISORt criteria for a diagnosis of IAC being met. Evidence is accumulating in recent years that this subgroup of PSC with elevated IgG4-values has a significantly inferior transplant-free survival (Mendes 2006, Zhou 2021). It is not yet clear whether this subgroup would also benefit from anti-inflammatory treatment with corticosteroids.

There is a large number of different aetiologies of bile duct damage, which all share morphologic features of sclerosing cholangitis and should always be considered before the diagnosis of PSC can be made. Secondary sclerosing cholangitis can be caused by ischemic or traumatic bile duct injuries, as well as different immunologic or infectious diseases, which are summarised in Figure 1.

Clinical course of PSC and risk assessment

The clinical course of PSC is generally characterised by an increased frequency of episodic cholestatic symptoms such as jaundice, pruritus, and right-sided upper abdominal pain. Moreover, inflammatory-fibrotic strictures of the large and middle-sized bile ducts favour the development of ascending cholangitis up to severe cholangiosepsis. In advanced disease stage – but not in every patient – chronic cholangitis leads to biliary hepatic fibrosis and liver cirrhosis with complications of portal hypertension such as oesophageal varices and ascites. The overall disease course in PSC is highly variable, with some patients requiring transplantation shortly after diagnosis, while others live almost without symptom for decades. Depending on whether data from transplant centres (Broome 2002, Tischendorf 2007) or from large epidemiologic studies are analysed (Boonstra 2013), the median transplant-free survival after initial diagnosis is estimated between 10 and 20 years. Only about one third of patients die of liver failure, whereas carcinoma of the biliary tract or colon is the cause of death in more than 40% of patients (Bergquist 2002, Boonstra 2013, Claessen 2009).

Assessment of individual prognosis is difficult in a disease like PSC with a highly variable and often relapsing course. Several cohort studies identified the following clinical parameters as predictors of an unfavourable course with reduced transplant-free survival: older age at first diagnosis, coexisting ulcerative colitis, coexisting extrahepatic and extraintestinal autoimmune disease, splenomegaly, hepatomegaly, variceal hemorrhage, high-grade ("dominant") strictures in the cholangiogram, extent of cholangiographic bile duct changes (Amsterdam score), liver elastography and extent of histologic changes (De Vries 2017, Kim 2000, Ponsioen 2010, Rupp, Tischendorf 2007, Corpechot 2014, Eaton 2016). In addition, the following biomarkers have been shown to be useful for prognostic assessment: Alkaline phosphatase (AP), bilirubin, aspartate aminotransferase (AST), and serum albumine (de Vries, Beuers, and Ponsioen 2015). Several prognostic scores for estimating prognosis in PSC have been developed: The revised Mayo-Risk-Score (Kim 2000) was the first risk score and calculates survival probability at 1 and 4 years based on patient age, bilirubine, albumine, AST and history of variceal bleeding. The Amsterdam-Oxford-Model (de Vries 2018) has also been validated in independent cohorts and calculates long-term overall survival at 5-, 10- and 15 years based on bilirubine, albumine, AST, alkaline phosphatase, platelets, large-duct-involvement and age at first diagnosis.

PSC and IBD

There is a clear association of PSC with IBD, and especially ulcerative colitis as the predominating subtype. IBD associated with PSC has typical features, particularly right-sided colitis with frequent "backwash ileitis" and rectal sparring (Loftus 2005). Conversely, PSC was found in 0.75% to 5.4% of patients with ulcerative colitis and in 1.2% to 3.4% of patients with Crohn's disease (Gizard 2014). Usually, IBD is diagnosed first and PSC later in the course of the disease or both diseases are diagnosed almost simultaneously; but sometimes IBD can manifest even years after the initial diagnosis of PSC. In order not to miss a clinically inapparent IBD, it is recommended that a complete ileocolonoscopy with random stepwise biopsies is always performed following the initial diagnosis of PSC.

The pathophysiological cause of this striking association of PSC and IBD is thought to be an aberrant homing of lymphocytes activated in the intestine, which migrate via the endothelium of the liver sinusoids into the liver and are involved in the establishment of a chronic hepatobiliary inflammatory process (Adams and Eksteen 2006).

Nevertheless, activity of both diseases does not show a regular pattern and it cannot be postulated that high activity of one disease leads to higher (or lower) activity of the other one. Furthermore, effective treatment of IBD does not have an impact on the course of PSC, even not with the α4β7-integrin-antagonists vedolizumab (Lynch 2020). Therefore, treatment strategies for IBD associated with PSC do not differ from those for IBD without PSC, with one exception: The risk of colorectal carcinoma in IBD patients is about 5 times higher and the carcinomas occur earlier in the course of the disease and are more frequently localised on the right side. Hence, international guidelines recommend yearly surveillance colonoscopies in all patients with IBD, as soon as additional PSC has been diagnosed (Magro 2017).

PSC as a risk factor for hepatobiliary malignancies

Even more than the risk of colorectal cancer, the risk of hepatobiliary malignancies is dramatically increased in PSC. According to population-based studies (de Valle, Bjornsson, and Lindkvist 2012, Boonstra 2013), the cumulative 10-year risk of cholangiocarcinoma is 6%-11%. In the very large cohort of the International PSC Study Group, recruiting mainly from tertiary centres, the annual incidence rate of hepatobiliary malignancies was 1.4/100 Pat. years. The risk for hepatobiliary malignancies was even higher in male patients, in patients with ulcerative colitis (compared to no

IBD or Crohn's disease) and in patients with classical PSC (compared to the small-duct variant or the PSC/AIH-variant) (Weismuller 2017). In addition to the more than hundred-fold increased risk of cholangiocarcinoma of the bile ducts including the gallbladder, a Swedish study also found an increased risk of pancreatic cancer (Bergquist 2002). Hepatocellular carcinomas (HCC), on the other hand, occurs comparatively rarely in PSC even in a cirrhotic stage of the disease (Zenouzi 2014).

Role of surveillance strategies

Given the markedly increased risk of malignancy, surveillance strategies for the early detection of carcinomas with the aim of enabling curative therapy are an important aspect in the management of PSC (Figure 4). Annual Colonoscopies to screen for colorectal neoplasia in all PSC patients with IBD are established and reduce significantly the colorectal cancer associated mortality (Boonstra 2013).

For cholangiocarcinoma, however, current publications on surveillance seem to paint a contradictory picture. In a prospective multicentre study from Sweden annual imaging with MRI/MRCP followed by ERCP and cytology/histology was not able to detect malignancy early enough to improve long-term survival (Villard 2023). In another international retrospective study including 2975 PSC-patients from 28 centres, different surveillance strategies were compared. With regular scheduled imaging overall survival improved and patients diagnosed with hepatobiliary malignancy were more likely to be treated with potentially curative therapies (surgical resection or liver transplantation) (Bergquist 2023).

The diagnosis of cholangiocarcinoma in a curable stage (CC) remains a challenging task because imaging studies have a limited sensitivity due to the often intramural growth pattern of CCA in PSC. Therefore, CCA are visible as stenosis or tumour only in late stages precluding curative therapeutic approaches. Furthermore, stenoses upon cholangiography may be caused by inflammatory activity as well as neoplasia, so that also biochemical tests and intraductal biopsy procedures have a low sensitivity and specificity. Newer techniques with direct visualisation through single-operator cholangioscopy might be a promising approach.

Despite those difficulties in diagnosing CCA in PSC, international practice guidelines recommend yearly high quality MRI with MRCP and/or liver ultrasound (Figure 4). Furthermore, a clinical evaluation every 6-12 months and serum liver-related tests including bilirubin, ALP, AST, platelets, and PT are recommended. Carbohydrate antigen 19-9 (CA 19-9) is not suggested for surveillance but should be done in case of suspected CCA. When a high-grade stricture is suspicious for CCA, invasive evaluation with ERC and forceps biopsy or brush cytology should be performed. Fluorescence in situ hybridisation (FISH) or equivalent chromosomal assessments can be considered when brush cytology and/or histology are equivocal. Due to their low sensitivity strictures should be reevaluated after 3 months when malignancy or dysplasia was not confirmed.

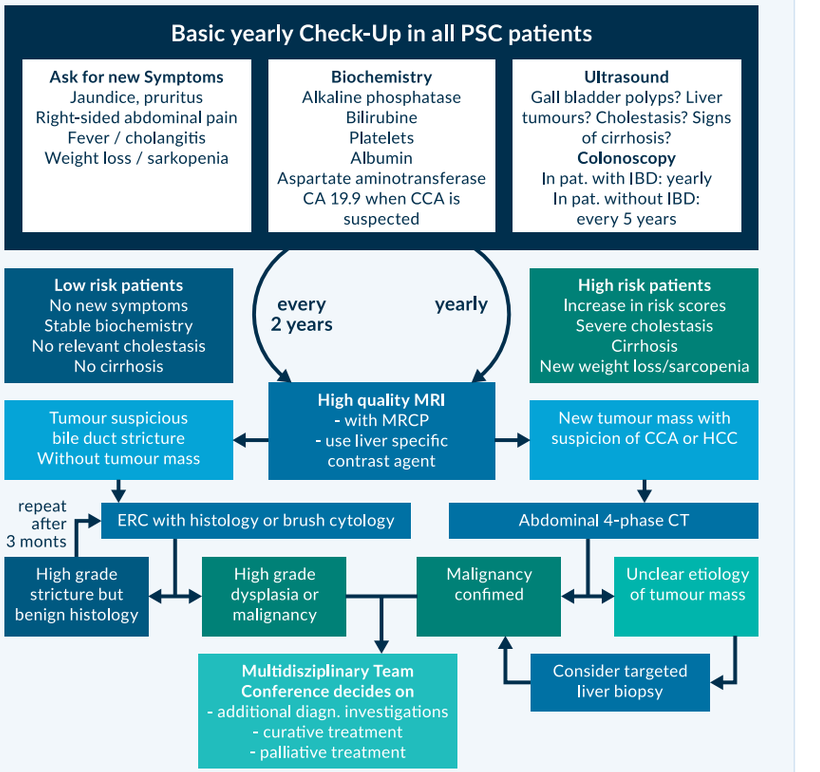

Figure 4. Surveillance algorithm for PSC
Abbreviations: PSC: Primary Sclerosing Cholangitis, IBD: Inflammatory Bowel Disease, CCA: Cholangiocarcinoma, HCC: hepatocellular carcinoma, MRI: Magnetic Resonance Imaging, MRCP: Magnetic Resonance Cholangiopancreaticography, ERC: Endoscopic Retrograde Cholangiography, CT: Computer Tomography

Medical treatment

The pathogenesis of PSC is largely unknown and, accordingly, a causal medical therapy for the disease is not yet available. Only antibiotic therapy for acute infectious cholangitis and endoscopic interventional therapy for obstructive cholestasis are established (Weismuller and Lankisch 2011).

Ursodeoxycholic acid (UDCA), a bile acid with choleretic, antiapoptotic, and antiinflammatory properties, has been used for cholestatic diseases including PSC for more than three decades, although evidence for a significant improvement in transplant-free survival has (in contrast to PBC) not yet been demonstrated in any PSC study. With a very high dosage of 28-30 mg/kg BW, even an opposite effect including disease progression was observed (Lindor 2009). In the studies with moderate dosages of UDCA (17-23 mg/kg BW), there were no significant improvements in hard endpoints, but at least a reduction in cholestasis parameters, especially AP. Subsequent subgroup analyses demonstrated that patients who experienced a significant reduction in AP with UDCA had significantly better transplant-free survival (Lindstrom 2013). Therefore, it is hypothesised that UDCA therapy at a moderate dose could improve prognosis in patients with a good biochemical response.

Despite ample evidence of an immunologically mediated pathogenesis of the disease, several smaller, but methodologically questionable (nonrandomised, nonplacebo-controlled) studies have failed to demonstrate prognostic improvement in PSC with the use of immunosuppressive or immunomodulatory agents (Culver and Chapman). However, there are two subgroups or variants of patients with PSC in whom immunosuppression is required: first, patients with coexisting autoimmune hepatitis (AIH) should be treated with immunosuppression according to current recommendations. A German retrospective multicentre study showed that PSC patients receiving immunosuppressive treatment already had more frequent signs of cirrhosis and elevated serum immunoglobulin G at diagnosis; also, the simplified AIH score and the modified histologic activity index were significantly elevated at therapy initiation (Schulze 2015). On the other hand, patients with IgG4-associated cholangitis (IAC) also benefit from immunosuppressive therapy and then show rapid regression of strictures on cholangiogram; however, it is unclear whether patients with PSC and only moderately elevated serum IgG4 also benefit from immunosuppression.

Antibiotics are an indispensable part of the therapy of acute bacterial cholangitis. In addition, the long-term use of various antibiotics such as metronidazole or vancomycin was evaluated in pilot studies and showed at least an improvement of biochemical, and in some cases also clinical and histological parameters (Davies 2008, Farkkila 2004, Tabibian 2014, Tabibian 2013). An adaptation of the antibiotic therapy strategy to the respective biliary germ spectrum seems to be reasonable at least in case of acute cholangitis (Negm 2010).

The management of cholestatic pruritus in PSC includes endoscopic treatment of relevant bile duct strictures and general measures such as moisturising creams and cooling. As medical first-line treatment option bezafibrate (400 mg daily) should be considered, taking into account relevant side effects (myalgias, myopathies, kidney dysfunction or worsening of liver parameters). In a randomised, placebo-controlled study, bezafibrate led to a reduction in pruritus of more than 40% within 3 weeks in 45% of participants in a mixed PBC and PSC cohort (de Vries 2021). Rifampicin (150-300 mg/d) is an alternative treatment option, but should initially only be given under close monitoring of liver values due to the risk of drug-induced toxic hepatitis (up to 12% of patients after 4-12 weeks) (European Association for the Study of the Liver 2022).

Endoscopic treatment

Fibrotic strictures of the bile ducts with consecutive bile duct dilatations characterise PSC, promote ascending cholangitis, and lead to cholestasis. Mechanical balloon dilatation (Figure 5) of these strictures using ERC can effectively resolve cholestasis and relieve symptoms of cholestasis (Gluck 2008, Gotthardt 2010). According to a recently published international randomised trial (Ponsioen 2018), short-term stent insertion is not less effective than ballon dilatation but was associated with significantly more complications. Therefore, balloon dilatation should be the preferred method, and stent implantation of PSC-associated bile duct strictures should be used cautiously only in selected cases. Choledocholithiasis, which is occasionally associated with PSC, can also be treated endoscopically by means of balloon or basket assisted stone removal or mechanical or electrohydraulic lithotripsy.

Apart from the therapy of cholestasis, ERC also holds an important role in the diagnostic work-up of new biliary strictures suspicious for malignancy. For this purpose, imaging techniques such as cholangioscopy and intraductal ultrasound, as well as brush or forceps biopsy to obtain cells and tissue are common methods (Aabakken 2017). The European Association for the Study of the Liver recommends in its current guideline (European Association for the Study of the Liver 2022) performing an ERC in patients with relevant (symptomatic) strictures and in cases of suspected cholangiocarcinoma, but not for routine surveillance.

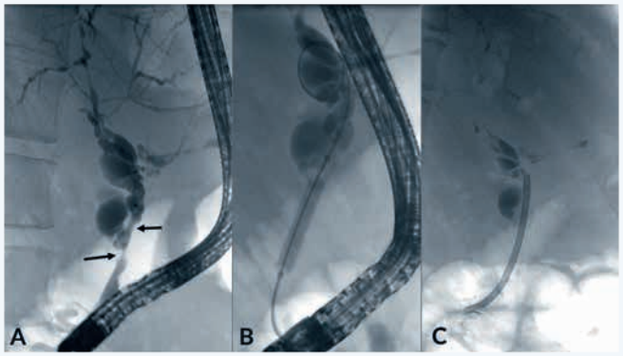

Figure 5. Endoscopic treatment of a high-grade stricture (A) with either balloon dilatation (B) or stenting (C). Combination of both methods is also frequently applied.

Liver transplantation for PSC

In the absence of definitive drug or endoscopic treatment options, liver transplantation (LT) remains the only curative therapy for PSC. Currently between five and fifteen percent of liver transplants in Europe are performed for this indication, depending on the region (Adam 2018, Fosby 2015). Against the background of the variable disease course and the incalculable risk of malignancy, the greatest challenge for an optimal prognosis for PSC-patients is to ensure that a donor organ is available at the right time. Compared with other hepatopathies, PSC progresses rather slowly but can also worsen acutely in the setting of cholangiosepsis. On the other hand, preemptive liver transplantation carries a higher short-term mortality risk of LT itself than the short-term natural course of the disease. However, when cholangiocarcinoma (CCA) is detected during disease progression, which is expected in 10-15% of patients, this is often advanced and therefore a contraindication to transplantation.

PSC patients should therefore be listed for LT when life expectancy and quality of life are so limited due to portal hypertension, liver failure, recurrent cholangitis or refractory pruritus that transplantation represents the lower risk compared to spontaneous progression (Martin and Levy 2017). Of note, the urgency of liver transplantation is not adequately reflected by the MELD score, which was designed for cirrhotic patients but underrates the main mortality factors in PSC like pronounced cholestasis, frequent cholangitis, acute cholangiosepsis and CCA.

Hence, many transplant allocation systems established exceptional points for PSC-patients, when they fulfill certain criteria, which reflect urgency better than the MELD-Score alone. This allows higher priority for PSC patients on the waiting list and allows a large proportion of PSC patients to be provided with a donor organ in a timely manner and keeps waiting list mortality low.

Long-term survival of organ recipients, most of whom are relatively young for this indication, is comparatively good with 79% to 85% after 5 years and 70%-80% after 10 years (Hildebrand 2016, Ravikumar 2015). However, biliary strictures, including PSC recurrence, occur in up to 36% of recipients transplanted for PSC and significantly affect both graft and patient survival. In case of cholestatic biochemistry following LT, it is recommended to initiate appropriate diagnostic steps without delay (MRI, in severe cholestasis also ERC, or liver biopsy); the treatment strategies in case of recurrent PSC do not differ from PSC-management in the pretransplant situation.

Risk factors for PSC recurrence in retrospective analyses were donor and/or recipient age, recipient INR prior to LT, cold ischaemia time, rejection and immunosuppression with tacrolimus. However, while these parameters could not be confirmed in meta-analyses (Buchholz 2018), almost all analyses identified (active) chronic inflammatory bowel disease as the most important risk factor for PSC recurrence. Whether intensified IBD therapy or even a protective colectomy could prevent recurrence is still under debate. The role of "prophylactic" continued UDCA therapy after LT is also unclear. The type of biliary anastomosis does not influence the risk of recurrence, so that no general recommendation is given for the creation of a biliodigestive anastomosis.

Even after LT, the risk of IBD-associated colon cancer is significantly increased. Annual screening colonoscopies are therefore strongly recommended. If no IBD is present, screening colonoscopies should be performed at least every 5 years, due to the increased risk of malignancy after LT.

References

Aabakken, L., T. H. Karlsen, J. Albert, M. Arvanitakis, O. Chazouilleres, J. M. Dumonceau, M. Farkkila, P. Fickert, G. M. Hirschfield, A. Laghi, M. Marzioni, M. Fernandez, S. P. Pereira, J. Pohl, J. W. Poley, C. Y. Ponsioen, C. Schramm, F. Swahn, A. Tringali, and C. Hassan. 2017. 'Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline', Endoscopy, 49: 588-608.

Adam, R., V. Karam, V. Cailliez, O. Grady JG, D. Mirza, D. Cherqui, J. Klempnauer, M. Salizzoni, J. Pratschke, N. Jamieson, E. Hidalgo, A. Paul, R. L. Andujar, J. Lerut, L. Fisher, K. Boudjema, C. Fondevila, O. Soubrane, P. Bachellier, A. D. Pinna, G. Berlakovich, W. Bennet, M. Pinzani, P. Schemmer, K. Zieniewicz, C. J. Romero, P. De Simone, B. G. Ericzon, S. Schneeberger, S. J. Wigmore, J. F. Prous, M. Colledan, R. J. Porte, S. Yilmaz, D. Azoulay, J. Pirenne, P. D. Line, P. Trunecka, F. Navarro, A. V. Lopez, L. De Carlis, S. R. Pena, E. Kochs, C. Duvoux, centers all the other 126 contributing, Liver the European, and Association Intestine Transplant. 2018. '2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation', Transpl Int, 31: 1293-317.

Adams, D. H., and B. Eksteen. 2006. 'Aberrant homing of mucosal T cells and extra-intestinal manifestations of inflammatory bowel disease', Nat Rev Immunol, 6: 244-51.

Bergquist, A., A. Ekbom, R. Olsson, D. Kornfeldt, L. Loof, A. Danielsson, R. Hultcrantz, S. Lindgren, H. Prytz, H. Sandberg-Gertzen, S. Almer, F. Granath, and U. Broome. 2002. 'Hepatic and extrahepatic malignancies in primary sclerosing cholangitis', J Hepatol, 36: 321-7.

Bergquist, A., T. J. Weismuller, C. Levy, C. Rupp, D. Joshi, J. S. Nayagam, A. J. Montano-Loza, E. Lytvyak, E. Wunsch, P. Milkiewicz, R. Zenouzi, C. Schramm, N. Cazzagon, A. Floreani, I. F. Liby, M. Wiestler, H. Wedemeyer, T. Zhou, C. P. Strassburg, E. Rigopoulou, G. Dalekos, M. Narasimman, X. Verhelst, H. Degroote, M. Vesterhus, A. E. Kremer, B. Bundgens, F. Rorsman, E. Nilsson, K. K.

Jorgensen, E. von Seth, M. Cornillet Jeannin, N. Nyhlin, H. Martin, S. Kechagias, K. Wiencke, M. Werner, B. T. Beretta-Piccoli, M. Marzioni, H. Isoniemi, J. Arola, A. Wefer, J. Soderling, M. Farkkila, H. Lenzen, and P. S. C. Study Group International. 2023. 'Impact on follow-up strategies in patients with primary sclerosing cholangitis', Liver Int, 43: 127-38.

Bjornsson, E., R. Olsson, A. Bergquist, S. Lindgren, B. Braden, R. W. Chapman, K. M. Boberg, and P. Angulo. 2008. 'The natural history of small-duct primary sclerosing cholangitis', Gastroenterology, 134: 975-80.

Boberg, K. M., R. W. Chapman, G. M. Hirschfield, A. W. Lohse, M. P. Manns, and E. Schrumpf. 2011. 'Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue', J Hepatol, 54: 374-85.

Boonstra, K., R. K. Weersma, K. J. van Erpecum, E. A. Rauws, B. W. Spanier, A. C. Poen, K. M. van Nieuwkerk, J. P. Drenth, B. J. Witteman, H. A. Tuynman, A. H. Naber, P. J. Kingma, H. R. van Buuren, B. van Hoek, F. P. Vleggaar, N. van Geloven, U. Beuers, and C. Y. Ponsioen. 2013. 'Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis', Hepatology, 58: 2045-55.

Bowlus, C. L., L. Arrive, A. Bergquist, M. Deneau, L. Forman, S. I. Ilyas, K. E. Lunsford, M. Martinez, G. Sapisochin, R. Shroff, J. H. Tabibian, and D. N. Assis. 2023. 'AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma', Hepatology, 77: 659-702.

Broome, U., H. Glaumann, E. Lindstom, L. Loof, S. Almer, H. Prytz, H. Sandberg-Gertzen, S. Lindgren, F. T. Fork, G. Jarnerot, and R. Olsson. 2002. 'Natural history and outcome in 32 Swedish patients with small duct primary sclerosing cholangitis (PSC)', J Hepatol, 36: 586-9.

Broome, U., R. Olsson, L. Loof, G. Bodemar, R. Hultcrantz, A. Danielsson, H. Prytz, H. Sandberg-Gertzen, S. Wallerstedt, and G. Lindberg. 1996. 'Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis', Gut, 38: 610-5.

Buchholz, B. M., P. M. Lykoudis, R. Ravikumar, J. M. Pollok, and G. K. Fusai. 2018. 'Role of colectomy in preventing recurrent primary sclerosing cholangitis in liver transplant recipients', World J Gastroenterol, 24: 3171-80.

Claessen, M. M., F. P. Vleggaar, K. M. Tytgat, P. D. Siersema, and H. R. van Buuren. 2009. 'High lifetime risk of cancer in primary sclerosing cholangitis', J Hepatol, 50: 158-64.

Corpechot, C., F. Gaouar, A. El Naggar, A. Kemgang, D. Wendum, R. Poupon, F. Carrat, and O. Chazouilleres. 2014. 'Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis', Gastroenterology, 146: 970-9; quiz e15-6.

Culver, E. L., and R. W. Chapman. 'Systematic review: management options for primary sclerosing cholangitis and its variant forms - IgG4-associated cholangitis and overlap with autoimmune hepatitis', Aliment Pharmacol Ther, 33: 1273-91.

Davies, Y. K., K. M. Cox, B. A. Abdullah, A. Safta, A. B. Terry, and K. L. Cox. 2008. 'Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic', J Pediatr Gastroenterol Nutr, 47: 61-7.

de Valle, M. B., E. Bjornsson, and B. Lindkvist. 2012. 'Mortality and cancer risk related to primary sclerosing cholangitis in a Swedish population-based cohort', Liver Int, 32: 441-8.

de Vries, E., R. Bolier, J. Goet, A. Pares, J. Verbeek, M. de Vree, J. Drenth, K. van Erpecum, K. van Nieuwkerk, F. van der Heide, N. Mostafavi, J. Helder, C. Ponsioen, R. Oude Elferink, H. van Buuren, U. Beuers, and Group Netherlands Association for the Study of the Liver-Cholestasis Working. 2021. 'Fibrates for Itch (FITCH) in Fibrosing Cholangiopathies: A Double-Blind, Randomized, Placebo-Controlled Trial', Gastroenterology, 160: 734-43 e6.

de Vries, E. M., U. Beuers, and C. Y. Ponsioen. 2015. 'Biomarkers for disease progression of primary sclerosing cholangitis', Curr Opin Gastroenterol, 31: 239-46.

De Vries, E. M., M. de Krijger, M. Farkkila, J. Arola, P. Schirmacher, D. Gotthardt, B. Goeppert, P. J. Trivedi, G. M. Hirschfield, H. Ytting, B. Vainer, H. R. van Buuren, K. Biermann, M. H. Harms, O. Chazouilleres, D. Wendum, A. D. Kemgang, R. W. Chapman, L. M. Wang, K. D. Williamson, A. S. Gouw, V. Paradis, C. Sempoux, U. Beuers, S. Hubscher, J. Verheij, and C. Ponsioen. 2017. 'Validation of the Prognostic Value of Histologic Scoring Systems in Primary Sclerosing Cholangitis; An International Cohort Study', Hepatology.

de Vries, E. M., J. Wang, K. D. Williamson, M. M. Leeflang, K. Boonstra, R. K. Weersma, U. Beuers, R. W. Chapman, R. B. Geskus, and C. Y. Ponsioen. 2018. 'A novel prognostic model for transplant-free survival in primary sclerosing cholangitis', Gut, 67: 1864-69.

Deneau, M. R., W. El-Matary, P. L. Valentino, R. Abdou, K. Alqoaer, M. Amin, A. Z. Amir, M. Auth, F. Bazerbachi, A. Broderick, A. Chan, J. Cotter, S. Doan, M. El-Youssef, F. Ferrari, K. N. Furuya, M. Gottrand, F. Gottrand, N. Gupta, M. Homan, B. M. Kamath, K. M. Kim, K. L. Kolho, A. Konidari, B. Koot, R. Iorio, O. Ledder, C. Mack, M. Martinez, T. Miloh, P. Mohan, N. O'Cathain, A. Papadopoulou, A. Ricciuto, L. Saubermann, P. Sathya, E. Shteyer, V. Smolka, A. Tanaka, R. Varier, V. Venkat, B. Vitola, M. B. Vos, M. Woynarowski, J. Yap, and M. K. Jensen. 2017. 'The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration', Hepatology, 66: 518-27.

Eaton, J. E., B. Dzyubak, S. K. Venkatesh, T. C. Smyrk, G. J. Gores, R. L. Ehman, N. F. LaRusso, A. A. Gossard, and K. N. Lazaridis. 2016. 'Performance of magnetic resonance elastography in primary sclerosing cholangitis', J Gastroenterol Hepatol, 31: 1184-90.

European Association for the Study of the Liver. 2022. 'EASL Clinical Practice Guidelines on sclerosing cholangitis', J Hepatol, 77: 761-806.

Farkkila, M., A. L. Karvonen, H. Nurmi, H. Nuutinen, M. Taavitsainen, P. Pikkarainen, and P. Karkkainen. 2004. 'Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: a randomized placebo-controlled trial', Hepatology, 40: 1379-86.

Fosby, B., E. Melum, K. Bjoro, W. Bennet, A. Rasmussen, I. M. Andersen, M. Castedal, M. Olausson, C. Wibeck, M. Gotlieb, H. Gjertsen, L. Toivonen, S. Foss, H. Makisalo, A. Nordin, T. Sanengen, A. Bergquist, M. E. Larsson, G. Soderdahl, G. Nowak, K. M. Boberg, H. Isoniemi, S. Keiding, A. Foss, P. D. Line, S. Friman, E. Schrumpf, B. G. Ericzon, K. Hockerstedt, and T. H. Karlsen. 2015. 'Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013', Scand J Gastroenterol, 50: 797-808.

Gizard, E., A. C. Ford, J. P. Bronowicki, and L. Peyrin-Biroulet. 2014. 'Systematic review: The epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease', Aliment Pharmacol Ther, 40: 3-15.

Gluck, M., N. R. Cantone, J. J. Brandabur, D. J. Patterson, J. E. Bredfeldt, and R. A. Kozarek. 2008. 'A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis', J Clin Gastroenterol, 42: 1032-9.

Gotthardt, D. N., G. Rudolph, P. Kloters-Plachky, H. Kulaksiz, and A. Stiehl. 2010. 'Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment', Gastrointest Endosc, 71: 527-34.

Hildebrand, T., N. Pannicke, A. Dechene, D. N. Gotthardt, G. Kirchner, F. P. Reiter, M. Sterneck, K. Herzer, H. Lenzen, C. Rupp, H. Barg-Hock, P. de Leuw, A. Teufel, V. Zimmer, F. Lammert, C. Sarrazin, U. Spengler, C. Rust, M. P. Manns, C. P. Strassburg, C. Schramm, T. J. Weismuller, and P. S. C. Study Group German. 2016. 'Biliary strictures and recurrence after liver transplantation for primary sclerosing cholangitis: A retrospective multicenter analysis', Liver Transpl, 22: 42-52.

Kaplan, G. G., K. B. Laupland, D. Butzner, S. J. Urbanski, and S. S. Lee. 2007. 'The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis', Am J Gastroenterol, 102: 1042-9.

Karlsen, T. H., T. Folseraas, D. Thorburn, and M. Vesterhus. 2017. 'Primary sclerosing cholangitis - a comprehensive review', J Hepatol, 67: 1298-323.

Kim, W. R., T. M. Therneau, R. H. Wiesner, J. J. Poterucha, J. T. Benson, M. Malinchoc, N. F. LaRusso, K. D. Lindor, and E. R. Dickson. 2000. 'A revised natural history model for primary sclerosing cholangitis', Mayo Clin Proc, 75: 688-94.

Lindkvist, B., M. Benito de Valle, B. Gullberg, and E. Bjornsson. 2010. 'Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden', Hepatology, 52: 571-7.

Lindor, K. D., K. V. Kowdley, V. A. Luketic, M. E. Harrison, T. McCashland, A. S. Befeler, D. Harnois, R. Jorgensen, J. Petz, J. Keach, J. Mooney, C. Sargeant, J. Braaten, T. Bernard, D. King, E. Miceli, J. Schmoll, T. Hoskin, P. Thapa, and F. Enders. 2009. 'High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis', Hepatology, 50: 808-14.

Lindstrom, L., R. Hultcrantz, K. M. Boberg, I. Friis-Liby, and A. Bergquist. 2013. 'Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis', Clin Gastroenterol Hepatol, 11: 841-6.

Loftus, E. V., Jr., G. C. Harewood, C. G. Loftus, W. J. Tremaine, W. S. Harmsen, A. R. Zinsmeister, D. A. Jewell, and W. J. Sandborn. 2005. 'PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis', Gut, 54: 91-6.

Lohr, J. M., M. Vujasinovic, J. Rosendahl, J. H. Stone, and U. Beuers. 2022. 'IgG4-related diseases of the digestive tract', Nat Rev Gastroenterol Hepatol, 19: 185-97.

Lynch, K. D., R. W. Chapman, S. Keshav, A. J. Montano-Loza, A. L. Mason, A. E. Kremer, M. Vetter, M. de Krijger, C. Y. Ponsioen, P. Trivedi, G. Hirschfield, C. Schramm, C. H. Liu, C. L. Bowlus, D. J. Estes, D. Pratt, C. Hedin, A. Bergquist, A. C. de Vries, C. J. van der Woude, L. Yu, D. N. Assis, J. Boyer, H. Ytting, E. Hallibasic, M. Trauner, H. U. Marschall, L. M. Daretti, M. Marzioni, K. K. Yimam, N. Perin, A. Floreani, B. T. Beretta-Piccoli, J. K. Rogers, Group International Primary Sclerosing Cholangitis Study, and C. Levy. 2020. 'Effects of Vedolizumab in Patients With Primary Sclerosing Cholangitis and Inflammatory Bowel Diseases', Clin Gastroenterol Hepatol, 18: 179-87 e6.

Magro, F., P. Gionchetti, R. Eliakim, S. Ardizzone, A. Armuzzi, M. Barreiro-de Acosta, J. Burisch, K. B. Gecse, A. L. Hart, P. Hindryckx, C. Langner, J. K. Limdi, G. Pellino, E. Zagorowicz, T. Raine, M. Harbord, F. Rieder, Crohn's European, and Organisation Colitis. 2017. 'Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders', J Crohns Colitis, 11: 649-70.

Martin, E. F., and C. Levy. 2017. 'Timing, Management, and Outcomes of Liver Transplantation in Primary Sclerosing Cholangitis', Semin Liver Dis, 37: 305-13.

Mendes, F. D., R. Jorgensen, J. Keach, J. A. Katzmann, T. Smyrk, J. Donlinger, S. Chari, and K. D. Lindor. 2006. 'Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis', Am J Gastroenterol, 101: 2070-5.

Negm, A. A., A. Schott, R. P. Vonberg, T. J. Weismueller, A. S. Schneider, S. Kubicka, C. P. Strassburg, M. P. Manns, S. Suerbaum, J. Wedemeyer, and T. O. Lankisch. 2010. 'Routine bile collection for microbiological analysis during cholangiography and its impact on the management of cholangitis', Gastrointest Endosc, 72: 284-91.

Ponsioen, C. Y., U. Arnelo, A. Bergquist, E. A. Rauws, V. Paulsen, P. Cantu, I. Parzanese, E. M. De Vries, K. N. van Munster, K. Said, O. Chazouilleres, B. Desaint, A. Kemgang, M. Farkkila, S. Van der Merwe, W. Van Steenbergen, H. U. Marschall, P. O. Stotzer, D. Thorburn, S. P. Pereira, and L. Aabakken. 2018. 'No Superiority of Stents vs Balloon Dilatation for Dominant Strictures in Patients With Primary Sclerosing Cholangitis', Gastroenterology, 155: 752-59 e5.

Ponsioen, C. Y., J. B. Reitsma, K. M. Boberg, L. Aabakken, E. A. Rauws, and E. Schrumpf. 2010. 'Validation of a cholangiographic prognostic model in primary sclerosing cholangitis', Endoscopy, 42: 742-7.

Ravikumar, R., E. Tsochatzis, S. Jose, M. Allison, A. Athale, F. Creamer, B. Gunson, V. Iyer, M. Madanur, D. Manas, A. Monaco, D. Mirza, N. Owen, K. Roberts, G. Sen, P. Srinivasan, S. Wigmore, G. Fusai, B. Fernando, and A. Burroughs. 2015. 'Risk factors for recurrent primary sclerosing cholangitis after liver transplantation', J Hepatol, 63: 1139-46.

Rupp, C., A. Mummelthei, P. Sauer, K. H. Weiss, P. Schirmacher, A. Stiehl, W. Stremmel, and D. N. Gotthardt. 'Non-IBD immunological diseases are a risk factor for reduced survival in PSC', Liver Int, 33: 86-93.

Schulze, K., T. J. Weismuller, M. Bubenheim, P. Huebener, R. Zenouzi, H. Lenzen, C. Rupp, D. Gotthardt, P. de Leuw, A. Teufel, V. Zimmer, F. P. Reiter, C. Rust, L. Tharun, A. Quaas, S. A. Weidemann, F. Lammert, C. Sarrazin, M. P. Manns, A. W. Lohse, C. Schramm, and P. S. C. Study Group German. 2015. 'Criteria Used in Clinical Practice to Guide Immunosuppressive Treatment in Patients with Primary Sclerosing Cholangitis', PLoS One, 10: e0140525.

Tabibian, J. H., A. Gossard, M. El-Youssef, J. E. Eaton, J. Petz, R. Jorgensen, F. B. Enders, A. Tabibian, and K. D. Lindor. 2014. 'Prospective Clinical Trial of Rifaximin Therapy for Patients With Primary Sclerosing Cholangitis', Am J Ther.

Tabibian, J. H., E. Weeding, R. A. Jorgensen, J. L. Petz, J. C. Keach, J. A. Talwalkar, and K. D. Lindor. 2013. 'Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis - a pilot study', Aliment Pharmacol Ther, 37: 604-12.

Tischendorf, J. J., H. Hecker, M. Kruger, M. P. Manns, and P. N. Meier. 2007. 'Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: A single center study', Am J Gastroenterol, 102: 107-14.

Trivedi, P. J., C. L. Bowlus, K. K. Yimam, H. Razavi, and C. Estes. 2022. 'Epidemiology, Natural History, and Outcomes of Primary Sclerosing Cholangitis: A Systematic Review of Population-based Studies', Clin Gastroenterol Hepatol, 20: 1687-700 e4.

Tsaitas, C., A. Semertzidou, and E. Sinakos. 2014. 'Update on inflammatory bowel disease in patients with primary sclerosing cholangitis', World J Hepatol, 6: 178-87.

Villard, C., I. Friis-Liby, F. Rorsman, K. Said, A. Warnqvist, M. Cornillet, S. Kechagias, N. Nyhlin, M. Werner, I. Janczewska, T. Hagstrom, E. Nilsson, and A. Bergquist. 2023. 'Prospective surveillance for cholangiocarcinoma in unselected individuals with primary sclerosing cholangitis', J Hepatol, 78: 604-13.

Weismuller, T. J., and T. O. Lankisch. 2011. 'Medical and endoscopic therapy of primary sclerosing cholangitis', Best Pract Res Clin Gastroenterol, 25: 741-52.

Weismuller, T. J., P. J. Trivedi, A. Bergquist, M. Imam, H. Lenzen, C. Y. Ponsioen, K. Holm, D. Gotthardt, M. A. Farkkila, H. U. Marschall, D. Thorburn, R. K. Weersma, J. Fevery, T. Mueller, O. Chazouilleres, K. Schulze, K. N. Lazaridis, S. Almer, S. P. Pereira, C. Levy, A. Mason, S. Naess, C. L. Bowlus, A. Floreani, E. Halilbasic, K. K. Yimam, P. Milkiewicz, U. Beuers, D. K. Huynh, A. Pares, C. N. Manser, G. N. Dalekos, B. Eksteen, P. Invernizzi, C. P. Berg, G. I. Kirchner, C. Sarrazin, V. Zimmer, L. Fabris, F. Braun, M. Marzioni, B. D. Juran, K. Said, C. Rupp, K. Jokelainen, M. Benito de Valle, F. Saffioti, A. Cheung, M. Trauner, C. Schramm, R. W. Chapman, T. H. Karlsen, E. Schrumpf, C. P. Strassburg, M. P. Manns, K. D. Lindor, G. M. Hirschfield, B. E. Hansen, K. M. Boberg, and P. S. C. Study Group International. 2017. 'Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associate With Course of Primary Sclerosing Cholangitis', Gastroenterology, 152: 1975-84 e8.

Zenouzi, R., T. J. Weismuller, P. Hubener, K. Schulze, M. Bubenheim, N. Pannicke, C. Weiler-Normann, H. Lenzen, M. P. Manns, A. W. Lohse, and C. Schramm. 2014. 'Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis', Clin Gastroenterol Hepatol, 12: 1733-8.

Zhou, T., H. Lenzen, L. Dold, B. Bundgens, H. Wedemeyer, M. P. Manns, M. A. Gonzalez-Carmona, C. P. Strassburg, and T. J. Weismuller. 2021. 'Primary sclerosing cholangitis with moderately elevated serum-IgG4 - characterization and outcome of a distinct variant phenotype', Liver Int, 41: 2924-33.

13. Primary biliary cholangitis

Heike Bantel, Andreas E. Kremer

Abstract

Primary biliary cholangitis (PBC) is a chronic inflammatory cholestatic liver disease that can result in end-stage biliary cirrhosis and associated complications. Because of its characteristic autoantibody signature, immune-mediated biliary injury and genetic risk factors, PBC is considered as autoimmune liver disease, although immunosuppressive therapy is ineffective. Treatment strategies have therefore focused on cholestatic consequences and symptom burden. PBC-associated symptoms such as pruritus, sicca syndrome and fatigue as well as extrahepatic immune-mediated co-morbidities, e.g. thyreopathy or rheumatoid arthritis, can strongly impair quality of life. The diagnosis is based on serological detection of elevated cholestasis parameters, especially alkaline phosphatase, and PBC-specific anti-mitochondrial/anti-nuclear antibodies. Liver biopsy is only required if PBC is suspected despite negative autoantibody diagnostic or to clarify liver comorbidities, such as autoimmune hepatitis or metabolic dysfunction-associated steatotic liver disease. The treatment goal is to prevent disease progression with ursodeoxycholic acid (UDCA) as approved standard therapy of PBC. Treatment response should be assessed latest after 6 to 12 months of standard therapy by blood-based response criteria. In case of inadequate treatment response, a second line therapy with licensed novel PPAR agonists or off-label use of bezafibrate under continuation of UDCA therapy is possible for patients without decompensated cirrhosis. In summary, it is important to consider PBC in the differential diagnosis of cholestatic liver disease in order to enable early diagnosis of this rare liver disease and thus to create the best conditions for effective treatment and prevention of disease progression and complications.

Introduction

Primary biliary cholangitis is an immune-mediated, chronic cholestatic disease of the liver with a female predominance characterised by selective destruction of the small intrahepatic bile ducts resulting in non-suppurative destructing cholangitis (Lleo A 2020). It is characterised by anti-mitochondrial antibodies or PBC-specific anti-nuclear antibodies, progressive cholestasis, and characteristic histological features (European

Association for the Study of the Liver 2017). Untreated, PBC can progress from lymphocytic cholangitis and progressive ductopenia to biliary cirrhosis (Lleo A 2020). In 2016, the term "primary biliary cirrhosis" was replaced by "primary biliary cholangitis" as currently most patients never develop cirrhosis anymore, as the cirrhosis stigmatised many patients, and caused association with alcohol consumption. The acronym PBC, however, remains unchanged (Beuers 2015).

The prevalence of PBC varies regionally and ranges between 1.9 and roughly 40 per 100,000 inhabitants (Liu 2010, Selmi 2011, Younossi 2019). The age at diagnosis is usually around the 5th decade of life, although cases have been described as early as the 2nd decade of life. In 90% of cases women are affected by the disease (Lu 2018). It is estimated that 0.5% of the normal population is AMA positive (Mattalia 1998). In a French prospective study, the 5-year PBC incidence rate for patients with positive AMA detection and normal AP was 16% (Dahlqvist 2017). The majority of these patients with a later diagnosis of PBC were women (89%) and the median age of diagnosis was 62 years. In another European long-term follow-up study in patients with AMA detection without further laboratory evidence of PBC at baseline, only about 10% developed PBC at follow-up > 6 years (Zandanell 2020). The probability of developing PBC was even lower in a retrospective Chinese study, with a 7.8% 5-year PBC incidence rate in patients with a positive AMA titer and no evidence of liver disease at the time of AMA detection (Duan W 2022).

Pathophysiology

The pathophysiology of primary biliary cholangitis is still not fully understood. It is believed that multiple endogenous and exogenous factors mutually interact and synergistically promote the initiation and progression of primary biliary cholangitis. The clinical observation of a broad array of immune-mediated phenomena suggests the disease to be of autoimmune aetiology. Still, the question remains whether pathophysiological alterations within and damage of the small intrahepatic biliary epithelial cells (BECs), such as dysfunction of the protective biliary bicarbonate-rich umbrella, cause a subsequent immune reaction or whether a direct immune attack, e.g. due to a molecular mimicry following an infection, results in the non-suppurative destructive cholangitis. A loss of immune tolerance to the E2 subunit of pyruvate dehydrogenase complex (PDC-E2), that is located on the inner membrane of mitochondria, results in a multi-lineage immune response. Despite the ubiquitous presence of mitochondria, selectively BECs within the small intrahepatic bile ducts are attacked by the immune system. Without therapy, this immune reaction results in a progressive and irreversible destruction and loss of small interlobular and septal bile ducts with formation of a biliary fibrosis and finally cirrhosis. Genome-wide association studies (GWAS) proofed important immunoregulatory pathways, such as IL-12 and IFN-ɣ (Hirschfield 2009, Gerussi 2021). More recently, a X-wide association study (XWAS) identified a risk locus on the X chromosome that underlines the importance of Treg cells (Asselta 2021). Finally, epigenetic modifications of the X chromosome could lead to closing the missing heritability gap and shed light on the biology of female predisposition.

Diagnosis of PBC

The diagnosis of PBC should be considered in the presence of elevated alkaline phosphatase (AP) after exclusion of obstructive (e.g. by ultrasound) and other causes of cholestatic liver diseases (Table 1), especially in women above the age of 30 who reveal a higher PBC prevalence compared to men (9:1 ratio) (Lu 2018). The diagnosis is confirmed if anti-mitochondrial antibodies (AMAs) can be detected in the presence of AP elevation. AMAs can be found in 90–95% of PBC patients (Vergani 2004). Approximately 5–10% of PBC patients remain AMA negative in immunofluorescence technique (Kaplan 2005). In some of those patients, antibodies against the major M2 components (pyruvate dehydrogenase complex-E2 and 2-oxoglutaric acid dehydrogenase complex) can be detected by ELISA or Western Blotting. More than 30% of PBC patients negative for AMA by indirect immunofluorescence technique reveal PBC-specific anti-nuclear antibodies (ANAs), including sp-100 and gp-210 (Vergani 2004; Hirschfield 2008). Therefore, in case of AMA-negativity, detection of PBC-specific ANAs by ELISA and immunofluorescence is recommended.

If PBC is suspected in patients negative for AMAs and PBC-specific ANAs, liver biopsy should be performed. PBC is histologically characterised by chronic, non-suppurative cholangitis and destruction of interlobular bile ducts. In addition, epithelioid granuloma can be observed. Inflammatory bile duct damage can result in ductopenia and collagen deposition (fibrosis development) which can be divided into four disease stages according to Ludwig and Scheuer (Ludwig 1978, Scheuer 1998). The four-stage histological model according to Nakanuma et al. considers cholestasis and bile duct loss in addition to fibrosis and might be of higher prognostic relevance compared to the classical PBC-staging (Nakanuma 2010).

The diagnosis PBC is confirmed when two of the three criteria – AP elevation, presence of AMAs or PBC-specific ANAs and histological characteristics of PBC – are met (Lindor 2019).

PBC-associated symptoms

Although PBC can be asymptomatic, a substantial proportion of patients develop symptoms, usually between 2 and 4 years following diagnosis (Roll 1983). The classical symptoms of PBC are fatigue, pruritus, and sicca syndrome, which affect more than 50% of patients (Hegade 2019, Mang 1997, Cauch-Dudek K 1998).

Fatigue can strongly impair quality of life and is not related to severity of liver disease with the exception of end-stage liver disease and associated hepatic encephalopathy (Poupon 2004; Huet 2000). Further causes of fatigue should be excluded, such as hypothyroidism, anaemia, coeliac disease, depression, nighttime pruritus, and sleep disturbance.

Pruritus represents a characteristic cholestatic symptom in PBC, which can occur at any disease stage and can dramatically impair quality of life (Beuers 2014). Patients with a ductopenic course of the disease being at risk for advanced disease progression are especially affected by severe pruritus (Vleggaar 2001). With respect to the increased risk of gall stones and associated complications in PBC, bile duct obstruction must be excluded (e.g. by ultrasound) as cause of pruritus.

Sicca symptoms, including dry eyes and / or mouth are typical signs in PBC and can reduce quality of life (Fox 2008). Most PBC patients have sicca-like symptoms without fulfillment of the characteristics of a primary Sjögren's Syndrome. Enlargement of the parotid gland is, however, indicative of primary Sjögren's Syndrome and should be further clarified.

As in other cholestatic liver diseases, hyperlipidaemia can also be observed in PBC and can be associated with xanthomas and xanthelasma. Increased levels of LDL cholesterol (mainly composed of non-artherogenic lipoprotein X) are usually not related with an increased cardiovascular risk in PBC patients if other further risk factors, such as arterial hypertension, diabetes mellitus, smoking or familial risk are excluded (Jahn 1985). In PBC patients with concomitant cardiovascular risk factors, however, lipid diagnostic and risk-adapted treatment of hyperlipidaemia are recommended (Cash 2013).

PBC patients have an increased risk of osteopenia and osteoporosis compared to age- and sex-matched controls, which can further negatively impact quality of life due to bone and joint alterations and associated pain (Menon 2001). Bone mineral density testing is therefore recommended at diagnosis and in regular follow-up intervals according to the individual risk (Lindor 2019). Musculoskeletal changes and associated discomfort can also be caused by rheumatologic comorbidities in PBC, which have to be considered in the diagnostic approach (Table 2).

Table 1. Differential Diagnoses of Cholestatic Liver Diseases

1) Cholestatic Liver Diseases
Primary biliary cholangitis
Primary / secondary sclerosing cholangitis
IgG4-related cholangiopathy
Drug-/toxin-induced cholestasis
Viral cholangitis (e.g. CMV, HIV)
Obstructive cholangiopathy (e.g. bile duct stones, intra-/extra-hepatic malignancies)
Ductal plate malformation (e.g. Caroli syndrome)
Vanishing-bile-duct syndrome
Ischemic type biliary lesion (e.g. after liver transplantation)
Cystic fibrosis-associated cholangiopathy
Intrahepatic cholestasis of pregnancy
Hereditary cholestasis syndromes (e.g. FIC1-, BSEP- or MDR3-deficiency), Alagille syndrome, erythropoetic protoporphyria
Sarcoidosis, storage diseases, amyloidosis
Nodular regenerative hyperplasia

Extrahepatic immune-mediated diseases in PBC

PBC patients reveal an increased risk for the development of extrahepatic immune-mediated diseases (Chalifoux 2017, Efe 2021, Floreani 2018, Gershwin 2005), such as Sjögren's syndrome, Raynaud syndrome or systemic sclerosis/CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and teleangectasia) syndrome, as well as rheumatoid arthritis and autoimmune thyroid diseases, especially Hashimoto thyroiditis (Table 2).

Table 2.

2) Immune-mediated co-morbidities associated with PBC
Sjögren's Syndrome
Autoimmune Thyreoiditis
Rheumatoid Arthritis
Systemic sclerosis / CREST syndrome
Raynaud Syndrome

Risk factors of PBC progression and prognosis

Several risk factors are associated with disease progression and a higher risk of mortality or need for liver transplantation in PBC. For instance, younger age (< 50 years) at diagnosis of PBC is related with an unfavourable prognosis (Carbone 2013). Whereas AMA levels are not of prognostic relevance, detection of PBC-specific ANAs such as gp210 antibodies are associated with faster disease progression (Nakamura 2007), in particular in patients with an inadequate response to UDCA (Haldar 2021).

The efficacy of the standard therapy (UDCA) on disease progression has been proven by several placebo-controlled and long-term observational studies (Leuschner 1989, Poupon 1994, Poupon 1997, Corpechot 2000). A meta-analysis of the global PBC study group including 4845 PBC patients demonstrated that UDCA-treated patients reveal a significant better transplantation-free survival compared to untreated PBC patients (Lammers 2014). Patients with insufficient response to UDCA therapy, who does not fulfill biochemical response criteria (e.g. Paris-II criteria: AP and AST < 1.5-fold upper limit of normal and normal bilirubin after 12 month of UDCA treatment) have a worse prognosis compared to patients with treatment response (Corpechot 2011). Furthermore, transplantation-free survival of patients with early PBC responding to UDCA therapy is comparable with a healthy control population (Corpechot 2011, Pares 2006).

In PBC patients who received a liver biopsy, fibrosis stage and ductopenia (> 50% bile duct loss) are of prognostic relevance. Importantly, PBC patients with histologically progressed liver fibrosis (F3/F4) reveal a reduced transplantation-free survival independent of treatment response (Kumagi 2010, Murillo Perez 2019).

Prognostic scores from the UK PBC Research Group or the Global PBC Study Group (GLOBE score) can be used to estimate the individual risk of disease progression and the development of associated complications (Lammers 2015, Carbone 2016). These scores consider the disease stage (alkaline phosphatase, albumin, bilirubin and platelet count) as well as age at diagnosis as important risk factors (Gatselis 2020, Carbone 2013). A GLOBE score > 0.30 after one year of standard therapy is associated with a significant shorter transplantation-free survival of PBC patients compared to healthy individuals (Lammers 2015). In multicentre PBC cohorts, it could also be demonstrated that patients who achieved normalisation of AP or low-normal bilirubin levels (≤ 0.6-fold of upper limit of normal range) on standard therapy had significantly higher survival rates compared to patients with AP or bilirubin levels above this threshold (Murillo Perez 2020). Thus, at least in younger patients or those with risk factors normalisation of laboratory parameters is the novel, optimal treatment goal.

Risk stratification of PBC patients by liver stiffness measurement

In addition to blood-based parameters and scores, liver stiffness measurement is useful for risk stratification of PBC patients. Initially, a cut-off value of > 9.6 kPa could be identified for liver stiffness measurement by vibration-controlled transient elastography (VCTE) in PBC patients, which was associated with an increased risk for liver decompensation, mortality or need for liver transplantation (Corpechot 2012). A multicentre PBC study identified a similar VCTE cut-off value (10.2 kPa) for the prediction of liver decompensation independently from treatment response and GLOBE score (Osman 2021). A recent guideline from the European Association for the Study of the Liver (EASL) therefore recommends VCTE for risk stratification in PBC and suggests a threshold of 10 kPa for prediction of advanced fibrosis in PBC (EASL 2021). A further multicentre study identified a low (8 kPa) and a high (15 kPa) VCTE threshold for risk stratification of PBC patients in terms of low or high risk of developing clinical outcomes such as liver-related complications, liver transplantation or death (Corpechot 2022). Of note, body mass index and liver biochemistry did not affect liver stiffness measurement in PBC (Cristoferi 2021). Liver stiffness measurement therefore represents a reliable method for monitoring of PBC progression and further improved risk stratification in addition to GLOBE score or criteria of treatment response (Paris-II) (Corpechot 2012, Corpechot 2022).

Hepatocellular carcinoma risk and surveillance in PBC

PBC patients with liver cirrhosis have an increased risk for developing hepatocellular carcinoma (HCC), although the general risk is lower compared to end-stage liver diseases of other etiologies such as chronic hepatitis B or C virus infection (Natarajan 2021, Lindor 2019). In addition to progressed fibrosis, male sex, and inadequate treatment response have been identified as risk factors for HCC development in PBC. Surveillance with regular (bi-annual) imaging modalities and alpha fetoprotein (AFP) is recommended in international guidelines for patients with liver cirrhosis independently of aetiology and was associated with better clinical outcome of PBC patients who developed HCC (Lindor 2019, Bitzer 2023, Trivedi 2014, Silveira 2008).

Therapeutic options in PBC

First-line therapy

The drug of choice for slowing the progression of the disease is consistent drug therapy of PBC with the bile acid ursodeoxycholic acid (UDCA). Thus, UDCA is the recommended first-line therapy in all patients diagnosed with PBC. All patients should receive a dosage of 13-15 mg/kg body weight/day that should be titrated and divided into two daily doses at least during the first three months of therapy. According to current knowledge, lifelong therapy is indicated. UDCA is a physiological bile acid that accounts for up to 3% of the bile acid pool in healthy individuals. Oral supplementation will increase this proportion to around 50% (Beuers 2006). As an endogenous substance, UDCA is very well tolerated. Occasionally an increased stool frequency can occur, especially at the start of therapy, which is why a gradual dosage is recommended. Other side effects are rare and are generally due to additives in the drug. A change of preparation can therefore be tried in the event of intolerance. The mere detection of AMA, sp100 or gp210 in the absence of increased cholestasis parameters does not justify therapy.

Several placebo-controlled studies underline the efficacy of UDCA in patients with PBC (Poupon 1991, Poupon 1994, Poupon 1997, Lindor 1996, Lammert 2014). Prognostically important laboratory parameters such as AP, AST and bilirubin improved in these studies. Liver histology was also positively influenced and histological progression was delayed (Angulo 1999), while a smaller placebo-controlled study was unable to demonstrate any histological effects of UDCA treatment in PBC patients after 2 years (Batts 1996). In patients with advanced PBC, transplant-free survival improved (Angulo 1999). Patients with early-stage disease and a good response to UDCA did not differ in transplant-free survival from a healthy control population (Pares 2006, Corpechot 2011). The number needed to treat (NNT) without or with cirrhosis to avoid liver transplantation or death with UDCA is only 20 and 4, respectively. In patients with an AP above 4 times the norm, the NNT is 5 (Harms 2020). Long-term studies have demonstrated that this first-line treatment standard leads to a significant improvement in the prognosis of patients with PBC (EASL 2017). The proportion of patients requiring a PBC-related liver transplant fell from 20% in 1986 to 4% in 2015 compared to other indications for a liver transplant. The largest proportion of the decline took place from 1986 to 1996, after which the number of PBC patients receiving liver transplants remained largely stable (Harms 2019). This indicates a relevant group of patients in whom it is not possible to prevent advanced liver disease or in whom PBC was only diagnosed in the context of decompensation of liver cirrhosis. PBC patients requiring transplantation tend to be marginally older (56 vs. 54 years) than 30 years ago (Harms 2019).

The treatment response to UDCA is usually assessed after 6 or 12 months at the latest. Biochemical parameters are used as surrogate markers to define the treatment response, in particular alkaline phosphatase (AP), total bilirubin and transaminases (EASL 2017). They are part of several dichotomous criteria for UDCA response (e.g. Barcelona, Paris I or Paris II criteria) (Pares 2006, Corpechot 2008, Corpechot 2011) or continuous scoring systems (e.g. GLOBE score) (Lammers 2015), which were developed to define an inadequate UDCA response. Depending on the response criteria used, up to 30–40% of UDCA-treated patients have an inadequate response to treatment. These patients have an increased risk of developing liver cirrhosis (Carey 2015, EASL 2017). However, which response criteria best define an inadequate UDCA response and should be applied in everyday clinical practice is left open in the guidelines (Jones 2022). This heterogeneity can lead to uncertainties that make it difficult to identify patients at risk of disease progression. Correct risk stratification can also be difficult if the surrogate markers are in the borderline range between "low" and "high" risk of progression (Jones 2022). More recent data indicate that a response to first-line UDCA therapy can be defined even more narrowly: patients who achieve a low-normal bilirubin value of ≤ 0.6x ULN (upper limit of normal), or a normal-value AP (≤ 1x ULN) under UDCA therapy, have the lowest risk of liver transplantation or death after 10 years (Murillo Perez 2020). A rule of thumb can be derived from this, which should be easier to apply for risk stratification in everyday clinical practice (Figure 1): According to this, normalisation of AP and bilirubin should be aimed for under UDCA (Murillo Perez 2020). If this aim is not achieved with UDCA, there are below standing second-line treatment options available (Figure 1).

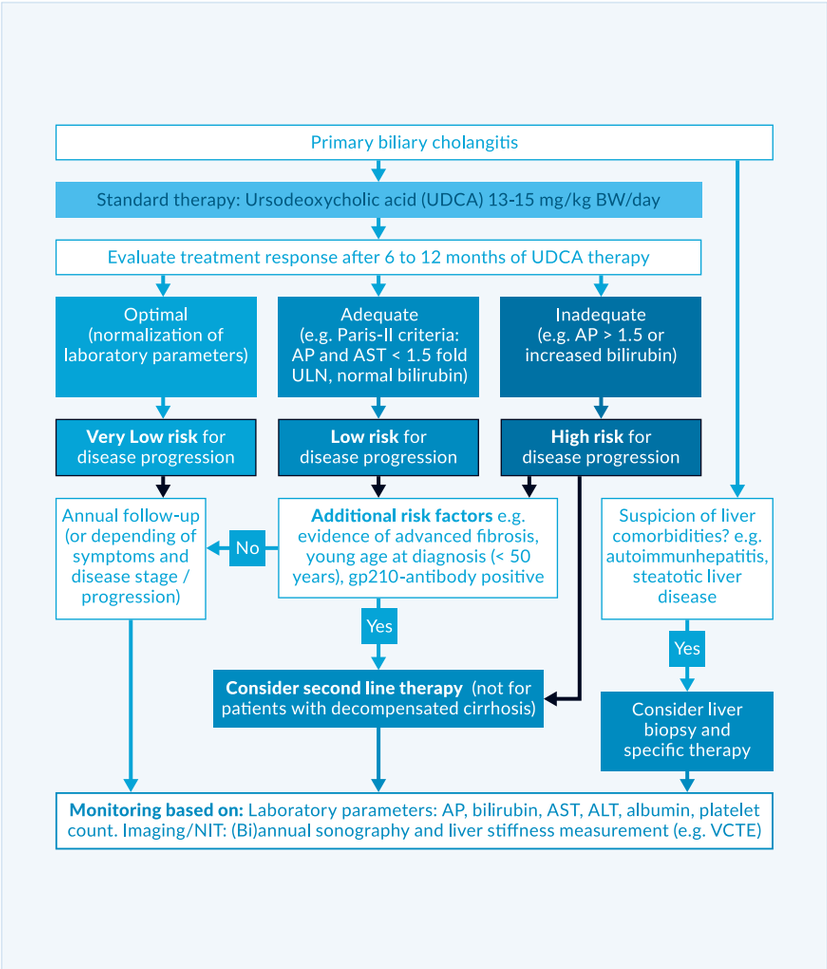

Figure 1. Management of PBC patients according to standard therapy response. NIT, non-invasive test; VCTE, vibration-controlled transient elastography; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Second-line therapy

In 2016, obeticholic acid (OCA) was approved as second-line therapy in combination with UDCA for patients with PBC who do not respond adequately to UDCA, or – clinically necessary in only a few cases – as monotherapy in cases of UDCA intolerance (Nevens 2016). OCA is a semisynthetic bile acid that represents the first highly selective and high-affinity first-in-class agonist of the nuclear farnesoid X receptor (FXR). It exhibits anti-cholestatic, anti-inflammatory, anti-fibrotic and hepatoprotective properties (Forman 1995, Gadaleta 2011). The clinical data on OCA is very extensive and includes 2 dose-finding studies (Hirschfield 2015; Kowdley 2018), a phase 3 study (POISE) (Nevens 2016) plus data from an open extension phase (POISE LTSE) (Trauner 2019). The primary combined endpoint of the POISE study was defined as biochemical response with an AP < 1.67x ULN, an AP reduction of at least 15% and normalisation of total bilirubin (Nevens 2016). The proportion of patients who achieved the primary combined endpoint after 12 months with OCA was 46% (5-10 mg/day) and 47% (10 mg/day), respectively, compared to 10% in the placebo arm (Nevens 2016). The treatment response was maintained even after 72 months of long-term treatment with OCA (Nevens 2019). The proportion of patients reaching the primary endpoint increased to over 50 % and led to significant, sustained reductions in AP, GGT and transaminases (ALT, AST). Bilirubin levels remained stable over 6 years. Liver stiffness stabilised in all subgroups of patients in the same period and there were no new safety signals with OCA therapy. Treatment discontinuation due to pruritus occurred in only 4% of patients during the extension phase (Nevens 2019, Trauner 2019). Finally, in a subgroup of patients (n=16) in whom paired liver biopsies were available (before the start of the double-blind study and after approximately 3 years of OCA therapy) collagen morphometry was clearly indicated to be improved in a post-hoc analysis (Bowlus 2020).

There are also real-world studies in international patient cohorts underlining the efficacy and safety of OCA (Roberts 2020, D`Amato 2021, Abbas N 2023). In addition, a recently published comparative analysis also provided important evidence for the improvement of clinical endpoints under OCA: using the propensity matching method, OCA-treated patients from the POISE study (6-year follow-up) were compared with UDCA-treated patients from two real-world cohorts. In the cross-study comparison, treatment with OCA resulted in significantly superior transplant-free survival (HR [hazard ratio]: 0.29 [95% CI: 0.10–0.83] for POISE vs. global PBC and HR: 0.30 [95% CI: 0.12–0.75] for POISE vs. UK PBC) (Murillo Perez 2022).

The FDA has recommended a contraindication in decompensated liver cirrhosis and also in compensated liver cirrhosis with signs of portal hypertension. These recommendations are based on case reports of acute liver failure, presumably as a result of an OCA overdose (Eaton 2020). In June 2024, EMA recommended revoking conditional marketing authorisation of OCA as the benefits would no longer outweigh its risks. This decision is based on the results of the COBALT study (Phase 3b; OCA vs. placebo over 8 years), which did not show significant differences in the primary composite endpoint, i.e. time to death, liver transplant, MELD score ≥ 15 or hepatic decompensation, between the treatment groups. However, it should be mentioned that many drop-outs and therapeutic switches of patients in the placebo group due to insufficient treatment response and ethical reasons confounded the results (Jones 2024, Kowdley 2022). In November 2024, OCA finally lost its conditional marketing authorisation in the European Union.

Fibrates are nuclear peroxisome proliferator activated receptor (PPAR) agonists that are approved for the treatment of hyperlipidaemia. A meta-analysis of phase 2 studies and several cohort studies indicated that a combination therapy of fenofibrate or bezafibrate and UDCA significantly reduced biochemical markers such as AP and serum bilirubin in patients with an inadequate response to UDCA (Honda 2013, Honda 2019, Grigorian 2015, Tanaka 2015). In the BEZURSO trial, a randomised phase 3 study, 100 patients who had not adequately responded to UDCA therapy according to the Paris II criteria were treated either with a combination of 400 mg bezafibrate per day and UDCA or with UDCA and placebo. The endpoint of normal AST, ALT, AP, modified prothrombin time and normal bilirubin was achieved in 31% of patients in the bezafibrate group compared to 0% in the placebo group. Two thirds of the bezafibrate-treated patients exhibited a complete normalisation of their AP values. Furthermore, a decrease in liver stiffness and some benefit in pruritus were observed (Corpechot C 2018). In a Japanese cohort, transplant-free survival also improved with bezafibrate (Tanaka A 2021). A smaller, non-randomised study reported that additional fibrate therapy in PBC patients with an inadequate response to UDCA can reduce the risk of developing liver cirrhosis or liver decompensation (Chung 2019). In addition to the low costs, the anti-pruritogenic effect of bezafibrate speaks for its use. However, fibrates are not approved for PBC therapy.

Side effects of fibrates include myalgia, gastrointestinal complaints, and increase in retention parameters; hepatotoxicity was observed in 6–10% of cases, some of which required steroid therapy (Corpechot 2018, Abbas N 2023). Appropriate monitoring under bezafibrate is therefore necessary. Furthermore, bezafibrate should be applied with caution in patients with advanced disease stages and is not recommended in cases of portal hypertension, decompensated liver cirrhosis, or impaired renal function.

There are few but promising data on the possible additive effect of triple therapy with UDCA, OCA and fibrates in PBC patients who have not responded adequately to second-line therapy (UDCA+OCA or UDCA+fibrate) (Smets 2021, Soret 2021, Reig 2021). First data from two randomised, placebo-controlled, phase 2, dose-finding studies have further indicated the stronger anti-cholestatic benefit for directly combining obeticholic acid plus bezafibrate (Hejda 2023, Levy 2023a). Larger phase 3 trials and clinical end point studies are warranted to support such an approach in the real-life setting. However, it remains unclear whether OCA will receive a new marketing authorisation for this application.

Currently, there are three further PPAR agonists, elafibranor, seladelpar, and saroglitazar being investigated as second line therapy in combination with UDCA in large, randomised, placebo-controlled phase 3 studies. The PPARα/δ agonist elafibranor at a daily dose of 80 mg achieved the primary endpoint (defined as an AP < 1.67x ULN, with a reduction of ≥ 15% from baseline, and normal total bilirubin levels at week 52) in 51% of patients compared to 4% in the placebo arm. Fifteen percent of elafibranor-treated patients achieved AP normalisation (Kowdley 2024). In October 2024, elafibranor received conditional marketing authorisation in the European Union for the treatment of PBC patients insufficiently responding to UDCA therapy. The selective PPARδ agonist seladelpar achieved at a daily dose of 10 mg the same primary endpoint (month 12) in 61.7% compared to 20% in the placebo arm. Seladelpar (10 mg/day) resulted in AP normalisation in 25% of patients compared to 0% in the placebo group (Hirschfield 2024). Furthermore, the benefit of pruritus improvement seems stronger under seladelpar therapy compared to elafibranor. European Union marketing authorisation of seladelpar for second line treatment of PBC was granted February 2025. Data on the phase 3 study of the PPARα/ɣ agonist saroglitazar have not been published to date. These new therapeutic options will significantly diversify the treatment options for PBC patients in the future. In addition to the laboratory response, effective symptom control will move into the focus of future therapeutic developments.

Extrahepatic manifestations and quality of life

Around 60% of patients are discovered as a result of abnormal laboratory findings and are often still asymptomatic at the time of diagnosis. According to a larger cohort analysis (n = 770) from England, however, the prognosis of PBC is not better if the patients are symptom-free at the time of diagnosis. In addition, patients almost invariably become symptomatic with increasing disease duration, with around 95% becoming symptomatic after 20 years (Prince 2004). In PBC, the severity of the clinical symptoms does not correlate with the stage of the underlying disease. Treatment with UDCA generally does not improve the symptoms of pruritus, fatigue and sicca syndrome (EASL 2017; Hirschfield 2018).

Patients with PBC often suffer from a wide range of different symptoms. Extrahepatic manifestations can lead to a significant reduction in quality of life (Mells 2013). The most common primary extrahepatic symptoms of PBC include fatigue and pruritus. The world's largest PBC patient cohort on symptom burden to date is the UK-PBC National Study Cohort with 2353 patients. Fatigue and symptoms of social dysfunction were independently associated with reduced quality of life (Mells 2013). The younger the patients were, the more their quality of life was impaired (Dyson 2016). In a study on the perception of quality of life, female patients with PBC rated their quality of life even lower than female patients with type II diabetes mellitus (Untas 2015). Even stronger, PBC patients with severe pruritus had a comparable EQ-5D quality of life measure compared to severe

Parkinson`s Disease (Smith 2025). Against this background, the European guideline on the diagnosis and treatment management of patients with PBC emphasises the importance of clinical symptoms. It recommends an "active evaluation" and "active management of PBC-associated symptoms", namely pruritus, fatigue, sicca symptoms, bone changes and comorbid autoimmune diseases (EASL 2017).

Pruritus

For many patients, pruritus is particularly agonising and significantly impairs their quality of life (EASL 2017; Düll 2019). Pruritus is considered chronic if it persists for longer than 6 weeks. In the largest collection of data to date on cholestatic pruritus in 2194 PBC patients, 73% of patients reported pruritus at some point during the course of the disease and 34% reported chronic persistent pruritus. At the onset of PBC, pruritus was already moderate to severe in 28% of patients. However, almost half of the patients with severe pruritus had not yet received a single guideline-oriented drug therapy (Hegade 2019).

With increasing duration, pruritus persists independently of the underlying disease and acquires independent disease value as chronic pruritus. Cholestatic pruritus is often characterised by a circadian rhythm and increases significantly at night and in warm weather. Women often experience an increase in symptoms depending on their menstrual cycle, during late pregnancy or under hormone replacement therapy. The extremities are most frequently affected, especially the palms of the hands and soles of the feet (Beuers 2014). Severe courses restrict everyday activities, lead to a lack of sleep and thus to an increase in existing fatigue. This leads to adjustment, anxiety and depressive disorders, and even suicide (Tajiri 2017; Ständer 2022). In practice, regular recording of the symptom using a numerical rating scale (NRS) or verbal rating scale (VRS) is recommended for the assessment of the course (Ständer 2013). The psychological burden of pruritus should not be underestimated. Patients should therefore be specifically asked about their quality of life and sleep.

Current guidelines recommend a structured approach to pruritus management in stages. As a first step, patients are advised on basic therapeutic measures with moisturising and hydrating skin care products. Potential ingredients include urea, menthol, camphor, lidocaine, polidocanol or calcineurin inhibitors (off-label use). Topical therapy can be used alone or in combination with systemic therapies and/or UV phototherapy. Antihistamines are not recommended as a specific therapy, even though they can occasionally have non-specific antipruritic effects (EASL 2017). With the exception of the anion exchange resin cholestyramine, none of the systemic treatment options mentioned below are approved for cholestatic pruritus.

The side effect profile is considered favourable with adequate patient education, but the antipruritic efficacy of cholestyramine has only been investigated in small, uncontrolled studies (EASL 2017, Düll 2022). The recommended dose ranges from 4–16 g/d, 2-4 hours before or after other medications (EASL 2017). Patients should be carefully informed about possible interactions of the exchange resin with other drugs taken at the same time such as UDCA, digitoxin, oral anticoagulants and fat-soluble vitamins. As an alternative first-line off-label therapy, bezafibrate is recommended at a dose of 400 mg/day. The antipruritic efficacy of bezafibrate was underlined in the randomised, placebo-controlled study FITCH, in which 45% of the study participants achieved at least a 50% reduction in pruritus intensity within 3 weeks (de Vries 2021). Further case series also reported beneficial effects of bezafibrate on pruritus (Reig 2018) and in the BEZURSO-Trial bezafibrate had a trend towards improved pruritus albeit the baseline itch intensity was low with a NRS of 1 (Corpechot 2018). For potential adverse events see paragraph on second-line therapies.

If cholestyramine and/or bezafibrate is not tolerated or ineffective after two to four weeks, the anti-tuberculosis antibiotic and PXR-agonist rifampicin is considered as second-line therapy. The antipruritic efficacy of rifampicin was demonstrated in 4 prospective, randomised and placebo-controlled studies and confirmed by meta-analyses (EASL 2017, Tandon 2007). In most cases, low doses of 150–300 mg/day are sufficient for effective relief of pruritus. There are also increased interaction risks with rifampicin, e.g. with oral anticoagulants, oral contraceptives or antiepileptics. In a large real-life cohort of over 100 patients, treatment-induced hepatitis with liver dysfunction was observed in 5% of patients, indicating that transaminases should be monitored after 2, 6 and 12 weeks after start of therapy or dose modifications (Webb 2018). Patients should also be made aware of an orange-reddish discoloration of the urine and tear fluid.

Further anti-pruritic treatment options are the orally available opioid receptor antagonist naltrexone that was associated with moderate antipruritic effects in pruritus in randomised controlled trials and case reports (EASL 2017, Düll 2022). However, to avoid opioid withdrawal-like symptoms, naltrexone should be dosed gradually up to a dose of 50–100 mg/day. In particular for hospitalised patients or patients with decompensated liver cirrhosis, intravenous naloxone (0.002–0.2 µg/kg bw/min) represents a suitable alternative (Ständer 2022). An antipruritic effect has also being discussed for anticonvulsants such as gabapentin and pregabalin. They are preferably recommended for nephrogenic and neuropathic pruritus, but can also be considered for pruritus of other origins according to guideline recommendations (EASL 2017, Ständer 2022, Düll 2022). Selective serotonin

reuptake inhibitors (SSRIs) such as sertraline (50-100 mg/day) are used empirically in patients in whom previous treatment attempts have failed: The available evidence on the efficacy of sertraline in cholestatic pruritus is limited to small individual studies (Browning 2003, Mayo 2007). The tetracyclic antidepressant mirtazapine (7.5–30 mg/day) with additional H1-antihistaminergic and serotonin-antagonistic effects is not listed in the European PBC guideline, but has been described as antipruritic in case series in cholestasis (Davis 2003). Mirtazapine can therefore be used as further off-label use option in the evening at doses from 7.5-30 mg/day (Ständer 2022).

Novel anti-pruritic therapeutic approaches that are currently investigated in phase 2 and 3 randomised placebo-controlled trials in PBC are ileal bile acid transporter (IBAT) inhibitors (Levy 2023b), Mas-related G protein-coupled receptor (MRGPR) X4 antagonists and κ-opioid receptor (KOR) agonists (Fishbane 2020, Düll 2022).

Invasive, experimental approaches that have been published in case reports also include extracorporeal albumin dialysis, plasmapheresis and biliary drainage using a nasobiliary tube. Case reports also describe positive effects of physical therapy measures such as UV phototherapy (UVA, UVB) or bright light therapy (EASL 2017, Ständer 2022, Düll 2022).

Fatigue

Fatigue also occurs regardless of the severity of the liver disease and can significantly impair the quality of life of patients with PBC. More than half of patients with PBC report fatigue, 20% of which is severe (EASL 2017). Fatigue should not be confused with chronic fatigue syndrome (CFS) that refers to a feeling of persistent exhaustion, the inability to cope with everyday activities and reduced mental and physical performance. Other internal causes such as hypothyroidism, anaemia, celiac disease, and heart failure or medication side effects such as antihistamines and beta blockers should be considered in the differential diagnosis. Severe, especially nocturnal pruritus with sleep disturbances can also contribute significantly to fatigue. Successful relief of nocturnal pruritus also improves the symptoms of fatigue. The exact pathomechanisms of this complex syndrome with peripheral and central components are not yet understood (EASL 2017).

There are still no specific or approved intervention options available. There is also no evidence that treating the underlying disease with UDCA improves fatigue. In particularly severe cases, treatment with the centrally acting sympathomimetic modafenil, which is approved for the treatment of narcolepsy, may be considered (EASL 2017). However, treatment with modafenil in patients with PBC-associated fatigue exhibited no demonstrable benefit over placebo in a randomised, double-blind study (Silveira 2017). Fatigue is not an indication for liver transplantation, as, unlike pruritus, fatigue is usually not significantly improved. Patients can benefit from a structured, multidisciplinary and integrated approach to improve quality of life (including fatigue) (Jones 2008) as well as learning coping strategies and avoiding social isolation (EASL 2017). Novel treatment approaches may include the blockade of NADPH oxidase 1/4 inhibitors as a post-hoc analysis of a phase 2 study using setanaxib in PBC indicated a benefit in patients with moderate to severe fatigue (Jones 2023).

Sicca symptoms

Patients with PBC often complain of sicca symptoms. The dryness can affect almost all mucous membranes, most frequently in the eye and/or mouth area. Keratoconjunctivitis sicca is treated symptomatically with tear substitutes and, in the case of refractory symptoms, additionally with eye drops containing parasympathomimetics such as pilocarpine or cevimeline. Pronounced dry mouth (xerostomia) leads to problems with prolonged speaking and chewing. Due to the increased risk of tooth decay, which is around twice as prevalent as in the general population, those affected should be encouraged to pay more attention to oral hygiene. In addition, the risk of oral candidiasis is 10fold higher in this patient group (EASL 2017). Mouth sprays containing carmellose can provide subjective relief, while chewing gum and lozenges stimulate saliva production. Vaginal moisturisers are available for women with vaginal sicca syndrome – however, local hormone-containing substances should only be prescribed in consultation with a gynecologist (EASL 2017).

Bone health: osteopenia and osteoporosis

The majority of patients with PBC have reduced bone density (Hirschfield 2018). In a Spanish study (185 women with PBC), the prevalence of osteoporosis (T-score: -2.5) in the lumbar spine was 30.6% compared to 11.2 % in an age-matched healthy control population. Overall, 37% of patients with PBC had developed osteoporosis (Guanabens 2010). Furthermore, an increased rate of bone fractures was observed with elafibranor (6%) and seladelpar (4%) compared to 0% in the placebo groups (see FDA prescribing information for elafibranor and seladelpar 2024). The European PBC guideline recommends considering the risk of osteoporosis in all PBC patients (EASL 2017). To this end, osteodensitometry should be performed at the time of diagnosis. Depending on the extent of the cholestasis and

the individual risk profile, this should be repeated approximately every 1–5 years (EASL 2017). In patients with normal nutritional status and lack of features of calcium malabsorption calcium supplementation is not recommended (EASL 2017). Nevertheless, care should be taken to ensure sufficient calcium intake (1000 mg/day). In the absence of contraindications (e.g. history of kidney stones), primary prophylactic substitution with 25-OH vitamin D3 (1000 IU/day) or 20`000 IU/every second week can be given to increase the success of the intake and to achieve normal vitamin D levels in serum (Lindor 2019). For the treatment of osteoporosis, reference is made to corresponding guidelines. In case of intolerance to anti-resorptive bisphosphonate therapy, the involvement of osteoporosis specialists is recommended (Hirschfield 2018).

Cholestasis and nutritional advice

In the case of pronounced PBC-associated cholestasis, the risk of malabsorption of lipids and fat-soluble vitamins increases (EASL 2017). However, a manifest deficiency of fat-soluble vitamins is not commonly observed. Nevertheless, a significant number of patients with PBC exhibit reduced 25-OH vitamin D3 levels. Supplementation of fat-soluble vitamins should therefore be done on an individual basis (EASL 2017). Parenteral vitamin K supplementation may be considered in cases of impaired coagulation prior to surgery (EASL 2017).

The hypercholesterolaemia that regularly occurs in patients with PBC does not generally require treatment. The underlying mechanisms in PBC appear to differ from other cardiovascular risk diseases as lipoprotein X (LpX) is typically increased. The LpX fraction runs within the LDL fraction which results in false high LDL levels. However, LpX seems not to be of artherosclerotic potential (Longo 2002, Mach 2020). Only in case of additional cardiovascular risk such as arterial hypertension, diabetes mellitus or smoking, cholesterol-lowering pharmacological therapy should be applied (EASL 2017). The recommendations from the current European guidelines on dyslipidaemia management can be used for a risk-adapted approach in everyday practice (Mach F 2020).

Outlook

The treatment landscape for PBC is developing very positively. The pipeline of further second-line therapies is rapidly expanding, with further PPAR agonists and a first in class NOX1/4-inhibitor entering phase 3 trials. Thus, it will be possible to aspire for normal liver biochemistry, low symptom burden, and avoidance of liver transplantation. Beyond the classical anti-cholestatic and anti-inflammatory treatment regimen, there are currently also attempts at inducing immune tolerance to an encapsulated PDC-E2 antigen and reprograming the immune system (NCT05104853). Treatment of pruritus will further be strengthened by novel PPAR agonists but also by approaches targeting IBAT, KOR and MRGPRX4. The approval of drug for the treatment of symptom burden will further increase awareness of the symptom burden and the need for appropriate treatment of affected patients. Solely fatigue remains a difficult-to-treat symptom if moderate to severe. Novel approaches may include the NOX1/4-inhibitor setanaxib or golexanolone antagonising neurosteroids at the GABA receptor level. In summary, the future for patients with PBC is promising, remains dynamic and will improve the lives of many patients.

Key Messages

- Diagnosis of PBC should be considered in case of elevated alkaline phosphatase (AP) levels after imaging-based exclusion of obstructive cholestasis.
- PBC diagnosis is based on elevated AP levels in the presence of PBC-specific anti-mitochondrial or anti-nuclear antibodies or in case of non-detectable autoantibodies and PBC compatible liver histology.
- Ursodeoxycholic acid (UDCA 13–15 mg/kg bw) represents the standard first-line therapy in PBC and is of prognostic relevance.
- Treatment response is evaluated after 6 to 12 months of UDCA therapy by using response criteria based on laboratory parameters, e.g. AP, AST < 1.5x ULN and normal bilirubin (Paris-II response criteria).
- In case of inadequate response to the standard therapy, second line therapy with licensed novel PPAR agonists or with bezafibrate (off-label use) in addition to UDCA should be considered for PBC patients without decompensated liver cirrhosis.
- Monitoring of treatment efficacy and disease progression by laboratory parameters and, if available, by liver stiffness measurement is recommended.
- Monitoring of symptom burden such as fatigue, pruritus and sicca-syndrom should be performed regularly and treated consequently.

References

Abbas N, Culver EL, Thorburn D, et al. UK-wide multicenter evaluation of second-line therapies in primary biliary cholangitis. Clin Gastroenterol Hepatol. 2023;21(6):1561-1570.

Angulo P, Batts KP, Therneau TM, Jorgensen RA, Dickson ER, Lindor KD. Long-term ursodeoxycholic acid delays histological progression in primary biliary cirrhosis. Hepatology 1999;29(3):644-647.

Asselta R, Paraboschi EM, Gerussi A, et al. X chromosome contribution to the genetic architecture of primary biliary cholangitis. Gastroenterology 2021;160(7):2483-2495.

Batts KP, Jorgensen RA, Dickson ER, Lindor KD. Effects of ursodeoxycholic acid on hepatic inflammation and histological stage in patients with primary biliary cirrhosis. Am J Gastroenterol. 1996;91(11):2314-2317.

Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(6):318-328.

Beuers U, Kremer AE, Bolier R, Elferink RP. Pruritus in cholestasis: facts and fiction. Hepatology 2014;60:399-407.

Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. J Hepatol. 2015;63(5):1285-1287.

Bitzer M, Groß S, Albert J, et al. S3-Leitlinie Diagnostik und Therapie biliärer Karzinome. Z Gastroenterol. 2023;61(4):420-440.

Bowlus CL, Pockros PJ, Kremer AE, et al. Long-term obeticholic acid therapy improves histological endpoints in patients with primary biliary cholangitis. Clin Gastroenterol Hepatol. 2020;18(5):1170-1178.

Browning J, Combes B, Mayo MJ. Long-term efficacy of sertraline as a treatment for cholestatic pruritus in patients with primary biliary cirrhosis. Am J Gastroenterol. 2003;98(12):2736-2741.

Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology 2013;144:560-569.

Carbone M, Sharp SJ, Flack S, et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology 2016;63(3):930-950.

Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. Lancet 2015;386(10003):1565-1575.

Cauch-Dudek K, Abbey S, Stewart DE et al. Fatigue in primary biliary cirrhosis. Gut 1998;43:705-710.

Cash WJ, O'Neill S, O'Donnell ME et al. Randomized controlled trial assessing the effect of simvastatin in primary biliary cirrhosis. Liver Int. 2013;33:1166-1174.

Chalifoux SL, Konyn PG, Choi G et al. Extrahepatic manifestations of primary biliary cholangitis. Gut Liver 2017;11:771-780.

Cauch-Dudek K, Abbey S, Stewart DE, Heathcote EJ. Fatigue in primary biliary cirrhosis. Gut 1998;43(5):705-710.

Chung SW, Lee JH, Kim MA, et al. Additional fibrate treatment in UDCA-refractory PBC patients. Liver Int. 2019;39(9):1776-1785.

Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology 2000;32(6):1196-1199.

Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 2008;48(3):871-877.

Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol. 2011;55:1361-1367.

Corpechot C, Carrat F, Poujol-Robert A, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology 2012;56(1):198-208.

Corpechot C, Chazouillères O, Rousseau A, et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. N Engl J Med 2018;378(23):2171-2181.

Corpechot C, Carrat F, Gaouar F, et al. Liver stiffness measurement by vibration-controlled transient elastography improves outcome prediction in primary biliary cholangitis. J Hepatol. 2022;77:1545-1553.

Cristoferi L, Calvaruso V, Overi D, et al. Accuracy of transient elastography in assessing fibrosis at diagnosis in naïve patients with primary biliary cholangitis: a dual cut-off approach. Hepatology 2021;74(3):1496-1508.

Dahlqvist G, Gaouar F, Carrat F, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology 2017;65(1):152-163.

D'Amato D, De Vincentis A, Malinverno F, et al. Real-world experience with obeticholic acid in patients with primary biliary cholangitis. JHEP Rep. 2021;3(2):100248.

Davis MP, Frandsen JL, Walsh D, Andresen S, Taylor S. Mirtazapine for pruritus. J Pain Symptom Manage. 2003;25(3):288-291.

de Vries E, Bolier R, Goet J, et al. Fibrates for itch (FITCH) in fibrosing cholangiopathies: A double-blind, randomized, placebo-controlled trial. Gastroenterology 2021;160(3):734-743.

Duan W, Chen S, Li S, et al. The future risk of primary biliary cholangitis (PBC) is low among patients with incidental anti-mitochondrial antibodies but without baseline PBC. Hepatol Commun. 2022;6(11):3112-3119.

Düll MM, Kremer AE. Treatment of pruritus secondary to liver disease. Curr Gastroenterol Rep. 2019;21(9):48.

Düll MM, Kremer AE. Evaluation and management of pruritus in primary biliary cholangitis. Clin Liver Dis. 2022;26(4):727-745.

Dyson JK, Wilkinson N, Jopson L, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. Aliment Pharmacol Ther. 2016;44(10):1039-1050.

Eaton JE, Vuppalanchi R, Reddy R, Sathapathy S, Ali B, Kamath PS.

Liver injury in patients with cholestatic liver disease treated with obeticholic ccid. Hepatology 2020;71(4):1511-1514.

Efe C, Torgutalp M, Henriksson I et al. Extrahepatic autoimmune diseases in primary biliary cholangitis: Prevalence and significance for clinical presentation and disease outcome. J Gastroenterol Hepatol. 2021;36:936-942.

European Association for the Study of the Liver. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75:659-689.

European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145-172.

Fishbane S, Mathur V, Germain MJ, et al. Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients. Kidney Int Rep. 2020;5(5):600-610.

Floreani A, Cazzagon N. PBC and related extrahepatic diseases. Best Pract Res Clin Gastroenterol. 2018;34-35:49-54.

Forman BM, Goode E, Chen J, et al. Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 1995;81(5):687-93.

Fox PC, Bowman SJ, Segal B et al. Oral involvement in primary sjogren syndrome. J Am Dent Assoc. 2008;139:1592-1601.

Gadaleta RM, van Erpecum KJ, Oldenburg B, et al. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. Gut 2011;60(4):463-472.

Gatselis NK, Goet JC, Zachou K et al. Factors associated with progression and outcomes of early stage primary biliary cholangitis. Clin Gastroenterol Hepatol. 2020;18:684-692 e686.

Gershwin ME, Selmi C, Worman HJ et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology 2005;42:1194-1202.

Gerussi A, Carbone M, Corpechot C, Schramm C, Asselta R, Invernizzi P. The genetic architecture of primary biliary cholangitis. Eur J Med Genet. 2021;64(9):104292.

Grigorian AY, Mardini HE, Corpechot C, Poupon R, Levy C. Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: A meta-analysis. Clin Res Hepatol Gastroenterol. 2015;39(3):296-306.

Guañabens N, Cerdá D, Monegal A, et al. Low bone mass and severity of cholestasis affect fracture risk in patients with primary biliary cirrhosis. Gastroenterology 2010 ;138(7):2348-2356.

Haldar D, Janmohamed A, Plant T, et al. Antibodies to gp210 and understanding risk in patients with primary biliary cholangitis. Liver Int 2021;41(3):535-544.

Harms MH, Janssen QP, Adam R, et al. Trends in liver transplantation for primary biliary cholangitis in Europe over the past three decades. Aliment Pharmacol Ther. 2019;49(3):285-295.

Harms MH, de Veer RC, Lammers WJ, et al. Number needed to treat with ursodeoxycholic acid therapy to prevent liver transplantation or death in primary biliary cholangitis. Gut 2020;69(8):1502-1509.

Hegade VS, Mells GF, Fisher H et al. Pruritus Is Common and Undertreated in Patients With Primary Biliary Cholangitis in the United Kingdom. Clin Gastroenterol Hepatol. 2019;17:1379-1387.

Hejda V, Louvet A, Civitarese A, Szczech L, Zou H, Nevens F. Results from a planned interim analysis of a randomized, double-blind, active-controlled trial evaluating the effects of obeticholic acid and bezafibrate on serum biomarkers in primary biliary cholangitis. J Hep. 2023; 78(S1):S45

Hirschfield GM, Heathcote EJ. Antimitochondria antibody-negative primary biliary cirrhosis. Clin Liver Dis. 2008;12:323-331.

Hirschfield GM, Liu X, Xu C,et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N Engl J Med. 2009;360(24):2544-2555.

Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology 2015;148(4):751-761.

Hirschfield GM, Dyson JK, Alexander GJM, et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut 2018;67(9):1568-1594.

Hirschfield GM, Bowlus CL, Mayo MJ et al. A phase 3 trial of seladelpar in primary biliary cholangitis. N Engl J Med 2024; 390(9):783-794.

Honda A, Ikegami T, Nakamuta M, et al. Anticholestatic effects of bezafibrate in patients with primary biliary cirrhosis treated with ursodeoxycholic acid. Hepatology 2013;57(5):1931-1941.

Honda A, Tanaka A, Kaneko T, et al. Bezafibrate Improves GLOBE and UK-PBC scores and long-term outcomes in patients with primary biliary cholangitis. Hepatology 2019;70(6):2035-2046.

Huet PM, Deslauriers J, Tran A et al. Impact of fatigue on the quality of life of patients with primary biliary cirrhosis. Am J Gastroenterol. 2000;95:760-767.

Jahn CE, Schaefer EJ, Taam LA, et al. Lipoprotein abnormalities in primary biliary cirrhosis. Association with hepatic lipase inhibition as well as altered cholesterol esterification. Gastroenterology 1985;89(6):1266-1278.

Jones DE, Sutcliffe K, Pairman J, Wilton K, Newton JL. An integrated care pathway improves quality of life in Primary Biliary Cirrhosis. QJM 2008;101(7):535-543.

Jones DEJ, Wetten A, Barron-Millar B, et al. The relationship between disease activity and UDCA response criteria in primary biliary cholangitis: A cohort study. EBioMedicine 2022;80:104068.

Jones D, Carbone M, Invernizzi P, et al. Impact of setanaxib on quality of life outcomes in primary biliary cholangitis in a phase 2 randomized controlled trial. Hepatol Commun. 2023;7(3):e0057.

Jones DEJ, Beuers U, Bonder A, et al. Primary biliary cholangitis drug evaluation and regulatory approval: where do we go from here? Hepatology 2024; 80(5):1291-1300.

Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med. 2005;353:1261-1273.

Kowdley KV, Luketic V, Chapman R, et al. A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis. Hepatology 2018;67(5):1890-1902.

Kowdley KV, Brookhart AM, Hirschfield GM, et al. Efficacy of obeticholic acid (OCA) vs placebo and external controls on clinical outcomes in primary biliary cholangitis (PBC). Am J Gastroenterol. 2024; online ahead of print.

Kowdley KV, Bowlus CL, Levy C et al. Efficacy and safety of elafibranor in primary biliary cholangitis. N Engl J Med. 2024;390(9):795-805.

Kumagi T, Guindi M, Fischer SE et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. Am J Gastroenterol. 2010;105:2186-2194.

Lammers WJ, van Buuren HR, Hirschfield GM et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147:1338-1349.

Lammers WJ, Hirschfield GM, Corpechot C et al. Development and validation of a scoring system to predict outcomes of patients with primary biliary cirrhosis receiving ursodeoxycholic acid therapy. Gastroenterology 2015;149:1804-1812.

Lammert C, Juran BD, Schlicht E, et al. Biochemical response to ursodeoxycholic acid predicts survival in a North American cohort of primary biliary cirrhosis patients. J Gastroenterol. 2014;49(10):1414-1420.

Leuschner U, Fischer H, Kurtz W et al. Ursodeoxycholic acid in primary biliary cirrhosis: results of a controlled double-blind trial. Gastroenterology 1989;97:1268-1274.

Levy C, Hejda V, Louvet A et al. Combined effect of obeticholic acid and bezafibrate in patients with primary biliary cholangitis and inadequate response to or intolerance of ursodeoxycholic acid: results from two phase 2 clinical trials. Hepatology 2023a;78 (S1):5019-C

Levy C, Kendrick S, Bowlus CL, et al. GLIMMER: A randomized phase 2b dose-ranging trial of linerixibat in primary biliary cholangitis patients with pruritus. Clin Gastroenterol Hepatol. 2023b;21(7):1902-1912.

Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Dickson ER. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. Gastroenterology 1996;110(5):1515-1518.

Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69(1):394-419.

Liu H, Liu Y, Wang L, et al. Prevalence of primary biliary cirrhosis in adults referring hospital for annual health check-up in Southern China. BMC Gastroenterol. 2010;10:100.

Lleo A, Wang GQ, Gershwin ME, Hirschfield GM. Primary biliary cholangitis. Lancet 2020;396(10266):1915-1926.

Longo M, Crosignani A, Battezzati PM, et al. Hyperlipidaemic state and cardiovascular risk in primary biliary cirrhosis. Gut 2002;51(2):265-9.

Lu M, Li J, Haller IV; FOLD Investigators. Factors associated with prevalence and treatment of primary biliary cholangitis in United States health systems. Clin Gastroenterol Hepatol. 2018;16(8):1333-1341.

Ludwig J, Dickson ER, McDonald GS. Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). Virchows Arch A Pathol Anat Histol. 1978;379:103-112.

Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188.

Mang FW, Michieletti P, O'Rourke K et al. Primary biliary cirrhosis, sicca complex, and dysphagia. Dysphagia 1997;12:167-170.

Mattalia A, Quaranta S, Leung PS, et al. Characterization of antimitochondrial antibodies in health adults. Hepatology 1998;27(3):656-661.

Mayo MJ, Handem I, Saldana S, et al. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology 2007;45(3):666-674.

Mells GF, Pells G, Newton JL, et al. Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. Hepatology 2013;58(1):273-283.

Menon KV, Angulo P, Weston S et al. (2001) Bone disease in primary biliary cirrhosis: independent indicators and rate of progression. J Hepatol. 2001;35:316-323.

Murillo Perez CF, Hirschfield GM, Corpechot C et al. Fibrosis stage is an independent predictor of outcome in primary biliary cholangitis despite biochemical treatment response. Aliment Pharmacol Ther. 2019;50:1127-1136.

Murillo Perez CF, Harms MH, Lindor KD et al. Goals of treatment for improved survival in primary biliary cholangitis: Treatment target should be bilirubin within the normal range and normalization of alkaline phosphatase. Am J Gastroenterol. 2020;115(7):1066-1074.

Murillo Perez CF, Fisher H, Hiu S, et al. Greater transplant-free survival in patients receiving obeticholic acid for primary biliary cholangitis in a clinical trial setting compared to real-world external controls. Gastroenterology 2022;163(6):1630-1642.

Nakanuma Y, Zen Y, Harada K et al. Application of a new histological staging and grading system for primary biliary cirrhosis to liver biopsy specimens: Interobserver agreement. Pathol Int. 2010;60:167-174.

Nakamura M, Kondo H, Mori T et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology 2007;45:118-127.

Natarajan Y, Tansel A, Patel P et al. Incidence of Hepatocellular carcinoma in primary biliary cholangitis: A systematic review and meta-analysis. Dig Dis Sci. 2021;66:2439-2451.

Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016;375(7):631-643.

Nevens F, Shiffmann ML, Drenth JPH et al. Durable response in the markers of cholestasis through 5 years of open-label extension study of obeticholic acid in primary biliary cholangitis. Hepatology 2019; 70:S1:LB06

Nevens F, Trauner M, Manns MP. Primary biliary cholangitis as a roadmap for the development of novel treatments for cholestatic liver diseases. J Hepatol. 2023;78(2):430-441.

Osman KT, Maselli DB, Idilman IS et al. Liver stiffness measured by either magnetic resonance or transient elastography is associated with liver fibrosis and is an independent predictor of outcomes among patients with primary biliary cholangitis. J Clin Gastroenterol. 2021;55:449-457.

Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology 2006;130:715-720.

Poupon RE, Balkau B, Eschwège E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med. 1991;324(22):1548-1554.

Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. New Engl J Med. 1994;330(19):1342-1347.

Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997; 113:884-890.

Poupon RE, Chretien Y, Chazouilleres O et al. Quality of life in patients with primary biliary cirrhosis. Hepatology 2004;40:489-494.

Prince MI, Chetwynd A, Craig WL, Metcalf JV, James OF. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. Gut 2004;53(6):865-870.

Reig A, Sesé P, Parés A. Effects of Bezafibrate on Outcome and Pruritus in Primary Biliary Cholangitis With Suboptimal Ursodeoxycholic Acid Response. Am J Gastroenterol. 2018;113(1):49-55.

Reig A, Álvarez-Navascués C, Vergara M, et al. Obeticholic acid and fibrates in primary biliary cholangitis: Comparative effects in a multicentric observational study. Am J Gastroenterol. 2021;116(11):2250-2257

Roberts SB, Ismail M, Kanagalingam G, et al. Real-World Effectiveness of Obeticholic Acid in Patients with Primary Biliary Cholangitis. Hepatol Commun. 2020;4(9):1332-1345.

Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. N Engl J Med. 1983; 6;308(1):1-7.

Scheuer PJ. Ludwig Symposium on biliary disorders--part II. Pathologic features and evolution of primary biliary cirrhosis and primary sclerosing cholangitis. Mayo Clin Proc. 1998;73:179-183.

Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. Lancet 2011;377(9777):1600-1609.

Silveira MG, Suzuki A, Lindor KD. Surveillance for hepatocellular carcinoma in patients with primary biliary cirrhosis. Hepatology 2008;48(4):1149-56.

Silveira MG, Gossard AA, Stahler AC, et al. A randomized, placebo-controlled clinical trial of efficacy and safety: Modafinil in the treatment of fatigue in patients with primary biliary cirrhosis. Am J Ther. 2017;24(2):e167-e176.

Smets L, Verbeek J, Korf H, van der Merwe S, Nevens F. Improved Markers of Cholestatic Liver Injury in Patients With Primary Biliary Cholangitis Treated With Obeticholic Acid and Bezafibrate. Hepatology 2021;73(6):2598-2600.

Smith H, McLaughlin MM, Das S et al. The devastating impact of severe pruritus in primary biliary cholangitis; Hepatol Comm. 2025; online ahead of print.

Soret PA, Lam L, Carrat F, et al. Combination of fibrates with obeticholic acid is able to normalise biochemical liver tests in patients with difficult-to-treat primary biliary cholangitis. Aliment Pharmacol Ther 2021;53(10):1138-1146.

Ständer S, Augustin M, Reich A, et al. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials. Acta Derm Venereol. 2013;93(5):509-514.

Ständer S, Zeidler C, Augustin M, et al. S2k guideline: Diagnosis and treatment of chronic pruritus. J Dtsch Dermatol Ges. 2022;20(10):1387-1402.

Tajiri K, Shimizu Y. Recent advances in the management of pruritus in chronic liver diseases. World J Gastroenterol. 2017;23(19):3418-3426.

Tanaka A, Hirohara J, Nakanuma Y, Tsubouchi H, Takikawa H. Biochemical responses to bezafibrate improve long-term outcome in asymptomatic patients with primary biliary cirrhosis refractory to UDCA. J Gastroenterol. 2015;50(6):675-682.

Tanaka A, Hirohara J, Nakano T, et al. Association of bezafibrate with transplant-free survival in patients with primary biliary cholangitis. J Hepatol. 2021;75(3):565-571.

Tandon P, Rowe BH, Vandermeer B, Bain VG. The efficacy and safety of bile Acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. Am J Gastroenterol. 2007;102(7):1528-1536.

Trauner M, Nevens F, Shiffman ML, et al. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. Lancet Gastroenterol Hepatol. 2019;4(6):445-453.

Trivedi PJ, Lammers WJ, van Buuren HR et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut 2016;65:321-329.

Untas A, Boujut E, Corpechot C, et al. Quality of life and illness perception in primary biliary cirrhosis: a controlled cross-sectional study. Clin Res Hepatol Gastroenterol 2015;39(1):52-58.

Vergani D, Alvarez F, Bianchi FB, et al. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. J Hepatol. 2004;41(4):677-83.

Vleggaar FP, van Buuren HR, Zondervan PE et al. Jaundice in non-cirrhotic primary biliary cirrhosis: the premature ductopenic variant. Gut 2001;49:276-281.

Webb GJ, Rahman SR, Levy C, Hirschfield GM. Low risk of hepatotoxicity from rifampicin when used for cholestatic pruritus: a cross-disease cohort study. Aliment Pharmacol Ther. 2018;47(8):1213-1219.

Yagi M, Tanaka A, Namisaki T, et al. Is patient-reported outcome improved by nalfurafine hydrochloride in patients with primary biliary cholangitis and refractory pruritus? A post-marketing, single-arm, prospective study. J Gastroenterol. 2018;53(10):1151-1158.

Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and management of primary biliary cholangitis. Am J Gastroenterol. 2019;114(1):48-63.

Zandanell S, Strasser M, Feldman A, et al. Low rate of new-onset primary biliary cholangitis in a cohort of anti-mitochondrial antibody-positive subjects over six years of follow-up. J Intern Med. 2020;287(4):395-404.

14. Alcohol-associated hepatitis

Julian Allgeier, Claus Niederau, Johannes Sauter, Christian M. Lange

Harmful alcohol use and its global burden

Alcohol consumption remains one of the leading risk factors for disease worldwide. In 2018, the Global Burden of Disease collaboration considered 32, 5% of people (25% of females, 39% of males) to be current drinkers, with prevalence highest in regions with high socio-demographic index (SDI) like north western Europe, Australia, Russia or Canada (Collaborators 2018). In 2016, alcohol use was the seventh leading risk factor for premature death and disability and accounted for 2, 8 million deaths (Collaborators 2018). Europe has the highest attributable burden of all WHO regions (Collaborators 2018) with a significant gender gap: the attributable burden in men is 11, 0% whereas it is only 1, 8% in women (Collaborators 2018). While there is some evidence that moderate alcohol consumption may have protective effects in disease entities including ischemic heart disease and diabetes, the all-cause relative mortality risk increased monotonically with the amount of daily alcohol drinks (Collaborators 2018). Excessive alcohol consumption, whether in the form of heavy drinking or binge drinking, is responsible for about 50% of all liver-related deaths (Stein 2016); alcohol-associated liver disease culminates in cirrhosis in about 10-20% of cases in the United States (Singal 2021).

The onset of the COVID-19 pandemic aggravated these alcohol-associated effects; sale of alcoholic beverages increased significantly both remotely and online in 2020, the first year of the pandemic (Grossman 2020). Microsimulation modeling has estimated that this one-year increase will have resulted in 8000 ALD-related deaths, 18.700 cases of decompensated cirrhosis, 1.000 additional cases of HCC and 8, 9 million disability-adjusted life years by 2080 (Julien 2022). In the U.S. mortality rates for alcoholic liver disease dramatically increased between 2010-2019 and 2020-2021 during the COVID-19 pandemic, while the rates for NAFLD slightly increased and those for hepatitis B and C decreased (Gao 2023); the later study also showed that alcoholic liver disease was the most common cause of liver related mortality in the U.S. accounting for 55% of deaths, followed by HCV (33%), NAFLD (9%), and HBV (3%).

Definitions for what is considered hazardous alcohol use differ; the National Institute on Alcohol Use and Alcoholism (NIAAA) considers non-hazardous alcohol consumption as less than one drink for women and less than two drinks for men per day, with one drink defined as 14 g of alcohol

(2018). Yet, there is no threshold of safe alcohol consumption and even lower amounts confer a risk of alcohol-associated liver disease in the long-term (Collaborators 2022). Moreover, various drinking patterns confer an increased risk for liver injury, specifically binge drinking, more than four or five drinks for women and men, respectively, in less than two hours, and heavy drinking, more than seven or fourteen drinks for women and men, respectively, in a week (NIAAA 2018).

Key aspect to all strategies to reduce alcohol-related morbidity is prevention. A Swedish register study tracking more than 43.000 men enlisted for military service between 1969 and 1970 for 38 years found found that alcohol consumption in adolescence predicts liver related morbidity significantly later in life in a dose-dependent manner even at doses below those defined by various agencies as non-hazardous (Hagstrom 2018). Thus, education about the effects of alcohol consumption on somatic and psychological health needs initiation early in life. There is evidence that this should include brief behavioral counseling interventions to reduce unhealthy alcohol use in adults >18 years (O'Connor 2018) while evidence for those aged 17 and under is still lacking. To identify those at risk for alcohol use disorder (AUD), any drinking that results in impairment of mental of physical health, screening tools and questionnaires are helpful. The alcohol use disorders identification test (AUDIT) remains the gold standard for identifying hazardous and harmful drinkers (Bohn 1995), but a variety of other screening and assessment tools have arisen and are widely available online and through various agencies. Regulating availability of alcohol by amending legal drinking age, restricting access through reducing places of sale, higher taxes or bans on advertising might all positively impact alcohol-related morbidity, but more research is warranted to assess their individual and collective impact on harmful alcohol consumption.

Pathogenesis of alcohol-related liver disease (ALD)

There is significant individual variability in the relationship between extent of alcohol consumption and onset and severity of ALD. Predisposition to ALD is mediated by environmental, genetic and epigenetic factors; for the development of more severe forms such as alcoholic hepatitis-associated liver failure, conclusive causative scientific evidence is still lacking (Bataller 2022).

Hepatic injury in the setting of excessive alcohol consumption is a consequence of direct toxicity of ethanol-metabolites, but also of intestinal dysbiosis, damage of intestinal barriers and local and systemic inflammatory responses.

(1) Direct hepatic injury mediated by ethanol

Ethanol is oxidised by various enzymatic and nonenzymatic pathways. In hepatocytes, the most important pathway is oxidation of ethanol via alcohol dehydrogenase (ADH) to acetaldehyde; in mitochondria, acetaldehyde is converted to acetate and in turn acetate is converted to acetyl CoA, which leads the two-carbon molecule into the TCA (tricarboxylic acid cycle). The human genome encodes for five different classes of ADH, the majority of which are found in hepatic tissue (Sultatos 2004); however, alcohol metabolism mediated by ADH initiates not there but in the gastric epithelium (Sultatos 2004). Ethanol oxidation generates reducing equivalents, primarily reduced nicotinamide adenine dinucleotide (NAD), i.e., NADH. Changes in the NADH–NAD+ potential in the liver inhibit both fatty acid oxidation and the TAC and may thereby increase lipogenesis (You 2004). Ethanol has also been proven to increase lipid metabolism by inhibiting peroxisome proliferator–activated receptor α (PPARα) and AMP kinase as well as by stimulation of sterol regulatory element-binding protein (Fischer 2003, Ji 2006, You 2004), all mechanisms that favour presence of hepatic steatosis.

Ethanol may also activate Fas and TNF receptor 1 (TNF-R1) thereby activating caspase 8, causing mitochondrial injury and opening the mitochondrial transition pore (MTP), releasing cytochrome c, and activating caspases; all these processes contribute to apoptosis. Activation of TNF-R1 leads to nuclear factor kappa B (NFkB) activation (Schaffert 2009). TRIF-dependent signaling may contribute to alcohol-induced liver damage mediated by TLR4 (Hritz 2008). Animal models have also shown that alcohol increases various markers of oxidative stress (Meagher 1999, Wu 2009). Studies in rats and mice suggest that activated Kupffer cells and hepatocytes are the main sources of alcohol-induced free radicals (Bailey 1998, Kamimura 1992). Oxidative stress may mediate alcohol-induced liver injury in part via cytochrome P450 2E1 (Pessayre 1999, Lu 2008), leading to mitochondrial damage, activation of endoplasmic reticulum–dependent apoptosis, and up-regulation of lipid synthesis (Ji 2003, Yin 2001).

Other enzymatic pathways involved in ethanol metabolism include catalase and the Microsomal Ethanol Oxidising System (MEOS), a distinct structural unit of the endoplasmatic reticulum involved in metabolism of ethanol to acetaldehyde and utilising reduced NADH generated by cytosolic ADH activity (Teschke 2018).

The major propagating factor of alcohol-induced liver damage is formation of reactive oxygen species (ROS) and their consecutive direct damage to cellular and subcellular structures resulting in hepatocyte death and an inflammatory response by the host; virtually all systems, also those not explicitly named here, cause formation of ROS (Wu 2003).

(2) The gut-liver axis

Ethanol directly and indirectly affects the intestinal epithelial barrier and as such, the translocation of intraluminal contents to the portal venous system and by extension to the liver (Szabo 2015). High concentrations of intraluminal ethanol cause cell death in intestinal epithelium; systemic ethanol also downregulates mRNA levels of proteins associated with function and integrity of tight junctions in intestinal epithelium, resulting in impaired intestinal barrier function (Keshavarzian 1999). Acetaldehyde exhibits similar intraluminal effects (Dunagan 2012). Of note, ethanol consumption leads to profound intestinal dysbiosis, characterised by intestinal bacterial overgrowth, enrichment of pathogenic bacterial species, and of species more characteristic for the oral microbiome (Bajaj 2019). These changes are accompanied by changes in the intestinal virome and by fungal dysbiosis in alcoholic hepatitis (Lang 2020, Jiang 2020). Importantly, intestinal dysbiosis induces intestinal inflammation (mediated among others by TNF-alpha), which increases intestinal permeability (Chen 2015). Furthermore, a milestone study has shown that cytolysin, secreted by Enterococcus faecalis can cause hepatocyte death and liver injury (Duan 2019). This finding is particularly important since cytolytic Enterococcus faecalis can be therapeutically targeted by bacteriophages.

These changes in barrier integrity result in translocation of inflammatory mediators to the hepatic circulation, including pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) like lipopolysaccharide (LPS), the prototypical bacterial endotoxin (Szabo 2015), in most cases independent of consumption pattern (Bala 2014). Binding of LPS to CD14 in Kupffer cells and activation of toll-like receptors, specifically toll-like-receptor-4 (TLR-4) propagates inflammatory cascades in the liver (Schaffert 2009). Inhibition of this pathway in mice deficient of either TLR4 or CD14 has mediated protection to the detrimental hepatic effects of alcohol (Hritz 2008, Uesugi 2001, Petrasek 2010). Activation of TLR4 additionally results in downstream activation of the NFK-β pathway and increased production of a variety of pro- and anti-inflammatory cytokines including TNF-α and IL-1b, two molecules also involved in increased gut permeability, constituting a feedback-loop for further aggravation of alcohol-induced translocation of intestinal contents (Yoseph 2013).

Historically, the role of TNF-α has attracted significant attention as a potential treatment target in alcoholic hepatitis, but this approach has failed in clinical studies. Activated Kupffer cells also release TNF-α. Circulating TNF-α concentrations are higher in patients with alcoholic hepatitis than in heavy drinkers with inactive cirrhosis, heavy drinkers who do not have liver disease and people who do not drink alcohol and who do not have liver disease (Adachi 1994, Bird 1990). Circulating TNF-α concentrations are associated with high mortality (Bird 1990). In animal studies, knockouts of the TNF receptor 1 and administration of the anti-TNF-α agent thalidomide both ameliorated alcohol-induced liver injury (Yin 1999, Enomoto 1999). Ethanol was also shown to release mitochondrial cytochrome c and to induce expression of the Fas ligand that may then cause apoptosis via the caspase-3 activation pathway (Zhou 2001). Both TNF-α and Fas-mediated signals may increase the vulnerability of hepatocytes (Minagawa 2004).

(3) Genetic factors

While much remains unknown about the genetic thumbprint that predisposes to the development or progression of ALD in individuals with risky alcohol use, some risk variations have been identified. There is ample evidence that women develop ALD more quickly than men (Becker 1996, Sato 2001). In 2008, two genome-wide association (GWAS) studies linked the rs738409 polymorphism (I148M) of patatin-like phospholipase domain containing 3 (PNPLA3) with hepatic fat content and ALT levels (Romeo 2008, Yuan 2008). Further studies corroborated this association between the I148M polymorphism and NAFLD in almost all ethnic and age groups (Baclig 2014, DiStefano 2015, Buch 2015, Trepo 2014). The I148M polymorphism also seems to predispose to cirrhosis (Shen 2015) and hepatocellular carcinoma (Trepo 2014, Burza 2014, Valenti 2013). More recently, it has been suggested that the IL48M PNPLA3 polymorphism also accelerates fibrosis progression and HCC incidence in alcoholic liver disease (Buch 2015, Trepo 2012, Nault 2014, Falleti 2016, Stickel 2015). Another GWAS confirmed PNPLA3 and identified TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis (Buch 2015). All three loci are known to have a role in lipid processing, suggesting that lipid turnover is important in the pathogenesis of alcohol-related cirrhosis. An investigation into the interaction between PNPLA3 rs738409 and TM6SF2 rs58542926 as risk variants for HCC development showed that TM6SF2 C/T or T/T in conjunction with PNPLA3 G/G variants may be potential genetic risk factors for developing HCC in alcohol-related cirrhosis (Falleti 2016). In addition, carriage of the heterozygous alpha1-antitrypsin Pi*Z strongly increases the risk of alcohol-associated liver disease (Strnad 2019).

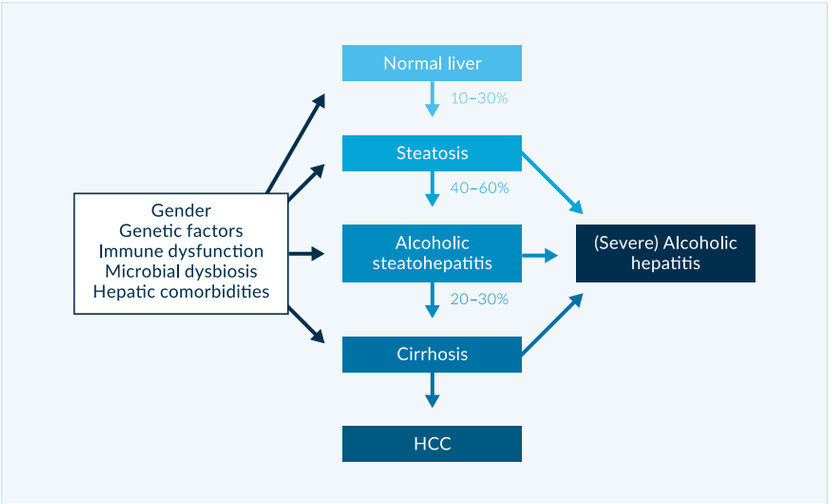

Figure 1. Effects of alcohol overconsumption on the liver

Diagnosis

The clinical spectrum of alcohol-associated liver disease ranges from steatosis and steatohepatitis to severe alcoholic hepatitis, liver cirrhosis and hepatocellular carcinoma (Figure 1). Severe alcoholic hepatitis is a syndrome that can emerge in patients with or without liver cirrhosis. Common features include jaundice, ascites, peripheral edema and hepatomegaly; in the presence of portal hypertension and associated sequelae, patients can also present with hematemesis or other signs of gastrointestinal hemorrhage. Hepatic encephalopathy (HE) is common, but caution is warranted as alcohol withdrawal syndrome represents an important differential diagnosis and differs in treatment. Overt HE is associated with poorer prognosis (Sujan 2018). In patients with liver cirrhosis, alcoholic hepatitis is a frequent cause of acute-on-chronic liver failure (i.e. acute decompensation of cirrhosis in combination with specific organ failures).

While the diagnosis of alcohol-associated hepatitis remains a clinical one, a variety of criteria have been recommended over time, most recently by the government-funded Alcoholic Hepatitis Consortia. The following conditions are employed (Crabb 2016):

Criteria for diagnosis of alcoholic hepatitis

1. Onset of Jaundice within eight weeks of presentation to medical professional
2. Ongoing excessive alcohol consumption
   - Females: three drinks or > 40 g alcohol/diem
   - Males: four drinks or > 50 g alcohol/diem
3. Abstinence (if so reported) of less than 60 days
4. Total Bilirubin >3 mg/dL
5. Aspartate Aminotransferase (AST) >50 U/L + AST/ALT ratio of 1.5 AND both AST and ALST < 400 U/L
6. Exclusion of other causes of acute liver injury

A major adjustment in comparison to previous sets of criteria has been inclusion of moderate cases of alcohol-associated hepatitis as evidenced by lowering the threshold of inclusion of total bilirubin from 5 mg/dL to 3 mg/dL (Bataller 2022). Seemingly insignificant, this enables inclusion of a subgroup of alcoholic hepatitis cases that has significant short and medium term mortality (<7% at three months and <20% at one year) (Clemente-Sanchez 2021) and would benefit from medical surveillance primarily aimed at promoting cessation of alcohol consumption (Bataller 2022).

Ruling out competing differential diagnoses should include exclusion of biliary or vessel obstruction via imaging (ultrasound, CT/MRT), viral hepatitis (HAV/HBV/HCV/HEV and other hepatotropic viruses), autoimmune hepatitis (autoimmune serology), ischaemia and drug-induced liver injury (DILI).

Liver biopsy, preferably transjugular, is not required but has its place in the setting of diagnostic uncertainty. Biopsy can only identify presence of steatohepatitis and while certain characteristics tend to appear more readily in alcoholic hepatitis, is not the appropriate diagnostic modality to differentiate it from nonalcoholic steatohepatitis (Kleiner 2012). Acute steatohepatitis generally features ballooned hepatocytes, presence of Mallory-Denk bodies, a neutrophilic infiltrate, ductular reactions, bilirubinostasis and pericellular and sinusoidal fibrosis (Bataller 2022).

If performed, liver biopsy can deliver important prognostic information. Altamirano et al developed a semiquantitative scoring system called the Alcoholic Hepatitis Histologic-Score (AHHS) (Altamirano 2014). Their primary analysis included data from 121 patients in Barcelona, Spain; its development continued through a test set of 96 patients from five academic centres in the United States and Europe. The system was validated with an independent group of 109 patients. Degree of fibrosis, neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria were independently associated with 90-day mortality. The AHHS identifies patients with a low (0–3 points), moderate (4–5 points), or high (6–9 points)

risk of death within 90 days (3%, 19%, and 51%, respectively; p < 0.0001). It estimated 90-day mortality in the training and test sets with an area under the receiver operating characteristic analysis of 0.77 (95% confidence interval 0.71–0.83), thus proving its potential clinical use for identifying high risk individuals (Altamirano 2014).

Similarly, Lackner et al. recently developed a scoring system under the umbrella of the Study of Alcohol-related Liver Disease Study Group (SALVE); their scoring system, just like the AHHS, clearly demonstrates increased mortality in the setting of present cirrhosis (Lackner 2021).

Predictive modeling and indication for therapy

Disease-related mortality for alcoholic hepatitis varies depending on project (?, was ist mit project gemeint?) and is generally approximated between 20-50% after three months (Cohen 2009, Arab 2021).

Most prominently, Maddrey's discriminant function (MDF) and the Model for End-Stage Liver Disease (MELD) score are employed for stratification and help to identify patients who can benefit from treatment with corticosteroids. MDF is calculated using the following equation (Maddrey 1978):

MDF >32 indicates benefit from corticosteroid treatment in the setting of alcoholic hepatitis (Maddrey 1978). MELD is useful specifically in clinical settings in which PT is not a parameter routinely determined. Patients with MDF <32 usually have milder disease with short term survival >90% and generally do not benefit from treatment with corticosteroids. In patients with acute-on-chronic liver failure, the CLIF-C ACLF score can be informative (https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf).

Other less commonly employed scoring systems that have shown ability to predict mortality in the alcoholic hepatitis cohort include the Glasgow Alcoholic Hepatitis Score (GAHS) (Forrest 2007) and the ABIC Score (Age; Bilirubin; INR; Creatinine) (Dominguez 2008). Patients with a Maddrey's discriminant function >32 and a GAHS of >9 who were treated with corticosteroids had an 84-day survival of 59%, while untreated patients had a 38% survival (Forrest 2007).

The GAHS adjudicates points for the following categories:

GAHS categories

- Age
- White Blood Cell Count (WBC)
- BUN
- Total Bilirubin
- PT

ABIC uses the following equations for calculation:

ABIC = (Age, years, × 0.1) + (Total Bilirubin (mg/dl) x 0.08) + (INR × 0.8) + (Creatinine (mg/dl) × 0.3)

A variety of retrospective analyses have recently concluded that MELD prognosticates mortality more accurately than MDF, making it the score of choice for approximating usefulness of corticosteroid treatment at the present time (Dunn 2005, Srikureja 2005, Morales-Arraez 2022, Forrest 2018). Maximum benefit from corticosteroids is derived in a MELD range between 25 – 39 (Bataller 2022).

As corticosteroids increase the risk of infection which is one of the major complications contributing to mortality in the presence of alcoholic liver failure, the Lille Score has been useful in predicting lack of response to corticosteroids and is calculated on day 7 after initiation of treatment (Louvet 2007). Calculations can also be performed on day 4 (Garcia-Saenz-de-Sicilia 2017).

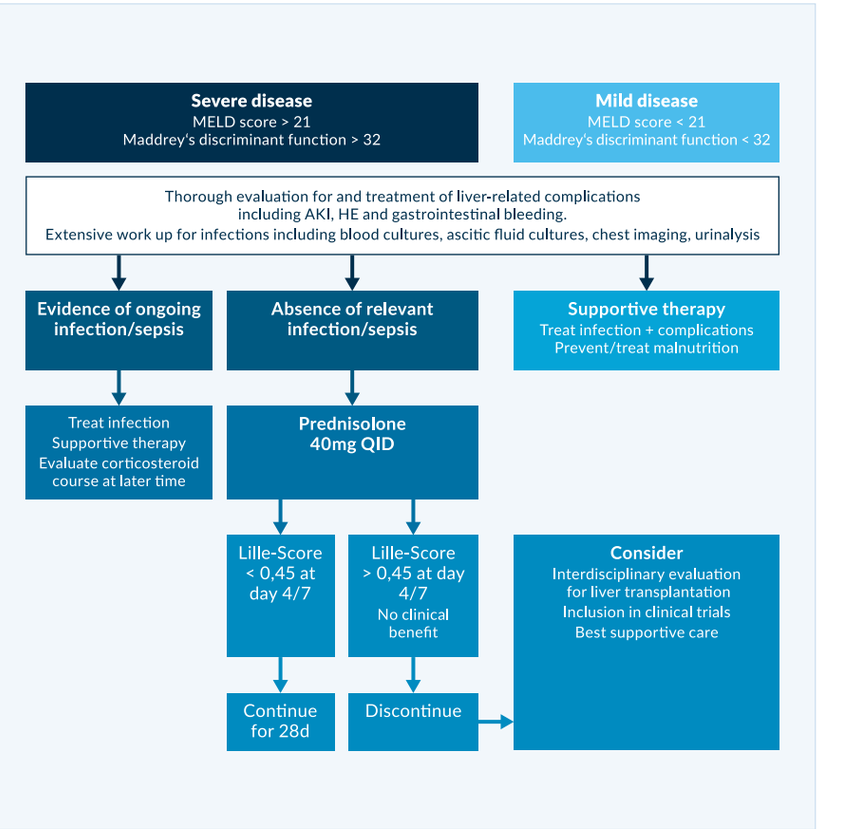

Figure 2.

Therapy

(1) Corticosteroids

Historically, studies and meta-analyses have shown controversial results for the use of corticosteroids in alcoholic hepatitis (Imperiale 1990, Imperiale 1999, Rambaldi 2008, Christensen 1999). Generally, it is accepted that corticosteroids have not been shown to increase survival, in particular during longer follow-up (Rambaldi 2008) except in a subgroup of patients with a Maddrey's discriminant function >32 or in those presenting with hepatic encephalopathy (Rambaldi 2008, Mathurin 2002). A meta-analysis of three studies corroborated that corticosteroids given for 28 days increase 1-month survival by 20% in severe alcoholic hepatitis (Maddrey's discriminant function >32) (Mathurin 2002). Prednisolone was generally administered at 40 mg per day for 28 days, with (Imperiale 1999) or without (Mathurin 2003) tapering regimens employed.

In the STOPAH trial, the largest double-blind RCT comparing prednisolone (and pentoxifylline, details below) conducted thus far, primary end-point analysis of data of 1053 patients yielded a moderate improvement of short-term mortality (1 month) in the prednisolone-group, but no significant differences in 3 month and 1 year mortality (Thursz 2015).

The mechanisms by which corticosteroids improve short-term survival in severe alcoholic hepatitis are not fully understood but are generally thought to be by disruption of inflammatory response. In general, corticosteroids inhibit various inflammatory processes by acting on activator protein 1 and NFkB (Barnes 1997). In patients with alcoholic hepatitis, some studies reported that corticosteroids were associated with a decrease in circulating levels of proinflammatory cytokines such as interleukin-8, TNF-α and others (Taieb 2000, Spahr 2001). Corticosteroid use is considered contraindicated in the presence of sepsis, severe infection, or gastrointestinal bleeding (O'Shea 2006).

MDF, MELD, and Lille Score are used to stratify whether corticosteroid therapy is indicated; its continuation beyond a seven day treatment course is warranted in the setting of alcoholic hepatitis (Maddrey 1978, Louvet 2007, Lucey 2009) with an MDF >32, or a MELD >21 respectively, indicating a short term benefit (Figure 2).

(2) Pentoxifylline

Pentoxifylline, a diphosphoesterase inhibitor, has been assessed in several clinical trials in severe alcoholic hepatitis.

Initial studies indicated a possible benefit as pentoxifylline (administered at 400 mg TID for 28 days) reduced short-term mortality in severe alcoholic hepatitis (MDF>32); mortality was 24% in the pentoxifylline group and 46% in the placebo group (p <0.01) (Akriviadis 2000); this effect is likely due to significant differences in deaths attributed to hepatorenal syndrome (HRS) (placebo: 22/24, 92%; treatment group: 6/12, 50%), suggesting that its effect is orchestrated through preventing HRS.

In 2014 however, a randomised, non-inferiority trial that included 121 patients with severe alcoholic hepatitis with MDF >32 found no significant differences in 1-month survival, 6-month survival, treatment response as defined by the Lille Model and hepatic complications, concluding that prednisolone remains the preferred treatment option (Park 2014).

Salvage therapy with pentoxifylline after lack of response to prednisolone hads no beneficial effects on treatment outcome (Louvet 2008); similarly, combination of prednisolone and pentoxifylline did not have an effect on 1-month and 6-month survival (Sidhu 2012, Mathurin 2013).

Finally, in the above mentioned STOPAH trial no benefit of pentoxifylline was observed (Thursz 2015). Overall, Pentoxifylline cannot currently be recommended for the treatment of alcoholic hepatitis.

(3) TNF-α inhibition

While initial pre-clinical data and experience from pilot studies concerning the effectiveness of TNF-α inhibition to alleviate hepatic necrosis seemed promising (Tilg 2003, Menon 2004, Sharma 2009, Limuro 1997), trials investigating the use of infliximab and etanercept in severe alcoholic hepatitis had to be terminated prematurely due to a significant increase in severe infections (Naveau 2004) and a decrease in 6-month survival (Boetticher 2008), perhaps because TNF-α is required for liver regeneration. Current guidelines do not recommend their use in severe alcoholic hepatitis (Singal 2018, EASL 2012).

(4) N-acetyl cysteine (NAC) and other antioxidants

In a large trial, the combination of NAC and prednisolone for severe alcoholic hepatitis showed only significant reductions of mortality at the 1-month interval (n=7/85 (8.2%) vs. 21/89 (23.6%), p=0.005) and after two months (13/85 (15.3%) vs. 29/89 (32.6%), p=0.007) but not at three or six months (19/85 (22.4%) vs. 30/89 (33.7%), p=0.095) (23/85 (27.1%) vs. 34/89 (38.2%) (Nguyen-Khac 2011). Nevertheless, further studies are justified to explore the benefits of NAC in addition to prednisolone in severe alcoholic hepatitis, because this trial may have been underpowered.

Other antioxidant drugs, such as vitamin E, have shown to be ineffective at improving outcome or survival for patients with severe alcoholic hepatitis (Phillips 2006, Stewart 2007, Mezey 2004)

(5) G-CSF

In 2014, a RCT evaluated the hypothesis that treating patients with severe alcoholic hepatitis with granulocyte colony-stimulating factor (G-CSF) might mobilise bone marrow-derived stem cells and promote hepatic regeneration and thereby improve survival (Singh 2014). 46 patients were randomised to one treatment arm receiving standard medical treatment (SMT) (n=23) and another arm receiving G-CSF (n=23) at a dose of 5 µg/kg subcutaneously every 12 h for 5 consecutive days.

There was a statistically significant increase in the number of CD34+ cells in the peripheral blood in the G-CSF arm as compared with the SMT arm after 5 days of therapy. Concurrently, 1-month survival was significantly improved in the G-CSF arm (78.3% vs. 30.4%, p=0.001). There was also a significant reduction in Child-Pugh and MELD scores and MDF at 1-, 2-, and 3-month intervals between the groups favouring G-CSF (Singh 2014).

Unfortunately, a recent meta-analysis that included more recent follow-up studies has reported high heterogeneity between studies with geographical differences indicating results ranging from lack of efficiency to even higher mortality with G-CSF in European studies, indicating the need for further, high-quality evidence (Marot 2020).

(6) Nutrition and supportive therapy

Signs of malnutrition and clinically apparent sarcopenia are common in patients with AUD and alcoholic liver disease, underscoring the importance of including nutritional strategies in the treatment approach for this patient collective. Alcoholic beverages have high caloric but poor nutritional value. Malnutrition is associated with high mortality in severe alcoholic hepatitis (Mendenhall 1984, Mendenhall 1986, Stickel 2003).

An RCT compared enteral nutrition with 2000 kcal/day via feeding tube with corticosteroid treatment (Prednisolone 40 mg QD, 28 days) in severe alcoholic hepatitis, finding similar 1-month and 1-year survival rates in both groups (Cabre 2000). A small pilot study in 2004 combined corticosteroid therapy with total enteral nutrition and suggested it could be a useful strategy in patients with severe alcoholic hepatitis (Alvarez 2004).

More recently, the combination of corticosteroid therapy and enteral nutrition was compared against corticosteroid therapy alone in a RCT, enrolling 136 patients with a history of risky alcohol consumption, recent onset of jaundice, and steatohepatitis proven by biopsy; they were assigned randomly (1:1) to groups that received either intensive enteral nutrition plus methylprednisolone or conventional nutrition plus methylprednisolone (Moreno 2016). In the intensive enteral nutrition group, enteral nutrition was given via feeding tube for 14 days. The primary end point was 6-month survival. In the intention-to-treat analysis, there was no significant difference between groups in 6-month cumulative mortality: 44.4% in the enteral nutrition group vs. 52.1% in the controls (p= 0.406). Intensive enteral nutrition was difficult to implement and did not improve survival (Moreno 2016) However, further analysis showed that low daily energy intake was associated with greater mortality, so adequate nutritional intake should remain a goal for treatment.

Current guidelines recommend a daily protein intake of 1.2 – 1.5 g/kg and a daily caloric intake of 35 kcal/kg for patients with severe alcoholic hepatitis with an additional replenishment of thiamine and B complex vitamins as well as zinc and other trace elements (Singal 2018).

Furthermore, a comprehensive infection work-up should be performed to rule out concomitant infection, a major source of decompensation in the setting of alcoholic liver disease. Special attention must be given to differentiating community-acquired from healthcare-associated infections and even without culture positive infection, the threshold for initiating broad spectrum anti-infective therapy should be low (Singal 2018).

(7) Liver transplantation (LT)

In some countries (e.g. in Germany) in patients with decompensated alcoholic cirrhosis, a minimum sobriety interval of six months is required for consideration for liver transplantation (though exceptions are possible). This is, however, a requirement that cannot be afforded to patients in acute liver failure secondary to alcoholic hepatitis, given that the 1-month mortality lies between 20-50% (Singal 2014) and promising conservative treatment options offering improvement are lacking.

In 2011, a pivotal study from Belgium and France showed for the first time that transplanting highly selected patients with severe alcoholic hepatitis that were non-responders to corticosteroid therapy and had a favourable psychosocial profile can strongly improve survival compared to conservative treatment (6-month survival in LT: 77% vs. SMT: 23%, p<0.001) (Mathurin 2011). Relapse rate was low and comparable to historical cohorts (Mathurin 2011). The ACCELERATE-AH study confirmed these results, with survival rates of 94% after one year and 84% after three years; relapse rate for sustained alcohol abuse was 10% and 17% after one and three years,

respectively, comparable to those seen after posttransplant for in other transplant indications (Lee 2018). Other cohorts have shown higher rates of relapse in these early transplantation cohorts compared to the traditional approach however (Bataller 2022), and its association with increased mortality warrants further attention. For this purpose, the Sustained Alcohol Use Post Liver Transplant (SALT) Score has been developed and has shown usefulness in predicting low risk for relapse (Lee 2019). It includes four variables: >10 drinks/day at time of initial hospitalisation, multiple previous rehabilitation attempts, alcohol-related legal issues, and illicit substance abuse (Lee 2019).

Cohorts in the United States and in Italy have confirmed that LT significantly improves the outcome of patients with severe alcoholic hepatitis while also reporting similar relapse rates of alcohol consumption (Louvet 2022, Germani 2022). Nevertheless, LT should be considered as the first line treatment in the setting of severe, non-steroid responsive alcoholic hepatitis in highly selected patients after careful evaluation of their psychosocial profile.

(8) Miscellaneous and emerging therapy options

Historically, drugs that target the liver's capacity to regenerate such as oxandrolone, propylthiouracil, insulin and glucagon have failed to provide a mortality benefit (Halle 1982, Trinchet 1992, Bird 1991).

More recently, the IL-22 agonist F-652 has shown promising ability to reduce MELD and Lille-scores and ameliorate hepatic inflammation after 28 days (Arab 2020) (Table 1). Exploiting the increasingly attention-seizing connection between the liver and the gut microbiome, a pilot study on fecal microbiota transplantation has reported a reduction in mortality compared to historical cohorts (Philips 2017). Another phase 1 clinical trial evaluated effects of FMT in patients with alcoholic cirrhosis and continuous, problematic drinking habits evidenced by AUDIT-10 >8 and reported safety of FMT and also significant reduction in craving; FMT increased microbial diversity and significantly reduced inflammatory parameters such as IL-6 compared to the placebo group (Bajaj 2021).

Other modalities targeting the dysfunction of the gut-liver axis currently under investigation for severe alcoholic hepatitis include broad-spectrum antibiotics and bovine colostrum (Bataller 2022).

Anakinra, in combination with pentoxifylline and zinc has not proven to increase 6-month survival in patients with severe alcoholic hepatitis compared to standard corticosteroid therapy (Szabo 2022), and Anakinra without pentoxifylline and zinc was associated with increased mortality compared to prednisolone in another trial (Gawrieh S. et al. AASLD 2022 late-breaking abstract).

The ISAIAH trial is currently investigating the proficiency of the IL-1 Antagonist canakinumab in severe alcoholic hepatitis (Vergis 2021). The apoptosis inhibitors selonsertib and emricasan are also being evaluated as treatment options (Bataller 2022).

Table 1.

Emerging therapies + ongoing trials	
Therapy Modality	**Evidence/ Trial Number**
Fecal Microbiome Transfer (FMT)	Philips 2017; Bajaj 2021; NCT04758806
Bovine Colostrum	NCT01968382; NCT02473341
F-652 (recombinant IL-22)	NCT02655510
Canakinumab (IL-1 Inhibitor)	NCT03775109
Selonsertib (ASK-1 Inhibitor)	NCT02854631

(9) AUD and abstinence

Abstinence remains the factor with the highest impact on morbidity and mortality in patients with AUD and alcoholic liver disease. There is consensus that these patients should be managed within a multidisciplinary team that includes addiction specialists (Arab 2022). Identification of underlying psychiatric comorbidities is essential. For AUD, a variety of drugs with alcohol anticraving properties are available but should be used with caution in the setting of alcoholic hepatitis and its sequelae; baclofen is considered safe in ALD, while disulfiram, acamprosate, and naltrexone should all be avoided in patients with advanced liver disease (Arab 2022).

Rehabilitation should be initiated as soon as possible. Initiation during in-patient treatment of alcoholic hepatitis or within 30 days of initial presentation significantly reduces readmission, alcohol relapse and death (Peeraphatdit 2020) and while most outpatient hepatologists remain reluctant to prescribe medical treatment for AUD, their out-patient use has been associated with lower rates of disease progression (Vannier 2022, Vannier 2022).

Summary

Alcoholic hepatitis is a clinical syndrome for which diagnosis is established based on patient history of heavy alcohol consumption, jaundice, signs of liver failure, and the absence of other reasonable causes of liver injury. A liver biopsy may be helpful but is not required either

to determine the diagnosis or enable prognosis. Abstinence is the most important factor for recovery and rehabilitation and should be initiated during hospitalisation. Patients with severe alcoholic hepatitis (Maddrey's discriminant function >32 or MELD score >21) should receive corticosteroid therapy in the absence of contraindications. Benefit from corticosteroid therapy should be evaluated after four to seven days using the Lille model (Louvet 2007). Traditionally, pentoxifylline has been employed as a secondary treatment option, but its use is not universally recommended without clear evidence for impact on mortality. In non-steroid responsive alcoholic hepatitis, carefully selected patients may benefit from liver transplantation. Emerging therapies aiming to improve intestinal dysbiosis as an important element in the pathogenesis of alcoholic hepatitis seem promising and deserve further investigation.

References

Collaborators GBDA. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. Sep 22 2018;392(10152):1015-1035. doi:10.1016/S0140-6736(18)31310-2

Stein E, Cruz-Lemini M, Altamirano J, et al. Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. J Hepatol. Nov 2016;65(5):998-1005. doi:10.1016/j.jhep.2016.06.018

Singal AK, Mathurin P. Diagnosis and Treatment of Alcohol-Associated Liver Disease: A Review. JAMA. Jul 13 2021;326(2):165-176. doi:10.1001/jama.2021.7683

Grossman ER, Benjamin-Neelon SE, Sonnenschein S. Alcohol Consumption during the COVID-19 Pandemic: A Cross-Sectional Survey of US Adults. Int J Environ Res Public Health. Dec 9 2020;17(24)doi:10.3390/ijerph17249189

Julien J, Ayer T, Tapper EB, Barbosa C, Dowd WN, Chhatwal J. Effect of increased alcohol consumption during COVID-19 pandemic on alcohol-associated liver disease: A modeling study. Hepatology. Jun 2022;75(6):1480-1490. doi:10.1002/hep.32272

Drinking Levels Defined. NIAAA. 2018. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking

Collaborators GBDA. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. Lancet. Jul 16 2022;400(10347):185-235. doi:10.1016/S0140-6736(22)00847-9

Hagstrom H, Hemmingsson T, Discacciati A, Andreasson A. Alcohol consumption in late adolescence is associated with an increased risk of severe liver disease later in life. J Hepatol. Mar 2018;68(3):505-510. doi:10.1016/j.jhep.2017.11.019

O'Connor EA, Perdue LA, Senger CA, et al. Screening and Behavioral Counseling Interventions to Reduce Unhealthy Alcohol Use in Adolescents and Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. Nov 13 2018;320(18):1910-1928. doi:10.1001/jama.2018.12086

Bohn MJ, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. J Stud Alcohol. Jul 1995;56(4):423-32. doi:10.15288/jsa.1995.56.423

Bataller R, Arab JP, Shah VH. Alcohol-Associated Hepatitis. N Engl J Med. Dec 29 2022;387(26):2436-2448. doi:10.1056/NEJMra2207599

Sultatos LG, Pastino GM, Rosenfeld CA, Flynn EJ. Incorporation of the genetic control of alcohol dehydrogenase into a physiologically based pharmacokinetic model for ethanol in humans. Toxicol Sci. Mar 2004;78(1):20-31. doi:10.1093/toxsci/kfh057

You M, Crabb DW. Recent advances in alcoholic liver disease II. Minireview: molecular mechanisms of alcoholic fatty liver. Am J Physiol Gastrointest Liver Physiol. Jul 2004;287(1):G1-6. doi:10.1152/ajpgi.00056.2004

Fischer M, You M, Matsumoto M, Crabb DW. Peroxisome proliferator-activated receptor alpha (PPARalpha) agonist treatment reverses PPARalpha dysfunction and abnormalities in hepatic lipid metabolism in ethanol-fed mice. J Biol Chem. Jul 25 2003;278(30):27997-8004. doi:10.1074/jbc.M302140200

Ji C, Chan C, Kaplowitz N. Predominant role of sterol response element binding proteins (SREBP) lipogenic pathways in hepatic steatosis in the murine intragastric ethanol feeding model. J Hepatol. Nov 2006;45(5):717-24. doi:10.1016/j.jhep.2006.05.009

You M, Matsumoto M, Pacold CM, Cho WK, Crabb DW. The role of AMP-activated protein kinase in the action of ethanol in the liver. Gastroenterology. Dec 2004;127(6):1798-808. doi:10.1053/j.gastro.2004.09.049

Schaffert CS, Duryee MJ, Hunter CD, et al. Alcohol metabolites and lipopolysaccharide: roles in the development and/or progression of alcoholic liver disease. World J Gastroenterol. Mar 14 2009;15(10):1209-18. doi:10.3748/wjg.15.1209

Hritz I, Mandrekar P, Velayudham A, et al. The critical role of toll-like receptor (TLR) 4 in alcoholic liver disease is independent of the common TLR adapter MyD88. Hepatology. Oct 2008;48(4):1224-31. doi:10.1002/hep.22470

Meagher EA, Barry OP, Burke A, et al. Alcohol-induced generation of lipid peroxidation products in humans. J Clin Invest. Sep 1999;104(6):805-13. doi:10.1172/JCI5584

Wu D, Cederbaum AI. Oxidative stress and alcoholic liver disease. Semin Liver Dis. May 2009;29(2):141-54. doi:10.1055/s-0029-1214370

Bailey SM, Cunningham CC. Acute and chronic ethanol increases reactive oxygen species generation and decreases viability in fresh, isolated rat hepatocytes. Hepatology. Nov 1998;28(5):1318-26. doi:10.1002/hep.510280521

Kamimura S, Gaal K, Britton RS, Bacon BR, Triadafilopoulos G, Tsukamoto H. Increased 4-hydroxynonenal levels in experimental alcoholic liver disease: association of lipid peroxidation with liver fibrogenesis. Hepatology. Aug 1992;16(2):448-53. doi:10.1002/hep.1840160225

Pessayre D, Mansouri A, Haouzi D, Fromenty B. Hepatotoxicity due to mitochondrial dysfunction. Cell Biol Toxicol. 1999;15(6):367-73. doi:10.1023/a:1007649815992

Lu Y, Zhuge J, Wang X, Bai J, Cederbaum AI. Cytochrome P450 2E1 contributes to ethanol-induced fatty liver in mice. Hepatology. May 2008;47(5):1483-94. doi:10.1002/hep.22222

Ji C, Kaplowitz N. Betaine decreases hyperhomocysteinaemia, endoplasmic reticulum stress, and liver injury in alcohol-fed mice. Gastroenterology. May 2003;124(5):1488-99. doi:10.1016/s0016-5085(03)00276-2

Yin M, Gabele E, Wheeler MD, et al. Alcohol-induced free radicals in mice: direct toxicants or signaling molecules? Hepatology. Nov 2001;34(5):935-42. doi:10.1053/jhep.2001.28888

Teschke R. Alcoholic Liver Disease: Alcohol Metabolism, Cascade of Molecular Mechanisms, Cellular Targets, and Clinical Aspects. Biomedicines. Nov 12 2018;6(4)doi:10.3390/biomedicines6040106

Wu D, Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res Health. 2003;27(4):277-84.

Szabo G. Gut-liver axis in alcoholic liver disease. Gastroenterology. Jan 2015;148(1):30-6. doi:10.1053/j.gastro.2014.10.042

Keshavarzian A, Holmes EW, Patel M, Iber F, Fields JZ, Pethkar S. Leaky gut in alcoholic cirrhosis: a possible mechanism for alcohol-induced liver damage. Am J Gastroenterol. Jan 1999;94(1):200-7. doi:10.1111/j.1572-0241.1999.00797.x

Dunagan M, Chaudhry K, Samak G, Rao RK. Acetaldehyde disrupts tight junctions in Caco-2 cell monolayers by a protein phosphatase 2A-dependent mechanism. Am J Physiol Gastrointest Liver Physiol. Dec 15 2012;303(12):G1356-64. doi:10.1152/ajpgi.00526.2011

Bajaj JS. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol. Apr 2019;16(4):235-246. doi:10.1038/s41575-018-0099-1

Lang S, Duan Y, Liu J, et al. Intestinal Fungal Dysbiosis and Systemic Immune Response to Fungi in Patients With Alcoholic Hepatitis. Hepatology. Feb 2020;71(2):522-538. doi:10.1002/hep.30832

Jiang L, Lang S, Duan Y, et al. Intestinal Virome in Patients With Alcoholic Hepatitis. Hepatology. Dec 2020;72(6):2182-2196. doi:10.1002/hep.31459

Chen P, Starkel P, Turner JR, Ho SB, Schnabl B. Dysbiosis-induced intestinal inflammation activates tumour necrosis factor receptor I and mediates alcoholic liver disease in mice. Hepatology. Mar 2015;61(3):883-94. doi:10.1002/hep.27489

Duan Y, Llorente C, Lang S, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature. Nov 2019;575(7783):505-511. doi:10.1038/s41586-019-1742-x

Bala S, Marcos M, Gattu A, Catalano D, Szabo G. Acute binge drinking increases serum endotoxin and bacterial DNA levels in healthy individuals. PLoS One. 2014;9(5):e96864. doi:10.1371/journal.pone.0096864

Uesugi T, Froh M, Arteel GE, Bradford BU, Thurman RG. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. Hepatology. Jul 2001;34(1):101-8. doi:10.1053/jhep.2001.25350

Petrasek J, Mandrekar P, Szabo G. Toll-like receptors in the pathogenesis of alcoholic liver disease. Gastroenterol Res Pract. 2010;2010doi :10.1155/2010/710381

Yoseph BP, Breed E, Overgaard CE, et al. Chronic alcohol ingestion increases mortality and organ injury in a murine model of septic peritonitis. PLoS One. 2013;8(5):e62792. doi:10.1371/journal.pone.0062792

Adachi Y, Bradford BU, Gao W, Bojes HK, Thurman RG. Inactivation of Kupffer cells prevents early alcohol-induced liver injury. Hepatology. Aug 1994;20(2):453-60.

Bird GL, Sheron N, Goka AK, Alexander GJ, Williams RS. Increased plasma tumour necrosis factor in severe alcoholic hepatitis. Ann Intern Med. Jun 15 1990;112(12):917-20. doi:10.7326/0003-4819-112-12-917

Yin M, Wheeler MD, Kono H, et al. Essential role of tumour necrosis factor alpha in alcohol-induced liver injury in mice. Gastroenterology. Oct 1999;117(4):942-52. doi:10.1016/s0016-5085(99)70354-9

Enomoto N, Yamashina S, Kono H, et al. Development of a new, simple rat model of early alcohol-induced liver injury based on sensitisation of Kupffer cells. Hepatology. Jun 1999;29(6):1680-9. doi:10.1002/hep.510290633

Becker U, Deis A, Sorensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology. May 1996;23(5):1025-9. doi:10.1002/hep.510230513

Sato N, Lindros KO, Baraona E, et al. Sex difference in alcohol-related organ injury. Alcohol Clin Exp Res. May 2001;25(5 Suppl ISBRA):40S-45S. doi:10.1097/00000374-200105051-00007

Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. Dec 2008;40(12):1461-5. doi:10.1038/ng.257

Yuan X, Waterworth D, Perry JR, et al. Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes. Am J Hum Genet. Oct 2008;83(4):520-8. doi:10.1016/j.ajhg.2008.09.012

Baclig MO, Lozano-Kuhne JP, Mapua CA, Gopez-Cervantes J, Natividad FF, St Luke's Liver Diseases Study G. Genetic variation I148M in patatin-like phospholipase 3 gene and risk of non-alcoholic fatty liver disease among Filipinos. Int J Clin Exp Med. 2014;7(8):2129-36.

DiStefano JK, Kingsley C, Craig Wood G, et al. Genome-wide analysis of hepatic lipid content in extreme obesity. Acta Diabetol. Apr 2015;52(2):373-82. doi:10.1007/s00592-014-0654-3

Buch S, Stickel F, Trepo E, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet. Dec 2015;47(12):1443-8. doi:10.1038/ng.3417

Trepo E, Nahon P, Bontempi G, et al. Association between the PNPLA3 (rs738409 C>G) variant and hepatocellular carcinoma: Evidence from a meta-analysis of individual participant data. Hepatology. Jun 2014;59(6):2170-7. doi:10.1002/hep.26767

Shen JH, Li YL, Li D, Wang NN, Jing L, Huang YH. The rs738409 (I148M) variant of the PNPLA3 gene and cirrhosis: a meta-analysis. J Lipid Res. Jan 2015;56(1):167-75. doi:10.1194/jlr.M048777

Burza MA, Molinaro A, Attilia ML, et al. PNPLA3 I148M (rs738409) genetic variant and age at onset of at-risk alcohol consumption are independent risk factors for alcoholic cirrhosis. Liver Int. Apr 2014;34(4):514-20. doi:10.1111/liv.12310

Valenti L, Dongiovanni P, Ginanni Corradini S, Burza MA, Romeo S. PNPLA3 I148M variant and hepatocellular carcinoma: a common genetic variant for a rare disease. Dig Liver Dis. Aug 2013;45(8):619-24. doi:10.1016/j.dld.2012.12.006

Trepo E, Guyot E, Ganne-Carrie N, et al. PNPLA3 (rs738409 C>G) is a common risk variant associated with hepatocellular carcinoma in alcoholic cirrhosis. Hepatology. Apr 2012;55(4):1307-8. doi:10.1002/hep.25518

Nault JC, Nahon P. Genetic predisposition to hepatocellular carcinoma in alcoholic cirrhosis: the NCAN-PNPLA3-lipid connection? J Hepatol. Nov 2014;61(5):971-2. doi:10.1016/j.jhep.2014.08.001

Falleti E, Cussigh A, Cmet S, Fabris C, Toniutto P. PNPLA3 rs738409 and TM6SF2 rs58542926 variants increase the risk of hepatocellular carcinoma in alcoholic cirrhosis. Dig Liver Dis. Jan 2016;48(1):69-75. doi:10.1016/j.dld.2015.09.009

Stickel F, Hampe J, Trepo E, Datz C, Romeo S. PNPLA3 genetic variation in alcoholic steatosis and liver disease progression. Hepatobiliary Surg Nutr. Jun 2015;4(3):152-60. doi:10.3978/j.issn.2304-3881.2014.11.04

*Strnad P, Buch S, Hamesch K, et al. Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis. Gut. Jun 2019;68(6):1099-1107. doi:10.1136/gutjnl-2018-316228*

Sujan R, Cruz-Lemini M, Altamirano J, et al. A Validated Score Predicts Acute Kidney Injury and Survival in Patients With Alcoholic Hepatitis. Liver Transpl. Dec 2018;24(12):1655-1664. doi:10.1002/lt.25328

Crabb DW, Bataller R, Chalasani NP, et al. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology. Apr 2016;150(4):785-90. doi:10.1053/j.gastro.2016.02.042

Clemente-Sanchez A, Oliveira-Mello A, Bataller R. Moderate Alcoholic Hepatitis. Clin Liver Dis. Aug 2021;25(3):537-555. doi:10.1016/j.cld.2021.03.001

Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. Semin Liver Dis. Feb 2012;32(1):3-13. doi:10.1055/s-0032-1306421

Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology. May 2014;146(5):1231-9 e1-6. doi:10.1053/j.gastro.2014.01.018

Lackner C, Stauber RE, Davies S, et al. Development and prognostic relevance of a histologic grading and staging system for alcohol-related liver disease. J Hepatol. Oct 2021;75(4):810-819. doi:10.1016/j.jhep.2021.05.029

Cohen SM, Ahn J. Review article: the diagnosis and management of alcoholic hepatitis. Aliment Pharmacol Ther. Jul 2009;30(1):3-13. doi:10.1111/j.1365-2036.2009.04002.x

Arab JP, Diaz LA, Baeza N, et al. Identification of optimal therapeutic window for steroid use in severe alcohol-associated hepatitis: A worldwide study. J Hepatol. Nov 2021;75(5):1026-1033. doi:10.1016/j.jhep.2021.06.019

Maddrey WC, Boitnott JK, Bedine MS, Weber FL, Jr., Mezey E, White RI, Jr. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology. Aug 1978;75(2):193-9.

Forrest EH, Morris AJ, Stewart S, et al. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. Gut. Dec 2007;56(12):1743-6. doi:10.1136/gut.2006.099226

Dominguez M, Rincon D, Abraldes JG, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol. Nov 2008;103(11):2747-56. doi:10.1111/j.1572-0241.2008.02104.x

Dunn W, Jamil LH, Brown LS, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology. Feb 2005;41(2):353-8. doi:10.1002/hep.20503

Srikureja W, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. J Hepatol. May 2005;42(5):700-6. doi:10.1016/j.jhep.2004.12.022

Morales-Arraez D, Ventura-Cots M, Altamirano J, et al. The MELD Score Is Superior to the Maddrey Discriminant Function Score to Predict Short-Term Mortality in Alcohol-Associated Hepatitis: A Global Study. Am J Gastroenterol. Feb 1 2022;117(2):301-310. doi:10.14309/ajg.0000000000001596

Forrest EH, Atkinson SR, Richardson P, et al. Application of prognostic scores in the STOPAH trial: Discriminant function is no longer the optimal scoring system in alcoholic hepatitis. J Hepatol. Mar 2018;68(3):511-518. doi:10.1016/j.jhep.2017.11.017

Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology. Jun 2007;45(6):1348-54. doi:10.1002/hep.21607

Garcia-Saenz-de-Sicilia M, Duvoor C, Altamirano J, et al. A Day-4 Lille Model Predicts Response to Corticosteroids and Mortality in Severe Alcoholic Hepatitis. Am J Gastroenterol. Feb 2017;112(2):306-315. doi:10.1038/ajg.2016.539

Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomised trials. Ann Intern Med. Aug 15 1990;113(4):299-307. doi:10.7326/0003-4819-113-4-299

Imperiale TF, O'Connor JB, McCullough AJ. Corticosteroids are effective in patients with severe alcoholic hepatitis. Am J Gastroenterol. Oct 1999;94(10):3066-8. doi:10.1111/j.1572-0241.1999.03066.x

Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis--a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. Aliment Pharmacol Ther. Jun 2008;27(12):1167-78. doi:10.1111/j.1365-2036.2008.03685.x

Christensen E, Gluud C. Glucocorticosteroids are not effective in alcoholic hepatitis. Am J Gastroenterol. Oct 1999;94(10):3065-6. doi:10.1111/j.1572-0241.1999.03065.x

Mathurin P, Mendenhall CL, Carithers RL, Jr., et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomised placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol. Apr 2002;36(4):480-7. doi:10.1016/s0168-8278(01)00289-6

Mathurin P, Abdelnour M, Ramond MJ, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology. Dec 2003;38(6):1363-9. doi:10.1016/j.hep.2003.09.038

Thursz MR, Forrest EH, Ryder S, investigators S. Prednisolone or Pentoxifylline for Alcoholic Hepatitis. N Engl J Med. Jul 16 2015;373(3):282-3. doi:10.1056/NEJMc1506342

Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med. Apr 10 1997;336(15):1066-71. doi:10.1056/NEJM199704103361506

Taieb J, Mathurin P, Elbim C, et al. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. J Hepatol. Apr 2000;32(4):579-86. doi:10.1016/s0168-8278(00)80219-6

Spahr L, Rubbia-Brandt L, Pugin J, et al. Rapid changes in alcoholic hepatitis histology under steroids: correlation with soluble intercellular adhesion molecule-1 in hepatic venous blood. J Hepatol. Nov 2001;35(5):582-9. doi:10.1016/s0168-8278(01)00190-8

O'Shea R, McCullough AJ. Steroids or cocktails for alcoholic hepatitis. J Hepatol. Apr 2006;44(4):633-6. doi:10.1016/j.jhep.2006.01.011

Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med. Jun 25 2009;360(26):2758-69. doi:10.1056/NEJMra0805786

Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology. Dec 2000;119(6):1637-48. doi:10.1053/gast.2000.20189

Park SH, Kim DJ, Kim YS, et al. Pentoxifylline vs. corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial. J Hepatol. Oct 2014;61(4):792-8. doi:10.1016/j.jhep.2014.05.014

Louvet A, Diaz E, Dharancy S, et al. Early switch to pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids. J Hepatol. Mar 2008;48(3):465-70. doi:10.1016/j.jhep.2007.10.010

Sidhu SS, Goyal O, Singla P, et al. Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE trial). Dig Dis Sci. Jun 2012;57(6):1664-71. doi:10.1007/s10620-012-2097-4

Mathurin P, Louvet A, Duhamel A, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomised clinical trial. JAMA. Sep 11 2013;310(10):1033-41. doi:10.1001/jama.2013.276300

Tilg H, Jalan R, Kaser A, et al. Anti-tumour necrosis factor-alpha monoclonal antibody therapy in severe alcoholic hepatitis. J Hepatol. Apr 2003;38(4):419-25. doi:10.1016/s0168-8278(02)00442-7

Menon KV, Stadheim L, Kamath PS, et al. A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis. Am J Gastroenterol. Feb 2004;99(2):255-60. doi:10.1111/j.1572-0241.2004.04034.x

Sharma P, Kumar A, Sharma BC, Sarin SK. Infliximab monotherapy for severe alcoholic hepatitis and predictors of survival: an open label trial. J Hepatol. Mar 2009;50(3):584-91. doi:10.1016/j.jhep.2008.10.024

Iimuro Y, Gallucci RM, Luster MI, Kono H, Thurman RG. Antibodies to tumour necrosis factor alfa attenuate hepatic necrosis and inflammation caused by chronic exposure to ethanol in the rat. Hepatology. Dec 1997;26(6):1530-7. doi:10.1002/hep.510260621

Naveau S, Chollet-Martin S, Dharancy S, et al. A double-blind randomised controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology. May 2004;39(5):1390-7. doi:10.1002/hep.20206

Boetticher NC, Peine CJ, Kwo P, et al. A randomised, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology. Dec 2008;135(6):1953-60. doi:10.1053/j.gastro.2008.08.057

Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol. Feb 2018;113(2):175-194. doi:10.1038/ajg.2017.469

European Association for the Study of L. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol. Aug 2012;57(2):399-420. doi:10.1016/j.jhep.2012.04.004

Nguyen-Khac E, Thevenot T, Piquet MA, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med. Nov 10 2011;365(19):1781-9. doi:10.1056/NEJMoa1101214

Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. J Hepatol. Apr 2006;44(4):784-90. doi:10.1016/j.jhep.2005.11.039

Stewart S, Prince M, Bassendine M, et al. A randomised trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol. Aug 2007;47(2):277-83. doi:10.1016/j.jhep.2007.03.027

Mezey E, Potter JJ, Rennie-Tankersley L, Caballeria J, Pares A. A randomised placebo controlled trial of vitamin E for alcoholic hepatitis. J Hepatol. Jan 2004;40(1):40-6. doi:10.1016/s0168-8278(03)00476-8

Singh V, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomised pilot study. Am J Gastroenterol. Sep 2014;109(9):1417-23. doi:10.1038/ajg.2014.154

Marot A, Singal AK, Moreno C, Deltenre P. Granulocyte colony-stimulating factor for alcoholic hepatitis: A systematic review and meta-analysis of randomised controlled trials. JHEP Rep. Oct 2020;2(5):100139. doi:10.1016/j.jhepr.2020.100139

Mendenhall CL, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. Am J Med. Feb 1984;76(2):211-22. doi:10.1016/0002-9343(84)90776-9

Mendenhall CL, Tosch T, Weesner RE, et al. VA cooperative study on alcoholic hepatitis. II: Prognostic significance of protein-calorie malnutrition. Am J Clin Nutr. Feb 1986;43(2):213-8. doi:10.1093/ajcn/43.2.213

Stickel F, Hoehn B, Schuppan D, Seitz HK. Review article: Nutritional therapy in alcoholic liver disease. Aliment Pharmacol Ther. Aug 15 2003;18(4):357-73. doi:10.1046/j.1365-2036.2003.01660.x

Cabre E, Rodriguez-Iglesias P, Caballeria J, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomised trial. Hepatology. Jul 2000;32(1):36-42. doi:10.1053/jhep.2000.8627

Alvarez MA, Cabre E, Lorenzo-Zuniga V, Montoliu S, Planas R, Gassull MA. Combining steroids with enteral nutrition: a better therapeutic strategy for severe alcoholic hepatitis? Results of a pilot study. Eur J Gastroenterol Hepatol. Nov 2004;16(12):1375-80. doi:10.1097/00042737-200412000-00023

Moreno C, Deltenre P, Senterre C, et al. Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids. Gastroenterology. Apr 2016;150(4):903-10 e8. doi:10.1053/j.gastro.2015.12.038

Singal AK, Kamath PS, Gores GJ, Shah VH. Alcoholic hepatitis: current challenges and future directions. Clin Gastroenterol Hepatol. Apr 2014;12(4):555-64; quiz e31-2. doi:10.1016/j.cgh.2013.06.013

Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. Nov 10 2011;365(19):1790-800. doi:10.1056/NEJMoa1105703

Lee BP, Mehta N, Platt L, et al. Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis. Gastroenterology. Aug 2018;155(2):422-430 e1. doi:10.1053/j.gastro.2018.04.009

Lee BP, Vittinghoff E, Hsu C, et al. Predicting Low Risk for Sustained Alcohol Use After Early Liver Transplant for Acute Alcoholic Hepatitis: The Sustained Alcohol Use Post-Liver Transplant Score. Hepatology. Apr 2019;69(4):1477-1487. doi:10.1002/hep.30478

Louvet A, Labreuche J, Moreno C, et al. Early liver transplantation for severe alcohol-related hepatitis not responding to medical treatment: a prospective controlled study. Lancet Gastroenterol Hepatol. May 2022;7(5):416-425. doi:10.1016/S2468-1253(21)00430-1

Germani G, Angrisani D, Addolorato G, et al. Liver transplantation for severe alcoholic hepatitis: A multicenter Italian study. Am J Transplant. Apr 2022;22(4):1191-1200. doi:10.1111/ajt.16936

Halle P, Pare P, Kaptein E, Kanel G, Redeker AG, Reynolds TB. Double-blind, controlled trial of propylthiouracil in patients with severe acute alcoholic hepatitis. Gastroenterology. May 1982;82(5 Pt 1):925-31.

Trinchet JC, Balkau B, Poupon RE, et al. Treatment of severe alcoholic hepatitis by infusion of insulin and glucagon: a multicenter sequential trial. Hepatology. Jan 1992;15(1):76-81. doi:10.1002/hep.1840150115

Bird G, Lau JY, Koskinas J, Wicks C, Williams R. Insulin and glucagon infusion in acute alcoholic hepatitis: a prospective randomised controlled trial. Hepatology. Dec 1991;14(6):1097-101.

Arab JP, Sehrawat TS, Simonetto DA, et al. An Open-Label, Dose-Escalation Study to Assess the Safety and Efficacy of IL-22 Agonist F-652 in Patients With Alcohol-associated Hepatitis. Hepatology. Aug 2020;72(2):441-453. doi:10.1002/hep.31046

Philips CA, Pande A, Shasthry SM, et al. Healthy Donor Fecal Microbiota Transplantation in Steroid-Ineligible Severe Alcoholic Hepatitis: A Pilot Study. Clin Gastroenterol Hepatol. Apr 2017;15(4):600-602. doi:10.1016/j.cgh.2016.10.029

Bajaj JS, Gavis EA, Fagan A, et al. A Randomised Clinical Trial of Fecal Microbiota Transplant for Alcohol Use Disorder. Hepatology. May 2021;73(5):1688-1700. doi:10.1002/hep.31496

Szabo G, Mitchell M, McClain CJ, et al. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. Hepatology. Oct 2022;76(4):1058-1068. doi:10.1002/hep.32478

Vergis N, Patel V, Bogdanowicz K, et al. IL-1 Signal Inhibition In Alcoholic Hepatitis (ISAIAH): a study protocol for a multicentre, randomised, placebo-controlled trial to explore the potential benefits of canakinumab in the treatment of alcoholic hepatitis. Trials. Nov 11 2021;22(1):792. doi:10.1186/s13063-021-05719-2

Arab JP, Izzy M, Leggio L, Bataller R, Shah VH. Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation. Nat Rev Gastroenterol Hepatol. Jan 2022;19(1):45-59. doi:10.1038/s41575-021-00527-0

Peeraphatdit TB, Kamath PS, Karpyak VM, et al. Alcohol Rehabilitation Within 30 Days of Hospital Discharge Is Associated With Reduced Readmission, Relapse, and Death in Patients With Alcoholic Hepatitis. Clin Gastroenterol Hepatol. Feb 2020;18(2):477-485 e5. doi:10.1016/j.cgh.2019.04.048

Vannier AGL, Przybyszewski EM, Shay J, et al. Psychotherapy for Alcohol Use Disorder Is Associated With Reduced Risk of Incident Alcohol-Associated Liver Disease. Clin Gastroenterol Hepatol. Aug 11 2022;doi:10.1016/j.cgh.2022.08.001

Vannier AGL, Shay JES, Fomin V, et al. Incidence and Progression of Alcohol-Associated Liver Disease After Medical Therapy for Alcohol Use Disorder. JAMA Netw Open. May 2 2022;5(5):e2213014. doi:10.1001/jamanetworkopen.2022.13014

Gao X, Lv F, He X, et al. Impact of the COVID-19 pandemic on liver disease-related mortality rates in the United States. J Hepatol 2023; 78(1):16-27.

15. Vascular liver disease

Matthias J. Bahr

"It is impossible to explain or to understand the morbid appearances of the liver, without referring to its intimate structure, and as some points relating to this have been only lately made out, I shall commence with a short account of it."

Georg Budd, Diseases of the Liver, 1853

Vascular liver diseases comprise a heterogeneous group of mostly rare hepatic disorders – some of them exceedingly rare.

Every single part of the hepatic vasculature may be affected, i.e., hepatic sinusoids, portal vein, hepatic artery and liver veins. The clinical presentation varies widely depending on the type of disease but also within the individual disease entities. Vascular liver diseases may present as acute disorders or chronic liver disease, as hepatocellular necrosis or cholestasis, as tumour-like lesions or portal hypertension.

The spectrum of underlying causes is wide, and in many cases multiple risk factors will concur in the development of clinically significant disease (Table 1).

Table 1. Classification and predisposing factors for vascular liver disease

Hereditary disorders	• Inherited thrombophilia, e.g., factor V Leiden mutation, mutations of prothrombin, protein C, protein S, antithrombin III • Hereditary hemorrhagic teleangiectasia • SP110-associated sinusoidal obstruction syndrome
Congenital or acquired malformations	• Webs, shunts, aneurysms
Acquired cellular defects	• Myeloproliferative neoplasms • Paroxysmal nocturnal hemoglobinuria • Malignancy
Inflammatory disease, immune-mediated disorders	• Focal inflammatory lesions, e.g., pancreatitis, diverticulitis, appendicitis, cholecystitis, abscesses, inflammatory bowel disease • Vasculitis, e.g., polyarteritis nodosa, Behçet's disease • Rheumatic disease
External factors	• Toxicity, radiation, trauma

Disorders of the hepatic sinusoid

Hepatic sinusoidal disease may present as luminal obstruction (i.e., sinusoidal obstruction syndrome), as luminal enlargement (i.e., peliosis hepatis) or as perisinusoidal fibrosis. Whether the latter represents a separate disease entity is debatable, as perisinusoidal fibrosis is also observed in common diseases such as steatohepatitis. Both sinusoidal obstruction syndrome as well as peliosis hepatis are not strictly confined to the hepatic sinusoids but may extend to the hepatic venous system.

Sinusoidal obstruction syndrome (Hepatic veno-occlusive disease)

Sinusoidal obstruction syndrome (SOS), also referred to as hepatic veno-occlusive disease (VOD), is a circulatory disorder primarily affecting the hepatic sinusoids. Involvement of the hepatic central veins may occur, but studies after conditioning for hematopoietic cell transplantation have demonstrated that in more than 40% of patients with SOS the hepatic venous system is not involved. The proportion of exclusive sinusoidal affection falls to 25% in patients with progression to severe SOS (DeLeve 2009).

Pathophysiology

Sinusoidal obstruction syndrome may be triggered by a variety of factors (Valla 2016). By far the most common cause in the Western world are myeloablative regimens in preparation for hematopoietic stem cell transplantation (HSCTx), particularly when the transplant is for a malignancy. Historically, the proportion of patients with SOS after HSCTx varied from the single-digit percentage range up to 50% if highly toxic regimens were chosen. Currently, reported rates range between 1.8% at day 21 and 2.4% at day 100 (Ruutu 2023). Apart from conditioning regimens for HSCTx (high-dose chemotherapy plus total body irradiation), other drugs have been implicated in the development of SOS (Table 2). Among others and in addition to the intensity of the chemotherapy applied, additional risk factors appear to increase the risk for SOS: genetics, Karnofsky score, exposure to estroprogestatives in women, autologous or allogeneic type of HSCTx, prior myeloablative transplantation or preexistent liver disease (DeLeve 2009, Mohty 2016).

Originally, the syndrome was described in conjunction with the ingestion of herbal teas or foods containing pyrrolizidine alkaloids. Rarely, SOS is caused by hereditary SP110 defects additionally leading to immunodeficiency, VODI (Cliffe 2012). Whether immunodeficiency may give rise to infections facilitating secondary SOS is under debate. In addition, MTHFR mutations are suggested as a risk factor for SOS (Efrati 2014).

Both the histopathological changes and the clinical picture of SOS have been experimentally studied in a rat model using monocrotaline, a pyrrolizidine alkaloid directly toxic to sinusoidal endothelial cells. These experiments have confirmed the primary sinusoidal damage infrequently followed by central venous involvement (DeLeeve 1996, Mohty 2015). In addition, chemotherapy might interfere with sinusoidal repair by inhibiting mobilisation of bone marrow progenitors of endothelial cells (Vion 2015).

Table 2. Conditions associated with sinusoidal obstruction syndrome

• Pyrrolizidine alkaloid-containing herbs, e.g. comfrey, groundsel, rattlebox, traditional Chinese medicine preparations • Radiation exposure • Pregnancy	• Hereditary SP110 defects • MTHFR mutations • ABCB11 mutations
DRUGS	
• 6-mercaptopurine • 6-thioguanine • Actinomycin D (Dactinomycin) • Azathioprine** • Busulfan* • Cytosine arabinoside • Cyclophosphamide* • Dacarbazine • Doxorubicin (Adriamycin)	• Gemtuzumab ozogamicin • Irinotecan • Melphalan* • Mitomycin • Oxaliplatin, Carboplatin • Urethane • Vinblastine • Sirolimus • Isavuconazole

*Exclusively reported with conditioning regimens for HSCTx
**Reports for azathioprine-associated SOS included concurrent potential causes of SOS (modified according to DeLeve 2009, Thatishetty 2013, Tewari 2017)

Clinical presentation and diagnosis

SOS characteristically presents with weight gain (inconsistently associated with ascites), hepatomegaly with right upper quadrant pain, and jaundice. The onset of symptoms usually occurs between day 10 and day 20 after cyclophosphamide-containing regimens but can be delayed up to 1 month after conditioning therapy with other therapies.

SOS is a primarily clinical diagnosis presenting with the following characteristics: (1) hepatotoxic conditioning regimen for HSCTx with an appropriate temporal relation to the development of clinical signs and symptoms, (2) weight gain & hepatic pain & jaundice and, (3) negative work-up for other causes (Dignan 2013, Bajwa 2017). In patients meeting these criteria, diagnosis can be made with reasonable certainty and solely based on clinical judgement. Differential diagnoses comprise cholestatic

jaundice due to sepsis, drug-induced cholestasis, fluid overload due to renal failure or congestive heart failure, liver involvement by viral or fungal infections, and acute graft-versus-host disease.

However, in up to 20% of patients the diagnosis of SOS cannot reliably be made on clinical grounds (McDonald 1993 & 2004). This has promoted the development of scoring systems such as the Seattle or the Baltimore Criteria (Jones 1987; McDonald 1993) (Table 3). However, up to 50% of patients not meeting the Baltimore criteria may exhibit histological features of SOS (Shulman 1994). Measurement of various biomarkers was suggested as indicator and follow-up marker of SOS (e.g. von Willebrand factor, thrombomodulin, E-selectin, sICAM1, PAI-1). Their use, however, is still regarded as experimental (Dignan 2013, Bajwa 2017). In 2016 the European Society for Blood and Marrow Transplantation suggested revised criteria for diagnosis and severity of SOS (Mohty 2016). The latest revision is shown in Table 4 (Mohty 2023). Taking into account that the paediatric population significantly differs from adults, separate criteria were recently established for children (Corbacioglu 2018).

Table 3. Diagnosis of sinusoidal obstruction syndrome after HSCTx

Seattle criteria (McDonald 1993)	Baltimore criteria (Jones 1987)
At least two of the following findings within 20 days of transplantation:* • Bilirubin >34.2 µmol/L (2 mg/dL) • Hepatomegaly or right upper quadrant pain of liver origin • ≥2% weight gain due to fluid accumulation	**Hyperbilirubinaemia >34.2 µmol/L (2 mg/dL) plus ≥2 additional criteria** • Usually painful hepatomegaly • ≥5% weight gain • Ascites

*The 20-day rule applies to cyclophosphamide-containing regimens and should be adjusted according to the regimen actually used

Table 4. Revised EBMT criteria for diagnosis of sinusoidal obstruction syndrome in adults* (Mohty 2023)

Probable	Clinical	Proven
Two of the following criteria must be present: • Bilirubin >34 µmol/L (2 mg/dL) • Painful hepatomegaly • Weight gain >5% • Ascites • Ultrasound and/or elastography suggestive of SOS/VOD	• Bilirubin ≥34 µmol/L (2 mg/dL) **and two of the following criteria must be present:** • Painful hepatomegaly • Weight gain >5% • Ascites	• Histologically proven SOS/VOD or • hemodynamically proven (HVPG ≥10 mmHg)
Onset		
In the first 21 days after HSCT: classical SOS/VOD >21 days after HSCT: late onset SOS/VOD		

For any patient, these symptoms/signs should not be attributable to others causes.

The gold standard to confirm SOS is based on the combination of hepatic histology plus measurement of the wedged hepatic venous pressure gradient (HVPG >10 mmHg) (Gressens 2022). Both can be achieved during a single procedure via the transvenous route, especially as increased bleeding risk often precludes percutaneous liver biopsy. However, histology may be negative due to the sometimes patchy character of the disease.

Imaging techniques are used to confirm hepatomegaly or ascites and will help to rule out differential diagnoses such as biliary obstruction. A more specific sign is the finding of hepatic inflow blockage with reduced or reversed portal flow in colour Doppler ultrasound (Figure 1). In addition, attenuation of hepatic venous flow or gallbladder wall edema may be detected. Some authors suggest the use of composite ultrasound imaging scores (Lassau 2002). Though less specific, CT imaging (i.e. heterogeneous hypoattenuation and patchy enhancement in the portal venous or equilibrium phase) may be suggestive for SOS (Yang 2018).

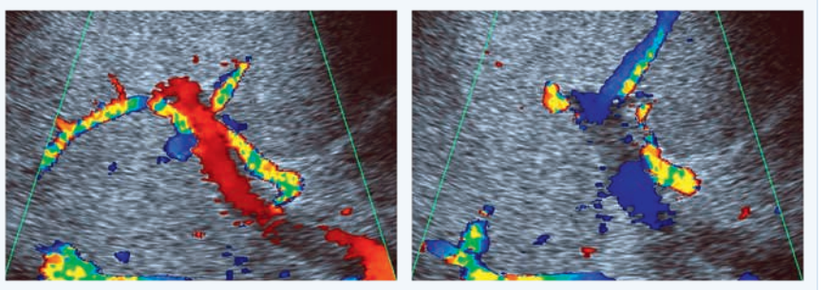

Figure 1. Doppler ultrasound in sinusoidal obstruction syndrome. Exemplary case showing undulating portal venous flow in a jaundiced patient after HSCTx

Severity of SOS varies from mild forms to rapidly progressing and eventually life-threatening disease (McDonald 1993). In patients without need for treatment of fluid excess or hepatic pain, SOS is considered mild and is associated with a self-limited course. Treatment associated with a complete remission within 100 days is considered moderate disease. If SOS does not resolve by day 100, it is categorised as severe. This classification, however, is retrospective and does not support clinical decision-making. The EBMT has proposed a modified classification system (Table 5).

Table 5. EBMT criteria for severity of sinusoidal obstruction syndrome in adults (Mohty 2016, Mohty 2023)

	Mild[a]	Moderate[a]	Severe	Very severe – MOD[b]
Time since first clinical symptoms of SOS [c]	>7 Days	5–7 Days	≤4 Days	Any time
Bilirubin (µmol/L)	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics			Doubling within 48 h	
Aminotransferases	≤2 x normal	>2 and ≤5 x normal	>5 and ≤8 x normal	>8 x normal
Weight increase			≥5% and <10%	≥10%
Renal function	baseline at transplant	<1.5 x baseline at transplant	≥1.5 and <2 x baseline at transplant	≥2 x baseline at transplant or signs of MOD/MOF[b]

[a] In two or more risk factors for SOS, patients should be in the upper grade
[b] Multiple organ dysfunction (MOD) is classified as very severe, MOD is defined as ≥2 organs from the SOFA score with a score ≥2 or an increase ≥2 or organ dysfunction for patients with underlying organ involvement
[c] Time between first signs/symptoms and fulfillment of SOS diagnostic criteria

Management and prognosis

Taking into account that SOS is probably under-diagnosed by solely employing clinical criteria, case fatality rates of detected SOS vary between 15 and 20% (DeLeve 2009). Apart from deep jaundice, additional signs of liver failure such as coagulopathy or hepatic encephalopathy may be missing. In contrast, systemic complications leading to multiple organ failure (renal, pulmonary) are the main reasons for death in these patients (Mohty 2015). This underlines the necessity of a closely supervised management concept. Highly toxic conditioning regimens should possibly be avoided. Meta-analysis support the use of ursodeoxycholic acid for SOS prophylaxis (Cheuk 2015, Mothy 2020). In high-risk patients, defibrotide may be used (Dignan 2013, Mohty 2015, Mothy 2020).

Several treatments have been suggested for established SOS, e.g., thrombolysis using tPA, defibrotide or methylprednisolone (DeLeve 2009, Dignan 2013, Richardson 2013). In addition, invasive strategies such as TIPS or liver transplantation have been evaluated. Primarily, fluid management should aim to control fluid overload (using diuretics, paracentesis, hemofiltration/hemodialysis) and adequate oxygenation should be provided (Mahadeo 2017, Ovchinsky 2018). Thrombolysis has not proved successful and was associated with severe complications.

Defibrotide, a mixture of single-stranded oligodeoxyribonucleotides derived from porcine intestinal mucosa, works as an endothelial protective agent (Palomo 2016). Defibrotide was successfully tested in phase II and III trials both in paediatric and adult settings (Richardson 2010, Corbacioglu 2012, Richardson 2016). This compound can also be used in multiple organ failure without substantially increasing the bleeding risk. Current data support defibrotide use as soon as SOS is diagnosed (Mothy 2020). Methylprednisolone may be considered as additional therapy (Dignan 2013).

Unlike Budd-Chiari syndrome, decompression of portal hypertension using TIPS does not improve SOS. For patients with favourable prognosis of the underlying hematopoietic disorder after HSCTx, liver transplant might possibly be considered.

Key messages – Sinusoidal obstruction syndrome (SOS)

- SOS is a potentially life-threatening disorder of the hepatic microcirculation
- In Western countries the majority of cases occurs after myoablative chemotherapy in the context of hematopoietic stem cell transplantation (HSCTx), other etiologies comprise toxins such as pyrrolizidine alkaloids and genetic factors
- Clinical parameters and scoring systems are first-line screening tools, ultrasound may support diagnosis, some cases require liver biopsy for confirmation
- Ursodeoxycholic acid is used for prophylaxis
- Mild disease may be treated symptomatically, while moderate to severe forms require early defibrotide therapy

Peliosis hepatis

Peliosis hepatis is a rare and potentially reversible disorder characterised by single or multiple blood-filled cystic cavities within the hepatic tissue. Whether it is related to nonobstructive sinusoidal dilatation is currently unclear (Marzano 2015). Prevalence of peliosis hepatis may vary between 0.03% in HIV infection, 0.2% in pulmonary tuberculosis up to 20% after renal transplantation. There is no favoured localisation of the peliotic lesions. It may occur at all ages, including a fetal form. The cavity size ranges from submillimetres to centimetres but rarely exceeds 3 cm. The histopathological appearance may show a missing endothelial cell lining with hepatocytes directly serving as boundary (parenchymal type). Alternatively, the endothelium may be preserved but the hepatic sinusoids appear dilated (phlebectatic type). The aneurysmal dilation may extend to the central vein (Yanoff 1964, Tsokos 2005).

Pathophysiology

Several risk factors have been suggested as promoters of peliosis hepatis, e.g., infections, drugs or malignant disorders (Table 6). However, the exact pathogenesis of peliosis is still unclear. Histology suggests endothelial damage leading to destruction of the endothelial lining. Other hypotheses favour an increased sinusoidal pressure resulting in the widening of the sinusoidal lumen with consecutive destruction of the sinusoidal endothelium or primary hepatocellular necrosis replaced by blood-filled cystic lesions. Fibrotic changes and even liver cirrhosis as well as regenerative nodules may be found, but it is unclear whether these features are directly linked to peliosis hepatis or whether they are just coincidental.

Table 6. Risk factors reported with peliosis hepatis

Infections	• Human immunodeficiency virus • Bartonella spp. (bacillary angiomatosis) • Tuberculosis
Drugs, toxins	• Azathioprine, cyclosporine • Anabolic steroids, glucocorticoids, oral contraceptives, tamoxifen • Vinyl chloride, arsenic, thorium oxide
Malignant and benign tumours	• Multiple myeloma, Waldenström disease • Hodgkin disease • Hepatocellular adenoma
Inflammatory disease	• Celiac disease • Systemic lupus erythematodes
Miscellaneous	• Renal or heart transplantation • Diabetes mellitus • Hereditary hemorrhagic telangiectasia • Pregnancy • No underlying disorder in up to 50%

Clinical presentation and diagnosis

Peliosis hepatis is mostly asymptomatic and incidentally detected by hepatic imaging. Rarely, the peliotic cysts may rupture leading to intrahepatic or intraabdominal hemorrhage. Individual cases with overt liver disease have been reported, characterised by hepatomegaly, jaundice, ascites, portal hypertension and liver failure. Extrahepatic manifestations may be found in organs of the mononuclear phagocytic system (e.g., spleen, lymph nodes, bone marrow) but also in the lungs, kidneys, parathyroid or adrenal glands, or other parts of the gastrointestinal tract.

Usually, peliosis hepatis is easily detected by imaging techniques (Ronot 2016). However, discrimination between peliosis and other benign or malignant lesions may turn difficult. Peliotic lesions miss a mass effect on the adjacent hepatic vasculature. Blood flow within the lesion is slow, resulting in a hypodense appearance after contrast application in CT. However, in some patients a ring-like accumulation of contrast media may be present. Using MRI, low intensity is seen in T1-weighted images while T2-weighted images show a high signal (Iannaccone 2006). In contrast-enhanced ultrasound (CEUS) both centrifugal as well centripetal contrast filling might be detected, in some cases even tumour-like behaviour occurs (Schuldes 2011). Though imaging techniques may assist the diagnosis of peliosis hepatis, liver biopsy is often required for final confirmation. Wedged hepatic venography may also be diagnostic, but its use needs strong suspicion.

Management and prognosis

Typically, peliosis hepatis will not progress to symptomatic disease. In these patients management has to concentrate on the identification and, if required, treatment of the underlying disease. Causal treatment is the therapeutic mainstay mostly leading to regression of the peliotic lesions. Individual cases may require surgery if the risk of cyst rupture and consecutive bleeding is estimated to be high. If liver failure or portal hypertension dominate the clinical picture liver transplantation might be considered provided aetiology does not pose a contraindication.

Disorders of the hepatic artery

Pathologies involving the hepatic artery may present differently (Table 7, Figure 2). Occlusion of the arterial lumen results in hypoxia of the supplied tissue. Though gross hepatocellular necrosis may follow, such as in ischemic hepatitis, preserved portal venous oxygen supply often prevents the most devastating damage. In contrast to the hepatic parenchyma, the biliary system is exclusively supplied arterially and, therefore, more susceptible to ischemic damage. Clinically, this may present as an elevation of cholestasis-associated liver enzymes (i.e., gamma GT, alkaline phosphatase). In more severe cases, structural damage to bile ducts may be irreversible (i.e., ischemic cholangiopathy). Especially after orthotopic liver transplantation ischaemia type biliary lesions (ITBL) still pose a major challenge for clinical management.

Table 7. Aetiology of hepatic artery disease

Obstruction or destruction of the hepatic artery	• Hepatic artery embolism or thrombosis • Vasculitis • Sickle cell disease • Thrombotic microangiopathy (e.g., hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, HELLP syndrome) • Chronic transplant rejection • Trauma
Aneurysms	• Congenital malformations • Polyarteritis nodosa (PAN) • Focal inflammation, trauma
Shunts	• Congenital malformations • Hereditary hemorrhagic teleangiectasia

Aneurysms and shunts represent other significant disease entities of the hepatic artery. Aneurysms are often detected incidentally by imaging. In the majority, they are asymptomatic but abdominal pain or – in rare cases – obstructive jaundice may develop. In about 20% of cases multiple aneurysms are present. Males are more often affected than women. The risk of rupture and subsequent hemorrhage is high and may reach up to 80% depending on the size of the aneurysm. Therefore, either radiological intervention or surgery needs to be evaluated (Hulsberg 2011, Christie 2011).

In contrast to aneurysms, shunts involving the hepatic artery are mostly symptomatic. The spectrum of symptoms is wide including abdominal pain, portal hypertension or signs of high-output heart failure. The therapeutic approach has to be individualised including radiological interventions or surgical procedures.

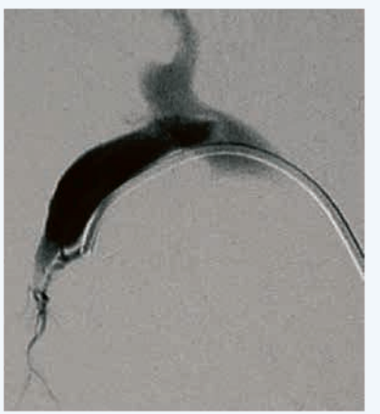

Figure 2. Spontaneous arterioportal shunt. Angiography in a patient with non-cirrhotic portal hypertension. A small arterioportal shunt is detected by superselective catheterisation of the hepatic artery

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)

Hereditary hemorrhagic telangiectasia (HHT) is a highly penetrant, autosomal dominant disease. The heterozygous prevalence is estimated between 1:5, 000 and 1:8, 000. HHT is characterised by progressive and multivisceral development of arteriovenous malformations (Govani 2009, Garg 2014, Arthur 2015).

Mutations in several genes interacting with transforming growth factor (TGF)-β receptor have been identified in HHT. According to the genes involved, different subtypes can be discriminated (Viteri-Noël 2022):

- HHT 1 (ENG encoding endoglin, chromosome 9q34.11),
- HHT 2 (ACVRL1 encoding activin A receptor type II-like kinase ALK-1, chromosome 12q13.13),
- HHT/juvenile polyposis syndrome (MADH4 encoding Smad4, chromosome 18q21.1),
- RASA-1 related disorders (RASA-1 encoding p120-RasGAP, chromosome 5q14.3),
- HHT-like (GDF2 encoding BMP-9, chromosome 10q11.22).

Liver involvement may be found in all subtypes but appears to be most frequent in HHT 2. Though hereditary, HHT is characterised by marked intrafamilial variation. Recently, the first case of tissue-specific mosaicism was reported (McDonald 2018).

Clinical presentation and diagnosis

HHT is a multivisceral disease. Apart from the nasopharnyx and the gastrointestinal tract, central nervous (~10%), pulmonary (~50%) and hepatic involvement occur at high frequency. Accordingly, the spectrum of clinical disease is wide, e.g., anaemia, seizures, subarachnoid hemorrhage, paraplegia, transient ischemic attacks/stroke, dyspnea, cyanosis, polycythaemia, abdominal pain and hepatic abscesses.

Symptoms develop progressively throughout life. Telangiectasias appear before the age of 20 in half, before 40 in two-thirds of the patients. Thereafter it takes one or two decades for the development of significant bleeding or symptomatic visceral involvement (Plauchu 1989, Govani 2009, Arthur 2015). Overall, life expectancy of patients suffering from HHT is two decades less than in the general population (Droege 2018).

The proportion of hepatic involvement in HHT reaches up to 75%. Hepatic malformations appear more frequently in females. However, less than 20% of patients with hepatic involvement are symptomatic (Singh 2014). The

clinical picture of liver involvement in HHT depends on the predominant type of malformation (i.e., arterioportal vs. arteriovenous shunts). Arteriovenous malformations increase cardiac output. In individual cases up to 20 L/min may be reached. These patients suffer from high output cardiac failure. In addition, symptoms of a mesenteric steal syndrome (e.g., postprandial abdominal pain) and complications of biliary ischaemia (e.g., biliary abscesses) may occur. As a consequence of ischaemia, nodular regeneration of the liver develops (HHT-associated pseudocirrhosis). In contrast, arterioportal malformations will cause portal hypertension (Buscarini 2006, Garcia-Tsao 2000).

Diagnosis of HHT is made using the Curaçao criteria, 3 of 4 of which need to be fulfilled (Shovlin 2000, Faughnan 2020):

- recurrent spontaneous epistaxis,
- telangiectasias, multiple and in typical localisation,
- positive family history,
- visceral arteriovenous malformations (lung, liver, brain, spine).

Current guidelines do endorse routine screening for hepatic vascular malformations (Faughnan 2020). A diagnostic score involving age, gender, hemoglobin and alkaline phosphatase was suggested to identify patients at risk for significant liver disease (Singh 2014). However, using Doppler ultrasound, screening is performed with high sensitivity and specificity (Table 8) (Caselitz 2003). Alternatively, CT or MR imaging may be applied.

Table 8. Ultrasound criteria for hepatic involvement in HHT*

Major criteria	• Dilated common hepatic artery >7 mm (inner diameter) • Intrahepatic arterial hypervascularisation
Minor criteria	• V_{max} of the proper hepatic artery >110 cm/s • RI of the proper hepatic artery <0.60 • V_{max} of the portal vein >25 cm/s • Tortuous course of the extrahepatic hepatic artery
Facultative findings	• Dilated portal vein >13 mm • Dilated liver veins >11 mm • Hepatomegaly >15 cm in midclavicular line • Nodular liver margin

*Two major criteria: definitive hepatic involvement in HHT, one major criterion plus minor criteria: probable hepatic involvement (modified according to Caselitz 2003)

If hepatic involvement is confirmed, cardiac output should be estimated (e.g., via echocardiography). Furthermore, in patients with liver involvement screening at regular intervals is advised to detect complications such as development of portal hypertension or biliary lesions.

Management of hepatic involvement in HHT

Intensive first-line treatment should be restricted to symptomatic patients or patients suffering from complications (Faughnan 2020).

Currently, no established medical therapy for HHT exists. In chronic GI bleeding the use of hormonal therapy (oestrogen-progesterone preparations, danocrine), antifibrinolytics (aminocaproic acid, tranexamic acid) and other experimental drugs (tamoxifen, interferon, thalidomide, sirolimus) were suggested (Ardelean 2015). However, no data supports the use of these drugs to treat hepatic vascular malformations.

A phase 2 trial evaluated bevacizumab to treat liver involvement in HHT (Dupuis-Girod 2012). Significant improvements in cardiac output, epistaxis and SF-36 scores were achieved. However, long-term effects, dosing and necessity of maintenance therapy are still unclear (Ardelean 2015, Chavan 2017). Registry data comparing thalidomide and bevacizumab show positive effects on transfusion dependency, GI bleeding and epistaxis for both drugs while only bevacizumab was helpful in treating vascular malformations (Buscarini 2019). Current guidelines support bevacizumab as a second-line treatment in patients with hepatic malformations due to HHT (Faughnan 2020).

Single cases using kinase inhibition (i.e., sunitinib, nintedanib) were reported, but still have to be regarded experimental.

Limited data exist for the use of hepatic artery embolisation and liver transplantation (Buscarini 2006, Chavan 2013, Felli 2017). Due to the invasiveness and complication rates of these approaches only patients with moderate to severe symptoms should be regarded as candidates for interventional therapy. Hepatic artery embolisation can be used to reduce shunt flow in patients with arteriovenous hepatic shunts leading to significant reduction of cardiac output and improvement of associated symptoms. However, complications such as hepatic and biliary necrosis or acute cholecystitis have been described. Success of hepatic artery embolisation very much depends on adequate patient selection. Current guidelines do not endorse general use of embolisation outside experienced centres but do favour liver transplantation in advanced hepatic involvement of HHT (Faughnan 2020).

Key messages – Hereditary hemorrhagic telangiectasia (HHT)

- HHT is diagnosed using the Curaçao criteria based on clinical evaluation and imaging
- Hepatic involvement is easily diagnosed using Doppler ultrasound, CT or MRI are similarly sensitive
- Treatment of hepatic HHT lesions should only be considered for symptomatic patients or complicated disease
- After symptomatic therapy, bevacizumab may be considered as second-line treatment
- Interventional treatment is considered experimental

Disorders of the portal vein

Portal vein thrombosis is a common disease located within the main portal vein and its larger branches. Additionally, rare affections of the medium-sized and preterminal portal vein branches have been identified. The nomenclature for the latter has been inconsistent and descriptive. Recently, the term porto-sinusoidal vascular disease was suggested replacing and incorporating the different previously decribed terms.

Portal vein thrombosis

Portal vein thrombosis (PVT) is the most frequent disorder affecting the hepatic vasculature. Autopsy studies report a prevalence range between 0.05% and 1%. In compensated cirrhosis PVT may be found in 1% of cases, while a prevalence between 8% and 26% is reported for decompensated cirrhosis.

PVT is of heterogeneous aetiology. It is promoted by both local and systemic risk factors (Tables 9 & 11). In about 20 to 30% of patients a local risk factor can be identified. Systemic risk factors are found in 50-70% (DeLeve 2009, Plessier 2010). The obesity epidemic disclosed central obesity as a major risk factor for idiopathic PVT (Bureau 2016). In up to one third of the patients a combination of several predisposing conditions is found.

Table 9. Local risk factors for portal vein thrombosis

Malignancy	Primary hepatic or abdominal cancer Metastatic disease
Focal inflammation	Neonatal omphalitis, umbilical vein catheterisation Pancreatitis, duodenal ulcer, cholecystitis Diverticulitis, appendicitis, inflammatory bowel disease Tuberculosis, CMV hepatitis
Portal venous injury	Cholecystectomy, splenectomy, colectomy, gastrectomy Surgical portosystemic shunting, TIPS Oesophageal sclerotherapy Liver transplantation, hepatobiliary surgery Abdominal trauma, exercise
Vascular haemodynamics	Cirrhosis with impaired hepatic inflow Budd-Chiari syndrome Constrictive pericaridtis

Clinical presentation

Portal vein thrombosis may present as acute or chronic disease, representing successive stages of the disease. As management depends on PVT aetiology, non-cirrhotic, non-malignant PVT needs to be regarded separately from (a) thrombi resulting from slowed portal venous flow in liver cirrhosis, (b) thrombi by tumours invading the portal venous circulation, and (c) septic thrombi also known as pylephlebitis (DeLeve 2009, Plessier 2010).

A classification focusing on anatomico-functional aspects of PVT has found wide resonance (Table 10) (Sarin 2016).

Table 10. Sarin classification of portal vein thrombosis (Sarin 2016)

Site of PVT	Type 1: trunk only Type 2: branch only: 2a, one branch; 2b, both branches Type 3: trunk and branches
Extent of PV system occlusion	S: splenic vein M: mesenteric vein SM: both
Degree of portal venous system occlusion	O: occlusive, no visible flow in PV lumen on imaging/Doppler study NO: non-occlusive, flow visible in PV lumen on imaging/Doppler study
Duration and presentation	R: recent (previously patent PV, hyperdense thrombus, absent/limited collaterals, dilated PV at the site of occlusion) Ch: chronic (previously diagnosed PVT, no hyperdense thrombus, portal cavernoma, portal hypertension) As: asymptomatic S: symptomatic
Type of underlying liver disease	Cirrhotic Non-cirrhotic Hepatobiliary malignancy Local malignancy Posttransplant Associated conditions

The typical clinical presentation of acute PVT includes abdominal or lumbar pain of sudden onset or progressing over a few days. Depending on the extent of the thrombosis the pain may be severe and colicky. The diminished mesenteric outflow leads to intestinal congestion. Paralytic ileus may develop. Moderate distension of the abdomen is common. However, peritoneal signs are usually absent unless intestinal infarction develops. Fever and a marked systemic inflammatory response may develop even without systemic infection. This is accompanied by elevated laboratory markers of inflammation. In contrast, liver function – apart from intermittent elevation of aminotransferases – is usually not substantially affected by acute PVT unless significant liver damage pre-exists. Clinical features should improve within 5-7 days. Otherwise transmural intestinal ischaemia has to be suspected.

Cases without resolution of acute portal vein thrombosis progress to the chronic stage. The obstructed portal vein is replaced by collateral veins bridging the thrombotic part, known as portal cavernoma (also addressed as Extra Hepatic Portal Venous Obstruction, EHPVO). There is wide variation in the clinical picture of portal cavernoma. It may rarely lead to obstruction of the extrahepatic bile ducts (i.e., portal cholangiopathy/biliopathy, portal cavernoma cholangiopathy), which may be associated with marked jaundice (Dhiman 2014, Khuroo 2016). However, the leading symptom of chronic PVT are the facets of portal hypertension (e.g., portosystemic collaterals such as gastric or oesophageal varices). As liver function is usually not impaired, complications such as hepatic encephalopathy or ascites are substantially less frequent than in liver cirrhosis. Hepatopulmonary syndrome may be found in up to 10% of patients.

Diagnosis

Both acute PVT and portal cavernoma are easily detected using sonography, CT or MR imaging. Acute PVT presents as intraluminal hyperechoic material in ultrasound, while Doppler imaging demonstrates a lack of blood flow (Figure 3). Using contrast-enhanced ultrasound (CEUS), vascularisation of the thrombus may be used to identify malignant thrombi. As PVT may extend to the mesenteric or splenic veins, thorough assessment of the splanchnic tributaries is mandatory. For detailed assessment of thrombus extension, CT or MR angiography are more sensitive than Doppler sonography.

Portal cavernoma presents as serpiginous vessel structures, while the main portal vein or its branches are not visible. As a compensatory mechanism hepatic arteries are usually enlarged. Depending on the individual location and appearance of portal cavernoma it may be mistaken as part of the surrounding organs or as tumour.

Management and prognosis

In acute PVT, timely recanalisation of the obstructed veins should be aspired. Causal factors require correction whenever possible. Complications need to be appropriately addressed.

Spontaneous recanalisation without anticoagulation occurs infrequently (<10%). Therefore, anticoagulation is the most commonly used strategy to reopen the obstructed portal vein. Most data were gained using heparin either unfractionated or LMW followed by vitamin K antagonists. Prospective data suggest success rates between 25% and 80%. Response increases if neither the splenic vein is involved nor ascites is detectable. Anticoagulation should be initiated as early as possible – delay might be associated with treatment failure. Major complications are reported in less than 5% of treated patients (DeLeve 2009, Plessier 2010, Hall 2011). Depending on whether a transient or a persistent risk factor has facilitated PVT development, anticoagulation should be maintained for 6 months or long-term, respectively (EASL 2016).

In recent years, many reports on the use of direct oral anticoagulants (DOAC) in PVT have appeared (Monaco 2023). The response rates are claimed higher than with heparin/VKA regimens. Resolution rates beyond 80-90% have been reported. While the EASL guidelines of 2016 do not recommend DOAC in PVT (EASL 2016), the more recent guidelines from the AASLD and the BAVENO conference both present DOAC as a treatment option in PVT (Northup 2021, de Franchis 2022).

Experience with other treatment modalities is limited (e.g., systemic/local thrombolysis, surgical thrombectomy, transjugular intrahepatic portosystemic stent [TIPS]). Systemic thrombolysis appears largely ineffective. Although performed successfully in some centres, major procedure-related complications and even death have been reported for local thrombolysis. A meta-analysis attested that TIPS placement is technically highly feasible, effective and safe (Rodrigues 2018). Emergency surgical intervention is indicated in suspected intestinal infarction. In these cases, surgical thrombectomy can be performed.

If treatment is initiated early in acute PVT the outcome is favourable. Symptoms may sometimes disappear within hours after start of therapy and portal hypertension rarely develops. Overall mortality is well below 10% (DeLeve 2009, Plessier 2010).

In patients with portal cavernoma, prevention of gastrointestinal bleeding due to portal hypertension is the main focus of therapy (Chaudhary 2013). The use of non-selective beta-blockers is incompletely evaluated in portal cavernoma. However, an approach similar to portal hypertension in liver cirrhosis is supported by current guidelines and appears to improve prognosis (DeLeve 2009). Recently, small series employing interventional

recanalisation of the chronically obstructed portal vein have been published with favourable results (Artru 2022).

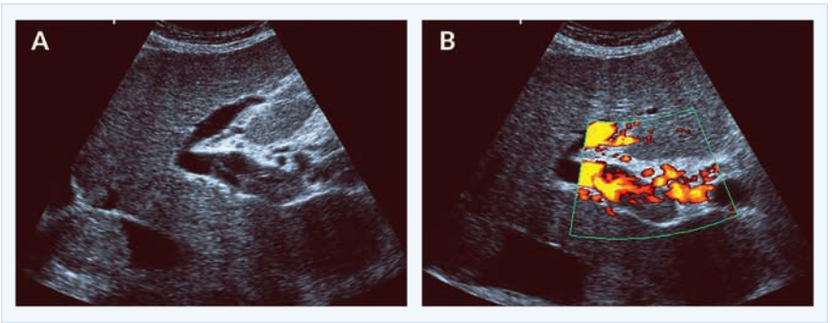

Figure 3. Acute portal vein thrombosis. Ultrasound of a patient with acute PVT. (A) Hyperechoic material is located within the main portal vein. (B) Using the power mode for flow detection, blood flow is limited to those parts of the portal vein without hyperechoic material

Portal vein thrombosis secondary to liver cirrhosis

PVT is a common complication of liver cirrhosis with an increasing prevalence in more advanced disease stages (Abergel 2020). It needs to be discriminated from portal venous obstruction caused by hepatocellular carcinoma.

Pathophysiologically, PVT in cirrhosis arises as a consequence of reduced hepatic inflow leading to diminished flow velocity and eventually stasis within the portal vein (Anton 2022). Therefore, thrombi are often partial and development of portal cavernoma is less common. In addition, endothelial injury appears to be of importance (Driever 2021).

The use of non-selective beta-blockers (NSBB) in cirrhosis may increase the risk of PVT development by more than 4-fold (Xu 2019). However, PVT is not regarded as a contraindication for NSBB use. In patients with cirrhosis, a newly developed ascites or significant worsening of existing ascites should trigger the search for PVT.

The therapeutic approach in patients with PVT associated with liver cirrhosis has to be regarded separate from non-cirrhotic PVT. Whether PVT increases mortality in patients with cirrhosis has been a case of ongoing discussions (Berry 2015, Cool 2019, Zhang 2020, Chen 2021). Thus, the indication for therapeutic interventions is less clear than in non-cirrhotic patients. However, recently the pendulum appeared to move towards a more aggressive therapeutic approach (Senzolo 2021, Guerrero 2023).

Anticoagulation was shown safe both in the prophylactic as well as in the therapeutic setting (Villa 2012, Delgado 2012). Use of enoxaparin as primary prophylaxis completely prevented the development of PVT. In subacute PVT, anticoagulation (using either vitamin K antagonists or LMWH) achieved complete recanalisation in nearly half of the patients, while at least partial response was seen in 2/3 of cases. Similarly, DOAC were used successfully in cirrhosis-associated PVT (De Gottardi 2017). A recent meta-analysis even saw slight advantages for DOAC in comparison to vitamin K antagonists (Zhang 2022).

Interventional therapy using TIPS appears even more effective than medical approaches showing complete response in 57% and at least partial response nearly in all patients. Technical feasibility is high and long-term stent patency is achieved in the majority of patients (Luca 2011, Rössle 2014, Guo 2022).

Portal vein thrombosis secondary to malignoma

Malignant PVT resulting from hepatocellular carcinoma should not lead to therapeutic nihilism. While systemic therapy (e.g. sorafenib) is the recommended strategy in Western countries, experience from Asia favours resection to TACE or conservative treatment (Lu 2019, Zhang 2019). Portal vein stenting has been reported for malignant PVT, however, the effect on patient relevant end-points is unclear.

Pylephlebitis

Pylephlebitis (septic / suppurative portal vein thrombosis) is an entity separate from classical PVT (Kanellopoulou 2010, Choudhry 2016, Jevtic 2022, Fusaro 2023). Pylephlebitis typically develops secondary to a primary site of inflammation and infection (e.g., diverticulitis, appendicitis, pancreatitis).

It is characterised by high, spiking fever with chills, a painful liver, and sometimes shock. Blood cultures should be taken (often Bacteroides spp., E. coli ± other enteric species). Infected thrombi give rise to hepatic microabscesses.

If pylephlebitis is suspected antibiotic therapy must be commenced immediately. Additional anticoagulation appears to improve outcomes in this setting (Naymagon 2020). In addition, the primary focus of infection needs to be addressed.

Key messages – Portal vein thrombosis (PVT)

- Non-cirrhotic, non-malignant PVT needs to be discriminated from PVT secondary to cirrhosis, malignoma or pylephlebitis
- Doppler ultrasound detects PVT with high sensitivity and specificity in first-line screening
- CT and MRI are superior for staging extended PVT
- In acute non-cirrhotic PVT timely anticoagulation is recommended either using heparin/VKA or DOAC
- Highly symptomatic cases may qualify for interventional or surgical treatment
- Chronic PVT is characterised by complications of portal hypertension and sometimes portal biliopathy
- PVT due to cirrhosis does not substantially affect the clinical course
- However, anticoagulation was shown to improve prognosis in cirrhotic PVT
- Pylephlebitis is an vascular emergency

Porto-sinusoidal vascular disease (PSVD)

The nomenclature of the small branch portal affections has been modified several times in recent years. First, ambiguous descriptions including hepatoportal sclerosis, non-cirrhotic portal fibrosis, idiopathic portal hypertension, incomplete septal cirrhosis, nodular regenerative hyperplasia and obliterative portal venopathy were replaced by idiopathic non-cirrhotic portal hypertension (INCPH) (EASL 2016). However, according to the observation that pathological features of INCPH may be present prior to the development of portal hypertension an even more comprehensive nomenclature was proposed, i.e., porto-sinusoidal vascular disease (PSVD) (De Gottardi 2019).

The histopathological correlate is an affection of the medium-sized and preterminal portal venous branches generating different morphological features that exist side by side (Guido 2019):

(a) Occlusion of the portal venous branches induces hypotrophy of the supplied tissue. As a compensatory reaction, growth of appropriately perfused liver tissue gives rise to the development of regenerative nodules. This combination of hypotrophic and hypertrophic liver tissue without signs of fibrosis is the equivalent of nodular regenerative hyperplasia (Wanless 1990).

(b) As a second type of reaction, portal veins are not just destroyed but replaced by filiform fibrotic strands penetrating the hepatic tissue. These fibrotic strands are strictly confined to the portal tracts and do not form fibrotic septae (Aggarwal 2013, Nakanuma 2001). This feature is equivalent to hepatoportal sclerosis.

Nodular regenerative hyperplasia is found in 14-27% of cases with non-cirrhotic portal hypertension (Naber 1991, Nakanuma 1996). In autopsy studies the prevalence is 3.1/100, 000, one third of which are associated with portal hypertension (Colina 1989). The picture of hepatoportal sclerosis less frequently described in the Western world but is more common in Asia (e.g., India, Japan).

A number of associated pathologies have been suggested to promote PSVD: Immune and hematologic disorders, e.g., rheumatoid arthritis, Felty's syndrome, other connective tissue disorders, CVID, HIV infection, myeloproliferative and lymphoproliferative disease. PSVD has been described in infective endocarditis, inflammatory bowel disease and after kidney transplantation. Furthermore, it may occur in conjunction with chemotherapy, HAART, other drugs and after toxin exposure (e.g., arsenic, vinyl chloride). Also, a hereditary component is discussed (Albuquerque 2013, Ghabril 2014, Hartleb 2011, Matsumoto 2000, Sarin 2007, Schouten 2011, Schouten 2015, Vilarinho 2016).

Clinically, PSVD presents with complications of portal hypertension. Liver function is usually not significantly impaired, although individual cases with liver failure and liver transplantation have been described. The prognosis depends on the underlying disorder and on the control of portal hypertension (Ataide 2013, Blendis 1978, Dumortier 2001, Naber 1990, Sarin 2007, Schouten 2015, Siramolpiwat 2014). TIPS has proven an effective measure in PSVD (Bissonnette 2016).

The diagnostic criteria for the diagnosis of PSVD are largely based on histology (De Gottardi 2022): including specific signs (obliterative portal venopathy, nodular regenerative hyperplasia, incomplete septal fibrosis) and non-specific features (portal tract abnormalities, architectural disturbance, non-zonal sinusoidal dilatation, mild perisinusoidal fibrosis). Portal hypertension characterises later stages of the disease. Hepatic vein affections (Budd-Chiari syndrome) or diseases affecting the portal tracts (sarcoidosis, congenital hepatic fibrosis, sinusoidal obstruction syndrome) are excluded.

The above criteria point to the importance of liver biopsy for the diagnosis of PSVD. However, interobserver agreement in histology evaluation is variable (Jharab 2015). Even more, histological features of PSVD may be found in up to 10% of the general population (Zuo 2017). In imaging studies, differentiation between nodular regenerative hyperplasia and cirrhosis may be impossible. In ultrasound, "atoll-like lesions" have been described as a characteristic imaging feature (Caturelli 2011). The

value of non-cirrhotic transient elastography results for the diagnosis of PSVD has been emphasised (Seijo 2012).

Therapy is guided by the extent of portal hypertension as the main complication of PSVD. Furthermore, the underlying causative conditions and risk factors should be addressed.

Key messages – Porto-sinusoidal vascular disease (PSVD)

- PSVD is defined by affections of the smallest portal vein branches
- The diagnosis is mainly based on characteristic histological features and exclusion of concomitant defined liver disease
- Risk factors and causative agents are variable
- Therapy is based on the treatment of portal hypertension and the specific aetiology and risk factors

Disorders of the hepatic veins

Budd-Chiari syndrome is the only defined entity of hepatic venous disease. However, other disorders such as the sinusoidal obstruction syndrome or peliosis hepatis may also affect the hepatic venous system. Furthermore, hepatic congestion due to cardiac or pericardial disease shares clinical similarities with Budd-Chiari syndrome.

Budd-Chiari syndrome

Budd-Chiari syndrome (BCS) is defined as hepatic venous outflow obstruction at any level from the small hepatic veins to the junction of the inferior vena cava (IVC) and the right atrium, regardless of the cause of obstruction (Janssen 2003). Obstructions caused by sinusoidal obstruction syndrome and cardiac or pericardial disorders are excluded by this definition. BCS is a rare disorder with an estimated incidence of 1 per million and a prevalence of 11 per million (Li 2019). Data from hospital admissions in the US suggest that the incidence of BCS might be increasing (Alukal 2021). However, improved imaging methods and increased diagnostic alertness might contribute to higher detection rates.

Pathophysiology

Obstruction of the hepatic outflow may arise from endoluminal lesions, e.g., thrombosis, webs, endophlebitis (primary BCS) or from outside the venous system by luminal invasion or by extrinsic compression, e.g., tumour, abscess, cysts (secondary BCS) (Janssen 2003).

On rare occasions, BCS originates from congenital malformations, e.g., webs or stenotic vessels (Ciesek 2010, Darwish Murad 2009). However, outflow obstruction is usually caused by thrombosis. Prevalence of thrombophilic risk factors is shown in Table 11. However, the underlying etiologies may vary in different parts of the world (Qi 2016).

Thrombi are exclusively located within the hepatic veins in 49% of patients, exclusively within IVC in 2%, and as combined thrombosis of hepatic veins and IVC in 49%. In 8-18% a concomitant portal vein thrombosis is identified (Darwish Murad 2009, Alukal 2021).

Obstruction of hepatic outflow leads to congestion of the drained tissue. Over time this will induce hypotrophy of affected and consecutive regenerative growth of non-affected parts of the liver. A typical area of hypertrophy is located in liver segment 1 (caudate lobe), favoured by the separate venous drainage into the IVC. Regenerative nodules may occasionally progress to hepatocellular carcinoma. In addition, intrahepatic collaterals may develop.

Table 11. Prevalence of thrombophilic risk factors in acute and chronic portal vein thrombosis and in primary Budd-Chiari syndrome*

Risk factor	Portal vein thrombosis	Budd-Chiari syndrome
Myeloproliferative neoplasms	21% – 40%	40% – 50%
Atypical	14%	25% – 35%
Classical	17%	10% – 25%
Paroxysmal nocturnal hemoglobinuria	0% – 2%	0% – 19%
Antiphospholipid syndrome	6% – 19%	4% – 25%
Factor V Leiden mutation	3% – 32%	6% – 32%
Factor II (prothrombin) mutation	14% – 40%	3% – 7%
Protein C deficiency	0% – 26%	4% – 30%
Protein S deficiency	2% – 30%	3% – 20%
Antithrombin deficiency	0% – 26%	0% – 23%
Plasminogen deficiency	0% – 6%	0% – 4%
Hyperhomocysteinaemia	11% – 22%	22% – 37%
TT677 MTHFR genotype	11% – 50%	12% – 22%
Recent pregnancy	6% – 40%	6% – 12%
Recent oral contraceptive use	12% – 44%	6% – 60%
Behçet's disease	0% – 31%	0% – 33%
Connective tissue disease	4%	10%

*Adult patients without malignancy or cirrhosis, (according to DeLeve 2009, Darwish Murad 2009, Plessier 2010, Garcia-Pagán 2023)

Clinical presentation and diagnosis

Depending on the location of outflow obstruction, the number of vessels involved and the temporal dynamics of BCS, the clinical presentation varies between subclinical disease to light symptoms, and dramatic acute complaints which may progress to acute liver failure. The disease might present with a progressively relapsing course successively involving different hepatic veins.

Symptoms of hepatic congestion are ascites (>80% of patients), abdominal pain (>60%) and oesophageal varices (>50%). Significant disturbance of liver function is rather rare, e.g., hepatic encephalopathy (<10%), as is involvement of extrahepatic organs, e.g., hepatorenal syndrome (<10%) (Darwish Murad 2009).

In the majority of cases, diagnosis of BCS can be obtained using Doppler ultrasound. If technical difficulties obviate sonographic diagnosis, MRI is the imaging method of choice. Only in rare cases, liver biopsy or hepatic venography is required to confirm the diagnosis (Janssen 2003). Ultrasound characteristics of BCS are clearly defined (Boozari 2008). They comprise specific signs such as direct visualisation of thrombi, stenosis, webs, replacement of hepatic veins by fibrotic strands or reversed flow in hepatic veins or IVC. Suggestive signs are hepatic collaterals that may be interposed between hepatic veins or may be located on the hepatic capsule. Widening of the caudate vein (>3 mm) is also regarded as suggestive for BCS. These signs serve in the diagnosis of BCS and may be accompanied by a myriad of non-specific changes (e.g., ascites, regenerative nodules, splenomegaly).

Several scoring systems have been proposed to evaluate prognosis and to guide therapy (Garcia-Pagán 2023). However, the widespread availability of TIPS procedures has substantially improved prognosis, thus invalidating scoring systems in clinical practice (Inchingolo 2020).

As regeneration nodules in BCS may progress to hepatocellular carcinoma, thorough imaging is mandatory. However, identification of malignant transformation may be difficult (Van Wettere 2019).

Management and prognosis

Treatment of BCS has to be adjusted to the aetiology and the severity of the clinical picture. If BCS is caused by congenital malformations such as webs, radiological interventions using balloon catheter-assisted dilation may succeed.

In case of a primary thrombotic event, anticoagulation is the mainstay of therapy (Janssen 2003, DeLeve 2009, Darwish Murad 2009, Seijo 2013, EASL 2015, Garcia-Pagán 2023). However, in long-term follow-up less than half of patients will be solely treated with anticoagulation and remain free of further interventions (Seijo 2013). Therefore, interventional techniques (e.g., TIPS, recanalisation) should be evaluated early, especially in patients with moderate to severe symptoms. With the advent of TIPS, the necessity for liver transplantation in BCS has declined sharply. Success rates of TIPS – both in the short-term and in the long-term – are high (Seijo 2013, Zhang 2015, Inchingolo 2020). Thus, surgical procedures (e.g., surgical shunt, liver transplantation) are only rarely performed.

With this approach, current data show that survival in BCS is above 70% after 5 years (Seijo 2013). However, population-based data from Sweden disclosed that the risk of death is tripled in patients with BCS compared to the general population (Åberg 2023).

Key messages – Budd-Chiari syndrome (BCS)

- BCS is defined as hepatic outflow obstruction between (a) the small hepatic veins and (b) the junction of the inferior vena cava (IVC) and the right atrium
- Risk factors and causative agents are variable with myeloproliferative disorders and hereditary coagulation defects being most common in Western countries
- Diagnosis is mainly based on imaging (Doppler ultrasound, CT, MRI)
- Therapy follows a step-wise approach according to disease severity – anticoagulation, recanalisation, TIPS, liver transplantation

References

Åberg F, Rajani R, Wester A, Widman L, Hagström H. Three-fold increased risk of death in Budd-Chiari syndrome compared to matched controls: A population-based cohort study. Clin Gastroenterol Hepatol 2023;21:995-1004.

Abergel A, Gasperment M, Giao F, et al. Extrahepatic portal vein obstruction (EHPVO) in cirrhosis. Clin Res Hepatol Gastroenterol 2020;44:497-502.

Aggarwal S, Fiel MI, Schiano TD. Obliterative portal venopathy: a clinical and histopathological review. Dig Dis Sci 2013;58:2767-76.

Albuquerque A, Cardoso H, Lopes J, Cipriano A, Carneiro F, Macedo G. Familial occurrence of nodular regenerative hyperplasia of the liver. Am J Gastroenterol 2013;108:150-1.

Alukal JJ, Zhang T, Thuluvath PJ. A nationwide analysis of Budd-Chiari syndrome in the United States. J Clin Exp Hepatol 2021;11:181-87.

Anton A, Campreciós G, Pérez-Campuzano V, Orts L, García-Pagán JC, Hernández-Gea V. The pathophysiology of portal vein thrombosis in cirrhosis: Getting deeper into Virchow's triad. J Clin Med 2022;11:800-1.

Ardelean DS, Letarte M. Anti-angiogenic therapeutic strategies in hereditary hemorrhagic telangiectasia. Front Genet 2015;6:1-7.

Artru F, Vietti-Violi N, Sempoux C, et al. Portal vein recanalisation alone to treat severe portal hypertension in non-cirrhotic patients with chronic extrahepatic portal vein obstruction. JHep Rep 2022;4:100511.

Arthur H, Geisthoff U, Gossage JR, et al. Executive summary of the 11th HHT international scientific conference. Angiogenesis 2015;18:511-24.

Ataide EC, dos Santos IN, Martins DL, et al. Liver failure and the need for transplantation in 6 patients with hepatoportal sclerosis. Transpl Proc 2013;45:1907-9.

Bajwa RPS, Mahadeo KM, Taragin BH, et al. Consensus report by paediatric acute lung injury and sepsis investigators and paediatric blood and marrow transplantation consortium joint working committees: Supportive care guidelines for management of veno-occlusive disease in children and adolescents, part 1: Focus on investigations, prophylaxis, and specific treatment. Biol Blood Marrow Transplant 2017;23:1817-1825.

Berry K, Taylor J, Liou IW, Ioannou GN. Portal vein thrombosis is not associated with increased mortality among patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:585-93.

Bissonnette J, Garcia-Pagán JC, Albillos A, et al. Role of the transjugular intrahepatic portosystemic shunt in the management of severe complications of portal hypertension in idiopathic noncirrhotic portal hypertension. Hepatology 2016;64:224-31.

Blendis LM, Lovell D, Barnes CG, Ritland S, Cattan D, Vesin P. Oesophageal variceal bleeding in Felty's syndrome associated with nodular regenerative hyperplasia. Ann Rheum Dis 1978;37:183-6.

Budd G. On diseases of the liver. Blanchard and Lea. Philadelphia 1853.

Buscarini E, Butella LM, Geisthoff U, et al. Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis 2019;14:28.

Buscarini E, Plauchu H, Garcia Tsao G, et al. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. Liver Int 2006;26:1040-6.

Bureau C, Laurent J, Robic MA, et al. Central obesity is associated with non-cirrhotic portal vein thrombosis. J Hepatol 2016;64:427-32.

Boozari B, Bahr MJ, Kubicka S, Klempnauer J, Manns MP, Gebel M. Ultrasonography in patients with Budd-Chiari syndrome – diagnostic signs and prognostic implications. J Hepatol 2008;49:572-80.

Caselitz M, Bahr MJ, Bleck JS, et al. Sonographic criteria for the diagnosis of hepatic involvement in hereditary hemorrhagic telangiectasia (HHT). Hepatology 2003;37:1139-46.

Caturelli E, Ghittoni G, Ranalli TV, Gomes VV. Nodular regenerative hyperplasia of the liver: coral atoll-like lesions on ultrasound are characteristic in predisposed patients. Br J Radiol 2011; 84:e129–e34.

Chavan A, Schumann-Binarsch S, Luthe L, et al. Systemic therapy with bevacizumab in patients with hereditary hemorrhagic telangiectasia (HHT). Vasa 2013;42:106-10.

Chavan A, Schumann-Binarsch S, Schmuck B, et al. Emerging role of bevacizumab in management of patients with symptomatic hepatic involvement in hereditary hemorrhagic telangiectasia. Am J Hematol 2017;92:E641-E647.

Chavan A, Luthe L, Gebel M, et al. Complications and clinical outcome of hepatic artery embolisation in patients with hereditary haemorrhagic telangiectasia. Eur Radiol 2013;23:951-7.

Chaudhary N, Mehrotra S, Srivastava M, Nundy S. Management of bleeding in extrahepatic portal venous obstruction. Int J Hepatol 2013;2013:784842.

Chen Z, Ran T, H Cao, Xu F, Zhou Z, He S. The impact of portal vein thrombosis on the prognosis of patients with cirrhosis: A retrospective propensity-score matched study. Front Med 2021;8:685944.

Cheuk DKL, Chiang AKS, Ha SY, Chan GCF. Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation. Cochrane Database Syst Rev 2015;5, CD009311:1-109.

Choudhry AJ, Baghdadi YMK,Amr MA, et al. Pylephlebitis: a review of 95 cases. J Gastrointest Surg 2016;20:656-61.

Christie AB, Christie DB, Nakayama DK, Solis MM. Hepatic artery aneurysms: evolution from open to endovascular repair techniques. Am Surgeon 2011;77:608-11.

Ciesek S, Rifai K, Bahr MJ, et al. Membranous Budd-Chiari syndrome in caucasians. Scand J Gastroenterol 2010;45:226-34.

Cliffe ST, Bloch DB, Suryani S, et al. Clinical, molecular, and cellular immunologic findings in patients with SP110-associated veno-occlusive disease with immunodeficiency syndrome. J Allergy Clin Immunol 2012;130:735-42.

Colina F, Alberti N, Solis JA, Martinez-Tello FJ. Diffuse nodular regenerative hyperplasia of the liver (DNRH). A clinicopathologic study of 24 cases. Liver 1989; 9:253-65.

Cool J, Rosenblatt R, Kumar S, et al. Portal vein thrombosis prevalence and associated mortality in cirrhosis in a nationally representative inpatient cohort. J Gastroenterol Hepatol 2019;34:1088-1092.

Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in paediatric patients: a new classification from the European society for blood and marrow transplantation. Bone Marrow Transplant 2018;53:138-45.

Corbacioglu S, Cesaro S, Faraci M, et al. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. Lancet 2012;379:1301-9.

Darwish Murad S, Plessier A, Hernandez-Guerra M, et al. Aetiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med 2009;151:167-75.

de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76:959-74.

De Gottardi A, Rautou PE, Schouten J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol Hepatol 2019;4:399-411.

De Gottardi A, Sempoux C, Berzigotti Al. Porto-sinusoidal vascular disorder. J Hepatol 2022;77:1124-35.

De Gottardi A, Trebicka J, Klinger C, et al. Antithrombotic treatment with direct-acting oral anticoagulants (DOACs) in patients with splanchnic vein thrombosis and cirrhosis. Liver Int 2017;37:694-9.

DeLeve LD, Valla DC, Garcia-Tsao G. AASLD practice guidelines. Vascular disorders of the liver. Hepatology 2009;49:1729-64.

DeLeve LD, Wang X, Kuhlenkamp JF, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. Hepatology 1996;23:589-99.

Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2012;10:776-83.

De Santis A, Moscatelli R, Catalano C, et al. Systemic thrombolysis of portal vein thrombosis in cirrhotic patients: a pilot study. Digest Liver Dis 2010;42:451-5.

Dhiman RK, Saraswaty VA, Valla DC, et al. Portal cavernoma cholangiopathy: Consensus statement of a working party of the Indian National Association for Study of the Liver. J Clin Exp Hepatol 2014;4:S2-S14.

Dignan FL, Wynn RF, Hadzic N, et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol 2013;163:444-57.

Driever EG, von Meijenfeldt FA, Adelmeijer J, et al. Non-malignant portal vein thrombi in patients with cirrhosis consist of intimal fibrosis with or without a fibrin-rich thrombus. Hepatology 2021;75:898-911.

Droege F, Thangavelu K, Stuck BA, et al. Life expectancy and comorbidities in patients with hereditary hemorrhagic telangiectasia. Vasc Med 2018;23:37-383.

Dumortier J, Bizollon T, Scoazec JY, et al. Orthotopic liver transplantation for idiopathic portal hypertension: indications and outcome. Scand J Gastroenterol 2001;36:417-22.

Dupuis-Girod S, Ginon I, Saurin JC, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA 2012;307:948-55.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol 2016;64:179-202.

Efrati E, Zuckerman T, Ben-Ami E, Krivoy N. MTHFR C677T/A1298C genotype: a possible risk factor for liver sinusoidal obstruction syndrome. Bone Marrow Transpl 2014;49:726-727.

Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. Ann Intern Med 2020;173:989-1001.

Felli E, Addeo P, Faitot F, et al. Liver transplantation for hereditary hemorrhagic telangiectasia: A systematic review. HPB 2017;19:567-72.

Fusaro L, Di Bella S, Martingano P, Saveria Crocè L, Giuffrè M. Pylephlebitis: A systematic review on aetiology, diagnosis, and treatment of infective portal vein thrombosis. Diagnostics 2023;13:429.

Garg N, Khunger M, Gupta A, Kumar N. Optimal management of hereditary hemorrhagic telangiectasia. J Blood Med 2014;5:191-206.

Garcia-Pagán JC, Valla DC. Primary Budd-Chiari syndrome. N Engl J Med 2023;388:1307-16.

Garcia-Tsao G, Korzenik JR, Young L, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 2000;343:931-6.

Ghabril M, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. Semin Liver Dis 2014;34:240-5.

Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. Eur J Hum Genet 2009;17:860-71.

Gressens SB, Cazals-Hatem D, Lloyd V, et al. Hepatic venous pressure gradient in sinusoidal obstruction syndrome: Diagnostic value and link with histological lesions. JHep Rep 2022;4:100558.

Guerrero A, del Campo L, Piscaglia F, et al. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: The IMPORTAL competing-risk meta-analysis. J Hepatol 2023;79:69-78.

Guido M, Alves VAF, Balabaud C et al. Histology of portal vascular changes associated with idiopathic non-cirrhotic portal hypertension: nomenclature and definition. Histopathology 2019;74:219-226.

Guo DF, Fan LW, Le Q, Huang CB, et al. Transjugular intrahepatic portosystemic shunt for the prevention of rebleeding in patients with cirrhosis and portal vein thrombosis: Systematic review and meta-analysis. Front Pharmacol 2022;13:968988.

Hall TC, Garcea G, Metcalfe M, Bilku D, Dennison AR. Management of acute non-cirrhotic and non-malignant portal vein thrombosis: a systematic review. World J Surg 2011;35:2510-20.

Hartleb M, Gutkowski K, Milkiewicz P. Nodular regenerative hyperplasia: Evolving concepts on underdiagnosed cause of portal hypertension. World J Gastroenterol 2011;17:1400-9.

Hulsberg P, de la Garza-Jordan J, Jordan R, Matusz P, Tubbs RS, Loukas M. Hepatic aneurysm: a review. Am Surg 2011;77:586-91.

Iannaccone R, Federle MP, Brancatelli G et al. Peliosis hepatis: Spectrum of imaging findings. AJR 2006;187:W43-W52.

Inchingolo R, Posa A, Mariappan M, et al. Transjugular intrahepatic portosystemic shunt for Budd-Chiari syndrome: A comprehensive review. World J Gastroenterol 2020;26:5060-73.

Janssen HLA, Garcia-Pagan JC, Elias E, et al. Budd-Chiari syndrome: a review by an expert panel. J Hepatol 2003;38:364-71.

Jharap B, van Asseldonk DP, de Boer NKH, et al. Diagnosing nodular regenerative hyperplasia of the liver is thwarted by low interobserver agreement. PLoS ONE 2015;10:DOI:10.1371/journal.pone.0120299.

Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987;44:778-83.

Jevtic D, Gavrancic T, Pantic I, et al. Suppurative thrombosis of the portal vein (pylephlebits): A systematic review of literature. J Clin Med 2022;11:4992.

Kanellopoulou T, Alexopoulou A, Theodossiades G, Koskinas J, Archimandritis AJ. Pylephlebitis: an overview of non-cirrhotic cases and factors related to outcome. Scand J Infect Dis 2010;42:804-11.

Khuroo MS, Rather AA, Khuroo NS, Khuroo MS. Portal biliopathy. World J Gastroenterol 2016; 22: 7973-82.

Lassau N, Auperin A, Leclere J, Bennaceur A, Valteau-Couanet D, Hartmann O. Prognostic value of doppler-ultrasonography in hepatic venoocclusive disease. Transplantation 2002;74:60-6.

Li Y, De Stefano V, Li H, et al. Epidemiology of Budd-Chiari syndrome: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2019;43:468-474.

Lu J, Zhang XP, Zhong BY, et al. Management of patients with hepatocellular carcinoma and portal vein tumour thrombosis: comparing east and west. Lancet Gastroenterol Hepatol 2019;4:721-30.

Luca A, Miraglia R, Caruso S, et al. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. Gut 2011;60:846-52.

Mahadeo KM, McArthur J, Adams RH, et al. Consensus report by the paediatric acute lung injury and sepsis investigators and paediatric blood and marrow transplant consortium joint working committees on supportive care guidelines for management of veno-occlusive disease in children and adolescents: Part 2 - focus on ascites, fluid and electrolytes, renal, and transfusion issues. Biol Blood Marrow Transplant 2017;23:2023-33.

Marzano C, Cazals-Hatem D, Rautou PE, Valla DC. The significance of nonobstructive sinusoidal dilatation of the liver: Impaired portal perfusion or inflammatory reaction syndrome. Hepatology 2015;62:956-63.

Matsumoto T, Kobayashi S, Shimizu H, et al. The liver in collagen diseases: pathologic study of 160 cases with particular reference to hepatic arteritis, primary biliary cirrhosis, autoimmune hepatitis and nodular regenerative hyperplasia of the liver. Liver 2000;20:366-73.

McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation – a cohort study of 355 patients. Ann Intern Med 1993;118:255-67.

McDonald GB. Liver disease of uncertain cause. Bone Marrow Transplant 2004;33:977-8.

McDonald J, Wooderchak-Donahue WL, Henderson K, et al. Tissue-specific mosaicism in hereditary hemorrhagic telangiectasia: Implications for genetic testing in families. Am J Med Genet 2018;176:1618-1621.

Monaco G, Bucherini L, Stefanini B, Piscaglia F, Foschi FG, Ielasi L. Direct oral anticoagulants for the treatment of splanchnic vein thrombosis: A state of art. 2023;29:4962-74.

Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives – A position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant

2015;50:781-9.

Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 2016;51:906-12.

Mohty M, Malard F, Abecassis M, et al. Prophylactic, preemptive, and curative treatment for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: A position statement from an international expert group. Bone Marrow Transplant 2020;55:485-95.

Mohty M, Malard F, Alaskar AS M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a refined classification from the European society for blood and marrow transplantation (EBMT). Bone Marrow Transplant 2023;58:749-54.

Naber AH, Van Haelst U, Yap SH. Nodular regenerative hyperplasia of the liver: an important cause of portal hypertension in non-cirrhotic patients. J Hepatol 1991;12:94-9.

Nakanuma Y, Hoso M, Sasaki M, et al. Histopathology of the liver in non-cirrhotic portal hypertension of unknown aetiology. Histopathology 1996; 28:195-204.

Nakanuma Y, Tsuneyama K, Ohbu M., Katayanagi K. Pathology and pathogenesis of idiopathic portal hypertension with an emphasis on the liver. Pathol Res Pract 2001;197:65-76.

Naymagon L, Tremblay D, Schiano T,·Mascarenhas J. The role of anticoagulation in pylephlebitis: a retrospective examination of characteristics and outcomes. J Thromb Thrombolysis 2020;49:325-31.

Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 Practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;73:366-413.

Ovchinsky N, Frazier W, Auletta JJ, et al. Consensus report by the paediatric acute lung injury and sepsis investigators and paediatric blood and marrow transplantation consortium joint working committees on supportive care guidelines for management of veno-occlusive disease in children and adolescents, part 3: Focus on cardiorespiratory dysfunction, infections, liver dysfunction, and delirium. Biol Blood Marrow Transplant 2018;24:204-18.

Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 1989;32:291-7.

Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al. Acute portal vein thrombosis unrelated to cirrhosis: A prospective multicenter follow-up study. Hepatology 2010;51:210-8.

Palomo M, Mir E, Rovira M, Escolar G, Carreras E, Diaz-Ricart M. What is going on between defibrotide and endothelial cells? Snapshots reveal the hot spots of their romance. Blood 2016;127:1719-27.

Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomised, dose-finding trial. Biol Blood Marrow Transplant 2010;16:1005-17.

Richardson PG, Ho VT, Cutler C, Glotzbecker B, Antin JH, Soiffer R. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: Novel insights to pathogenesis, current status of treatment and future directions. Biol Blood Marrow Transplant 2013;19:S88-S90.

Richardson PG, Corbacioglu S, Ho VT, et al. Drug safety evaluation of defibrotide. Expert Opin Drug Saf 2013;12:123-36.

Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. Blood 2016;127:1656-65.

Rodrigues SG, Sixt S, Abraldes JG, et al. Systematic review and meta-analysis: portal vein recanalisation and transjugular intrahepatic portosystemic shunt for portal vein thrombosis. Aliment Pharmacol Ther 2019;49:20-30.

Ronot M, Kerbaol A, Rautou PE, et al. Acute extrahepatic infectious or inflammatory diseases are a cause of transient mosaic pattern on CT and MR imaging related to sinusoidal dilatation of the liver. Eur Radiol 2016;26:3094-101.

Rössle M, Bausch B, Klinger C. Therapy algorithm for portal vein thrombosis in liver cirrhosis: The internist's point of view. Viszeralmedizin 2014;30:401-8.

Ruutu T, Peczynski C, Houhou M, et al. Current incidence, severity, and management of veno-occlusive ase/sinusoidal obstruction syndrome in adult allogeneic HSCT recipients: an EBMT Transplant Complications Working Party study. Bone Marrow Transpl 2023; online first.

Qi X, Han G, Guo X, et al. The aetiology of primary Budd-Chiari syndrome - differences between the West and China. Aliment Pharmacol Ther 2016;44:1152-67.

Sarin SK, Kumar A, Chawla YK, et al. Noncirrhotic portal fibrosis/idiopathic portal hypertension: APASL recommendations for diagnosis and treatment. Hepatol Int 2007;1:398-413.

Sarin SK, Philips CA, Kamath PS, et al. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. Gastroenterology 2016;151:574-77.

Schouten JNL, Garcia-Pagan JC, Valla DC, Janssen HLA. Idiopathic noncirrhotic portal hypertension. Hepatology 2011;54:1071-81.

Schouten JNL, Verheij J, Seijo S. Idiopathic non-cirrhotic portal hypertension: a review. Orphanet J Rare Dis 2015;10(67):1-8

Schuldes M, Weickert U. Kontrastmittelsonographie bei Verdacht auf Lebermetastasen. Dtsch Med Wochenschr 2011;136:1255-6.

Seijo S, Reverter E, Miquel R, et al. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. Dig Liver Dis 2012;44:855-60.

Seijo S, Plessier A, Hoekstra J, et al. Good long-term outcome of Budd-Chiari syndrome with a step-wise management. Hepatology 2013;57:1962-68.

Senzolo M, Garcia-Tsao G, García-Pagan JC. Current knowledge and management of portal vein thrombosis in cirrhosis. J Hepatol 2021;75:442-53.

Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-7.

Shulman HM, Fisher LB, Schoch HG, Henne KW, McDonald GB. Venoocclusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. Hepatology 1994;19:1171-80.

Singh S, Swanson KL, Hathcock MA, et al. Identifying the presence of clinically significant hepatic involvement in hereditary haemorrhagic telangiectasia using a simple clinical scoring index. J Hepatol 2014;61;124-31.

Siramolpiwat S, Seijo S, Miquel R, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatology 2014;59:2276-85.

Tewari P, Wallis W, Kebriaei P. Manifestations and management of veno-occlusive disease/sinusoidal obstruction syndrome in the era of contemporary therapies. Clin Adv Hematol Oncol 2017;15:130-9.

Thatishetty AV, Agresti N, O'Brien CB. Chemotherapy-induced hepatotoxicity. Clin Liver Dis 2013;17:671-86.

Tsokos M, Erbersdopler A. Pathology of peliosis. Forensic Sci Int 2005;149:25-33.

Van Wettere M, Purcell Y, Bruno O, et al. Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome. J Hepatol 2019;70:1123-32.

Valla DC, Cazals-Hatem D. Sinusoidal obstruction syndrome. Clin Res Hepatol Gastroenterol 2016;40:378-85.

Vilarinho S, Sari S, Yilmaz G, et al. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic noncirrhotic portal hypertension. Hepatology 2016;63:1977-86.

Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012;143:1253-60.

Vion AC, Rautou PE, Durand F, Boulanger CM, Valla DC. Interplay of inflammation and endothelial dysfunction in bone marrow transplantation: Focus on hepatic veno-occlusive disease. Semin Thromb Hemost 2015;41:629-43.

Viteri-Noël A, González-García A, Luis Patier J, et al. Hereditary hemorrhagic telangiectasia: Genetics, pathophysiology, diagnosis, and management. J Clin Med 2022;11:5245.

Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990;11:787-97.

Xu X, GuoX, De Stefano V, et al. Nonselective beta-blockers and development of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. Hepatol Int 2019;13:468-81.

Yang S, Wu J, Lei S. CT features of hepatic venoocclusive disease: A meta-analysis. Acad Radiol 2018;25:328-37.

Yanoff M, Rawson AJ. Peliosis hepatis. An anatomic study with demonstration of two variities. Arch Pathol 1964;77:159-65.

Zhang F, Wang C, Li Y. The outcomes of interventional treatment for Budd-Chiari syndrome: systematic review and meta-analysis. Abdom Imaging 2015;40:601-8.

Zhang Y, Xu BY, Wang XB, et al. Prevalence and clinical significance of portal vein thrombosis in patients with cirrhosis and acute decompensation. Clin Gastroenterol Hepatol 2020;18:2564-72.

Zhang ZY, Dong KS, Zhang EL, et al. Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: A systematic review and meta-analysis. Medicine 2019;98:e18362.

Zhang Z, Zhao Y, Han B, Zhu Z, Sun L, Cui X. The efficacy and safety of anticoagulants in the treatment of cirrhotic portal vein thrombosis: A systematic review and meta-analysis. Clin Appl Thromb Hemost 2022;28:1-10.

Zuo C, Chumbalkar V, Ells PF, et al. Prevalence of histological features of idiopathic noncirrhotic portal hypertension in general population: A retrospective study of incidental liver biopsies. Hepatol Int 2017;11:452-60.

16. Acute liver failure

Akif Altinbas, Josef Pospiech, Ali Canbay

Introduction

Acute liver failure (ALF), characterized by elevated liver enzymes in addition to hyperbilirubinemia, coagulopathy, and/ or hepatic encephalopathy, is a potentially life-threatening clinical condition that develops in the presence of a healthy liver. Preexisting chronic liver issues must be ruled out because the management and outcome of acute-on-chronic liver failure differ from ALF (Lemmer 2023).

The classical clinical picture is extensive hepatocyte death followed by loss of liver functions displaying prolonged INR and elevated bilirubin levels (Rutherford 2008). In animal studies, targeting ferroptosis, in addition to previously documented cell deaths of apoptosis, necrosis, and necroptosis, was recently found to have a limiting effect on acetaminophen-induced ALF (Yamada 2020). NLRP3 inflammasome was shown to play a crucial role in ALF by causing various cell deaths (Jiménez-Castro 2019). ALF is a potentially reversible disease that occurs in the body's most regeneratively skilled organ. In this dynamic process, the lost hepatocytes undergo healthy hepatocyte cell division and ductular structure proliferation while apoptotic bodies and cell debris are cleared out by inmate and newly recruited macrophages, along with the activated hepatic stellate cells, which play an important role in the progression of fibrosis (Cardoso 2017). The balance between the degree of cell death and the ability of hepatocytes to regenerate, as well as the severity of neutrophil infiltration and the amount of collagen produced, would define where the liver ends up. As a result, predicting which patients require more aggressive intervention, such as emergent liver transplantation, is in clinical practice difficult yet valuable.

Epidemiology

The overall incidence of ALF is estimated to be one to six cases per million people each year, and it accounts for up to 8% of all adult liver transplants (Bernal 2010, Rovegno 2019). Germany, with 800-1000 ALF cases annually, was found to be comparable with the US but significantly lower than East Asian countries such as Taiwan and Thailand (Weiler 2020). In Thailand, the incidence of ALF in was reported as 62.9 per million population per year, with just 0.005% of ALF patients undergoing liver transplantation

(Thanapirom 2019). However, comparing the results by income level would be inaccurate due to a lack of reliable data and some misclassifications, including alcohol-related liver failure labeled as ALF in middle- and low-income countries (Weiler 2020, Thanapirom 2019). The establishment of a registry in Asia to collect ALF-related data should be promoted.

In high-income countries, acetaminophen intoxication remains the most common cause of ALF (about 50%), whereas viral hepatitis and herbal medications are in low- and middle-income nations (Bernal 2010, Stravitz 2023, Vento 2023). Surprisingly, the Argentinian registry revealed that nearly half of ALF patients had indeterminate etiology or autoimmune hepatitis (Mendizabal 2019). The etiology, as well as the outcome, varied greatly depending on the country's income level. The more than 90% ALF-related deaths in the 1980s dropped to 29% in Western countries, however it still double the rate within the low-income regions (Vento 2023). Receiving timely and accurate diagnoses, as well as meeting general standards of care in ICU settings with transplantation options, makes a significant difference in outcome. The survival rates following liver transplantation continued to improve (e.g., 5 years survival rate was 63%) even though the age of the donors and recipients was advancing in Europe (Müller 2020).

With acetaminophen as the major cause, drug-induced ALF does have a central role with only minor changes in Western countries. Painkillers, such as acetaminophen, ibuprofen, and diclofenac, are comparable to the group of antibiotics followed by some herbal medicines (Weiler 2020, Tujios 2022). In the United States, 22% of ALF patients waiting for liver transplant had seronegative or indeterminate etiology, 34% as drug-induced etiology and 15% had viral hepatitis (Karvellas 2023). In Asia, the most common drugs for drug-induced ALF are herbals, traditional and anti-tuberculosis medicines (Jindal 2022). According to the literature, almost half of the acetaminophen-related ALF cases are unintentional (not suicidal), and half of them involve a combination with opioids (Larson 2005). Interestingly, in the United States, after limiting the dose of acetaminophen in this combination, the rate of ALF secondary to acetaminophen has decreased by 16% every year (Orandi 2023).

Viral hepatitis B and E, particularly HEV in pregnant women, which are still the leading causes of ALF in middle- and low-income countries, have begun to rise again following a steady drop thanks to widespread immunization campaigns. This recent spike was mostly attributed to the opioid crisis, injection drug use, and homelessness (Tujios 2022). There is always a need for updated approaches to prevent HBV reactivations as new biological, immune-suppressive, or immuno-modulatory therapies become available (Papatheodoridis 2022). Hepatitis A, on the other hand, is closely related to socioeconomic development level, poor access to healthcare or clean water, a rising number of immigrants, intravenous drug use, and sexual orientation (e.g., males having sex with men). Even though ALF occurs in less than 1% of HAV patients, once established, the mortality rate among adults can reach 30% and the outcome following liver transplantation, compared to HBV-induced ALF, is much worse (Jindal 2022, Manka 2016). HCV has not been identified as a cause of ALF; on the other hand, HDV requires the presence of HBV and is commonly identified as a cause of acute-on-chronic hepatitis/ liver failure.

Acute-onset severe AIH presentation is a rare cause of ALF (ranging from 7% to 32%), but transplant-free survival with the presentation of ALF was as low as 15% in U.S. and 20% in Brazil (Mendizabal 2019, Jindal 2022, Enke 2023).

Other causes of ALF, such as amanita toxin, Wilson's disease, Budd-Chiari syndrome, and acute fatty liver of pregnancy, may account for nearly 1% of all causes (Table 1) (Stravitz 2023). In Western countries, however, indeterminate, or idiosyncratic etiologies account for 7- 43% of ALF cases (Stravitz 2023, Mendizabal 2019, Müller 2020, Hadem 2012).

Table 1. Aetiology-specific diagnostic and treatment methods of ALF

Aetiology	Diagnostic method	Treatment method
Acetaminophen	Drug concentration in serum	Oral active charcoal N-acetylcysteine
Idiosyncratic drug toxicity	Drug concentrations in serum Eosinophil count in serum	N-acetylcysteine Corticosteroid Ursodeoxycholic acid
Acute viral hepatitis A	HAV Ig M	No specific therapy
Acute viral hepatitis B	HBsAg, HBc Ig M, HBV DNA	Entecavir, Tenofovir disoproxil or alafenamide
Acute viral hepatitis E	Anti- HEV, HEV RNA	Ribavirin
Herpes Simplex virus	HSV Ig M, HSV RNA	Acyclovir
Autoimmune hepatitis	ANA, ASMA, Ig G, LKM, SLA	Methylprednisolone
Wilson's disease	Urinary copper, ceruloplasmin in serum, slit-lamp examination	No specific therapy
Alpha 1 antitrypsin deficiency	AT level in serum, AT genotyping	No specific therapy
Haemochromatosis	Ferritin in serum, transferrin saturation	No specific therapy
Budd-Chiari syndrome	Ultrasound	Anticoagulation, transjugular intrahepatic portosystemic shunt
Acute fatty liver of pregnancy	Swansea criteria	Immediate delivery
Amanita	Amatoxins in urine, history	Oral active charcoal Silibinin

General standard of care

Traditionally, the time interval between the onset of symptoms and the development of coagulopathy and encephalopathy I used to classify patients as hyperacute (<7 days), acute (8-28 days), or subacute (28 days-6 months) groups. This classification would be useful in predicting not only the etiology, which is usually linked with hyperacute presentations such as APAP and ischemic etiologies, but also the outcome, as the longer the delay, the worse the outcome (O'Grady 1993). Recognizing ALF earlier and distinguishing it from acute-on-chronic liver diseases, transferring the patient to an intensive care unit (ICU), preferably in a specialized transplant center, defining the cause and initiating a specific therapy in addition to the standards of care, could be lifesaving. Therefore, the management plan should prioritize timely and evidence-based medicine treatment methods for ALF, including etiology-specific approaches as well as general standards of care with multi-disciplinary teams.

A race against the clock starts immediately after a presumed diagnosis of ALF. Preventing metabolic complications such as hypoglycemia or hyponatremia should be supported by monitoring for potential organ failures due to renal or lung involvement. As a result, monitoring urine output, ammonia and lactate levels, repeating finger stick glucose levels as well as electrolytes, kidney, and hepatic functions, and avoiding nephrotoxic agents, is critical in the management of ALF.

The initial workup should also include searching for possible underlying infections with a detailed physical evaluation, routine urinalysis, urine and blood cultures, and chest images. Providers should also bear in mind that the interpretation of inflammatory markers such as C-reactive protein (CRP) and procalcitonin may be challenging due to altered synthetic capacity of the liver. Routine antibiotic use without any evidence of infection is usually advised; nevertheless, given the high risk of infection evolving in sepsis and multi-organ failure quickly, the bar for initiating an empirical broad-spectrum antibiotic should be low (Lemmer 2023).

Close monitoring of vital signs alongside neurological impairments is essential in the context of ALF management. The most common used hepatic encephalopathy (HE) classification is the West Haven criteria which divided HE into 4 category where minimal and grade 1 represents clinically covert HE, whereas grade 3 and 4, clinically overt HE, present with somnolence or coma, respectively, are indicative for emergent liver transplantation in the setting of irreversible liver injury (Lemmer 2023, Weissenborn 2019). Because the elevated serum ammonia levels related to cerebral edema may result in cerebral herniation and death if intracranial pressure (ICP) exceeds 25mmHg, obtaining cranial computed tomography (CT) in patients with advanced hepatic encephalopathy and repeating the imaging in the event of neurological deterioration is now standard of care. It was reported that these complications of ALF are seen much less than before with the improvements in the standard of care and the modalities to detoxify ammonia. Furthermore, because of increased mental alteration and neurological dysfunction, avoiding aspiration risks is as important as avoiding benzodiazepines, particularly long-acting formulations.

Monitoring INR, aPTT, fibrinogen, and platelet counts in ALF patients is still part of assessing the severity of underlying hepatic functions and the risk of bleeding. However, given the recent concept of “rebalanced hemostasis,” it is widely agreed that the decision to transfuse any type of coagulation factor or blood products has not been made without obtaining viscoelastic tests (VET) such as ROTEM analyses (Lemmer 2023, Cohen 2020, Stravitz 2018). There is an overall decreased synthesis of both pro- and anti-coagulant factors in the context of ALF. Furthermore, despite having coagulopathy due to a pro-coagulant state, both mechanical and medical DVT prophylaxis, as well as routine vitamin K supplementation in the context of prolonged cholestasis, is recommended (Pereira 2005). On the other side, the risk of bleeding is mostly attributable to stress-induced GI mucosal injury and has been reported to be 10%, although only 2% relates to death (Stravitz 2018). Of note, platelet count could be a predictor of a poor outcome (Stravitz 2023).

Some scoring systems have been widely utilized predict the outcome of ALF (Table 2). The model for end-stage liver disease (MELD), which was originally designed to predict the outcome of cirrhotic patients undergoing transjugular portacaval shunt (TIPS) procedure, was found to be a better tool than King’s College (KCC) and Clichy criteria, and has since been widely used as an allocation tool in Europe and the United States (Lemmer 2023). While KCC outperformed MELD in predicting mortality from acetaminophen-related ALF, MELD was shown to be superior to KCC in non-acetaminophen-drug-related cases (Craig 2010, Fontana 2021). The ALFSG index was demonstrated to be better than the KCC and Clichy criterion (Koch 2016). In a recent observational cohort study, a bedside noninvasive breathing test (13C-methacetin) representing the metabolic function of the liver was shown to be a promising tool (Fontana et al. 2021). The combination of MicroRNAs combination in addition to clinical data was also found to be better than the ALFSG index, MELD, and KCC criteria (Tavabie 2021). Because the outcome of ALF is primarily defined by the impaired balance between the amount of hepatocyte cell death, the regenerative capacity of the hepatocytes and the synthetic function of the liver, incorporating the apoptotic or overall cell death markers of M30 or M65, respectively, into scoring systems, including a short-lived liver product of hepcidin or an activated liver progenitor cell marker reflecting the regenerative capacity of liver, could display better accuracy (Lemmer 2023). There is ongoing interest in and need for a more

accurate prognostic scoring method (Stravitz 2023).

Liver biopsy has been mostly replaced by non-invasive tests. However, in such circumstances, a liver biopsy is required to determine the presence of Ebstein-Barr virus (EBV), Herpes simplex virus (HSV), or Cytomegalovirus (CMV), or to diagnose autoimmune hepatitis or malignancies, or with the indeterminate cases when the prompt diagnosis may lead to a specific treatment. A liver biopsy could still be of benefit in predicting the outcome and the need for emergent liver transplantation in individualized cases.

Table 2. Current widely used and promising new scoring systems

Scoring systems	Aetiology specific	
King's College criteria	Acetaminophen	Arterial pH 7.25 or Two of the following criteria: INR <6.5, creatinine >300 µmol/L, grade 3-4 hepatic encephalopathy
	Non-acetaminophen	INR>6.5 or Three of the following criteria: age <10 or >40 years, unclear or drug-induced aetiology, onset-time between jaundice and encephalopathy >7 days, INR>3.5, bilirubin >300 µmol/L
Clichy criteria*		Grade 3-4 hepatic encephalopathy and factor V level <20% if <30 years old, or <30% if >30 years old
MELD		10 x [0.957 x ln (serum creatinine) + 0.378 x ln(total bilirubin) +1.12 x ln(INR+0.643)]
Modified MELD with CK-18		10 x [0.957 x ln (serum creatinine) + 0.378 x ln(CK18/ M65) + 1.12 x ln(INR + 0.643)]
BILE score	Addition or subtraction of point(s) based on aetiology	Bilirubin (µmol/L)/100 + Lactate (mmol/L) + 4 (for cryptogenic ALF, Budd-Chiari or Phenprocoumon induced) –2 (for acetaminophen-induced) +0 (for other causes)
ALFSG index		Coma grade, bilirubin, INR, phosphorus, $\log_{10}$ M30
ALFED model		Dynamic of variables over 3 days: HE 0–2 points; INR 0–1 point; arterial ammonia 0–2 points; serum bilirubin 0–1 point
Additionally,		Low T3, low HDL, or high ferritin and low transferrin levels were found to be related to worse outcome

* Validated to HBV aetiology
Adapted from Lemmer P et al. (1)

Aetiology specific approach

Drug-induced

This Western society's nightmare is nevertheless often an exclusion diagnosis either from an idiosyncratic reaction or a predicted acetaminophen dose-related liver damage. Acetaminophen intoxication is typically caused by suicidal intent, roughly half of the cases, and causes a dose-related hepatocellular liver injury (Larson 2005). Therefore, monitoring the drug concentration in serum would mostly be beneficial in the context of suicide attempt. If acetaminophen-induced ALF occurs after a suicide attempt, activated oral charcoal (1 g/kg) if appears within 4 hours accompanied by N-acetyl cysteine infusion to restore glutathione if presents within 24-36 hours can be beneficial (Table 1) (Hoofnagle 2019). N-acetyl cysteine intravenous infusion protocol involves 10 grams over 20 minutes followed by 10 grams over 24 hours or 5 grams if the body weight is less than 70 kg.

On the other hand, most of the non-acetaminophen-drug-induced ALFs have a significant latency period, even up to one year, making the diagnosis challenging. Thus, there is continued interest in developing scores such as the Revised Electronic Causality Assessment Method (RECAM) to obtain a diagnosis with a better sensitivity (Hayashi 2022). In the future, drug-specific HLA-based genetic analysis could play a role in reaching a precise diagnosis (Fontana et al. 2023a; Nicoletti 2023). Corticosteroids are frequently used in non-acetaminophen-drug-related ALF cases (Sanabria-Cabrera 2022). Despite the need for randomized controlled trials to assess the actual role of corticosteroids, it is suggested to use in patients presenting with moderate-severe ALF or with autoimmune hepatitis features (Björnsson 2022). Even though the usefulness of three days of N-acetylcysteine infusion in the context of non-acetaminophen-drug-induced ALF is still debated, it is commonly employed given the non-harmful feature along with possibility of benefit (Andrade 2019, Fontana 2023). Of note, there is no harm or any supportive benefit for the use of ursodeoxycholic acid even in the setting of cholestatic presentation of drug-induced liver injury (Bernal 2010, Andrade 2019).

Viral hepatitis

The impact of the recent large population migration should be observed closely in Western countries. The majority of immigrants are from the areas where national vaccination programs are less likely to be implemented or where access to clean water, sanitation, and healthcare is limited (Bernal 2010). Furthermore, young generations from recently industrialized

countries such as South Korea, may lack HAV-protective antibodies HAV (Yoon 2017). On the other hand, HEV infection should be considered in every ALF case because it is the most prevalent viral cause of ALF in Asian countries (20- 40%) and is becoming more common in developed nations (up to 10%) (Manka 2016). Initiating one of the oral anti-viral agents for acute severe acute hepatitis (entecavir 0.5- 1 mg per day or tenofovir disoproxil 245 mg per day or Tenofovir alafenamide 25 mg per day) has been demonstrated to be effective in decreasing mortality rate (Stravitz 2019). Moreover, there is no effective anti-viral medication against HAV, and the most often used anti-viral for HEV is ribavirin (up to 1200 mg per day per body weight) (Gabrielli 2023).

ALF can be caused by viruses other than the conventional A- E viral hepatitis viruses, such as herpes simplex virus (HSV), CMV, EBV, VZV, and Dengue virus. Disseminated primary HSV (type 1 or 2) infections or reactivation secondary to the use of various monoclonal antibodies (e.g., tocilizumab) has been shown to be a cause of ALF, with nearly 90% mortality rates if untreated (Busani 2021, Chaudhary 2017). The absence of mucocutaneous lesions may make the diagnosis more difficult. The standard treatment for HSV-induced ALF is intravenous acyclovir with a dose of 10 mg/ kg three times per day.

Autoimmune related

Earlier accurate diagnosis and initiation of steroid treatment can reduce the need for emergent liver transplantation in individuals with acute onset severe AIH patients. However, given the lack of precise diagnostic markers, the absence of classical autoimmune markers in the majority of the cases (almost 40% seronegativity rates), the difficulties in obtaining a liver biopsy, the significant limitations in applying the standard AIH diagnostic scoring systems to the acute settings, and the confusion with prior suspicious drug usage may prevent timely initiation of therapy (Weiler-Normann 2014). Even though there are still some debates about the definition of responsiveness, the treatment of AIH-induced ALF should begin as soon as underlying sepsis is excluded. The standard of care is administration of intravenous methylprednisolone 1-2 mg/kg per day.

Amanita intoxication

Administering activated charcoal enterally for gastrointestinal decompensation, accompanied by silibinin intravenously (20- 50 mg/ kg per day) as an amatoxin uptake inhibitor, are the major modalities to fight against Amanita phalloides-related poisoning (Olano 2021). Without obtaining urine test positivity for amatoxins, particularly in spring and early summer, the treatment should be initiated based on the mushroom consumption history. The first 24 hours are important for initiating treatment for the greatest efficacy, however since the days of 2-4 are critical for developing irreversible liver failure, monitoring these patients closely and transferring them to an institute capable of emergent liver transplantation is critical (Lemmer 2023).

Wilson disease

The presence of prominently high bilirubin levels alongside low alkaline phosphatase, relatively low transaminases with reduced hemoglobin levels secondary to Coomb's negative hemolysis, and cholinesterase activity may raise the suspicion of Wilson disease without awaiting the typical clinical presentation of Wilson disease. Because the classical treatment options for Wilson's disease, chelators and zinc tablets, are ineffective in the setting of ALF due to time limitation to take in action, practically almost all patients die without liver transplantation (Lee 2009). This uncommon reason for ALF, reportedly 1% in the US, is an autosomal recessive disease (Stravitz 2023).

Acute fatty liver of pregnancy

It is an uncommon (in 1 out of 7000-15000 pregnancies), but potentially fatal obstetric complication that typically seen in the third trimester of the pregnancy (Verma 2021). The diagnosis is determined when 6 out of 14 Swansea criteria met, and extreme precautions, including immediate delivery regardless of gestational age, should be taken. Newborns should be monitored for hypoglycemia and fatty liver carefully, while mothers should be monitored for liver failure, requiring emergent liver transplantation. Both mom and newborn may undergo long-chain 3-hydroxyacyl-coenzyme A dehydrogenase enzyme deficiency afterward.

Budd- Chiari syndrome

This rare cause of ALF, around 1%, occurs in the context of underlying hereditary or acquired hypercoagulable state (one-third), or secondary to oral contraceptive use or abdominal trauma, or idiopathic (one-fifth) (Stravitz 2023, Parekh 2017). Therefore, diagnostic investigations should

include myeloproliferative disorders, which vary from 30% to 50% of Budd-Chiari syndrome cases, and of utmost importance, the search for an undiagnosed malignancy before moving forward to emergent liver transplantation (Costa 2020).

Once the diagnosis of Budd-Chiari syndrome is established, the general standard of care is initiation of long-term anticoagulation therapy with low molecular weight heparin followed by vitamin K antagonists, if there is no contraindication such as pregnancy. If attempts to reduce the portal system outflow pressure with trans-jugular intrahepatic portosystemic shunt (TIPS) placement fail and ALF progresses, emergent liver transplantation is inevitable. Despite the advances in treatment modalities, even hospital mortality was almost 60%, and the classical scoring systems (MELD and King's College) were found to be inaccurate in predicting the survival of these patients with Budd-Chiari syndrome (Parekh 2017).

In addition to Continues Renal Replacement Therapy (CRRT), which has been linked to an improved neurological and overall outcome if initiated earlier, there are certain artificial liver support systems, promising plasma exchange therapy, and developing stem cell therapies (Lemmer 2023; Stravitz 2023). The common characteristic of these modalities is their non-etiology-specific features. They should be considered as part of the overall ALF management strategy.

Despite the fact that acute kidney injury is not rare in ALF patients, the success of CRRT is independent of AKI occurrence, and defined as efficacious in the context of sustained high ammonia levels (>150 mmol/L) (Cardoso 2018, Nanchal 2020, Tsipotis 2015). Albumin-bound toxin-adsorbing systems such as MARS and Prometheus could also be beneficial. However, given the conflicting data in the literature, it could be considered a bridge therapy to liver transplantation, particularly under clinical trials (Tsipotis 2015). Circuit thrombosis could be a possible issue to deal with when it comes to these systems.

An alternative to these liver support systems with the capacity to adsorb large amounts of protein-bound toxins is plasma exchange therapy (Stravitz 2023). Likely related to its capability to decrease the amount of damage-associated molecular patterns and the impact on monocyte function, plasma exchange was found to improve overall survival, even in patients who are too sick to undergo liver transplantation (Larsen 2016). MARS and plasma exchange were shown to be beneficial as a bridge to liver transplantation in Wilson disease patients (Jindal 2022). Given the high mortality rate of ALF presentation of Wilson disease, identifying even a bridge therapy toward emergent liver transplantation is important.

To enhance liver cell regeneration, adipose-derived stem cells are being used as promising hepatocyte cell sources and to enrich the immunological environment in individuals, whereas allogeneic macrophages were found to be limiting necrosis via increased clearance of apoptotic and necrotic cells in the liver in a mouse model (Götze 2019, Lewis 2020).

Liver transplantation

The main goal of ALF treatment is to prevent death and improve transplant-free survival. Access to emergent liver transplantation in the setting of ALF necessitates major resources, such as institutions with specialized human resources and advanced units, long-term follow-up with close social and medical support, and useful organ donors. The pressing concern for high-income countries is the limited number of liver donors. There are ongoing efforts to broaden the donor criteria by accepting livers from persons with advanced steatosis, as well as livers from circulating death donors, or by employing split grafts or living donors (Sharma 2022). While the percentage of living liver donors increased from 2.3% to 5% between 2017 and 2020 in the United States, the global average is 23% (Terrault 2023). Applying mechanical liver perfusion to increase graft viability and decrease posttransplantation complications has the potential to impact on the liver transplantation process (Da Sousa Silva 2022).

In other words, emergent liver transplantation is a game changer, particularly for ALF patients who do not respond to the standard of care. Predicting the outcome and taking precautions towards emergent liver transplantation in an earlier setting is an important step in the management of ALF. Therefore, the necessity of emergent liver transplantation should be assessed every day starting from admission day until the day of discharge.

It should be taken into account that, irrespective of etiology, overall survival in the context of ALF is around 65- 70%, with acetaminophen-induced ALF representing the highest possibility of transplantation-free recovery as well as the highest risk of death in the waitlist (Reddy et al. 2016). The transplant-free survival dropped to 20-30% with the etiologies of DILI, autoimmune, and HBV (Stravitz 2023).

References

Andrade, Raúl J.; Aithal, Guruprasad P.; Björnsson, Einar S.; Kaplowitz, Neil; Kullak-Ublick, Gerd A.; Larrey, Dominique et al. (2019): EASL Clinical Practice Guidelines: Drug-induced liver injury. In: Journal of hepatology 70 (6), S. 1222–1261. DOI: 10.1016/j.jhep.2019.02.014.

Bernal, William; Auzinger, Georg; Dhawan, Anil; Wendon, Julia (2010): Acute liver failure. In: Lancet (London, England) 376 (9736), S. 190–201. DOI: 10.1016/S0140-6736(10)60274-7.

Björnsson, Einar S. (2022): Role of Corticosteroids in Drug-Induced Liver Injury. A Systematic Review: Frontiers Media S.A.

Busani, Stefano; Bedini, Andrea; Biagioni, Emanuela; Serio, Lucia; Tonelli, Roberto; Meschiari, Marianna et al. (2021): Two Fatal Cases of Acute Liver Failure Due to HSV-1 Infection in COVID-19 Patients Following Immunomodulatory Therapies. In: Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 73 (1), e252-e255. DOI: 10.1093/cid/ciaa1246.

Cardoso, Filipe S.; Gottfried, Michelle; Tujios, Shannan; Olson, Jody C.; Karvellas, Constantine J. (2018): Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. In: Hepatology (Baltimore, Md.) 67 (2),

S. 711–720. DOI: 10.1002/hep.29488.

Cardoso, Filipe S.; Marcelino, Paulo; Bagulho, Luís; Karvellas, Constantine J. (2017): Acute liver failure: An up-to-date approach. In: Journal of critical care 39, S. 25–30. DOI: 10.1016/j.jcrc.2017.01.003.

Chaudhary, Dhruv; Ahmed, Shifat; Liu, Nanlong; Marsano-Obando, Luis (2017): Acute Liver Failure from Herpes Simplex Virus in an Immunocompetent Patient Due to Direct Inoculation of the Peritoneum. In: ACG case reports journal 4, e23. DOI: 10.14309/crj.2017.23.

Cohen, Tobias; Haas, Thorsten; Cushing, Melissa M. (2020): The strengths and weaknesses of viscoelastic testing compared to traditional coagulation testing. In: Transfusion 60 Suppl 6, S21-S28. DOI: 10.1111/trf.16073.

Costa, Ana Rita Gonçalves; Freitas, Inês; Raposo, Joana; Barbosa, Gustavo; Miranda, Helena P.; Nery, Filipe (2020): Budd-Chiari Syndrome and Acute Liver Failure: An Uncommon Presentation of Acute Myeloid Leukaemia. In: GE Portuguese journal of gastroenterology 28 (1), S. 62–66. DOI: 10.1159/000507335.

Craig, D. G. N.; Ford, A. C.; Hayes, P. C.; Simpson, K. J. (2010): Systematic review: prognostic tests of paracetamol-induced acute liver failure. In: Alimentary pharmacology & therapeutics 31 (10), S. 1064–1076. DOI: 10.1111/j.1365-2036.2010.04279.x.

Da Sousa Silva, Richard X.; Weber, Achim; Dutkowski, Philipp; Clavien, Pierre-Alain (2022): Machine perfusion in liver transplantation. In: Hepatology (Baltimore, Md.) 76 (5), S. 1531–1549. DOI: 10.1002/hep.32546.

Enke, Thomas; Livingston, Sherry; Rule, Jody; Stravitz, Todd; Rakela, Jorge; Bass, Nathan et al. (2023): Autoimmune hepatitis presenting as acute liver failure: A 20-year retrospective review of North America. In: Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 29 (6), S. 570–580. DOI: 10.1097/LVT.0000000000000105.

Fontana, Robert J.; Bjornsson, Einar S.; Reddy, Rajender; Andrade, Raul J. (2023a): The Evolving Profile of Idiosyncratic Drug-Induced Liver Injury. In: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 21 (8), S. 2088–2099. DOI: 10.1016/j.cgh.2022.12.040.

Fontana, Robert J.; Liou, Iris; Reuben, Adrian; Suzuki, Ayako; Fiel, M. Isabel; Lee, William; Navarro, Victor (2023b): AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. In: Hepatology (Baltimore, Md.) 77 (3), S. 1036–1065. DOI: 10.1002/hep.32689.

Fontana, Robert J.; Stravitz, R. Todd; Durkalski, Valerie; Hanje, James; Hameed, Bilal; Koch, David et al. (2021): Prognostic Value of the 13 C-Methacetin Breath Test in Adults with Acute Liver Failure and Non-acetaminophen Acute Liver Injury. In: Hepatology (Baltimore, Md.) 74 (2), S. 961–972. DOI: 10.1002/hep.31783.

Gabrielli, Filippo; Alberti, Francesco; Russo, Cristina; Cursaro, Carmela; Seferi, Hajrie; Margotti, Marzia; Andreone, Pietro (2023): Treatment Options for Hepatitis A and E: A Non-Systematic Review. In: Viruses 15 (5). DOI: 10.3390/v15051080.

Götze, Tobias; Krueger, Michael; Meutsch, Juliane; Dörfel, Max; Born, Stephan; Sowa, Jan-Peter; Canbay, Ali (2019): Three Cases of Alcohol-Induced Acute-On-Chronic Liver Failure With Successful Support by Adipose-Derived Stem Cells. In: Clinical and translational gastroenterology 10 (12), e00095. DOI: 10.14309/ctg.0000000000000095.

Hadem, Johannes; Tacke, Frank; Bruns, Tony; Langgartner, Julia; Strnad, Pavel; Denk, Gerald U. et al. (2012): Etiologies and outcomes of acute liver failure in Germany. In: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 10 (6), 664-9.e2. DOI: 10.1016/j.cgh.2012.02.016.

Hayashi, Paul H.; Lucena, M. Isabel; Fontana, Robert J.; Bjornsson, Einar S.; Aithal, Guruprasad P.; Barnhart, Huiman et al. (2022): A revised electronic version of RUCAM for the diagnosis of DILI. In: Hepatology (Baltimore, Md.) 76 (1), S. 18–31. DOI: 10.1002/hep.32327.

Hoofnagle, Jay H.; Björnsson, Einar S. (2019): Drug-Induced Liver Injury — Types and Phenotypes. In: The New England journal of medicine 381 (3), S. 264–273. DOI: 10.1056/NEJMra1816149.

Jiménez-Castro, Mónica B.; Cornide-Petronio, María Eugenia; Gracia-Sancho, Jordi; Peralta, Carmen (2019): Inflammasome-Mediated Inflammation in Liver Ischemia-Reperfusion Injury. In: Cells 8 (10). DOI: 10.3390/cells8101131.

Jindal, Ankur; Sarin, Shiv K. (2022): Epidemiology of liver failure in Asia-Pacific region. In: Liver international : official journal of the International Association for the Study of the Liver 42 (9), S. 2093–2109. DOI: 10.1111/liv.15328.

Karvellas, Constantine J.; Leventhal, Thomas M.; Rakela, Jorge L.; Zhang, Jingwen; Durkalski, Valerie; Reddy, K. Rajender et al. (2023): Outcomes of patients with acute liver failure listed for liver transplantation: A multicenter prospective cohort analysis. In: Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 29 (3), S. 318–330. DOI: 10.1002/lt.26563.

Koch, David G.; Tillman, Holly; Durkalski, Valerie; Lee, William M.; Reuben, Adrian (2016): Development of a Model to Predict Transplant-free Survival of Patients With Acute Liver Failure. In: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 14 (8), 1199-1206.e2. DOI: 10.1016/j.cgh.2016.03.046.

Larsen, Fin Stolze; Schmidt, Lars Ebbe; Bernsmeier, Christine; Rasmussen, Allan; Isoniemi, Helena; Patel, Vishal C. et al. (2016): High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. In: Journal of hepatology 64 (1), S. 69–78. DOI: 10.1016/j.jhep.2015.08.018.

Larson, Anne M.; Polson, Julie; Fontana, Robert J.; Davern, Timothy J.; Lalani, Ezmina; Hynan, Linda S. et al. (2005): Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. In: Hepatology (Baltimore, Md.) 42 (6), S. 1364–1372. DOI: 10.1002/hep.20948.

Lee, William M.; Hynan, Linda S.; Rossaro, Lorenzo; Fontana, Robert J.; Stravitz, R. Todd; Larson, Anne M. et al. (2009): Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. In: Gastroenterology 137 (3), 856-64, 864.e1. DOI: 10.1053/j.gastro.2009.06.006.

Lemmer, Peter; Sowa, Jan-Peter; Bulut, Yesim; Strnad, Pavel; Canbay, Ali E. (2023): Mechanisms and aetiology-dependent treatment of acute liver failure. Aachen: Universitätsbibliothek der RWTH Aachen.

Manka, Paul; Verheyen, Jens; Gerken, Guido; Canbay, Ali (2016): Liver Failure due to Acute Viral Hepatitis (A-E). In: Visceral medicine 32 (2), S. 80–85. DOI: 10.1159/000444915.

Mendizabal, Manuel; Tagliafichi, Viviana; Rubinstein, Fernando; Rojas, Paloma; Marciano, Sebastían; Yantorno, Silvina et al. (2019): Liver transplantation in adults with acute liver failure: Outcomes from the Argentinean Transplant Registry. In: Annals of hepatology 18 (2), S. 338–344. DOI: 10.1016/j.aohep.2018.11.003.

Müller, Philip C.; Kabacam, Gokhan; Vibert, Eric; Germani, Giacomo; Petrowsky, Henrik (2020): Current status of liver transplantation in Europe. In: International journal of surgery (London, England) 82S, S. 22–29. DOI: 10.1016/j.ijsu.2020.05.062.

Nanchal, Rahul; Subramanian, Ram; Karvellas, Constantine J.; Hollenberg, Steven M.; Peppard, William J.; Singbartl, Kai et al. (2020): Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary, and Renal Considerations. In: Critical care medicine 48 (3), e173-e191. DOI: 10.1097/CCM.0000000000004192.

Nicoletti, Paola; Dellinger, Andrew; Li, Yi Ju; Barnhart, Huiman X.; Chalasani, Naga; Fontana, Robert J. et al. (2023): Identification of Reduced ERAP2 Expression and a Novel HLA Allele as Components of a Risk Score for Susceptibility to Liver Injury Due to Amoxicillin-Clavulanate. In: Gastroenterology 164 (3), S. 454–466. DOI: 10.1053/j.gastro.2022.11.036.

O'Grady, J. G.; Schalm, S. W.; Williams, R. (1993): Acute liver failure: redefining the syndromes. In: Lancet (London, England) 342 (8866), S. 273–275. DOI: 10.1016/0140-6736(93)91818-7.

Olano, Jonathan de; Wang, Josh J.; Villeneuve, Eric; Gosselin, Sophie; Biary, Rana; Su, Mark K.; Hoffman, Robert S. (2021): Current fatality rate of suspected cyclopeptide mushroom poisoning in the United States. In: Clinical toxicology (Philadelphia, Pa.) 59 (1), S. 24–27. DOI: 10.1080/15563650.2020.1747624.

Orandi, Babak J.; McLeod, M. Chandler; MacLennan, Paul A.; Lee, William M.; Fontana, Robert J.; Karvellas, Constantine J. et al. (2023): Association of FDA Mandate Limiting Acetaminophen (Paracetamol) in Prescription Combination Opioid Products and Subsequent Hospitalizations and Acute Liver Failure. In: JAMA 329 (9), S. 735–744. DOI: 10.1001/jama.2023.1080.

Papatheodoridis, George V.; Lekakis, Vasileios; Voulgaris, Thodoris; Lampertico, Pietro; Berg, Thomas; Chan, Henry L. Y. et al. (2022): Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: A systematic review, meta-analysis, and expert opinion. In: Journal of hepatology 77 (6), S. 1670–1689. DOI: 10.1016/j.jhep.2022.07.003.

Parekh, Justin; Matei, Vlad M.; Canas-Coto, Alejandro; Friedman, Daniel; Lee, William M. (2017): Budd-chiari syndrome causing acute liver failure: A multicenter case series. In: Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 23 (2), S. 135–142. DOI: 10.1002/lt.24643.

Pereira, Stephen P.; Rowbotham, David; Fitt, Sarah; Shearer, Martin J.; Wendon, Julia; Williams, Roger (2005): Pharmacokinetics and efficacy of oral versus intravenous mixed-micellar phylloquinone (vitamin K1) in severe acute liver disease. In: Journal of hepatology 42 (3), S. 365–370. DOI: 10.1016/j.jhep.2004.11.030.

Reddy, K. Rajender; Ellerbe, Caitlyn; Schilsky, Michael; Stravitz, R. Todd; Fontana, Robert J.; Durkalski, Valerie; Lee, William M. (2016): Determinants of outcome among patients with acute liver failure listed for liver transplantation in the United States. In: Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 22 (4), S. 505–515. DOI: 10.1002/lt.24347.

Rovegno, Maximiliano; Vera, Magdalena; Ruiz, Alex; Benítez, Carlos (2019): Current concepts in acute liver failure. In: Annals of hepatology 18 (4), S. 543–552. DOI: 10.1016/j.aohep.2019.04.008.

Rutherford, Anna; Chung, Raymond T. (2008): Acute liver failure: mechanisms of hepatocyte injury and regeneration. In: Seminars in liver disease 28 (2), S. 167–174. DOI: 10.1055/s-2008-1073116.

Sanabria-Cabrera, Judith; Tabbai, Sara; Niu, Hao; Alvarez-Alvarez, Ismael; Licata, Anna; Björnsson, Einar et al. (2022): N-Acetylcysteine for the Management of Non-Acetaminophen Drug-Induced Liver Injury in Adults: A Systematic Review. In: Frontiers in pharmacology 13, S. 876868. DOI: 10.3389/fphar.2022.876868.

Sharma, Sonal; Saner, Fuat H.; Bezinover, Dmitri (2022): A brief history of liver transplantation and transplant anesthesia. In: BMC anesthesiology 22 (1), S. 363. DOI: 10.1186/s12871-022-01904-1.

Starkey Lewis, Philip; Campana, Lara; Aleksieva, Niya; Cartwright, Jennifer Ann; Mackinnon, Alison; O'Duibhir, Eoghan et al. (2020): Alternatively activated macrophages promote resolution of necrosis following acute liver injury. In: Journal of hepatology 73 (2), S. 349–360. DOI: 10.1016/j.jhep.2020.02.031.

Stravitz, R. Todd; Ellerbe, Caitlyn; Durkalski, Valerie; Schilsky, Michael; Fontana, Robert J.; Peterseim, Carolyn; Lee, William M. (2018): Bleeding complications in acute liver failure. In: Hepatology (Baltimore, Md.) 67 (5), S. 1931–1942. DOI: 10.1002/hep.29694.

Stravitz, R. Todd; Fontana, Robert J.; Karvellas, Constantine; Durkalski, Valerie; McGuire, Brendan; Rule, Jody A. et al. (2023): Future directions in acute liver failure. In: Hepatology (Baltimore, Md.) 78 (4), S. 1266–1289. DOI: 10.1097/HEP.0000000000000458.

Stravitz, R. Todd; Lee, William M. (2019): Acute liver failure. In: Lancet (London, England) 394 (10201), S. 869–881. DOI: 10.1016/S0140-6736(19)31894-X.

Tavabie, Oliver D.; Karvellas, Constantine J.; Salehi, Siamak; Speiser, Jaime L.; Rose, Christopher F.; Menon, Krishna et al. (2021): A novel microRNA-based prognostic model outperforms standard prognostic models in patients with acetaminophen-induced acute liver failure. In: Journal of hepatology 75 (2), S. 424–434. DOI: 10.1016/j.jhep.2021.03.013.

Terrault, Norah A.; Francoz, Claire; Berenguer, Marina; Charlton, Michael; Heimbach, Julie (2023): Liver Transplantation 2023: Status Report, Current and Future Challenges. In: Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 21 (8), S. 2150–2166. DOI: 10.1016/j.cgh.2023.04.005.

Thanapirom, Kessarin; Treeprasertsuk, Sombat; Soonthornworasiri, Ngamphol; Poovorawan, Kittiyod; Chaiteerakij, Roongruedee; Komolmit, Piyawat et al. (2019): The incidence, etiologies, outcomes, and predictors of mortality of acute liver failure in Thailand: a population-base study. In: BMC gastroenterology 19 (1), S. 18. DOI: 10.1186/s12876-019-0935-y.

Tsipotis, Evangelos; Shuja, Asim; Jaber, Bertrand L. (2015): Albumin Dialysis for Liver Failure: A Systematic Review. In: Advances in chronic kidney disease 22 (5), S. 382–390. DOI: 10.1053/j.ackd.2015.05.004.

Tujios, Shannan; Stravitz, R. Todd; Lee, William M. (2022): Management of Acute Liver Failure: Update 2022. In: Seminars in liver disease 42 (3), S. 362–378. DOI: 10.1055/s-0042-1755274.

Vento, Sandro; Cainelli, Francesca (2023): Acute liver failure in low-income and middle-income countries. In: The lancet. Gastroenterology & hepatology 8 (11), S. 1035–1045. DOI: 10.1016/S2468-1253(23)00142-5.

Verma, Dhruv; Saab, Adelaide M.; Saab, Sammy; El-Kabany, Mohamed (2021): A Systematic Approach to Pregnancy-Specific Liver Disorders. In: Gastroenterology & hepatology 17 (7), S. 322–329.

Weiler, Nina; Schlotmann, Andreas; Schnitzbauer, Andreas Anton; Zeuzem, Stefan; Welker, Martin-Walter (2020): The Epidemiology of Acute Liver Failure. In: Deutsches Arzteblatt international 117 (4), S. 43–50. DOI: 10.3238/arztebl.2020.0043.

Weiler-Normann, Christina; Lohse, Ansgar W. (2014): Acute autoimmune hepatitis: many open questions. In: Journal of hepatology 61 (4), S. 727–729. DOI: 10.1016/j.jhep.2014.06.030.

Weissenborn, Karin (2019): Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. In: Drugs 79 (Suppl 1), S. 5–9. DOI: 10.1007/s40265-018-1018-2.

Yamada, Naoya; Karasawa, Tadayoshi; Kimura, Hiroaki; Watanabe, Sachiko; Komada, Takanori; Kamata, Ryo et al. (2020): Ferroptosis driven by radical oxidation of n-6 polyunsaturated fatty acids mediates acetaminophen-induced acute liver failure. In: Cell death & disease 11 (2), S. 144. DOI: 10.1038/s41419-020-2334-2.

Yoon, Eileen L.; Sinn, Dong Hyun; Lee, Hyun Woong; Kim, Ji Hoon (2017): Current status and strategies for the control of viral hepatitis A in Korea. In: Clinical and molecular hepatology 23 (3), S. 196–204. DOI: 10.3350/cmh.2017.0034.

17. Complications of liver cirrhosis

Benjamin Maasoumy, Jonel Trebicka

Summary

This chapter deals with the development of complications in patients with end stage liver disease. Liver cirrhosis is the common in stage of any chronic liver injury. After a rather long period of compensated stage with increasing fibrosis and liver insufficiency, portal hypertension develops also progressively and drive complications. Especially development of collaterals including varices, as well as development of kidney dysfunction with the ascites are the most common complications of portal hypertension. Alongside with portal hypertension, a complex process of augmenting inflammatory state takes place, first limited to the liver and later taking over the organism in the form of systemic inflammation. Both portal hypertension and systemic inflammation drive decompensation, with this maximal form acute on chronic liver failure (ACLF), characterised by development of organ failures and very high short-term mortality. Despite substantial research work treatment options are limited to nonselective beta blockers, non-absorbable antibiotics, albumin, TIPS and liver transplantation.

Clinical stages and pathophysiology of liver cirrhosis

Liver cirrhosis is widely regarded as the final stage in the natural history of liver disease. However, complications and prognosis vary widely among the affected patients (D'Amico 2006, D'Amico 2018). In the past, patients have only been stratified into compensated and decompensated cirrhosis. However, this does not adequately reflect the complex pathomechanism and the wide variety of clinical phenotypes (Figure 1) (D'Amico 2018, Engelmann 2021). Modern classifications distinguish up to seven distinct stages in the natural history of cirrhosis (D'Amico 2018, Schulz 2024). In patients with compensated cirrhosis or compensated advanced chronic liver disease (cACLD), the development of portal hypertension plays a key role in disease progression and the development of clinical complications. Portal

hypertension is defined by a portosystemic pressure gradient (PPG) of ≥6 mmHg (de Franchis 2022). However, the risk of associated complications, i.e. hepatic decompensation, remains negligible until a threshold of 10 mmHg is reached. This threshold indicates a so called clinical significant portal hypertension (CSPH) (de Franchis 2022, Jachs 2024a, Jachs 2024b). In the absence of CSPH and if the underlying liver disease has been adequately treated, patients do not necessarily require any specialised follow-up other than surveillance for hepatocellular carcinoma (HCC) due to the overall excellent prognosis (de Franchis 2022, Jachs 2024b, Semmler 2022). In contrast, those cACLD patients with CSPH should usually be followed by hepatologists for hepatic decompensation and may benefit from early treatment with non-selective beta-blockers (NSBB) even in the absence of large varices (Semmler 2021, Villanueva 2019). The gold standard for the diagnosis of CSPH in cACLD patients is the invasive transjugular assessment of the hepatic venous pressure gradient (HVPG). However, in the recent years several non-invasive alternatives have been established based on either elastography, blood tests (e.g. VITRO (Jachs 2023, Semmler 2024), 3P/5P model (Reiniš 2023, Sandmann 2023)) or a combination of different clinical and laboratory data (e.g. ANTIPICATE model (Abraldes 2016, Pons 2021)). BAVENO VII proposed criteria based on liver stiffness and platelets, which have been best validated for chronic hepatitis C and are able to diagnose or rule-out CSPH in about 50% of the patients (Abraldes 2016, Semmler 2022). Sequential application or combination of different non-invasive tests as well as the introduction of new techniques (e.g. spleen elastography) may reduce the grey zone in the future (Dajti 2022, Jachs 2023, Odriozola 2023) (Table 1). Validation will be required for different etiologies (including rare diseases) and different clinical situations (cured vs. ongoing liver disease) (Jachs 2024b, Sandmann 2023).

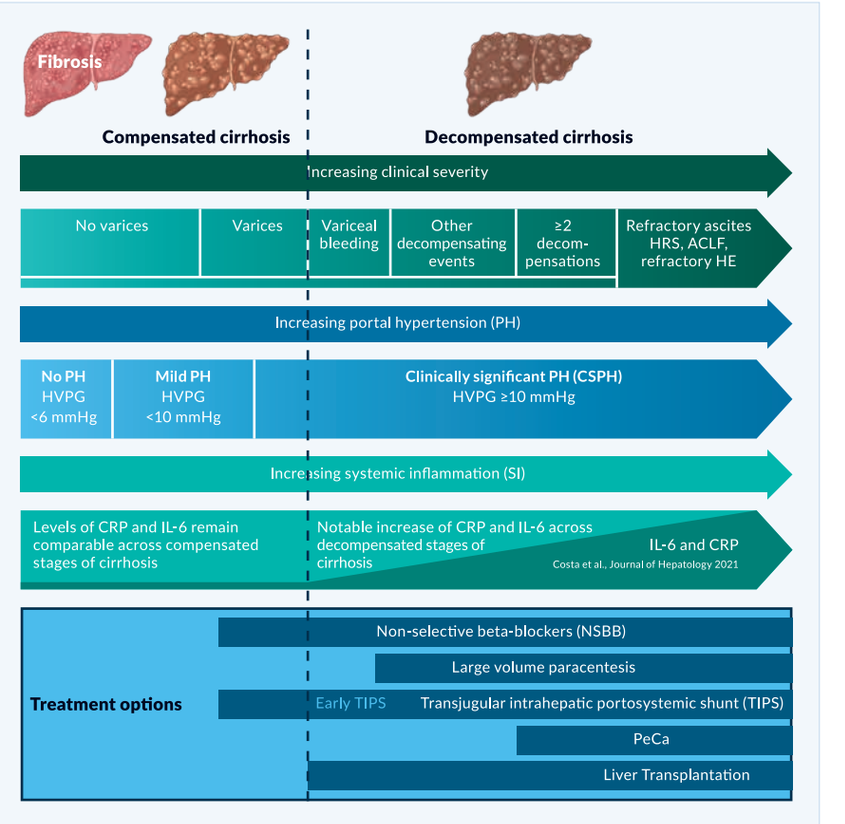

Figure 1. Modified after D'Amico et al., Journal of Hepatology 2018.

Table 1. Selection of non-invasive tests (NIT) for the detection of clinically significant portal hypertension (CSPH)

NIT model	Required Parameters	Output Categories	Cut-off values (if available)
ANTICIPATE[1] ANTICIPATE NASH[2]	LSM + PLT LSM + PLT + BMI	CSPH probability (%) CSPH probability (%) in obese MASLD/MetALD patients	
Baveno VII[3]	LSM + PLT	CSPH ruled-out, Grey zone, CSPH ruled-in	**CSPH Ruled out:** LSM ≤15 kPa + PLT ≥150x10^9/L **CSPH Ruled in:** LSM ≥25 kPa particularly validated for patients with virus- and/or alcohol-related cACLD and non-obese (BMI <30 kg/m^2) NASH-related cACLD
+ VITRO[4]	LSM + PLT + VWF/PLT ratio	CSPH ruled-out, Grey zone, CSPH ruled-in	**Baveno VII +** **CSPH Ruled out:** VITRO ≤1.5 **CSPH Ruled in:** VITRO ≥2.5
+ Spleen stiffness measurement (SSM)[5]	LSM + PLT + SSM	CSPH ruled-out, Grey zone, CSPH ruled-in	**CSPH Ruled out if at least two of the following present:** LSM ≤15 kPa; PLT ≥150 x 10^9/L; SSM ≤ 40kPa **CSPH Ruled in if at least two of the following present:** LSM >25 kPa; PLT <150 x 10^9/L; SSM > 40kPa
3P Model[6]	PLT + Bilirubin + INR	CSPH probability (%)	
5P Model[6]	PLT + Bilirubin + APTT + CHE + Gamma GT	CSPH probability (%)	

NASH: non-alcoholic steatotic liver disease, LSM: liver stiffness measurement, PLT: platelets, BMI: body mass index, CSPH: clinical significant portal hypertension, MASLD: metabolic dysfunction associated steatotic liver disease, cALCD: compensated advanced chronic liver disease, VWF: von Willebrandt factor, SSM: spleen stiffness measurement, INR: international normalised ratio

Citations

1: Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, Procopet B, Bosch J, Genesca J, Berzigotti A; Anticipate Investigators. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology. 2016 Dec;64(6):2173-2184. doi: 10.1002/hep.28824. Epub 2016 Oct 27. Erratum in: Hepatology. 2017 Jul;66(1):304-305. doi: 10.1002/hep.29201. PMID: 27639071.

2: Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, Stefanescu H, Ma MM, Mandorfer M, Mergeay-Fabre M, Procopet B, Schwabl P, Ferlitsch A, Semmler G, Berzigotti A, Tsochatzis E, Bureau C, Reiberger T, Bosch J, Abraldes JG, Genescà J. Noninvasive Diagnosis of Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease. Am J Gastroenterol. 2021 Apr;116(4):723-732. doi: 10.14309/ajg.0000000000000994. PMID: 33982942.

3: de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974. doi: 10.1016/j.jhep.2021.12.022. Epub 2021 Dec 30. Erratum in: J Hepatol. 2022 Jul;77(1):271. doi: 10.1016/j.jhep.2022.03.024. PMID: 35120736; PMCID: PMC11090185.

4: Jachs M, Hartl L, Simbrunner B, Bauer D, Paternostro R, Scheiner B, Balcar L, Semmler G, Stättermayer AF, Pinter M, Quehenberger P, Trauner M, Reiberger T, Mandorfer M. The Sequential Application of Baveno VII Criteria and VITRO Score Improves Diagnosis of Clinically Significant Portal Hypertension. Clin Gastroenterol Hepatol. 2023 Jul;21(7):1854-1863.e10. doi: 10.1016/j.cgh.2022.09.032. Epub 2022 Oct 14. PMID: 36244661.

5: Dajti E, Ravaioli F, Marasco G, Alemanni LV, Colecchia L, Ferrarese A, Cusumano C, Gemini S, Vestito A, Renzulli M, Golfieri R, Festi D, Colecchia A. A Combined Baveno VII and Spleen Stiffness Algorithm to Improve the Noninvasive Diagnosis of Clinically Significant Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease. Am J Gastroenterol. 2022 Nov 1;117(11):1825-1833. doi: 10.14309/ajg.0000000000001887. Epub 2022 Jul 21. PMID: 35973171.

6: Reiniš J, Petrenko O, Simbrunner B, Hofer BS, Schepis F, Scoppettuolo M, Saltini D, Indulti F, Guasconi T, Albillos A, Téllez L, Villanueva C, Brujats A, Garcia-Pagan JC, Perez-Campuzano V, Hernández-Gea V, Rautou PE, Moga L, Vanwolleghem T, Kwanten WJ, Francque S, Trebicka J, Gu W, Ferstl PG, Gluud LL, Bendtsen F, Møller S, Kubicek S, Mandorfer M, Reiberger T. Assessment of portal hypertension severity using machine learning models in patients with compensated cirrhosis. J Hepatol. 2023 Feb;78(2):390-400. doi: 10.1016/j.jhep.2022.09.012. Epub 2022 Sep 22. PMID: 36152767.

The progression of earlier stages of cirrhosis is directly correlated with the degree of portal hypertension (Costa 2021, Ripoll 2007). In the decompensated stage (dACLD), the absolute HVPG level becomes less important. Patients' prognosis and morbidity are determined by hepatic impairment, the presence of extrahepatic complications of cirrhosis and systemic inflammation (Angeli 2018, Costa 2021, D'Amico 2018, Engelmann 2021, Trebicka 2020d).

Hepatic impairment may include inadequate liver detoxification as indicated by elevated bilirubin or ammonia levels. Both are associated with patient survival. Bilirubin is widely used and included in several prognostic scores (Table 2). The value of ammonia has been controversial in the past. Limitations include interlaboratory variation. Recently, promising results have been published when local upper limits of normal are considered for interpretation (Ballester 2023, Tranah 2022). Hepatic synthetic capacity could be assessed by either INR or albumin. Serum cholinesterase may also be of value in certain situations (Stockhoff 2022).

Table 2. Scores for disease severity assessment in liver cirrhosis

Score	Included parameters	Interpretation	Comment
MELD Score[1]	Creatinine + Bilirubin + INR	Scores range from 6-40.	Predicts three-month survival in patients with liver cirrhosis. OPTN Score from 2002-2016.
MELD Na[2]	Creatinine + Bilirubin + INR + Sodium (Na)	Scores range from 6-40.	Predicts three-month survival in patients with liver cirrhosis. OPTN score from 2016-2022.
MELD 3.0[3]	Creatinine + Bilirubin + INR + Sodium (Na) + Albumin + Sex	Scores range from 6-40.	Predicts three-month survival in patients with liver cirrhosis. Current recommendation from the OPTN since 2022.
Child-Pugh[4]	Bilirubin + Albumin + Quick + Ascites + Hepatic encephalopathy	Scores range from 5-15. Child-Pugh class A (5-6 pts.), Child-Pugh class B (7-9 pts.), Child-Pugh class C (10-15 pts.)	Child-Pugh class correlate with one- and two-year patient survival. OPTN Score pre-2002.
CLIF-C AD[5]	Age + WBC + Creatinine + INR + Sodium (Na)	Scores range from 0-100. CLIF-C AD ≥60: high risk (3-month mortality >30%) CLIF-C AD ≤45: low risk (3-month mortality <2%)	CLIF-C acute decompensation (AD) score predicts survival of patients with acute decompensation of cirrhosis who do not have acute-on-chronic liver failure (ACLF)

It is generally preferable to use a validated online calculator to calculate each score as there are several caveats relating to minimum and maximum values assigned in the respective scores and subcategories, which make manual calculations prone to error.

Abbreviations

CLIF-C AD: Chronic Liver Failure Consortium Acute Decompensation; INR: International Normalised Ratio; MELD: Model for End-Stage Liver Disease; MELD Na: MELD score incorporating serum sodium; MELD 3.0: Updated MELD score incorporating sodium, albumin, and sex; Na: Sodium; OPTN: Organ Procurement and Transplantation Network; WBC: White blood cell count.

Citations

1: Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001 Feb;33(2):464-70. doi: 10.1053/jhep.2001.22172. PMID: 11172350.
2: Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006 May;130(6):1652-60. doi: 10.1053/j.gastro.2006.02.010. PMID: 16697729.
3: Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1-85. PMID: 4950264.
4: Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, Levesque E, Durand F, Angeli P, Caraceni P, Hopf C, Alessandria C, Rodriguez E, Solis-Muñoz P, Laleman W, Trebicka J, Zeuzem S, Gustot T, Mookerjee R, Elkrief L, Soriano G, Cordoba J, Morando F, Gerbes A, Agarwal B, Samuel D, Bernardi M, Arroyo V; CANONIC study investigators of the EASL-CLIF Consortium. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014 Nov;61(5):1038-47. doi: 10.1016/j.jhep.2014.06.012. Epub 2014 Jun 17. PMID: 24950482.

Various forms of hepatic decompensation (distinct cirrhosis-associated complications) can occur. However, the clinical and prognostic relevance differs between complications and also depends on the number of events, e.g. patients with a single event of variceal bleeding without ascites have a better outcome than those with ascites but without portal hypertensive bleeding (D'Amico 2014, D'Amico 2006). The current BAVENO VII criteria propose a distinction between first and subsequent hepatic decompensation. First hepatic decompensation could be either overt ascites, overt hepatic encephalopathy and/or variceal bleeding. Further decompensation is associated with higher mortality and is defined by the development of either a second decompensation event (ascites, encephalopathy or bleeding), jaundice, refractory ascites or hepatorenal syndrome (de Franchis 2022).

In the final stage of cirrhosis, systemic inflammation becomes an important part of the pathophysiology. CSPH is one of the key factors involved in this process. CSPH contributes to an impairment of the intestinal barrier ("leaky gut"). This leads to translocation of bacteria and bacterial compounds (pathogen-associated molecular patterns, PAMPs) (Trebicka 2021b). Hepatic and extrahepatic cell and tissue damage, such as that caused by underlying liver disease, leads to a systemic increase in damage-associated molecular patterns (DAMPs). PAMPs and DAMPs trigger the secretion of proinflammatory cytokines following systemic arterial vasodilation. This has the potential to further worsen portal pressure by increasing splanchnic and hepatic arterial inflow. However, this is limited by the cardiac capacity to compensate for the required hyperdynamic circulation (cirrhotic cardiomyopathy) (D'Amico 2018, Engelmann 2021) (Figure 2).

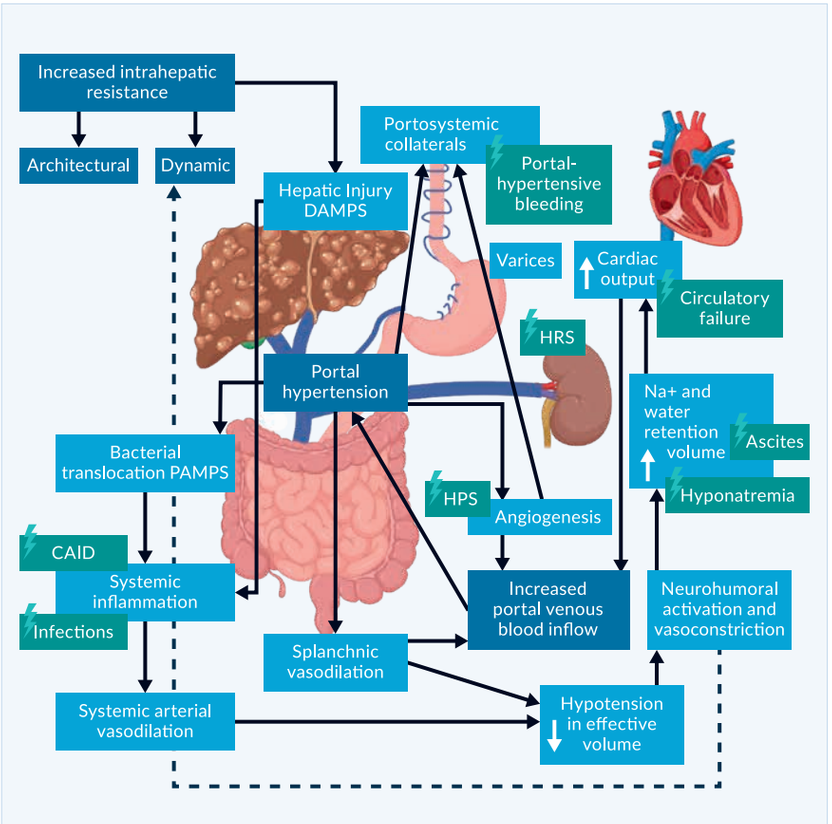

Figure 2. Adapted from Rodrigues et al., JHEP Reports 2020.

Pathophysiology and management of specific complications

Ascites

Clinical manifestation and relevance

Ascites is the most common event of first hepatic decompensation (18-48% of cases) (D'Amico 2018, Jepsen 2010, Planas 2004). The annual incidence in cACLD patients has been estimated to be 5-10% (Angeli 2018, Ginés 1987). It indicates a significant change in the natural history of liver cirrhosis with a dramatic increase in mortality (D'Amico 2006). Ascites is graded as mild (only detectable by ultrasound, grade 1), moderate (moderate abdominal distention, grade 2) and large (marked abdominal distention, grade 3) (Angeli 2018). While mild amounts of ascites are usually not associated with clinical symptoms, large amounts lead to significant morbidity. Clinical symptoms may include abdominal tightness, weight gain, loss of appetite, abdominal hernias and immobility. Ultimately, this leads to frailty, sarcopenia and a reduced health-related quality of life (HRQOL) (Hui 2024, Merli 2019). Small defects in the diaphragm can also accumulate in the pleural space as so-called hepatic hydrothorax, which can result in shortness of breath (Hui 2024).

Recurrent ascites is defined as ascites that occurs at least three times within 12 months. Refractory ascites is defined as ascites that cannot be mobilised despite adequate sodium restriction and diuretic treatment, either because of to non-response (diuretic-resistant) or intolerance of treatment (diuretic-intractable) (Angeli 2018, Arroyo 1996a). Refractory ascites indicates the final stage of liver cirrhosis and is linked to particularly poor survival (Salerno 1993, Tergast 2023, Tergast 2022). Therefore, patients with refractory ascites should be considered for liver transplantation (Angeli 2018).

Pathogenesis

Ascites is considered to be the consequence of CSPH, sodium and water retention as well as decreased oncotic pressure (Figure 3). CSPH and impaired venous drainage in portal system may increase capillary leakage and lead to drainage fluid into the abdominal cavity. Moreover, CSPH and inflammation results also leads to arterial vasodilation resulting in a decreased effective arterial blood volume. The physiological neurohumoral response to this is an activation of the renin-angiotensin-aldosterone system (RAAS) that mediates sodium and water retention in kidney. In the cirrhotic patient it will ultimately lead to sodium and water overload and is considered as the main driver of hydropic decompensation. Finally, impaired hepatic protein synthesis may contribute to ascites manifestation as the liver is the source of the majority of serum protein, in particular albumin.

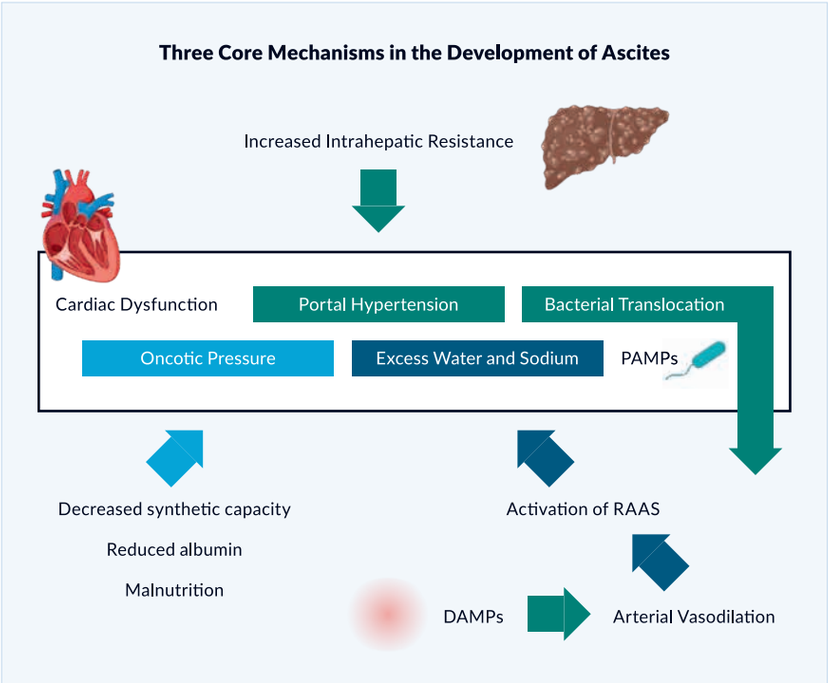

Figure 3. Adapted from Zakim and Boyers's Hepatology 6th edition; EASL „CPG decompensated cirrhosis", J Hepatol 2018; Bhathal PS, et al. J Hepatol 1985; Rockey DC, et al. Gastroenterology 1998.

Diagnostic work-up

First ascites manifestation requires a structured diagnostic work-up, which usually includes a diagnostic paracentesis. While cirrhosis is certainly the most common cause of ascites, other differential diagnoses such as heart failure, intra-abdominal malignancy, portal vein thrombosis must be ruled out at this stage. The general appearance of the ascites can already lead to assumptions about its origin (e.g. if it is red or milky). In addition, total ascites protein and albumin should be determined. Albumin levels can be used to calculate the simple serum ascites albumin gradient (SAAG). Using a threshold of 1.1 g/dL, the SAAG is supposed to differentiate ascites due to portal hypertension from other causes in more than 95% of the cases (Runyon 1992). Low ascites protein levels support the suspicion of a classic transudate, e.g. due to CSPH, and levels below 1.5 g/dL indicate an increased risk for spontaneous bacterial peritonitis (SBP) (Guarner 1999, Llach 1992, Moreau 2018, Runyon 1986). Levels above 2.5 g/dL are suspicious for other causes of ascites (Runyon 1992). If malignancy is suspected, cytology should be performed on samples of at least 50-100 mL (Angeli 2018, Arroyo 1996b). Ascites level of cholesterol and carcinoembryonic antigen levels may be useful in case repeated cytology remains inconclusive (Angeli 2018, Gulyás 2001). After ascites has been attributed to liver cirrhosis and CSPH, subsequent episodes do not always require the same level of work-up. However, any worsening or new onset of ascites should raise the question of a possible precipitating event of hepatic decompensation (e.g., infection) that requires specific treatment (de Franchis 2022, Jalan 2014b, Moreau 2013).

Treatment

Therapeutic strategies are directly derived from the pathomechanisms discussed above and include nutritional, pharmaceutical and interventional measures. In general, a stepwise approach should be followed. However, presentation with grade 3 ascites may also justify direct initiation of combination therapy.

Nutrition

Sodium restriction is considered to be the treatment of choice in patients with ascites targeting the RAAS-induced retention of sodium and free water. However, overall efficacy is limited and a certain degree of natriuresis is required. Current EASL guidelines recommend limiting salt intake to 4.6-6.9 g per day (Angeli 2018). While more restrictive regimens may result in faster resolution of ascites, they are associated with impaired caloric intake and increased risk of renal failure. Moreover, it remains almost impossible for patients to follow such recommendations in their daily routine, as it is not possible to calculate the exact amount of salt in all meals. A more practical approach is to advise them not to add extra salt to their regular meals.

Fluid restriction is often used to treat ascites. However, its role is widely overestimated. In particular, there are no data that convincingly support its widespread use. In addition, fluid restriction has the same disadvantages as sodium restriction in terms of reducing overall caloric intake. At present, it is only recommended for severe hyponatraemia (<125 mmol/L) (Angeli 2018, Gerbes 2019).

In contrast, the importance of overall calory and in particular protein intake seems to be widely underestimated. Malnutrition and sarcopenia is frequent among cirrhotic patients and independently linked to an increased morbidity and mortality. In non-obese patients a calory intake of 30-35 kcal/kg body weight including 1-1.5g/kg body weight is indicated. This should be accompanied by late evening snack to avoid hypoglycemic and katabolic phases during the night, which provokes encephalopathy as well as further detoriation of sarcopenia and ascites (Merli 2019).

Diuretics

The first line of treatment is aldosterone antagonists, which directly target hyperaldosteronism and are superior to loop diuretics as monotherapy. Spironolactone is the most widely used drug and can be used up to a dosage of 400mg per day (Angeli 2018). Common side effects include hyperkalaemia, renal impairment and gynecomastia. In patients with severe gynecomastia, eplerenone can be used as an alternative and equally effective treatment. However, the approved dosage is limited to 50 mg/day. In case of inadequate response or severe ascites and/or hyperkalaemia on monotherapy, loop diuretics may be added (Angeli 2018). The dosage should be limited to the equivalent of 160mg of oral furosemide per day. Torasemide may offer a more favourable pharmacokinetic profile. However, there are no data to support that this translates into a superior outcome in cirrhotic patients. Combination therapy with spironolactone and loop diuretics is more effective, offers a better control of protassium levels, but is also more frequently associated with an excessive response with the need for dose reductions (Angeli 2010, Santos 2003). Treatment should be aimed at weight loss of 500-1000 g per day and should be adjusted after ascites control is achieved (Angeli 2018).

Large volume paracentesis (LVP)

In patients with refractory ascites, repeated LVP can be performed to control clinical symptoms. LVP is generally a safe procedure. Major bleeding is rare and routine assessment of the patient`s coagulation status is therefore not required (Lin 2005, Villa 2022). However, ultrasound guidance is recommended to avoid inadvertent punction of abdominal vessels. While, a maximum drainage volume has not been established, there is a certain risk of a circulatory dysfunction following LVP of more than 5 litres, as indicated by a decrease in mean arterial pressure, increase in aldosterone levels and the risk of acute kidney injury (AKI) (Ginès 1988). This can be prevented by albumin infusion of 6-8 g/L of removed ascites (Angeli 2018, Bernardi 2012, Sola-Vera 2003). However, the longer term administration of albumin in patients with severe ascites, requiring paracentesis, has been shown to improve survival (Caraceni 2018b).

Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS insertion is the most effective treatment for CSPH after liver transplantation. Ascites control can be achieved in more than 70% of patients (García-Pagán 2020). A stent graft is placed through the jugular vein to create a bypass between a hepatic vein and a portal vein branch. This results in an immediate decrease in PPG, usually below the threshold of CSPH. Initially, there were some safety concerns due to a significant mortality rate and complications such as liver failure and encephalopathy (Lebrec 1996). Since then, significant benefits have been achieved, including technical safety, stent patency rates, and patient selection. In the past, TIPS malfunction was a common problem. However, this changed when bare metal stents were replaced by PTFE-coated stents (Bureau 2004). There has been a long-lasting debate as to whether TIPS is only a symptomatic treatment in patients with refractory and recurrent ascites. Finally, an individual patient meta-analysis (refractory ascites) and a well-designed randomised trial (recurrent ascites) convincingly demonstrated an improved survival compared to repeated LVP (Bureau 2017a, Salerno 2007). Thus, today, TIPS is considered the first-line treatment for patients with refractory or recurrent ascites (Angeli 2018, de Franchis 2022). The survival benefit underscores the ability of TIPS to alter the natural history of ACLD by curing CSPH, a major driver of disease progression. TIPS reduces the risk of further decompensation (Larrue 2023) and may prevent hepatic decompensation in patients with ACLD undergoing extrahepatic surgery (Piecha 2024). In addition, some studies suggest that there is a decrease in systemic inflammation after TIPS (Berres 2015, Kornfehl 2024, Tiede 2024), which is linked to an improved survival, ascites control and improvement of sarcopenia (Hey 2023, Kornfehl 2024, Tiede 2024). However, disadvantages need to be considered and patients must be carefully selected (García-Pagán 2020) (Table 3). The most discussed complication of TIPS may be hepatic encephalopathy. Spontaneous portosystemic shunts (SPSS) and their absolute size are linked to the risk of encephalopathy (Praktiknjo 2020a). Therefore, it seems obvious that this is also the case when TIPS is used as an iatrogenic shunt. In fact, the incidence of post-TIPS HE ranges from 35 to 50% (Bureau 2021, Ehrenbauer 2023, Montagnese 2022). While post-TIPS HE does necessarily increase mortality, it certainly does affect quality of life, in associated with rehospitalisation and is one of the most common reasons for the need of TIPS diameter reduction (Agrawal 2015, Gairing 2022, Nardelli 2024, Pereira 2016). Refractory or recurrent HE is usually considered as a contraindication for TIPS (Angeli 2018). However, the mechanisms of HE are complex and TIPS has both negative and positive effects in this regard (e.g. reduction of bleeding, inflammation and sarcopenia). Recent studies suggest that with fully covered stents and subsequently a marginal risk of dysfunction, the benefits and disadvantages of TIPS may even be balanced, as the HE incidence was not different from patients treated with LVP (Bureau 2017a). Overall, it remains difficult to predict the occurrence and course of HE after TIPS. Some authors stated that assessment for minimal HE may help to select patient selection (Berlioux 2014, Nardelli 2016). However, this has not been confirmed by others (Ehrenbauer 2023). More

relevant seems to be the stage of liver cirrhosis as indicated by MELD, serum cholinesterase or the new Freiburg index of post TIPS survival (FIPS) (Bettinger 2021, Cai 2022, Stockhoff 2022). The use of stents with a smaller diameter can reduce the risk for post-TIPS HE (Schepis 2018, Wang 2018) . 8 mm instead of 10 mm is now widely considered as the standard of care, especially due to improved outcome (Trebicka 2019b, Praktiknjo 2021b). Treatment efficacy remains similar as long as a 50% PPG reduction is achieved (Queck 2023, Wang 2018). In high-risk patients underdilatation to 6 or 7 mm or a reduction of preexisting SPSS may be considered (Lv 2022, Praktiknjo 2021a, Schepis 2018). Recently, an individualised approach has been suggested. A PPG reduction of 60-80% was identified as the optimal target to maximise the chance of ascites control without increase in the incidence of Post-TIPS HE (Kabelitz 2025). Finally, primary prophylaxis with rifaximin significantly reduced post-TIPS HE in a recently published randomised controlled trial (Bureau 2021). While the risk of HE may be overestimated, many physicians tend to underestimate the risk for cardiac decompensation, which can be expected in 20% of patients (Billey 2019, Schneider 2023). Due to the newly introduced shunt, the cardiac index increases by approximately 50% (Huonker 1999), at least in the early phase after TIPS. Therefore, patients with significant cardiac impairment and moderate or severe pulmonary hypertension should not undergo TIPS insertion (Angeli 2018). In addition, the presence of aortic valve stenosis seems to be associated with a particularly high risk (Billey 2019). Different risk scores have been proposed in the past with varying degrees of prognostic accuracy. In general, the prevalence of diastolic dysfunction seems to be a valid parameter that is associated with the likelihood of decompensation (Billey 2019, Schneider 2023). Thus, echocardiography should be performed prior to TIPS. Smaller diameter stents may help to further reduce the risk of decompensation. TIPS results in reduced portal blood flow. In rare cases this can lead to hepatic infarction (Tuifua 2022). Insufficient arterial perfusion must be ruled out when evaluating patients for TIPS. However, the more common clinical challenge is the reduction of liver function leading to hepatic failure with progressive increase in bilirubin levels. High grades of intrahepatic inflammation, serum bilirubin, serum cholinesterase as well as low albumin levels have been associated with poor post-TIPS survival (Bettinger 2021, Bureau 2011, Stockhoff 2021, Stockhoff 2022). Therefore, patients with very advanced stages of liver disease may not be suitable candidates for TIPS. However, most of these studies lack a control group. Thus, it remains unclear whether TIPS treatment impairs survival or whether the poorer outcome does rather reflect the prognosis of the more advanced liver cirrhosis (Bettinger 2021, Bureau 2011, Stockhoff 2021, Stockhoff 2022). In fact, some retrospective studies suggest that in patients with very advanced liver disease (e.g. as indicated by FIPS or CHE) survival is not impaired, but also no longer improved by TIPS insertion (Stockhoff 2021, Stockhoff 2022). Thus, TIPS could still be considered as a symptomatic treatment in these cases when liver transplantation is not available. Importantly, these studies also did not include patients with end-stage liver disease (e.g., bilirubin levels >100 µmol/L). While TIPS may not necessarily worsen prognosis in advanced stages of cirrhosis, it certainly becomes less effective and is associated with more complications. Current guidelines recommend to use TIPS for ascites only as soon as patients enter the stage of recurrent or refractory ascites. However, the required frequency of paracentesis is linked to higher rate of ascites persistence after TIPS (Piecha 2024). Given the positive effects at earlier stages including the reduction of further decompensation, future studies need to determine whether it should be considered earlier in the natural history of cirrhosis.

Table 3. Absolute and relative contraindications for TIPS insertion

Relative TIPS contraindications
• Cardiac ◦ Mild aortic valve stenosis ◦ E/A > 2 or E/A < 0.8 ◦ Two of the following: ▪ E/e´> 14 ▪ LAVI > 34 mL/m2 ▪ TR > 2.8 m/s ▪ sep e´ < 7 cm/s or lat e´< 10 cm/s
• Liver function ◦ MELD ≥ 18 ◦ Bilirubin ≥ 50 µmol/L ◦ Platelets ≤ 75.000/µL
• Primary or metastatic hepatic malignancy
• Contrast agent allergy
• Hyperthyreosis
• Age ≥ 65 years old
Absolute TIPS contraindications
• Cardiac ◦ LVEF ≤ 30% ◦ Moderate to severe aortic or pulmonary valve stenosis
• Renal ◦ Chronic kidney failure > CKD4, except hepatorenal syndrome
• Hepatic encephalopathy ◦ Acute ≥ 2. grade ◦ Recurrent/chronic encephalopathy ≥ 2. grade without specific trigger ▪ ≥ 2 episodes within 6 months
• Liver function ◦ Bilirubin ≥ 80 µmol/L
• Life expectancy ≤ 1 year
• Unrelieved biliary obstruction
• Active infection
• Significant pulmonary hypertension (mPAP >35 mmHg)
• Extensive primary or metastatic hepatic malignancy

Citations

1. Billey C, Billet S, Robic MA, et al. A Prospective Study Identifying Predictive Factors of Cardiac Decompensation After Transjugular Intrahepatic Portosystemic Shunt: The Toulouse Algorithm. Hepatology. 2019;70(6):1928-1941. doi:10.1002/hep.30934
2. Schneider H, Berliner D, Stockhoff L, et al. Diastolic dysfunction is associated with cardiac decompensation after transjugular intrahepatic portosystemic shunt in patients with liver cirrhosis. United European Gastroenterol J. 2023;11(9):837-851. doi:10.1002/ueg2.12471
3. Stockhoff L, Schultalbers M, Tergast TL, et al. Safety and feasibility of transjugular intrahepatic portosystemic shunt in elderly patients with liver cirrhosis and refractory ascites. PLoS One. 2020;15(6):e0235199. Published 2020 Jun 25. doi:10.1371/journal.pone.0235199
4. Tripathi D, Stanley AJ, Hayes PC, et al. Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension. Gut. 2020;69(7):1173-1192. doi:10.1136/gutjnl-2019-320221
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406-460. doi:10.1016/j.jhep.2018.03.024

Home-based ascites drainage systems

In patients who are not candidates for TIPS, continuous or daily ascites drainage may be considered as an alternative treatment to repeated LVP. In contrast to TIPS, CSPH and ascites formation are altered. However, ascites control can be achieved without the need for repeated medical interventions. There are mainly two different systems available. The first one is an implantable pump that drains fluid from the peritoneal cavity to the bladder (alfapump). The subcutaneous system can be charged and programmed with an external device. Early studies reported a higher incidence of renal failure and infections (Bellot 2013, Bureau 2017b, Solbach 2018, Stirnimann 2017). The frequency of these complications decreased with more experience and the use of prophylactic antibiotics. Continuous ascites drainage has been associated with less need for paracentesis and improved quality of life (Bellot 2013, Bureau 2017b, Solbach 2018, Stirnimann 2017, Wong 2020). However, the pump comes with significant cost and the need for surgery. Moreover, it is currently not available in Europe. The other option is a tunneled peritoneal catheter (PeCa). These are widely used for drainage of malignancy-associated fluid collections in the abdominal and pleural cavities (Lungren 2013, Maleux 2016). The system is less expensive, can be easily implanted with local anesthesia or light sedation, and can be removed in the same manner. It can therefore also be used as a bridging treatment (e.g. until transplantation or TIPS is available). Studies in patients with cirrhosis have shown a reduced need for paracentesis (Macken 2019, Solbach 2017) and an overall good control of ascites. Infections are frequent in the treated patients. However, randomised controlled trials are lacking and it remains uncertain whether PeCa implantation itself increases the risk for peritonitis. Of note, a retrospective study found no significant differences in the rate of infection between patients with PeCa and those treated with LVP. However, the detection rate of pathogens in the ascites was higher and more gram positive bacteria were found (Tergast 2022). Recently, a new PeCa version has been introduced that uses a silver coating. Preliminary data suggest that this significantly reduces the risk for peritonitis and the need for PeCa explantation (Schütte 2024) . Due to the continuous or intermittent daily drainage of ascites, both PeCa and the ascites pump are associated with hyponatraemia and renal impairment. In contrast to the more common hypervolemic hyponatraemia, these patients have a true sodium depletion due to the loss via ascites drainage. Sodium replacement may be required (Tergast 2023, Tergast 2022). Both

hyponatraemia and renal impairment correlate with the amount of fluid that is removed per day. If possible, drainage volume should be limited to a maximum of 1.5 L/day (Tergast 2023).

Portal hypertensive bleeding

Clinical manifestation and relevance

Oesophageal and gastric varices are very common and are present in approximately 40% of patients with CHILD A and 70% of those with CHILD B/C cirrhosis (Kovalak 2007). However, varices due to portosystemic shunts may also be present at various sites in the gastrointestinal tract (Jansson-Knodell 2021, Kochar 2008, Norton 1998). Patients remain asymptomatic and eventually present with variceal hemorrhage, which is a traumatic and life-threatening event (Reverter 2014). After ascites and encephalopathy, it is one of the most frequent events of hepatic decompensation (Jepsen 2010, Mandorfer 2021). Improvement in endoscopic and medical management have reduced short-term mortality from 30-50% to 10-20% (Chalasani 2003, D'Amico 1997, Graham 1981, Reverter 2014, Stokkeland 2006). However, recurrent bleeding is associated with significant morbidity related to other cirrhosis-associated complications such as encephalopathy, hydropic decompensation and hospitalisation (Angeli 2018, Garcia-Tsao 2024, Montagnese 2022). Bleeding of gastric varices is less frequent than from oesophageal varices. However, when bleeding does occur, it is often more difficult to control and is associated with higher mortality (Sarin 1992). Besides varices, recurrent bleeding may also occur in portal hypertension, gastropathy and intestinopathy (Merli 2004, Urrunaga 2014).

Pathogenesis

The development of oesophageal and ectopic varices is the result of CSPH and the need for portosystemic collaterals. The risk of varices is closely related to HVPG levels. The risk of bleeding increases with values >15mmHg (Ripoll 2007).

Diagnostic work-up

Endoscopy is necessary to diagnose oesophageal and gastric varices. The risk of bleeding is closely related to the size of the varices, liver function and the presence of red colour signs (de Franchis 2022, Villa 2022). Thus, during endoscopy oesophageal varices should be classified as either small or large (>5 mm). In addition, they can be classified according to Paquet as grade I (varices extending just above the mucosal level), II (varices not completely compressed after air insufflation), or III (varices varices protruding more than one third of the luminal diameter and/or are in contact with each other) (Angeli 2018, Paquet 1982).

Gastroesophageal varices (GOV) and isolated gastric varices (IGV) are usually classified according to Sarin depending on their localisation as GOV1 and GOV2, as well as IGV 1 and IGV2 (Sarin 1992). These may differ in their bleeding risk and associated mortality rate (Angeli 2018).

Treatment

Acute variceal bleeding

Acute variceal bleeding demands urgent treatment. Initially, immediate resuscitation is required, including placement of large intravenous lines to prevent organ failure (Angeli 2018, Cárdenas 2001, de Franchis 2022). The most important factor in bleeding control in portal hypertensive hemorrhage is control of portal hypertension. In the emergency setting, the quickest way to lower portal pressure is to use vasoactive drugs that cause arterial splanchnic vasoconstriction and, thus decrease portal inflow. In general, terlipressin and somtatostatin (analogues) can be used (Angeli 2018, Avgerinos 1997, de Franchis 2022, Levacher 1995). Doing so before the endoscopy facilitates the subsequent sclerosing therapy or endoscopic variceal ligation (EVL). It is usually recommended that these medications be continued for five days, as this covers the time period of highest risk for rebleeding (Angeli 2018, de Franchis 2022, Dell'Era 2008). However, in low-risk patients, 24 hours may also be sufficient (Azam 2012). Blood (Angeli 2018, Mallet 2017) transfusion should usually not be given unless the hemoglobin level falls below 7 g/dL or the patient develops symptomatic anaemia (Villanueva 2013). Immediate antibiotic treatment (e.g., ceftriaxone) improves bleeding control and reduces the risk of rebleeding (Bernard 1995, Bernard 1999, Hou 2004). In addition, initiation of HE prophylaxis with lactulose is recommended (de Franchis 2022, Sharma 2011). Rifaximin is an alternative treatment option (Maharshi 2015). Routine use of procoagulant factors is usually not required. In fact, fresh frozen plasma can easily lead to volume overload, which further aggravate CSPH (Angeli 2018, de Franchis 2022). There is also no need to use proton pump inhibitors (PPI) in the absence of gastric ulcers. PPIs may be associated with smaller post-ligation ulcers. However, they do not alter the risk of rebleeding (Shaheen 2005). Their role in preventing ulcers in patients in the intensive care unit has

also been questioned, recently (Krag 2018). Whether they are even harmful in cirrhotic patients still remains a matter of debate (Gairing 2024, Peña Rodríguez 2024, Tergast 2018). There are conflicting data regarding the use of tranexamic acid. In a large randomised trial in patients with upper GI bleeding, no effect on survival. However, patients treated with tranexamic acid experienced venous thromboembolic events at a higher frequency (Afolabi 2020). Importantly, nearly half of the patients had suspected variceal bleeding. In contrast, a smaller randomised trial in patients with cirrhosis found a greater chance to control variceal bleeding. However, survival remained unchanged (Kumar 2024).

After initial resuscitation, patients should undergo endoscopy to confirm the diagnosis, achieve bleeding control (if necessary) and prevent early rebleeding. However, the optimal timing of endoscopy remains to be determined. A recent study showed that for upper gastrointestinal bleeding, there was no benefit to performing endoscopy within 6h compared to 6-24h. However, less than 10% of the patients enrolled had variceal bleeding (Lau 2020). If bleeding control cannot be achieved and/or in case of early treatment failure (within) 24hour, the patient should be considered for treatment with rescue TIPS and/or coiling/sclerosis of the varices. If an interventional radiologist is not immediately available, balloon tamponade can be used as bridging therapy (Angeli 2018, de Franchis 2022). However, it comes with the need for endotracheal intubation and the risk of oesophageal necrosis or perforation. A better alternative in this case is the application of a self-expanding metal stent (SEMS). SEMS has been associated with a better bleeding control and survival when compared to balloon tamponade (Escorsell 2016). All patients, regardless from initial bleeding control, should be evaluated for preemptive TIPS ("early TIPS"). There are compelling data that patients with a CHILD B cirrhosis and active bleeding at index endoscopy or CHILD C cirrhosis (<14 points) benefit from TIPS insertion within 72h after variceal bleeding (García-Pagán 2010, Nicoară-Farcău 2021). This is also the case in patients with acute-on-chronic liver failure (ACLF). Elevated bilirubin levels and acute hepatic encephalopathy do not necessarily represent a contraindication for TIPS under these circumstances (Trebicka 2020a).

Primary prophylaxis

Either NSBB or EVL can be used for primary prophylaxis of variceal bleeding. The likelihood of bleeding is not different between the two options. However, NSBB do have other advantages as they also treat the underlying CSPH (Shah 2014, Villanueva 2019). NSBB may reduce intestinal permeability and systemic inflammation (Jachs 2021, Reiberger 2013a). The combination of EVL and NSBB was not superior to NSBB treatment alone in the majority of prospective studies (Lo 2010). However, a recent large prospective trial from India suggested a lower risk of bleeding in patients with decompensated liver cirrhosis and high-risk varices. NSBBs cause arterial splanchnic vasoconstriction via b2 blockade and cardiodepression via b1 blockade (Tevethia 2024). Both act synergistically to reduce portal pressure. Carvedilol, which also has an additional a1 blockade, has been shown to be more effective than propranolol (Kim 2016, Reiberger 2013b). It is also easier to titrate it to an effective dose (Turco 2023). Primary prophylaxis of variceal bleeding is indicated in patients with either large varices or small varices and red spots or CHILD C cirrhosis (de Franchis 2022). If primary prophylaxis with NSBB is established and well tolerated, follow-up endoscopy is not required at least among those with compensated cirrhosis. Of note, in patients with only small varices and CHILD A/B cirrhosis, NSBB does neither prevent bleeding nor the development of large varices (Groszmann 2005). However, the prospective PREDESCI study and a recent meta-analysis data demonstrated that NSBB may still prevent hepatic decompensation (i.e., ascites) in patients with CSPH (Villanueva 2019, Villanueva 2022). While this was especially true for those with small varices, some recently proposed algorithms support the use of NSBB when CSPH is diagnosed with non-invasive tools (i.e., LSM). This may eliminate the need for endoscopy (Garcia-Tsao 2021). There has been an intense debate about the safety of NSBB in advanced stages of cirrhosis (Sersté 2010), suggesting the existence of a therapeutic window (Ge 2014). In those with cirrhosis-associated circulatory dysfunction, additional cardiodepression and a1 blockade certainly have detrimental effects with an increased risk of acute kidney injury (Téllez 2020, Tergast 2019). However, the question remains as how to define the window. Some have suggested the presence of refractory ascites or SBP, but this has not been confirmed by others (Leithead 2015, Mandorfer 2014, Sersté 2010, Tergast 2019). Even in the case of ACLF, NSBBs have shown beneficial effects (Mookerjee 2016, Tergast 2019). However, systemic arterial pressure seems to be good indicator. In patients with a systolic pressure below 90 mmHg or a MAP of <65 mmHg patients have an increased risk of AKI but not beneficial effect on ACLF or survival (Tergast 2019).

Secondary prophylaxis

In contrast to the setting of primary prophylaxis, the combination of NSBB and EVL is widely accepted to be superior to either NSBB or EVL alone (Puente 2014). This affects both mortality and the risk of rebleeding. Patients should also be evaluated for TIPS insertion, which should be performed if secondary prophylaxis fails or if adequate secondary prophylaxis is not possible for any reason. If TIPS is chosen as a treatment option, it should

be used as soon as possible after the bleeding event. It has been shown to be highly effective in preventing rebleeding and it improves survival (de Franchis 2022, Sauerbruch 2015). If TIPS is not an option, patients may be considered for retrograde balloon-assisted obliteration of portosystemic shunts (e.g., BRTO) (Table 4).

Table 4.

Primary prophylaxis	Acute portal hypertensive bleeding	Secondary prophylaxis	Recurrent bleeding
Indication • Large Varices (>5 mm) • Small Varices (<5 mm) and CHILD C or red spots • Evidence for CSPH (only NSBB!) **Treatment** • NSBB or EVL NSBB and EVL can be considered in CPS B/C?	**Initial treatment** • Resuscitation • Blood Transfusion if HB <7 g/dL or by clinical indication • Terlipressin (1-2 mg i.v.) • Antibiotic Treatment • Lactulose • PPI only if gastric ulcers suspected **Hemostasis** • Endoscopy within 12 h • Danis-Stent • Rescue-TIPS	**Early/preemptive TIPS** • Within 72h if – CHILD C (<14) – CHILD B (≥8) + active bleeding in index endoscopy **Conservative** • Combination of NSBB and EVL • BRTO	**TIPS**

Hepatic encephalopathy

Clinical manifestation and relevance

Hepatic encephalopathy (HE) describes a clinical syndrome characterised by a broad spectrum of neuropsychiatric abnormalities in patients with liver disease. Patients may present with overt HE defined by obvious, clinically apparent changes that can range from impaired orientation to coma. In contrast, those with covert HE can usually be only be diagnosed by a careful history or, in the case of minimal HE (mHE), only by a specific neuropsychometric assessment (Montagnese 2022, Vilstrup 2014). HE is highly prevalent among patients with cirrhosis. The annual incidence of overt HE cirrhotic patients has been estimated to be around 2-10% (Benvegnù 2004, Tapper 2019) with a considerable range depending on the severity of liver disease and the underlying aetiology (Rose 2020, Vilstrup 2014). In patients with decompensated liver cirrhosis overt HE is prevalent in 10-14% at the time of diagnosis (Jepsen 2010, Saunders 1981). Minimal HE may be diagnosed in approximately 40% of patients with cirrhosis (Ehrenbauer 2024, Gairing 2023). HE is associated with impaired quality of life, significantly increased morbidity and health-care related costs (Hirode 2019, Lv 2024, Shaheen 2019). The recurrence rate is high despite the use of prophylactic measures (Kang 2017, Sharma 2009). Even mHE can be linked to signficant impairments of activities in daily living including driving skills (Redfield 2024). Moreover, mHE is a risk factor for the subsequent development of overt HE (Redfield 2024). After the first episode of overt HE, mortality increases up to 85% within five years (Jepsen 2010).

Pathogenesis

The pathogenesis of HE is complex and, so far, still incompletely understood. Several factors may contribute to the development of HE. However, there are two components that widely are considered to be central to the pathophysiology: impaired hepatic detoxification and portosystemic shunts (Praktiknjo 2020a, Rose 2020). According to the EASL guidelines, HE can be classified as type A, B or C depending on the pathogenesis. Type A is present in acute liver failure where impaired detoxification plays a major role. Type B occurs in those with large portosystemic shunts, which impair outcome, especially if their cumulative area exceeds 83 mm^2 (corresponding to a single shunt with a diameter of 10 mm) (Praktiknjo 2020b). Type C HE is present in cirrhosis (mixture of SPSS and impaired liver function) (Montagnese 2022). Regardless of the predominant cause of HE ammonia is one of the central molecules involved in the pathogenesis. The main source of ammonia is the gut where it is a product of protein digestion and bacteria urease activity. However, it is also produced and required in certain amino acid metabolisms in several organs including the liver itself. Excess ammonium is usually eliminated in the liver via the urea cycle. In case of excess production or impaired elimination i.e. due to hepatic impairment or portosystemic shunts, ammonium molecules may enter the brain and subsequently the astrocytes, where it is metabolised to glutamine. The resulting increase in intracellular osmotic pressure forces fluid into the astrocytes, causing swelling and dysfunction. This can be exacerbated by hypoosmotic serum, for example as a result of hypoproteinaemia and hyponatraemia (Rose 2020, Gallego-Durán 2024). Ammonia detoxification via the glutamine dehydrogenase may also be accompanied by increased neuronal levels of the inhibitory neurotransmitter ɣ-aminobutyricacid (GABA) (Sørensen 2024). Furthermore, ammonia has been linked to oxidative stress resulting from neutrophil dysfunction, which increases neuronal vulnerability and neuroinflammation. Increased systemic inflammation also contributes to neuroinflamamtion (Rose 2020, Gallego-Duran 2024) (Figure 4).

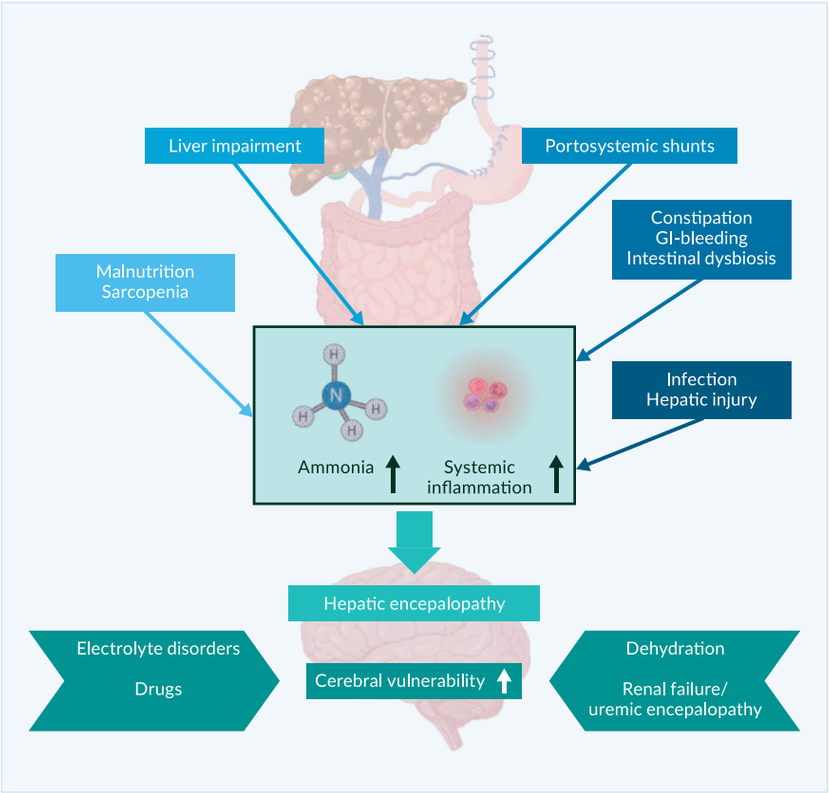

Figure 4.

Diagnostic work-up

The diagnosis of HE requires the exclusion of all relevant differential diagnoses. Contributing factors such as hyponatraemia and gastrointestinal bleeding must also be identified. The diagnostic relevance of ammonia has been debated over decades. However, its measurement can help to attribute neurocognitive impairment to cirrhosis or rule in differential diagnoses (Montagnese 2022). Moreover, elevated serum ammonia levels indicate a higher risk of overt HE development (Ballester 2023). Given the high inter-laboratory variability, recent studies have suggested using the ratio of ammonia to the local upper limit of normal rather than absolute ammonia levels (Ballester 2023, Tranah 2022).

However, at this stage, overt HE remains a diagnosis to be made clinically. It should be graded according to the West Haven criteria. This can be challenging and time consuming in routine clinical practice. The joint EASL/AASLD guidelines suggest a more practical approach based on the patient's level of orientation. Those with impaired orientation regarding the time are considered to have HE grade II, while an insufficient orientation with regard to space can be classified as HE grade III. HE grade IV is characterised by hepatic coma in which the patient is unresponsive to painful stimuli (Vilstrup 2014). To diagnose HE grade I, clinicians need to be familiar with the patient's usual cognitive level (e.g. with the help of a relative), as neurocognitive impairment is by definition not obvious (Table 5) (Vilstrup 2014).

Table 5. Suggested application of West Haven Criteria for Hepatic Encephalopathy in clinical practice.

West Haven Criteria	Description	Suggested criteria for clinical practice
Unimpaired	No history of HE and no current encephalopathy	Tested and proved to be normal
Minimal	• Descret motor and cognitive impairment as detected by psychometric or neuropsychological tests • Neurophysiological alteration without clinical evidence of mental change	• Abnormal results of established psychometric or neuropsychological tests • No clinical manifestations
Grade I	• Trivial lack of awareness • Phases of euphoria or anxiety • Shortened attention span • Impaired performance of basic math (addition or subtraction)	Patient presents with cognitive or behavioral decline with respect to his or her standard on clinical examination but is oriented in time and space
Grade II	• Lethargy or apathy • Disorientation for time • Obvious changes in personality • Occurrence of inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time whilst the other symptoms mentioned might also occur
Grade III	• Somnolence to semi-stupor, but responsive to stimuli • Confusion • Gross disorientation	Disoriented for space whilst the other symptoms mentioned might also occur
Grade IV	• Comatose state (unresponsive to verbal or noxious stimuli)	No response even to painful stimuli

Adapted from: Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., Weissenborn, K., and Wong, Philip. (2014). Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology 60 (2): p 715-735. DOI: 10.1002/hep.27210

Specific neuropsychometric tests must be used to assess mHE. The gold standard is the Psychometric Hepatic Encephalopathy Score (PHES), which can be obtained using the Portosystemic Encephalopathy Syndrome Test (PSE), which consists of a comprehensive test battery of 5 subtests (Weissenborn 2001). The PSE may provide the most comprehensive and accurate assessment of neurocognitive status. However, it is also quite time-consuming. A number of alternative tests have been proposed in the past, varying in their diagnostic accuracy for mHE and their predictive value for oHE (Table 6) (Ehrenbauer 2024). Among these, the Animal Naming Test (ANT) has been shown to be of significant value when used as a screening tool in clinical practice. Patients are asked to name as many animals as possible in one minute. Adjustments, e.g. for the educational level, need to be considered when using this test and different norms have been suggested for different regions (Campagna 2017, Ehrenbauer 2024, Labenz 2019). Another app-based alternative is the stroop test, which showed a high correlation with PHES and can be done by patients without supervision by dedicated staff and is also available in an abbreviated version (Acharya 2023, Ehrenbauer 2024, Labenz 2024).

Table 6. Selected tests for mHE assessment

Test	Test description	Time and equipment required	Cut-off values
PSE Syndrome Test	The PSE-Syndrome Test, yielding the Psychometric hepatic encephalopathy score (PHES) is a neuropsychological paper-pencil based test which is the surrogate goldstandard for diagnosing mHE. The test is evaluating psychomotor speed and visuomotor and -spatial orientation in 5 subtests. It is validated in numerous languages/ countries.	15–20 minutes Timer, pencil, test sheets	Score < -4 to -3 depending on regional norm values
Animal Naming Test (ANT)	The ANT is a word-fluency test in which patients had to name in one minute as many animals as possible. Recent studies recommend ANT for selecting patients for further HE diagnostics. It is the only bedside test.	2–3 minutes with explanation Timer	Age and education norms avilable only for Italy <23 animals (Germany) <14 animals (India) <20 animals (China)
EncephalApp (Stroop)	The EncephalApp is a smartphone-based version of the classic paper-based Stroop test that assesses psychomotor speed and cognitive flexibility. Here, patients had to react on a coloured font of a word that names a different color.	5–15 minutes Smartphone and EncephalApp	Age and education norms avilable only for USA >185.1s (Germany)
Critical Flicker Frequency (CFF)	A psychophysiological test in which patients have to react to a rapidly flickering light when it seems flickering to them. Problems can arise due to high variability of the test runs. There are competing study results with regard to the predictive value.	5–15 minutes HEPAtonorm analyzer	<39 Hz Age and education norms avilable only for Germany
Inhibitory Control Test (ICT)	The ICT is a computer-based test which evaluates working memory and sustained attention. Difficulties with the test are complex test clarification and long duration.	20 minutes Computer and ICT software (via www.hecme.tv, curently offline)	>24 Weighted Lures Age and education norms avilable only for Germany and USA
Continuous Reaction Time Test (CRT)	CRT measures the time between an auditory stimulus and a motor response. The score, the CRT index, looks at the variability of reaction times. Here, a high variability should indicate a cognitive deficit. One advantage of this test is its independence of age and education.	15 minutes Computer and EKHO CRT equipment	CRT-Index <1.9

Treatment

If the trigger of HE can be identified, it should be treated first. This includes correcting electrolyte ibalances and stopping certain medications (Montagnese 2022, Vilstrup 2014). Most of the available specific medical treatments for HE target ammonia (Rose 2020).

Lactulose

Lactulose is a non-resorbable disaccharide that has long been used as a symptomatic treatment for constipation. Its mode of action consists of acceleration of intestinal transit time as an osmotic laxative and of the decrease of the intestinal pH. The latter results in a higher proportion of NH_4^+ compared to NH_3, which leads to a lower ammonium resorption. It also leads to favourable changes in the gut microbiota (Elkington 1969). Lactulose has proven efficacy in the treatment of acute HE as well as in secondary prophylaxis (Als-Nielsen 2004, Gluud 2016). Intra-rectal administration can be used in the treatment of acute HE. Oral dosing is usually titrated up to a target of 2-3 soft bowel movements per day. However, tolerance is limited, especially for long-term treatment, as it is often associated with abdominal discomfort. A small but randomised trial documented that a single dose of polyethylene glycol led to an even faster resolution of HE than standard treatment with lactulose (Rahimi 2014).

Rifaximin

Rifaximin is an antibiotic that is only minimally absorbed in the gut. It is thought to work by decontaminating the gut, which is associated with reduced ammonia production by gut bacteria. In severe cases, rifaximin might help speed recovery from HE and might even reduce mortality when added to lactulose (Sharma 2013). More importantly, rifaximin has been shown to be effective for secondary prophylaxis in combination with lactulose (Bass 2010, Kang 2017).

L-ornithine-L-aspartate (LOLA)

LOLA contains two amino acids that are required for urea synthesis and glutamine synthesis, both of which are natural pathways for ammonia elimination. It has therefore been suggested that LOLA supports ammonia detoxification. There has been a long ongoing debate about the efficacy of LOLA in HE therapy, particularly when used as an oral preparation (Vilstrup 2014). A well-conducted meta-analysis including 36 trials and 2377 patients found a significant positive impact of LOLA on mortality and HE resolution when compared with placebo or no intervention. However, the authors noted that the quality of the individual studies included was limited (Goh 2018). Recently, a well-performed prospective double-blind, randomised controlled trial demonstrated the efficacy of intravenous LOLA in severe HE (grade III+IV) when added to rifaximin + lactulose. Treated patients benefited from faster HE recovery and lower mortality (Jain 2022).

Branched-chain amino acids (BCAA)

BCAA facilitate albumin and muscle protein biosynthesis, which may help to reduce ammonia production (Kawaguchi 2013). Meta-analyses support the beneficial effect of BCAA on HE recovery, while mortality remains unchanged (Gluud 2017).

Embolisation of portosystemic shunts

If medical treatment fails, embolisation of SPPS is an effective treatment that should be considered (Montagnese 2022). The procedure is generally safe (Ke 2022, Laleman 2013, Privitera 2018). However, it also worsens portal hypertension and may subsequent complication such as ascites.

Dialysis

In cases of severe HE, hemodialysis can remove ammonia very quickly. This also leads to electrolytes rebalance and removal of urea, which may contribute to encephalopathy in patients with renal impairment. Systems that use albumin and its binding capacity may be even more effective (Hassanein 2007).

Fecal microbiota transplant (FMT)

FMT may be a future treatment option for patients with recurrent HE. Some promising pivotal studies have been published, showing improvements in PHES and other psychometric tests (Bajaj 2017, Bajaj 2019). However, more studies are needed before this can be recommended for routine clinical practice.

Acute kidney injury in cirrhosis

Clinical manifestation and relevance

Kidney disfunction is very common in advanced stages of liver cirrhosis affecting 27-53% of hospitalised patients (Pose 2024). Kidney dysfunction is a continuum in cirrhosis and increasing creatinine levels correlate with the risk of short-term mortality. Thus, serum creatinine is part of several prognostic scores in cirrhosis including the MELD score and its squeals, which determine donor liver allocation in several eras of the world (Martin 2024). However, due to the low muscle mass in patients with liver cirrhosis, kidney dysfunction may also be present at lower creatinine levels (Angeli 2018). Therefore, a rapid rise in serum creatinine or a significant decrease in urine output should prompt immediate diagnostic and therapeutic intervention, even before a specific threshold is reached. Acute Kidney Injury (AKI) is defined as an increase in serum creatinine by more than 50% from the baseline within one week or an increase of ≥ 26.4 µmol/L (≥ 0.3 mg/dL) within 24 (48) hours (Nadim 2024). While the majority of AKI episodes are mild (AKI 1), even the distinction between AKI1a (serum creatinine <1.5mg/dL) and AKI1b (serum creatinine ≥1.5 mg/dL) has important prognostic implications (Huelin 2017) . Renal failure in patients with acute decompensation of liver cirrhosis is indicated by serum creatinine levels above 2 mg/dL and should not be confused with HRS, as HRS indicates a very poor prognosis (Nadim 2024). Renal failure is also the most common manifestation (> 50%) of Acute-on-Chronic Liver Failure (ACLF), a specific form of acute decompensation associated with very high short-term mortality (Moreau 2013). Patients may also present with a slow rise in serum creatinine referred to as Non-AKI (NAKI). Chronic kidney disease is defined by a glomerular filtration rate (GFR) of < 60 mL/min, calculated using the Modification of Diet in Renal Disease 6 (MDRD6) formula, persisting for at least three months (Nadim 2024) (Table 7).

Table 7. Diagnostic criteria for kidney dysfunction in advanced liver cirrhosis

Subject	Definition		
Definition of Baseline sCr	• A value of sCr obtained in the previuos three months, when available, can be used as baseline sCr. • In patients with more than one value within the previous three months, the value closest to the admission time should be used as baseline. • In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or, • A percentage increase sCr ≥50% which is knwon, or presumed, to have occured wihtin the prior seven days		
Staging of AKI	• Stage 1: increase in sCr up to 2-fold from baseline ◦ 1a: sCr< 1.5 mg/dL ◦ 1b: sCr ≥1.5 mg/dL • Stage 2: increase in sCr >2-fold to 3-fold from baseline • Stage 3: increase of sCr >3-fold from baseline or sCr≥4.0 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dL (≥26.5 µmol/L) or initiation of renal replacement therapy		
Progression of AKI	Progression		Regression
	Progression of AKI to a higher stage and/ or need for RRT		Regression of AKI to a lower stage
Response to treatment	No response	Partial response	Full response
	No regression of AKI	Regression of AKI with a reduction of sCr to ≥0.3 mg/dL (≥26.5 µmol/L) above the baseline value	Return of sCr to a value within ≥0.3 mg/dL (≥26.5 µmol/L) of the baseline value
Diagnostic Criteria for HRS	• Presence of advanced cirrhosis and ascites • No improvement in sCr and/or urine output within 24 h following adequate volume resuscitation • Absence of strong evidence for an alternative explanation HRS-AKI: HRS + AKI criteria fulfilled HRS-AKD: HRS + increase in sCr ≥50%, or GFR <60 mL/min/1.73 m² or markers of kidney damage ≤90d HRS-CKD: HRS + GFR <60 ml/min/1.73 m² and/or markers of kidney damage for >90d		

AKI: acute kidney injury; sCr: serum creatinine; RRT: renal replacement therapy

Citations: EASL Guideline cirrhosis AND Position Paper

Pathogenesis

There are various types of AKI and triggers of kidney damage. However, patients with cirrhosis are particularly susceptible for AKI, which is a result of the systemic inflammation and hemodynamic alterations that can be observed among patients with CSPH and advanced liver cirrhosis and may even be further enhanced by comorbidities or treatment related effects e.g. LVP or diuretic treatment. The decrease in systemic arterial blood pressure leads to activation of RAAS and the sympathetic nervous system and vasoconstriction of the renal artery and afferent glomerular arterioles (Adebayo 2023, Pose 2024). This results in renal hypoperfusion. In the recent years, it became evident that systemic inflammation and in particular the inflammatory driving factors, namely PAMPs and DAMPs, have direct deteriorating effects on renal function. PAMPs and DAMPs may enter the renal blood flow and cause renal inflammation (Pose 2024, Solé 2019). Besides direct cellular damage this leads to further decrease of renal blood flow. Ultimately, the changes linked to CSPH, systemic inflammation and circulatory dysfunction will lead to renal damage that is called hepatorenal syndrome (HRS-AKI).

Diagnostic work-up

In all patients with cirrhosis and AKI the potential trigger should be identified and removed as soon as possible. Those progressing to stage 1b or higher should be assesssed for the presence of HRS. HRS represents the maximal renal dysfunction in liver cirrhosis and is potentially reversible. Generally, two forms are still distinguished: HRS type I (HRS-AKI) is characterised by rapid renal failure, defined as a doubling of serum creatinine over 2.5 mg/dL (226 mmol/L) within less than two weeks. HRS type II (HRS-NAKI) is often associated with refractory ascites and shows moderate renal failure with serum creatinine levels between 1.5 and 2.5 mg/dL (133 to 226 mmol/L) with a stable or slowly progressive course. However, HRS is cannot be diagnosed immediately, serum creatinine must be > 1.5 mg/dL (> 133 mmol/L) and there must be no improvement after at least one day of withdrawal of all diuretics and adequate volume resuscitation (Nadim 2024). In the past, HRS was strictly diagnosed by exclusion, not associated with shock, nephrotoxic medications, parenchymal kidney disease (proteinuria > 500 mg/d, abnormal urine sediment, microhematuria, pathological kidney ultrasound). It is now accepted that HRS-AKI can also occur in the presence of other (chronic) kidney disease. Therefore, the absence of strong evidence for an alternative explanation as the primary cause of AKI is sufficient to establish the HRS-AKI diagnosis (Nadim 2024) (Figure 5).

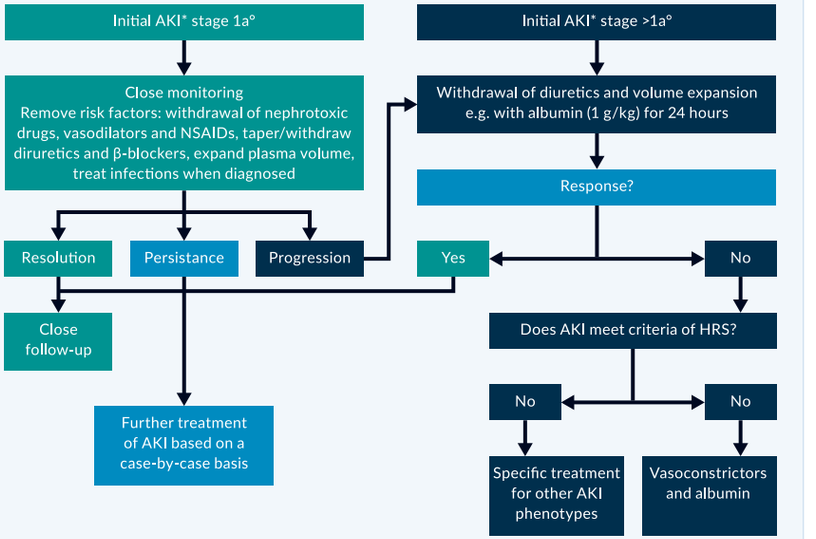

Figure 5. *AKI at the first fullfillment of KDIGO criteria.

Treatment

Any AKI should be treated by removing the precipitating factor and all nephrotoxic medications. The specific treatment of HRS type I (HRS-AKI) includes intravenous albumin administration of 20-40 g/day and additional therapy with vasoconstrictors. If there are no contraindications, terlipressin is the drug of choice, as it significantly improves short-term survival in combination with albumin infusions. This therapy should start with a terlipressin dose of 2–4 mg/day and be continued for at least three days. Terlipressin should be used at a maximum dose of 12 mg/day (Angeli 2018, Nadim 2024). Instead of repeated bolus application, terlipressin can also be given as a continuous infusion in HRS (initial dose 3 mg over 24 hours), which may reduce the required dose and side effects (Cavallin 2016). In patients under intensive care supervision, continuous norepinephrine administration may also be effective, although not in combination with terlipressin (Singh 2012, Wong 2021). Other vasoconstrictors are not recommended due to insufficient data.

While the administration of terlipressin in patients with HRS type I (HRS-AKI) is recommended in most guidelines worldwide, including Europe, the use of terlipressin as a vasoconstrictor for the treatment of HRS has not yet been approved in the United States. A recently published phase 3 study (CONFIRM) was designed to confirm the efficacy and safety

of terlipressin in combination with albumin in patients with HRS Type I. The study was randomised 1:2 with a placebo control for 14 days. The primary endpoint was the reversal of HRS, defined as two consecutive measurements of creatinine below 1.5 mg/dL, taken more than 2 hours apart, with survival without dialysis for at least 10 days after the completion of treatment. A total of 300 patients were randomised, 199 to terlipressin and 101 to placebo. Terlipressin led to a reversal of HRS in 32% of patients, while the primary endpoint was achieved in only 17% of patients in the placebo group. Liver transplantation was performed in 46 patients (23%) in the terlipressin group and 29 patients (29%) in the placebo group, with 50% vs. 45% mortality. Respiratory deterioration within 90 days accounted for 11% of deaths in the terlipressin group and 2% of deaths in the placebo group. The cardiodepressive effect of terlipressin is an additional side effect that may have influenced the results of the CONFIRM study (Wong 2021). This was particularly present among those with ACLF grade 3. Moreover, terlipressin was not linked to a higher rate of reversal of renal failure in this group but even a numerically higher mortality. Therefore, the use in ACLF grade 3 may not be recommended (Wong 2022).

In a recently published Danish study, 25 patients with ascites and impaired kidney function were randomised 2:2:1, group A received terlipressin combined with dobutamine, group B received dobutamine and terlipressin as sequential monotherapies, and group C received placebo. Dobutamine monotherapy increased cardiac output without affecting GFR. Terlipressin alone improved GFR and mean arterial pressure but decreased cardiac output. The combination of dobutamine and terlipressin had a favourable effect on cardiac output, but no additional effect on mean arterial pressure or GFR . This study showed that dobutamine alone does not have a favourable effect on systemic or renal hemodynamics in patients with ascites. However, it suggests that the combination with dobutamine may be an option for patients with terlipressin and cardiodepressive side effects (Israelsen 2020).

Patients with HRS type II (NAKI-HRS) are unlikely to benefit from this therapy and are treated similarly to patients with refractory ascites. Especially in these patients, but generally in all patients with HRS, a TIPS could be considered. Renal replacement therapy is indicated only in the presence of dialysis criteria, mainly as a bridge to liver transplantation, the only potentially curative treatment for HRS. For intended liver transplantation, albumin and terlipressin should be administered, as patients with renal insufficiency have a significantly poorer postoperative prognosis. In patients with HRS and prolonged dialysis dependency, the indication for sequential liver/kidney transplantation should be considered (Angeli 2018, Nadim 2024).

Infections and cirrhosis-associated immune dysfunction (CAID)

Clinical manifestation and relevance

Advanced liver cirrhosis is accompanied by a complex and, so far, not completely understood cirrhosis-associated immune dysfunction (CAID) (Albillos 2014, Albillos 2022). As a result, the incidence of infection is 4-6 times higher than in non-cirrhotic individuals (Fernández 2002, Fernández 2021). In the event of infection, mortality is 4x increased (Arvaniti 2010, Jalan 2014a) and the prognosis remains impaired even after the infections resolved (Kimmann 2019). Many cirrhotic patients develop multiple infections during hospitalisation and mortality almost doubles with each infectious episode (Bajaj 2012, Schultalbers 2020). Bacterial infections are a major cause of hepatic decompensation (e.g. variceal bleeding and worsening of ascites) (Fernández 2019, Moreau 2023) and the most common trigger of (ACLF) (Arroyo 2015, Moreau 2013). The most frequent sites of infection are spontaneous bacterial peritonitis (SBP) and urinary tract infections (UTI) (Schultalbers 2020). A particular threat is the emergence of multi-drug resistant bacteria (MDRB) (Fernández 2019, Hillert 2021, Piano 2019). These are highly prevalent in nosocomial infections and are associated with the development of sepsis and a poor survival (Fernández 2019, Piano 2019). The detrimental effects of infections are not limited to bacterial pathogens. More serious causes have also been documented for viral infections such as COVID-19 or influenza (Qiu 2020, Schütte 2019, Singh 2020). A particular poor prognosis has been described for invasive Candida infections (Barros 2023).

Pathogenesis

The liver and its resident immune cells play a central role in the immune system. They mediate immune tolerance, recognises systemic and gut-derived pathogens and orchestrate appropriate responses such as the production of pro-inflammatory cytokines and acute phase proteins. In patients with cirrhosis, liver dysfunction, reduced intestinal barrier function and increased systemic inflammation are the key drivers in the pathogenesis of CAID (Albillos 2022, Hasa 2022). Portal hypertension and intestinal dysbiosis facilitate translocation of gut bacteria and bacterial products into the portal vein. The resulting hepatic and systemic inflammation as indicated by increased levels of several pro-inflammatory cytokines such as TNF, IL-6 and IL-8. This is associated with the transition

from the compensated to the decompensated stage of cirrhosis and with the degree hepatic impairment (Albillos 2022, Hasa 2022). Ultimately the persistent inflammation leads to a compensatory but excessive immunosuppressive response (e.g. mediated by IL-10) that turns into a state of immune paralysis and immune cell exhaustion, making patients particularly vulnerable for infections (Albillos 2022, Hasa 2022). However, the mechanisms of CAID are much more complex as there are several other important contributing factors. The distortion of liver histology, the lower amount of total liver tissue as well as the increasing number of porto-systemic shunts interfere with the liver`s role as an immune filter and initial place of antigen recognition (Albillos 2022, Hasa 2022). Impaired hepatic function lowers the capability of the synthesis of acute phase and complement proteins (Homann 1997). Functional changes can also be documented at the cellular level, affecting various innate and adaptive immune cells, including monocytes, neutrophils and lymphocytes. Overall, the number of circulating monocytes is increased but functionally impaired, with reduced phagocytic capacity and lysosomal enzyme production (Albillos 2022, Nakagawara 1984). Neutrophils are characterised by a higher degree of respiratory burst but lower phagocytic capacity and reduced circulating levels (Albillos 2022, Shawcross 2008). Circulating CD4+ T helper cells are also reduced, while certain subsets of CD8+ T cells are increased (Albillos 2022). T-helper cell impairment leads to reduced B-cell function and lower immunoglobulin levels in advanced stages of cirrhosis (Basho 2021). Importantly, these decreased IgG levels are associated with a higher risk of ACLF and death in patients with decompensated liver cirrhosis (Tergast 2021).

Diagnostic work-up

Early diagnosis and prompt initiation of an adequate treatment is crucial to limit morbidity and maximise patients' chances of survival (Jalan 2014a). In the case of SBP, every hour of delay is associated with a 3% increase in mortality (Kim 2014). However, the clinical diagnosis of an infection in a cirrhotic patient can be challenging. Symptoms of hepatic decompensation, such as hepatic encephalopathy or worsening of ascites, may dominate the clinical picture. Thus, any new onset of hepatic decompensation or worsening of cirrhosis-related complications should be considered as an alarm signal and the patient should be evaluated for the presence of an infection, including a diagnostic paracentesis (Angeli 2018, Jalan 2014a). There has been a long debate about the utility of biomarkers. Pancytopenia is highly prevalent in patients with liver cirrhosis, limiting the value of leucocytosis. C-reactive protein (CRP) can indicate the presence of infection. However, as it is produced in the liver, false negatives must be considered (Park 2005). In contrast, systemic inflammation leads to chronic elevations of CRP even in the absence of infection (Jalan 2014a). Unlike CRP, procalcitonin (PCT) levels are less dependent on liver function. While PCT correlates with infection in cirrhosis, e.g. SBP (Yang 2015), as well as with the outcome of infections (Girardi 2024), it can also be elevated due to systemic or hepatic inflammation (Sato 2020, Simbrunner 2023). Some other biomarkers such as presepsin and resistin have been suggested, but their role still remains to be determined (Fischer 2019). Overall, biomarkers are not able to replace careful clinical evaluation at this stage. If an infection is suspected, the diagnostic work-up should include a diagnostic paracentesis and culture of ascites fluid (if ascites is present), urine sediment examination and a chest x-ray (Fernández 2021).

Treatment

Spontaneous bacterial peritonitis (SBP)

SBP is diagnosed when the ascitic polymorphonuclear count exceeds 250/µL (Angeli 2018). Antibiotic treatment should be started immediately, but must be chosen carefully. An inappropriate choice of the antibiotic leads to a more than twofold increase in mortality (Fernández 2019). A small prospective randomised trial demonstrated a superior survival when patients were treated aggressively with daptomyicin and meropenem instead of ceftazidime (Piano 2016). However, the widespread use of broad-spectrum antibiotics is certainly followed by a further emergence of MRBD (Piano 2019). Therefore, an individualised, risk-based approach seems necessary. As nosocomial infection has been confirmed as the most relevant risk factor for MRBD across different studies (Fernández 2012, Fernández 2019, Fernández 2021, Piano 2019), current EASL guidelines recommend a stratification into community-acquired, healthcare associated and nosocomial SBP (Angeli 2018). In addition, the severity of infection (e.g. sepsis and/or ACLF) should be taken into account. Third-generation cephalosporins appear to be sufficient for community-acquired SBP. However, if the infection is nosocomial and/or associated with organ failure, more aggressive treatment, e.g. a carbapenem +/- a glycopeptide antibiotic, should be used (Angeli 2018). Carbapenems have shown to be highly effective, including excellent and rapid distribution into the ascites fluid (Griemsmann 2022, Piano 2016). Glycopeptides should be considered particularly if there is an increased risk of infections with gram positive species (e.g. with enterococci) (Angeli 2018). This is the case, for example, among patients treated with high doses of PPIs (Tergast 2018, Wellhöner 2019), those with PeCa (Tergast 2022) and recent endoscopic procedures (Reuken 2012), and in alcoholic liver disease, where Enterococcus

faecalis is closely linked to disease progression (Duan 2019, Llorente 2017). The efficacy of antibiotics should be monitored by a diagnostic paracentesis 48 hours after treatment initiation, which should show a reduction in PMN count of at least 25% (Angeli 2018). Patients with SBP benefit from albumin treatment, which can counteract circulatory dysfunction in these patients (Mandorfer 2014, Salerno, Navickis, Wilkes 2013, Sort 1999). 1.5 g/kg body weight on day 1 followed by 1g/kg body weight on day 3 is usually recommended based on the original study protocol by Sort et al (Angeli 2018, Sort 1999). Once the SBP has resolved antibiotic prophylaxis should be initiated for as long as the ascites persists (Angeli 2018, Ginés 1990, Titó 1988). Some patients may even benefit from primary SBP prophylaxis (Fernández 2007) . A potential risk factor for SBP is a low ascites protein level (Guarner 1999, Llach 1992, Runyon 1986). A recent prospective, multicentre study showed that primary prophylaxis with norfloxacine may improve survival among patients with CHILD C cirrhosis. However, this was only the case if the ascites protein level was below 1.5 g/dL (Moreau 2018). Norfloxacin is usually recommended for SBP prophylaxis based on the available studies (Angeli 2018, Cohen 2009, Mücke 2020a). Some concerns have been raised about the emergence of infection and in terms of side effects (Mücke 2020b). Rifaximin is an alternative and promising treatment option (Facciorusso 2019, Wang 2019). However, current data remain insufficient to recommend it as the first-line treatment.

Urinary tract infection

UTI are among the most common types of infections in patients with decompensated liver cirrhosis (Fernández 2002, Schultalbers 2020). While the rate of clinical complications and mortality may be lower compared to other sites of infection, UTI may still trigger AKI and ACLF in a considerable proportion of patients (Angeli 2018, Merli 2016, Moreau 2013, Mücke 2018). Antibiotic treatment is generally recommended (Angeli 2018). Similar to SBP, the risk for MDR hast to be considered when choosing the anti-infective drug. However, a prospective randomised study demonstrated that a broad-spectrum antibiotic treatment is only required in case of a severe infections, i.e. sepsis (Merli 2016). For uncomplicated UTI, fosfomycin or nitrofurantoin may be considered as a sufficient treatment attempt (Angeli 2018). The use of albumin is not recommended in the absence of HRS-AKI (Angeli 2018, Guevara 2012, Thévenot 2015).

Pneumonia

Pneumonia is a particularly dangerous form of infection in cirrhosis (Merli 2016). Conversely, the likelihood of mortality in patients with pneumonia is dramatically increased in the presence of liver cirrhosis (Boivin 2019, Di Pasquale 2013). Given the impact of the initial use of an inadequate antibiotic treatment and the considerable risk of MDR in nosocomial infections in these patients, an aggressive approach seems to be reasonable (Piano 2019). Thus, carbapenems could be considered early in nosocomial pneumonia and at least third-generation cephalosporins and/or piperacillin/tacobactam in healthcare-associated pneumonia (Angeli 2018, Jalan 2014a). However, local prevalence of MDR must be taken into account as well. As with other non-SBP infections, the use of albumin is not recommended and it may even complicate pneumonia due to the higher incidence of pleural and pulmonary edema (Angeli 2018, China 2021, Maiwall 2022).

Pulmonary complications

Clinical manifestation and relevance

There are four main pulmonary complications that can be linked to liver cirrhosis. Pneumonia as a result of CAID, hepatic hydrothorax, as atypical localisation of ascites related to small defects in the diaphragm, portopulmonary hypertension (PPHT) and hepatopulmonary syndrome (HPS). Pneumonia/CAID and hepatic hydrothorax/ascites are discussed above. PPHT is defined by an increase in the mean pulmonary arterial pressure (mPAP) to a level of more than 20 mmHg due to increased pulmonary vascular resistance (PVR) in patients with portal hypertension in the absence of other causes of pulmonary hypertension (Simonneau 2019). It may be present in 5-10% of patients with end-stage liver cirrhosis and is associated with poor survival (Colle 2003, Kawut 2008, Krowka 2006, Sussman 2006). Depending on the severity of PPHT, liver cirrhosis as well as cardiac and pulmonary comorbidities, patients may present with severe hypoxia and/or clinical signs of right heart failure (DuBrock 2023). HPS is defined by the presence of chronic liver disease (most commonly cirrhosis), intrapulmonary shunts (IPS) and either hypoxaemia or an increased alveolar-arterial oxygen gradient indicating impairment of intrapulmonary blood oxygenation (Angeli 2018). The presence of HPS is widely underestimated. However, in patients with decompensated cirrhosis, IPS and HPS can be found in up to 50% and 36%, respectively (Mauz 2024). Patients are often asymptomatic but may become clinically apparent with dyspnoea (Angeli 2018, Raevens 2022). However, the most specific symptom is platypnea, i.e. improvement of symptoms when lying down. Of note, HPS impairs survival regardless of the severity of liver disease (Raevens 2022).

Pathogenesis

The pathophysiology of PPHT is still incompletely understood. However, it is hypothesised that portosystemic shunting allows bypassing of the increased vasoactive substances (which are a response to the increased portal pressure, hepatic resistance and inflammation) from the portal tract to the systemic blood circulation. As a result, increased levels of vasoactive substances may also be present in the pulmonary arterial system, leading to vasodilation also at the capillary level. Intrapulmonary blood flow is increased while the capacity for oxygen exchange remains unchanged, resulting in a functional shunting from the right to the left heart. This is thought to be one of the key components of HPS (Thomas 2020, Zaka 2025). In addition, both systemic vasodilation and intrapulmonary result in a hyperdynamic state. Increased blood flow is accompanied by increased shear stress on the endothelial wall. In response, endothelin-1 is secreted leading to smooth muscle cell proliferation and/or increased muscle tone and intimal fibrotic changes (Farber 2004, Porres-Aguilar 2012, Thomas 2020). Ultimately, this may significantly contribute to PHHT (Neuhofer 2006) (Figure 6).

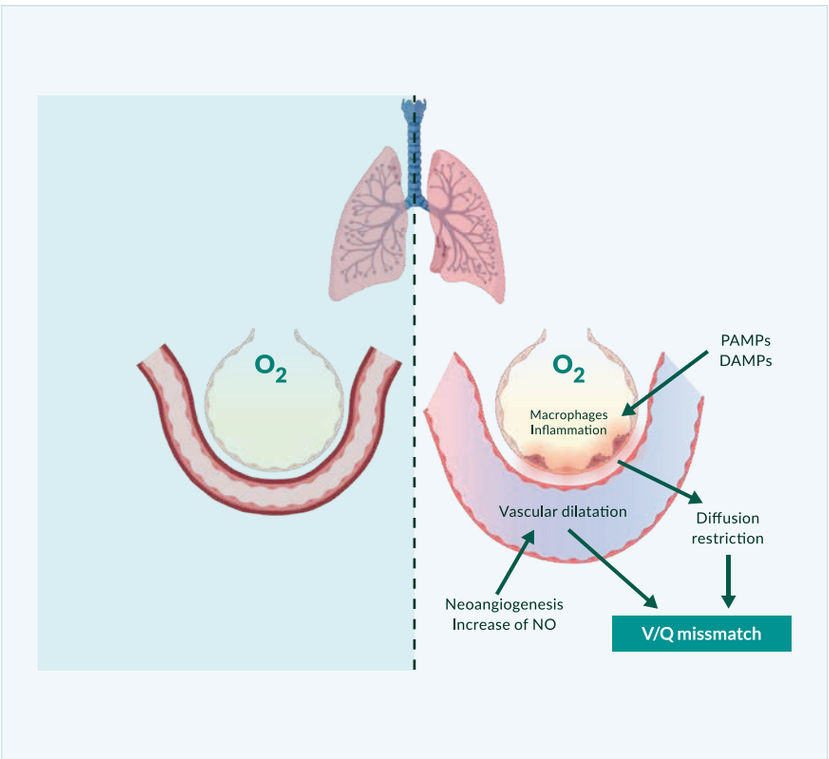

Figure 6.

Diagnostic work-up

PPHT: Elevated right ventricular pressure (>40-50 mmHg) on echocardiography will raise suspicion of PPHT and can be used as a screening criterion for further investigation (DuBrock 2023). However, to establish the diagnosis of PPHT a right heart catheterisation is required. PPHT is characterised by a precapillary pulmonary hypertension. Diagnosic criteria include a mPAP >20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and PVR ≥2 WU (Humbert 2023). Other causes of PAH need to be excluded. Patients with PAH can be divided into three risk categories, as it is the case for PPHT. The risk categories are defined by clinical symptoms, specific results of echocardiography and hemodynamic parameters (Table 8) (Humbert 2023).

Table 8. Portopulmonary hypertension: Diagnostic criteria

I – Presence of portal hypertension
II – Elevated pulmonary arterial pressure compatible with pulmonary hypertension (mPAP in right-heart catheterisation >20 mmHg)
III – Increased pulmonary vascular resistance (>240 dyne s-1cm-5; >2 Wood Units)
IV – normal pulmonary occlusion pressure (PAWP ≤15 mmHg)
V – absence of other causes of pulmonary artery or venosus hypertension hypertension (i.e., chronic thromboembolism, chronic lung disease/hypoxia, chronic left heart disease)

Degree of severity is determined by mPAP in right-heart catheterisation as mild (mPAP <34 mmHg), moderate (mPAP =35-44) or severe (mPAP ≥45 mmHg).

Abbreviations
mPAP: Mean pulmonary arterial pressure; PAWP: Pulmonary arterial wedge pressure; PVR: Pulmonary vascular resistance.

Citations
Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet. 2004 May 1;363(9419):1461-8. doi: 10.1016/S0140-6736(04)16107-2. PMID: 15121411.
European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024. Epub 2018 Apr 10. Erratum in: J Hepatol. 2018 Nov;69(5):1207. doi: 10.1016/j.jhep.2018.08.009. PMID: 29653741.

HPS: Given the high prevalence, all cirrhotic patients with hypoxaemia should undergo screening for HPS. The first step is to assess for IPS. This can be done by contrast-enhanced echocardiography using microbubbles of >10 µm in diameter. In a healthy individual, these bubbles should remain and be absorbed in the pulmonary capillaries. In patients with IPS, bubbles appear in the left heart atrium within 3 to 6 cardiac cycles (Angeli 2018,

Raevens 2022). This easy and diagnostic tool cannot be used in the presence of intracardiac shunts (e.g. due to a patent foramen ovale). In this case, bubbles will appear in the left atrium after 1 or 2 cardiac cycles. In patients with IPS, the diagnosis of HPS requires the exclusion of other lung diseases, which usually requires a chest CT scan and functional lung assessments such as maximal forced expiratory volume and carbon monoxide diffusing capacity (Table 9) (Angeli 2018, Raevens 2022).

Table 9. Hepatopulmonary syndrome: Diagnostic criteria

I – Liver disease and/or portal hypertension
II – Pulmonary vascular defect with positive finding on contrast-enhanced echocardiography (i.e., microbubble opacification of the left heart chambers three to six cycles after right atrial passage) or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
III – Hypoxia with partial pressure of oxygen <80 mmHg or alveolar-arterial oxygen gradient >15 mmHg in ambient air (≥20 mmHg in patients older than 65 years)

III)The abbreviated formula for the alveolar-arterial gradient is as follows: $P(A\text{-}a)O_2$ = (FIO_2 (Patm-PH_20)-($PaCO_2$/0.8))-PaO_2, where PAO_2 denotes partial pressure of alveolar oxygen, PaO_2 partial pressure of arterial oxygen, FIO_2 fraction of inspired oxygen, Patm atmospheric pressure, PH_20 partial pressure of water vapor at body temperature, and $PaCO_2$ partial pressure of arterial carbon dioxide.
Severity classification of HPS is based on the partial pressure of oxygen in arterial blood gas without supplementary oxygen (PaO_2) as mild (PaO_2 ≥80 mmHg), moderate (PaO_2 60–79 mmHg), severe (PaO_2 50–59 mmHg) or very severe (PaO_2 <50 mmHg).

Abbreviations
HPS: Hepatopulmonary syndrome; $P(A\text{-}a)O_2$: Alveolar-arterial oxygen gradient; PaO_2: Partial pressure of arterial oxygen; PAO_2: Partial pressure of alveolar oxygen; $PaCO_2$: Partial pressure of arterial carbon dioxide; FIO_2: Fraction of inspired oxygen; Patm: Atmospheric pressure; PH_2O: Partial pressure of water vapor at body temperature.

Citations
European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024. Epub 2018 Apr 10. Erratum in: J Hepatol. 2018 Nov;69(5):1207. doi: 10.1016/j.jhep.2018.08.009. PMID: 29653741.
Raevens S, Boret M, Fallon MB. Hepatopulmonary syndrome. JHEP Rep. 2022 Jul 4;4(9):100527. doi: 10.1016/j.jhepr.2022.100527. PMID: 36035361; PMCID: PMC9403489.

Treatment

PPHT: In general, treatment strategy follows the clinical assessment of the risk category and the presence or absence of cardiovascular comorbidities (Humbert 2023). Medical treatment options include endothelin receptor antagonists, phosphodiesterase subtype 5 inhibitors and prostacyclin analouges (Angeli 2018, Humbert 2023). However, while treatment is associated with improvement in hemodynamic parameters, all of these drugs can lead to decrease in systemic arterial pressure, which limits their tolerability in advanced liver cirrhosis, particularly when combination treatment is required (DuBrock 2023, Savale 2020). Best treatment results can be achieved by liver transplantation (Savale 2020). However, not all patients are suitable candidates, mainly because of the risk of right heart failure. Patients with mPAP of > 45-50 mmHg at the time of liver transplantation, have a posttransplant mortality of up to 100% (Krowka 2000). In contrast, transplantation appears to be safe in patients with mPAP of < 35 mmHg or of 35-45 mmHg but a PVR of < 3 WU (Angeli 2018, DuBrock 2023).

HPS: Up till now, there is no pharmacological treatment available. Patients with hypoxaemia can be treated with continuous oxygen supply (Angeli 2018, Raevens 2022). Moreover, coil embolisation of ateriovenous malformations has been suggested. However, complications such as pulmonary infarction and infections need to be considered (Grady 2015). Liver transplantation remains the only effective treatment option. Although perioperative mortality is higher compared with non-HPS patients, arterial oxygenation and six-minute walk distance significantly improves significantly. Recent data suggest that HPS can be expected to resolve in approximately 95% of cases (Aragon Pinto 2021, Raevens 2022).

Acute-on-chronic liver failure

Clinical manifestation and relevance

The poor prognosis of liver cirrhosis (Lange 2023) is particularly due to acute decompensations (AD), which represent a situational worsening of the disease state (Jalan 2021). These are characterised by the rapid onset of ascites, gastrointestinal bleeding, hepatic encephalopathy, bacterial infections, or a combination of these complications (Gu 2022). The CANONIC study demonstrated that there is a subgroup of patients with acutely decompensated liver cirrhosis who have a significantly worse prognosis (Moreau 2013). This subgroup of patients was termed ACLF, which is the most severe form of acute decompensation (Schulz 2022). ACLF was defined by the European Association for the Study of the Liver (EASL)–Chronic Liver Failure (CLIF) Consortium based on the results of the CANONIC study. The CANONIC study is a prospective observational study involving more than 1300 patients with acute decompensation (Moreau 2013). Various organ systems were classified into organ failure or organ dysfunction based on clinical and laboratory parameters. Analogous to the Sequential Organ Failure Assessment (SOFA) Score, the CLIF-C Organ Failure (OF) Score was

calculated (https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf). This score includes the function of the liver and kidneys (creatinine and bilirubin levels), cognition (West Haven criteria), circulation (MAP and catecholamine requirement), and coagulation (INR) (Table 10).

Table 10.

Organ system	Diagnostic criterium	Points		
		1	2	3
	Bilirubin	<106 µmol/L	106–205 µmol/L	**>205 µmol/L**
		<6 mg/d	6–12 mg/dL	**>12 mg/dL**
	Creatinine	<177 µmol/L	**177–310 µmol/L**	**>310 µmol/L**
		<2 mg/dL	**2–3.5 mg/dL**	**>3.5 mg/dL**
	Hepatic encephalopathy	Grade 0 (WH)	Grade I, II (WH)	**Grade III, IV (WH)**
	INR	<2.0	2.0–2.4	**≥2.5**
	Mean arterial pressure	>70 mmHg	<70 mmHg	**Vasopressors**
	S_pO_2/F_iO_2	>357	214–357	**≥214**
	p_aO_2/F_iO_2	>300	300–200	**<200**

Bold = Organ failure

Organ failure is defined as a score of 3 in the respective organ system. An exception is made for the kidneys, where organ failure is defined with a CLIF-C-OF score of 2 (corresponding to a creatinine level of > 2 mg/dL) (Jalan 2014b) (Figure 7). Patients with more than one organ failure or isolated kidney failure meet the criteria for ACLF. Additionally, isolated organ failures combined with kidney dysfunction (creatinine 1.5–1.9 mg/dL) or hepatic encephalopathy (grade I/II) are classified as ACLF Grade I. Patients with two manifest organ failures show ACLF Grade II, and those with three or more organ failures have ACLF Grade III. The 28-day mortality rate increases with the grade, reaching 68% in patients with four or more organ failures (Arroyo 2020). A more precise prognosis for ACLF can be made using the CLIF-C ACLF Score, which also considers age and leukocyte count (Jalan 2014b). Although the EASL-CLIF definition has been validated worldwide, two other definitions exist in the USA and Asia: the North American Consortium for the Study of End-stage Liver Disease (NACSELD) and the Asian Pacific Association for the Study of the Liver (APASL). Both definitions are similar to the EASL-CLIF, with the distinction that NACSELD defines ACLF only when there are two manifest organ failures, whereas APASL does not consider extrahepatic triggers and organ failures (Arroyo 2020).

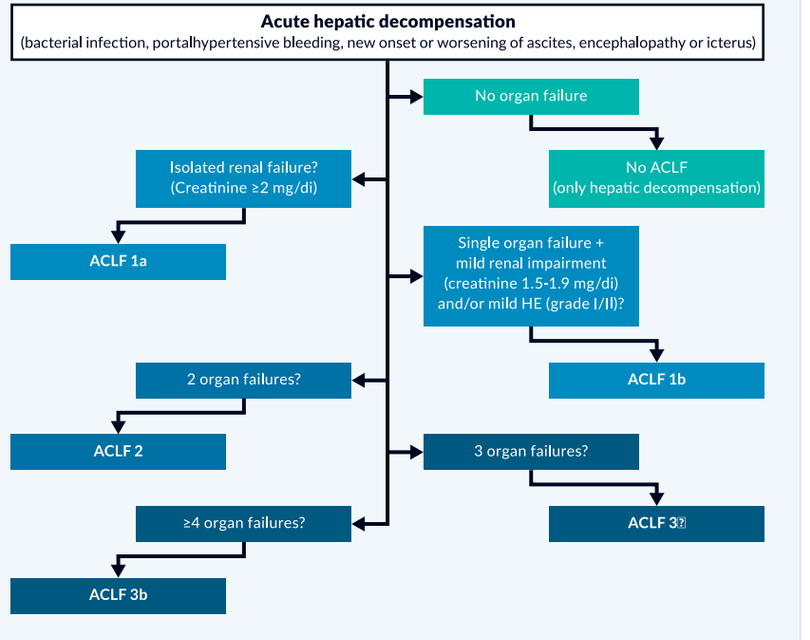

Figure 7.

Pathogenesis

ACLF affects approximately one in four patients (23%) hospitalised for decompensated liver cirrhosis. About 20% of patients admitted without ACLF develop ACLF within the following 90 days (so-called pre-ACLF), with 60% of these cases occurring within the next three weeks, as shown in the PREDICT study (Trebicka 2020b). Pre-ACLF patients exhibit a significantly elevated inflammatory profile (increased leukocyte counts and CRP levels) (Trebicka 2020b). Risk factors for the development of ACLF include the presence of ascites, low mean arterial pressure, anaemia, and a high MELD score. In addition, younger patients appear to be more commonly affected (Angeli 2018). The onset of ACLF is primarily attributed

to two pathophysiological phenomena: portal hypertension and systemic inflammation (Trebicka 2020b). Patients with ACLF show significantly higher concentrations of pro-inflammatory cytokines (Trebicka 2019a). The occurrence of events, especially infections, severe gastrointestinal bleeding, or alcoholic hepatitis, can lead to further reductions in effective blood volume, thereby inducing hypoperfusion of various organs (Trebicka 2021a). The kidney and brain are particularly early affected, thus playing a special role in the definition of dysfunction. These events are known as precipitating factors or triggers and play a crucial role in the prevention and treatment of ACLF. However, in 40% of cases no trigger can be identified (Trebicka 2021a).

Diagnostic work-up and treatment of triggers

A trigger can be identified in 60% of patients with ACLF (Trebicka 2021a). Possible triggers include liver-related factors such as alcoholic steatohepatitis (ASH) or a flare of viral hepatitis, as well as extrahepatic triggers such as infections. Combinations are also not uncommon (Trebicka 2021a). Any patient admitted with ACLF or who develops ACLF during hospitalisation should undergo a systematic examination for the presence of the most common triggers, including documented bacterial infections, alcohol-related hepatitis, gastrointestinal bleeding with hemodynamic instability, a flare of hepatitis B virus infection, recent intake of medication known to cause brain failure, and recent intake of medication known to cause kidney failure (Figure 8) (Moreau 2023).

Patients for whom systematic examination fails to identify expected triggers should be investigated based on clinical context and using a comprehensive list of all potential unusual cases (Figure 8) (Moreau 2023). The causal treatment of potential triggers plays a key role in preventing ACLF, as no specific preventive therapy has been established so far (Angeli 2018, Moreau 2023). The concepts of treating the most critical triggers are outlined below.

Infections can represent both a trigger and a complication of ACLF. Typically, these are bacterial infections, less commonly mycoses. When choosing antibiotic therapy, patient-specific factors, the suspected focus, and local resistance patterns should be considered (see above) (Moreau 2023). Patients with ACLF and suspected bacterial infections should receive broad-spectrum empirical antibiotic therapy as soon as possible, in line with local epidemiology. A rapid and comprehensive evaluation for infection is recommended for patients with ACLF and suspected bacterial infections (Moreau 2023). An empirical antifungal therapy may be indicated for ACLF patients developing nosocomial septic shock with additional risk factors for fungal infection (Moreau 2023).

One of the most common triggers in Western countries is alcoholic hepatitis due to active alcoholism or an alcohol binge. Here, corticosteroids remain the treatment of choice, although their efficacy is still under debate. Severe cases with increased short-term mortality can be identified using the modified Maddrey score. In cases with a score > 32, steroid therapy with 40 mg of prednisolone/day can be initiated. Due to potential steroid-associated side effects, identifying patients who do not benefit from steroid therapy is essential. This can be assessed using the Lille score, calculated based on age, albumin, prothrombin time, creatinine, and bilirubin levels at the start and after seven days of prednisolone therapy (Trebicka 2022). With increasing severity of ACLF, the response to corticosteroids decreases, while the risk of infection increases. Therefore, corticosteroids are not recommended for patients with severe alcoholic hepatitis and ACLF-3, nor for patients with uncontrolled bacterial infections. If corticosteroids are administered to patients with severe alcoholic hepatitis and ACLF, close monitoring for infections is necessary (Moreau 2023, Trebicka 2022).

Acute variceal bleeding, accounting for 70% of upper gastrointestinal bleeding episodes in cirrhosis, has been identified as a common cause of death and ACLF in cirrhotic patients. Recent treatment advances, including endoscopic treatment, pharmacotherapy, and TIPS, have led to a decrease in the frequency of variceal bleeding over the past decade. However, ACLF significantly worsens survival in these patients. Indeed, ACLF doubles the risk of rebleeding and serves as a simple criterion for identifying patients at risk of rebleeding (Moreau 2023). Two independent studies have shown that TIPS, either preemptive/early or emergency, improves survival in patients with ACLF-1 or ACLF-2 and variceal bleeding, although few patients with ACLF-3 were included in these studies (Kumar 2021, Trebicka 2020a). Therefore, TIPS should be considered in the treatment of patients with ACLF and variceal bleeding, even in those with bilirubin levels over 5 mg/dL. As a result, affected patients should be transferred to hospitals with access to TIPS, potentially reducing their mortality rate by up to 75%. This data is well supported by a recent study showing that the survival benefit from preemptive/early TIPS increases with a higher MELD score (Moreau 2023).

Other triggers can include a flare of known viral hepatitis. Acute infections with hepatitis A or E can also be potential triggers. Therefore, patients with liver cirrhosis should be vaccinated against hepatitis A and B as appropriate (Moreau 2023). For patients with HBV-related ACLF, the use of nucleoside analogues is recommended as the treatment of choice (Moreau 2023).

Drug-induced liver injury (DILI) is often implicated as a potential trigger. Physicians should especially inquire about recent new medications,

including over-the-counter, natural remedies, and dietary supplements (Moreau 2023).

There is a high likelihood of having more than one trigger in patients with ACLF. Identifying these triggers is crucial for targeted treatment and preventing disease progression. Therefore, it is important to differentiate between the treatment of trigger-related complications and the treatment of ACLF itself (Moreau 2023).

Specific therapy and supportive measures

Specific therapy for ACLF aims to address the pathophysiology, particularly the inflammatory response. To date, only the use of Albumin is evidence-based in ACLF. Albumin binds to endotoxins and acts as a scavenger of reactive oxygen species. Its effectiveness is likely due to its positive effect on hemodynamics and inflammatory response (Klein 2020).

The ANSWER study demonstrated the positive effects of long-term albumin therapy in patients with decompensated liver cirrhosis. Patients who received weekly albumin infusions in addition to standard therapy showed significantly improved transplant-free survival. Additionally, fewer severe infections and complications occurred (Caraceni 2018a).

The ATTIRE study did not show a benefit of albumin infusion on 28-day mortality in patients with decompensated liver cirrhosis, despite achieving normal albumin levels. This study did not explicitly differentiate between patients with ACLF and those with AD. However, there was a lower number of patients with new or existing organ failures among patients who achieved normal albumin levels (China 2021). The RESOLVE trial, currently enrolling patients, aims to clarify the significance of long-term albumin therapy in patients with ACLF.

As albumin levels and concentrations are often significantly reduced in patients with ACLF, albumin infusion is recommended for treating ascites, prevention of HRS, and in cases of confirmed SBP.

Patients with ACLF, particularly those in ACLF Grade III, require intensive care. Guidelines for supportive therapy are not specific to ACLF and are derived from those for severe sepsis and multiple organ failure in non-cirrhotic patients. However, significant differences exist in the application of general guidelines to patients with liver cirrhosis. (Gustot 2015). Special attention is given to the risk of overhydration and tissue edema. To maintain adequate organ perfusion, slightly increased MAP values should be targeted. Isotonic crystalloids should be preferred over colloids in volume resuscitation (Gustot 2015, Garnacho-Montero 2015). Vasopressor use, especially norepinephrine, should be considered early in ACLF patients with septic shock (Choudhury 2017). Non-invasive ventilation (NIV) and extracorporeal membrane oxygenation (ECMO) are considered in patients with respiratory failure, while renal replacement therapy is indicated in cases of renal failure, particularly in the presence of HRS or metabolic complications (Moreau 2023).

Liver transplantation remains the definitive treatment for patients with ACLF, offering potential for improved survival and quality of life. Early evaluation for liver transplantation is recommended, especially in patients with ACLF Grade II and III (Moreau 2023, Trebicka 2020c).

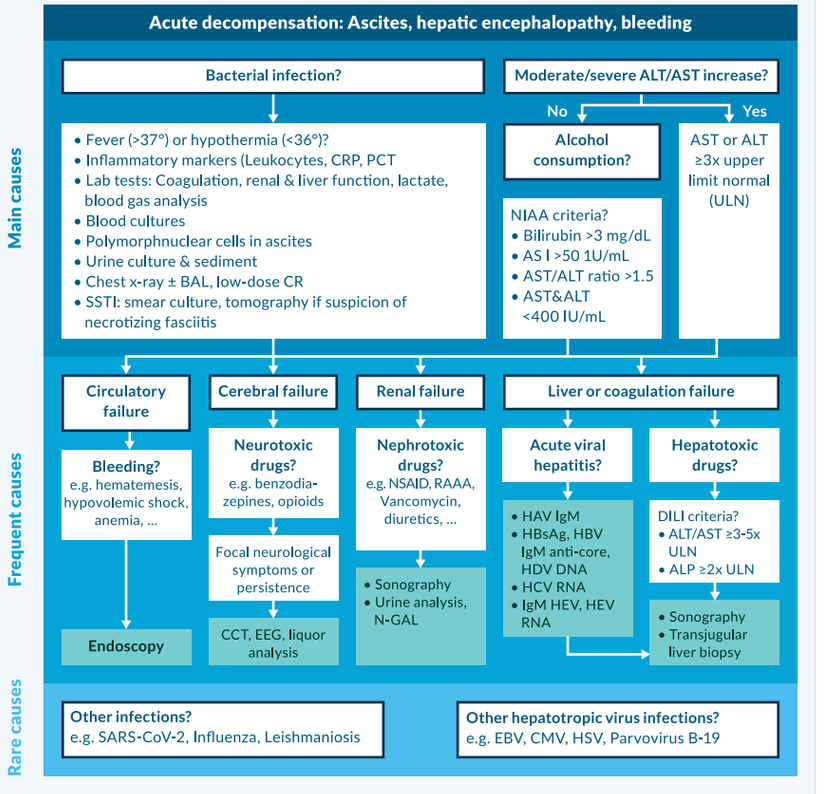

Figure 8.

Acknowledgements

The authors thank Julius Egge, Laura Buttler, Martin Kabelitz, Jim Mauz, Sarah Schütte and Lea Wagner for their assistance regarding figure and table design.

References

Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, Procopet B, Bosch J, Genesca J, Berzigotti A. 2016. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "anticipate" study. Hepatology. 64(6):2173–84.

Acharya C, Shaw J, Duong N, Fagan A, McGeorge S, Wade JB, Thacker LR, Bajaj JS. 2023. QuickStroop, a shortened version of EncephalApp, detects covert hepatic encephalopathy with similar accuracy within one minute. Clin Gastroenterol Hepatol. 21(1):136–42.

Adebayo D, Wong F. 2023. Pathophysiology of hepatorenal syndrome – acute kidney injury. Clin Gastroenterol Hepatol. 21(10):S1–S10.

Afolabi A, Kayani A, Simmons J, Soomro M, Veitch A, Henry D, Gray R, Edwards P, Manno D, Austin E, et al. 2020. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): An international randomised, double-blind, placebo-controlled trial. The Lancet. 395(10241):1927–36.

Agrawal S, Umapathy S, Dhiman RK. 2015. Minimal hepatic encephalopathy impairs quality of life. J Clin Exp Hepatol. 5(Suppl 1):S42–8.

Albillos A, Lario M, Álvarez-Mon M. 2014. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. J Hepatol. 61(6):1385–96.

Albillos A, Martin-Mateos R, Van der Merwe S, Wiest R, Jalan R, Álvarez-Mon M. 2022. Cirrhosis-associated immune dysfunction. Nat Rev Gastroenterol Hepatol. 19(2):112–34.

Als-Nielsen B, Gluud LL, Gluud C. 2004. Non-absorbable disaccharides for hepatic encephalopathy: Systematic review of randomised trials. BMJ. 328(7447):1046–50.

Angeli P, Fasolato S, Mazza E, Okolicsanyi L, Maresio G, Velo E, Galioto A, Salinas F, D'Aquino M, Sticca A, et al. 2010. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: Results of an open randomised clinical trial. Gut. 59(1):98–104.

Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, Krag A, Laleman W, Gines P. 2018. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 69(2):406–60.

Aragon Pinto C, Iyer VN, Albitar HAH, Anderson A, Cajigas H, Simonetto DA, Krowka MJ, DuBrock HM, Gallo de Moraes A. 2021. Outcomes of liver transplantation in patients with hepatopulmonary syndrome in the pre and post-MELD eras: A systematic review. Respir Med and Res. 80:100852.

Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. 1996a. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 23(1):164–76.

Arroyo V, Fernandez-Esparrach G, Gines P. 1996b. Diagnostic approach to the cirrhotic patient with ascites. Oxford: Elsevier. 35 p.

Arroyo V, Moreau R, Jalan R, Ginès P. 2015. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. J Hepatol. 62(1):S131–43.

Arroyo V, Moreau R, Jalan R. 2020. Acute-on-chronic liver failure. N Engl J Med. 382(22):2137–45.

Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. 2010. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 139(4):1246,1256.e5.

Avgerinos A, Nevens F, Raptis S, Fevery J. 1997. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: The european acute bleeding oesophageal variceal episodes (ABOVE) randomised trial. Lancet. 350(9090):1495–9.

Azam Z, Hamid S, Jafri W, Salih M, Abbas Z, Abid S, Shah H. 2012. Short course adjuvant terlipressin in acute variceal bleeding: A randomized double blind dummy controlled trial. J Hepatol. 56(4):819–24.

Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, Brown G, Noble NA, Thacker LR, Kamath PS. 2012. Second infections independently increase mortality in hospitalized cirrhotic patients: The NACSELD experience. Hepatology. 56(6):2328–35.

Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, Kheradman R, Heuman D, Wang J, Gurry T, et al. 2017. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology. 66(6):1727–38.

Bajaj JS, Salzman NH, Acharya C, Sterling RK, White MB, Gavis EA, Fagan A, Hayward M, Holtz ML, Matherly S, et al. 2019. Fecal microbial transplant capsules are safe in hepatic encephalopathy: A phase 1, randomized, Placebo-Controlled trial. Hepatology. 70(5):1690–703.

Ballester MP, Tranah TH, Balcar L, Fiorillo A, Ampuero J, Kerbert AJC, Thomsen KL, Escudero MD, Mandorfer M, Reiberger T, et al. 2023. Development and validation of the AMMON-OHE model to predict risk of overt hepatic encephalopathy occurrence in outpatients with cirrhosis. J Hepatol. 79(4):967–76.

Barros N, Rosenblatt RE, Phipps MM, Fomin V, Mansour MK. 2023. Invasive fungal infections in liver diseases. Hepatol Commun. 7(9):e0216.

Basho K, Zoldan K, Schultheiss M, Bettinger D, Globig A, Bengsch B, Neumann-Haefelin C, Klocperk A, Warnatz K, Hofmann M, et al. 2021. IL-2 contributes to cirrhosis-associated immune dysfunction by impairing follicular T helper cells in advanced cirrhosis. J Hepatol. 74(3):649–60.

Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, et al. 2010. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 362(12):1071–81.

Bellot P, Welker M, Soriano G, von Schaewen M, Appenrodt B, Wiest R, Whittaker S, Tzonev R, Handshiev S, Verslype C, et al. 2013. Automated low flow pump system for the treatment of refractory ascites: A multi-center safety and efficacy study. J Hepatol. 58(5):922–7.

Benvegnù L, Gios M, Boccato S, Alberti A. 2004. Natural history of compensated viral cirrhosis: A prospective study on the incidence and hierarchy of major complications. Gut. 53(5):744–9.

Berlioux P, Robic MA, Poirson H, Métivier S, Otal P, Barret C, Lopez F, Péron JM, Vinel JP, Bureau C. 2014. Pre-transjugular intrahepatic portosystemic shunts (TIPS) prediction of post-TIPS overt hepatic encephalopathy: The critical flicker frequency is more accurate than psychometric tests. Hepatology. 59(2):622–9.

Bernard B, Cadranel J, Valla D, Escolano S, Jarlier V, Opolon P. 1995. Prognostic significance of bacterial infection in bleeding cirrhotic patients: A prospective study. Gastroenterology. 108(6):1828–34.

Bernard B, Grangé J, Khac EN, Amiot X, Opolon P, Poynard T. 1999. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: A meta-analysis. Hepatology. 29(6):1655–61.

Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. 2012. Albumin infusion in patients undergoing large-volume paracentesis: A meta-analysis of randomized trials. Hepatology. 55(4):1172–81.

Berres M, Asmacher S, Lehmann J, Jansen C, Görtzen J, Klein S, Meyer C, Strunk HM, Fimmers R, Tacke F, et al. 2015. CXCL9 is a prognostic marker in patients with liver cirrhosis receiving transjugular intrahepatic portosystemic shunt. J Hepatol. 62(2):332–9.

Bettinger D, Sturm L, Pfaff L, Hahn F, Kloeckner R, Volkwein L, Praktiknjo M, Lv Y, Han G, Huber JP, et al. 2021. Refining prediction of survival after TIPS with the novel freiburg index of post-TIPS survival. J Hepatol. 74(6):1362–72.

Billey C, Billet S, Robic MA, Cognet T, Guillaume M, Vinel JP, Péron JM, Lairez O, Bureau C. 2019. A prospective study identifying predictive factors of cardiac decompensation after transjugular intrahepatic portosystemic shunt: The toulouse algorithm. Hepatology. 70(6):1928–41.

Boivin Z, Perez MF, Atuegwu NC, Anzueto A, Mortensen EM. 2019. Impact of cirrhosis on pneumonia-related outcomes in hospitalized older veterans. Am J Med Sci. 357(4):296–301.

Bureau C, Garcia-Pagan Jc, Otal P, Pomier-Layrargues G, Chabbert V, Cortez C, Perreault P, Péron Jm, G. Abraldes J, Bouchard L, et al. 2004. Improved clinical outcome using polytetrafluoroethylene-coated stents for tips: Results of a randomized study. Gastroenterology. 126(2):469–75.

Bureau C, Métivier S, D'Amico M, Péron JM, Otal P, Pagan JCG, Chabbert V, Chagneau-Derrode C, Procopet B, Rousseau H, et al. 2011. Serum bilirubin and platelet count: A simple predictive model for survival in patients with refractory ascites treated by TIPS. J Hepatol. 54(5):901–7.

Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, Mathurin P, Otal P, Cabarrou P, Péron JM, et al. 2017a. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. Gastroenterology. 152(1):157–63.

Bureau C, Adebayo D, de Rieu MC, Elkrief L, Valla D, Peck-Radosavljevic M, McCune A, Vargas V, Simon-Talero M, Cordoba J, et al. 2017b. Alfapump system vs. large volume paracentesis for refractory ascites: A multicenter randomized controlled study. J Hepatol. 67(5):940–9.

Bureau C, Thabut D, Jezequel C, Archambeaud I, D'Alteroche L, Dharancy S, Borentain P, Oberti F, Plessier A, De Ledinghen V, et al. 2021. The use of rifaximin in the prevention of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt : A randomized controlled trial. Ann Intern Med. 174(5):633–40.

Cai W, Zheng B, Lin X, Wu W, Chen C. 2022. Prediction of patient hepatic encephalopathy risk with freiburg index of post-TIPS survival score following transjugular intrahepatic portosystemic shunts: A retrospective study. Int J Gen Med. 15:4007–16.

Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, De Rui M, Pasquale C, Nardelli S, Pentassuglio I, Merkel C, et al. 2017. The animal naming test: An easy tool for the assessment of hepatic encephalopathy. Hepatology. 66(1):198–208.

Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, Levantesi F, Airoldi A, Boccia S, Svegliati-Baroni G, et al. 2018a. Long-term albumin administration in decompensated cirrhosis (ANSWER): An open-label randomised trial. Lancet. 391(10138):2417–29.

Caraceni P, Riggio O, Angeli P, et al. 2018b. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial [published correction appears in Lancet. 2018 Aug 4;392(10145):386. Lancet. 2018;391(10138):2417–2429.

caraCárdenas A, Ginès P, Uriz J, Bessa X, Salmerón JM, Mas A, Ortega R, Calahorra B, De Las Heras D, Bosch J, et al. 2001. Renal failure after upper gastrointestinal bleeding in cirrhosis: Incidence, clinical course, predictive factors, and short-term prognosis. Hepatology. 34(4):671–6.

Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, Gola E, Morando F, Stanco M, Rosi S, et al. 2016. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology. 63(3):983–92.

Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, Pandya P, Sitaraman S, Shen J. 2003. Improved patient survival after acute variceal bleeding: A multicenter, cohort study. Am J Gastroenterol. 98(3):653–9.

China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, Portal AJ, Becares Salles N, Gilroy DW, O'Brien A. 2021. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. N Engl J Med. 384(9):808–17.

Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, Sharma MK, Bhadoria AS, Kumar G, Joshi YK, et al. 2017. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int. 37(4):552–61.

Cohen MJ, Sahar T, Benenson S, Elinav E, Brezis M, Soares-Weiser K, Cohen MJ. 2009. Antibiotic prophylaxis for spontaneous bacterial peritonitis in cirrhotic patients with ascites, without gastro-intestinal bleeding. Cochrane Database Syst Rev. 2010(1):CD004791.

Colle IO, Moreau R, Godinho E, Belghiti J, Ettori F, Cohen-Solal A, Mal H, Bernuau J, Marty J, Lebrec D, et al. 2003. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: A prospective study. Hepatology. 37(2):401–9.

Costa D, Simbrunner B, Jachs M, Hartl L, Bauer D, Paternostro R, Schwabl P, Scheiner B, Stättermayer AF, Pinter M, et al. 2021. Systemic inflammation increases across distinct stages of advanced chronic liver disease and correlates with decompensation and mortality. J Hepatol. 74(4):819–28.

Dajti E, Ravaioli F, Marasco G, Alemanni LV, Colecchia L, Ferrarese A, Cusumano C, Gemini S, Vestito A, Renzulli M, et al. 2022. A combined baveno VII and spleen stiffness algorithm to improve the noninvasive diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol. 117(11):1825–33.

D'Amico G, Lucas A. 1997. Natural history. clinical-haemodynamic correlations. prediction of the risk of bleeding. Baillieres Clin Gastroenterol. 11(2):243–56.

D'Amico G, Garcia-Tsao G, Pagliaro L. 2006. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 44(1):217–31.

D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, Tinè F, Giannuoli G, Traina M, Vizzini G, et al. 2014. Competing risks and prognostic stages of cirrhosis: A 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther. 39(10):1180–93.

D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. 2018. Clinical states of cirrhosis and competing risks. J Hepatol. 68(3):563–76.

de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, Albillos A, Baiges A, Bajaj J, Bañares R, et al. 2022. Baveno VII – renewing consensus in portal hypertension. J Hepatol. 76(4):959–74.

Dell'Era A, MD, de Franchis R, MD, Iannuzzi F, MD. 2008. Acute variceal bleeding: Pharmacological treatment and primary/secondary prophylaxis. Best Pract Res Clin Gastroenterol. 22(2):279–94.

Di Pasquale M, Esperatti M, Crisafulli E, Ferrer M, Bassi GL, Rinaudo M, Escorsell A, Fernandez J, Mas A, Blasi F, et al. 2013. Impact of chronic liver disease in intensive care unit acquired pneumonia: A prospective study. Intensive Care Med. 39(10):1776–84.

Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, White RC, Clarke TH, Nguyen K, Torralba M, et al. 2019. Bacteriophage targeting of

gut bacterium attenuates alcoholic liver disease. Nature. 575(7783):505–11.

DuBrock HM. 2023. Portopulmonary hypertension: Management and liver transplantation evaluation. Chest. 164(1):206–14.

Ehrenbauer AF, Schneider H, Stockhoff L, Tiede A, Lorenz C, Dirks M, Witt J, Gabriel MM, Wedemeyer H, Hinrichs JB, et al. 2023. Predicting overt hepatic encephalopathy after TIPS: Value of three minimal hepatic encephalopathy tests. JHEP Rep. 5(9):100829.

Ehrenbauer AF, Egge JFM, Gabriel MM, Tiede A, Dirks M, Witt J, Wedemeyer H, Maasoumy B, Weissenborn K. 2024. Comparison of 6 tests for diagnosing minimal hepatic encephalopathy and predicting clinical outcome: A prospective, observational study. Hepatology. 80(2):389-402.

Elkington SG, Floch MH, Conn HO. 1969. Lactulose in the treatment of chronic portal-systemic encephalopathy. N Engl J Med. 281(8):408–12.

Engelmann C, Clària J, Szabo G, Bosch J, Bernardi M. 2021. Pathophysiology of decompensated cirrhosis: Portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. J Hepatol. 75(Suppl 1):S49–66.

Escorsell À, Pavel O, Cárdenas A, Morillas R, Llop E, Villanueva C, Garcia-Pagán JC, Bosch J. 2016. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology. 63(6):1957–67.

Facciorusso A, Papagiouvanni I, Cela M, Buccino VR, Sacco R. 2019. Comparative efficacy of long-term antibiotic treatments in the primary prophylaxis of spontaneous bacterial peritonitis. Liver Int. 39(8):1448–58.

Farber HW, Loscalzo J. 2004. Pulmonary arterial hypertension. N Engl J Med. 351(16):1655–65.

Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. 2002. Bacterial infections in cirrhosis: Epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology. 35(1):140–8.

Fernández J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V, et al. 2007. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. 133(3):818–24.

Fernández J, Acevedo J, Castro M, Garcia O, Rodríguez de Lope C, Roca D, Pavesi M, Sola E, Moreira L, Silva A, et al. 2012. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: A prospective study. Hepatology. 55(5):1551–61.

Fernández J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, Deulofeu C, Garcia E, Acevedo J, Fuhrmann V, et al. 2019. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in europe. J Hepatol. 70(3):398–411.

Fernández J, Piano S, Bartoletti M, Wey EQ. 2021. Management of bacterial and fungal infections in cirrhosis: The MDRO challenge. J Hepatol. 75:S101–17.

Fischer P, Grigoras C, Bugariu A, Nicoara-Farcau O, Stefanescu H, Benea A, Hadade A, Margarit S, Sparchez Z, Tantau M, et al. 2019. Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis? Dig Liver Dis. 51(12):1685–91.

Gairing SJ, Müller L, Kloeckner R, Galle PR, Labenz C. 2022. Review article: post-TIPSS hepatic encephalopathy—current knowledge and future perspectives. Aliment Pharmacol Ther. 55(10):1265–76.

Gairing SJ, Mangini C, Zarantonello L, Gioia S, Nielsen EJ, Danneberg S, Gabriel M, Ehrenbauer AF, Bloom PP, Ripoll C, et al. 2023. Prevalence of minimal hepatic encephalopathy in patients with liver cirrhosis: A multicenter study. Am J Gastroenterol. 118(12):2191–200.

Gairing SJ, Mangini C, Zarantonello L, Jonasson E, Dobbermannn H, Sultanik P, Galle PR, Labenz J, Thabut D, Marquardt JU, et al. 2024. Proton pump inhibitor use and risk of hepatic encephalopathy: A multicenter study. JHEP Rep. 6(8):101104.

Gallego-Durán R, Hadjihambi A, Ampuero J, Rose CF, Jalan R, Romero-Gómez M. 2024. Ammonia-induced stress response in liver disease progression and hepatic encephalopathy. Nat Rev Gastroenterol Hepatol. (11):774-791

García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, Abraldes JG, Nevens F, Vinel JP, Mössner J, et al. 2010. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 362(25):2370–9.

García-Pagán JC, Saffo S, Mandorfer M, Garcia-Tsao G. 2020. Where does TIPS fit in the management of patients with cirrhosis? JHEP Rep. 2(4):100122.

Garcia-Tsao G, Abraldes JG. 2021. Nonselective beta-blockers in compensated cirrhosis: Preventing variceal hemorrhage or preventing decompensation? Gastroenterology. 161(3):770–3.

Garcia-Tsao G, Abraldes JG, Rich NE, Wong VW. 2024. AGA clinical practice update on the use of vasoactive drugs and intravenous albumin in cirrhosis: Expert review. Gastroenterology. 166(1):202–10.

Garnacho-Montero J, Fernández-Mondéjar E, Ferrer-Roca R, Herrera-Gutiérrez ME, Lorente JA, Ruiz-Santana S, Artigas A. 2015. Crystalloids and colloids in critical patient resuscitation. Med Intensiva. 39(5):303–15.

Ge PS, Runyon BA. 2014. When should the β-blocker window in cirrhosis close? Gastroenterology. 146(7):1597–9.

Gerbes AL, Labenz J, Appenrodt B, Dollinger M, Gundling F, Gülberg V, Holstege A, Lynen-Jansen P, Steib CJ, Trebicka J, et al. 2019. Updated S2k-guideline "complications of liver cirrhosis". german society of gastroenterology (DGVS). Z Gastroenterolog. 57(5):611.

Ginés P, Quintero E, Arroyo V, Terés J, Bruguera M, Rimola A, Caballería J, Rodés J, Rozman C. 1987. Compensated cirrhosis: Natural history and prognostic factors. Hepatology. 7(1):122–8.

Ginès P, Titó L, Arroyo V, Planas R, Panés J, Viver J, Torres M, Humbert P, Rimola A, Llach J, et al. 1988. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology. 94(6):1493–502.

Ginés P, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forne M, Miranda ML, Llach J, Salmerón JM, et al. 1990. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis : Results of a double - blind, placebo controlled trial. Hepatology. 12(4):716–24.

Girardi P, Buono R, Bisazza C, Marchi L, Angeli P, Di Pascoli M. 2024. Prognostic value of procalcitonin in patients with cirrhosis hospitalized for acute infection. Dig Liver Dis. 56(5):810–7.

Gluud LL, Vilstrup H, Morgan MY. 2016. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev. 2016(5):CD003044.

Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, Vilstrup H, Gluud LL. 2017. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2020(3):CD001939.

Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY, Morgan MY. 2018. L-ornithine l-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev. 2019(6):CD012410.

Grady K, Gowda S, Kingah P, Soubani AO. 2015. Coil embolization of pulmonary arteries as a palliative treatment of diffuse type I hepatopulmonary syndrome. Respir Care. 60(2):e20–5.

Graham DY, Smith JL. 1981. The course of patients after variceal hemorrhage. Gastroenterology. 80(4):800–9.

Griemsmann M, Grote-Koska D, Cornberg M, Schmidt JJ, Maasoumy B, Book T, Bremer B, Schulte B, Manns MP, Wedemeyer H, et al. 2022. Plasma and ascites pharmacokinetics of meropenem in patients with decompensated cirrhosis and spontaneous bacterial peritonitis. J Hepatol. 76(1):230–3.

Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, et al. 2005. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 353(21):2254–61.

Gu W, Hortlik H, Erasmus H, Schaaf L, Zeleke Y, Uschner FE, Ferstl P, Schulz M, Peiffer K, Queck A, et al. 2022. Trends and the course of liver cirrhosis and its complications in germany: Nationwide population-based study (2005 to 2018). Lancet Reg Health Eur. 12:100240.

Guarner C, Solà R, Soriano G, Andreu M, Novella MT, Vila MC, Sàbat M, Coll S, Ortiz J, Gómez C, et al. 1999. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. Gastroenterology. 117(2):414–9.

Guevara M, Terra C, Nazar A, Solà E, Fernández J, Pavesi M, Arroyo V, Ginès P. 2012. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol. 57(4):759–65.

Gulyás M, Kaposi AD, Elek G, Szollár LG, Hjerpe A. 2001. Value of carcinoembryonic antigen (CEA) and cholesterol assays of ascitic fluid in cases of inconclusive cytology. J Clin Pathol. 54(11):831–5.

Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrief L, Hopf C, et al. 2015. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 62(1):243–52.

Hasa E, Hartmann P, Schnabl B. 2022. Liver cirrhosis and immune dysfunction. Int Immunol. 34(9):455–66.

Hassanein TI, Tofteng F, Brown RS, McGuire B, Lynch P, Mehta R, Larsen FS, Gornbein J, Stange J, Blei AT. 2007. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 46(6):1853–62.

Hey P, Chapman B, Wong D, Gow P, Testro A, Terbah R, Sinclair M. 2023. Transjugular intrahepatic portosystemic shunt insertion improves muscle mass but not muscle function or frailty measures. Eur J Gastroenterol Hepatol. 35(9):997–1003.

Hillert A, Schultalbers M, Tergast TL, Vonberg R, Rademacher J, Wedemeyer H, Cornberg M, Ziesing S, Maasoumy B, Höner zu Siederdissen C. 2021. Antimicrobial resistance in patients with decompensated liver cirrhosis and bacterial infections in a tertiary center in northern germany. BMC Gastroenterol. 21(1):1–296.

Hirode G, Vittinghoff E, Wong RJ. 2019. Increasing burden of hepatic encephalopathy among hospitalized adults: An analysis of the 2010–2014 national inpatient sample. Dig Dis Sci. 64(6):1448–57.

Homann C, Varming K, Høgåsen K, Mollnes TE, Graudal N, Thomsen AC, Garred P. 1997. Acquired C3 deficiency in patients with alcoholic cirrhosis predisposes to infection and increased mortality. Gut. 40(4):544–9.

Hou M, Lin H, Liu T, Kuo BI, Lee F, Chang F, Lee S. 2004. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: A randomized trial. Hepatology. 39(3):746–53.

Huelin P, Piano S, Solà E, Stanco M, Solé C, Moreira R, Pose E, Fasolato S, Fabrellas N, de Prada G, et al. 2017. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. Clin Gastroenterol and Hepatol. 15(3):438,445.e5.

Hui Y, Wang H, Guo G, Yang W, Wang X, Cui B, Fan X, Sun C. 2024. Health-related quality of life and frailty in liver cirrhosis. BMJ Support Palliat Care. 14(e3):e2880-e2887.

Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al. 2023. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 61(1):2200879.

Huonker M, Schumacher YO, Ochs A, Sorichter S, Keul J, Rössle M. 1999. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. Gut. 44(5):743–8.

Israelsen M, Dahl EK, Madsen BS, Wiese S, Bendtsen F, Møller S, Fialla AD, Jensen BL, Krag A. 2020. Dobutamine reverses the cardio-suppressive effects of terlipressin without improving renal function in cirrhosis and ascites: A randomized controlled trial. Am J Physiol Gastrointest Liver Physiol. 318(2):G313–21.

Jachs M, Hartl L, Schaufler D, Desbalmes C, Simbrunner B, Eigenbauer E, Bauer DJM, Paternostro R, Schwabl P, Scheiner B, et al. 2021. Amelioration of systemic inflammation in advanced chronic liver disease upon beta-blocker therapy translates into improved clinical outcomes. Gut. 70(9):1758–67.

Jachs M, Hartl L, Simbrunner B, Bauer D, Paternostro R, Scheiner B, Balcar L, Semmler G, Stättermayer AF, Pinter M, et al. 2023. The sequential application of baveno VII criteria and VITRO score improves diagnosis of clinically significant portal hypertension. Clin Gastroenterol and Hepatol. 21(7):1854,1863.e10.

Jachs M, Hartl L, Simbrunner B, Semmler G, Balcar L, Hofer BS, Schwarz M, Bauer D, Stättermayer AF, Pinter M, et al. 2024a. Prognostic performance of non-invasive tests for portal hypertension is comparable to that of hepatic venous pressure gradient. J Hepatol. 80(5):744–52.

Jachs M, Sandmann L, Hartl L, Tergast T, Schwarz M, Bauer DJM, Balcar L, Ehrenbauer A, Hofer BS, Cornberg M, et al. 2024b. Validation of baveno VII criteria and other non-invasive diagnostic algorithms for clinically significant portal hypertension in hepatitis delta. J Hepatol. 81(2):248-257.

Jain A, Sharma BC, Mahajan B, Srivastava S, Kumar A, Sachdeva S, Sonika U, Dalal A. 2022. L-ornithine l-aspartate in acute treatment of severe hepatic encephalopathy: A double-blind randomized controlled trial. Hepatology. 75(5):1194–203.

Jalan R, D'Amico G, Trebicka J, Moreau R, Angeli P, Arroyo V. 2021. New clinical and pathophysiological perspectives defining the trajectory of cirrhosis. J Hepatol. 75:S14–26.

Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, Gustot T, Bernardi M, Canton R, et al. 2014a. Bacterial infections in cirrhosis: A position statement based on the EASL special conference 2013. J Hepatol. 60(6):1310–24.

Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, Levesque E, Durand F, Angeli P, Caraceni P, et al. 2014b. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 61(5):1038–47.

Jansson-Knodell CL, Calderon G, Weber R, Ghabril M. 2021. Small intestine varices in cirrhosis at a high-volume liver transplant center: A retrospective database study and literature review. Am J Gastroenterol. 116(7):1426–36.

Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. 2010. Clinical course of alcoholic liver cirrhosis: A danish population-based cohort study. Hepatology. 51(5):1675–82.

Kabelitz MA, Hartl L, Schaub G, Tiede A, Rieland H, Kornfehl A, Hübener P, Jachs M, Hinrichs J, Schütte SL, et al. 2025. Identification

of optimal portal pressure decrease to control ascites while minimizing hepatic encephalopathy after TIPS: A multicenter study. Hepatology. Epub ahead of print.

Kang SH, Lee YB, Lee J-, Nam JY, Chang Y, Cho H, Yoo J-, Cho YY, Cho EJ, Yu SJ, et al. 2017. Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. Aliment Pharmacol Ther. 46(9):845–55.

Kawaguchi T, Taniguchi E, Sata M. 2013. Effects of oral branched-chain amino acids on hepatic encephalopathy and outcome in patients with liver cirrhosis. Nutr Clin Pract. 28(5):580–8.

Kawut SM, Krowka MJ, Trotter JF, Roberts KE, Benza RL, Badesch DB, Taichman DB, Horn EM, Zacks S, Kaplowitz N, et al. 2008. Clinical risk factors for portopulmonary hypertension. Hepatology. 48(1):196–203.

Ke Q, Wang Z, Huang X, Li L, Wu W, Qiu L, Jiao Y, Xie Y, Peng X, Liu J, et al. 2022. Splenic vein embolization as a feasible treatment for patients with hepatic encephalopathy related to large spontaneous splenorenal shunts. Ann Hepatol. 27(5):100725.

Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, Runyon BA. 2014. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. Am J Gastroenterol. 109(9):1436–42.

Kim SG, Kim TY, Sohn JH, Um SH, Seo YS, Baik SK, Kim MY, Jang JY, Jeong SW, Lee B, et al. 2016. A randomized, multi-center, open-label study to evaluate the efficacy of carvedilol vs. propranolol to reduce portal pressure in patients with liver cirrhosis. Am J Gastroenterol. 111(11):1582–90.

Kimmann M, Tergast TL, Schultalbers M, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B. 2019. Sustained impact of nosocomial-acquired spontaneous bacterial peritonitis in different stages of decompensated liver cirrhosis. PloS One. 14(8):e0220666.

Klein LM, Chang J, Gu W, Manekeller S, Jansen C, Lingohr P, Praktiknjo M, Kalf JC, Schulz M, Spengler U, et al. 2020. The development and outcome of Acute-on-Chronic liver failure after surgical interventions. Liver Transpl. 26(2):227–37.

Kochar N, Tripathi D, McAvoy NC, Ireland H, Redhead DN, Hayes PC. 2008. Bleeding ectopic varices in cirrhosis: The role of transjugular intrahepatic portosystemic stent shunts. Aliment Pharmacol Ther. 28(3):294–303.

Kornfehl A, Tiede A, Hemetsberger P, Kappel J, Müllner-Bucsics T, Stockhoff L, Rieland H, Reider L, Dominik N, Kramer G, et al. 2024. Decreasing interleukin-6 levels after TIPS predict outcomes in decompensated cirrhosis. JHEP Rep. 101308.

Kovalak M, MD, Lake J, MD, Mattek N, MPH, Eisen, Glenn, MD, MPH, Lieberman D, MD, Zaman, Atif, MD, MPH. 2007. Endoscopic screening for varices in cirrhotic patients: Data from a national endoscopic database. Gastrointest Endosc. 65(1):82–8.

Krag M, Marker S, Perner A, Wetterslev J, Wise M, Schefold JC, Keus F, Guttormsen AB, Bendel S, Borthwick M, et al. 2018. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med. 379(23):2199–2208.

Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RAF. 2000. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transpl. 6(4):443–50.

Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. 2006. Portopulmonary hypertension: Results from a 10-year screening algorithm. Hepatology. 44(6):1502–10.

Kumar M, Venishetty S, Jindal A, Bihari C, Maiwall R, Vijayaraghavan R, Saggere Muralikrishna S, Arora V, Kumar G, Sarin SK. 2024. Tranexamic acid in upper gastrointestinal bleed in patients with cirrhosis: A randomized controlled trial. Hepatology. 80(2):376-388.

Kumar R, Kerbert AJC, Sheikh MF, Roth N, Calvao JAF, Mesquita MD, Barreira AI, Gurm HS, Ramsahye K, Mookerjee RP, et al. 2021. Determinants of mortality in patients with cirrhosis and uncontrolled variceal bleeding. J Hepatol. 74(1):66–79.

Labenz C, Beul L, Toenges G, Schattenberg JM, Nagel M, Sprinzl MF, Nguyen-Tat M, Zimmermann T, Huber Y, Marquardt JU, et al. 2019. Validation of the simplified animal naming test as primary screening tool for the diagnosis of covert hepatic encephalopathy. Eur J Intern Med. 60:96–100.

Labenz C, Gairing SJ, Kaps L, Ehrenbauer AF, Schleicher EM, Mengel S, Egge JFM, Gabriel MM, Galle PR, Wedemeyer H, et al. 2024. QuickStroop for screening for minimal hepatic encephalopathy in patients with liver cirrhosis. JHEP Rep. 101298.

Laleman W, Simon-Talero M, Maleux G, Perez M, Ameloot K, Soriano G, Villalba J, Garcia-Pagan J, Barrufet M, Jalan R, et al. 2013. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: A multicenter survey on safety and efficacy. Hepatology. 57(6):2448–57.

Lange CM, Trebicka J, Gerbes A, Canbay A, Geier A, Merle U, Peck-Radosavljevic M, Tacke F, Vogelmann T, Theis S, et al. 2023. Limited access to liver transplantation and TIPS despite high mortality, healthcare resource use and costs of cirrhosis in germany. Liver Int. 43(11):2503–12.

Larrue H, D'Amico G, Olivas P, Lv Y, Bucsics T, Rudler M, Sauerbruch T, Hernandez-Gea V, Han G, Reiberger T, et al. 2023. TIPS prevents further decompensation and improves survival in patients with cirrhosis and portal hypertension in an individual patient data meta-analysis. J Hepatol. 79(3):692–703.

Lau JYW, Yu Y, Tang RSY, Chan HCH, Yip H, Chan SM, Luk SWY, Wong SH, Lau LHS, Lui RN, et al. 2020. Timing of endoscopy for acute upper gastrointestinal bleeding. N Engl J Med. 382(14):1299–308.

Lebrec D, Giuily N, Hadengue A, Vilgrain V, Moreau R, Poynard T, Gadano A, Lassen C, Benhamou JP, Erlinger S. 1996. Transjugular intrahepatic portosystemic shunts: Comparison with paracentesis in patients with cirrhosis and refractory ascites: A randomized trial. french group of clinicians and a group of biologists. J Hepatol. 25(2):135–44.

Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, Ferguson JW. 2015. Non-selective [beta]-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut. 64(7):1111.

Levacher S, Blaise M, Pourriat J, Letoumelin P, Lapandry C, Pateron D. 1995. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. Lancet. 346(8979):865–8.

Lin CH, Shih FY, Ma MH, Chiang WC, Yang CW, Ko PC. 2005. Should bleeding tendency deter abdominal paracentesis? Dig Liver Dis. 37(12):946–51.

Llach J, Rimola A, Navasa M, Ginès P, Salmerón JM, Ginès A, Arroyo V, Rodés J. 1992. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: Relevance of ascitic fluid protein concentration. Hepatology. 16(3):724–7.

Llorente C, Jepsen P, Inamine T, Wang L, Bluemel S, Wang HJ, Loomba R, Bajaj JS, Schubert ML, Sikaroodi M, et al. 2017. Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal enterococcus. Nat Commun. 8(1):837–15.

Lo G, Chen W, Wang H, Lee C. 2010. Controlled trial of ligation plus nadolol versus nadolol alone for the prevention of first variceal bleeding. Hepatology. 52(1):230–7.

Lungren MP, MD, Kim CY, MD, Stewart JK, MD, Smith TP, MD, Miller MJ, MD. 2013. Tunneled peritoneal drainage catheter placement for refractory ascites: Single-center experience in 188 patients. J Vasc Interv Radiol. 24(9):1303–8.

Lv X, Lu Q, Deng K, Yang J, Yang L. 2024. Prevalence and characteristics of covert/minimal hepatic encephalopathy in patients with liver cirrhosis: A systematic review and meta-analysis. Am J Gastroenterol. 119(4):690–9.

Lv Y, Chen H, Luo B, Bai W, Li K, Wang Z, Xia D, Guo W, Wang Q, Li X, et al. 2022. Concurrent large spontaneous portosystemic shunt embolization for the prevention of overt hepatic encephalopathy after TIPS: A randomized controlled trial. Hepatology. 76(3):676–88.

Macken L, Hashim A, Mason L, Verma S. 2019. Permanent indwelling peritoneal catheters for palliation of refractory ascites in end-stage liver disease: A systematic review. Liver Int. 39(9):1594–607.

Maharshi S, Sharma BC, Srivastava S, Jindal A. 2015. Randomised controlled trial of lactulose versus rifaximin for prophylaxis of hepatic encephalopathy in patients with acute variceal bleed. Gut. 64(8):1341–2.

Maiwall R, Kumar A, Pasupuleti SSR, Hidam AK, Tevethia H, Kumar G, Sahney A, Mitra LG, Sarin SK. 2022. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. J Hepatol. 77(3):670–82.

Maleux G, Indesteege I, Laenen A, Verslype C, Vergote I, Prenen H. 2016. Tenckhoff tunneled peritoneal catheter placement in the palliative treatment of malignant ascites: Technical results and overall clinical outcome. Radiol Oncol. 50(1):1–7.

Mallet M, Rudler M, Thabut D. 2017. Variceal bleeding in cirrhotic patients. Gastroenterol Rep. 5(3):185–92.

Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, Hagmann M, Blacky A, Ferlitsch A, Sieghart W, et al. 2014. Nonselective β blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 146(7):1680,1690.e1.

Mandorfer M, Simbrunner B. 2021. Prevention of first decompensation in advanced chronic liver disease. Clin Liver Dis. 25(2):291–310.

Martin ED, Berg T, Berenguer M, Burra P, Fondevila C, Heimbach JK, Pageaux G, Sanchez-Fueyo A, Toso C. 2024. EASL clinical practice guidelines on liver transplantation. J Hepatol. 81(6):1040–86.

Mauz JB, Schneider H, Berliner D, Tiede A, Stockhoff L, Hinrichs JB, Wedemeyer H, Meyer BC, Olsson KM, Maasoumy B, et al. 2024. High prevalence and clinical relevance of intrapulmonary vascular dilatations in patients undergoing TIPS implantation. Clin Gastroenterol Hepatol. 22(9):1867-1877.e4.

Merli M, Nicolini G, Angeloni S, Gentili F, Attili AF, Riggio O. 2004. The natural history of portal hypertensive gastropathy in patients with liver cirrhosis and mild portal hypertension. Am J Gastroenterol. 99(10):1959–65.

Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L, Plauth M, Parés A. 2019. EASL clinical practice guidelines on nutrition in chronic liver disease. J Hepatol. 70(1):172–93.

Merli M, Lucidi C, Di Gregorio V, Lattanzi B, Giannelli V, Giusto M, Farcomeni A, Ceccarelli G, Falcone M, Riggio O, et al. 2016. An empirical broad spectrum antibiotic therapy in health-care–associated infections improves survival in patients with cirrhosis: A randomized trial. Hepatology. 63(5):1632–9.

Montagnese S, Rautou P, Romero-Gómez M, Larsen FS, Shawcross DL, Thabut D, Vilstrup H, Weissenborn K. 2022. EASL clinical practice guidelines on the management of hepatic encephalopathy. J Hepatol. 77(3):807–24.

Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, Coenraad M, Sperl J, Gines P, Moreau R, et al. 2016. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol. 64(3):574–82.

Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, et al. 2013. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 144(7):1426,1437.e9.

Moreau R, Elkrief L, Bureau C, Perarnau J, Thévenot T, Saliba F, Louvet A, Nahon P, Lannes A, Anty R, et al. 2018. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology. 155(6):1816,1827.e9.

Moreau R, Tonon M, Krag A, Angeli P, Berenguer M, Berzigotti A, Fernandez J, Francoz C, Gustot T, Jalan R, et al. 2023. EASL clinical practice guidelines on acute-on-chronic liver failure. J Hepatol. 79(2):461–91.

Mücke MM, Rumyantseva T, Mücke VT, Schwarzkopf K, Joshi S, Kempf VAJ, Welsch C, Zeuzem S, Lange CM. 2018. Bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality. Liver Int. 38(4):645–53.

Mücke MM, Mücke VT, Graf C, Schwarzkopf KM, Ferstl PG, Fernandez J, Zeuzem S, Trebicka J, Lange CM, Herrmann E. 2020a. Efficacy of norfloxacin prophylaxis to prevent spontaneous bacterial peritonitis: A systematic review and meta-analysis. Clin Transl Gastroenterol. 11(8):e00223.

Mücke MM, Mayer A, Kessel J, Mücke VT, Bon D, Schwarzkopf K, Rüschenbaum S, Queck A, Göttig S, Vermehren A, et al. 2020b. Quinolone and multidrug resistance predicts failure of antibiotic prophylaxis of spontaneous bacterial peritonitis. Clin Infect Dis. 70(9):1916–24.

Nadim MK, Kellum JA, Forni L, Francoz C, Asrani SK, Ostermann M, Allegretti AS, Neyra JA, Olson JC, Piano S, et al. 2024. Acute kidney injury in patients with cirrhosis: Acute disease quality initiative (ADQI) and international club of ascites (ICA) joint multidisciplinary consensus meeting. J Hepatol. 81(1):163–83.

Nakagawara A, Inokuchi K, Ikeda K, Kumashiro R, Tamada R. 1984. Decreased superoxide (O2-)-generating activity of blood monocytes from patients with hepatic cirrhosis. Hepatogastroenterology. 31(5):201–3.

Nardelli S, Gioia S, Pasquale C, Pentassuglio I, Farcomeni A, Merli M, Salvatori FM, Nikolli L, Torrisi S, Greco F, et al. 2016. Cognitive impairment predicts the occurrence of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Am J Gastroenterol. 111(4):523–8.

Nardelli S, Riggio O, Marra F, Gioia S, Saltini D, Bellafante D, Adotti V, Guasconi T, Ridola L, Rosi M, et al. 2024. Episodic overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt does not increase mortality in patients with cirrhosis. J Hepatol. 80(4):596–602.

Neuhofer W, Gülberg V, Gerbes AL. 2006. Endothelin and endothelin receptor antagonism in portopulmonary hypertension. Eur J Clin Invest. 36(s3):54–61.

Nicoară-Farcău O, Rudler M, Angrisani D, Torres F, Casanovas G, Bosch J, Lv Y, Thabut D, Fan D, García-Pagán JC, et al. 2021. Effects of early placement of transjugular portosystemic shunts in patients with high-risk acute variceal bleeding: A meta-analysis of individual patient data. Gastroenterology. 160(1):193,205.e10.

Norton ID, Andrews JC, Kamath PS. 1998. Management of ectopic varices. Hepatology. 28(4):1154–8.

Odriozola A, Puente Á, Cuadrado A, Iruzubieta P, Arias-Loste MT, Redondo C, Rivas C, Fábrega E, Crespo J, Fortea JI. 2023. High accuracy of spleen stiffness measurement in diagnosing clinically significant portal hypertension in metabolic-associated fatty liver disease. Liver Int. 43(7):1446–57.

Paquet KJ. 1982. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices - A prospective controlled randomized trial.

Endoscopy. 14(1):4–5.

Park WB, Lee K, Lee CS, Jang HC, Kim HB, Lee H, Oh M, Choe KW. 2005. Production of C-reactive protein in escherichia coli-infected patients with liver dysfunction due to liver cirrhosis. Diagn Microbiol Infect Dis. 51(4):227–30.

Peña Rodríguez M, Fagan A, Sikaroodi M, Gillevet PM, Bajaj JS. 2024. Proton pump inhibitor use and complications of cirrhosis are linked with distinct gut microbial bacteriophage and eukaryotic viral-like particle signatures in cirrhosis. Clin Transl Gastroenterol. 15(2):e00659.

Pereira K, Carrion AF, Salsamendi J, Doshi M, Baker R, Kably I. 2016. Endovascular management of refractory hepatic encephalopathy complication of transjugular intrahepatic portosystemic shunt (TIPS): Comprehensive review and clinical practice algorithm. Cardiovasc Intervent Radiol. 39(2):170–82.

Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, Cavallin M, Gola E, Sticca A, Loregian A, et al. 2016. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. Hepatology. 63(4):1299–309.

Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, Soares EC, Kim DJ, Kim SE, Marino M, et al. 2019. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology. 156(5):1368,1380.e10.

Piecha F, Vonderlin J, Frühhaber F, Graß J, Ozga A, Harberts A, Benten D, Hübener P, Reeh M, Riedel C, et al. 2024. Preoperative TIPS and in-hospital mortality in patients with cirrhosis undergoing surgery. JHEP Rep. 6(1):100914.

Planas R, Ballesté B, Antonio Álvarez M, Rivera M, Montoliu S, Anton Galeras J, Santos J, Coll S, Maria Morillas R, Solà R. 2004. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol. 40(5):823–30.

Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, Stefanescu H, Ma MM, Mandorfer M, Mergeay-Fabre M, et al. 2021. Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol. 116(4):723–32.

Porres-Aguilar M, Altamirano JT, Torre-Delgadillo A, Charlton MR, Duarte-Rojo A. 2012. Portopulmonary hypertension and hepatopulmonary syndrome: A clinician-oriented overview. Eur Respir Rev. 21(125):223–33.

Pose E, Piano S, Juanola A, Ginès P. 2024. Hepatorenal syndrome in cirrhosis. Gastroenterology. 166(4):588,604.e1.

Praktiknjo M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, Baiges A, Low G, Llop E, Maurer MH, et al. 2020a. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. J Hepatol. 72(6):1140–50.

Praktiknjo M, Simón-Talero M, Römer J, et al. 2020b. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. J Hepatol. 72(6):1140-1150.

Praktiknjo M, Abu-Omar J, Chang J, Thomas D, Jansen C, Kupczyk P, Schepis F, Garcia-Pagan JC, Merli M, Meyer C, et al. 2021a. Controlled underdilation using novel VIATORR® controlled expansion stents improves survival after transjugular intrahepatic portosystemic shunt implantation. JHEP Rep. 3(3):100264.

Praktiknjo M, Abu-Omar J, Chang J, et al. 2021b. Controlled underdilation using novel VIATORR® controlled expansion stents improves survival after transjugular intrahepatic portosystemic shunt implantation. JHEP Rep. 3(3):100264.

Privitera G, Figorilli F, Jalan R, Mehta G. 2018. Portosystemic shunt embolization and recurrent ascites: A single-center case series. Gastroenterology. 155(5):1649–50.

Puente A, Hernández-Gea V, Graupera I, Roque M, Colomo A, Poca M, Aracil C, Gich I, Guarner C, Villanueva C. 2014. Drugs plus ligation to prevent rebleeding in cirrhosis: An updated systematic review. Liver Int. 34(6):823–33.

Qiu H, Wander P, Bernstein D, Satapathy SK. 2020. Acute on chronic liver failure from novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Liver Int. 40(7):1590–3.

Queck A, Schwierz L, Gu W, Ferstl PG, Jansen C, Uschner FE, Praktiknjo M, Chang J, Brol MJ, Schepis F, et al. 2023. Targeted decrease of portal hepatic pressure gradient improves ascites control after TIPS. Hepatology. 77(2):466–75.

Raevens S BM, Fallon MB. 2022. Hepatopulmonary syndrome JHEP Rep. 4(9):100527.

Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. 2014. Lactulose vs polyethylene glycol 3350-electrolyte solution for treatment of overt hepatic encephalopathy: The HELP randomized clinical trial. JAMA Intern Med. 174(11):1727–33.

Redfield R, Latt N, Munoz SJ. 2024. Minimal hepatic encephalopathy. Clin Liver Dis. 28(2):237-252.

Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, Lammert F, Trauner M, Peck-Radosavljevic M, Vogelsang H. 2013a. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol. 58(5):911–21.

Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, Heinisch BB, Trauner M, Kramer L, Peck-Radosavljevic M. 2013b. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut. 62(11):1634–41.

Reiniš J, Petrenko O, Simbrunner B, Hofer BS, Schepis F, Scoppettuolo M, Saltini D, Indulti F, Guasconi T, Albillos A, et al. 2023. Assessment of portal hypertension severity using machine learning models in patients with compensated cirrhosis. J Hepatol. 78(2):390–400.

Reuken PA, Pletz MW, Baier M, Pfister W, Stallmach A, Bruns T. 2012. Emergence of spontaneous bacterial peritonitis due to enterococci - risk factors and outcome in a 12-year retrospective study. Aliment Pharmacol Ther. 35(10):1199–208.

Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, Keough A, Llop E, González A, Seijo S, et al. 2014. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 146(2):412,419.e3.

Ripoll C, Groszmann R, Garcia–Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia–Pagan JC, Makuch R, Patch D, et al. 2007. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 133(2):481–8.

Rose CF, Amodio P, Bajaj JS, Dhiman RK, Montagnese S, Taylor-Robinson SD, Vilstrup H, Jalan R. 2020. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatol. 73(6):1526–47.

Runyon BA. 1986. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. Gastroenterology. 91(6):1343–6.

Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. 1992. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med. 117(3):215–20.

Salerno F, Borroni G, Moser P, Badalamenti S, Cassara L, Maggio A, Fusini M, Cesana B. 1993. Survival and prognostic factors of cirrhotic patients with ascites: A study of 134 outpatients. Am J Gastroenterol. 88(4):514–9.

Salerno F, Cammà C, Enea M, Rössle M, Wong F. 2007. Transjugular intrahepatic portosystemic shunt for refractory ascites: A meta-analysis of individual patient data. Gastroenterology. 133(3):825–34.

Salerno F, Navickis RJ, Wilkes MM. 2013. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: A meta-analysis of randomized trials. Clin Gastroenterol Hepatol. 11(2):123,130.e1.

Sandmann L, Tergast TL, Wedemeyer H, Deterding K, Maasoumy B. 2023. 3P and 5P models of limited value for the detection of clinically significant portal hypertension in patients with hepatitis delta. J Hepatol. 79(1):e47–9.

Santos J, Planas R, Pardo A, Durández R, Cabré E, Morillas RM, Granada ML, Jiménez JA, Quintero E, Gassull MA. 2003. Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety. J Hepatol. 39(2):187–92.

Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. 1992. Prevalence, classification and natural history of gastric varices: A long-term follow-up study in 568 portal hypertension patients. Hepatology. 16(6):1343–9.

Sato S, Sato S, Tsuzura H, Ikeda Y, Hayashida S, Takahashi S, Amano N, Murata A, Shimada Y, Iijima K, et al. 2020. Elevated serum procalcitonin levels and their association with the prognosis of patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 32(9):1222–8.

Sauerbruch T, Mengel M, Dollinger M, Zipprich A, Rössle M, Panther E, Wiest R, Caca K, Hoffmeister A, Lutz H, et al. 2015. Prevention of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents versus hemodynamically controlled medical therapy. Gastroenterology. 149(3):660,668.e1.

Saunders JB, Walters JR, Davies AP, Paton A. 1981. A 20-year prospective study of cirrhosis. Br Med J. 282(6260):263–6.

Savale L, Guimas M, Ebstein N, Fertin M, Jevnikar M, Renard S, Horeau-Langlard D, Tromeur C, Chabanne C, Prevot G, et al. 2020. Portopulmonary hypertension in the current era of pulmonary hypertension management. J Hepatol. 73(1):130–9.

Schepis F, Vizzutti F, Garcia-Tsao G, Marzocchi G, Rega L, De Maria N, Di Maira T, Gitto S, Caporali C, Colopi S, et al. 2018. Under-dilated TIPS associate with efficacy and reduced encephalopathy in a prospective, non-randomized study of patients with cirrhosis. Clin Gastroenterol Hepatol. 16(7):1153,1162.e7.

Schneider H, Berliner D, Stockhoff L, Reincke M, Mauz JB, Meyer B, Bauersachs J, Wedemeyer H, Wacker F, Bettinger D, et al. 2023. Diastolic dysfunction is associated with cardiac decompensation after transjugular intrahepatic portosystemic shunt in patients with liver cirrhosis. United European Gastroenterol J. 11(9):837–51.

Schultalbers M, Tergast TL, Simon N, Kabbani A, Kimmann M, zu Siederdissen CH, Gerbel S, Manns MP, Cornberg M, Maasoumy B. 2020. Frequency, characteristics and impact of multiple consecutive nosocomial infections in patients with decompensated liver cirrhosis and ascites. United European Gastroenterol J. 8(5):567–76.

Schulz M, Trebicka J. 2022. Acute-on-chronic liver failure: A global disease. Gut. 71(1):5–6.

Schulz MS, Angeli P, Trebicka J. 2024. Acute and non-acute decompensation of liver cirrhosis (47/130). Liver Int. Epub ahead of print.

Schütte A, Ciesek S, Wedemeyer H, Lange CM. 2019. Influenza virus infection as precipitating event of acute-on-chronic liver failure. J Hepatol. 70(4):797–9.

Schütte SL, Wedemeyer H, Maasoumy B, Tergast TL. 2024. Silver-coating of tunneled peritoneal drainage system is associated with a lower incidence of spontaneous bacterial peritonitis and device explanation. J Hepatol. 80:S202–3.

Semmler G, Binter T, Kozbial K, Schwabl P, Hametner-Schreil S, Zanetto A, Gavasso S, Chromy D, Bauer DJM, Simbrunner B, et al. 2021. Noninvasive risk stratification after HCV eradication in patients with advanced chronic liver disease. Hepatology. 73(4):1275–89.

Semmler G, Lens S, Meyer EL, Baiges A, Alvardo-Tapias E, Llop E, Tellez L, Schwabl P, Mauro E, Escudé L, et al. 2022. Non-invasive tests for clinically significant portal hypertension after HCV cure. J Hepatol. 77(6):1573–85.

Semmler G, Hartl L, Mendoza YP, Simbrunner B, Jachs M, Balcar L, Schwarz M, Hofer BS, Fritz L, Schedlbauer A, et al. 2024. Simple blood tests to diagnose compensated advanced chronic liver disease and stratify the risk of clinically significant portal hypertension. Hepatology. 80(4):887-900.

Sersté T, Melot C, Francoz C, Durand F, Rautou P, Valla D, Moreau R, Lebrec D. 2010. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 52(3):1017–22.

Shah HA, Azam Z, Rauf J, Abid S, Hamid S, Jafri W, Khalid A, Ismail FW, Parkash O, Subhan A, et al. 2014. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: A multicentre randomized controlled trial. J Hepatol. 60(4):757–64.

Shaheen A, Nguyen HH, Congly SE, Kaplan GG, Swain MG. 2019. Nationwide estimates and risk factors of hospital readmission in patients with cirrhosis in the united states. Liver Int. 39(5):878–84.

Shaheen NJ, Stuart E, Schmitz SM, Mitchell KL, Fried MW, Zacks S, Russo MW, Galanko J, Shresta R. 2005. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: A randomized, controlled trial. Hepatology. 41(3):588–94.

Sharma BC, Sharma P, Agrawal A, Sarin SK. 2009. Secondary prophylaxis of hepatic encephalopathy: An open-label randomized controlled trial of lactulose versus placebo. Gastroenterology. 137(3):885,891.e1.

Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. 2013. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. Am J Gastroenterol. 108(9):1458–63.

Sharma P, Agrawal A, Sharma BC, Sarin SK. 2011. Prophylaxis of hepatic encephalopathy in acute variceal bleed: A randomized controlled trial of lactulose versus no lactulose. J Gastroenterol Hepatol. 26(6):996–1003.

Shawcross DL, Wright GA, Stadlbauer V, Hodges SJ, Davies NA, Wheeler-Jones C, Pitsillides AA, Jalan R. 2008. Ammonia impairs neutrophil phagocytic function in liver disease. Hepatology. 48(4):1202-12.

Simbrunner B, Hartl L, Jachs M, Bauer DJM, Scheiner B, Hofer BS, Stättermayer AF, Marculescu R, Trauner M, Mandorfer M, et al. 2023. Dysregulated biomarkers of innate and adaptive immunity predict infections and disease progression in cirrhosis. JHEP Rep. 5(5):100712.

Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. 2019. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 53(1):1.

Singh S, Khan A. 2020. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the united states: A multicenter research network study. Gastroenterology. 159(2):768,771.e3.

Singh V, Ghosh S, Singh B, Kumar P, Sharma N, Bhalla A, Sharma AK, Choudhary NS, Chawla Y, Nain CK. 2012. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: A randomized study. J Hepatol. 56(6):1293–8.

Sola-Vera J, Miñana J, Ricart E, Planella M, González B, Torras X, Rodrı́guez J, Such J, Pascual S, Soriano G, et al. 2003. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. Hepatology. 37(5):1147–53.

Solbach P, Höner zu Siederdissen C, Taubert R, Ziegert S, Port K, Schneider A, Hueper K, Manns M, Wedemeyer H, Jaeckel E. 2017. Home-based drainage of refractory ascites by a permanent-tunneled peritoneal catheter can safely replace large-volume paracentesis. Eur J Gastroenterol Hepatol. 29(5):539–46.

Solbach P, Höner zu Siederdissen C, Wellhöner F, Richter N, Heidrich B, Lenzen H, Kerstin P, Hueper K, Manns M, Wedemeyer H, et al. 2018. Automated low-flow ascites pump in a real-world setting: Complications and outcomes. Eur J Gastroenterol Hepatol. 30(9):1082–9.

Solé C, Solà E, Huelin P, Carol M, Moreira R, Cereijo U, Mas J, Graupera I, Pose E, Napoleone L, et al. 2019. Characterization of inflammatory response in hepatorenal syndrome: Relationship with kidney outcome and survival. Liver Int. 39(7):1246–55.

Sørensen M, Andersen JV, Bjerring PN, Vilstrup H. 2024. Hepatic encephalopathy as a result of ammonia-induced increase in GABAergic tone with secondary reduced brain energy metabolism. Metab Brain Dis. 2024;40(1):19.

Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, et al. 1999. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 341(6):403–9.

Stirnimann G, Berg T, Spahr L, Zeuzem S, McPherson S, Lammert F, Storni F, Banz V, Babatz J, Vargas V, et al. 2017. Treatment of refractory ascites with an automated low-flow ascites pump in patients with cirrhosis. Aliment Pharmacol Ther. 46(10):981–91.

Stockhoff L, Schneider H, Tergast TL, Cornberg M, Maasoumy B. 2021. Freiburg index of post-TIPS survival (FIPS) a valid prognostic score in patients with cirrhosis but also an advisor against TIPS? J Hepatol. 75(2):487–9.

Stockhoff L, Muellner-Bucsics T, Markova AA, Schultalbers M, Keimburg SA, Tergast TL, Hinrichs JB, Simon N, Gerbel S, Manns MP, et al. 2022. Low serum cholinesterase identifies patients with worse outcome and increased mortality after TIPS. Hepatol Commun. 6(3):621–32.

Stokkeland K, Brandt L, Ekbom A, Hultcrantz R. 2006. Improved prognosis for patients hospitalized with esophageal varices in sweden 1969–2002. Hepatology. 43(3):500–5.

Sussman N, Kaza V, Barshes N, Stribling R, Goss J, O'Mahony C, Zhang E, Vierling J, Frost A. 2006. Successful liver transplantation following medical management of portopulmonary hypertension: A Single-Center series. Am J Transplant. 6(9):2177–82.

Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. 2019. Incidence of and risk factors for hepatic encephalopathy in a Population-Based cohort of americans with cirrhosis. Hepatol Commun. 3(11):1510–9.

Téllez L, Ibáñez-Samaniego L, Pérez del Villar C, Yotti R, Martínez J, Carrión L, Rodríguez de Santiago E, Rivera M, González-Mansilla A, Pastor Ó, et al. 2020. Non-selective beta-blockers impair global circulatory homeostasis and renal function in cirrhotic patients with refractory ascites. J Hepatol. 73(6):1404–14.

Tergast TL, Wranke A, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B. 2018. Dose-dependent impact of proton pump inhibitors on the clinical course of spontaneous bacterial peritonitis. Liver Int. 38(9):1602–13.

Tergast TL, Kimmann M, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B. 2019. Systemic arterial blood pressure determines the therapeutic window of non-selective beta blockers in decompensated cirrhosis. Aliment Pharmacol Ther. 50(6):696–706.

Tergast TL, Schultalbers M, Wedemeyer H, Cornberg M, Maasoumy B. 2021. IgG, a novel predictor for acute-on-chronic liver failure and survival in patients with decompensated cirrhosis? J Hepatol. 75(1):229–31.

Tergast TL, Griemsmann M, Stockhoff L, Heidrich B, Schirmer H, Lenzen H, Wedemeyer H, Cornberg M, Jaeckel E, Maasoumy B. 2022. Home-based, tunnelled peritoneal drainage system as an alternative treatment option for patients with refractory ascites. Aliment Pharmacol Ther. 56(3):529–39.

Tergast TL, Griemsmann M, Stockhoff L, Port K, Heidrich B, Cornberg M, Wedemeyer H, Lenzen H, Richter N, Jaeckel E, et al. 2023. Daily low-volume paracentesis and clinical complications in patients with refractory ascites. JAMA Netw Open. 6(7):e2322048.

Tevethia HV, Pande A, Vijayaraghavan R, Kumar G, Sarin SK. 2024. Combination of carvedilol with variceal band ligation in prevention of first variceal bleed in child-turcotte-pugh B and C cirrhosis with high-risk oesophageal varices: The 'CAVARLY TRIAL'. Gut. 73(11):1844–53.

Thévenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, Rudler M, Heurgué-Berlot A, Rosa I, Talbodec N, et al. 2015. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol. 62(4):822–30.

Thomas C, Glinskii V, de Jesus Perez V, Sahay S. 2020. Portopulmonary hypertension: From bench to bedside. Frontiers in Medicine. 7:569413.

Tiede A, Stockhoff L, Liu Z, Rieland H, Mauz JB, Ohlendorf V, Bremer B, Witt J, Kraft A, Cornberg M, et al. 2024. TIPS insertion leads to sustained reversal of systemic inflammation in patients with decompensated liver cirrhosis. Clin Mol Hepatol. Epub ahead of print.

Titó L, Rimola A, Ginès P, Llach J, Arroyo V, Rodés J. 1988. Recurrence of spontaneous bacterial peritonitis in cirrhosis: Frequency and predictive factors. Hepatology. 8(1):27–31.

Tranah TH, Ballester M, Carbonell-Asins JA, Ampuero J, Alexandrino G, Caracostea A, Sánchez-Torrijos Y, Thomsen KL, Kerbert AJC, Capilla-Lozano M, et al. 2022. Plasma ammonia levels predict hospitalisation with liver-related complications and mortality in clinically stable outpatients with cirrhosis. J Hepatol. 77(6):1554–63.

Trebicka J, Amoros A, Pitarch C, Titos E, Alcaraz-Quiles J, Schierwagen R, Deulofeu C, Fernandez-Gomez J, Piano S, Caraceni P, et al. 2019a. Addressing profiles of systemic inflammation across the different clinical phenotypes of acutely decompensated cirrhosis. Front Immunol. 10:476.

Trebicka J, Bastgen D, Byrtus J, et al. 2019b. Smaller-Diameter Covered Transjugular Intrahepatic Portosystemic Shunt Stents Are Associated With Increased Survival. Clin Gastroenterol Hepatol. 2019;17(13):2793-2799.e1.

Trebicka J, Gu W, Ibáñez-Samaniego L, Hernández-Gea V, Pitarch C, Garcia E, Procopet B, Giráldez Á, Amitrano L, Villanueva C, et al. 2020a. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol. 73(5):1082–91.

Trebicka J, Fernandez J, Papp M, Caraceni P, Giovo I, Uschner FE, Jimenez C, Gustot T, Albillos A, Bañares R, et al. 2020b. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol. 73(4):842–54.

Trebicka J, Sundaram V, Moreau R, Jalan R, Arroyo V. 2020c. Liver transplantation for Acute-on-Chronic liver failure: Science or fiction? Liver Transpl. 26(7):906–15.

Trebicka J, Fernandez J, Papp M, et al. 2020d. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. J Hepatol. 73(4):842-854.

Trebicka J, Papp M, Caraceni P, Laleman W, Gambino C, Giovo I, Uschner FE, Jansen C, Jimenez C, Mookerjee R, et al. 2021a. PREDICT identifies precipitating events associated with the clinical course of acutely decompensated cirrhosis. J Hepatol. 74(5):1097–108.

Trebicka J, Bork P, Krag A, Arumugam M. 2021b. Utilizing the gut microbiome in decompensated cirrhosis and acute-on-chronic liver failure. Nat Rev Gastroenterol Hepatol. 2021;18(3):167-180.

Trebicka J, Louvet A, Arroyo V, Jalan R, Shah VH, Moreau R. 2022. Severe alcoholic hepatitis as precipitant for organ failure and ACLF. Z Gastroenterol. 60(1):67–76.

Tuifua TS, Partovi S, Remer EM, Ragheb J, Bullen JA, Kattan MW, Kapoor B. 2022. Assessment of clinical outcomes, clinical manifestations, and risk factors for hepatic infarction after transjugular intrahepatic portosystemic shunt placement (TIPS): A retrospective comparative study. Cardiovasc Intervent Radiol. 45(10):1512–23.

Turco L, Reiberger T, Vitale G, La Mura V. 2023. Carvedilol as the new non-selective beta-blocker of choice in patients with cirrhosis and portal hypertension. Liver Int. 43(6):1183–94.

Urrunaga, Nathalie H., MD, MS, Rockey DC, MD. 2014. Portal hypertensive gastropathy and colopathy. Clin Liver Dis. 18(2):389–406.

Villa E, Bianchini M, Blasi A, Denys A, Giannini EG, de Gottardi A, Lisman T, de Raucourt E, Ripoll C, Rautou P. 2022. EASL clinical practice guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol. 76(5):1151–84.

Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, et al. 2013. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 368(1):11–21.

Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, Bañares R, Morillas RM, Poca M, Peñas B, et al. 2019. B blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): A randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 393(10181):1597–608.

Villanueva C, Torres F, Sarin SK, Shah HA, Tripathi D, Brujats A, Rodrigues SG, Bhardwaj A, Azam Z, Hayes PC, et al. 2022. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. J Hepatol. 77(4):1014–25.

Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. 2014. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the american association for the study of liver diseases and the european association for the study of the liver. Hepatology. 60(2):715–35.

Wang J, Yu Y, Li G, Shen C, Meng Z, Zheng J, Jia Y, Chen S, Zhang X, Zhu M, et al. 2018. Relationship between serum HBV-RNA levels and intrahepatic viral as well as histologic activity markers in entecavir-treated patients. J Hepatol. 68(1):16–24.

Wang W, Yang J, Liu C, Song P, Wang W, Xu H, Xia X. 2019. Norfloxacin, ciprofloxacin, trimethoprim–sulfamethoxazole, and rifaximin for the prevention of spontaneous bacterial peritonitis: A network meta-analysis. Eur J Gastroenterol Hepatol. 31(8):905–10.

Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. 2001. Neuropsychological characterization of hepatic encephalopathy. J Hepatol. 34(5):768–73.

Wellhöner F, Döscher N, Tergast TL, Vital M, Plumeier I, Kahl S, Potthoff A, Manns MP, Maasoumy B, Wedemeyer H, et al. 2019. The impact of proton pump inhibitors on the intestinal microbiota in chronic hepatitis C patients. Scand J Gastroenterol. 54(8):1033–41.

Wong F, Bendel E, Sniderman K, Frederick T, Haskal ZJ, Sanyal A, Asrani SK, Capel J, Kamath PS. 2020. Improvement in quality of life and decrease in Large-Volume paracentesis requirements with the automated Low-Flow ascites pump. Liver Transpl. 26(5):651–61.

Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, Gonzalez SA, Mumtaz K, Lim N, Simonetto DA, et al. 2021. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med. 384(9):818–28.

Wong F, Pappas SC, Reddy KR, Vargas H, Curry MP, Sanyal A, Jamil K. 2022. Terlipressin use and respiratory failure in patients with hepatorenal syndrome type 1 and severe acute-on-chronic liver failure. Aliment Pharmacol Ther. 56(8):1284–93.

Yang Y, Li L, Qu C, Zeng B, Liang S, Luo Z, Wang X, Zhong C. 2015. Diagnostic accuracy of serum procalcitonin for spontaneous bacterial peritonitis due to end-stage liver disease: A meta-analysis. Medicine (Baltimore). 94(49):e2077.

Zaka AZ, Mangoura SA, Ahmed MA. 2025. New updates on hepatopulmonary syndrome: A comprehensive review. Respir Med. 236:107911.

18. Diagnosis, prognosis & therapy of hepatocellular carcinoma

Ursula Ehmer, Jens U. Marquardt

Summary

Hepatocellular carcinoma (HCC) is one of the most common and deadliest cancers worldwide. Historically, viral hepatitis and alcohol abuse constitute dominant risk factors of HCC development. However, non-alcoholic fatty liver disease is a rapidly evolving cause of HCC in the Western world. In cirrhotic patients, diagnosis of HCC can be reliably established by dynamic imaging modalities. However, the relevance of histology becomes increasingly recognised due to improved precision medicine approaches. A variety of treatment options is now available, and treatments depend on the stage of disease as well as the degree of liver function impairment. However, despite established surveillance by ultrasound, the majority of cases are still diagnosed at advanced tumour stages when treatment options are limited. Curative treatment approaches include liver transplantation, surgical resection, percutaneous ablation, and radiation, whereas different local and systemic therapies are available in advanced stages. Thus, HCC is a hallmark for multidisciplinary dialogue in tumour boards. Further, the landscape of systemic therapies significantly evolved with the advent of targeted therapies and immune checkpoint inhibitors over the recent years. Currently, combination therapies are the gold standard for upfront therapy in eligible patients at advanced stages of the disease and steadily improved overall survival over the last decade. Nevertheless, prognosis of HCC patients is still limited and there remains an urgent need for novel diagnostic and predictive biomarkers as well as improved therapies.

Epidemiology, Screening and Prevention

Liver cancer ranks among the most common cancers and is the third most frequent cause of cancer-related death worldwide (Vogel 2022). Hepatocellular carcinomas (HCC) represent about 90% of primary liver cancers and show a significant increase in all age populations over the last decades. Globally, primary liver cancer accounts for around 7% of all cancers and affected more than 905 000 patients in 2020 (Ferlay 2021). Further,

mortality rates equal incidence rates and, thus, HCC advanced to a major global health care problem. Notably, HCC is characterised by a significant geographic heterogeneity that is associated with incidence rates of the major risk factors. Worldwide, the most frequent underlying etiologies are chronic viral hepatitis (B and C), alcohol abuse, aflatoxin as well as inherited or acquired metabolic diseases, including haemochromatosis, alpha-1-antitrypsin deficiency as well as non-alcoholic steatohepatitis (NASH). The latter showing the most prominent increase in incidence rates in Western countries due to a sharp rise in metabolic syndrome, obesity, and diabetes mellitus type 2.

In the majority of HCC cases, advanced liver fibrosis or cirrhosis can be detected and, thus, the presence of liver cirrhosis remains the most important risk factor for the development of HCC. Overall, annual incidence among patients with cirrhosis is 1-8%, depending on the underlying etiological risk factor. In addition, co-existing risk factors as well as other patient-related factors resembling age, male gender as well as the degree of portal hypertension aggravate the risk for liver cancer development. Interestingly, although a significant number of non-alcoholic fatty liver disease (NAFLD)/NASH patients also show overlapping alcohol abuse, HCC in the background of metabolic inflammation can be induced in the absence of cirrhosis in a sizeable number of patients, which underlines the increasing importance of metabolic liver diseases in the Western world.

Most important preventive measure in the context of chronic liver diseases (CLDs) is early detection as well as prevention of cirrhosis development. Besides vaccination and treatment in chronic Hepatitis B, consequent treatment of HCV as well as elimination of noxes are particularly important. Notably, the role of screening for CLDs in the general population remains a matter of ongoing discussion and should be addressed in global health care programmes (Labenz 2022). Besides the mentioned measures, daily coffee consumption seems to have beneficial effects in CLD. In addition, metformin shows positive effects on the development of HCC in patients at risk but should only be given in case of a medical indication, i.e., diabetes mellitus type 2.

Surveillance of patients at high risk

According to general recommendations, surveillance should be performed in patients at high risk for HCC development with a high probability of curative treatment options (Voesch 2022). In general, an annual incidence of 1.5% warrants surveillance in cirrhotic patients irrespective of the aetiology and, thus, the majority of patients with liver cirrhosis should be enrolled in specific surveillance programmes when liver function is still compensated, i.e. CHILD A/B or CHILD C on the waiting list for transplantation. In Caucasian patients with HBV, risk assessment can be reliably achieved by implementing the PAGE-B score. Surveillance should be installed for patients with intermediate or high risk, i.e. PAGE-B score >10 (Papatheodoridis 2016). Surveillance in the absence of cirrhosis should be reserved to patients with an age <50 years and chronic HBV infection in patients of African and Asian descent. Notably, the relevance of surveillance in non-cirrhotic NASH and HCV patients remains unclear and is a matter of scientific interest. However, in case of suspected advanced fibrosis, an increased risk for HCC development is documented and regular surveillance seems warranted.

Surveillance is generally recommended by means of bi-annual abdominal ultrasound and should be performed by experienced personnel. The use of other dynamic imaging technologies including computer tomography or MRI have a high false positive rate and, thus, does not seem to be cost effective for the majority of patients. However, if ultrasound is not feasible due to patient factors, e.g., obesity or abdominal gas, contrast enhanced dynamic imaging can be considered. Serological markers including repeated AFP measurements can optionally be used to complement ultrasound, but the overall diagnostic sensitivity remains poor. Thus, novel biomarkers for early detection are urgently needed and are the focus of ongoing studies.

Diagnosis of hepatocellular carcinoma

HCC differs from most other tumour entities as it can be reliably diagnosed based on specific characteristics by MRI or CT imaging in cirrhotic patients. Nevertheless, in non-cirrhotic patients or whenever diagnostic criteria for HCC are not fulfilled by imaging, diagnosis should be confirmed by biopsy. As the interventional risks in obtaining liver biopsies are small, some centres aim to secure diagnosis by histopathology in all palliative cases also when radiologic characteristics confirm the presence of HCC (European Association for the Study of the Liver 2018). However, increased risk of bleeding after liver biopsy should be considered in cirrhotic patients with severely impaired plasmatic coagulation or low platelets as well as in patients with clinically meaningful perihepatic ascites. Another concern is needle-track seeding of tumour cells, which is reported to occur in less than 3% of patients. Seeding metastasis can be treated by resection or radiation therapy in most cases (Silva 2008). Most importantly, there seems to be no influence on the oncologic outcome or overall survival. Therefore, histological confirmation is desired and should not be restricted to unclear situations (Fuks 2014).

Clinical presentation

Early and even intermediate stage HCC are mostly asymptomatic. Liver nodules at these stages are often detected by surveillance ultrasound in patients at risk, by routine medical check-up, or during imaging for other medical conditions. At more advanced tumour stages, patients can present with tumour-specific symptoms such as pain, weight loss and fatigue as well as worsening of liver function and other cirrhosis-related symptoms – mostly ascites or variceal bleeding – due to increased portal pressure or macrovascular invasion into the main portal vein. More rarely, intraabdominal hemorrhage from rupture of subcapsular liver tumours leads to the diagnosis of HCC (Sahu 2019). Consequently, diagnostic work-up of a worsening of liver function in cirrhotic patients – including de-novo ascites – should always rule out an underlying HCC.

Imaging-based diagnosis

With the prominent role of imaging in the diagnosis and staging of HCC, refined algorithms for radiologic work-up of liver nodules in the patients with cirrhosis have been developed. Specific changes in vascularisation are observed during HCC development – i.e. hypervascularisation in the (late) arterial phase together with a wash-out in the portal venous and/or delayed venous phases – and are the backbone of imaging-based HCC diagnosis. Multi-phase contrast-enhanced imaging methods can detect these chances with high sensitivity and specificity in nodules ≥ 1 cm. MRI is currently considered the most sensitive imaging method (Di Martino 2013). Sensitivity increases with size of the tumour nodule, ranging between 62% and 71% (MRI), or 62% and 68% (CT), respectively, for small nodules < 20 mm and up to 95% (MRI) or 92% (CT) in larger nodules (Aube 2017, Lee 2015). Apart from "classic" imaging features, several other criteria can be helpful to establish the diagnosis of HCC. In MRI, consideration of diffusion-weighted imaging (DWI) and the use hepatobiliary contrast agents increase the specificity of diagnosis. In addition to classical arterial hyperenhancement and portal venous or delayed phase washout, the Liver Imaging Reporting and Data System (LI-RADS) criteria for HCC diagnosis include further features such as enhancing capsule appearance, size, threshold growth by ≥50% in ≤6 months, and restricted diffusion to categorise lesions in cirrhotic patients. LI-RADS categories reflect the likelihood of any nodule for malignancy and specifically for HCC (Lee 2021). The LI-RADS criteria also consider that sensitivity and specificity of radiologic imaging will likely never reach 100% and even "probably benign" lesions (LI-RADS 2) have a probability of HCC in 1 out of 10 patients. Therefore, biopsies should be performed in all doubtful cases to avoid any delay in treatment. Contrast-enhanced ultrasound (CE-US) may help to establish the diagnosis of HCC but is considered less sensitive and – especially in differentiation from cholangiocarcinoma – less specific than radiologic imaging (Piscaglia 2017). However, due to its low cost and easy application, CE-US remains a relevant diagnostic tool in many centres, but it should not be used as sole imaging method in the diagnosis of HCC.

In small liver lesions below 1 cm, sensitivity and specificity of imaging-based diagnosis remains low and sampling for histopathology can provide a technical challenge. In these cases, HCC diagnosis cannot be reliably established. With a high risk of progression of these nodules towards unambiguous HCC in cirrhotic patients, follow-up by imaging every three months is strongly recommended (Khalili 2011). Of note, all imaging features of HCC should only be used for diagnosis in cirrhotic patients and in patients at high risk for HCC – such as patients with chronic HBV – due to the high pre-test probability in these cohorts. In all other cases, diagnosis should be confirmed by biopsy even if imaging is highly suggestive of HCC.

Whenever HCC diagnosis is confirmed either by imaging or histopathology, a complete tumour staging including CT scan of the lung and abdomen – if not already covered by diagnostic MRI of the liver – should be obtained to rule out metastatic disease.

Due to the unique vascular pattern of intrahepatic HCC, assessment of treatment response should not only consider changes in tumour size, but also changes in vascularisation pattern. Especially in intra-arterial treatment approaches (TACE or TARE), loss of arterial (hyper-)enhancement is considered a criterion for treatment response. This feature is included in modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC (Llovet 2020). Further adaption of the mRECIST criteria might be needed to account for specific changes observed with immunotherapeutic treatment approaches to accurately describe tumour response.

Histology and biomarkers

Histological Classification of malignant liver tumours is the basis for subsequent diagnostic and therapeutic approaches. By histology, several specific subtypes of HCC have been identified. The revised WHO classification distinguishes eight specific subtypes found in up to 35% of HCC (steatohepatitic, clear cell, macrotrabecular-massive, scirrhous, chromophobe, fibrolamellar, neutrophil-rich, and lymphocyte-rich), while the remaining tumours (approx. 65%) are classified as "not-otherwise-specified" HCC (NOS-HCC). Some subtypes are associated with distinct genetic changes and characterised by a better or worse prognosis in

comparison to NOS-HCC. However, subtyping currently does not affect clinical decision making (Lokuhetty).

A diagnostic challenge – particularly in early HCC – remains the distinction between dysplastic nodules and well-differentiated HCC. In these cases, an immunohistochemistry panel consisting of glypican 3, HSP70 and glutamine synthetase can confirm malignant tumour growth with high specificity and a sensitivity of 70% (Di Tommaso 2009). Therapeutically relevant is the differentiation of HCC from other malignant liver tumours. In samples where differentiation of HCC and intrahepatic cholangiocarcinoma (iCCA) is not possible by histomorphology, immunohistochemistry of cell-type specific markers such as HepPar-1 and arginase 1 (hepatocytes) or CK7 and CK19 (bile duct cells) can be used to establish diagnosis. Tumours with biliary differentiation components in addition to the hepatocellular differentiation should be delineated as combined HCC/(i)CCA. Histology is also crucial in the differentiation of highly differentiated HCC from precursor lesions, i.e., dysplastic nodules, as well as non-malignant hepatocellular adenoma and focal nodular hyperplasia.

Though elevated AFP levels are suggestive of HCC, a relatively low sensitivity of 60% for AFP levels >20 ng/mL renders it unsuitable as a sole marker for early detection. However, APF levels >100 ng/mL are highly specific for HCC (98%) and might help to establish diagnosis in unclear cases where biopsy is deemed too risky for the patient. Several serologic biomarkers for early diagnosis of HCC as well as for monitoring of therapeutic response are currently under investigation, including AFP-L3, DCP or neutrophil/lymphocyte ratio. However, no reliable markers have been established in clinical routine so far. Additionally, the concept of "liquid biopsy" – using blood samples to detect circulating tumour cells, extracellular vesicles, and circulating tumour DNA (ctDNA) – has gained more attention in recent years. While still far from clinical application, this approach might give future opportunities for early detection of HCC and provide diagnostic tools for estimating prognosis and therapeutic response (Pinero 2020).

Classification of HCC

Clinical staging of HCC aims to stratify patients with respect to specific prognosis and to select the optimal therapeutic options for the respective stage. Herein, the Barcelona Clinic Liver Cancer (BCLC) classification has been adopted as the international standard, which is recommended by both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) (Table 1) (European Association for the Study of the Liver 2018). Unlike other classification schemes the BCLC staging system does not exclusively rely on tumour characteristic and spread, but also includes performance status as well as severity of liver disease (Llovet 1999). Importantly, the classification also provides information on median survival of patients as well as recommendations for specific therapeutic options (Table 1). Importantly, given the increase in therapeutic options in advanced stages of HCC, a current update included a clinical decision-making tool for the recommendation that considers individual patients preferences as well as co-morbidities (Reig 2022). Despite intense research activities, molecular characteristics are not yet able to reliably assess individual prognosis or response prediction of patients with HCC.

Table 1. BCLC Staging System

BCLC Stage	ECOG	Tumour Characteristics	Child-Pugh Stage	Prognosis
0	0	Single <2cm	A	>5 years
A	0	Single <5cm or ≤3 nodules <3cm	A	>5 years
B	0	Multinodular	A	>2.5 years
C	1-2	Macrovascular invasion, extrahepatic spread	A	>2 years
D	3-4	any	B9 – C	3 months

Notably, the BCLC classification might be less accurate in Asian patients with a distinct etiological background. An alternative classification, the Hong Kong Liver Cancer Staging System (HKLC), has been recently introduced and might be more accurate in predicting survival of affected Asian patients (Yau 2014). Several other classification schemes to predict prognosis of patients have been introduced over the recent years. Particularly relevant for both prognosis as well as stage-dependent response to therapy is the so-called ALBI score that combines serum albumin and bilirubin. Validity of the score could be confirmed in geographically distinct cohorts of patients as well as different disease stages (Johnson 2015).

Treatment allocation according to the BCLC staging system

The BCLC staging systems provides guidance for the choice of treatment in HCC patients (Figure 1) as outlined in more detail below. However, many patients do benefit from treatment strategies that do not strongly adhere to the staging system. More specifically, curative treatment options might not be available for all patients with very early or early HCC due to tumour or patient characteristics. In these cases, locoregional treatment options

can be more suitable and offer good tumour control. Likewise, in patients with intermediate stage HCC (BCLC B) vascular anatomy might preclude the use of intraarterial therapies and justify systemic treatment, as does insufficient response to locoregional treatment approaches. On the other hand, superior response to systemic or locoregional treatments might deem tumours confined to the liver resectable and therefore amenable for curation in BCLC B patients. The adaptation of BCLC treatment recommendations to individual tumour characteristics have been recognised as the concept of "stage migration" and highlight the importance of an individualised therapy tailored to each HCC patient (Reig 2022).

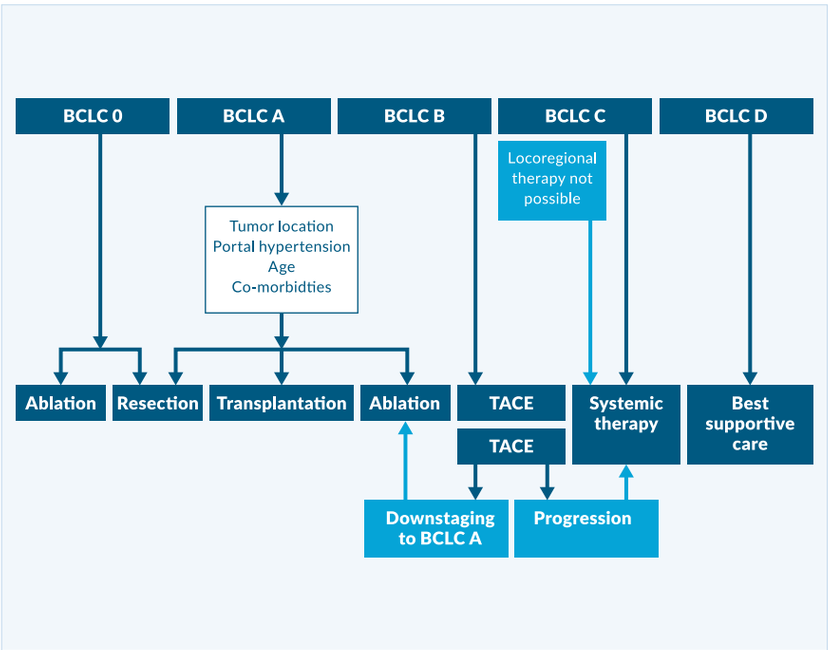

Figure 1. BCLC treatment algorithm for HCC

Curative treatment approach in BCLC stages 0-A

Established curative treatment approaches in HCC include surgical resection, liver transplantation and local ablation of tumour nodules. The choice of treatment depends on multiple factors that include size and location to the tumour, presence of multifocal lesions, liver function and liver functional reserve, presence of portal hypertension, age, performance status, and any medical preconditions that might influence the therapeutic outcome for a certain procedure.

Surgical resection

In BCLC stages 0 and A, resection is the therapy of choice as long as complete removal of the tumour(s) is possible and save for the patient, i.e., liver function is preserved. Additionally, tumours beyond Milan criteria can be evaluated for surgery if there is no evidence of metastasis or macrovascular invasion. Especially in non-cirrhotic HCC patients, extensive resections are possible due to the comparatively large functional reserve of the remaining liver (Zhou 2014). In general, tumour growth beyond the liver and the presence of extrahepatic metastases are strong indicators of a poor prognosis and high recurrence rates. Therefore, patients with these more advanced tumours should not be considered for surgery.

Recent advances in locoregional and systemic therapies have resulted in an increasing percentage of patients with an excellent tumour response – rendering previously unresectable tumours suitable for potentially curative surgery in many cases. The term conversion therapy has been established for this relatively novel treatment strategy in HCC. However, the benefits of this approach are still considered as controversial since reliable outcome predictors are lacking (Sun 2021). Especially in more advanced tumour stages such as those tumours with macrovascular invasion, further studies are needed to identify tumour characteristics that can predict which patients will benefit from conversion therapy.

Reduced functional liver reserve after resection remains the main predictor of peri-operative mortality in HCC patients with liver cirrhosis. The extend of resection that is feasible and save for the patient depends on liver function and the presence of portal hypertension. Reduced platelets (< 100, 000/µl), increased liver stiffness (> 12-14 kPa), and mildly impaired liver function (MELD ≥ 9 and/or reduced hepatic indocyanine green kinetics (ICG test)) are non-invasive predictors of an increased risk for post-operative hepatic decompensation or even liver failure. Similarly, the presence of oesophageal varices or an increased hepatic venous pressure gradient (HVPG > 10 mmHg) is associated with an unfavourable outcome after surgery. In these patients, only minor liver resections of <3 segments should be performed (Citterio 2016). In patients with a more severely impaired liver function (Child-Pugh B or above), even small surgical resections cannot be considered as save and are associated with a high mortality.

Despite these challenges, the boundaries set by liver cirrhosis have been pushed towards more extensive surgeries in the recent years. Minimal-invasive resections are associated with lower complication and mortality rates in comparison to open resections while displaying comparable recurrence and survival rates (Andreou 2018). Thus, minimal-invasive approaches should be implemented whenever feasible. In addition, preserving liver function remains a key prognostic factor in surgery in HCC

patients. Extra-anatomic versus anatomic resections save liver parenchyma but might be associated with a higher rate of tumour recurrence as part of the tumour-bearing portal region remains in situ (Jiao 2020). Additionally, techniques to increase the functional reserve of the future liver remnant have been successfully used in patients with and without liver cirrhosis. Among those, pre-operative portal vein embolisation and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) are established techniques. However, due to the high mortality rate of up to 30%, these approaches should be only a considered in selected patients (Allaire 2020).

Even though surgical resection is considered as a curative treatment approach, recurrence rates are high with a global 5-year recurrence-free survival of only approx. 35% and a limited overall survival of less than 60%, respectively (Reveron-Thornton 2022). Tumour recurrence rates are associated with larger size and number of tumour nodules as well as poor differentiation, the presence of microvascular invasion, and high alpha-fetoprotein levels. Current guidelines recommend follow-up of HCC patients after surgery as most recurrent tumours are amenable to treatment (European Association for the Study of the Liver 2018). Most HCC recurrences are intrahepatic, and many centres implement CT or MRI imaging every 3 – 6 months after resection for 2 years or longer, though recommendations for follow-up vary between guidelines.

Liver transplantation

Liver transplantation should be considered in all patients with unresectable HCC within Milan criteria (BCLC A) as long as there are no contraindications. Even in cirrhotic patients after curative surgery, liver transplantation might be considered due to the high rate of tumour recurrence. The option for liver transplantation is implemented into most current guidelines as the treatment of choice in early unresectable HCC. However, many patients will not be considered for transplantation due to advanced age or the presence of relevant co-morbidities. While advanced age is not considered as contra-indication for liver transplantation, the overall fitness or "biological age" is still relevant to predict post-operative mortality. However, with a peak HCC incidence at approximately 70 years of age (El-Serag 2011), probability of concomitant cardiovascular disease or secondary malignancies is relevant in this cohort, resulting to the exclusion of many patients from liver transplantation. The rising incidence of HCC in non-alcoholic fatty liver disease is also associated with a higher rate of cardiovascular diseases, diabetes, and severe obesity that can increase the risk of post-operative complications and result in poor long-term outcomes. As a shortage of donor organs presents a challenge in many countries, candidates for liver transplantation are carefully selected and a tight control of any risk factors is mandatory in patients considered for liver transplantation.

Despite these limitations, tumour-related long-term outcome after liver transplantation is excellent, generally exceeding 80% 5-year survival rate, and recurrence rates are low for patients within the Milan criteria (BCLC A) (Mazzaferro 1996). While the size limits of Milan or United Network of Organ Sharing (UNOS) T2 criteria, respectively, have been implemented into transplant guidelines more than 20 years ago, it is now acknowledged that patients with larger tumours and a higher number of tumour nodules will have a comparable outcome to BCLC A patients if tumours meet specific criteria. There are a number of "extended criteria" that focus on identifying patients with tumours beyond Milan criteria but with a low risk of recurrence, most prominently the UCSF criteria (single tumour ≤ 6.5 cm or no more than 3 tumours with the largest one not exceeding 4.5 cm and a combined tumour diameter of no more than 8 cm) and up-to-7 criteria (single tumour ≤ 7 cm or multiple tumours with the sum of the diameter of the larges tumour and the number of tumours ≤ 7). Both lead to an excellent 5-year survival rate of more than 70% after liver transplantation (Mazzaferro 2009, Yao 2001). On the other hand, even patients within Milan criteria might have a high risk of recurrence if they have high AFP levels. Currently, AFP levels > 1, 000 ng/mL (persisting after downstaging) are considered as a contraindication for liver transplantation and some extended criteria include AFP levels into their calculation (Duvoux 2012, Mazzaferro 2018). Even with the development more refined extended criteria, liver transplantation is not considered for patients with macrovascular invasion or even metastasis due an unfavourable cancer biology and poor prognosis after transplantation (Roayaie 2004).

Independent of the initial tumour extent, long waiting times for a donor organ due to organ shortage present a relevant risk for tumour progression in HCC patients (Bhoori 2010). To minimise this risk, locoregional "bridging" therapies such a transarterial chemoembolisation (TACE), radioembolisation, ablation, or stereotactic body radiation (SBRT) are used to prevent tumour progression. Importantly, response to these bridging therapies can be used as a predictor for outcome as good responders are characterised by low recurrence rates after transplant (Beal 2016, Rubinstein 2017). Down-staging of tumours to meat Milan criteria has also been implemented into transplant allocation systems in several countries as outcomes in these patients are comparable to those who were always with Milan criteria (Marrero 2018, Yao 2015).

Even with optimal patient selection, tumour recurrence after transplantation presents an eminent risk. With the lack of adjuvant therapies

in HCC suitable for transplant patients, the choice of immunosuppression has been studied as an influencing factor for tumour recurrence. Inhibitors of mTOR such as sirolimus and everolimus have anti-tumour as wells as immunosuppressive properties. Though no significant survival benefit could be shown in a large randomised controlled trial for the treatment with sirolimus-containing combination therapy (Geissler 2016), several retrospective studies indicate that HCC patients benefit from the use of mTOR inhibitors in combination with reduced calcineurin inhibitors in their immunosuppressive regimen (Yan 2022). Due to considerable side effects such as thrombosis of the hepatic artery and impaired wound healing, mTOR inhibitors should not be started earlier than one month after liver transplantation.

With limited evidence for standardised follow-up imaging for tumour recurrence, sonography as well as CT or MRI might be used for up to 5 years after transplant depending on the individual recurrence risk based on explant histology.

Ablation

Thermal ablation is an alternative treatment approach with curative intent that is considered equal to surgical resection in smaller tumours of up to 2 cm (Wang 2014). However, ablation leads to lower recurrence-free and overall survival rates in larger tumours (Shin 2021, Uhlig 2019). During procedures using thermal ablation, a probe is inserted into the tumour under CT or ultrasound guidance with subsequent destruction of tumour tissue by heat. Radiofrequency ablation (RFA) and microwave ablation (MWA) are both thermo-ablative techniques with comparable outcome. Recurrence from tumour margins and a cooling effect from adjacent large blood vessels that are believed to counteract ablation – commonly called the "heat sink" phenomenon – both likely contribute to inferior outcome of ablation in comparison to surgical resection in tumours larger than 15 mm (Kang 2018). Additionally, tumour location is important and not all tumours are eligible for ablation: tumour nodules close to the hilus or to heat-sensitive organs such as the gall bladder or colon are not ideal candidates for ablation. However, treatment in most subcapsular nodules is safe and efficient (Kang 2016).

As ablation seems to be well tolerated even in cirrhotic patients or patients with a high perioperative risk profile, this approach can also be considered in in larger tumours up to 5 cm in cases where the risk of surgery is high. In addition to an adequate safety margin in ablation, a combination of TACE and ablation improves recurrence-free and overall survival in lesions up to 7 cm in comparison to RFA alone (Peng 2013).

Other techniques that are less commonly used and are often technically challenging are cryoablation, irreversible electroporation (IRE), laser induced thermal therapy (LITT), and high-intensity focused ultrasound (HIFU). Though data from controlled trials is limited, efficiency might be comparable to RFA and MWA in smaller tumours (Qian 2021). In centres experienced in these techniques, they can present alternative treatment strategies when thermal ablation is not possible.

Adjuvant therapy

Until recently, there was no sufficient evidence for a benefit of an adjuvant therapy after curative resection. Prophylactic TACE after resection that targets the resection margins is primarily applied in some centres in China, but only selected patients seem to benefit from this approach and there no data from controlled studies so far (Wang 2021). The randomised controlled phase 3 STORM-trial showed no benefit of adjuvant Sorafenib in a large patient cohort after curative ablation or resection (Bruix 2015). The first phase 3 trial in adjuvant treatment of HCC that met its primary endpoint is the IMbrave 050 trial that investigated an adjuvant combination therapy with atezolizumab and bevacizumab in HCC patients with high-risk of recurrence after ablation or resection (Qin 2023). In this study, post-operative or post-interventional treatment with atezolizumab and bevacizumab in patients with high-risk tumours (tumour size >5 cm, more than 3 tumours, presence of microvascular invasion or limited macrovascular invasion, and/or poor tumour differentiation) significantly improved recurrence-free survival in comparison to placebo. In addition, results from several trials investigating adjuvant immunotherapy are currently pending. Importantly, adjuvant immunotherapies should strictly be avoided after liver transplantation due to the high risk of fatal rejection.

Locoregional therapies in BCLC stages B and C

For large or multinodular tumours that cannot be treated by surgery, several locoregional therapies, which can achieve long-term disease control, are used for palliative treatment. In BCLC stage B, improvements in locoregional and systemic therapies have led to an increase in survival to > 2.5 years (Reig 2022). In selected cases such as limited macrovascular invasion in tumours confined to the liver, patients with BCLC C stage HCC can also benefit from locoregional therapies. However, with the availability of highly efficient systemic therapies, locoregional treatments are now less commonly used in advanced HCC.

TACE and DEB-TACE

TACE is considered the gold standard in the treatment of intermediate stage HCC. Several trials report a survival benefit in comparison to symptomatic treatment (Llovet 2002). Though treatment protocols are poorly standardised, a combination of chemotherapy and embolising agent delivered through transarterial catheter into the liver presents the cornerstone of all TACE procedures. Chemotherapeutic agents commonly used in conventional TACE – or cTACE – are doxorubicin, epirubicin or cisplatin which are injected in an emulsion containing lipiodol, an iodised oil with embolising properties (Lencioni 2016), and can be combined with other embolising agents. As an alternative approach, TACE can also be performed with drug-eluting beads (DEB-TACE), where chemotherapeutic agents are bound to embolic microspheres and slowly released into the tumour microenvironment. While initially developed to reduce systemic exposure to chemotherapeutic agents, several studies now indicate that clinical outcomes of cTACE and DEB-TACE are comparable (Gao 2013).

Unselective TACE is associated with a higher rate of side effects – most prominently a decrease in liver function and post-embolisation syndrome with fever and abdominal pain. Thus, selective and supra-selective TACE are now the standard of care. Treatment should be applied as selectively as possible to target tumour-feeding vessels while protecting surrounding liver tissue from ischemic injury (European Association for the Study of the Liver 2018). TACE is most effective in limited multinodular disease. Depending on the size of the tumour, TACE treatment can be repeated several times with the goal of complete devascularisation of the tumour. In patients with insufficient response to TACE – defined by tumour growth despite TACE or occurrence of multiple new intrahepatic lesions indicative of rapid tumour progression – treatment should be discontinued and a switch to systemic therapies is recommended.

Transarterial Radioembolisation (TARE)

TARE or selective internal radiotherapy (SIRT) presents an alternative intraarterial treatment with results comparable to TACE in intermediate stage HCC (Brown 2022, Kolligs 2015). A more recent phase II trial even showed improved time to progression and overall survival in patients treated with TARE in comparison to those treated with DEB-TACE (Dhondt 2022). However, TARE should not be used in advanced HCC, since several large trials showed no improvement in overall survival compared to systemic treatment with sorafenib and the emerging systemic treatment modalities in this stage (Chow 2018, Vilgrain 2017). Radioembolisation is usually performed using glass or resin microspheres loaded with yttrium-90 (90Y). Microspheres are delivered via the hepatic artery and emit high-energy beta-particles with a half-life of 64 hours. For adequate dosimetry and to exclude relevant misplacement of microspheres into non-tumour tissue within and outside the liver, angiographic evaluation using 99mTc macro-aggregated albumin (99mTc-MAA) is performed prior to TARE. A more recent development is the use of Holmium-166 (166Ho) coated microspheres. 166Ho is a beta-emitting radionuclide which also emits gamma photons – a characteristic that allows the use of the 166Ho microspheres for dosimetry at lower doses (Weber 2022). Similar to TACE, radioembolisation aims to target tumour nodules as selectively as possible, sparing non-tumourous liver tissue while applying high and if achievable ablative doses of the radionuclide to the tumour. In selected cases – especially when resection or ablation are not possible in smaller tumours – delivery of ablative doses to the tumour bearing segment can be used with a curative intent (SIRT segmentectomy). Treatment of a large volume of non-tumourous liver should be avoided as it poses a higher risk of radiation-induces liver disease (REILD) and of a long-term decrease in liver function. However, if one or more tumour nodules are restricted to one liver lobe, delivery of high-radiation doses can induce hypertrophy of the untreated lobe with a latency of several months. This approach can be used for downstaging may enable resection of the tumour in selected patients (Salem 2023).

Stereotactic body radiation therapy (SBRT)

Radiation therapies take advantage of the comparatively high radiation sensitivity of hepatocellular carcinoma. SBRT allows for focal delivery of high radiation doses to individual tumours. Due to the lack of randomised controlled trials, SBRT is not recommended as a fist line therapy in most guidelines. However, it can present an alternative treatment option if ablation is not possible. SBRT has shown excellent local control rates of >90% and an overall survival >70% after 3 years in smaller HCC <6cm in a meta-analysis of several observational studies (Long 2021) and seems to be relatively well tolerated in patients with impaired liver function (Feng 2018). Additionally, SBRT can be used as bridging to liver transplant in cases where tumours are not amenable for or do not respond to TACE or ablation. In addition to SBRT, other radiation-based therapies are currently under investigation such as brachytherapy and proton beam therapy, which are available at selected centres.

Systemic therapy in BCLC stage C

Historic view on systemic treatment options – the era of multi-tyrosine kinase inhibitors

Sorafenib – The gold standard in first-line therapy for more than 10 years

Until 2007, no effective treatments for patients diagnosed with advanced HCC or patients who progressed to this stage after failure of other therapies were available. The positive results of the randomised, controlled phase III SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol) trial evaluating sorafenib, an oral multi-tyrosine kinase inhibitor (TKI) with activity against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and RAF kinase for advanced HCC in a mainly Western cohort provided first evidence for the efficacy of anti-angiogenetic strategies in advanced HCC (Llovet 2008). Median OS in the sorafenib arm was 10.7 months versus 7.9 months in placebo-treated patients (hazard ratio [HR] 0.69; 95% CI 0.55–0.87; p = 0.00058). Similar results were not only demonstrated in a parallel phase III study involving mainly Asian, predominantly hepatitis B-infected patients, but also in eight subsequent phase III studies in which sorafenib served as the control treatment (Cheng 2009, Llovet 2021). On the basis of the positive results from both trials, sorafenib was approved and became the systemic standard of care across different therapeutic lines. Importantly, none of the following phase III trials could demonstrate superiority over sorafenib until recently. Although currently no predictive biomarkers for response exist, several clinical factors including chronic hepatitis C infection or side effects including early dermatological events or hypertension favour a better response to the treatment (Bruix 2019). Despite approval for all stages of liver disease, large non-interventional observational studies have shown that the survival of patients with CHILD class B cirrhosis is significantly shorter than those of patients with CHILD A cirrhosis. Since these studies did not provide conclusive evidence for a benefit in patients with severely impaired liver function, the use of sorafenib should in general be limited to patients with compensated stages of cirrhosis.

Lenvatinib – REFLECT Trial

Lenvatinib is another oral multi-tyrosine kinase inhibitor with activity against VEGFR1–3, fibroblast growth factor receptor (FGFR) 1–4, PDGF, RET and KIT. An open-label phase III study involving mainly Asian patients was conducted to demonstrate non-inferiority of lenvatinib in comparison with sorafenib in a first-line setting (Kudo 2018). The study reached its primary endpoint with a median OS of 13.6 months in the experimental lenvatinib arm versus 12.3 months in the sorafenib arm (HR 0.92; 95% CI 0.79–1.06). An interesting observation of this trial was the high objective response rate (ORR) for lenvatinib with 24.1% versus 9.2% for sorafenib despite the similar OS. Further, surrogate characteristics for survival such as progression-free survival (PFS) and time to progression (TTP) were consistently higher in the lenvatinib arm than in the sorafenib arm (PFS: 7.4 months vs 3.7 months; TTP: 8.9 months vs 3.7 months). Adverse effects were overall slightly more pronounced in lenvatinib-treated patients, particularly hypertension and thrombocytopenia. Importantly, the study excluded patients with adverse prognostic tumour characteristics such as main branch portal vein thrombosis or tumours involving > 50% of the liver. Nevertheless, results from the trial encouraged the use of lenvatinib as an effective first-line alternative in advanced HCC, leading to its inclusion in recent EASL and European Society for Medical Oncology (ESMO) guidelines.

Compounds in first-line treatment with no therapeutic benefits in phase 3 trials

Following the approval of sorafenib, several other first-line substances have been tested either against sorafenib (brivanib, linifanib, sunitinib) or in combination with sorafenib (sorafenib plus erlotinib, sorafenib plus doxorubicin). Despite positive signals from phase II trials, none of the studies achieved their primary endpoint and demonstrated a meaningful survival benefit over sorafenib alone.

A new era of therapies – first-line immunotherapy with checkpoint inhibitor monotherapy and combination therapy

The recent advances in immune-oncological therapies spiked great hopes for their efficacy for treatment of HCC patients. In the first large phase III study, the so-called Checkmate-459 study, monotherapy with nivolumab (anti-PD-1 antibody) was tested in comparison to sorafenib in patients with advanced HCC in first-line therapy (Yau 2022). Although an improved survival of 16.4 months versus 14.7 months was achieved, the study did not reach statistical significance and missed its primary endpoint (hazard ratio 0.85 [95% confidence interval (CI) 0.72-1.02]; p=0.075). Based on the results of the trial, it was reasonable to assume that monotherapy with a checkpoint inhibitor might not be sufficiently effective in HCC. Accordingly, subsequent studies targeted combination of immune-oncology (IO) therapy

with different partners. Combinations of dual immunotherapy combining PD-1/PD-L1 and CTLA4, immunotherapy with anti-VEGF antibodies or TKIs are currently investigated (Heinrich 2018). The recently concluded IMbrave 150 trial (Finn 2020) investigated the combination of the PD-L1 antibody atezolizumab (Atezo) and the VEGF antibody bevacizumab (Bev). Treatment with the new combination resulted in an overall survival of 19.2 versus 13.2 months with sorafenib (HR 0.58) and prolonged progression-free survival (6.8 months with Atezo/Bev vs. 4.3 months with sorafenib; HR 0.59). Following FDA and, subsequently, EMA approval in November 2020, the combination with Atezo/Bev is now the new standard of care in first-line systemic therapy for eligible patients with advanced HCC (Figure 2). A key advantage of the new combination therapy is that it is usually very well tolerated in clinical practice and maintains patients' quality of life for a long time. However, the risk of bleeding, especially fulminant bleeding from oesophageal varices, represents a serious clinical challenge. Thus, a thorough screening should be obligatorily before therapy initiation. Of note, a necessary variceal ligation prior to therapy initiation may delay the start of systemic therapy and potentially cause tumour progression. Hence, lenvatinib and sorafenib remain important alternative treatment options in non-eligible patients, i.e., following liver transplantation or uncontrolled autoimmune disease (Figure 2).

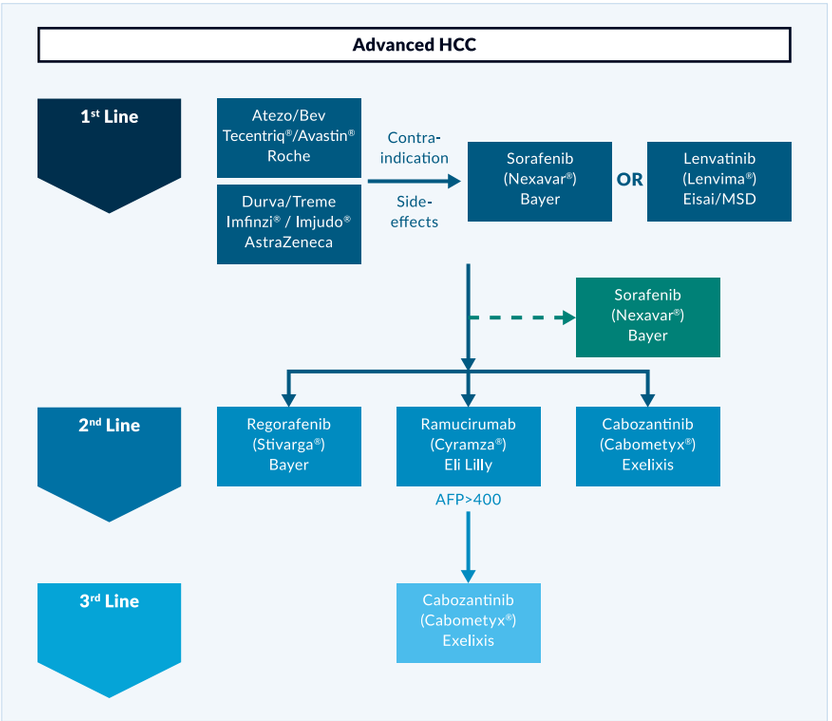

Figure 2. Systemic treatment lines in advanced HCC

In the recent phase III HIMALAYA trial, both combination therapy of the PD-L1 inhibitor durvalumab (anti-PD-L1 antibody) in combination with a single dose of tremelimumab (antibody against cytotoxic T-lymphocyte-associated protein 4) were investigated in the so-called STRIDE protocol (Single Tremelimumab Regular Interval Durvalumab) in first-line treatment of advanced HCC as well as durvalumab monotherapy against a comparator arm with the previous standard of care sorafenib. Initial results of the trial were presented at the ASCO-GI Congress in January 2022 (https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070). Median overall survival was 16.43 months (95% CI, 14.16 – 19.58) with STRIDE, 16.56 months (95% CI, 14.06 – 19.12) with durvalumab, and 13.77 months (95% CI, 12.25 – 16.13) with sorafenib. The hazard ratio for STRIDE versus sorafenib was 0.78 ($p = 0.0035$) and survival with durvalumab mono was non-inferior to therapy with sorafenib (HR 0.86). In terms of adverse events, combination therapy also showed a significant improvement in patients' quality of life compared with sorafenib. The combination was approved by the FDA in the United States in October 2022, followed by EMA approval in the EU in February 2023. The results of the Himalaya study, thus, underscore the efficacy of IO combination therapy for HCC.

Besides the combination of anti-VEGF and PD-1/PD-L1 inhibitor and immunotherapy combinations, other strategies involve the combination of TKI and PD-1/PD-L1 inhibitors. The role of the combination is currently unclear and has to be demonstrated in future clinical phase III trials (Llovet 2022).

Second-Line Therapies
Regorafenib – RESORCE Trial

Regorafenib is an oral TKI, that is structurally a fluorinated sorafenib analogue with a similar spectrum of molecular targets. Besides a profound anti-proliferative effect on the tumour cells, regorafenib significantly inhibits neo-angiogenesis and, thus, modulates the tumour microenvironment. The randomised controlled RESORCE phase III trial evaluated the role of regorafenib in patients with advanced HCC that progressed under sorafenib therapy (Bruix 2017). The main inclusion criteria were a preserved liver function (CHILD A), progressive disease under sorafenib as well as tolerability to sorafenib (defined as receiving sorafenib ≥ 400 mg for at least 20 days of the last 28 days of treatment). The study further rigorously stratified for region, portal-vein thrombosis, alpha-fetoprotein (AFP) levels and extrahepatic tumour manifestation. This highly selective strategy was performed to avoid toxicity and unequal distribution of prognostically adverse characteristics. The study reached its primary endpoint and

demonstrated a significantly improved OS for regorafenib (10.6 months) versus placebo (7.8 months) (HR 0.63; 95% CI 0.50–0.79; p < 0.0001) as well as an increase in the median TTP (3.2 months vs 1.5 months; HR 0.44; 95% CI 0.36–0.55; p < 0.001). In addition, regorafenib significantly extended the tumour control rates as well as ORR. The spectrum of adverse events was comparable to side effects described for sorafenib, including hypertension, hand-foot syndrome, fatigue, and diarrhoea, but were overall manageable. Based on the results of the RESORCE trial, regorafenib was approved by the FDA and the EMA in patients with advanced HCCs previously treated with sorafenib. Notably, a retrospective evaluation of the sequential treatment effect of sorafenib followed by regorafenib revealed a median OS from the beginning of the systemic therapy of 26 months versus 19.6 months for placebo (Finn 2018). These data obtained in a well selected patient population provided, for the first time, evidence that sequential application of systemic therapies in Barcelona Clinic Liver Cancer-stage C (BCLC C) patients can reach comparable survival times observed in phase III trials of TACE in BCLC-B patients. Thus, a sequential treatment strategy should be prospectively implemented and evaluated in suitable patients (Marquardt 2019).

Cabozantinib – CELESTIAL Trial

Cabozantinib is another oral multi-tyrosine kinase inhibitor with activity against MET, VEGFR2, and RET. Following its approval for the treatment of thyroid and renal cell carcinomas by both the EMA and the FDA, cabozantinib has most recently been granted approval as a second-line treatment in HCC Child–Pugh A patients by the EMA and the FDA (Abou-Alfa 2018). The phase III CELESTIAL trial compared the benefit of cabozantinib (60 mg daily) with placebo in second- and third-line treatment for advanced HCC with preserved liver function and good performance status (i.e., Child–Pugh A, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0/1). The study was stopped after the second interim analysis due to proven efficacy. Overall, an improvement in OS from 8.0 months to 10.2 months could be demonstrated for cabozantinib compared with placebo. Mean PFS was 5.4 months versus 1.9 months (HR 0.44; 95% CI 0.36–0.52; p < 0.001). Further, the disease control rate was 64% for cabozantinib versus 33.4% in placebo (p < 0.001) with a low ORR rate of 4% versus 0.4% according to RECIST 1.1 (p = 0.0086). Similar to the other TKIs, grade 3/4 side effects occurred in 68% of patients and predominantly involved hand-foot syndrome (17 vs 0%), hypertension (12 vs 2%), transaminase elevation (12 vs 7%), and fatigue (10 vs 4%). Interestingly, nearly 30% of patients in the study had received more than one pre-treatment, albeit most of these patients had been treated with chemotherapy in addition to sorafenib. Nevertheless, the results of the CELESTIAL study suggest that cabozantinib could also have a place in later therapy lines (Figure 2). Interestingly, a recent analysis confirmed the efficacy of cabozantinib over placebo in patients with different AFP levels, but most prominently in patients with AFP levels ≥ 400 ng/mL, which determines a poor prognosis subgroup of patients. In this cohort, the median OS was 8.5 months compared with 5.2 months with cabozantinib or placebo, respectively (HR 0.71; 95% CI 0.54–0.94) [21].

Ramucirumab – REACH-2

Ramucirumab is a recombinant monoclonal antibody that specifically binds to the VEGFR2 domain, thereby preventing the binding of VEGF ligands. Similar to other compounds, such as sunitinib and brivanib, ramucirumab initially showed promising results in a small phase II study for advanced HCC (Nault 2018). Based on these results, the randomised controlled phase III REACH study was initiated as a second-line therapy after sorafenib failure (Zhu 2015). However, the REACH study failed to demonstrate a significant improvement in median OS for all patients and did not meet its primary endpoint. Despite these initial discouraging results, a subgroup analysis suggested that ramucirumab improves survival in patients with elevated baseline AFP levels above 400 ng/mL. Subsequently, the REACH II study was initiated in this patient population (Zhu 2019). In this selected cohort, ramucirumab improved the median OS from 7.3 months to 8.5 months versus placebo (HR 0.710; 95% CI 0.53–0.95; p = 0.019) and PFS from 1.6 months to 2.8 months (HR 0.452; 95% CI 0.40–0.60; p < 0.0001). A combined analysis of the REACH I and II study confirmed the survival benefit of ramucirumab compared with placebo (Delta: 3.1 months; HR 0.69; 95% CI 0.57–0.84; p = 0.0002). Thus, ramucirumab is an interesting second-line option in patients with high AFP levels and a poor prognosis. Notably, ramucirumab is the first intravenous, non-TKI drug with proven anti-angiogenetic efficacy in second line for advanced HCC. Accordingly, the side-effect spectrum deviates substantially from multi-tyrosine kinase inhibitors. With respect to grade 3/4 side effects, only hypertension (12.7% vs 3.8%) and proteinuria (1.3% vs 0%) occurred more frequently with ramucirumab compared with placebo.

Several other compounds were evaluated against placebo in second-line settings for advanced HCC. Neither brivanib, everolimus nor tivantinib showed a significant improvement in OS.

Second-line checkpoint inhibitor monotherapy and combination therapy.

Initial evidence on the efficacy of checkpoint inhibition with pembrolizumab in the second-line setting after failure or intolerance of lenvatinib were revealed by the KEYNOTE-224 trial (Zhu 2018). Building on the results of this trial, the phase III KEYNOTE-240 trial was initiated (Finn 2019). Despite a significantly improved OS (13.9 months for pembrolizumab compared with 10.6 months for placebo (HR: 0.781; 95% CI: 0.611 to 0.998; p = 0.0238), the study did not reach the prespecified significance level and is, therefore, formally negative, despite showing comparable benefit to the phase II study and clear clinical benefit in terms of durable response in patients who responded to treatment.

The single-arm phase 1/2 CheckMate 040 study evaluated the combination of nivolumab and ipilimumab (El-Khoueiry 2017). The study included patients previously treated with sorafenib for advanced HCC were randomised to 3 treatment arms: arm 1: nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks; arm 2: nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks; and arm 3: nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks. The primary endpoints were safety and tolerability, and secondary endpoints included ORR, DOR, DCR, and OS. In arm 1, ORR was 31%, with 7 patients achieving complete tumour response; OS was 23 months. The combination was well tolerated, with 37% treatment-related grade 3/4 adverse events (mostly pruritus and rash). Based on the results of this phase 1/2 study, the nivolumab-ipilimumab combination received accelerated approval from the FDA, but has not received approval from the EMA.

Agent	Type	Line	FDA	EMA
Nivolumab	Anti-PD-1	2L	09/2017	–
Pembrolizumab	Anti-PD-1	2L	11/2018	–
Atezolizumab (in combination with Bevacizumab)	Anti-PD-L1	1L	05/2020	11/2020
Ipilimumab (in combination with Nivolumab)	Anti-CTLA-4	2L	3/2020	–
Durvalumab (in combination with Tremelimumab)	Anti-PD-L1	1L	10/2022	02/2023

Table 2. Approved immunotherapies for advanced HCC

Supportive therapy in end-stage liver disease – BCLC stage D

Maintaining liver function is the key dogma in HCC and constitutes the most significant prognostic factor. Irrespective of the treatment modality, clinical outcomes are undoubtfully better in patients with preserved liver function. Thus, any treatment that can result in a decrease in liver function, such as unselective TACE or TARE, might – even if temporally tolerated – diminish long-term outcome. In systemic therapy with sorafenib, Child-Pugh B patients have a poorer outcome compared to patients with preserved liver function (Child-Pugh A) and are more likely to discontinue treatment due to side effects (Marrero 2016). If these findings hold true in combination immunotherapies that are better tolerated than sorafenib remains to be investigated. More recent evidence indicates that systemic therapy with atezolizumab and bevacizumab is reasonably tolerated in Child-Pugh B patients and there is currently no rational to withhold treatment from this subset of patients (D'Alessio 2022).

Nevertheless, treatment of liver cancer should be mostly restricted to patients with preserved liver function. For this reason, terminal stage HCC (BCLC D) is not defined by tumour size or extension, but rather by presence of severely impaired liver function (Child-Pugh C). In this subset of patients, survival is believed to depend on liver function und is estimated to be shorter than 3 months. Therefore, these patients should only receive supportive therapy as any tumour-directed treatments will not result in a survival benefit but, conversely, reduce liver function even further. As a more accurate predictor of liver functional reserve in HCC patients, the ALBI score – which is calculated from albumin and bilirubin levels – has been developed. ALBI grade 3 corresponds to an impaired liver function and as in Child-Pugh C patients, no benefit from tumour-specific therapies can be expected (Pinato 2017). Needless to say, an exception from this rule are patients awaiting liver transplantation. In those patients, control of the tumour is more important than a decrease in liver function as long as the patient remains fit for transplant.

Key points

- The majority of HCC develop in cirrhotic or fibrotic livers – with alcohol abuse, chronic viral hepatitis, and non-alcoholic fatty liver disease (NAFLD) presenting the main risk factors for cirrhosis and HCC development.
- HCC diagnosis in cirrhotic livers can be based on characteristic imaging criteria, but histological confirmation of HCC is recommended in palliative cases.
- The BCLC treatment algorithm is the backbone of stage-adapted HCC therapy in the Western world.
- Curative treatment options in very early (BCLC 0) and early (BCLC A) HCC include resection, ablation, and liver transplantation.
- Locoregional treatment approaches including transarterial chemoembolisation (TACE) and transarterial radioembolisation (TARE) are used in multifocal HCC confined to the liver (intermediate stage HCC, BCLC B)
- In advanced stage HCC – characterised by macrovascular tumour invasion and/or metastatic spread (BCLC C) – systemic combination immunotherapies present the standard of care in first line treatment, while different tyrosine kinase inhibitors are available as alternative or second line therapeutic options.
- All tumour-directed therapies should be restricted to patients with preserved liver function.

References

Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018;379(1):54-63.

Allaire M, Goumard C, Lim C, Le Cleach A, Wagner M, Scatton O. New frontiers in liver resection for hepatocellular carcinoma. JHEP Rep. 2020;2(4):100134.

Andreou A, Struecker B, Raschzok N, et al. Minimal-invasive versus open hepatectomy for hepatocellular carcinoma: Comparison of postoperative outcomes and long-term survivals using propensity score matching analysis. Surg Oncol. 2018;27(4):751-758.

Aube C, Oberti F, Lonjon J, et al. EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. Liver Int. 2017;37(10):1515-1525.

Beal EW, Dittmar KM, Hanje AJ, et al. Pretransplant Locoregional Therapy for Hepatocellular Carcinoma: Evaluation of Explant Pathology and Overall Survival. Front Oncol. 2016;6:143.

Bhoori S, Sposito C, Germini A, Coppa J, Mazzaferro V. The challenges of liver transplantation for hepatocellular carcinoma on cirrhosis. Transpl Int. 2010;23(7):712-722.

Brown AM, Kassab I, Massani M, et al. TACE versus TARE for patients with hepatocellular carcinoma: Overall and individual patient level meta analysis. Cancer Med. 2022.

Bruix J, da Fonseca LG, Reig M. Insights into the success and failure of systemic therapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2019;16(10):617-630.

Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.

Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015;16(13):1344-1354.

Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25-34.

Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018;36(19):1913-1921.

Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic Interaction of Factors Associated With Liver Decompensation After Resection for Hepatocellular Carcinoma. JAMA Surg. 2016;151(9):846-853.

D'Alessio A, Fulgenzi CAM, Nishida N, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: A real-world study. Hepatology. 2022;76(4):1000-1012.

Dhondt E, Lambert B, Hermie L, et al. (90)Y Radioembolisation versus Drug-eluting Bead Chemoembolisation for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomised Controlled Trial. Radiology. 2022;303(3):699-710.

Di Martino M, De Filippis G, De Santis A, et al. Hepatocellular carcinoma in cirrhotic patients: prospective comparison of US, CT and MR imaging. Eur Radiol. 2013;23(4):887-896.

Di Tommaso L, Destro A, Seok JY, et al. The application of markers (HSP70 GPC3 and GS) in liver biopsies is useful for detection of hepatocellular carcinoma. J Hepatol. 2009;50(4):746-754.

Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology. 2012;143(4):986-994 e983; quiz e914-985.

El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017.

El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365(12):1118-1127.

European Association for the Study of the Liver E. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.

Feng M, Suresh K, Schipper MJ, et al. Individualised Adaptive Stereotactic Body Radiotherapy for Liver Tumors in Patients at High Risk for Liver Damage: A Phase 2 Clinical Trial. JAMA Oncol. 2018;4(1):40-47.

Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021.

Finn RS, Merle P, Granito A, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. J Hepatol. 2018;69(2):353-358.

Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-1905.

Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomised, Double-Blind, Phase III Trial. J Clin Oncol. 2019:JCO1901307.

Fuks D, Cauchy F, Fusco G, Paradis V, Durand F, Belghiti J. Preoperative tumour biopsy does not affect the oncologic course of patients with transplantable HCC. J Hepatol. 2014;61(3):589-593.

Gao S, Yang Z, Zheng Z, et al. Doxorubicin-eluting bead versus conventional TACE for unresectable hepatocellular carcinoma: a meta-analysis. Hepatogastroenterology. 2013;60(124):813-820.

Geissler EK, Schnitzbauer AA, Zulke C, et al. Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomised, Multicenter, Open-Label Phase 3 Trial. Transplantation. 2016;100(1):116-125.

Heinrich B, Czauderna C, Marquardt JU. Immunotherapy of Hepatocellular Carcinoma. Oncol Res Treat. 2018;41(5):292-297.

Jiao S, Li G, Zhang D, Xu Y, Liu J, Li G. Anatomic versus non-anatomic resection for hepatocellular carcinoma, do we have an answer? A meta-analysis. Int J Surg. 2020;80:243-255.

Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550-558.

Kang TW, Lim HK, Cha DI. Percutaneous ablation for perivascular hepatocellular carcinoma: Refining the current status based on emerging evidence and future perspectives. World J Gastroenterol. 2018;24(47):5331-5337.

Kang TW, Lim HK, Lee MW, et al. Long-term Therapeutic Outcomes of Radiofrequency Ablation for Subcapsular versus Nonsubcapsular

Hepatocellular Carcinoma: A Propensity Score Matched Study. Radiology. 2016;280(1):300-312.

Khalili K, Kim TK, Jang HJ, et al. Optimisation of imaging diagnosis of 1-2 cm hepatocellular carcinoma: an analysis of diagnostic performance and resource utilisation. J Hepatol. 2011;54(4):723-728.

Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomised trial of selective internal radiation therapy vs. chemoembolisation in unresectable hepatocellular carcinoma. Liver Int. 2015;35(6):1715-1721.

Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-1173.

Labenz C, Arslanow A, Nguyen-Tat M, et al. Structured Early detection of Asymptomatic Liver Cirrhosis: Results of the population-based liver screening programme SEAL. J Hepatol. 2022;77(3):695-701.

Lee YJ, Lee JM, Lee JS, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology. 2015;275(1):97-109.

Lee YT, Wang JJ, Zhu Y, Agopian VG, Tseng HR, Yang JD. Diagnostic Criteria and LI-RADS for Hepatocellular Carcinoma. Clin Liver Dis (Hoboken). 2021;17(6):409-413.

Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolisation for hepatocellular carcinoma: A systematic review of efficacy and safety data. Hepatology. 2016;64(1):106-116.

Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329-338.

Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol. 2022;19(3):151-172.

Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7(1):6.

Llovet JM, Lencioni R. mRECIST for HCC: Performance and novel refinements. J Hepatol. 2020;72(2):288-306.

Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734-1739.

Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390.

Lokuhetty D, White VA, Watanabe R, Cree IA, World Health Organization., International Agency for Research on Cancer. Digestive system tumours. Fifth edition. ed.

Long Y, Liang Y, Li S, et al. Therapeutic outcome and related predictors of stereotactic body radiotherapy for small liver-confined HCC: a systematic review and meta-analysis of observational studies. Radiat Oncol. 2021;16(1):68.

Marquardt JU, Saborowski A, Czauderna C, Vogel A. The Changing Landscape of Systemic Treatment of Advanced Hepatocellular Carcinoma: New Targeted Agents and Immunotherapies. Target Oncol. 2019;14(2):115-123.

Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140-1147.

Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750.

Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35-43.

Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693-699.

Mazzaferro V, Sposito C, Zhou J, et al. Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma. Gastroenterology. 2018;154(1):128-139.

Nault JC, Galle PR, Marquardt JU. The role of molecular enrichment on future therapies in hepatocellular carcinoma. J Hepatol. 2018;69(1):237-247.

Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol. 2016;64(4):800-806.

Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolisation in the treatment of hepatocellular carcinoma: a prospective randomised trial. J Clin Oncol. 2013;31(4):426-432.

Pinato DJ, Sharma R, Allara E, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 2017;66(2):338-346.

Pinero F, Dirchwolf M, Pessoa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. Cells. 2020;9(6).

Piscaglia F, Wilson SR, Lyshchik A, et al. American College of Radiology Contrast Enhanced Ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) for the diagnosis of Hepatocellular Carcinoma: a pictorial essay. Ultraschall Med. 2017;38(3):320-324.

Qian K, Zhang F, Allison SK, Zheng C, Yang X. Image-guided locoregional non-intravascular interventional treatments for hepatocellular carcinoma: Current status. J Interv Med. 2021;4(1):1-7.

Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023.

Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681-693.

Reveron-Thornton RF, Teng MLP, Lee EY, et al. Global and regional long-term survival following resection for HCC in the recent decade: A meta-analysis of 110 studies. Hepatol Commun. 2022;6(7):1813-1826.

Roayaie S, Schwartz JD, Sung MW, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl. 2004;10(4):534-540.

Rubinstein MM, Kaubisch A, Kinkhabwala M, Reinus J, Liu Q, Chuy JW. Bridging therapy effectiveness in the treatment of hepatocellular carcinoma prior to orthotopic liver transplantation. J Gastrointest Oncol. 2017;8(6):1051-1055.

Sahu SK, Chawla YK, Dhiman RK, et al. Rupture of Hepatocellular Carcinoma: A Review of Literature. J Clin Exp Hepatol. 2019;9(2):245-256.

Salem R, Padia SA, Lam M, et al. Clinical, dosimetric, and reporting considerations for Y-90 glass microspheres in hepatocellular carcinoma: updated 2022 recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging. 2023;50(2):328-343.

Shin SW, Ahn KS, Kim SW, Kim TS, Kim YH, Kang KJ. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. Ann Surg. 2021;273(4):656-666.

Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut. 2008;57(11):1592-1596.

Sun HC, Zhu XD. Downstaging Conversion Therapy in Patients With Initially Unresectable Advanced Hepatocellular Carcinoma: An Overview. Front Oncol. 2021;11:772195.

Uhlig J, Sellers CM, Stein SM, Kim HS. Radiofrequency ablation versus surgical resection of hepatocellular carcinoma: contemporary treatment trends and outcomes from the United States National Cancer Database. Eur Radiol. 2019;29(5):2679-2689.

Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18(12):1624-1636.

Voesch S, Bitzer M, Blodt S, et al. Z Gastroenterol. 2022;60(1):e131-e185.

Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400(10360):1345-1362.

Wang L, Lin N, Lin K, et al. The Clinical Value of Postoperative Transarterial Chemoembolisation for Resectable Patients with Intermediate Hepatocellular Carcinoma After Radical Hepatectomy: a Propensity Score-Matching Study. J Gastrointest Surg. 2021;25(5):1172-1183.

Wang Y, Luo Q, Li Y, Deng S, Wei S, Li X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomised and nonrandomised controlled trials. PloS one. 2014;9(1):e84484.

Weber M, Lam M, Chiesa C, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging. 2022;49(5):1682-1699.

Yan X, Huang S, Yang Y, et al. Sirolimus or Everolimus Improves Survival After Liver Transplantation for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Liver Transpl. 2022;28(6):1063-1077.

Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumour size limits does not adversely impact survival. Hepatology. 2001;33(6):1394-1403.

Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumours within Milan criteria. Hepatology. 2015;61(6):1968-1977.

Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022;23(1):77-90.

Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 2014;146(7):1691-1700 e1693.

Zhou Y, Lei X, Wu L, Wu X, Xu D, Li B. Outcomes of hepatectomy for noncirrhotic hepatocellular carcinoma: a systematic review. Surg Oncol. 2014;23(4):236-242.

Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940-952.

Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282-296.

Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859-870.

19. Transplant hepatology: a comprehensive update

Richard Taubert, Theresa Kirchner
(based on the previous issue by Susanne Beckebaum et al.)

Abstract

Liver transplantation (LT) is the only life-saving therapy in patients with advanced liver disease, cirrhosis or acute liver failure. Although LT is a true success story, a multiprofessional team in a specialised centre is needed for patient selection, waiting list monitoring and surveillance after LT. In nowadays new techniques expand the pool of organs in times of organ shortage. Individualised immunosuppression regimes should be used to improve graft and patient survival and to reduce side effects due to immunosuppressive medication. Treatment of recurrence of underlying disease could be challenging.

Hereinafter we will give an overview over indications for LT, pre- and posttransplant patient management, risk factors before and after LT and treatment of complications.

Introduction

Over the past 30 years major advances have been made in the field of organ transplantation due to improvements in surgical techniques and organ conservation as well as optimisation of intensive care and immunosuppressive management. This chapter focuses on important issues in the field of transplant hepatology and may provide helpful information to physicians involved in the care of adult liver transplant (LT) recipients. It includes indications for LT, current organ allocation policy, pretransplant evaluation, management while on the waiting list, living donor liver transplantation (LDLT) and management of early and long-term complications post-LT.

Timing and indications for liver transplantation

Appropriate selection of candidates and timing of LT is crucial in reducing mortality and improving outcomes in LT recipients. A patient

is considered too healthy to undergo LT if the expected survival is longer without surgery. Therefore, criteria are needed in order to select patients with priority for LT who can most benefit from transplantation. In 2002, the Organ Procurement and Transplantation Network along with the United Network of Organ Sharing (UNOS) developed a system based on the model for end-stage liver disease (MELD) (Table 1) to prioritise patients on the waiting list. In the Eurotransplant countries, the Child-Pugh Turcotte (CPT) score was replaced by the MELD score in December 2006.

The lab MELD score using the three laboratory parameters depicted in Table 1 ranges from 6 (less ill) to 40 (severely ill). It estimates mortality in patients with end stage liver disease within 90 days (Kwong 2015). The MELD score is used for candidates 12 years of age or older and the Paediatric End Stage Liver Disease Model (PELD) score is used for patients <12 years of age. The MELD score includes creatinine, total bilirubin and INR, age is added to PELD. In a large study (Merion 2005) looking at the survival benefit of LT candidates, those transplanted with a MELD score <15 had a significantly higher mortality risk as compared to those remaining on the waiting list, while candidates with a MELD score of 18 or higher had a significant transplant benefit.

Table 1. Calculation of the MELD* Score

MELD Score =	10x (0,957 x ln [creatinine mg/dL] + 0,378 x ln [total bilirubine mg/dL] + 1,12 x ln [INR**] + 0,643)

*Model of End-stage Liver Disease, **International Normalised Ratio

The MELD score does not accurately predict mortality in approximately 15-20% of patients. Therefore MELD-based allocation allows exceptions for patients whose score may not reflect the severity of their liver disease. These exceptions include e.g. hepatocellular carcinoma (HCC), nonmetastatic hepatoblastoma, adult polycystic liver degeneration, primary hyperoxaluria type 1, small-for-size syndrome, cystic fibrosis, familial amyloid polyneuropathy, hepatopulmonary syndrome, portopulmonary hypertension, urea cycle disorders, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), hemangioendothelioma of the liver, biliary sepsis, primary sclerosing cholangitis (PSC) and cholangiocarcinoma. Patients with standard exceptions will be assigned a higher MELD score (match MELD) than that assigned by the patient's laboratory test results (lab MELD). Consequently, this resulted in an increasing proportion of patients transplanted for HCC and other exceptions over time (Massie 2011).

MELD has proved to be accurate as a predictor of waiting list mortality, but has shown to be less accurate in predicting posttransplant outcome (Kaltenborn 2015). For instance, MELD allocation resulted in decreased waiting list mortality; whereas posttransplant morbidity has increased due to transplantation of a higher proportion of sicker recipients with MELD scores >30 (Dutkowski 2011). Moreover, the quality of donor organs has been impaired over the last two decades (Schlitt 2011).

Creatinine values exert a systematic bias against women due to their lower creatinine values conditioning a longer waiting time for an organ (Rodríguez-Castro 2014). Thus women are disadvantaged by use of MELD score in terms of access to LT. The question has been raised whether additional candidate characteristics should be explicitly incorporated into the prioritisation of waiting list candidates (Sharma 2012). It has also been suggested to take into account not only pretransplant mortality but also donor-related factors for estimation of the donor risk index (DRI) (Feng 2006) and posttransplant mortality. Furthermore, standardisation of laboratory assays and variants of MELD including incorporation of parameters such as sodium or cholinesterase have been proposed to overcome the limitations of the current scoring system (Choi 2009, Weissmüller 2008, Vitale 2012). The Hong Kong transplant group aimed to establish additional criteria to predict short-term mortality in severe flares of chronic hepatitis B virus (HBV) infection (Fung 2019). Their results revealed that HBV-infected patients with MELD ≥28 should be worked up for LT, and those with MELD 28-32 with 3-4 at-risk criteria (age ≥52 years, ALT >217 U/L, platelets <127, and abnormal baseline imaging), or MELD ≥32 should be listed.

UNOS made a policy change and revised the MELD scoring system on January 11, 2016 by incorporating the serum sodium value (MELD-Na) because patients with hyponatraemia have significantly higher mortality rates compared with those with normal serum sodium levels. But the MELD-Na also appears to disadvantage women in the waiting list. Because of this Wood et al. designed a corrected MELD-Na that eliminates sex disparities (Wood 2021).

Candidates for LT must have irreversible acute or chronic end-stage liver disease. Alcohol-induced liver disease (ALD, 35.2%) and viral infections (34.9%) have been the most common disease indications in adults with liver cirrhosis (https://www.eltr.org) during the last decades (Figure 1). Non-alcoholic fatty liver disease (NAFLD) is a frequent aetiology of liver disease in western countries and has become a leading indication for LT in the United States (US) and Europe; whereas the proportion of transplant waitlist additions for HCV-associated disease has declined since the introduction of interferon-free, direct-acting antiviral (DAA) therapy (Cotter 2019). Data from the UNOS and Organ Procurement and Transplantation Network registry from 2004 through 2013 revealed that the number of adults with non-alcoholic steatohepatitis (NASH) awaiting LT has almost tripled since 2004 (Wong 2015).

Other indications include cholestatic liver disorders (primary biliary

cirrhosis [PBC], PSC), HBV infection, autoimmune hepatitis (AIH), inherited metabolic diseases (Wilson's Disease, haemochromatosis, α-1-antitrypsin deficiency), HCC, and acute or acute-on-chronic hepatic failure. In children, biliary atresia and metabolic liver diseases are the most common indications. Contraindications for LT include extrahepatic malignancies, sepsis, uncontrolled pulmonary hypertension, and coexistent medical disorders such as severe cardiopulmonary condition, technical or anatomical barriers such as thrombosis of the entire portal and superior mesenteric venous system. Previous malignancy history must be carefully considered and likelihood of recurrence estimated. Active alcohol consumption is a relative contraindication, because more and more studies show the life saving effect with acceptable alcohol relapse rates after liver transplantation in severe and refractory manifestations of alcoholic hepatitis in highly selected patients (Mathurin 2011, Lee (c) 2018, Carrique 2021).

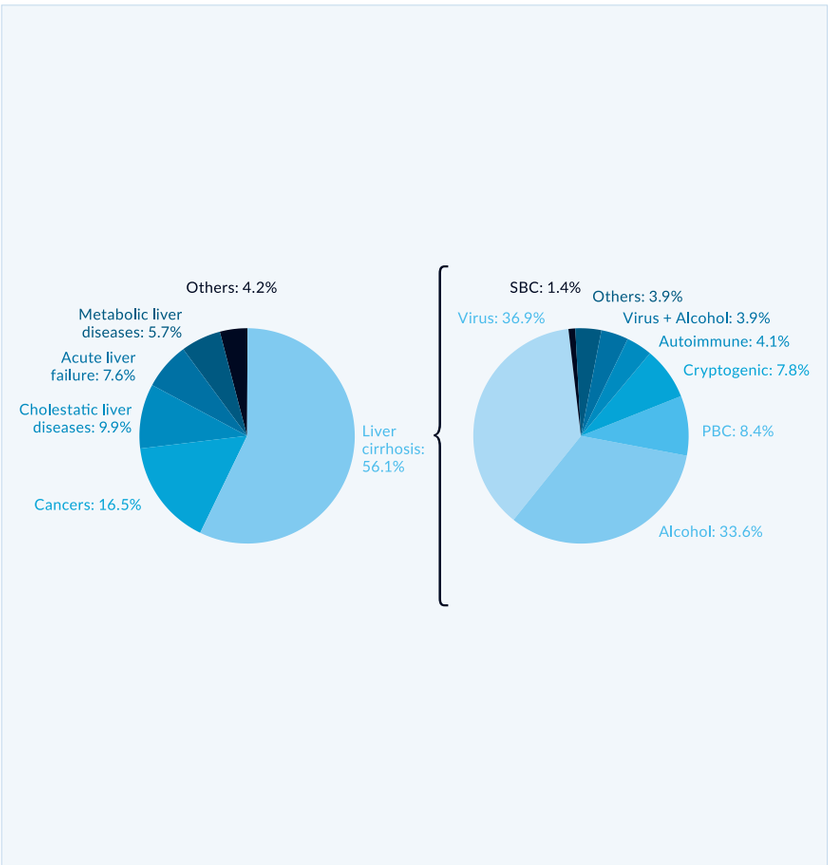

Figure 1. Indications for liver transplantation (LT). Primary diseases leading to LT in Europe, 1988–2015 (Data kindly provided from European Liver Transplant Registry, https://www.eltr.org)

PBC = primary biliary cholangitis **SBC** = secondary biliary cirrhosis

Patient evaluation

Evaluation of a potential transplant candidate is a complex and time-consuming process that requires a multidisciplinary approach. Requirements for evaluation may differ slightly between transplant centres. The evaluation process must identify extrahepatic diseases that may exclude the patient from transplantation or require treatment before surgical intervention. The protocol we use for evaluation of potential transplant candidates is shown in Table 2.

Pretransplant management issues

In cases of recurrent variceal hemorrhage despite prior interventional endoscopic therapy (and non-selective beta-blockade) or refractory ascites, transjugular intrahepatic portosystemic shunts (TIPS) have been used to lower portal pressure and as bridging therapy for transplant candidates. The identification of predisposing factors and medication such as lactulose and rifaximin, a minimally absorbed antibiotic, are effective for prophylaxis and management of hepatic encephalopathy (HE) (Mullen 2014).

Hepatorenal syndrome (HRS) represents a complication of end-stage liver disease and is a risk factor for acute kidney injury (AKI) in the early post-operative phase (Saner 2012). It is classified into type 1 HRS characterised by a rapid impairment of renal function with a poor prognosis; type 2 HRS is a moderate steady renal impairment. Vasoconstrictors including terlipressin in combination with volume expansion are commonly used and have been shown to be effective for restoration of arterial blood flow and serve as bridging therapy to LT (Hinz 2013). Extracorporeal liver support systems based on exchange or detoxification of albumin have been successfully employed in indicated cases.

Beyond MELD, other parameters such as frailty and sarcopenia might be essential to consider suitable patients for the waiting list. Sarcopenia is part of the frailty complex present in cirrhotic patients. According to the operational definition by the European Working Group on Sarcopenia in Older People (EWGSOP), the diagnosis of sarcopenia comprises the presence of both low muscle mass and low muscle function in terms of low muscle strength or low physical performance. Muscle wasting is considered one of the major complications of end-stage liver cirrhosis and may be caused by a variety of factors such as reduced nutrient intake, dietary restrictions in sodium and water in decompensated liver disease, reduced protein intake for hepatic encephalopathy, reduced intestinal absorption secondary to maldigestion caused by pancreatic exocrine insufficiency or to intestinal bacterial overgrowth due to small bowel motility disorders

and a hypermetabolic state with increased energy consumption and high protein catabolism.

Sarcopenia was highly associated with waitlist mortality and negative perioperative outcome (Kahn 2018, Meeks 2017). This was in particular an issue in patients who were listed with low priority based on a low MELD score (van Vugt 2017).

After waitlisting, laboratory values must be updated according to the recertification schedule shown in Table 3.

Table 2. Basic (not exhausted) evaluation protocol for potential transplant candidates

Physical examination
Diagnostic tests (baseline laboratory testing; serologic, tumour/virologic, and microbiological screening; coagulation tests, autoantibodies; thyroid function tests)
Abdominal ultrasound with vascular Doppler/Duplex
Abdominal MRI or computer tomography (CT) scan
Chest X-rays
Electrocardiogram (ECG), cardio CT in patients ≥50 years or > 2 cardiological risk factors, cononary angiography only if indicated and after cardio CT, Swan-Ganz catheterisation, Doppler/Duplex carotid arteries
Upper and lower endoscopy
Pulmonary function testing
Mammography (in females >50 years)
Physician consultations (anesthesiologist, gynecologist, urologist, cardiologist, neurologist, dentist, ear, nose, and throat specialist)
A meticulous psychosocial case review (medical specialist in psychosomatic medicine, psychiatry or psychology)

Table 3. Recertification schedule of MELD data

Score	Recertification	Lab values
≥25	every 7 days	≤48 hours old
24–19	every 30 days	≤7 days old
18–11	every 90 days	≤14 days old
≤10	every year	≤30 days old

Special attention regarding specific, disease-related therapy prior to surgery should be given to transplant candidates undergoing LT for HCC or virally-related liver diseases.

Waiting list monitoring of patients with ALD

ALD is currently the most common indication for LT in many European and US LT centres. The 6-month abstinence requirement (the so-called '6-month rule') is a common practise requiring candidates abstinent from alcohol for at least 6 months to be eligible for transplant.

ALD is associated with a lower risk of waitlist removal for deterioration (HR 0.84, 95%CI 0.81-0.86, p<0.001) and a higher risk of waitlist removal for improvement (HR 2.91, 95%CI 2.35-3.61 p<0.001) as compared to non-ALD (Giard 2019).

Alcoholic hepatitis (AH) represents a subpopulation of patients with ALD with short term mortality approaching 70% in severe cases. The thresholds for amount and duration of alcohol use leading to severe AH (SAH) are not clearly defined. However, an average consumption of more than 40 g per day for women and 50–60 g per day for men are estimated minimum thresholds for the diagnosis of SAH. Heavy alcohol use has usually occurred for >6 months (typically for several years) with <2 months of abstinence before clinical presentation of jaundice.

Until recently, LT as a treatment for SAH has been a taboo in most transplant centres owing to concerns about the limited organ supply and the risk that the SAH liver recipient will return to harmful drinking. Moreover, there has been a controversial discussion in literature about LT in SAH (Fung 2017, Lucey 2017, Barosa 2017, Daswani 2018, Kubiliun 2018, Lee (a) 2018, Zhu 2018, Mitchell 2019, Thursz 2018), and this issue has been debated in national and international conferences and liver societies (Addolorato 2016, Martin 2014, EASL CPG 2018: management of alcohol-related liver disease, Graziadei 2016).

The change in attitude has been launched by a French-Belgian study group (Mathurin 2011) which favoured early LT in SAH as a reasonable rescue option for patients who failed to respond to conservative therapy. The authors selected patients who had no prior episodes of AH and had scores ≥0.45 according to the Lille model or rapid deterioration of liver function despite medical therapy. Only patients were selected who had family support, no severe comorbidities and were commited to alcohol abstinence. Only 2.9% of available grafts were considered for this indication. The cumulative 6-month survival rate (±SE) was significantly higher among patients undergoing early LT than among those who were not placed on the waiting list (77 ± 8% vs. 23 ± 8%, P<0.001). This was also true through 2 years of follow-up (hazard ratio, 6.08; P = 0.004). Three patients had an alcohol relapse at 720 days, 740 days, and 1140 days after LT.

A lively international debate about the selection criteria in patients with ALD was sparked in 2012. An advantage of the 6-month period of abstinence before listing is avoidance of unnecessary LT in patients who

will spontaneously improve and a commitment of the patient to abstinence giving the opportunity to implement preventive strategies against future relapse episodes (Im 2019). Arguments in favour for LT is the risk of death in patients with severe ALD/AH, the fact that the 6-month rule as a single predictor of abstinence is debatable and may discriminate patients with favourable prognosis and low risk of recurrence. A multicentre control study from French and Belgian with 149 patients cannot conclude non-inferiority in terms of rate of alcohol relapse post-transplant between early liver transplantation and standard transplantation (after at least six month of abstinence). The prospective controlled study confirms the important survival benefit in early liver transplantation in patients with severe alcohol-related hepatitis but high alcohol intake is more frequent after early liver transplantation (Louvet 2022).

The majority of LT recipients after LT for AH maintains long-term abstinence, but younger age, multiple prior rehabilitation attempts and overt encephalopathy were associated with post-LT alcohol use (Lee (d) 2022). Further suggested predictors of recurrence include positive family history of substance use, alcohol-related comorbidity, history of prior alcohol-related legal issues, history of substance abuse (other than alcohol), lack of social support, lack of familiar support, denial of drug-related problems and addiction length and intensity of ALD. Prognostic instruments used to predict future drinking after LT include the University of Michigan Alcoholism Prognosis score, the Alcohol Relapse Risk score, the High Risk Alcoholism Relapse (HRAR) score and the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) (Im 2019). However these scores were not specifically developed for the LT setting. Therefore, Lee et al. (b) (2019) developed a new prognostic score (SALT score) using 4 pretransplant variables to identify AH candidates at low risk for alcohol relapse after early LT. A multidisciplinary approach including psychosocial and medical assessment and integration of an addiction specialist may be a crucial prerequisite to properly determine suitability of the ALD patient for LT. In nowadays even artificial intelligence is used to identify harmful alcohol use after LT by psychological profiles (Lee (e) 2022).

Results of several studies and retrospective analyses resulted in a paradigm shift in therapy for highly selected patients with SAH who are not responding to medical therapy. The UNOS, the EASL Clinical Practise Guideline on alcohol-related liver disease (2018) and the American College of Gastroenterology (ACG) Clinical Guideline (Singal 2018) therefore suggest that the decision for waitlisting should not be based only on the 6-month abstinence rule. Presently, in case of non-response to conservative therapy, highly selected patients can therefore be considered for early LT in European and US transplant centres (Antonini 2018, Lee (c) 2018, Thurs 2019, Carrique 2021).

Addiction rehabilitation programmes should be implemented prior to LT, and post-LT contracting, for alcohol after care and counseling should be considered in patients who are too sick to attend pretransplant rehabilitation treatment.

Management of patients with ALD in the context of LT is an ongoing debate in Germany. According to legally binding guidelines of the German Medical Association abstinence must be proven by negative urine ethyl glucuronide (uETG) tests (and hair-ETG/carbohydrate-deficient Transferrin (CDT) if applicable) during the 6 months before possible waitlisting (https://www.bundesaerztekammer.de/fileadmin/user_upload/BAEK/Ueber_uns/Richtlinien_Leitlinien_Empfehlungen/RiliOrgaWlOvLeberTx20230121.pdf). Furthermore, a positive psychiatric assessment with potential recommendations for psychotherapeutic measures is mandatory before listing. As soon as a patient is on the waiting list due to ALD, ETG testing is required at every visit in the LT outpatient clinic (at least every 3 months).

The majority of patients with severe SAH already reveal cirrhotic changes of the liver in terms of acute on chronic liver failure and do not meet the 6-months rule. In exceptional urgent cases the transplant conference of the corresponding German LT centre can deviate from the 6-months rule (https://www.bundesaerztekammer.de/fileadmin/user_upload/BAEK/Ueber_uns/Richtlinien_Leitlinien_Empfehlungen/RiliOrgaWlOvLeberTx20230121.pdf). This presupposes a request by the transplant centre for an alcohol audit which is carried out by a committee of specialists nominated by the German Medical Association. Eurotransplant organises the audit process consisting of 3 auditors who give an expert opinion (independently of each other). A positive vote is achieved if all 3 auditors agree to an exceptional listing. However, after completion of the audit process the transplant conference takes the final decision to list or not to list the patient

Psychosocial interventions should be routinely used in the medical management of ALD prior to and after LT (EASL CPG: Liver transplantation [2016]). Once listed, patients with ALD should be monitored for alcohol use by clinical interviewing and random biochemical testing. The specific biochemical test used in different countries and transplant centres will depend on availability, programme resources and costs. Currently, anticraving drugs (except baclofen) and disulfiram are not recommended in patients with advanced ALD, because of the potential side effects and insufficient experience in this population.

Waiting list monitoring and treatment of viral hepatitis B and C in liver transplant candidates

The treatment of viral hepatitis B and C is well established and patients should be treated according to actual guidelines. In all viremic patients with viral hepatitis B on the waiting list efficient therapy should be started. The goal of antiviral therapy in HBV patients on the waiting list is to achieve viral suppression to undetectable HBV DNA levels using sensitive tests (Cornberg 2011, Beckebaum 2013a). Several studies have demonstrated clinical benefits in patients with decompensated cirrhosis with viral suppression as reflected by a decrease in CPT score, improvement of liver values and resolution of clinical complications (Kapoor 2000, Schiff 2007). Moreover, initiation of nucleos(t)ide analogue (NUC) treatment prior to LT has markedly reduced HBV recurrence posttransplantation.

The success of direct-acting antivirals (DAAs) has dramatically changed the landscape for HCV and liver transplantation. The diagnosis of a decompensated liver cirrhosis with replicative hepatitis C is rarity nowadays. Only very few patients have to be transplanted with a replicative hepatitis C and need a DAA therapy after liver transplantation. Nearly all liver transplant patients with a reinfection of HCV in the past reached a sustained virological response with DAA therapy.

According to the European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C (2020), patients without cirrhosis and with compensated (Child-Pugh A) cirrhosis without HCC awaiting LT with a MELD score <18-20 should be treated prior to LT; whereas those without HCC and a MELD score ≥18-20 should be transplanted first without antiviral treatment. Patients with decompensated cirrhosis (Child-Pugh B or C) without HCC awaiting LT with a MELD score <18–20 have an indication for antiviral treatment with the fixed-dose combination of sofosbuvir, velpatasvir and daily ribavirin. In HCV transplant candidates with HCC timing of antiviral therapy should not interfere with the management on the waiting list, it must be decided on a case-by-case basis. Patients with HCC without cirrhosis or with compensated cirrhosis should be treated for HCV infection prior to LT.

Based on available data and according to EASL recommendations (2020) the use of HCV-infected organs is acceptable in patients at high risk of death on the waiting list but should not be offered to non-infected recipients with a MELD score <20 if there is no access to anti-HCV therapy.HCV negative patients receiving a HCV positive organ should be treated in any case.

Adjunct treatment and staging of HCC transplant candidates

LT should be considered in early or intermediate stage HCC (Reig (b) 2022). A 5-year survival rate of 75–80% can be achieved in patients with HCC undergoing LT (Vogel (b) 2022). Under MELD allocation, patients must meet the Milan criteria (one tumour ≤5 cm in diameter or up to three tumours, all ≤3 cm, no extrahepatic manifestation, no macrovascular infiltration) to qualify for exceptional HCC waiting list consideration. Diagnosis of HCC is confirmed if the following criteria are met according to the German Medical Association (https://www.bundesaerztekammer.de/fileadmin/user_upload/BAEK/Ueber_uns/Richtlinien_Leitlinien_Empfehlungen/RiliOrgaWlOvLeberTx20230121.pdf): (1) liver biopsy-proven alone or (2) two contrast-enhanced (CE) imaging techniques (CE-magnetic resonance imaging [MRI], CE- computed tomography [CT] or CE-ultrasound [US]) in tumours 1 cm up to ≤2 cm; (3) one contrast-enhanced imaging technique (CE-MRI, CE-CT) in tumours >2 cm; (4) arterial hypervascularisation with rapid venous wash out, displaying contrast reversal in comparison to the surrounding liver tissue in 3-phase cross-sectional imaging techniques. Initial imaging (before downstaging with interventional therapy or resection) has to be used for diagnosis. Patients are registered at a MELD score equivalent to a 15% probability of pretransplant death within 3 months. Patients will receive additional MELD points equivalent to a 10% increase in pretransplant mortality to be assigned every 3 months until these patients receive a transplant or become unsuitable for LT due to progression of their HCC. The listing centre must enter an updated MELD score exception application in order to receive additional MELD points.

Pre-listing, the patient should undergo a thorough assessment to rule out extrahepatic spread and/or vascular invasion. The assessment should include CT scan or MRI of the abdomen, pelvis and chest. We perform trimonthly routine follow-up examinations (MRI or CT scan) of waitlisted HCC patients for early detection of disease progression. Underestimation of HCC burden before LT has shown to be frequent despite advanced imaging technologies. This has been reconfirmed in a study conducted by Ecker et al. (2018). The authors collected HCC patients who underwent LT after preoperative MRI in a prospective institutional database (January 2003 to December 2013). Patients were subdivided in those “within” or “outside” Milan criteria by both imaging and explant pathologic evaluation. Of 318 patients with HCC meeting Milan criteria by MRI at the time of LT, only 248 (78.0%) remained within Milan on explant examination.

Waiting list drop-out rates can be reduced by the application of bridging therapies such as transarterial chemoembolisation (TACE) or radiofrequency ablation (Roayie 2007, Reig (b) 2022). In patients treated with transarterial chemoembolisation before LT for HCC Response

Evaluation Criteria in Solid Tumours (RECIST) have shown to be superior to EASL criteria at 1 month follow-up for predicting long-term survival (Shuster 2013). Transarterial radionuclide therapies such as Yttrium-90 microsphere transarterial radioembolisation (TARE) have been tested for bridging therapy in selected cases (Toso 2010).

Kulik et al. (2018) aimed to investigate the effectiveness of locoregional therapy (LRT) in LT candidates with HCC on the LT waitlist. They conducted a systematic review and metaanalysis considering multiple databases from 1996 to April 25, 2016, for studies that enrolled adults with cirrhosis awaiting LT and treated with bridging or down-staging therapies before LT. LRT included TACE, transarterial radioembolisation, ablation, and radiotherapy. The authors showed that in LT candidates with HCC, the use of LRT is associated with a nonsignificant trend toward improved waitlist and posttransplant outcomes. Bridging therapy should be considered in particular in patients outside the Milan criteria, with a likely waiting time of longer than 6 months, and those within the Milan criteria with high-risk characteristics of HCC. Sorafenib has been administered in a few studies before LT to investigate the safety and efficacy of this oral multikinase inhibitor in the neoadjuvant setting (Fijiki 2011, Di Benedetto 2011). A systematic review of the few available studies showed that perioperative use of sorafenib did not improve patient survival and could even lead to a worse prognosis (Qi 2015). Moreover, sorafenib is frequently associated with side effects such as fatigue, weight loss, skin rash/desquamation, hand–foot skin reaction, alopecia and diarrhoea, requiring dose reduction or treatment discontinuation. Accurate discrimination of HCC patients with good and poor prognosis by specific criteria (genomic or molecular strategies) is highly warranted to select appropriate treatment options (Bittermann 2014, Tournoux-Facon 2011).

Lately immune check point inhibitors were established in the individualised HCC treatment as standard of care (Vogel (b) 2022). The combination of atezolizumab with bevacizumab is currently the firt choice first-line treatment, liver function has to be preserved and bleeding risk should be low in this patient group (Reig 2022). There is still an ongoing discussion if check point inhibitors should be used before transplantation and when.

Liver transplantation in autoimmune hepatitis and cholestatic liver diseases

In Europe 4% of cirrhosis patients were transplanted due to AIH and 8% due to PBC, based on the data from the European Liver Transplant Registry (https://www.ELTR.org).

An international multicentre study of 3, 902 PBC patients, Harms et al (2019) found that treatment with UDCA is associated with prolonged liver transplant-free survival.

On the one hand AIH could lead to chronic liver failure due to cirrhotic liver impairment but on the other hand acute severe autoimmune hepatitis can lead to acute liver failure. The management and the right timing for LT in patients with severe acute AIH is still challenging. In a retrospective multicentre study by De Martin et al (De Martin 2021) acute severe AIH was diagnosed by definite or probable AIH based on the simplified AIH score, an INR ≥ 1.5 and/or bilirubin >200 µmol/L, no previous history of AIH and a histologically proven AIH. The study showed that in patients with acute severe AIH the INR at the introduction of corticosteroids and the evolution of INR and bilirubin are predictive of LT or death. A new scoring system (SURFASA score) was built. The score comprised three parameters: INR at baseline, change in INR over 3 days and change in total bilirubin over 3 days after beginning of steroid treatment, the cut off point was <-0.9. Responding rate on steroid therapy was 75% below this cut off and with a score >1.75 the risk of dying or LT was 85-100%. The score was validated later, but the authors highlight that traditional MELD score were equally accurate (Lin 2022).

PSC, accounting for approximately 5% of all transplant cases, is a rather small indication group on the waiting list. According to the actual Guidelines of the German Medical Association, patients with PSC who fulfil the standard exception criteria receive a match MELD reflecting the sum of 3-month mortality according to lab MELD and a 15% 3-month mortality at listing and then they are upgraded every three months following every 10% increase of the 3-month mortality (https://www.bundesaerztekammer.de/fileadmin/user_upload/BAEK/Ueber_uns/Richtlinien_Leitlinien_Empfehlungen/RiliOrgaWlOvLeberTx20230121.pdf). A large retrospective study with 286 PSC patients by Rupp et al showed that the rate of transplantation-free survival was higher in patients receiving scheduled ERCP compared to patients with ERCP on demand (Rupp 2019). However benefit was only significant in patients with the initial or later diagnosis of a dominant stenosis, even if asymptomatic. Another large multicentre study (2975 PSC patients from 27 centres) highlights that scheduled imaging (ultrasound and/or MRI) improves survival in PSC (Bergquist 2023). Asymptomatic patients with cholangiocellular carcinoma hat a better survival if scheduled imaging had been performed (Bergquist 2023).

Living donor liver transplantation: indications, donor evaluation, and outcome

LDLT was introduced in 1989 in a successful series of paediatric patients (Broelsch 1991). Adult-to-adult LDLT (ALDLT) was first performed in Asia where cadaveric organ donation is rarely practiced (Sugawara 1999, Kawasaki 1998). LDLT peaked in the US in 2001 (Qiu 2005) but thereafter the numbers declined by 30% over the following years (Vagefi 2012, Carlisle 2012). A decline over time was also observed in Europe, whereas LDLT activity increased in Asia. Recently published studies showed good survival rates in HCC-patients with LDLT beyond Milan compared to those within Milan (Alim 2021, Liang 2021). In the last years LDLT is increasingly mentioned in various indications.

In selected cases, LDLT offers significant advantages over deceased donor LT (Quintini 2013). The evaluation of donors is a cost-effective and time-consuming process. Clinical examinations, imaging studies, special examinations, biochemical parameters, and psychosocial evaluation prior to donation varies from centre to centre and has been described elsewhere (Valentin-Gamazo 2004). Using Germany as an example, the expenses for evaluation, hospital admission, surgical procedure, and follow-up examinations of donors are paid by the recipient's insurance. Due to the increasing number of potential candidates and more stringent selection criteria, rejection of potential donors has been reported in 69-86% of cases (Valentin-Gamazo 2004, Pascher 2002). The advantages of LDLT include the feasibility of performing the operation when medically indicated and the short duration of cold ischaemia time.

LDLT is associated with surgical risks for the recipient AND donor (Baker 2017). The surgical procedures for LDLT are more technically challenging than those for deceased donor LT. In the recipient operation, bile duct reconstruction has proven to be the most challenging part of the procedure with biliary complications ranging from 15% to 60% (Sugawara 2005).

Regarding donor outcome, morbidity rates vary considerably in the literature (Patel 2007, Beavers 2002, Shiraz 2016). Possible complications include wound infection, pulmonary problems, vascular thrombosis with biliary leaks, strictures, and incisional hernia. A major concern related to LDLT is still donor safety because an operative procedure with potential risks must be carried out on a healthy individual (Baker 2016). Biliary complications are the most common postoperative complication in LDLT and occur in up to 7% of donors (Perkins 2008, Sugawara 2005). Liver regeneration can be documented with imaging studies and confirmed by normalisation of bilirubin, liver enzymes, and synthesis parameters. Morbidity rates are strongly related to the experience of the surgical team and should be performed only by established transplant centres with appropriate medical expertise. The currently reported postoperative mortality rates for left and right hepatectomy are 0.1% and 0.5%, respectively. Outcome in patients undergoing LDLT is similar if not even better than in those undergoing deceased donor LT (Nadalin 2015, Alim 2021).

Perioperative complications

Cardiac decompensation, respiratory failure following reperfusion, and kidney failure in the perioperative LT setting constitute major challenges for the intensive care unit. Acute kidney injury (AKI) has a major impact on short- and long-term survival in LT patients. For instance, Pulitano et al. (2018) found that AKI was associated with increased risk of early allograft dysfunction and chronic kidney disease stage ≥ 2 posttransplant.

There is no currently accepted uniform definition of AKI, which would facilitate the standardisation of care of patients with AKI and improve and enhance collaborative research efforts. Biomarkers such as neutrophil gelatinase-associated lipocalin or kidney injury molecule-1 have been developed for the prevention of delayed AKI treatment (Saner 2012). Moreover, genetic profiling of post-reperfusion milieu showed that endothelin-1 and interleukin-18 serum levels on postoperative day 1 were independent predictors of AKI in multivariate analysis (Pulitano 2018).

Early dialysis has been shown to be beneficial in patients with severe AKI (stage III according to the classification of the Acute Kidney Injury Network) (Bellomo 2004), whereas treatment with dopamine or loop diuretics have shown to be associated with worse outcome. Preventative strategies of AKI include avoidance of volume depletion and maintenance of a mean arterial pressure >65 mm Hg (Saner 2012).

Despite advances in organ preservation and technical procedures, postoperative complications due to preservation/reperfusion injury have not markedly decreased over the past several years. Typical histological features of preservation and reperfusion injury include centrilobular pallor and ballooning degeneration of hepatocytes. Bile duct cells are more sensitive to reperfusion injury than hepatocytes (Washington 2005) resulting in increased serum levels of bilirubin, gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (AP). A recently published randomised trial showed that hypothermic Machine Perfusion in LT leads to a lower risk of non-anastomotic biliary strictures after LT and reduces the rate of postreperfusion syndrome and early allograft dysfunction (van Rijn 2021). Machine perfusion expands the pool of usable livers dramatically and improves graft function (Sousa Da Silva 2022; Czigany 2021, Brüggenwirth 2022).

Vascular complications continue to have devastating effects. In deceased LT, overall vascular complications such as hepatic artery thrombosis (HAT) have been reported in 1.6-4% of patients. Shiraz et al. (2016) retrospectively analysed the trends observed in vascular complications with changing protocols in adult LDLT (A-LDLT) and paediatric LDLT (P-LDLT) over 10 years. Depending on the era of LT the authors stratified the cohort in Group I (n= 391, Jan. 2006- Dec.2010) and Group II (n=741, Jan. 2011- Oct. 2013) patients. With a minimum follow up of 2 years, incidence of HAT in adults has reduced significantly from 2.2% in Group I to 0.5% to Group II, p = 0.02. In Group II non-significantly more adult patients (75%) with HAT could be salvaged compared to only 25% patients in Group I (p=0.12). Incidence of portal vein thrombosis (PVT) has been remained similar (p=0.2) in the two eras.

Yang et al. (2014) found that independent risk factors associated with early HAT were recipient/donor weight ratio ≥1.15 (OR=4.499), duration of hepatic artery anastomosis >80 min (OR=5.429), number of units of blood received intraoperatively ≥7 (OR=4.059) and postoperative blood transfusion (OR=6.898). After logistic regression, duration of operation >10 h (OR=6.394), re-transplantation (OR=21.793) and rejection reactions (OR=16.936) were identified as independent risk factors associated with early HAT. Graft type (whole/living-donor/split), duration of operation >10 h, re-transplantation, rejection episodes, recipients with diabetes preoperatively and recipients with a high level of blood glucose or diabetes postoperatively had a higher risk of late HAT in the univariate analysis. Doppler exams of the hepatic artery and portal vein are frequently performed in the early postoperative setting. HAT in the early postoperative period can be managed with thrombectomy. Late HAT with complication of bile duct strictures is managed by interventional endoscopic retrograde cholangiography (ERC) but requires re-transplantation in the majority of patients. Early portal vein thrombosis is rare (<1%) but may lead to graft loss if not revascularised.

Primary non-functioning graft (PNFG) may be clinically obvious immediately after revascularisation of the allograft. Early signs of liver dysfunction include prolonged coagulation times, elevated liver enzymes (transaminases, cholestasis parameters) without a downward trend, rising lactate, and hypoglycemic episodes. PNFG is a critical situation and requires immediate re-transplantation.

Infections occurring during the first month post-LT are usually nosocomial, donor-derived, or due to perioperative complications (Hernandez 2015). Death within the first year after LT is often associated with bacterial infections. Management of infections due to multidrugresistant gram positive pathogens represents a major therapeutic challenge in the transplant setting (Radunz 2011).

Overall incidence of fungal infections in LT recipients has declined due to early identification and treatment of high-risk patients. However, overall mortality rate for invasive candidiasis and aspergillosis remains high (Liu 2011).

The clinical symptoms of early T-cell mediated rejection (TCMR) are non-specific, may not be apparent or may manifest as fever, right upper quadrant pain, and malaise. A liver biopsy is indispensable for confirming the diagnosis. High dose corticosteroids (3 days of 500-1000 mg methylprednisolone) are the first-line treatment for moderate and severe TCMR. A small study (n=28) by Volpin et al compares a high dose methylprednisolone schedule (1000mg for 3 consecutive days) to a lower dose protocol (single 1000mg of methylprednisolone followed by a 6-day taper from 200 to 20mg/day) (Volpin 2002). The treatment response was evaluated by a second liver biopsy. The taper protocol was more effective and safer that the 3 days high dose schedule and corticosteroid side effects were lower. In selected TCMR cases antibody-depleting therapy may be necessary. Mild, moderate and severe TCMR should be treated by an increase in CNI. Diagnosis of acute antibody-mediated rejection (AMR) requires a liver biopsy demonstrating classic histology and C4d+ staining (Demetris 2016). Mild AMR should be treated with steroid boluses. Moderate to severe cases can include plasmapheresis and intravenous immunoglobulins with or without anti-B cell agents. In contrast to late TCMR early TCMR (<6 weeks after LT) is not associated with reduced patient or graft survival after LT when treated adequately, but patients with moderate-to-severe early TCMR are at an increased risk for late TCMR (Jadlowiec 2019).

Subclinical TCMR (subTCMR) describes the presence of histological features of TCMR but without relevant elevation of liver enzymes. subTCMR is seen in up to 25% after liver transplantation and has a good short-term prognosis even without any specific therapy. There is no therapy needed if transaminases <2 ULN because there is no progression in fibrosis reported but immunosuppressive therapy should not be reduced. Positivity for donor-specific antibodies (DSA) in subTCMR is associated with an impaired graft and patient survival due to an upregulation of rejection associated transcripts (Höfer 2020).

Long-term complications after liver transplantation

Management issues for the long term include opportunistic infections, chronic ductopenic rejection, side effects due to immunosuppression including cardiovascular complications and renal dysfunction, *de novo* malignancies, biliary complications, osteoporosis and disease recurrence.

Opportunistic infections

Opportunistic infections in the medium and long term after LT are primarily viral and fungal in origin. Opportunistic bacterial infections are uncommon after 6 months in patients receiving stable and reduced maintenance doses of immunosuppression with good graft function. There is still a need for prospective interventional trials assessing the potential effects of preventive and therapeutic strategies against bacterial and fungal infection for reducing or delaying the development of chronic allograft dysfunction.

Cytomegalovirus (CMV) infection plays an important role in the LT setting (Mumtaz 2014) (Figure 2). CMV DNA assay is the commonly used laboratory tool to diagnose and monitor CMV infection. Current guidelines recommend antiviral prophylaxis over pre-emptive therapy in preventing CMV disease in high-risk LT recipients (CMV-seronegative recipients of organs from CMV-seropositive donors [D+/R-], [Kotton 2018]) as antiviral prophylaxis, compared with preemptive therapy, is superior in controlling CMV infections without an increased risk of rejection or opportunistic infections (Yadav 2022). The period of prophylaxis should be no shorter than 3 months in D+/R- patients. Delayed-onset CMV disease occurs in 15-38% of CMV D+/R- LT patients after prophylactic treatment for 3 months (Eid 2010, EASL 2016).

The procedure in the transplant centres is inconsistent for intermediate risk (R+) patients. If a preemptive strategy is adopted, screening for CMV every 1-2 weeks in the first 3 months post-LT is not entirely achievable in routine clinical practice in most centres. If prophylaxis is carried out in D+/R+ or D-/R+ patients, this should last 3 months. D-/R- patients have the lowest risk of CMV infection and disease.

A controlled clinical trial demonstrated that valganciclovir, an oral prodrug of ganciclovir, is as effective and safe as intravenouos (IV) ganciclovir for the prophylaxis of CMV disease in solid organ (including liver) transplant recipients (Paya 2004). In a published study by Kim et al. (2015) LT patients experiencing CMV infection were administered oral valganciclovir (900 mg/day) daily or IV ganciclovir (5 mg/kg twice daily) as antiviral preemptive treatment. A total of 83 patients had preemptive antiviral therapy, of those 61 patients received ganciclovir and 22 patients received valganciclovir. The median time from LT to CMV infection in the IV ganciclovir group was shorter than in the oral valganciclovir group (21 days vs. 30 days, p = 0.001). Recurrent CMV infection rates after treatment were 14.8% in the ganciclovir and 4.5% in the valganciclovir group (p=0.277). None of the patients in either group experienced CMV disease. The authors concluded that oral valganciclovir was equally effective as IV ganciclovir in preemptive treatment of CMV infection following LT.

Therapies for refractory CMV-infections are limited by toxicities. In 2022 Maribavir was authorised for patients after stem cell or solid organ transplantation with or without resistence. Maribavir is an oral antiviral medication and was superior to (val)ganciclovir for CMV viraemia clearance in the SOLSTICE trial (Avery 2022).

Occurrence of posttransplant lymphoproliferative disease (PTLD) in the first year after solid-organ transplantation is typically related to EpsteinBarr virus (EBV) infection. Incidence ranges between 3 and 21% (Choudhary 2021). EBV-seronegativity of the recipient before infection, high EB viral load, intensity of immunosuppression and young age have been reported as risk factors for PTLD (Smets 2002). Outcomes have improved since rituximab has been incorporated into treatment regimens (Kamdar 2011). Therapeutic management options include reduction of immunosuppression, rituximab, combination chemotherapy and adoptive immunotherapy. The use of CD19 chimeric antigen receptor T-cell (CAR-T) therapy for relapsed/refreactory PTLD is possible. A lately published retrospective multicentre study by McKenna et al showed an overall response rate of 64% with a two-year overall survival rate of 58% respectively (McKenna 2023).

Oral reactivation of human herpes simplex virus-1 (HSV-1) after LT is common. Development of varicella-zoster virus (HHV-3) after LT is typically related to intense immunosuppressive therapy and its therapy does not differ from the non-transplant setting. There is a vaccination against varicella-zoster virus. In Germany the vaccination with a dead vaccine is recommended from the age of 50 (Gross 2020).

Human herpesvirus 6 (HHV-6A and HHV-6B) can cause primary or reactive infection in LT recipients and may often be restricted to the infected organ and asymptomatic but it can also display a variety of clinical syndromes, including fever, hepatitis, and higher rates of graft dysfunction. It may have indirect effects including increased risks of mortality and fibrosis as well as hepatitis C progression. Recipients with inherited chromosomally integrated HHV-6 (ciHHV-6) may have an increased risk of graft rejection and opportunistic infections (Phan 2018). HHV-6 and HHV-7 may have a potential role as co-pathogens in the direct and indirect illnesses caused by CMV. HHV-6 infection can be determined by quantifying viral DNA in plasma or blood, however, biopsy remains the gold standard for diagnosis. Clinically significant tissue-invasive infections can be treated with ganciclovir, foscarnet or cidofovir.

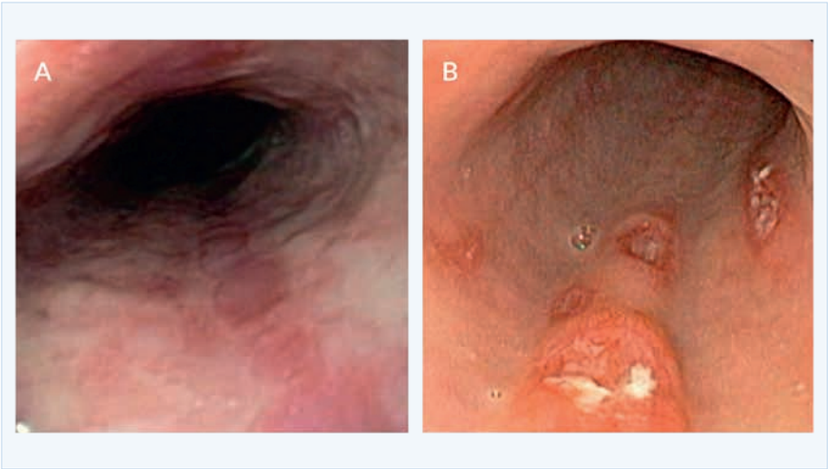

Figure 2. Cytomegalovirus (CMV) infection of the upper gastrointestinal tract. A. Livertransplanted patient complaining of dysphagia and epigastric discomfort with multiple longitudinal oesophageal ulcers seen at upper endoscopy. B. Endoscopic findings of deep oesophageal ulcerations with fibrinoid necrosis in another immunocompromised patient. In both cases, lesions were caused by CMV infection. Diagnosis depends on a positive mucosal biopsy, which should include specimens from the ulcer margins and ulcer base. Hematoxylin and eosin staining typically reveals "owl's eye" cytoplasmic and intranuclear inclusion bodies.

Hepatitis E

There is often a multifactorial pathogenesis for allograft hepatitis in LT patients. It is advisable to incorporate HEV RNA determination into the differential diagnostic investigation where patients have unexplained elevated liver enzymes or histological signs of allograft hepatitis (Borg 2016). Recently, molecular testing was suggested for HEV in transplant liver biopsies for evaluating patients with elevated transaminases of unknown origin (Protzer 2015).

Treatment of acute HEV infection with RBV may be indicated in specific cases of acute infection with severe liver dysfunction or extrahepatic manifestations. Chronic disease courses with HEV infections as well as reactivation after apparent cure have been reported in organ transplant patients. In the transplant setting, HEV Guidelines from UK (McPherson 2018) define diagnosis of persistent HEV infection leading to chronic hepatitis when HEV RNA is detectable in blood or stool for more than three months after the onset of relevant symptoms, raised liver enzymes, or from the first positive HEV RNA test.

The risk of HEV infection becoming chronic in immunocompromised (transplanted) patients is high, at around 60-65% (Kamar 2010a 2011, Legrand-Abravanel 2010, McPherson 2018). Quantification of HEV viral load is useful before initiation of antiviral therapy. HEV diagnosis should be bases on PCR techniques (Markakis 2022). A baseline quantitative HEV RNA assessment is undertaken on both plasma and stool at the start of treatment. A strong decrease of viral load may predict viral elimination.

A group from the Hannover Transplant Centre performed HEV serology tests in 226 LT patients, 129 non-transplanted patients with liver disease, and 108 healthy controls (Pischke 2010). HEV antibodies were detectable in 4% of the transplant group, 3% of the group with liver disease and 1% of the healthy control group. Three patients from the transplant group were HEV RNA positive, two of whom developed HEV viral persistence. Anti-HEV seroconversion was observed no earlier than four months after detection of HEV RNA.

The outcome, progression and individual variables associated with HEV infection becoming chronic were analysed in a retrospective study (Kamar 2011) including data from 17 transplant centres. The vast majority of the patients had received kidney (n=48) or liver (n=27) allografts. Chronification of HEV infection was defined as persistently elevated liver enzymes and positive detection of HEV replication in serum and/or feces over a minimum of six months. 65/85 patients (65.9%) developed a chronic disease. All 59 patients who underwent HEV genotyping had genotype 3. In contrast to the non-immunosuppressed patients, transaminases were usually only moderately elevated. Anti-HEV IgM was detectable in only 41% and IgG was detectable in 80.8%. 14.3% of the patients developed cirrhosis of the liver by the final follow-up.

In a recently published review of the literature sustained virological response was achieved by reduction of immunosuppression alone and by ribavirin regiments in 15% and 83% respectively (Markakis 2022).

With regard to PEG-interferon α treatment of HEV infection (Abbas 2014, Kamar 2010c), there is little data available for LT patients and this treatment approach should not be used as first line therapy. HEV RNA testing in plasma and stool at day 7 and monthly after RBV treatment initiation is recommended. A 3-month course of RBV monotherapy seems to be an appropriate treatment duration if stool tests are negative for HEV RNA at month 3 on two occasions (McPherson 2018). If HEV RNA is positive at month 3, RBV is continued until stool tests are negative for HEV RNA on two occasions one month apart or RBV is continued for 6 months. A test of SVR is conducted by testing plasma and stool samples for HEV RNA at three and six months after cessation of antiviral therapy.

Chronic rejection (TCMR and AMR)

Advances in immunosuppressive regimens have greatly reduced the incidence of chronic rejection and allograft failure. Chronic rejection

begins within weeks to months or years after LT and accounts for a small proportion of late graft dysfunction (Suhling 2016). It affects about 4% to 8% of patients (Neuberger 1999).

Sub-therapeutic immunosuppression and nonadherence to immunosuppressive therapy also coincides with increased risk of rejection, substantial increases in the rates of graft loss and death. Special attention should be posed on immunosuppression-related physical side effects as a major reason for non-adherence. Multidisciplinary evaluation, in particular by transplant hepatologists and psychologists are warranted to improve adherence before and after LT. Chronic TCMR and AMR may appear indolently and might only become apparent as liver test injury abnormalities (GGT, AP, bilirubin, transaminases). The diagnosis needs to be confirmed by histopathologic examination. Chronic TCMR results in potentially irreversible bile duct and vascular injury. Treatment is difficult. Patients on cyclosporine (CSA) should be switched to tacrolimus (TAC). Diagnosis of chronic AMR includes inflammation with low grade interface activity, fibrosis and C4d+ staining (Demetris 2016). There is currently no defined treatment strategy. Switching the baseline immunosuppression from CSA to TAC and initiating mycophenolate mofetil (MMF) rescue therapy represents a treatment option in these patients (Daly 2002).

Calcineurin inhibitor-induced nephrotoxicity and alternative immunosuppressive protocols

Despite the introduction of new immunosuppressive agents (Table 4), calcineurininhibitors(CNI)remainthekeydrugsinmostimmunosuppressive regimens. Both CSA and TAC inhibit the calcineurincalmodulin complex and therefore IL-2 production in T lymphocytes. TAC is available as traditional twice-daily immediate-release tacrolimus and once-daily prolonged/extended released formulations. Renal failure, mainly due to CNI nephrotoxicity, is the most common complication following orthotopic LT. The incidence of chronic renal dysfunction characterised by arteriolar hyalinosis resulting in a variety of tubulointerstitial and glomerular lesions has been reported in up to 70% of patients in the long term after LT and varies widely depending on the length of follow-up, the definition of chronic kidney disease and the intensity of immunosuppressive therapy (Beckebaum 2013b). End stage renal disease has been described in 18% of patients during a posttransplant follow-up of 13 years (Gonwa 2001).

Randomised trials have shown that induction therapy maintains immunosuppressive efficacy in steroid-free regimens. For instance, delayed CNI initiation (e.g. to days 4-5 posttransplant) can prevent deterioration of renal function posttransplant, but requires induction with an interleukin-2 antagonist receptor (IL-2RA) agent or rabbit antithymocyte globulin (rATG) to maintain early immunosuppressive efficacy.

A group from Regensburg initiated a single arm pilot study to determine the safety and efficacy of a CNI-free combination therapy (basiliximab induction/MPA and delayed [10 days posttransplant] SRL in patients with impaired renal function (GFR <50 mL/min and/or serum creatinine >1.5 mg/dL) at LT (Schnitzbauer 2015). Renal function improved significantly ($p = 0.006$). The critical time period for relevant improvement of kidney function seemed to be the first month, independently from SRL administration.

In LT patients with CNI-induced nephrotoxicity, a complete replacement of CNI with conversion to MMF has shown conflicting results with respect to the occurence of rejection, anywhere from 0% to 60% (Creput 2007, Schmeding 2011, Moreno 2004). MMF inhibits inosine monophosphate dehydrogenase, a critical enzyme in the *de novo* pathway of purine synthesis. Results from previous studies with immunosuppressive regimens including MMF and minimal CNI treatment suggest a significant improvement in renal function in this patient group (Beckebaum 2011, Cicinnati 2007a, Beckebaum 2004a, Cantarovich 2003, Garcia 2003, Raimondo 2003).

De novo immunosuppression with MMF combined with induction therapy and delayed CNI introduction is another approach to reduce CNI related nephrotoxicity especially in patients with higher MELD score or significant renal dysfunction. In a randomised clinical trial, a daclizumab/MMF/delayed low-dose TAC-based regimen was compared with a standard TAC/MMF regimen (Yoshida 2005). In both study arms, corticosteroids were tapered over time. Statistically significant higher median GFR was found in the delayed CNI group, although acute rejection episodes were not statistically significant different between the groups. Similar results were seen in two retrospective studies in LT patients receiving thymoglobulin induction therapy and a delayed initiation of CNI (Bajjoka 2008, Soliman 2007).

Another approach to maintain renal preservation is replacement of CNI by mTOR inhibitors such as SRL or everolimus (EVL) (Sanchez 2005, Harper 2011, Kawahara 2011, Hüsing (a) 2015) particularly in HCC-patients due to antitumour effects.

An Italian consensus Transplant panel even recommended routine use of EVL in predefined clinical scenarios, particularly in light of posttransplant nephrotoxicity (de Simone (a) 2016).

In the multicentre randomised (1:1) controlled PROTECT study (CRAD001HDE10) *de novo* patients were treated with CNI (CSA or TAC) + basiliximab ± steroids for 4-8 weeks after LT and were then randomised to an EVL-based treatment arm or a CNI-based control arm (Fischer 2012). In the EVL-based treatment arm (n=101), a 70% reduction of CNI (± steroids) was carried out over a period of 2 months, followed by treatment with EVL ± steroids. In the control arm (n=102) treatment with CNI (standard dose ±

steroids) was continued. Using the MDRD equation, the endpoint could be achieved with a difference in calculated GFR of at least 8 mL/min between the two treatment arms (p=0.02). The incidence of graft rejection, graft loss and death were not significantly different between the two treatment arms. A 24-month extension phase was performed in 81 patients to month 35 post-randomisation. The adjusted mean eGFR benefit from randomisation to month 35 was 9.4 mL/min/1.73 m2 with MDRD. The difference in favour of the CNI-free regimen increased gradually over time due to a small progressive decline in eGFR in the CNI group (Sterneck 2014).

A study by Hanover transplant centre outlined that a surveillance biopsy guided personalised immunosuppression programme leads to immunosuppression reduction and a significantly better kidney function (Saunders 2021).

Efficacy and safety of a TAC-free and a TAC-reduced regimen were compared with a TAC standard dose (TAC-C) regimen in a multinational, randomised controlled licensing trial (CRAD001H2304) in *de novo* LT recipients (Saliba 2011b). After a 1-month run-in phase on TAC-based immunosuppression (+/-MMF), patients were randomised to an EVL/prednisone/TAC-free group (TAC-WD) including TAC withdrawal at 4 months post-LT, an EVL/prednisone/reduced TAC group (EVL+rTAC) or a standard TAC control group (TAC-C). The primary combined endpoint included biopsy-confirmed acute rejection, allograft loss or death, and the secondary endpoint was renal function at 1 year. The TAC-WD arm was stopped prematurely due to a significantly higher incidence of biopsyconfirmed acute rejections (19.9% [TAC-WD] vs. 4.1% [EVL+rTAC] vs. 10.7% [TAC-C]).

At 1 year, significantly more patients in the TAC-C group had reached the combined primary endpoint compared to the EVL+rTAC group (9.7% vs. 6.7%; p<0.001). Kidney function was significantly better (p<0.001) in the EVL+rTAC arm than in the TAC-C arm. The increased rejection rate in the TAC-WD group at month 4 may be caused by the immunosuppressive strategy used. Unlike the CRAD001HDE10 study, no induction therapy with an anti-IL-2 inhibitor was performed and there was no weaning of CNI over 2 months. Instead, CNI were stopped abruptly.

Lin (2016) conducted a systematic review and meta-analysis of randomised controlled trials (RCT) analysing the effect of EVL on renal function in patients (EVL n=465, control n=428) with baseline GFR >30 mL/min undergoing a CNI minimisation or withdrawal protocol. Based on these results, EVL use with CNI minimisation in LT recipients was associated with improved renal function at 12 months (95% CI 2.75-17.8) but not associated with an increased risk of biopsy proven acute rejection (RR 0.68, 95% CI 0.31-1.46), graft loss (RR 1.60, 95% CI 0.51-5.00), or mortality (RR 1.34, 95% CI 0.62-2.90). However, it was associated with an increased risk of overall infections (RR 1.45, 95% CI 1.10-1.91).

In the randomised controlled multicentre SiLVER trial the per protocol analysis identified LT recipients with early CNI minimisation and introduction of SRL within 4 to 6 weeks after LT with significantly superior eGFR and lowest rate of chronic kidney disease (≥ stage 3) from year 1 during a follow-up period of 5-years (Buchholz 2020).

Early institution at one month of EVL in combination with low dose TAC (≤5 ng/mL) for preserving kidney function has also been recommended by the International Liver Transplant Society Consensus guidelines on immunosuppression in LT recipients (Charlton [c] 2019).

In future, there might be further development of cell therapeutic approaches and mesenchymal stem cells to launch tolerogenicity rather than development of new immunosuppressive drugs (Charlton [c] 2019).

Table 4. Clinically used immunosuppressive agents in liver transplantation

Immunosuppressant class	Immunosuppressive agent
Corticosteroids	Prednisone, prednisolone, methylprednisolone
Calcineurin inhibitors	Cyclosporin, tacrolimus
Antimetabolites	Mycophenolate mofetil, azathioprine
mTOR Inhibitors	Sirolimus, everolimus
Polyclonal antibodies	Antithymocyte globulin
Monoclonal anti-CD3 antibodies	Muromonab-CD3 (OKT3)
Chimeric monoclonal antibodies	Anti-IL-2 receptor inhibitor (basiliximab)
Monoclonal anti-CD52 antibodies	Alemtuzumab (campath-1H)

Other side effects of CNI

Besides potential nephrotoxicity, CNI therapy is associated with side effects that include cardiovascular complications, tremor, headache, electrolyte abnormalities, hyperuricaemia, hepatotoxicity, and gastrointestinal symptoms. Neurotoxicity, including tremor, paresthesia, muscle weakness, and seizures, more often occurs in TAC-treated patients; gingival hyperplasia, a rare event, and hirsutism are associated with CSA treatment.

Cardiovascular side effects due to CNI and steroids include hyperlipidaemia, arterial hypertension, and diabetes (Beckebaum 2004b).

The prevalence of new-onset diabetes mellitus after LT has been reported to occur in 9-21% of patients (John 2002, Konrad 2000). The prevalence of posttransplant diabetes is even higher if cofactors such as hepatitis C are present. In various studies, the diabetogenic potential has been reported to be higher in patients receiving TAC than in those receiving CSA. In

contrast, CSA has a more pronounced effect on lipid levels. CSA can act by modulating the activity of the LDL receptor or by inhibiting the bile acid 26-hydroxylase that induces bile acid synthesis from cholesterol.

Numerous studies aimed to determine the most effective immunosuppressive protocols while minimising drug-related side effects. These protocols often combine several drugs with different mechanisms of action and toxicities allowing dose adjustment. There is also a trend towards tailored immunosuppressive regimens following the aetiology of liver disease and comorbidities such as renal dysfunction and cardiovascular disease

A systematic review by Bzeizi et al including eight studies with 769 patients compared Everolimus alone or in combination with reduced CNI dose and showed a better renal function in patients with reduced CNI dose levels (Bzeizi 2021). A better long-term renal outcome was also shown for selected LT patients with Sirolimus-based immunosuppression and CNI reduction (Buchholz 2020).

Corticosteroid minimisation/avoidance protocols and additional strategies to reduce metabolic complications

There is ongoing discussion of steroid avoidance due to dyslipidaemia, osteoporosis, development of cataracts, weight gain, hypertension, and a deleterious impact on glucose control. As cardiovascular disease is the second leading cause of death in the late transplant period, steroidminimised/free regimens may be favoured in particular in patients with high risk of metabolic syndrome.

A metaanalysis including 16 studies with 1347 participants showed that glucocorticosteroid avoidance or withdrawal appears to reduce diabetes mellitus and hypertension (Fairfield 2018). In a study, Yoo et al. (2015) evaluated outcomes of 500 consecutive LT recipients who received a steroid-free protocol with rATG induction and a single dose of methylprednisolone given before the first dose of rATG. Mean MELD at transplantation was 22 ± 6. MMF was initiated postoperatively with delayed TAC initiation at 4.79 ± 13.3 days. TAC was replaced by SRL if serum creatinine remained above 2.0 mg/dL after 1 week. Patients were switched to TAC or SRL monotherapy at 12 weeks. Posttransplant peak creatinine was at 1 month 1.43 ± 0.95 mg/dL and improved to 1.26 ± 0.60 mg/dL ($p< 0.05$) at 2.5 years. Lowest GFR rate was observed at 1 month (65.6 ± 30.0) and improved by 12 months (72.7 ± 28.2, $p< 0.01$). One-year patient and graft survival were 92.8% and 89.6%, respectively. Rejection occurred in 22.8% of patients, 6.6% of patients had steroid-dependent rejection.

Other research groups have reported encouraging findings with steroidfree protocols including basiliximab induction therapy (Filipponi 2004, Llado 2008, Becker 2008). In a multicentre, 24-week, randomised, open-label, phase IIIb trial (DIAMOND study) renal function was investigated with once-daily, prolonged-release TAC-based immunosuppression in *de novo* LT recipients. Patients were administered prolonged-release TAC (initial dose 0.2 mg/kg/day); prolonged-release TAC (0.15-0.175 mg/kg/day) plus basiliximab or prolonged-release TAC (0.2 mg/kg/day delayed until Day 5) plus basiliximab. All patients had comedication with MMF plus a bolus of corticosteroids. Lower dose prolonged-release TAC (0.15–0.175 mg/kg/day) immediately posttransplant in combination with basiliximab and MMF was associated with lower TAC exposure, significantly reduced renal function impairment and biopsy-confirmed acute rejection incidence vs. prolongedrelease TAC (0.2 mg/kg/day) administered immediately after LT. Delayed higher-dose prolonged-release TAC exposure significantly reduced renal impairment compared with immediate administration (Trunecka 2015).

A published literature review (Lerut 2009) analysed the actual status of corticosteroid minimisation protocols in LT based on a detailed analysis of 51 peer-reviewed and 6 non-peer-reviewed studies. Results from the majority of studies showed that these protocols have clear metabolic benefits and are safe with respect to graft and patient survival. These results are in line with a recent metaanalysis of 16 studies with 1347 participants demonstrating that metabolic complications such as diabetes and hypertension were statistically significantly less frequent in patients undergoing steroid avoidance or withdrawal protocols vs. steroidcontaining immunosuppression (Fairfield 2018).

A healthy diet and regular exercise represent additional effective strategies to avoid or reduce serious cardiovascular complications. In patients with dyslipidaemia, hydrophilic statins such as pravastatin and fluvastatin should be preferred as they are not metabolised by cytochrome P450–3A4.

De novo malignancies

Incidence of malignancies is higher in transplant patients and depends on the length of follow-up, characteristics of the transplant population, choice of immunosuppressive therapy and the era when the LT was performed (Buell 2005, Fung 2001). A cumulative risk has been reported of 10%, 24%, 32% and 42% at 5, 10, 15 and 20 years, respectively, for development of *de novo* cancers after LT (Finkenstedt 2009). The highest risks in the transplant setting are non-melanoma skin cancers (21.7%) (Saglam 2022), mainly squamous cell carcinoma and basal cell carcinoma (Figure 3). Regular cancer surveillance programmes have been proposed by several groups; however, scientific evidence is lacking and surveillance programmes may

vary from centre to centre.

Bhat et al. (2018) investigated potential risk factors for malignancies after LT analysing data from the Scientific Registry of Transplant Recipients database comprising 108, 412 LT recipients. During median follow-up of 6.95 years malignancies during follow-up were 4, 483 (41.3%) skin, 1, 519 (14.0%) hematologic, and 4, 842 (44.7%) solid organ. The 10-year probability of *de novo* malignancy was 11.5% (11.3-11.8%). Multivariable analysis showed that age by decade, male gender, Caucasian race, multiorgan transplant, previous malignancy and alcohol-related, autoimmune-related, and NASH-related liver disease and PSC pre-LT (compared to HCV, p<0.001) were associated with higher risk of post-LT malignancy. There was no correlation between type of immunosuppression and risk of cancer. Findings were confirmed by Launoy et al (Launoy 2021).

Patients with replicative EBV infection and immunosuppressive regimens, i.e. ATG, are at a higher risk of developing PTLD. These patients may present with lymphoadenopathy and/or fever, weight loss and night sweats, and meticulous examination, serologic and imaging tests are required. Diagnosis and classification of PTLD is currently based on histologic criteria, and a multidisciplinary team is required including hematologists and transplant hepatologists for treatment of PTLD, monitoring of immunosuppressive therapy and preservation of allograft function.

In a prospective single-centre study the relationship between the development of solid organ cancers following LT and the level of CNI exposure was assessed (Carenco 2015). Data are based on 247 TAC-treated LT recipients who survived at least 1 year posttransplant. Study results showed that 43 (17.4%) patients developed *de novo* solid cancers. Mean TAC concentration during the first year after LT was significantly higher in patients who developed solid malignancies (10.3 ± 2.1 vs. 7.9 ± 1.9 ng/mL, p < 0.0001). Independent risk factors in multivariate analysis were tobacco consumption pretransplant (OR = 5.42; 95% CI [1.93-15.2], p = 0.0014) and mean annual TAC concentration during the first 12 months posttransplant (p < 0.0001; OR = 2.01; 95% CI [1.57-2.59], p < 0.0001). Similar results have been shown in a subgroup of patients exposed to TAC continuously for ≥3 years. Premalignant lesions such as actinic keratoses are mostly located on sun-exposed areas. Squamous cell carcinoma and basal cell carcinoma are increased by factors of ~65-200 and ~10, respectively, in organ transplant recipients as compared to the immunocompetent population (Ulrich 2008). An annual routine dermatologic follow-up exam, limitation of sun exposure and protective measures including sunscreens are highly recommended for transplant patients. Due to a higher incidence of colon cancer in patients transplanted for PSC and concomitant inflammatory bowel disease (Hanouneh 2011) an adequate colonoscopic surveillance is required at regular intervals (annual colonoscopy) even in the absence of active disease (Fevery 2012). A trend has recently been reported toward an increased incidence of advanced colon polyps and colon carcinoma in patients transplanted for diseases other than PSC after LT. However, larger studies are needed to determine whether posttransplant colon cancer surveillance should be performed more frequently than in the non-transplant setting (Rudraraju 2008).

Studies have reported a significantly higher incidence of aerodigestive cancer including lung cancer among patients who underwent LT for alcohol-related liver disease (Vallejo 2005, Jimenez 2005). These patients should undergo a more intensive surveillance protocol for the detection of upper gastrointestinal and oropharyngeal-laryngeal malignancies (Benlloch 2004). In cases of positive smoking history surveillance for lung cancer should be implemented. In a retrospective study, conversion from CNI to an mTOR inhibitor (EVL) improved the prognosis of *de novo* malignancies after LT for alcoholic cirrhosis (Thimonier 2014). One- and five-year survival was 77.4% and 35.2% in the EVL cohort vs. 47.2% and 19.4% in the non-EVL cohort, respectively (p=0.003).

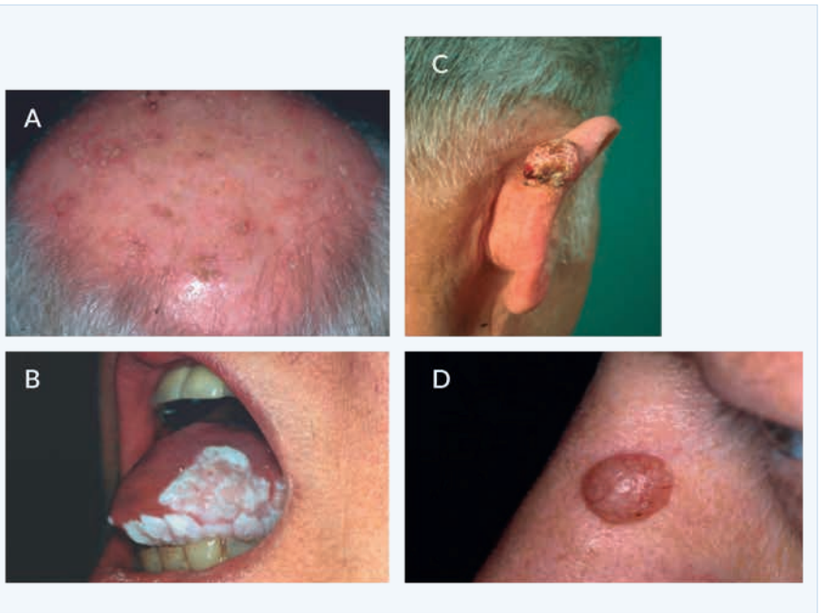

Figure 3. Non-melanoma skin scancers and liver transplantation (LT). Organ transplant recipients have an increased risk of development of non-melanoma skin cancers as compared to the non-transplant setting. Premalignant lesions such as actinic keratoses [A] are predominantly located on sun-exposed areas. Squamous cell carcinoma [B,C] is the most frequent skin cancer after LT followed by basal cell carcinoma [D] (Photographs kindly provided by Prof. Dr. Hillen, Transplant Dermatology Outpatient Unit, Department of Dermatology, University Hospital Essen, Germany)

Studies have shown that mTor inhibitors (SRL, EVL) exert antiangiogenic activities that are linked to a decrease in production of vascular endothelial growth factor (VEGF) and to a markedly inhibited response of vascular endothelial cells to stimulation by VEGF (Guba 2002). Furthermore, the ability of mTor inhibitors to increase the expression of E-cadherin suggests a mechanism for blocking regional tumour growth and for inhibiting metastatic progression. Therefore, we give special consideration for mTOR inhibitor-based immunosuppressive regimens not only in patients transplanted for HCC (Kang 2021) but also those with *de novo* malignancies after LT. There is evidence from meta-analyses and studies performed mainly in the kidney transplant setting that switching from CNI to mTOR-based immunosuppression is associated with a lower incidence of non-melanoma skin cancers (Euvrard 2012, Caroti 2012, Gu 2012, Adelmalek 2012). A multicentre study involving CNI-treated patients with a previous history of at least one squamous cell carcinoma randomly allocated patients to an arm in which CNI was replaced by SRL, or to an arm in which the CNI-based immunosuppression was continued (Euvrard 2012). The squamous cell carcinoma-free survival was significantly longer in the SRL group than in the CNI control group. The authors concluded that SRL obviously has an antitumour effect regarding the reappearance or the new appearance of non-melanoma skin cancers.

Biliary complications

The clinical outcome of patients posttransplant can be significantly affected by biliary complications (Lisotti 2015). Biliary leaks generally present as an early posttransplant complication and occur in 5% to 10% of deceased donor LT (Kapoor 2015) and in 10% to 15% of LDLT (Iida 2010). Biliary leaks are typically treated with placement of a biliary stent to bridge the leak, usually with sphincterotomy. In patients with biliary stones, endoscopic sphincterotomy and stone extraction are the treatment of choice. Biliary stone disease and in particular formation of biliary casts is common in the setting of LT and may occur without or in the setting of strictures due to impaired biliary flow. The exact aetiology of biliary cast disease is unknown but ischaemia and strictures have been described as predisposing factors (Pereira 2018). In a retrospective study complication rate during the first 15 days after endoscopic sphincterotomy were assessed in patients who underwent conventional or precut endoscopic sphincterotomy (Hüsing (b) 2015). A total of 24 complications (15.2%) were reported, including pancreatitis, bleeding, and perforation. Complication rates were not significantly different between the two sphincterotomy techniques.

Damage (ischaemia, infectious complications or rejection) of the biliary tree mucosa can provoke cast which consists of desquamated epithelial cells mixed with bile products within the biliary system and occurs in 3% to 18% of LT patients (Shah 2003).

Biliary strictures are one of the most common complications after LT, with a reported incidence of 5.8-34% (Graziadei 2006). Early anastomotic strictures usually have a technical origin, while strictures appearing later have a multifactorial origin. Non-anastomotic strictures without underlying hepatic artery thrombosis are commonly referred to as ischemic-type biliary lesions (ITBL). Hypothermic oxygenated machine perfusion led a lower risk of non-anastomotic strictures cardiac death (van Rijn 2021).

Risk factors for ITBL include preservation-induced injury, prolonged cold and warm ischaemia times, altered bile composition, ABO blood incompatibility and immunologic injury (Verdonk 2007, Buis 2009). A german transplant group found that specific chemokine receptor polymorphisms of the recipient are associated with the development of post-LT biliary strictures (Iacob 2012). Moreover, screening of anti-HLA antibodies might be useful for early identification of at-risk patients who could benefit from closer surveillance and tailored immunosuppressive regimen (Iacob 2012).

ERC or percutaneous transhepatic cholangiography (PTC) have typically been used as the primary approach, leaving surgical intervention for those who are non-responsive to endoscopic interventions or who have diffuse intrahepatic bile duct damage. Radiological methods such as magnetic resonance cholangiopancreatography (MRCP) have been introduced as an additional diagnostic tool for biliary complications. In cases of biliary cast and ischemic cholangiopathy, endoscopic ultrasound (EUS) was found to be diagnostically superior to ERCP and had a significant impact on clinical decision-making. EUS was less reliable when diagnosing anastomotic strictures (Hüsing 2015). EUS can complement ERCP to improve diagnosis of biliary complications after LT and impact on treatment decision.

The long-term efficacy and safety of endoscopic techniques have been evaluated in various transplant centres (Qin 2006, Zoepf 2012, Pascher 2005). Non-anastomotic strictures are commonly associated with a less favourable response to interventional endoscopic therapy in comparison to anastomosis stenosis (Figure 4). An Austrian group found anastomotic strictures in 12.6% of patients transplanted between October 1992 and December 2003 and non-anastomotic strictures in 3.7% during a mean follow-up of 53.7 months after LT (Graziadei 2006). Interventional endoscopic procedures were effective in 77% of patients with anastomosis stenosis, while treatment of non-anastomotic strictures showed long-term effectiveness in 63% of patients. A surgical approach was required in 7.4% of transplant recipients.

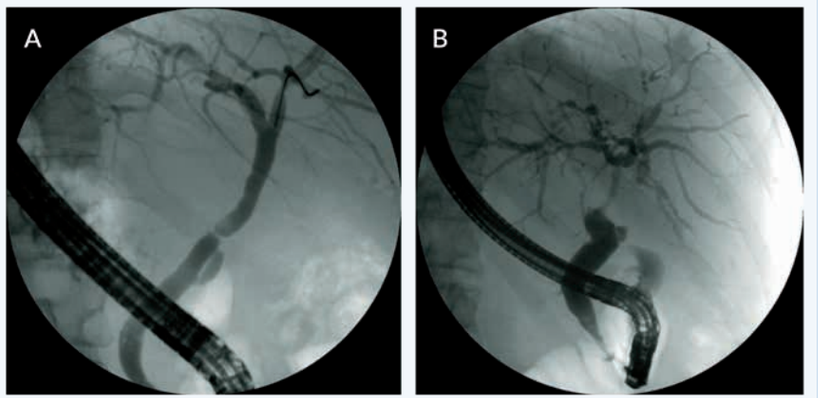

Figure 4. Biliary tract complications after liver transplantation. A. Endoscopic retrograde cholangiography (ERC) showing posttransplant short filiform anastomotic biliary stricture in a 46-year-old patient transplanted for hepatitis C virus (HCV) infection and alcohol-related cirrhosis 6 months earlier. Therapy sessions include dilatation and an increasing number of bile duct endoprostheses at short intervals of every 2-3 months. Prior to endoscopic therapy an endoscopic sphincterotomy is performed. B. ERC of a 41-year-old patient transplanted for HCV diagnosed with ischemic-type biliary lesions (type 3) with long non-anastomotic stricture extending proximally from the site of the anastomosis and strictures throughout the entire liver.

Results from 75 transplanted patients undergoing ERC for suspected anastomotic strictures were retrospectively analysed (Zoepf 2006). Balloon dilatation alone and combined dilatation and endoprosthesis placement was efficacious in 89% and 87% of cases respectively, but recurrence occurred in 62% and 31% of cases respectively. However, results of these strategies are inconsistent in the literature. Repeated ERC sessions are commonly performed with increasing endoprosthesis diameter every three months and double or triple parallel stenting in selected cases. Up to 75% of patients are stent-free after 18 months of endoscopic intervention (Tung 1999).

Medical treatment for bile duct strictures consists of ursodeoxycholic acid (UDCA) and additional antibiotic treatment in stricture-induced cholangitis. Complications related to bilioenteric anastomosis require PTC or surgical intervention.

Metabolic bone disease

Liver cirrhosis, heavy alcohol use, smoking, poor nutrition, hypogonadism, cholestatic liver disease, and therapy with corticosteroids, older age, lower-pre-L BMI are risk factors for the development of osteoporosis in pretransplant patients (Schreiber 2018, Lim 2021). In a study assessing both vertebral and nonvertebral (rib, pelvic, and femur) fractures in pretransplant patients with PBC and PSC, 20% and 1, 4% of the patients had experienced fracturing and avascular necrosis, respectively (Guichelaar 2007). Screening with bone densitometry using dual-energy x-ray absorptiometry should begin prior to LT (Wibaux 2011).

A further increase in bone turnover has been described after LT going along with bone density decrease within the first 3 to 6 months after transplant. Bone density gradually returns to pretransplant levels thereafter (Singh 2015). Posttransplant bone disease contributes significantly to patients' morbidity and mortality after transplantation and plays a role for their quality of life (Nel 2016). Factors favouring spinal bone gain from 4 to 24 months after transplantation include lower baseline and/or 4-month bone density, premenopausal status, lower cumulative glucocorticoids, no ongoing cholestasis, and higher levels of vitamin D and parathyroid hormone (Guichelaar 2006). CNI administration is a risk factor for osteoporosis after LT (Moreira Kulak 2010).

The risk of osteoporotic vertebral and nonaxial fractures was 14% and 21% at 1 and 2 years posttransplant, decreased with time, and was highest in patients with pretransplant osteopenia and cholestatic liver disease (Singh 2015).

A cumulative incidence of fractures at 1 year and at 8 years posttransplant was reported in 30% and 46% of patients transplanted for PBC and PSC (Guichelaar 2007). Nine percent experienced avascular necrosis after LT. This event was positively correlated with pretransplant and posttransplant lipid metabolism, bone mineral density and fracturing, and posttransplant glucocorticoid administration (Guichelaar 2007).

EASL Clinical Practice Guidelines focusing on Liver Transplantation (http://dx.doi.org/10.1016/j.jhep.2015.10.006) recommends bone mineral density screening yearly for patients with pre-existing osteoporosis and osteopenia, every 2-3 years in patients with normal bone mineral density and further screening intervals depending on impairment of bone mineral density and on risk factors. Regular bone mineral density screening may be hampered in some countries as it is not necessarily covered by (statutory) health insurances. There are no specific therapies for posttransplant osteoporosis besides those for non-transplanted patients. General interventions to reduce fracture risk include adequate intake of calcium and vitamin D. Secondary hyperparathyroidism and adverse lifestyle factors should be addressed and corrected. Bisphosphonates are currently the most effective agents for treatment of posttransplant osteoporosis (Moreira Kulak 2010) (www.dv-osteologie.org). A meta-analysis and systematic review of randomised controlled trials demonstrated that bisphosphonate therapy in the first 12 months post-LT is associated with reduced accelerated bone loss and improved bone mineral density at the lumbar spine (Kasturi 2010).

Recurrent diseases after liver transplantation

Disease recurrence may occur in patients transplanted for viral hepatitis, tumour disease, autoimmune or cholestatic or alcohol-related liver diseases.

Recurrence of hepatitis B in the allograft

HBV recurrence using combined prophylactic regimens is less than 5%. However, recurrence rates differ among various studies as most of them are small, with varying proportions of patients with active viral replication at LT and varying follow-up periods after LT. Combined use of hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogs (NUC) has emerged as treatment of choice in transplanted HBV recipients (Figure 5) (Cai 2012) and its efficacy has been investigated extensively. There is a high variability (dose, duration and method of HBIG administration) in the prophylactic protocols. According to the German guidelines (Cornberg 2021) patients receive 10, 000 IU HBIG IV in the anhepatic phase followed by 2000 IU a day during the first posttransplant week and 1000-2000 IU a month in the first year after LT. For long-term HBIG prophylaxis, trough anti-HBs levels at or above 100 IU/L should be maintained. For LT-patients with hepatitis B and D coinfection combined regime should be administered for a longer period (Orfanidou 2021).

The European Commission granted a marketing authorisation valid throughout the European Union for subcutaneous (SC) HBIG in 2009, and it has been launched in the last years in many European countries. SC HBIG application has advantages over intramuscular (IM) and IV administration (Yahyazadeh 2011, Beckebaum 2012, Beckebaum 2013c). It can be performed by patients at home, which is an important factor in improving patients' flexibility and mobility in daily life, lowering the frequency of physician consultations and avoiding AEs attributable to high peak and low trough serum anti-HBs levels compared with IV administration (Yahyazadeh 2011, Beckebaum 2012, Beckebaum 2013c).

De Simone et al. (b) (2016) demonstrated that early introduction of SC HBIg administration by week 3 posttransplantation, combined with HBV virostatic prophylaxis, is safe and effective for prevention of HBV reinfection.

Data from a retrospective study including 371 adults transplanted for HBV-related disease at 20 European centres and treated with IV HBIG (n=299), SC HBIG (n=236), and other HBIG preparations for 12 months ± NUC therapy were analysed (Beckebaum 2018). The majority (93.5%) received NUC therapy. Recurrence was 16/371 (4.3%) (annual rate 0.65%); 5/16 patients with recurrence had discontinued HBIG and 7/16 had low anti-HBs titre (<100 IU/L). The recurrence rate in HBIG-treated patients was 1 per 2069 months. Risk of HBV recurrence in patients who discontinued HBIG was increased by 5.2-fold as compared to those on SC HBIG therapy.

Economic issues have led to a conduct of studies investigating whether NUC therapy instead of combined long-term NUC/HBIG is sufficient for antiviral prophylaxis (Cholongitas 2014, Teperman 2013, Buti 2007, Angus 2007, Knighton 2013, Gane 2007, Stravitz 2012, Wesdorp 2012, Fung 2011).

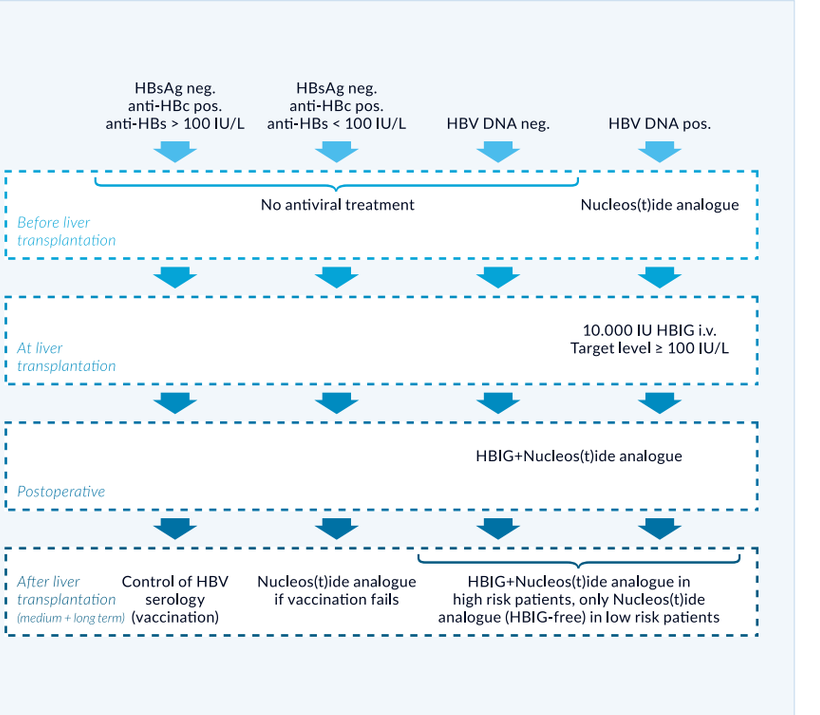

Figure 5. Prophylaxis of HBV recurrence after liver transplantation (LT). Postoperative combined use of nucleos(t)ide analog(s) and hepatitis B immunoglobulin (HBIG) is still the gold standard for prophylaxis of HBV reinfection early after LT. HBIG therapy can be withdrawn in the medium and long term after LT in low-risk patients. Those who are anti-hepatitis B core (anti-HBc) positive and without detectable anti-hepatitis B surface (anti-HBs) titres or with anti-HBs titres <100 IU/L should be vaccinated. In case of no or little response (anti-HBs <100 IU/L) to vaccination, lamivudine (LAM) monotherapy can be initiated. In patients who have protective anti-HBs titres of >100 IU/L, antiviral therapy is not necessary but long-term monitoring of HBV serology including anti-HBs titres is required. Neg., negative; pos., positive

Monotherapy with entecavir or tenofovir in HBIG-free prophylactic regime have shown promising outcome in preventing HBV recurrence after LT (Orfanidou 2021). The efficacy of a switch after at least 12 months of HBIG/LAM to combination therapy with an oral nucleoside and nucleotide analogue was investigated (Saab 2011). Estimated HBV reinfection rate was 1.7% at 1 year after HBIG withdrawal.

A prospective, multicentre study in which 20 HBV patients received 800 IU HBIG (IM) in the anhepatic phase and for another 7 days after transplant surgery was published (Gane 2013). Patients with genotypic detection of LAM resistance and creatinine levels ≥ 1.8 mg/dL were excluded. ADV was administered as add-on therapy to existing LAM treatment. Previously untreated patients received combined ADV plus LAM treatment, which was continued after transplantation. Serum HBsAg and anti-Hbs were measured monthly in the first 3 months, then every 3 months. HBV DNA determination was only performed annually and at the end of the follow-up observation period. HBV recurrence was defined as the reappearance of HBsAg or detection of HBV DNA. The median follow-up was 57 months (range 27–83 months). At transplantation 68% of patients had demonstrable virus replication and 26% had viral replication >4 $\log_{10}$ IU/mL. After the end of the study, another 28 HBV patients received a liver allograft. The patients (n=18) who had HBV DNA <3 $\log_{10}$ IU/mL at transplantation were given no posttransplant HBIG therapy at all. The median follow-up was 22 months (range 10-58 months). Looking at both cohorts it was shown that there was a loss of HBsAg in 47/48 patients within 8 weeks posttransplantation and in one patient within 6 months after transplantation. In one patient with recurrence of HCC, there was a transient reappearance of HBsAg in the follow-up period.

In a randomised, prospective, controlled phase 2 trial, patients (n=40) received emtricitabine, TDF and HBIG for 24 weeks (Teperman 2013). Subsequently all patients who were negative for HBsAg and HBV DNA (<400 copies/mL) were randomly allocated to continue with all three drugs or to an arm with emtricitabine and TDF but without HBIG. The median period of time from LT was 3.4 years (range 1.9–5.6 years). During an observation period of 72 weeks, no HBV recurrence in terms of HBsAg or HBV DNA detection was observed in any of the patients.

Most HBV prophylactic posttransplant studies to date are limited, small and with short follow-up periods. EASL Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection (2017) recommend combined hepatitis B immunoglobulin (HBIG) and NUC for prevention of recurrent HBV infection after LT.

As a life-long therapy, this accounts in particular for patients with a high risk for HBV recurrence (HBV DNA positive at the time of LT, HBeAg positive, HBV underlying HCC, and HDV or HIV coinfection). A study by Saidy et al investigates the discontinuation of HBIG in patients after LT for combined HBV and HDV infection (Saidy 2021). In this small study 17 patients discontinued HBIG for various reasons. Graft function, overall survival and histopathological findings from routine liver biopsies were compared. No significant differences were found regarding the clinical course, histopathological findings or graft and patient survival. The authors assume that the duration of HBIG administration must be questioned. Other studies confirm that HBIG-free prophylaxis is not associated with a worse outcome (Dobrindt 2020). Suitable for this the EASL Clinical Practice Guidelines determine that patients with a low risk of recurrence can discontinue HBIG and proceed with indefinite nucleos(t)ide analogue monoprophylaxis.

According to updated AASLD Hepatitis B Guidance (Terrault 2018) prophylaxis with or without HBIG for 5-7 days and NUCs posttransplant followed by long-term potent NUC therapy in low-risk patients is an appropriate approach. ETV or TDF, an ester prodrug of tenofovir (TFV) or TAF, a phosphonate prodrug of TFV, with more favourable renal and bone safety than TDF are preferred antiviral drugs because of their low rate of resistance with long-term use. Combination antiviral therapy and HBIG is recommended by Terrault et al. (2018) for those with high risk of recurrent disease posttransplant (HDV- and HIV-coinfected patients and nonadherent patients).

For HBsAg negative LT recipients receiving HBsAg negative, anti-HBc–positive allografts, the reported risk of HBV transmission varies with the HBV immune status of the recipient. Those who have detectable anti-HBs titres have a significant lower risk as compared to those without detectable anti-HBc or anti-HBs titre. EASL Clinical Practice HBV Guidelines (2017) recommend LAM as prophylactic approach; whereas AASLD Hepatitis B Guidance (Terrault 2018) positively emphasises highly potent ETV, TDF or TAF for long-term prophylactic use in this scenario.

There is no rationale for continuing HBIG therapy in case of viral breakthrough with detectable HBV DNA. The choice of antiviral therapy in patients with HBV recurrence depends on the current antiviral medication, the viral load, and the resistance profile. Antiviral drug resistance can easily be established by genotypic assays that identify specific mutations known to be associated with decreased susceptibility to particular drugs.

Recurrence of hepatitis C in the allograft

HCV infection always recurs in the allograft in patients with detectable serum HCV RNA and according to EALS Practice Guidelines every recurrence should be treated (EASL 2020). The severity of HCV reinfection can be determined by liver biopsy. Transient elastography (TE) and acoustic radiation force impulse (ARFI) play a substantial complementary role for measurement of fibrosis in HCV and non-HCV transplant recipients (Cross 2011, Beckebaum 2010).

Antiviral treatment initiated after LT may be favourable after postoperative convalescence (approximately 3 months after LT). Patients with elevated liver enzymes and hepatic inflammation, portal

hypertension, and/or the risk of rapid fibrosis progression should be treated earlier. Moreover, fibrosing cholestatic hepatitis (FCH) represents an urgent treatment indication. Studies based on smaller patient cohorts demonstrated excellent results in patients with FCH treated with sofosbuvir/ Ledipasvir and ribavirin for 12 or 24 weeks (Charlton (a) 2015, Manns 2016). Treatment of severe recurrence after primary LT may therefore reduce the need for re-transplantation. Re-transplantation should be mentioned in acute liver failure after LT due to HCV-reinfection.

According to EASL Recommendations on Treatment of Hepatitis C (EASL 2020) patients with posttransplant HCV recurrence with non-cirrhotic changes of the allograft or with compensated cirrhosis (Child-Pugh A) should be treated with either: fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (no need for immunosuppressive drug adjustment) or fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (need for monitoring of drug levels and maybe adjustment of immunosuppressive medication). In patients with decompensated cirrhosis and recurrence of HCV fixed-dose combination of sofosbuvir and velpatasvir with daily weight-based ribavirin should be used for 12 weeks. In case of contraindications for ribavirin or poor tolerance to ribavirin on treatment sofosbuvir and velpatasvir should be used for 24 weeks without ribavirin.

The high level of safety and efficacy of direct-acting antiviral agents for HCV-treatment opens the opportunity to transplant organs from HCV positive patients into non-HCV positive patients, because these organs usually come from younger donors (Levitsky (b) 2017). HCV negative patients who receive an HCV positive organ should be treated in any case.

Recurrence of cholestatic liver disease and autoimmune hepatitis

Data on the frequency of recurrent cholestatic and AIH-related liver disease vary in the literature depending on the follow-up period and criteria chosen for definition of disease recurrence which may be more aggressive than the original disease in some transplant patients (Carbone 2014). The posttransplant prognosis for PBC patients is excellent, with an approximately 80% 5-year survival reported by most large centres (Carbone 2011, Silveira 2010). It has been reported that HLA-A, -B, and -DR mismatches between the donor and the recipient decrease the risk of disease recurrence in PBC patients (Morioka 2007a, Hashimoto 2001). A published study with long term follow-up data reported recurrent PBC in one-third of patients at 11-13 years posttransplant (Charatcharoenwitthaya 2007).

Diagnosis of PBC in the transplanted liver is usually more challenging than diagnosis in the native liver. Anti-mitochondrial antibodies (AMA) often persist, and elevated cholestatic enzymes may be due to other causes of bile duct damage such as ischemic cholangiopathy or chronic ductopenic rejection. Recurrent PBC is a histological diagnosis, typically appearing as granulomatous cholangitis or duct lesions. The frequency of recurrence will be considerably underestimated if a liver biopsy is carried out only when clinical features are apparent.

In a Japanese multicentre study, recipient aged 61 years or older, HLA mismatches of four or more (maximum of six), graft: recipient weight ratio less than 0.8, and husband donor were reported as negative predictors of patient survival in PBC patients after LDLT (Egawa 2016). Some investigators have found that CSA-based immunosuppressive therapy is associated with lower PBC recurrence rates as compared to TAC-based immunosuppression (Wong 1993, Montano-Loza 2010). However, long-term survival has been shown to be not significantly different between CSA- and TAC-treated patients (Silveira 2010). Recent data show that younger age at the time of PBC diagnosis or at LT, TAC use, and biochemical markers of cholestasis after LT are risk factors for PBC recurrence by the Global PBC Study Group (Montana-Loza 2019).

In the Mayo Clinic transplant cohort, 50% of recurrent PBC patients receiving UDCA showed normalisation of serum alkaline phosphatase and alanine aminotransferase levels over a 36-month period compared to 22% of untreated patients (Charatcharoenwitthaya 2007). Although no significant differences in the rate of histological progression was detected between the treated and untreated subgroups, the proportion of individuals with histological progression was significantly lower in those that showed improvement of biochemical parameters regardless of treatment.

A recently published multicentre study by Corpechot et al points out that preemptive therapy with UDCA is associated with reduced risk of disease recurrence, graft loss and liver- related and all-cause mortality (Corpechot 2020).

German Guidelines for autoimmune related liver diseases recommend use of UDCA in patients with recurrent PBC (Strassburg 2017). EASL Clinical Practise Guidelines on Liver Transplantation (2016) do not recommend so far prophylactic use of UDCA in patients transplanted for PBC and PSC (https://dx.doi.org/10.1016/j. jhep.2015.10.006).

Obeticholic acid (OCA) is a promising new therapy that has been shown to substantially improve the long-term outcomes of PBC patients with inadequate response or intolerance to UDCA in the non-transplant setting. However, data are awaited to examine the effects of OCA on clinical outcome in patients with recurrent PBC and the need for an alternative treatment option other than UDCA. Since bile salts are responsible for the secondary toxic consequences, bile salt and nuclear hormone directed therapies may improve secondary toxic injury and are under current investigation. However, so far, these drugs are not available yet.

The reported recurrence rates for PSC after LT range between 9% and 37% (Cholongitas 2008, Alabraba 2009, Vera 2002, Graziadei 1999, Goss 1997). Biliary complications and diagnosis of recurrent PSC can be easily managed in patients with duct-to-duct biliary reconstruction. While Roux-en-Y hepaticojejunostomy was previously the common anastomotic technique for LT in patients with PSC, duct-to-duct reconstruction is currently recommended if there is no evidence of pathological changes of the common bile duct.

German Guidelines for Autoimmune Related Liver Diseases state that UDCA can be used for patients transplanted for PSC as randomised controlled studies on the efficacy of UDCA in patients transplanted for PSC are not available (Strassburg 2017). UDCA does not seem to have an influence on PSC recurrence rates. Preclinical studies in the non-transplant setting suggest that FXR- and PPAR-agonists, inhibitors of the apical sodium-dependent bile salt transporter (ASBT-inhibitors) and the C23 UDCA derivative nor-UDCA are promising agents for the treatment of PSC. However, data from studies targeting new therapeutic approaches in LT patients with recurrent PSC are not available.

In patients who underwent LT for PSC tacrolimus is associated with a better patient and graft survival compared to cyclosporine, tacrolimus should be the standard calcineurin inhibitor in those patients (Aberg, 2024).

Various risk factors for PSC recurrence have been identified including the presence of cholangiocarcinoma prior to LT; presence of certain human leukocyte antigen (HLA) such as HLA-DRB1*08, HLA DR52 in the recipient or donor; male recipient, a recipient-donor gender mismatch; recipient age, an intact colon in the recipient prior to LT, the presence of ulcerative colitis and early cholestasis after LT; use of extended donor criteria grafts; acute cellular rejection, steroid-resistant acute cellular rejection or use of OKT3; maintenance of steroid therapy for ulcerative colitis for more than 3 months; and CMV infection in the recipient (Faisal 2015, Montano-Loza 2016). An increased risk of recurrence has been reported in recipients of grafts from first-degree living related donors in two small single centre series from Japan (Tamura 2007, Haga 2007). A recently published study by Visseren et al detected specific difference in the gut microbiome pre transplantant in patients with recurrence of PSC and those without after LT (Visseren 2020). No difference in the alpha- or beta diversity were observed between recurrence and no-recurrence, but many over-represented bacterial features were detected in patients with recurrence of PSC. Further investigation in bacterial difference in needed.

Recurrent PSC is diagnosed by histology and/or imaging of the biliary tree and exclusion of other causes of non-anastomotic biliary strictures. Histopathological findings in PSC include fibrous cholangitis, fibroobliterative lesions, ductopenia, and biliary fibrosis.

It has been described that recurrence of PBC and AIH does not significantly impact long term outcome including overall survival whereas recurrent PSC has been associated with a higher re-transplantation rate (Tanaka 2020).

A British LT group found significantly better recurrence-free survival rates in patients who underwent colectomy before or during LT and in those with with non-extended donor criteria allografts (Alabraba 2009).

Interestingly, despite immunosuppression, a significantly higher corticosteroid requirement was reported in the transplant compared to the non-transplant setting, with 20% of PSC patients with concomitant PSC becoming corticosteroid dependent after LT (Ho 2005). A recent study reported that maintenance steroids (>3 months) for ulcerative colitis post-LT were a risk factor for recurrent PSC (Cholongitas 2008). A Scandinavian group studied the risk of colorectal neoplasia among 439 PSC patients, 80% of whom had chronic inflammatory bowel disease prior to LT and 3% of whom had developed *de novo* chronic inflammatory bowel disease (Jørgensen 2012). The median history of chronic inflammatory bowel disease was 15 years (range 0–50 years) and the follow-up period posttransplantation was 5 years (range 0–20 years). A fourth of the PSC patients who additionally had bowel involvement developed colorectal neoplasias. This frequency was twice as high postoperatively than before LT. Patients receiving TAC and MMF had a significantly higher risk of chronic inflammatory bowel disease-associated active inflammation than patients taking CSA and azathioprine (Jørgensen 2013). Morover, a Swedish study (Lindström 2018) TAC was reported as an independent risk factor for PSC recurrence. However, due to conflicting results in literature, impact of immunosuppression on PSC recurrence needs further investigation.

AIH recurrence was 20% after 5 and 31% after 10 years respectively in a recently published multicentre study (Montano-Loza 2022). Recurrence of AIH was associated with younger age at transplantation, immunosuppressive therapy with mycophenolate mofetil, sex mismatch and high immunoglobuline G before LT. Recurrence of AIH is a risk factor for impaired graft function and overall survival.

Transplantation centres commonly maintain AIH patients on prednisone after LT to reduce rejection and recurrence rates. However, there is limited evidence for this approach (Stirnimann 2019) and impact of type and dosing of immunosuppressive drugs on outcome needs further investigation. Survival rates post-LT are approximately 90% and 70% at 1 and 5 years (Montano-Loza 2016). A long-term follow-up study (>10 years) by a French group found AIH recurrence in 41% of the patients. The authors recommended regular liver biopsies, because histological signs precede abnormal biochemical liver values in about one-fourth of patients (Duclos-Vallee 2003). The diagnosis of recurrent AIH may include

histological features, the presence of autoantibodies, and increased gamma globulins. Histological signs of recurrence include interface hepatitis, lymphoplasmacytic infiltration, and/or lobular involvement. The majority of published studies did not confirm a posttransplant prognostic role of antibodies in patients undergoing LT for AIH. Conflicting data exist regarding the presence of specific HLA antigens that predispose patients to AIH recurrence after LT (Gonzalez-Koch 2001, Molmenti 2002).

Recurrent AIH must be distinguished from *de novo* AIH, which is a clinical entity resembling AIH and develops in LT recipients transplanted for other liver disorders. It was originally described in children after LT. The incidence of *de novo* AIH is variable because multiple descriptions have been used in case series. The Banff working group on liver allograft pathology has recently suggested that the nomenclature '*de novo* AIH' should be replaced by the terminology 'plasma-cell rich rejection' (Montano Loza 2016, Demetris 2016).

Outcome and recurrence in patients transplanted for hepatic malignancies

The results of early studies of LT for HCC were disappointing. More than 60% of patients developed tumour recurrence within the first two years posttransplant (Ringe 1989). Currently, there are recurrence rates of 10-15% in patients fulfilling the Milan criteria (Zavaglia 2005) and the majority of recurrence occurs within the first two years after LT (Stras 2022). A recurrence after five years is rare. In analyses of predictors of survival histological grade of differentiation, macroscopic vascular invasion and satellitosis were identified as independent predictors of survival and tumour recurrence (Zavaglia 2005, Hoyos 2015). Others identified MELD score >22, AFP >400 ng/mL and age >60 years as negative predictors for survival in HCC (Sotiropoulos 2008b, Jelic 2010). Several retrospective cohort studies are published in literature which demonstrated statistically significant differences in survival and recurrence between different RECIST criteria after LT (Morris 2016). AFP independently predicts tumour recurrence and correlates with vascular invasion and differentiation (Duvoux 2016). A French group of researchers developed a selection model called the AFP score. This score allows patients with HCC not meeting Milan criteria but scored 2 or lower, with AFP levels less than 100 ng/mL and a low 5-year risk of recurrence to be transplanted with excellent results (Duvoux 2016). In another study, Notarpaolo (2016) tested this AFP score in a population of non-French patients transplanted for viral hepatitis underlying HCC. The authors concluded that in this specific population, the AFP model better selects patients with HCC as compared to Milan criteria and that the AFP score can also be implemented in countries with an important burden of HCC occurring on post-hepatitic cirrhosis.

For patients having an indication for LT despite exceeding the Milan criteria, the use of marginal grafts or performance of LDLT has been considered as a reasonable option.

Expansion beyond the Milan criteria to University of California San Francisco (UCSF) criteria (single tumour <6.5 cm; two to three tumours, none >4.5 cm or total diameter <8 cm, no vascular invasion) or even more liberal criteria (no portal invasion, no extrahepatic disease) have been discussed widely (Sotiropoulos 2007, Silva 2011, Jelic 2010). Centres such as the San Francisco Transplant Group as well as the UCLA Transplant Group have demonstrated 5-year survival rates of 50-80% after LT for tumours beyond the Milan criteria but within UCSF criteria (Duffy 2007, Yao 2007). In a recently published study (Victor 2020) from the Houston transplant group, 220 HCC patients were transplanted, 138 inside Milan, 23 inside UCSF, and 59 beyond UCSF criteria. Interestingly, patient survival was similar at 1, 3, or 5 years despite pathologic tumour size.

The 'up to seven' criteria (7 being the sum of the size and number of tumours for any given HCC) was suggested as an approach to include additional HCC patients as transplant candidates. However, acceptance of a more liberal organ allocation policy would result in a further increase of HCC patients on the waiting list and in denying the use of these organs to other non-HCC patients.

The existence of several scoring systems in this era of LT shows on the one hand the widely held conviction of the transplant community that the well-established Milan criteria are too restrictive, not allowing many HCC patients the LT opportunity; on the other hand, this situation reflects some limitations of the existing pretransplant radiological evaluation (Sotiropoulos 2009). Multiple reports in the radiology literature address nodule detection in cirrhotic livers by means of CT, MRI, or ultrasonography. Many of them conclude that contrast-enhanced MRI is the most sensitive technique for detecting liver nodules (Teefey 2003, Tokunaga 2012). MRI has been shown to depict only 39 of 118 HCC in cirrhosis, for an overall sensitivity of 33% (Krinsky 2002). Detection of small tumours was inadequate, with only 11 of 21 lesions (52%) between 1 and 2 cm and 3 of 72 lesions (4%) <1 cm correctly classified. The sensitivity in the series from Essen was similarly poor, 0% for tumours <1 cm and 21% for tumours between 1 and 2 cm (Sotiropoulos 2005). Similar findings have been reported (Bhartia 2003) with the conclusion that the identification rate of tumours <1 cm is still limited. The presence of microvascular invasion and, in some cases, macrovascular invasion of segmental branches can usually be determined by pathologic inspection of the explanted liver. This, together with inaccurate tumour detection, leads to upgrading of the tumour stage or the classification according to the different sorts of criteria in the posttransplant period, compared to assumed stages by radiological

evaluation. More important, however, is the fact that some patients might not be given the opportunity to undergo LT on the basis of inaccurate radiological and clinical preoperative staging.

Mazzaferro et al. (2018) found that patients with HCC achieve a 70% chance of HCC-specific survival 5 years after LT, if AFP level are <200 ng/mL and the sum of number and tumour size (in centimeters) do not exceed 7. The authors created a model comprising level of AFP, tumour size, and tumour number, to determine the risk of death from HCC-related factors after LT and to define selection criteria for LT in HCC patients. For this purpose they provided an online calculator to predict 5-year survival and risk of HCC-related death.

Expansion of criteria in the LDLT setting is even more challenging due to the donor risk and the risk of selection of tumours with unfavourable biology following the concept of fast-tracking (Hiatt 2005). Novel molecular biology techniques, such as genotyping for HCC, may become relevant for determining recurrence-free survival and improving patient selection, but these biomarkers can not yet be used for clinical decision making.

A potential survival benefit was reported in studies and a meta-analysis of controlled clinical trials with SRL-based immunosuppression in patients transplanted for HCC (Kneteman 2004, Zimmerman 2008, Toso 2007, Liang 2012). These results are in line with a retrospective analysis based on the Scientific Registry of US Transplant Recipients, which included 2491 HCC LT recipients and 12, 167 recipients with non-HCC diagnoses. Moreover, the SILVER Study, a large prospective RCT, comparing SRL-containing versus SRL-free immunosuppression showed a benefit in recurrence-free survival and overall survival in the SRL group in the first 3 to 5 years, in particular in low risk patients, but did not improve long-term recurrence-free survival beyond 5 years (Geissler 2016).

Sorafenib (SOR) is currently used for HCC recurrence after LT when patients are not suitable for surgical/locoregional treatments. Repeated LT is not recommended (Stras 2022). In an Italian study (Invernizzi 2019) treatment response was obtained in 16% and stable disease in 50% in those treated with SOR (74% were on mTOR inhibitors). Median time to radiological progression was 6 months. Baseline predictors of overall survival were SOR+mTOR inhibitors, previous curative treatments and AFP>100 ng/mL. In addition Lenvatinib is used for recurrence treatment in some centres.

Although initial post-LT survival rates were poor in patients with unresectable hilar CCA outcomes, after introduction of the Mayo Clinic protocol, outcomes have been more promising. Neoadjuvant chemoradiation and subsequent LT has shown promising results for patients with localised, unresectable hilar cholangiocellular carcinoma (CCC) (Welling 2014, Masuoka 2011). In a published US study, the outcome of 38 patients who underwent LT was compared to that of 19 patients who underwent combined radical bile duct resection with partial hepatectomy (Hong 2011). The tumour was located in the intrahepatic bile duct in 37 patients and in the hilar bile duct in 20 patients. Results demonstrated that LT combined with neoadjuvant and adjuvant therapies is superior to partial hepatectomy with adjuvant therapy. Challenges of LT attributable to neoadjuvant therapy include tissue injury from radiation therapy and vascular complications including HAT. Predictors of response to the neoadjuvant protocol prior to LT need to be determined (Heimbach 2008). Increasing age, high pretransplant tumour marker, residual tumour size in the explant >2 cm, tumour grade, previous cholecystectomy and perineural invasion were identified as predictors of recurrence following LT (Knight 2007).

Machairas et al. (2020) conducted a systematic review investigating longterm outcomes of patients (n=698) with hilar CCC undergoing LT. A total of 13 studies were included in this systematic review. The majority (74.4%) received neoadjuvant therapy (combined chemotherapy and radiation). One-, 3- and 5-year overall survival rates ranged between 58%-92%, 31%80% and 20%-74%, respectively. Recurrence rates ranged widely between 16% and 61%, and perioperative mortality ranged between 0% and 25.5%. Results revealed that LT could provide acceptable long-term outcomes in the setting of neoadjuvant therapy using strict patient selection criteria.

Metastatic lesions originating from neuroendocrine tumours (NET) may be hormone-producing (peptide hormones or amines) or may present as nonfunctional tumours (Frilling 2006). They are characterised by slow growth and frequent metastasis to the liver, and their spread may be limited to the liver for protracted periods of time. Most studies in patients transplanted for NET are limited and usually restricted to small numbers of patients. An analysis based on the UNOS database including patients transplanted for NET between October 1988 and January 2008 showed that long-term survival of NET patients was similar to that of patients with HCC. Excellent results can be obtained in highly selected patients and a waiting time for LT longer than 2 months (Gedaly 2011). A recently published study with 32 patients showed excellent long-term survival rates even in patients with post-LT NET recurrence (particulary in late recurrence >24 month after LT) in particular by aggressive surgical treatment (Sposito 2021). Long-term results from prospective studies are needed to further define selection criteria for patients with NET for LT, to identify predictors for disease recurrence, and to determine the influence of the primary tumour site on patient posttransplant survival.

Recurrent alcohol abuse after liver transplantation for alcoholic liver disease

Recent trials have shown that uEtG or hair-EtG determinations are reliable markers for detection of alcohol relapse after LT (Staufer K 2011). Reported rates of returning to drinking after LT for ALD vary in the literature. Studies revealed a mean incidence of relapse in one-third of patients ranging from 10% to 50% in up to 5 years of follow-up (EASL CPG Management of alcohol-related liver disease [2018]). Approximately 10% to 15% of patients with recurrent ALD resume heavy drinking with damage of the new liver (Marroni 2018). There are psychological scoring systems to assess the relapse risk in patients with alcohol abuse but a prospective validation is missing (Shenoy 2021). Among other things the Sustained Alcohol Use Post-LT (SALT) score score by Lee et al was published (Lee (b) 2019). This prognostic score using four objective pretransplant variables (>10 drinks per day at initial hospitalisation, multiple prior rehabilitation attempts, prior alcohol-related legal issues and prior illicit substance abuse) identifies candidates with AH for early LT who are at low risk for sustained alcohol use posttransplant.

Marot et al. (2018) performed a systematic review and metaanalysis in patients with AH. Pooled estimated risk for alcohol relapse was 0.22. This risk was not statistically significant different between AH and AC with 6 months of abstinence. Pooled estimated rate for 6 month survival was 0.85 and similar between both groups.

Predictors of recurrence include positive family history of substance use, pretransplant abstinence, failed rehabilitation attempts, history of prior alcohol-related legal issues, history of substance abuse (other than alcohol), smoking, lack of social support, lack of familiar support, denial of drug-related problems and addiction, length and intensity of alcoholic liver disease and psychiatric comorbidities (Perney 2005, Dew 2008).

Patient and graft survival is excellent in those maintaining alcohol abstinence after LT. A study (Parrish 2019) considering SRTR data from patients (n=53.788) transplanted between 2014 and 2017 showed that patients with ALD and HCV had superior graft survival rates (90.7% at 1 year, 78.9% at 3 years and 90.0% at 1 year, 79% at 3 years, respectively) as compared to those with nonalcoholic steatohepatitis (NASH) (87.5% at 1 year, 77.9% at 3 years).

The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis analysed outcome of early LT for patients without mandatory period of sobriety with severe alcoholic hepatitis. Data derived from 12 centres from 8 UNOS regions (Lee (c) 2018). The authors reported a cumulative incidence of any alcohol use (slips or sustained alcohol use) of 25% at 1 year (95% CI, 18%-34%) and of 34% at 3 years (95% CI, 25%-44%) after LT. The cumulative incidence of sustained alcohol use was 10% at 1 year (95% CI, 6%-18%) and 17% at 3 years (95% CI, 10%-27%) after LT. Patients overall survival after 1 year (94%) and 3 years (84%) was not significantly worse compared to patients undergoing LT for other indications but sustained drinking after LT was associated with increased mortality (hazard ratio, 4.59; P=.01). A significant decrease of the medium- and long-term survival in severe chronic alcohol consumption after LT has also been shown in previous studies (Pfitzmann 2007).

For LT recipients with a history of ALD (and positive smoking history), a more intensive surveillance protocol including annual skin and ear nose throat (ENT) examinations as well as upper endoscopy (every 2–3 years) and abdominal ultrasound should be considered. Modifiable factors such as life style habits including cigarette smoking, physical inactivity, and obesity should be avoided. A systemic evaluation including malnutrition, vitamin and trace element deficiency, and osteoporosis is recommended.

According to results from the European Liver Transplant Registry (ELTR), mortality and graft failure were more often related to *de novo* tumours, cardiovascular and social factors in alcoholic LT patients as compared to patients transplanted for other etiologies (Burra 2010). LT recipients with a prior diagnosis of ALD might benefit from immunosuppressive regimens that minimise CNI exposure and favour mTOR-containing regimes. However, prospective studies are needed to gain more insight into this issue.

Recurrent non-alcoholic fatty liver disease

The increasing incidence of obesity and the metabolic syndrome throughout developed countries results in an increasing proportion of patients transplanted for NAFLD (Darwid Murash 2015). Younossi et al. (2016) constructed a steady-state prevalence model to quantify the economic and clinical burden of NAFLD in the United States and Europe. Data were validated using a computerised disease model. In the United States, over 64 million people are projected to have NAFLD, with an annual direct medical burden of approximately $103 billion ($1, 613 per patient). In Germany, France, Italy, and United Kingdom, the authors estimated ~52 million people with NAFLD with an annual cost of approximately €35 billion (from €354 to €1, 163 per patient). Life style interventions are of utmost importance and overweight patients who achieve significant reductions in body weight through physical activity and low caloric diet can decrease liver fat, visceral and subcutaneous adipose tissue (Copaci 2015). Treatment of NAFLD will likely involve a holistic, multidisciplinary and personalised approach (Malhotra 2015).

Patients transplanted for NAFLD had similar outcomes compared with patients transplanted for other indications (Burra 2014). Reported NAFLD

recurrence rates after LT vary in the literature, ranging between 20 and 40%. Villeret et al maintain that the recurrence of the underlying disease is inevitable and progressive in a large proportion of patients who underwent LT for NAFLD cirrhosis (Villeret 2023). This leads to a higher attention to life style changes after LT. The components of metabolic syndrome are often exacerbated following LT by factors such as immunosuppression requiring an aggressive management of cardiovascular complications after transplantation.

The transplant group from Stockholm (Tokodai 2019) conducting a retrospective study identified recipient age and 1-year BMI in multivariate analysis as independent risk factors for post-LT fatty liver disease development. Weight gain after LT is significantly greater in patients with older age (>50 years) and in those transplanted for chronic compared with fulminant liver failure. Thus, at least for steroid-free regimens, weight gain seems to be unrelated to any specific immunosuppressive drug. The greatest weight gain has been observed after the first 6 months posttransplant. Physical activity in LT recipients should be proposed as part of their therapeutic regimens. It also appears to improve health-related quality of life after LT (Battistella 2022), thus regular exercise programmes and a healthy diet may be incorporated to avoid cardiovascular morbidity and mortality and NAFLD recurrence (Cotter 2020).

There are continuous efforts on finding novel agents to help prevent and to slow down the progression of recurrent NAFLD (Younossi ZM 2019, Tang 2019). The importance of the gut microbiome in mediating hepatocyte inflammation and intestinal permeability may also offer future treatment options.

Pregnancy after liver transplantation

Adequate preconception counseling is crucial to provide optimal conditions for pregnancy and to modify immunosuppressive therapy if necessary to minimise risks for both the mother and the fetus. Female LT patients of reproductive age should preferentially use contraception during the first 12 months after transplantation. Immunosuppression therapy should be continuied during pregnancy, however, individual regimens could be possible (Rahim 2020). Fetal loss, prematurity, and low birth weight have been reported in women who have undergone transplantation (Valentin 2021), and maternal risks include hypertension, preeclampsia, gestational diabetes, and graft dysfunction. The rate of caesarean section is considerably higher in post-LT patients. Steroids, CNIs have not been reported to be teratogenic and should be maintained during pregnancy; whereas mycophenolate mofetil has shown to cause malformations in animal models and should be avoided. mTOR inhibitors may affect spermatogenesis in male recipients. More studies should be designed to investigate the role of immunosuppression on sexual dysfunction. In a retrospective study by Zaffar et al. (2018) 41 pregnancies in 28 transplanted women were considered. Mean transplant-to-pregnancy interval was 8.5±5.1 years. Immunosuppressive therapy consisted of TAC ± azathioprine (n=26), CSA (n=4) and prednisone with other immunosuppressive drugs (n=11). During pregnancy the following adverse events have been reported: hypertension (n=10), impairment of renal function (n=6), gestational diabetes (n=4), impairment of allograft function (n=2), and blood transfusion requiring anaemia (n=1). Two miscarriages, three stillbirths and one neonatal death occurred. Moreover, five small-for-gestational-age infants, one minor congenital anomaly and premature delivery in fourteen infants (38.9%) have been reported.

Although there is an increased risk for pregnancy-related complications as compared to the general population an appropriate multidisciplinary care, stable graft function at pregnancy onset and adherence to immunosuppressive regimens are a good prerequisite for a successful pregnancy and delivery after LT.

Experiences with liver transplantation in inherited metabolic liver diseases in adult patients

LT is regarded as an effective treatment strategy for patients with Wilson's Disease, which presents as deterioration of cirrhosis not responsive to treatment, as acute-on-chronic disease or fulminant hepatic failure (Moini 2010). LT reverses the abnormalities of copper metabolism by converting the copper kinetics from a homozygous to a heterozygous phenotype, thus providing an adequate increase of ceruloplasmin levels and a decrease of urinary copper excretion posttransplant. 1- and 5-year survival is excellent with 88% and 83% respectively (Ferrarese 2020). There are several reports in the literature indicating a reversal of neurological symptoms after LT (Martin 2008, Poujois 2020). However, the course of neurological symptoms remains unpredictable and it is still a matter of debate whether LT should be considered in patients with severe neurological impairment (Pabón 2008).

AAT deficiency is a common genetic reason for paediatric LT, but a rare indication in adults. The Z allele is most commonly responsible for severe deficiency and disease. LT corrects the liver disease and provides complete replacement of serum AAT activity. 567 AAT recipients who underwent LT between 1995 and 2004 were retrospectively investigated (Kemmer

2008). Survival rates after LT for AAT are excellent (1-year 93%, 5-year 90%, 20-year 82%) (Guillaud 2021).

In haemochromatosis, iron depletion therapy prior to LT may be associated with a better outcome after LT and is strongly recommended (Weiss 2007). It has been reported that the survival of patients who undergo LT for hereditary haemochromatosis is markedly lower in comparison to other indications (Dar 2009, Brandhagen 2001). Reduced posttransplant survival in patients with haemochromatosis has been attributed to cardiac problems and increased infectious complications. Findings derived from the UNOS database revealed 1- and 5-year survival rates of 75% and 64% in patients with iron overload, as compared to 83% and 70% in those without iron overload (Brandhagen 2001). More recent results from patients with haemochromatosis (n=217) transplanted between 1997 and 2006 revealed excellent 1- (86.1%), 3- (80.8%), and 5-year (77.3%) patient survival rates, which were not different from those transplanted for other liver diseases (Yu 2007).

LT halts production of mutated transthyretin (TTR) and therefore represents an accepted treatment for hereditary transthyretin (ATTR) amyloidosis, a systemic amyloidosis mainly affecting the peripheral nervous system and heart (Rocha 2016). Okumura et al. (2016) recently assessed 29 non-transplant and 36 transplant FAP V30M patients using an FAP clinical scoring system. They found that LT had beneficial effects on FAP clinical manifestations in these patients. However, the effects of transplantation on the clinical manifestations of FAP have not been systematically investigated and future studies are urgently warranted.

Outcome after liver transplantation for acute and acute-on-chronic liver failure

About half of acute hepatic failure (AHF) patients undergo LT. ALF accounts for 5-12% of LT activity worldwide and 7.3% in Europe (http://www.eltr.org/Overall-indication-and-results.html)

Of patients listed for transplantation, approximately one third will recover spontaneously without the need for grafting; thus, in as many as 20% of ALF patients LT is required (Lee 2012). Transplantation should be considered in those patients fulfilling Clichy or Kings College criteria (EASL CCPG on the Management of Acute (Fulminant) Liver Failure (2017); http://www.easl.eu/medias/cpg/ALF/English-report.pdf). Drug-induced liver injury due to acetaminophen overdose is the most common cause of LT for acute liver failure in developed countries (Craig 2010, Au 2011). Other etiologies comprise idiosyncratic drugs (such as isoniazid/rifampicin, cumarins, acetaminophen, ectasy, tricyclic antidepressants), Budd-Chiari syndrome, Wilson's Disease, hepatitis A, B and E infection or autoimmune disease.

Early postoperative complications in patients transplanted for AHF include sepsis, multisystem organ failure, and primary graft failure. Serum creatinine concentrations above 200 µmol/L pretransplant, non-white race of the recipient, donor body mass index >35 kg/m2 and recipient age >50 years have been suggested as risk factors for posttransplant mortality (Wigg 2005). Others reported that extended donor criteria rates and severe cerebral edema were associated with worse outcome (Chan 2009). The Edinburgh LT centre investigated the impact of perioperative renal dysfunction on posttransplant renal outcomes in AHF patients. They found that older age, female gender, hypertension, CSA and non-acetaminophen-induced AHF but not the severity of perioperative renal injury were predictive for the development of chronic kidney injury (Leithead 2011).

The results in patients transplanted for AHF have improved within the last decade due to the establishment of prognostic models, improved intensive care management and the option for LDLT which has a limited role in the US and Europe but plays a major role in Asia (Lo 2008). AHF was the indication for LDLT in more than 10% of the cohort reported by two Asian groups (Morioka 2007b, Lo 2004).

It has been reported that survival in patients with AHF is inferior to that of recipients with non-acute indications for LT in the first year but comparable in the long-term (Chan 2009, Wigg 2005). The US Acute Liver Failure Study Group found that two-year outcomes in initial survivors of AHF are generally good but that non-acetaminophen patients have a significantly lower survival, which may be related to pre-existing medical comorbidities (Fontana 2015).

Acute-on-chronic liver failure (ACLF) is characterised by acute decompensation of liver cirrhosis and is often combined with severe systemic inflammation, organ failure and a high mortality (transplantation-free-28-day mortality of 33%) (Schulz 2022). 1- year survival rates after LT for ACLF range from 70 to 80% depending on patient population and ALF severity. In recently published studies survival do not differ significantly from patients without ACLF (Schulz 2022). Further studies will be needed to improve current transplant allocation system for patients with this severe syndrome.

Conclusion

- LT is often the only life saving therapy in patients with acute liver disease, chronic liver disease or HCC
- Alcoholic and viral hepatitis are the most common reasons for LT worldwide, NAFLD is a strongly increasing
- The allocation system using the MELD score (creatinine, bilirubine and INR) optimises the priority of patients with severe liver disease
- Hypothermic machine perfusion expands the pool of usable livers
- Lifelong surveillance after LT is necessary to detect immunosuppression side-effect, graft failure or recurrence of underlying disease after LT
- Tailored immunsuppressive regims are necessary to improve graft and patient survival

LT is challenging due to a shortage of organs and a prolonged waiting-list time. The large disparity between the number of available deceased donor organs and recipients awaiting LT has created an ongoing debate regarding the appropriate selection criteria. A variety of approaches have been implemented to expand the organ donor pool including national efforts to expand deceased donor donation, split organ donations including LDLT, increased use of more elderly and obese donors and greater utilisation of expanded criteria donors. The rationale of allocation systems utilising the MELD score is to prioritise patients with severe liver dysfunction ("the sickest first"). This results in decreased waiting list mortality from 20 to 10% in the Eurotransplant region but also in a reduction of 1-year posttransplant survival by approximately 10%. A potential modification of the MELD allocation system or development of an improved prognostic scoring system is urgently warranted to optimise organ allocation in the future and to adjust gender difference.

Due to the availability of antiviral drugs, the survival of patients undergoing LT for HBV infection has dramatically improved and has become comparable to or even better than the survival of patients with nonvirus-related liver diseases. Protocols have been published in literature implementing withdrawal of HBIG or HBIG-free regimens, using only oral antivirals, in particular in patients at low risk of recurrence.

The availability of DAA all-oral combinations constitutes a substantial improvement in HCV therapy and in particular in patients formerly difficult-to-treat such as cirrhotic patients and in managing HCV infection after LT. SVR rates in LT patients are comparable with nontransplant patients and can be achieved with excellent tolerability.

Expansion of the donor pool by including HCV positive organs in the DAA era could substantially decrease waiting times and mortality rates for patients listed for LT. Mounting data demonstrate the safety of using organs from HCV-infected donors with subsequent treatment of HCV in the recipient. However, use of HCV positive donors in HCV negative LT recipients may currently be restricted to urgent situations and necessitates a robust informed consent process.

Data about the frequency of disease recurrence in cholestatic and autoimmune liver diseases vary in the literature. Diagnosis of disease relapse in cholestatic and autoimmune liver disease is more challenging than in the non-transplant setting. Most studies report excellent mediumterm and long-term results despite limited therapeutic options for disease recurrence.

LT in HCC patients provides excellent outcomes and low recurrence rates following the Milan criteria. Expansion of transplantation criteria beyond the Milan criteria has been discussed at length. The acceptance of a more liberal organ allocation policy may result in a further increase of the proportion of patients transplanted for HCC and denying the use of these organs to other patients for whom better results may be achieved. Recent developments in genomic and proteomic approaches may allow the identification of new biomarkers for prediction of HCC recurrence.

ALD is the leading indication for LT in European and US transplant centres. Early LT without fulfilling the 6-month abstinence rule should be restricted to those with severe disease who are not responding to medical therapy, have been subjected to a careful selection process and have a favourable addiction and psychosocial profile. German regulations require 6 months of alcohol sobriety in patients with ALD, however, in exceptional cases patients can get access to the waitlist through an audit process requested by the corresponding transplant centre and organised by Eurotransplant.

There should be psychosocial evaluation of the patient with ALD prior to LT considering possible risk factors for recurrence. Implementation of prognostic instruments for prediction of alcohol relapse are recommended. ALD patients on the waiting list should be monitored for alcohol use by regular clinical interviews and laboratory tests to confirm abstinence. However, standardisation and unified policy of the selection process may be helpful. Prospective studies are urgently needed to resolve the controversies that still surround the criteria for selection of those patients for LT.

The management of cardiovascular, renal, coagulopathic, cerebral and infectious complications in patients with AHF is clinically challenging. Prognostic models are helpful but not entirely accurate in predicting those who will require LT. Due to advances in intensive care medicine and surgical techniques, outcomes for patients with AHF have progressively improved over the last 2 decades.

CNI, at least at low doses, with or without other immunosuppressive

drugs, have been so far the cornerstone of immunosuppressive regimens in a substantial proportion of LT patients. Much attention has been directed to reducing CNI-associated long-term complications. Cardiovascular comorbidities due to metabolic complications such as diabetes mellitus, dyslipidaemia, obesity, and arterial hypertension account for 30-70% of long-term morbidity. Current trends of immunosuppressive strategies include CNI-sparing or CNI-free protocols including MMF- and/or mTOR-based immunosuppressive regimens and corticosteroid-avoidance protocols. mTOR-based immunosuppression should be used in HCC-patients due to antitumour effects. CNI delay with induction therapy for bridging the early postoperative phase should be considered especially in patients with high MELD scores. Finally, "individually tailored immunosuppressive" protocols may optimise drug efficacy, minimise drug toxicity and improve transplant outcome.

References

AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62(3):932-54. doi: 10.1002/hep.27950.

Abbas Z, Afzal R. Hepatitis E: when to treat and how to treat. Antivir Ther 2014;19(2):125-31.

Addolorato G, Bataller R, Burra P et al. Liver Transplantation for alcoholic liver disease. Transplantation 2016;100:981-98. doi:10.1097/, TP.0000000000001156.

Åberg F, Sallinen V, Tuominen S, European Liver and Intestine Transplant Association (ELITA). Cyclosporine vs. tacrolimus after liver transplantation for primary sclerosing cholangitis - a propensity score-matched intention-to-treat analysis. J Hepatol. 2024 Jan;80(1):99-108.

Alabraba E, Nightingale P, Gunson B, et al. A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. Liver Transpl 2009;15:330-40.

Alim A, Erdogan Y, Dayangac M, et al. Living Donor Liver Transplantation: The Optimal Curative Treatment for Hepatocellular Carcinoma Even Beyond Milan Criteria. Cancer Control. 2021.

Angus PW, Strasser SI, Patterson S, et al. A randomised study to assess the safety and efficacy of adefovir dipivoxil substitution for hepatitis B immune globulin in liver transplantation patients receiving long-term low dose IM HBIG and lamivudine prophylaxis. Hepatology 2007;46:238A.

ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol 2016;65(4):734-40.

Au JS, Navarro VJ, Rossi S. Drug-induced liver injury – its pathophysiology and evolving diagnostic tools. Aliment Pharmacol Ther 2011;34:11-20.

Avery RK, Alain S, Alexander BD; SOLSTICE Trial Investigators. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomised Clinical Trial. Clin Infect Dis. 2022 Sep 10;75(4):690-701.

Bajjoka I, Hsaiky L, Brown K, Abouljoud M. Preserving renal function in liver transplant recipients with rabbit anti-thymocyte globulin and delayed initiation of calcineurin inhibitors. Liver Transpl 2008;14:66-72.

Baker TB. Living liver donation, donor safety, and social media: Preparing for a new frontier. Liver Transpl 2017;23(2):131-132.

Barosa R, Teixeira C, Pinto J, E Branco JC. Early liver transplantation for severe alcoholic hepatitis - are we exploring all the tools? Liver Int 2017;37(9):1407-8.

Battistella S, D'Arcangelo F, Grasso M, et al. Liver Transplantation for NAFLD: indications and posttransplant management. Clin Mol Hepatol. 2022.

Beavers KL, Sandler RS, Shrestha R. Donor morbidity associated with right lobectomy for living donor liver transplantation to adult recipients. Liver Transpl 2002;8:110-7.

Beckebaum S (a), Cicinnati V, Brokalaki E, Frilling A, Gerken G, Broelsch CE. CNI-sparing regimens within the liver transplant setting: experiences of a single center. Clin Transpl 2004;215-20.

Beckebaum S (b), Cicinnati VR, Broelsch CE. Future directions in immunosuppression. Transplant Proc 2004;36:574S-6S.

Beckebaum S, Cicinnati V, Gerken G. Current concepts for prophylaxis and treatment of hepatitis B reinfection after liver transplantation. Med Klin (Munich) 2008;103:190-7.

Beckebaum S, Sotiropoulos G, Gerken G, Cicinnati V. Hepatitis B and liver transplantation: 2008 update. Rev Med Virol 2009;19:7-29.

Beckebaum S, Iacob S, Klein CG, et al. Assessment of allograft fibrosis by transient elastography and noninvasive biomarker scoring systems in liver transplant patients. Transplantation 2010;89:983-93.

Beckebaum S, Cicinnati VR. Conversion to combined mycophenolate mofetil and low-dose calcineurin inhibitor therapy for renal dysfunction in liver transplant patients: never too late? Dig Dis Sci 2011;56:4-6.

Beckebaum S (a), Kabar I, Cicinnati VR. Hepatitis B and C in liver transplantation: new strategies to combat the enemies. Rev Med Virol 2013;23(3):172-93.

Beckebaum S (b), Cicinnati VR, Radtke A, Kabar I. Calcineurin inhibitors in liver transplantation – still champions or threatened by serious competitors? Liver Int 2013;33(5):656-65.

Beckebaum S (c), Iacob S, Radtke A, Kabar I, Cicinnati VR. Body weight may not be sufficient for reliable estimation of subcutaneous hepatitis B immunoglobulin dose requirement. American Journal of Transplantation 2013;13:1615-16.

Beckebaum S, Herzer K, Bauhofer A, et al. Recurrence of hepatitis B infection in liver transplant patients receiving long-term hepatitis B immunoglobulin prophylaxis. Ann Transplant 2018;23:789-801.

Becker T, Foltys D, Bilbao I, et al. Patient outcomes in two steroid-free regimens using tacrolimus monotherapy after daclizumab induction and tacrolimus with mycophenolate mofetil in liver transplantation. Transplantation 2008;86:1689-94.

Benlloch S, Berenguer M, Prieto M, et al. De novo internal neoplasms after liver transplantation: increased risk and aggressive behavior in recent years? Am J Transplant 2004;4:596-604.

Bergquist A, Weismüller TJ, Levy C, Rupp C et al; International PSC Study Group. Impact on follow-up strategies in patients with primary sclerosing cholangitis. Liver Int. 2023 Jan;43(1):127-138.

Bethea E, Arvind A, Gustafson J et al. Immediate administration of antiviral therapy after transplantation of hepatitis C-infected livers into uninfected recipients: Implications for therapeutic planning. Am J Transplant 2019. doi: 10.1111/ajt.15768. [Epub ahead of print].

Bhartia B, Ward J, Guthrie JA, Robinson PJ. Hepatocellular carcinoma in cirrhotic livers: double-contrast thin-section MR imaging with pathologic correlation of explanted tissue. AJR Am J Roentgenol 2003;180:577-84.

Bhat M, Mara K, Dierkhising R, Watt KD. Gender, race and disease aetiology predict de novo malignancy risk following liver transplantation: Insights for future individualised cancer screening guidance. Transplantation 2018. doi: 10.1097/TP.0000000000002113. [Epub ahead of print].

Bittermann T, Hoteit MA, Abt PL, Forde KA, Goldberg D. Waiting time and explant pathology in transplant recipients with hepatocellular carcinoma: a novel study using national data. Am J Transplant 2014;14:1657-63.

Borg BB, Feng Z, Earl TM, Anderson CD. Hepatitis E in post-liver transplantation: is it time to routinely consider it? Clin Transplant 2016;30(9):975-9.

Brandhagen DJ. Liver transplantation for hereditary haemochromatosis. Liver Transpl 2001;7:663-7.

Broelsch CE, Whitington PF, Emond JC, et al. Liver transplantation in children from living related donors. Surgical techniques and results. Ann Surg 1991;214:428-37.

Brüggenwirth IMA, Mueller M, Lantinga VA, et al. Prolonged preservation by hypothermic machine perfusion facilitates logistics in liver transplantation: A European observational cohort study. Am J Transplant. 2022 Jul;22(7):1842-1851.

Buchholz BM, Ferguson JW, Schnitzbauer AA, et al. Liver and kidney recipient selection of hepatitis C virus viremic donors: Meeting consensus report from the 2019 controversies in transplantation. Transplantation 2020; 104(3):478-81.

Buchholz BM, Ferguson JW, Schnitzbauer AA et al.; International SiLVER study group. Randomised Sirolimus-based Early Calcineurin Inhibitor Reduction in Liver Transplantation: Impact on Renal Function. Transplantation. 2020 May;104(5):1003-1018.

Buell JF, Gross TG, Woodle ES. Malignancy after transplantation.Transplantation 2005;15:S254-64.

Buis CI, Geuken E, Visser DS, Kuipers F, Haagsma EB, Verkade HJ, et al. Altered bile composition after liver transplantation is associated with the development of nonanastomotic biliary strictures. J Hepatol 2009;50:69-79.

Burra P, Senzolo M, Adam R, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010;10:138-48.

Burra P, Germani G. Orthotopic liver transplantation In non-alcoholic fatty liver disease patients. Rev Recent Clin Trials. 2014;9(3):210-6.

Burton JR Jr, Terrault NA, Goldberg DS, et al. Liver and kidney recipient selection of HCV-viremic donors - Meeting Consensus Report from the 2019 Controversies in Transplantation. Transplantation 2019. doi: 10.1097/TP.0000000000003014. [Epub ahead of print].

Buti M, Mas A, Prieto M, et al. Adherence to lamivudine after an early withdrawal of hepatitis B immune globulin plays an important role in the long-term prevention of hepatitis B virus recurrence. Transplantation 2007;84:650-4.

Bzeizi KI, Smith R, Albenmousa A, et al. Long-Term Outcomes of Everolimus Therapy in De Novo Liver Transplantation: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Transplant Proc. 2021 Jan-Feb;53(1):148-158.

Cai CJ, Lu MQ, Chen YH, Zhao H, Li MR, Chen GH. Clinical study on prevention of HBV re-infection by entecavir after liver transplantation. Clin Transplant. Clin Transplant 2012;26(2):208-15.

Cantarovich M, Tzimas GN, Barkun J, Deschênes M, Alpert E, Tchervenkov J. Efficacy of mycophenolate mofetil combined with very low-dose cyclosporine microemulsion in long-term liver-transplant patients with renal dysfunction. Transplantation 2003;76:98-102.

Carbone M, Neuberger J. Liver transplantation in PBC and PSC: indications and disease recurrence. Clin Res Hepatol Gastroenterol 2011;35:446-54.

Carbone M, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatol 2014;60(1):210-23.

Carenco C, Assenat E, Faure S, Duny Y, Danan G, Bismuth M, Herrero A, Jung B, Ursic-Bedoya J, Jaber S, Larrey D, Navarro F, Pageaux GP. Tacrolimus and the risk of solid cancers after liver transplant: a dose effect relationship. Am J Transplant 2015;15(3):678-86.

Carlisle EM, Testa G. Adult to adult living related liver transplantation: Where do we currently stand? World J Gastroenterol 2012 Dec 14;18(46):6729-36.

Carrique L, Quance J, Tan A, et al. Results of Early Transplantation for Alcohol-Related Cirrhosis: Integrated Addiction Treatment With Low Rate of Relapse. Gastroenterology. 2021 Dec;161(6):1896-1906.e2.

Corpechot C, Chazouillères O, Belnou P, et al; Global PBC Study Group. Long-term impact of preventive UDCA therapy after transplantation for primary biliary cholangitis. J Hepatol. 2020 Sep;73(3):559-565.

Caroti L, Zanazzi M, Paudice N, et al. Conversion from calcineurin inhibitors to everolimus with low-dose cyclosporine in renal transplant recipients with squamous cell carcinoma of the skin. Transplant Proc 2012;44(7):1926-27.

Chan G, Taqi A, Marotta P, et al. Long-term outcomes of emergency liver transplantation for acute liver failure. Liver Transpl 2009;15:1696-702.

Charatcharoenwitthaya P, Pimentel S, Talwalkar, et al. Long-term survival and impact of ursodeoxycholic acid treatment for recurrent

primary biliary cirrhosis after liver transplantation. Liver Transpl 2007;13:1236-45.

Charlton M (a), Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015; 149: 649–59.

Charlton M (b), Gane E, Manns MP et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015;148(1):108-17.

Charlton M (c), Levitsky J, Aqel B et al. International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients. Transplantation 2019. doi: 10.1097/TP.0000000000002980.

Choi PC, Kim HJ, Choi WH, et al. Model for end-stage liver disease, model for end-stage liver disease-sodium and Child-Turcotte-Pugh scores over time for the prediction of complications of liver cirrhosis. Liver Int 2009;29:221-6.

Cholongitas E, Shusang V, Papatheodoridis GV, et al. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl 2008;14:138-43.

Cholongitas E, Goulis I, Antoniadis N, et al. New nucleos(t)ide analogue monoprophylaxis after cessation of hepatitis B immunoglobulin is effective against hepatitis B recurrence. Transpl Int 2014;27(10):1022-8.

Choudhary NS, Saigal S, Saraf N, Soin AS. Extrahepatic Malignancies and Liver Transplantation: Current Status. J Clin Exp Hepatol. 2021 Jul-Aug;11(4):494-500.

Cicinnati VR (a), Yu Z, Klein CG, et al. Clinical trial: switch to combined mycophenolate mofetil and minimal dose calcineurin inhibitor in stable liver transplant patients-assessment of renal and allograft function, cardiovascular risk factors and immune monitoring. Aliment Pharmacol Ther 2007;26:1195-208.

Copaci I, Lupescu I, Caceaune E, Chiriac G, Ismail G. Noninvasive Markers of improvement of liver steatosis achieved by weight reduction in patients with nonalcoholic fatty liver disease. Rom J Intern Med 2015;53(1):54-62.

Cornberg M, Protzer U, Petersen J, et al. Prophylaxis, diagnosis and therapy of hepatitis B virus infection – the German guideline. Z Gastroenterol 2011;49:871-930.

Cornberg M, Sandmann L, Protzer U et al.; Collaborators:. S3-Leitlinie der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) zur Prophylaxe, Diagnostik und Therapie der Hepatitis-B-Virusinfektion – (AWMF-Register-Nr. 021-11). Z Gastroenterol. 2021 Jul;59(7):691-776.

Cotter TG, Paul S, Sandıkçı B et al. Improved graft survival after liver transplantation for recipients with hepatitis C virus in the direct-acting antiviral era. Liver Transpl 2019;25(4):598-609. doi: 10.1002/lt.25424.

Cotter TG, Charlton M. Nonalcoholic steatohepatitis after liver transplantation. Liver Transpl 2020;26(1):141-59

Craig DG, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. Aliment Pharmacol Ther 2010;31:1064-76.

Créput C, Blandin F, Deroure B, et al. Long-term effects of calcineurin inhibitor conversion to mycophenolate mofetil on renal function after liver transplantation. Liver Transpl 2007;13:1004-10.

Crismale JF, Khalid M, Bhansali A,et al. Liver, simultaneous liver-kidney, and kidney transplantation from hepatitis C positive donors in hepatitis C negative recipients: A single-center study. Clin Transplant 2019:e13761.

Cross T, Jothimani D, Heneghan MA, Harrison PM. Non-invasive assessment of fibrosis in liver grafts due to hepatitis C virus recurrence. Clin Transplant 2011;25:345-51.

Czigany Z, Pratschke J, Froněk J, et al. Hypothermic Oxygenated Machine Perfusion Reduces Early Allograft Injury and Improves Post-transplant Outcomes in Extended Criteria Donation Liver Transplantation From Donation After Brain Death: Results From a Multicenter Randomised Controlled Trial (HOPE ECD-DBD). Ann Surg. 2021 Nov 1;274(5):705-712.

Dar FS, Faraj W, Zaman MB, Bartlett A, et al. Outcome of liver transplantation in hereditary haemochromatosis. Transpl Int 2009;22:717-24.

Darwish Murad S, Metselaar HJ. The invasion of fatty liver disease in liver transplantation. Transpl Int 2015; 29(4):416-7.

Daswani R, Kumar A, Sharma P, Singla V, Bansal N, Arora A. Role of liver transplantation in severe alcoholic hepatitis. Clin Mol Hepatol 2018;24(1):43-50.

Demetris AJ, Murase N, Lee RG, et al. Chronic rejection. A general overview of histopathology and pathophysiology with emphasis on liver, heart and intestinal allografts. Ann Transplant 1997;2:27-44.

De Martin E, Coilly A, Chazouillères O, et al.; FILFOIE consortium – France. Early liver transplantation for corticosteroid non-responders with acute severe autoimmune hepatitis: The SURFASA score. J Hepatol. 2021 Jun;74(6):1325-1334.

Demetris AJ, Bellamy C, Hubscher SG, et al. 2016 Comprehensive update of the Banff Working Group on liver allograft pathology: introduction of antibody-mediated rejection. Am J Transplant 2016;16:2816-35.

De Simone P (a), Fagiuoli S, Cescon M, De Carlis L, Tisone G, Volpes R, Cillo U; Consensus Panel. Use of everolimus in liver transplantation: Recommendations from a Working Group. Transplantation 2016;101(2):239-251.

De Simone P (b), Romagnoli R, Tandoi F, et l. Early introduction of subcutaneous Hepatitis B Immunoglobulin following liver transplantation for Hepatitis B virus infection: A prospective, multicenter study. Transplantation 2016;100(7):1507-12.

Dew MA, DiMartini AF, Steel J, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 2008;14:159-72.

Di Benedetto F, Tarantino G, Montalti R, et al. Sorafenib before liver transplantation for hepatocellular carcinoma: risk or give up. Transpl Int 2011;24(11):e97.

Dobrindt EM, Keshi E, Salim Y, et al. Hepatitis B Immunoglobulin discontinuation in long-term liver transplant patients. Transpl Infect Dis. 2020 Aug;22(4):e13303.

Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007;246:502-9.

Dutkowski P, Oberkofler CE, Béchir M, et al. The model for end-stage liver disease allocation system for liver transplantation saves lives, but increases morbidity and cost: a prospective outcome analysis. Liver Transpl 2011;17:674-84.

Duvoux C, Roudot-Thoraval F, Decaens T,et al; Liver Transplantation French Study Group. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143(4):986-94.

EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016;64:433-85.https://dx.doi.org/10.1016/j.jhep.2015.10.006.

EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol. 2020 Nov;73(5):1170-1218.

EASL Clinical Practise Guideline: Management of alcohol-related liver disease. J Hepatol 2018;69:154-81. https://www.easl.eu/medias/cpg/Alcoholic-LiverDisease/2018/English-report.pdf.

EASL Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection. J Hepatol 2017;67:370-98. https://www.easl.eu/medias/cpg/management-of-hepatitis-B-virus-infection/English-report.pdf.

EASL Clinical Practical Guidelines on the Management of Acute (Fulminant) Liver Failure. J Hepatol 2017;66:1047-81. https://www.easl.eu/medias/cpg/ALF/English-report.pdf

EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol 2018;68:1256-1271. https://www.journal-of-hepatology.eu/article/S0168-8278(18)30155-7/pdf.

Ecker BL, Hoteit MA, Forde KA, et al. Patterns of discordance between pretransplant imaging stage of hepatocellular carcinoma and posttransplant pathologic stage: A contemporary appraisal of the milan criteria. Transplantation 2018;102(4):648-55.

Egawa H, Sakisaka S, Teramukai S, Sakabayashi S, Yamamoto M, Umeshita K, Uemoto S. Long-term outcomes of living-donor liver transplantation for primary biliary cirrhosis: A Japanese multicenter Study. Am J Transplant 2016;16(4):1248-57.

Eid AJ, Razonable RR. New developments in the management of cytomegalovirus infection after solid organ transplantation. Drugs 2010;70:965-81.

Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med 2012;367(4):329-9.

Fairfield C, Penninga L, Powell J, Harrison EM, Wigmore SJ. Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients. Cochrane Database Syst Rev 2018;9:4:CD007606. doi: 10.1002/14651858.CD007606.pub4. [Epub ahead of print].

Faisal N, Renner EL. Recurrence of autoimmune liver diseases after liver transplantation. World J Hepatol 2015; 7(29): 2896–2905.

Fairfield C, Penninga L, Powell J, Harrison EM, Wigmore SJ. Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients. Cochrane Database Syst Rev 2018;4:CD007606.

Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006;6:783-90.

Ferrarese A, Morelli MC, Carrai P, et al. Outcomes of Liver Transplant for Adults With Wilson's Disease. Liver Transpl. 2020 Apr;26(4):507-516.

Fevery J, Henckaerts L, Van Oirbeek R, et al. Malignancies and mortality in 200 patients with primary sclerosering cholangitis: a long-term single-centre study. Liver Int 2012; 32:214-22.

Filipponi F, Callea F, Salizzoni M, et al. Double-blind comparison of hepatitis C histological recurrence rate in HCV+ liver transplant recipients given basiliximab + steroids or basiliximab + placebo, in addition to cyclosporine and azathioprine. Transplantation 2004;78:1488-95.

Finkenstedt A, Graziadei IW, Oberaigner W, et al. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. Am J Transplant 2009; 9:2355-61.

Fischer L, Klempnauer J, Beckebaum S, et al. A randomised, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation-PROTECT. Am J Transplant 2012;12:1855-65.

Fontana RJ, Ellerbe C, Durkalski VE, et al. Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicenter study. Liver Int 2015;35(2):370-80. doi: 10.1111/liv.12632. Epub 2014 Jul 28.

Frilling A, Malago M, Weber F, et al. Liver transplantation for patients with metastatic endocrine tumours. Liver Transpl 2006;12:1089-96.

Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De novo malignancies after liver transplantation: a major cause of late death. Liver Transpl 2001;7:S109-18.

Fung J, Cheung C, Chan SC, Yuen MF. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. Gastroenterology 2011;141:1212-9.

Fung JY. Liver transplantation for severe alcoholic hepatitis-The CON view. Liver Int 2017;37(3):340--2. doi: 10.1111/liv.13286.

Fung J, Mak LY, Chan AC, et al. Model for end-stage liver disease with additional criteria to predict short-term mortality in severe flares of chronic hepatitis B. Hepatology 2019. doi: 10.1002/hep.31086. [Epub ahead of print].

Gane E, Strasser SI, Patterson S, et al. A prospective study on the safety and efficacy of lamivudine and adefovir dipivoxil prophylaxis in HBsAg positive liver transplantation candidates. Hepatology 2007;46:479A.

Gane EJ, Patterson S, Strasser SI, McCaughan GW, Angus PW. Combination of lamivudine and adefovir without hepatitis B immune globulin is safe and effective prophylaxis against hepatitis B virus recurrence in hepatitis B surface antigen positive liver transplant candidates. Liver Transpl 2013;19(3):268-74.

Gane EJ, Robson RA, Bonacini M et al. Safety, anti-viral efficacy and pharmacokinetics (PK) of sofosbuvir (SOF) in patients with severe renal impairment. Hepatology 2014;60:667a-667.

Garcia CE, Ribeiro HB, Garcia RL, et al. Mycophenolate mofetil in stable liver transplant patients with calcineurin inhibitor-induced renal impairment: single-center experience. Transplant Proc 2003;35:1131-2.

Gedaly R, Daily MF, Davenport D, et al. Liver transplantation for the treatment of liver metastases from neuroendocrine tumours: an analysis of the UNOS database. Arch Surg 2011;146:953-8.

Geissler EK, Schnitzbauer AA, Zülke C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: A randomised, multicenter, open-label phase 3 trial. Transplantation 2016;100(1):116-25.

Giard JM, Dodge JL, Terrault N. Superior wait-list outcomes in patients with alcohol-associated liver disease compared to other indications for liver transplantation. Liver Transpl 2019. doi: 10.1002/lt.25485. [Epub ahead of print].

Gonwa TA, Mai ML, Melton LB, Hays SR, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. Transplantation 2001;72:1934-9.

Gonzalez-Koch A, Czaja AJ, Carpenter HA, et al. Recurrent autoimmune hepatitis after orthotopic liver transplantation. Liver Transpl 2001;7:302-10.

Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. Ann Surg 1997;225:472-81.

Graziadei IW, Wiesner RH, Marotta PJ, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. Hepatology 1999;30:1121-7.

Graziadei IW, Schwaighofer H, Koch R, et al. Long-term outcome of endoscopic treatment of biliary strictures after liver transplantation. Liver Transpl 2006;12:718-25.

Graziadei IW, Zoller H, Fickert P, et al. Indications for liver transplantation in adults: Recommendations of the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). Wien Klin Wochenschr 2016;128(19-20):679-90.

Gross GE, Eisert L, Doerr HW, et al. S2k-Leitlinie zur Diagnostik und Therapie des Zoster und der Postzosterneuralgie. J Dtsch Dermatol Ges. 2020 Jan;18(1):55-79.

Gu YH, Du JX, Ma ML. Sirolimus and non-melanoma skin cancer prevention after kidney transplantation: A meta-analysis. Asian Pac J Cancer Prev 2012;13(9):4335-9.

Guba M, von Breitenbuch P, Steinbauer M, et al. Rapamycin inhibits primary and metastatic tumour growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128-35.

Guichelaar MM, Kendall R, Malinchoc M, Hay JE. Bone mineral density before and after OLT: long-term follow-up and predictive factors. Liver Transpl 2006;12(9):1390-402.

Guichelaar MM, Schmoll J, Malinchoc M, Hay JE. Fractures and avascular necrosis before and after orthotopic liver transplantation: longterm follow-up and predictive factors. Hepatology 2007;46(4):1198-207.

Guillaud O, Jacquemin E, Couchonnal E, et al. Long term results of liver transplantation for alpha-1 antitrypsin deficiency. Dig Liver Dis. 2021 May;53(5):606-611.

Haga H, Miyagawa-Hayashino A, Taira K, Morioka D, Egawa H, Takada Y, Manabe T, Uemoto S. Histological recurrence of autoimmune liver diseases after living-donor liver transplantation. Hepatol Res 2007;37 Suppl 3:S463–S69.

Hanouneh IA, Macaron C, Lopez R. Risk of colonic neoplasia after liver transplantation for primary sclerosing cholangitis. Inflamm Bowel Dis 2012;18:269-74.

Harms MH, van Buuren HR, Corpechot C, et al.

Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol 2019;71(2):357-65.

Harper SJ, Gelson W, Harper IG, Alexander GJ, Gibbs P. Switching to sirolimus-based immune suppression after liver transplantation is safe and effective: a single-center experience. Transplantation 2011;91:128-32.

Hashimoto E, Shimada M, Noguchi S, et al. Disease recurrence after living liver transplantation for primary biliary cirrhosis: a clinical and histological follow-up study. Liver Transpl 2001;7:588-95.

Heimbach JK. Successful liver transplantation for hilar cholangiocarcinoma. Curr Opin Gastroenterol. 2008;24:384-8.

Hernandez Mdel P, Martin P, Simkins J. Infectious complications after liver transplantation. Gastroenterol Hepatol 2015;11(11):741-53.

Hiatt JR, Carmody IC, Busuttil RW. Should we expand the criteria for hepatocellular carcinoma with living-donor liver transplantation?-no, never. J Hepatol 2005;43:573-7.

Hinz M, Wree A, Jochum C et al High age and low sodium urine concentration are associated with poor survival in patients with hepatorenal syndrome. Ann Hepatol 2013;12(1):92-9.

Ho GT, Seddon AJ, Therapondos G, Satsangi J,Hayes PC. The clinical course of ulcerative colitis after orthotopic liver transplantation for primary sclerosing cholangitis: further appraisal of immunosuppression post transplantation. Eur J Gastroenterol Hepatol 2005;17:1379-85.

Höfer A, Jonigk D, Hartleben B, et al. DSA Are Associated With More Graft Injury, More Fibrosis, and Upregulation of Rejection-associated Transcripts in Subclinical Rejection. Transplantation. 2020 Mar;104(3):551-561.

Hong JC, Jones CM, Duffy JP, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. Arch Surg 2011;146:683-9.

Hoyos S, Escobar J, Cardona D, et al. Factors associated with recurrence and survival in liver transplant patients with HCC – a single center retrospective study. Ann Hepatol 2015;14(1):58-63.

Hüsing A, Cicinnati VR, Beckebaum S et al. Endoscopic ultrasound: valuable tool for diagnosis of biliary complications in liver transplant recipients? Surg Endosc 2015;29(6):1433-8.

Hüsing A (a), Schmidt M, Beckebaum S, Cicinnati VR, Koch R, Thölking G, Stella J, Heinzow H, Schmidt HH, Kabar I. Long-term renal function in liver transplant recipients after conversion from calcineurin inhibitors to mTOR Inhibitors. Ann Transplant 2015 26;20:707-13.

Hüsing A (b), Cicinnati VR, Maschmeier M, Schmidt HH, Wolters HH, Beckebaum S, Kabar I. Complications after endoscopic sphincterotomy in liver transplant recipients: A retrospective single-centre study. Arab J Gastroenterol 2015;16(2):46-9.

Hytiroglou P, Gutierrez JA, Freni M, et al. Recurrence of primary biliary cirrhosis and development of autoimmune hepatitis after liver transplant: A blind histologic study. Hepatol Res 2009;39:577-84.

Iacob S, Cicinnati VR, Dechêne A, et al. Genetic, immunological and clinical risk factors for biliary strictures following liver transplantation. Liver Int 2012;32(8):1253-61.

Iida T, Ogura Y, Oike F, Hatano E, Kaido T, Egawa H, Takada Y, Uemoto S. Surgery-related morbidity in living donors for liver transplantation. Transplantation 2010;89:1276–82.

Im GY, Kim-Schluger L, Shenoy A,et al. Early liver transplantation for severe alcoholic hepatitis in the United States-A single-center experience. Am J Transplant 2016;16(3):841-9. doi: 10.1111/ajt.13586.

Im GY, Cameron AM, Lucey MR. Liver transplantation for alcoholic hepatitis. J Hepatol 2019;70(2):328-34.

Invernizzi F, Iavarone M, Zavaglia C, et al.

Experience with early sorafenib treatment with mTOR inhibitors in hepatocellular carcinoma recurring after liver transplantation. Transplantation 2019 doi: 10.1097/TP.0000000000002955. [Epub ahead of print].

Jadlowiec CC, Morgan PE, Nehra AK, et al. Not All Cellular Rejections Are the Same: Differences in Early and Late Hepatic Allograft Rejection. Liver Transpl. 2019 Mar;25(3):425-435.

Jelic S, Sotiropoulos GC; ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:59-64.

Jimenez C, Marques E, Manrique A, al. Incidence and risk factors of development of lung tumours after liver transplantation. Transplant Proc 2005;37:3970-2.

Jørgensen KK, Lindström L, Cvancarova M, et al. Colorectal neoplasia in patients with primary sclerosing cholangitis undergoing liver transplantation: a Nordic multicenter study. Scand J Gastroenterol 2012;47(8-9):1021-9.

Jørgensen KK, Lindström L, Cvancarova M et al. Immunosuppression after liver transplantation for primary sclerosing cholangitis influences activity of inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11(5):517-23.

John PR, Thuluvath PJ. Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. Liver Transpl 2002;8:708-13.

Kahn J, Wagner D, Homfeld N, Müller H, Kniepeiss D, Schemmer P. Both sarcopenia and frailty determine suitability of patients for liver transplantation-A systematic review and meta-analysis of the literature. Clin Transplant 2018;32(4):e13226. doi: 10.1111/ctr.13226. [Epub ahead of print].

Kaltenborn A, Salinas R, Jäger MD, Lehner F, Sakirow L, Klempnauer J, Schrem H. Model of end-stage liver disease score and derived variants lack prognostic ability after liver transplantation. Ann Transplant 2015;20:441-8.

Kamar N (a), Abravanel F, Selves J, et al. Influence of immunosuppressive therapy on the natural history of genotype 3 hepatitis-E virus infection after organ transplantation. Transplantation 2010;89(3):353-60.

Kamar N (b), Rostaing L, Abravanel F,et al. Ribavirin therapy inhibits viral replication on patients with chronic hepatitis e virus infection. Gastroenterology 2010.;139(5):1612-8.

Kamar N (c) Rostaing L, Abravanel F,et al. Pegylated interferon-alpha for treating chronic hepatitis E virus infection after liver transplantation. Clin Infect Dis 2010;50(5):e30-e3.

Kamar N, Garrouste C, Haagsma EB, et al. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. Gastroenterology 2011;140(5):1481-9.

Kamar N, Izopet J, Tripon S, Bismuth M, Hillaire S, Dumortier J, Radenne S, Coilly A, Garrigue V, D'Alteroche L, Buchler M, Couzi L, Lebray P, Dharancy S, Minello A, Hourmant M, Roque-Afonso AM, Abravanel F, Pol S, Rostaing L, Mallet V. Ribavirin for chronic hepatitis E virus infection in transplant recipients. N Engl J Med 2014;370(12):1111-20.

Kamdar KY, Rooney CM, Heslop HE. Posttransplant lymphoproliferative disease following liver transplantation. Curr Opin Organ Transplant 2011;16:274-80.

Kang I, Lee JG, Choi SH, et al. Impact of everolimus on survival after liver transplantation for hepatocellular carcinoma. Clin Mol Hepatol. 2021 Oct;27(4):589-602.

Kapoor D, Guptan RC, Wakil SM, et al. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. J Hepatol 2000;33:308-12.

Kapoor VK. Bile duct injury repair – earlier is not better. Front Med 2015:9(4):508-11.

Kasturi KS, Chennareddygari S, Mummadi RR. Effect of bisphosphonates on bone mineral density in liver transplant patients: a metaanalysis and systematic review of randomised controlled trials. Transpl Int 2010;23(2):200-7.

Kawahara T, Asthana S, Kneteman NM. m-TOR inhibitors: What role in liver transplantation? J Hepatol 2011;55(6):1441-51.

Kawasaki S, Makuuchi M, Matsunami H, et al. Living related liver transplantation in adults. Ann Surg 1998;227:269-74.

Kemmer N, Kaiser T, Zacharias V, Neff GW. Alpha-1-antitrypsin deficiency: outcomes after liver transplantation. Transplant Proc 2008;40:1492-4.

Kim JM, Kwon CH, Joh JW, Ha YE, Sinn DH, Choi GS, Peck KR, Lee SK. Oral valganciclovir as a preemptive treatment for cytomegalovirus (CMV) Infection in CMV-seropositive liver transplant recipients. PLoS One 2015; 10(5):e0123554.doi: 10.1371/journal.pone.0123554. eCollection 2015.

Kneteman NM, Oberholzer J, Al Saghier M, et al. Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. Liver Transpl 2004;10:1301-11.

Knight SR, Friend PJ, Morris PJ. Role of transplantation in the management of hepatic malignancy. Br J Surg 2007;94:1319-30.

Knighton S, Agarwal K, Heneghan MA, et al. A pharmacist delivered stratified conversion protocol from hepatitis B immunoglobulin (HBIG) to tenofovir or entecavir is efficacious, safe and cost-effective for prevention of recurrence of hepatitis B virus (HBV) in liver transplant (LT) recipients. Hepatology 2012;54:619A.

Konrad T, Steinmüller T, Vicini P, et al. Regulation of glucose tolerance in patients after liver transplantation: impact of cyclosporin versus tacrolimus therapy. Transplantation 2000;69:2072-8.

Kotton CN, Kumar D, Caliendo AM,et al.; The Transplantation Society International CMV Consensus Group. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation 2018;102(6):900-31. doi: 10.1097/TP.0000000000002191.

Krinsky GA, Lee VS, Theise ND, et al. Transplantation for hepatocellular carcinoma and cirrhosis: sensitivity of magnetic resonance imaging. Liver Transpl 2002;8:1156-64.

Kubiliun M, Patel SJ, Hur C, Dienstag JL, Luther J. Early liver transplantation for alcoholic hepatitis: Ready for primetime? J Hepatol 2018;68(3):380-2.

Kulik L, Heimbach JK, Zaiem F et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology 2018 ;67(1):381-400.

Kwong AJ, Lai JC, Dodge JL, Roberts JP. Outcomes for liver transplant candidates listed with low model for end-stage liver disease score. Liver Transpl 2015;21(11):1403-9.

Kwong A, Kim WR, Mannalithara A, Heo NY, Udompap P, Kim D. Decreasing mortality and disease severity in hepatitis C patients awaiting liver transplantation in the United States. Liver Transpl 2017. doi: 10.1002/lt.24973. [Epub ahead of print].

Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 2009; 50:2001-6.

Lee BP (a), Terrault NA. Early liver transplantation for severe alcoholic hepatitis: moving from controversy to consensus. Curr Opin Organ Transplant 2018;23(2):229-36.

Lee BP (b), Vittinghoff E, Hsu C,et al. Predicting low-risk for sustained alcohol use after early liver transplant for acute alcoholic hepatitis: The sustained alcohol use post-liver transplant score. Hepatology 2019;69(4):1477-87.

Lee BP (c), Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. Gastroenterology 2018;155(2):422-30.e1.

Lee BP (d), Im GY, Rice JP, et al. Patterns of Alcohol Use After Early Liver Transplantation for Alcoholic Hepatitis. Clin Gastroenterol Hepatol. 2022 Feb;20(2):409-418.e5.

Lee BP (e), Roth N, Rao P, et al. Artificial intelligence to identify harmful alcohol use after early liver transplant for alcohol-associated

hepatitis. Am J Transplant. 2022 Jul;22(7):1834-1841.

Legrand-Abravanel F, Kamar N, Sandres-Saune K, Garrouste C, Dubois M, Mansuy JM, Muscari F, Sallusto F, Rostaing L, Izopet J. Characteristics of autochthonous hepatitis E virus infection in solid-organ transplant recipients in France. J Infect Dis 2010;202(6):835-44.

Leithead JA, Ferguson JW, Bates CM, Davidson JS, Simpson KJ, Hayes PC. Chronic kidney disease after liver transplantation for acute liver failure is not associated with perioperative renal dysfunction. Am J Transplant 2011;11:1905-15.

Lerut J, Bonaccorsi-Riani E, Finet P, Gianello P. Minimisation of steroids in liver transplantation. Transpl Int 2009; 22:2-19.

Levitsky J, Thudi K, Ison MG, Wang E, Abecassis M. Alemtuzumab induction in non-hepatitis C positive liver transplant recipients. Liver Transpl 2011;17:32-7.

Levitsky (b) J, Formica RN, Bloom RD, et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. Am J Transplant. 2017 Nov;17(11):2790-2802.

Liang W, Wang D, Ling X, et al. Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: A meta-analysis. Liver Transpl 2012;18(1):62-9.

Liang HR, Hsieh CE, Lin KH. Living donor liver transplantation for hepatocellular carcinoma beyond the Milan criteria: outcome of expanded criteria in tumour size. BMC Surg. 2021 Nov 19;21(1):401.

Liermann Garcia RF, Evangelista Garcia C, McMaster P, Neuberger J. Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single center. Hepatology 2001;33:22-7.

Lim WH, Ng CH, Ow ZGW, et al. A systematic review and meta-analysis on the incidence of osteoporosis and fractures after liver transplant. Transpl Int. 2021 Jun;34(6):1032-1043.

Lin M, Mittal S, Sahebjam F, Rana A, Sood GK. Everolimus with early withdrawal or reduced-dose Calcineurin-Inhibitors improves renal function in Liver Transplant Recipients: A systematic review and meta-analysis. Clin Transplant 2016, doi: 10.1111/ctr.12872. [Epub ahead of print].

Lin S, Hall A, Kumar R, Quaglia A, Jalan R. Validation of the SURFASA score to define steroid responsiveness in patients with acute autoimmune hepatitis. J Hepatol. 2022 Feb;76(2):485-487.

Lindström L, Jørgensen KK, Boberg KM et al. Risk factors and prognosis for recurrent primary sclerosing cholangitis after liver transplantation: a Nordic Multicentre Study. Scand J Gastroenterol. 2018 Mar;53(3):297-304.

Lisotti A, Fusaroli P, Caletti G. Role of endoscopy in the conservative management of biliary complications after deceased donor liver transplantation. World J Hepatol 2015;7(30):2927-32.

Liu X, Ling Z, Li L, Ruan B. Invasive fungal infections in liver transplantation. Int J Infect Dis 2011;15:e298-304.

Llado L, Fabregat J, Castellote J, et al. Impact of immunosuppression without steroids on rejection and hepatitis C virus evolution after liver transplantation: results of a prospective randomised study. Liver Transpl 2008;14:1752-60.

Lo CM, Fan ST, Liu CL, et al. Lessons learned from one hundred right lobe living donor liver transplants. Ann Surg 2004;240:151-8.

Lo CM, Liu CL, Lau GK, Chan SC, Ng IO, Fan ST. Liver transplantation for chronic hepatitis B with lamivudine-resistant YMDD mutant using add-on adefovir dipivoxil plus lamivudine. Liver Transpl 2005;11:807-13.

Lo CM. Liver transplantation for acute liver failure: not too early but never too late. Liver Transpl 2008;14:1243-4.

Lucey MR. Liver transplantation for severe alcoholic hepatitis - The PRO view. Liver Int 2017;37(3):343-344.

Machairas N, Kostakis ID, Tsilimigras DI, Prodromidou A, Moris D.

Liver transplantation for hilar cholangiocarcinoma: A systematic review. Transplant Rev (Orlando) 2020;34(1):100516.

Malhotra N, Beaton MD. Management of non-alcoholic fatty liver disease in 2015. World J Hepatol 2015;7(30):2962-7.

Manns M, Samuel D, Gane EJ et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicenter, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16(6):685-97.

Markakis GE, Papatheodoridis GV, Cholongitas E. Epidemiology and treatment of hepatitis E in the liver transplantation setting: A literature review. J Viral Hepat. 2022 Sep;29(9):698-718.

Marroni CA. Management of alcohol recurrence before and after liver transplantation. Clin Res Hepatol Gastroenterol 2015 Sep;39 Suppl 1:S109-14.

Marroni CA, Fleck AM Jr, Fernandes SA, Galant LH, Mucenic M, de Mattos Meine MH, Mariante-Neto G, Brandão ABM. Liver transplantation and alcoholic liver disease: History, controversies, and considerations. World J Gastroenterol 2018;24(26):2785-805.

Marot A, Dubois M, Trépo E, Moreno C, Deltenre P. Liver transplantation for alcoholic hepatitis: A systematic review with meta-analysis. PLoS One 2018;13(1):e0190823. doi: 10.1371/journal.pone.0190823

Martin AP, Bartels M, Redlich J, Hauss J, Fangmann J. A single center experience with liver transplantation for Wilson's disease. Clin Transplant 2008;22:216-21.

Martin P, DiMartini A, Feng S, Brown R, Jr, Fallon M. AASLD PRACTICE GUIDELINE. Evaluation for liver transplantation in adults: 2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59(3):1144-1165.

Massie AB, Caffo B, Gentry SE, Hall EC. MELD exceptions and rates of waiting list outcomes. Am J Transplant 2011;11:2362-71.

Masuoka HC, Rosen CB. Transplantation for cholangiocarcinoma. Clin Liver Dis 2011;15:699-715.

Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365(19):1790-1800.

Mazzaferro V, Sposito C, Zhou J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. Gastroenterology 2018;154(1):128-39.

McKenna M, Epperla N, Ghobadi A, et al. Real-world evidence of the safety and survival with CD19 CAR-T cell therapy for relapsed/refractory solid organ transplant-related PTLD. Br J Haematol. 2023 Jul;202(2):248-255

McPherson S, Elsharkawy AM, Ankcorn M, Ijaz S, Powell J, Rowe I, Tedder R, Andrews PA8. Summary of the British Transplantation Society UK Guidelines for Hepatitis E and Solid Organ Transplantation. Transplantation 2018; 102(1):15-20.

Meeks AC, Madill J. Sarcopenia in liver transplantation: A review. Clin Nutr ESPEN 2017;22:76-80.Memon K, Lewandowski RJ, Riaz A, Salem R. Yttrium 90 microspheres for the treatment of hepatocellular carcinoma. Recent Results Cancer Res 2013;190:207-24.

Merion RM, Schaubel DE, Dykstra DM, et al. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-13.

Merli M, Giannelli V, Gentili F, et al. Ribavirin priming improves the virological response to antiviral treatment in transplanted patients with recurrent hepatitis C: a pilot study. Antivir Ther 2011;16:879-85.

Mitchell MC, Maddrey WC. Changing Times in Liver Transplantation for alcohol-associated liver disease. JAMA Intern Med 2019;179(3):348-350.

Moini M, Mistry P, Schilsky ML. Liver transplantation for inherited metabolic disorders of the liver. Curr Opin Organ Transplant 2010;15:269-76.

Molmenti EP, Netto GJ, Murray NG, et al. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. Liver Transpl 2002;8:519-26.

Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A protects against primary biliary cirrhosis recurrence after liver transplantation. Am J Transplant 2010;10:852-8.

Montano-Loza AJ, Bhanji RA, Wasilenko S, Mason AL. Systematic review: recurrent autoimmune liver diseases after liver transplantation. Aliment Pharmacol Ther 2016;45:4:485-500.

Montano-Loza AJ, Ronca V, Ebadi M, et al; International Autoimmune Hepatitis Group (IAIHG). Risk factors and outcomes associated with recurrent autoimmune hepatitis following liver transplantation. J Hepatol. 2022 Jul;77(1):84-97.

Factors associated with recurrence of primary biliary cholangitis after liver transplantation and effects on graft and patient survival. Gastroenterology 2019;156(1):96-107.e1.

Moreira Kulak CA, Cochenski B, Borba VZ, Kulak J, et al. Posttransplantation osteoporosis. Arq Bras Endocrinol Metab 2010;54:143-9.

Moreno Planas JM, Cuervas-Mons Martinez V, Rubio Gonzalez E, et al. Mycophenolate mofetil can be used as monotherapy late after liver transplantation. Am J Transplant 2004;4:1650-5.

Morioka D (a), Egawa H, Kasahara M, et al. Impact of human leukocyte antigen mismatching on outcomes of living donor liver transplantation for primary biliary cirrhosis. Liver Transpl 2007;13:80-90.

Morioka D (b), Egawa H, Kasahara M, et al. Outcomes of adult-to-adult living donor liver transplantation. A single institution`s experience with 335 consecutive cases. Ann Surg 2007;245:315-25.

Morris PD, Laurence JM, Yeo D, Crawford M, et al. Can response to locoregional therapy help predict long-term survival after liver transplantation for hepatocellular carcinoma? A systematic review. Liver Transpl. 2016 Dec 22. doi: 10.1002/lt.24689.

Mullen KD, Sanyal AJ, Bass NM, et al. Rifaximin is safe and well tolerated for long-term maintenance of remission from overt hepatic encephalopathy. Clin Gastroenterol Hepatol 2014;12(8):1390-7.

Mumtaz K, Faisal N, Husain S, et al. Universal prophylaxis or preemptive strategy for cytomegalovirus disease after liver transplantation: A systematic review and meta-analysis. Am J Transplant 2015;15(2):472-81.

Nadalin S, Capobianco I, Königsrainer I, Harder B, Königsrainer A. Living liver donor: indications and technical aspects. Chirurg. 2015;86(6):609-21.

Naoumov NV, Lopes AR, Burra P, et al. Randomised trial of lamivudine versus hepatitis B immunoglobulin for long-term prophylaxis of hepatitis B recurrence after liver transplantation. J Hepatol 2001;34:888-94.

Nangia G, Borges K, Reddy KR. Use of HCV-infected organs in solid organ transplantation: An ethical challenge but plausible option. J Viral Hepat 2019;26(12):1362-71.

Nel JD, Epstein S. Metabolic Bone Disease in the Posttransplant Population: Preventative and Therapeutic Measures. Med Clin North Am 2016;100(3):569-86.

Neuberger J. Incidence, timing, and risk factors for acute and chronic rejection. Liver Transpl Surg 1999;5:S30-6.

Notarpaolo A, Layese R, Magistri P, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitisrelated cirrhosis who had received a liver transplant for HCC. J Hepatol 2017;66(3):552-559.

Okumura K, Yamashita T, Masuda T, et al. Long-term outcome of patients with hereditary transthyretin V30M amyloidosis with polyneuropathy after liver transplantation.Amyloid. 2016;23(1):39-45.

Orfanidou A, Papatheodoridis GV, Cholongitas E. Antiviral prophylaxis against hepatitis B recurrence after liver transplantation: Current concepts. Liver Int. 2021 Jul;41(7):1448-1461.

Pabón V, Dumortier J, Gincul R, et al. Long-term results of liver transplantation for Wilson's disease. Gastroenterol Clin Biol 2008;32:378-81.

Parrish NF, Feurer ID, Matsuoak LK, Rega SA, Perri R, Alexopoulos SP. The changing face of liver transplantation in the United States: The effect of HCV antiviral eras on transplantation trends and and outcomes. Transplantation Direct 2019;5(3):pe427.

Perney P, Bismuth M, Sigaud H,et al. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease? Transpl Int 2005;18(11):1292-129-7.

Pascher A, Sauer IM, Walter M, et al. Donor evaluation, donor risks, donor outcome, and donor quality of life in adult-to-adult living donor liver transplantation. Liver Transpl 2002;8:829-37.

Pascher A, Neuhaus P. Bile duct complications after liver transplantation. Transpl Int 2005;18:627-42.

Patel S, Orlaoff M, Tsoulfas G, et al. Living donor liver transplantation in the United States: identifying donors at risk for perioperative complications. Am J Transplant 2007;7:2344-9.

Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 2004;4:611-20.

Perkins JD. Biliary tract complications: The most common postoperative complication in living liver donors. Liver Transpl 2008:14:1372-7.

Perney P, Bismuth M, Sigaud H, et al. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease? Transpl Int 2005;18:1292-7.

Pereira P, Peixoto A. Biliary Complications - The "achilles heel" of orthotopic liver transplantation. J Gastroenterol 2018;25(1):1-3.

Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nüssler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007;13:197-205.

Pischke S, Suneetha PV, Baechlein C, et al. Hepatitis E virus infection as a cause of graft hepatitis in liver transplant recipients. Liver Transpl 2010;16(1):74-82.

Poujois A, Sobesky R, Meissner WG, et al. Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease. Neurology. 2020 May 26;94(21):e2189-e2202.

Protzer U, Böhm F, Longerich T, et al. Molecular detection of hepatitis E virus (HEV) in liver biopsies after liver transplantation. Mod Pathol 2015;28(4):523-32.

Pulitano C, Ho P, Verran D, et al. Molecular profiling of post-reperfusion milieu determines acute kidney injury after liver transplantation: a prospective study. Liver Transpl 2018; 23. doi: 10.1002/lt.25178. [Epub ahead of print].

Qi HL, Zhuang BJ, Li CS, Liu QY. Peri-operative use of sorafenib in liver transplantation: a time-to-event meta-analysis. World J Gastroenterol 2015;21(5):1636-40.

Qin YS, Li ZS, Sun ZX, Wu RP, Wang N, Yao YZ. Endoscopic management of biliary complications after orthotopic liver transplantation. Hepatobiliary Pancreat Dis Int 2006;5:39-42.

Qiu J, Ozawa M, Terasaki PI. Liver transplantation in the United States. Clin Transpl 2005:17-28.

Radunz S, Juntermanns B, Kaiser GM et al. Efficacy and safety of linezolid in liver transplant patients. Transpl Infect Dis 2011;13:353-8.

Rahim MN, Long L, Penna L, Williamson C, et al. Pregnancy in Liver Transplantation. Liver Transpl. 2020 Apr;26(4):564-581.

Raimondo ML, Dagher L, Papatheodoridis GV, et al. Long-term mycophenolate mofetil monotherapy in combination with calcineurin inhibitors for chronic renal dysfunction after liver transplantation. Transplantation 2003;75:186-90. .

Reig M (b), Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022 Mar;76(3):681-693.

Ringe B, Wittekind C, Bechstein WO, et al. The role of liver transplantation in hepatobiliary malignancy. A retrospective analysis of 95 patients with particular regard to tumour stage and recurrence. Ann Surg 1989;209:88-98.

Roayie K, Feng S. Allocation policy for hepatocellular carcinoma in the MELD era: room for improvement? Liver Transpl 2007;13:S36-43.

Ridruejo E, Silva MO. Safety of long-term nucleos(t)ide treatment in chronic hepatitis B. Expert Opin Drug Saf 2012; 11: 357-60.

Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: Characteristics and management related to kidney disease. Transplant Rev (Orlando) 2016; 31(2):115-120.

Rodríguez-Castro KI, De Martin E, Gambato M, Lazzaro S, Villa E, Burra P. Female gender in the setting of liver transplantation. World J Transplant 2014;4(4):229-42.

Rudraraju M, Osowo AT, Singh V, Carey EJ. Do patients need more frequent colonoscopic surveillance after liver transplantation? Transplant Proc 2008;40:1522-4.

Rupp C, Hippchen T, Bruckner T, et al. Effect of scheduled endoscopic dilatation of dominant strictures on outcome in patients with primary sclerosing cholangitis. Gut. 2019 Dec;68(12):2170-2178.

Saab S, Desai S, Tsaoi D, et al. Posttransplantation hepatitis B prophylaxis with combination oral nucleoside and nucleotide analogue therapy. Am J Transplant 2011;11:511-7.

Saglam K, Sahin TT, Ogut Z, et al. De Novo Malignancies After Liver Transplantation: Experience of a High-Volume Center. J Gastrointest Cancer. 2022 Dec;53(4):1020-1027.

Saidy RR, Sud I, Eurich F, et al. Discontinuation of Passive Immunisation Is Safe after Liver Transplantation for Combined HBV/HDV Infection. Viruses. 2021 May 13;13(5):904.

Saliba F (a), Dharancy S, Lorho R, et al. Conversion to everolimus in maintenance liver transplant patients: a multicenter, retrospective analysis. Liver Transpl 2011;17:905-13.

Saliba F (b), De Simone P, Nevens F et al. Efficacy and safety of everolimus with early reduction or elimination of tacrolimus in 719 de novo liver transplant recipients: 12 month results of a randomised, controlled study. Am J Transplant 2012;12(11):3008-20.

Sanchez EQ, Martin AP, Ikegami T, et al. Sirolimus conversion after liver transplantation: improvement in measured glomerular filtration rate after 2 years. Transplant Proc 2005;37:4416-23.

Saner FH, Cicinnati VR, Sotiropoulos G, Beckebaum S. Strategies to prevent or reduce acute and chronic kidney injury in liver transplantation. Liver Int 2012;32(2):179-88.

Satapathy SK, Joglekar K, Molnar MZ, et al. Achieving sustained virologic response in liver transplant recipients with hepatitis C decreases risk of decline in renal function. Liver Transpl 2018; doi: 10.1002/lt.25059. [Epub ahead of print].

Saunders EA, Engel B, Höfer A, et al. Outcome and safety of a surveillance biopsy guided personalised immunosuppression programme after liver transplantation. Am J Transplant. 2022 Feb;22(2):519-531.

Schiff E, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. Liver Transpl 2007;13:349-60.

Schlitt HJ, Loss M, Scherer M, et al. Current developments in liver transplantation in Germany: MELD-based organ allocation and incentives for transplant centres. Z Gastroenterol 2011;49:30-8.

Schmeding M, Kiessling A, Neuhaus R et al. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomised trial. Transplantation 2011;92:923-9.

Schnitzbauer AA, Sothmann J, Baier L, Bein T, Geissler EK, Scherer MN, Schlitt HJ. Calcineurin inhibitor free de novo immunosuppression in liver transplant recipients with pretransplant renal impairment: Results of a pilot study (PATRONo7). Transplantation 2015;99(12):2565-75.

Schreiber PW, Bischoff-Ferrari HA, Boggian K, et al. Bone metabolism dynamics in the early posttransplant period following kidney and liver transplantation. PLoS One 2018;13(1):e0191167. doi: 10.1371/journal.pone.0191167. eCollection 2018.

Schulz MS, Gu W, Schnitzbauer AA, Trebicka J. Liver Transplantation as a Cornerstone Treatment for Acute-On-Chronic Liver Failure. Transpl Int. 2022 Mar 17;35:10108.

Shah JN, Haigh WG, Lee SP, Lucey MR, Brensinger CM, Kochman ML, Long WB, Olthoff K, Shaked A, Ginsberg GG. Biliary casts after orthotopic liver transplantation: clinical factors, treatment, biochemical analysis. Am J Gastroenterol 2003;98:1861–1867.

Sharma P, Schaubel DE, Messersmith EE, Guidinger MK, Merion RM. Factors that affect deceased donor liver transplantation rates in the United States in addition to the model for end-stage liver disease score. Liver Transpl. 2012;18:1456-63.

Shenoy A, Dienstag A, Dienstag P, et al. Scoring systems to assess relapse risk in alcohol use disorder presenting for early liver transplantation: A systematic review. Gen Hosp Psychiatry. 2021 Sep-Oct;72:23-30.

Shiraz AR, Nayeem MA, Agarwal S, Goyal N, Gupta S. Vascular complications in living donor liver transplantation at a high volume centre: Evolving protocols and trends observed over 10 years. Liver Transpl 2016; 23(4):457-64.

Shuster A, Huynh TJ, Rajan DK, Marquez MA, Grant DR, Huynh DC, Jaskolka JD. Response Evaluation Criteria in Solid Tumours (RECIST) criteria are superior to European Association for Study of the Liver (EASL) criteria at 1 month follow-up for predicting long-term survival in patients treated with transarterial chemoembolisation before liver transplantation for hepatocellular cancer.J Vasc Interv Radiol 2013;24(6):805-12.

Silva MF, Sherman M. Criteria for liver transplantation for HCC: What should the limits be? J Hepatol 2011;55:1137-47.

Silveira MG, Talwalkar JA, Lindor KD, Wiesner RH. Recurrent primary biliary cirrhosis after liver transplantation. Am J Transplant 2010;10:720-6.

Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH, ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol 2018; 113:175t94.

Singh S, Watt KD. Long-term Medical Management of the Liver Transplant Recipient: What the Primary Care Physician Needs to Know. Mayo Clin Proc 2012; 87(8): 779–790.

Smets F, Sokal EM. Epstein-Barr virus-related lymphoproliferation in children after liver transplant: role of immunity, diagnosis, and management. Pediatr Transplant 2002;6:280-7.

Soliman T, Hetz H, Burghuber C. Short-term induction therapy with anti-thymocyte globulin and delayed use of calcineurin inhibitors in orthotopic liver transplantation. Liver Transpl 2007;13:1039-44.

Sotiropoulos GC, Malago M, Molmenti E, et al. Liver transplantation for hepatocellular carcinoma in cirrhosis: is clinical tumour classification before transplantation realistic? Transplantation 2005;79:483-7.

Sotiropoulos GC, Molmanti EP, Lösch C, Beckebaum S, Brolesch CE, Lang H. Meta-analysis of tumour recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases. Eur J Med Res 2007;12:527-34.

Sotiropoulos CG (a), Beckebaum S, Lang H, et al. Single-center experience on liver transplantation for hepatocellular carcinoma arising in alcoholic cirrhosis: results and ethical issues. Eur Surg Res 2008;40:7-13.

Sotiropoulos GC (b), Lang H, Sgourakis G, et al. Liberal policy in living donor liver transplantation for hepatocellular carcinoma: Lessons learned. Dig Dis Sci 2009;54(2):377-84.

Sotiropoulos GC, Molmenti EP, Lang H. Milan criteria, up-to-seven criteria, and the illusion of a rescue package for patients with liver cancer. Lancet Oncol 2009;10:207-8.

Sousa Da Silva RX, Weber A, Dutkowski P, Clavien PA. Machine perfusion in liver transplantation. Hepatology. 2022 Nov;76(5):1531-1549

Sposito C, Rossi RE, Monteleone M, et al. Postrecurrence Survival After Liver Transplantation for Liver Metastases From Neuroendocrine Tumors. Transplantation. 2021 Dec 1;105(12):2579-2586.

Staufer K, Andresen H, Vettorazzi E, et al. Urinary ethyl glucuronide as a novel screening tool in patients pre and post liver transplantation improves detection of alcohol consumption. Hepatology 2011;54(5):1640-9.

Sterneck M, Kaiser GM, Heyne N, et al. Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a randomised trial in liver transplantation. Am J Transplant 2014;14(3):701-10.

Stirnimann G, Ebadi M, Czaja AJ, Montano-Loza AJ. Recurrent and de novo autoimmune hepatitis. Liver Transpl 2019;25(1):152-66.

Straś WA, Wasiak D, Łągiewska B, et al. Recurrence of Hepatocellular Carcinoma After Liver Transplantation: Risk Factors and Predictive Models. Ann Transplant. 2022 Jan 26;27:e934924.

Strassburg CP, Susanne Beckebaum, Andreas Geier et al. Practice guideline autoimmune liver diseases - AWMF-Reg. No. 021-27]. Z Gastroenterol 2017;55:1135-1226.

Stravitz TR, Shiffman ML, Kimmel M, et al. Substitution of tenofovir/emtricitabine for hepatitis B immune globulin prevents recurrence of Hepatitis B after liver transplantation. Liver Int 2012;32(7):1138-45.

Sugawara Y, Makuuchi M. Technical advances in living-related liver transplantation. J Hepatobiliary Pancreat Surg 1999;6:245-53.

Sugawara Y, Makuuchi M. Living donor liver transplantation: present status and recent advances. Br Med Bull 2005;75-76:15-28.

Suhling H, Gottlieb J, Bara C, et al. Chronic rejection: Differences and similarities in various solid organ transplants. Internist (Berl) 2016;57(1):25-37.

Sutcliffe RP, Maguire DD, Muiesan P, et al. Liver transplantation for Wilson's disease: long-term results and quality-of-life assessment. Transplantation 2003;75:1003-6.

Sylvestre PB, Batts KP, Burgart LJ, Poterucha JJ, Wiesner RH. Recurrence of primary biliary cirrhosis after liver transplantation: Histologic estimate of incidence and natural history. Liver Transpl 2003;9:1086-93.

Tamura S, Sugawara Y, Kaneko J, Matsui Y, Togashi J, Makuuchi M. Recurrence of primary sclerosing cholangitis after living donor liver transplantation. Liver Int 2007;27:86–94.

Tanaka A, Kono H, Leung PSC, Eric Gershwin M. Recurrence of disease following organ transplantation in autoimmune liver disease and systemic lupus erythematosus. Cell Immunol 2020;347:104021.

Tang JT, Mao YM. Development of new drugs for the treatment of nonalcoholic steatohepatitis. J Dig Dis 2019. doi: 10.1111/1751-2980.12830.

Teefey SA, Hildeboldt CC, Dehdashti F, et al. Detection of primary hepatic malignancy in liver transplant candidates: prospective comparison of CT, MR imaging, US, and PET. Radiology 2003;226:533-42.

Teperman LW, Poordad F, Bzowej N, et al. Randomised trial of emtricitabine/tenofovir disoproxil fumarate after hepatitis B immunoglobulin withdrawal after liver transplantation. Liver Transpl 2013;19(6):594-601.

Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018;67(4),1560-99.

Testino G, Burra P, Bonino F, Piani F, et al.; Group of Italian Regions. Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: an Italian position statement. World J Gastroenterol 2014;20(40):14642-51.

Thimonier E, Guillaud O, Walter T, et al. Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver disease. Clin Transplant 2014;28(12):1339-48.

Thursz M, Kamath PS, Mathurin P, Szabo G, Shah VH. Alcohol-related liver disease: Areas of consensus, unmet needs and opportunities for further studies. J Hepatol 2019;70:521-30.

Thursz M, Allison M. Liver transplantation for alcoholic hepatitis: Being consistent about where to set the bar. Liver Transpl 2018;24(6):733-734.

Tokodai K, Karadagi A, Kjaernet F, Romano A, Ericzon BG, Nowak G. Characteristics and risk factors for recurrence of nonalcoholic steatohepatitis following liver transplantation. Scand J Gastroenterol 2019;54(2):233-239.

Tokunaga S, Koda M, Matono T, et al. Assessment of ablative margin by MRI with ferucarbotran in radiofrequency ablation for liver cancer: comparison with enhanced CT. Br J Radiol 2012;85:745-52.

Toniutto P, Fabris C, Fumo E, et al. Pegylated versus standard interferon-alpha in antiviral regimens for posttransplant recurrent hepatitis C: comparison of tolerability and efficacy. J Gastroenterol Hepatol 2005;20:577-82.

Toso C, Meeberg GA, Bigam DL, et al. De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects. Transplantation 2007;83:1162-8.

Toso C, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. J Hepatol 2010;52:930-6.

Tournoux-Facon C, Paoletti X, Barbare JC, et al. Development and validation of a new prognostic score of death for patients with hepatocellular carcinoma in palliative setting. J Hepatol 2011;54:108-14.

Tripathi D, Neuberger J. Autoimmune hepatitis and liver transplantation: indications, results, and management of recurrent disease. Semin Liver Dis 2009;29:286-96.

Trunecka P, Klempnauer J, Bechstein WO, Pirenne J, Friman S, Zhao A, Isoniemi H, Rostaing L, Settmacher U, Mönch C, Brown M, Undre N, Tisone G; DIAMOND study group. Renal function in de novo liver transplant recipients receiving different prolonged-release tacrolimus regimens-the DIAMOND Study. Am J Transplant 2015;15(7):1843-54.

Tung BY, Kimmey MB. Biliary complications of orthotopic liver transplantation. Dig Dis 1999;17:133-44.

Ulrich C, Degen A, Patel MJ, Stockfleth. Sunscreens in organ transplant patients. Nephrol Dial Transplant 2008;23:1805-8.

Vagefi PA, Ascher NL, Freise CE, Dodge JL, Roberts JP. The use of living donor liver transplantation varies with the availability of deceased donor liver transplantation. Liver Transpl 2012;18(2):160-5.

Valentin N, Guerrido I, Rozenshteyn F, et al. Pregnancy Outcomes After Liver Transplantation: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2021 Mar 1;116(3):491-504.

Valentin-Gamazo C, Malago M, Karliova M, et al. Experience after the evaluation of 700 potential donors for living donor liver transplantation in a single center. Liver Transpl 2004; 10: 1087-96.

Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation.Crit Rev Oncol Hematol 2005;56:87-99.

van Rijn R, Schurink IJ, de Vries Y,et al.; DHOPE-DCD Trial Investigators. Hypothermic Machine Perfusion in Liver Transplantation - A Randomised Trial. N Engl J Med. 2021 Apr 15;384(15):1391-1401.

van Vugt JLA, Alferink LJM, Buettner S, et al. A model including sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant candidates: a competing risk analysis in a national cohort. J Hepatol 2017;pii: S0168-8278(17)32474-1. doi: 10.1016/j.jhep.2017.11.030.

Vera A, Moledina S, Gunson B, et al. Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. Lancet 2002;360:1943-4.

Verdonk RC, Buis CI, van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 2: Management, outcome, and risk factors for disease progression. Liver Transpl 2007;13:725-32.

Victor DW, Monsour HP, Boktour M, et al. Outcomes of liver transplantation for hepatocellular carcinoma beyond the University of California San Francisco Criteria: A single-center experience. Transplantation 2020;104(1):113-121.

Vitale A, Bertacco A, Gambato M et al. Model for end-stage liver disease-sodium and survival benefit in liver transplantation. Transpl Int 2012;3.26(2):138-44.

Villeret F, Dharancy S, Erard D, et al. Inevitability of disease recurrence after liver transplantation for NAFLD cirrhosis. JHEP Rep. 2023 Jan 3;5(3):100668

Visseren T, Fuhler GM, Erler NS, et al. Recurrence of primary sclerosing cholangitis after liver transplantation is associated with specific changes in the gut microbiome pretransplant - a pilot study. Transpl Int. 2020 Nov;33(11):1424-1436.

Vogel A, Heinrich E, Bahr MJ, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant 2004;18:62-9.

Vogel A (b), Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022 Oct 15;400(10360):1345-1362.

Volpin R, Angeli P, Galioto A, et al. Comparison between two high-dose methylprednisolone schedules in the treatment of acute hepatic cellular rejection in liver transplant recipients: a controlled clinical trial. Liver Transpl. 2002 Jun;8(6):527-34

Washington K. Update on post-liver transplantation infections, malignancies, and surgical complications. Adv Anat Pathol 2005;12:221-6.

Weber NK, Forman LM, Trotter JF. HBIg discontinuation with maintenance oral anti-viral herapy and HBV vaccination in liver transplant recipients. Dig Dis Sci 2010;55:505-9.

Weiss KH, Gotthardt D, Schmidt J, et al. Liver transplantation for metabolic liver diseases in adults: indications and outcome. Nephrol Dial Transplant 2007;22, Suppl 8:viii9-12.

Weismüller TJ, Prokein J, Becker T, et al. Prediction of survival after liver transplantation by pretransplant parameters. Scand J Gastroenterol 2008;43:736-46.

Welling TH, Feng M, Wan S, et al. Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. Liver Transpl 2014;20(1):81-8.

Welzel TM, Reddy KR, Flamm SL et al. On-treatment HCV RNA in patients with varying degrees of fibrosis and cirrhosis in the SOLAR-

trial. Antivir Ther. 2016;21(6):541-546.

Wesdorp DJ, Knoester M, Coenraad MJ, et al. One-year results of tenofovir and emtricitabine without immunoglobulin to prevent hepatitis b recurrence after liver transplantation. J Hepatol 2012; 56 (Suppl. 2):S96-S97.

Wibaux C, Legroux-Gerot I, Dharancy S, et al. Assessing bone status in patients awaiting liver transplantation. Joint Bone Spine 2011; 78:387-91.

Wigg AJ, Gunson BK, Mutimer DJ. Outcomes following liver transplantation for seronegative acute liver failure: experience during a 12-year period with more than 100 patients. Liver Transpl 2005;11:27-34.

Wood NL, VanDerwerken D, Segev DL, Gentry SE. Correcting the sex disparity in MELD-Na. Am J Transplant. 2021 Oct;21(10):3296-3304

Wong PY, Portmann B, O'Grady JG, et al. Recurrence of primary biliary cirrhosis after liver transplantation following FK506-based immunosuppression. J Hepatol 1993;17:284-7.

Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading aetiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148(3):547-55.

Wu T, Morgan TR, Klein AS, Volk ML, Saab S, Sundaram V. Controversies in early liver transplantation for severe alcoholic hepatitis. Ann Hepatol 2018;17(5):759-68.

Yadav DK, Adhikari VP, Yadav RK, et al. Antiviral prophylaxis or preemptive therapy for cytomegalovirus after liver transplantation?: A systematic review and meta-analysis. Front Immunol. 2022 Nov 10;13:953210.

Yahyazadeh A, Beckebaum S, Cicinnati V, et al. Efficacy and safety of subcutaneous human HBV-immunoglobulin (Zutectra) in liver transplantation: an open, prospective, single-arm phase III study. Transpl Int 2011;24:441-50.

Yang Y, Zhao JC, Yan LN, et al. Risk factors associated with early and late HAT after adult liver transplantation. World J Gastroenterol. 2014;20(30):10545-52.

Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSFexpanded criteria based on preoperative imaging. Am J Transpl 2007;7:2587-96.

Yoo MC, Vanatta JM, Modanlou KA, et al. Steroid-free liver transplantation using rabbit antithymocyte globulin induction in 500 consecutive patients. Transplantation 2015;99(6):1231-5.

Yoshida H, Kato T, Levi DM, et al. Lamivudine monoprophylaxis for liver transplant recipients with non-replicating hepatitis B virus infection. Clin Transplant 2007;21:166-71.

Yoshida EM, Marotta PJ, Greig PD, et al. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen:

a multicenter randomised clinical trial. Liver Transpl 2005;11:1064-72.

Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64(5):1577-86.

Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, Bedossa P, Geier A, Beckebaum S, et al; REGENERATE Study Investigators. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394(10215):2184-2196.

Yu L, Ioannou GN. Survival of liver transplant recipients with haemochromatosis in the United States. Gastroenterology 2007;133:489-95.

Zaffar N, Soete E, Gandhi S, Sayyar P, Van Mieghem T,2, D'Souza R. Pregnancy outcomes following single and repeat liver transplantation: An international two-centre cohort. Liver Transpl 2018. doi: 10.1002/lt.25071. [Epub ahead of print].

Zavaglia C, De Carlis L, Alberti AB, et al. Predictors of long term survival after liver transplantation for hepatocellular carcinoma. Am J Gastroenterol 2005;100:2708-16.

Zhu J, Hussaini T, Yoshida EM. Early liver transplant for severe alcoholic hepatitis: establishing a new frontier by ignoring the rule? Ann Transl Med 2018;6(20):411.

Zimmerman MA, Trotter JF, Wachs M, et al. Sirolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. Liver Transpl 2008;14:633-8.

Zimmermann T, Beckebaum S, Berg C, et al. Expert recommendations: Hepatitis C and transplantation]. Z Gastroenterol 2016;54(7):665-84.

Zoepf T, Maldonado-Lopez EJ, Hilgard P, et al. Balloon dilatation vs. balloon dilatation plus bile duct endoprostheses for treatment of anastomotic biliary strictures after liver transplantation. Liver Transpl 2006;12:88-94.

Zoepf T, Maldonado de Dechêne EJ, Dechêne A, et al. Optimised endoscopic treatment of ischemic-type biliary lesions after liver transplantation. Gastrointest Endosc 2012;76:556-63.

20. Nutrition and liver diseases

Katharina Hupa-Breier, Andrea Schneider

Abbreviations

Branched-chain aminos acids (BCAA)
Hepatic encephalopathy (HE)
Aromatic aminod acids (AAA)
End stage liver disease (ESLD)

Abstract

The liver, as the central metabolic organ, is essentially responsible for nutrient homeostasis. Therefore, nutrition is a central aspect in liver diseases. On the one hand, patients with advanced liver diseases often suffer from malnutrition and sarcopenia, which have an important impact on the mortality and morbidity in these patients and affect the outcome after liver transplantation. Hence, early screening and implementation of nutritional therapy are crucial for these patients. On the other hand, malnutrition can also cause liver diseases such as fatty liver disease or parenteral nutrition-associated liver diseases.

In conclusion, nutrition and nutritional therapy is an important part in the field of hepatology.

Introduction

Patients with advanced liver disease, such as cirrhosis, often suffer from malnutrition and loss of muscle mass and functionality, which is referred to as sarcopenia. The prevalence of malnutrition is very high, affecting up to 80% of patients with cirrhosis. Numerous studies have shown that malnutrition and sarcopenia promote disease progression and worsen prognosis. This has been attributed to the increased rate of complications such as infections, hepatic encephalopathy, ascites, and hepatorenal syndrome. In addition, the outcome of liver transplantation is also significantly influenced by preoperative nutritional status (Bischoff 2020, EASL 2019, Plauth 2019).

In contrast, overweight or obesity in metabolic diseases is not only causally related to liver disease but also increases morbidity and mortality (Plauth 2024).

While malnutrition is usually obvious in advanced liver cirrhosis,

the risk of malnutrition in early liver disease and especially overweight sarcopenia is not perceived. In the final stage of liver cirrhosis, however, it is difficult to influence the nutritional status. Therefore, a structured assessment of the nutritional status at the first diagnosis of liver disease is crucial. It allows early detection of malnutrition and initiation of targeted nutritional therapy to prevent late complications and improve prognosis (Bischoff 2020, EASL 2019, Plauth 2019, Plauth 2024).

Screening and assessment of nutritional status

Screening and baseline assessment for malnutrition and obesity

In addition to the diagnosis and the stage of the presenting liver disease, the detailed history should include nutritional aspects (e.g. weight history, nausea, vomiting, reported dietary intake, digestive symptoms).

In addition to the physical examination, the basic assessment begins with the collection of the body mass index (BMI; body weight kg / body length m^2). According to the generally accepted rules, a BMI ≤18.5 is considered underweight (for patients older than 65 years a BMI ≤20) and a BMI ≥25 is considered overweight, a BMI ≥ 30 is considered obesity. However, when assessing BMI, it is important to keep in mind that ascites and oedema may confound the significance, and that malnutrition and sarcopenia may also be present in overweight or obese patients. A simple estimation correction formula can be used for patients with ascites: subtract 5% of body weight for small amounts of ascites, 10% for medium amounts, and 15% for large amounts of ascites (Plauth 2024).

Laboratory chemistry parameters can complement the examination and should be determined according to the underlying disease. For nutritional status, determination of liver synthesis parameters such as albumin, prealbumin, transferrin, minerals, and vitamins may be helpful.

Nutrition screening tools

All patients with chronic liver disease should be systematically screened for the presence of malnutrition using a validated tool at the time of diagnosis. This evaluation should then be repeated every 3-6 months according to the dynamics of the disease course (Lai 2021, Plauth 2024).

In clinical practice, the Nutritional Risk Score (NRS 2000) according to Kondrup is primarily used in addition to the Subjective Global Assessment Score (SGA) according to Detsky. Although both scores are clinically well established and the NRS has gained acceptance due to its relatively simple and examiner-independent collection, neither score has been evaluated in patients with liver disease. An NRS ≥3 indicates an increased risk of malnutrition (Bischoff 2020, Plauth 2024).

Two tools have been developed for liver-specific screening for malnutrition: the Royal Free Hospital Global Assessment (RFH-Ga) or Royal Free Hospital Nutritional Prioritising Tool (simplified form RFH-NPT), which has also been validated in patients with chronic liver disease, and the Liver Disease Undernutrition Screening Tool (LDUST). Both tools are recommended. The RFH-NPT is investigator-independent and correlates with cirrhosis severity, progression, and complication rate. The LDUST is relatively easy to collect due to the 6 questions asked of the patient, but is of limited value due to the patient's subjective assessment (Georgiou 2020, Boulhosa 2020, Plauth 2024).

Expanded nutritional assessment

All patients with alcohol-associated hepatitis (ASH), metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and those listed for transplantation should be screened for the presence of sarcopenia, as it is a strong predictor of morbidity and mortality. Several methods can be used for this purpose (Plauth 2024, Lai 2021).

Radiologic methods should be used to quantify muscle mass and quality as a prognostically important subcriterion of sarcopenia (e.g., when performed for other indications). Special software could be used to measure the area of the psoas and paravertebral muscles at the level of LWK 3 and relate it to body surface area. Skeletal muscle index values of < 50 in men and < 39 cm2/m2 can be used as cutoff values for the diagnosis of sarcopenia (Plauth 2024, Carey 2017).

Anthropometric measurements such as mid-arm circumference and triceps skinfold (TZF) are easy to obtain. All that is needed is a tape measure or, for TZF, a skinfold caliper. The TZF correlates with the body fat mass. These tests are of particular prognostic importance in disease progression. Matching with percentile tables taking into account sex and age allows assessment of nutritional status (malnutrition <15th percentile) (EASL 2019).

Since not only muscle mass is important for prognostic assessment but quite significantly muscle function, handgrip strength, walking speed, or chair stand-up test should be performed for quantification (Lai 2021, Plauth 2024).

To assess frailty as a multidimensional construct, a standardised instrument should be used that also allows graduation such as the Karnofsky Index and the Liver Frailty Index (Lai 2021, Plauth 2024).

One method for determining compartments is bioelectrical impedance analysis (BIA). In addition to determining body compartments, phase-sensitive devices in mono-frequency mode allow determination of the phase angle (PhA). PhA is of prognostic importance and represents an integral measure of cell mass and cell integrity. A PhA < 5 correlates with increased mortality (Ruiz-Margáin 2021, Plauth 2019, Plauth 2024).

- All patients with advanced liver disease should be screened for malnutrition and sarcopenia.
- NRS screening could be used for basic screening.

Nutritional management

Therapy of malnutrition

As the central metabolic organ, the liver is primarily responsible for nutrient homeostasis. Accordingly, advanced liver dysfunction results in catabolism due to increased gluconeogenesis and decreased ability to release glucose from glycogen during fasting periods.

Nutritional therapy should first consider the causes and incorporate individual needs into nutritional counseling. A helpful basis for expert nutritional counseling is the preparation of a food diary for at least 3 days. In any case, the nutritional therapy should be carried out by a nutrition expert (registered dietitian, ecotrophologist, bachelor of science dietitian).

If patients are unable to achieve their nutritional energy and protein goals through oral dietary intake even after all measures have been exhausted, there should be no hesitation to prescribe artificial nutrition. Here, sip feeds are available for oral nutrition supplementation (ONS), but enteral nutrition via tubes as well as parenteral nutrition (PE) should also be used to overcome the period of malnutrition as well as permanent home nutritional support (Bischoff 2020, Plauth 2019, Plauth 2024).

Energy requirements

Energy requirements are best determined by measuring resting energy expenditure (REE) using indirect calorimetry; if this method is not available, energy requirements can be estimated using formulas (Bischoff 2020, EASL 2019, Plauth 2019). The ideal weight or dry weight should be used as a reference. It should be taken into account that in liver cirrhosis patients the measured REE may differ from the estimated one by ± 500 kcal/d. Energy requirements depend on the underlying disease or stage of the disease and physical activity. Approximately 35% of patients with liver cirrhosis exhibit hypermetabolism, while up to 30% exhibit hypometabolism (Müller 1999, Limon-Miro 2022). Patients with acute liver failure have an 18-30% increased REE compared to healthy individuals (Walsh 2000). Sustained alcohol consumption increases REE by 26%, which decreases rapidly with abstinence (Levine 2000). Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) are more complex to assess because overweight or obesity, inflammatory activity, and pre-existing cirrhosis affect energy expenditure.

Thus, the recommendation can be derived to set the energy requirements for patients (without unusual physical activity) with liver cirrhosis, acute liver failure, ASH, and after liver transplantation (LT) at 1.3 times the dietary REE, which corresponds to 30 kcal/kgKG/d; for patients with MASLD without inflammation, 20-25 kcal/kgKG/d (Bischoff 2020, EASL 2019, Plauth 2019). For obese patients with MASLD an energy-restricted diet with exercise therapy should be implemented for weight loss, which can also be implemented with formulary diets *(see MASLD chapter)*.

Obese patients with chronic liver disease who are critically ill or facing surgery or liver transplantation should be fed hypocaloric, high-protein diet. The energy and protein targets are based on the recommendations for critically ill patients; for BMI 30-50, 22-25 kcal/kg/d and protein intake of 1.5 g/kg/d (amino acids 1.8 g/kg/d) are recommended; for BMI > 50, energy intake of 11-14 kcal/kg and protein intake of 1.5 g/kg (amino acids 1.8 g/kg/d) are calculated at ideal weight (Elke 2019).

Nutrient requirements

When calculating the macronutrients protein, carbohydrates and fats, the increased requirement in cirrhosis should be taken into account. Meals can be enriched with energy- and protein-dense additives (EASL 2019). Protein restriction even in encephalopathy is not recommended, except for severe encephalopathy with severely elevated ammonia, and then only for 24-48 hours. Early nutritional support should be provided to accelerate resolution of encephalopathy (Nardelli 2019). Thus, protein intake of 1.2-1.5 g/kgKG/d is recommended (EASL 2019, Plauth 2019, Plauth 2024). This is to stabilise the catabolic metabolic state that is often aggravated by protein losses. Plant proteins have a more favourable amino acid profile than animal products. Branched-chain amino acid (BCAA) supplementation in decompensated patients has been shown to have a positive effect in some studies (Dam 2018).

Carbohydrate intake is recommended at 50-60% of non-protein dependent energy requirements with a fat intake of 1g/kgKG/d. In cases of

fat malabsorption, such as chronic cholestasis, modification with medium-chain fatty acids may have a stabilising effect on malnutrition.

For patients with MASLD, the Mediterranean diet with whole grain products is particularly recommended *(see MASLD chapter)*. Patients with advanced liver disease should avoid alcohol altogether. Alcohol has a high energy density with no nutritional value and at the same time inhibits energy turnover, making it counterproductive for both weight loss and malnutrition. In addition, the risk of hepatocellular carcinoma and osteoporosis is increased (Bischoff 2020, EASL 2019) *(see ASH chapter)*.

Patients with advanced liver disease should generally be urged to eat 3 main meals and 3 snacks to avoid fasting periods longer than 4 hours. This can be implemented by a late-night snack (protein, carbohydrate) or anONS.

Salt-restricted diets are not recommended, because they increase the risk of worsening malnutrition. The EASL guideline recommends 5 g of salt added to the diet daily in cirrhotic patients with ascites (EASL 2019).

Certain micronutrients are critical in chronic liver disease especially with increased alcohol consumption and diseases associated with maldigestion-absorption (Llibre-Nieto 2021). If a deficiency exists or a high risk can be assumed, supplementation should be added to the diet. This concerns the fat-soluble vitamins, specifically the vitamin D (target > 30 ng/mL), and the water-soluble vitamins, namely folic acid and vitamin B1. The latter play a pathogenetic role for Wernicke's encephalopathy in alcohol dependence (Plauth 2024).

For minerals and trace elements, timely zinc and magnesium supplementation should be prescribed (Bischoff 2020, EASL 2019).

Protein supplementation

One the one hand, patient with end-stage liver disease and malnutrition have the need for a hypercaloric, high-protein diet, but on the other hand, they have a high risk for hyperammonaemia and hepatic encephalopathy (HE).

Branched-chain amino acids (BCAA), including leucine, isoleucine and valin are essential amino acids, which are mostly metabolised in the muscles, therefore they could be utilised even in end-stage liver disease (ESLD). In contrast, aromatic amino acids (AAA) could not sufficiently be metabolised any more in ESLD and accumulate. Therefore, the ratio between BCAA and AAA (BCAA to AAA ratio), which is normally 3.5:1, is altered, which seems to worsen HE. Furthermore, there is evidence that BCAA support the ammonia detoxification and have ammonia lowering effect (Plauth 2024). Clinical studies could demonstrate that BCAA reduce hepatic encephalopathy in ESLD and improve the incidence of post-LTc bacteremia and sepsis (Dam 2018). Besides these beneficial effects of BCAA, there is also some discussion about potential negative side effects. BCAA could impair liver fat content and insulin resistance (Plauth 2011). However, further studies are needed to confirm these data.

In conclusion, the current ESPEN guidelines recommend the use of BCAA in patients with HE and need for additional enteral nutrition (Bischoff 2020, Plauth 2019).

- Median energy requirement in patients with advanced liver disease is around 30 kcal/kgKG/d
- Energy requirement in patients with MASLD should be around 20-25 kcal/kgKG/d
- Protein intake should be 1.2-1.5 g/kgKG/d
- BCAA are recommended for patient with risk for clinical HE

Nutrition and liver transplantation

Before Liver transplantation

Malnutrition and sarcopenia are associated with an increased risk of morbidity and mortality in patients with end stage liver disease (Kim 2017). Furthermore, this is associated with increased mortality in patients on the waiting list and even affects the outcome after liver transplantation (Kalafateli 2017). A small pilot study showed that pre- and perioperative nutritional support may improve posttransplant outcomes (Plank 2005).

Therefore, it is recommended that patients on the waiting list should be carefully screened for malnutrition and sarcopenia. Early nutritional support should be implemented according to the current nutrition status and the recommended nutrition guidelines for patients with end stage liver disease. In short, a total energy intake of 30 kcal/kg/d and a protein intake of 1.2-1.5 g/kg/d are recommended (Bischoff 2020, Plauth 2019). Oral nutrition is preferred and should be accompanied by nutritional counseling. However, if the required energy intake cannot be achieved orally, further support with enteral or parenteral nutrition support should be provided at an early stage. In this case, enteral nutrition is the preferred route because it preserves the gut barrier and may therefore reduce the risk of bacterial translocation. However, this might be often challenging due to ascites. Therefore, parenteral nutrition is also recommended.

As obesity is an epidemic burden, it is an increasing problem also in the transplant setting. Diet and exercise are important treatment options, even in patients already on the waiting list. Weight loss in this group of patients should be achieved by reducing calories from carbohydrates and fat content, while maintaining a high amount of protein intake (2,0g/kg/ideal body

weight) to avoid sarcopenia (Moctezuma-Velazquez 2019). Total energy intake should be around 25 kcal/kg of ideal body weight. In the specific setting of liver transplantation, the use of BCAA is not recommended. In addition, the use of specific immunonutrition is not recommended.

After liver transplantation

With a new functional liver, nutritional and metabolic dysfunctions are expected to improve. However, the normalisation of malnutrition and sarcopenia may be prolonged and some alterations in body composition may persist. On the other hand, there is the risk for the development of other kind of malnutrition, such as obesity. Therefore, nutritional therapy is an important tool in terms of long-term outcome after LT (Hammad 2017a, Hammad 2015). Shortly after transplantation, enteral nutrition should be implemented after LT within 12-24 h as it could reduce the rate of infections (Hasse 1995). After the acute postoperative period, a total energy intake of about 30-35kcal/kg body weight with at least 1.2-1.5/kg body weight of protein is recommended in the current ESPEN guidelines (Bischoff 2020).

Recent studies have shown a significant reduction of infections by administration of pre- and probiotics such as Lactobacillus spp. (Plank 2005, Rayes 2002, Sugawara 2006). Specifically, the addition of synbiotics (combination of pro- and prebiotics) have been shown to restore macrophage function and modulate lymphocyte function, mainly through Lactobacillus. Furthermore, improving the intestinal barrier could prevent bacterial translocation from the gut. Therefore, the additional use of synbiotics after LT is recommended in the current guidelines.

Immunosuppression

The main change in lifestyle after LT is due to the lifelong intake of immunosuppression. Common immunosuppression after LT compromise steroids, calcineurin inhibitors such as cyclosporin or tacrolimus, and mycophenolat-mofetil. This therapy affects the diet by changing the metabolism, immune function and by food-drug interactions.

Metabolism

Corticosteroids could lead to overweight, as they increase appetite. Furthermore, they promote insulin resistance and dyslipidaemia and also influence the fat distribution (Noppe 2016). Their use is also associated with increased risk for liver steatosis (Sprinzl 2013). Calcineurin inhibitors, such as cyclosporin or tacrolimus, are associated with prediabetes (Perito 2017) and with significant weight gain after LT (Hammad 2017b). Furthermore, tacrolimus was associated with increased liver steatosis after LT. Therefore, weight gain is a current problem after LT. Obesity and new onset of diabetes are important risk factors for graft steatosis and increase the cardiovascular risk (Campos-Murguia 2024, Galvin 2019). Patients should be advised to aim for a normal body weight and avoid obesity. On the other hand, everolimus and sirolimus are associated with decrease in muscle mass (Hammad 2017a), which should be prevented by physical activity and sufficient protein intake.

Calcineurin inhibitors are known to affect the insulin secretion (Heit 2006, Vincenti 2007). Corticosteroids lead to insulin resistance with consecutive impaired hepatic glycogen metabolism and increased gluconeogenesis. As obesity further increases the risk of diabetes after LT (Chang 2018), obesity should be prevented.

While zincs deficiency regress in most cases, hypomagnesaemia often occurs after transplantation as a side effect of calcineurin inhibitors. Therefore, the intake of magnesium-rich food is encouraged, such as whole grain, nuts and seeds. In addition, steroids lead to hypocalcaemia and vitamin D deficiency, so vitamin D and optional Calcium substitution is recommended.

Immunosupression and food interaction

Food-drug interactions are mainly due to modification in the CYP3A4 and CYP 450 metabolism, which affects the immunosuppressive metabolism and therefore the blood concentration. The most important food is grapefruit, as it significantly increases calcineurin inhibitor levels in particular (Chan 2001). Particularly, the components bergamottin and naringenin act on the CYP3A4 pathway, which are also present in pomelo. One study showed that pomelo affected the cyclosporin levels (Grenier 2006). In addition, pomegranate juice has been shown to modulate CYP3A4 in animal models and *in vitro* (Mansoor 2023). However, a recent study in humans showed no significant alterations in cyclosporin levels (Anlamlert 2020). Another study further demonstrated, that all citrus fruits might affect the CYP3A4 pathway in a dose-dependent manner (Fujita 2008), as they all contain at least bergamottin or naringenin. In conclusion, patients should avoid eating grapefruit and should be educated about the potential risk of pomelo, cranberry and pomegranate to modify immunosuppressant levels in a dose-dependent manner.

Furthermore, St. John's wort affects the CYP4A3 and p-glycoprotein pathways and therefore affects the levels of tacrolimus and cyclosporine (Mannel 2004).

Immune systeme

Due to the immunosuppression, the transplant recipient is more susceptible to infections, especially food-borne infections, such as Shigella, Yersinia, Norovirus or Rotaviruses (Fagiuoli 2014). It is therefore important to avoid raw meat, fish, eggs and unpasteurised dairy products. Furthermore, vegetables and fruits should be washed thoroughly. In addition, food should be stored at appropriate temperatures and the kitchen should be hygienic and clean.

Furthermore, hepatitis E virus infection in liver transplant recipients is a serious infection because it can lead to chronic hepatitis with rapid progression to cirrhosis. Besides transmission via blood products, hepatitis E virus is mainly transmitted via undercooked meat and fish (Behrendt 2014). Meat should be cooked properly for at least 20 minutes.

In summary, good kitchen and food preparation hygiene is recommended to prevent food-borne infections.

Conclusion

In conclusion, nutritional therapy is an essential module in the treatment of patients before and after liver transplantation. Pre-operative malnutrition has a significant impact on the post-transplant outcome and should be treated as early as possible. Furthermore, nutritional therapy can prevent many side effects and complications after liver transplantation.

- Malnutrition and sarcopenia in patients on the liver transplant waiting have a significant impact on short- and long-term outcomes after liver transplantation and should be treated as early as possible.
- After liver transplantation, normal weight should be achieved, overweight should be avoided.
- As Immunosuppression influences the immune system, foodborne infections should be prevented.
- Due to interaction with immunosuppression, especially grapefruit and St. John´s wort intake should be avoided.

Nutrition-associated liver injury (NALI)

Severe malnutrition, such as in anorexia nervosa, can lead to liver damage and even acute liver failure due to the lack of protein in the diet. The reduced synthesis of apoproteins with fatty degeneration of the liver plays an important pathophysiological role. In addition, malnutrition also impairs other important liver functions and is able to induce hepatocellular autophagy processes (Bitetto 2010, Plauth 2019). It is not known whether fatty liver can progress to chronic liver disease because of malnutrition.

If nutrition resumes, there is a risk of acute liver damage from refeeding syndrome. This develops with a maximum rise in transaminases around day 27 and normalises in more than 80% of patients after 1 month (Rosen 2017).

Of increasing importance is liver damage up to acute liver failure due to malnutrition after bariatric surgery (Addeo 2019). Studies indicate that liver failure occurs at a median of 20 months. The incidence is highly dependent on the surgical procedure used and is highest with jejunoileal bypass and Scopinaro biliopancreatic diversion procedure. The cause is multifactorial, with bacterial overgrowth in the small intestine and severe protein amino acid deficiency thought to play an important role. In addition, it should be noted that the affected patient population already has a very high predisposition to MASLD. Therefore, in addition to monitoring nutritional status and liver function parameters, it is necessary to implement an adapted nutritional concept perioperatively. A nutritionist should accompany patients in this regard.

For information on liver damage due to hyperalimentation, see the chapter on MASLD.

Liver damage caused by medical nutrition

Parenteral nutrition (PE) can cause liver disease, which also manifests varies depending on the age of the patient and the type of intestinal failure. In infants and children, cholestatic liver disease called *Parenteral Nutrition Associated Cholestasis (PNAC)* may occur in addition to steatosis. Premature infants with low birth weight are particularly affected. Due to their different presentation and pathophysiology, PNAC in infants should be distinguished from PE-associated liver disease in adults (PNALD) (Koletzko 2010).

Adult PNALD is defined as a complication of PE administered for more than 14 days, which is usually biochemically associated with a 1.5-fold increase in the upper limit of normal or at least 2 of the following liver enzymes: AST, ALT, alkaline phosphatase. Often, this enzyme increase, which occurs 1-3 weeks after the onset of total PE, is accompanied by an increase in conjugated bilirubin of > 2 or 3 mg/dL (Żalikowska-Gardocka 2020). Histologically, there is predominantly evidence of small-mixed droplet fatty degeneration without nuclear shift, which is fundamentally different from classic MASLD. Progression is via steatohepatitis with periportal lymphocytic infiltration and hepatocellular necrosis to fibrosis and bile duct hyperplasia to cirrhosis (Buchman 2017). Prevalence and

disease progression depend on the duration of PE and the remaining length of the small bowel after bowel resection. Analyses showed that remaining small bowel length < 50 cm and fat administration > 1.0 g/kgKG/d were significantly associated with liver failure. Thus, pathophysiologically, liver damage is not only a consequence of PE but also of intestinal failure, which is why the literature often refers to "intestinal failure-associated liver disease" (IFALD), which is very difficult to differentiate in the clinic.

Prevention and treatment of NALI

For the prevention of NALI, specific nutritional protocols should be implemented in infants and children as well as adults with the aim of promoting enteral feeding patterns and intestinal rehabilitation in the best possible way (Bischoff 2020). The involvement of a qualified nutritionist is imperative in addressing these issues. Energy and nutrient intake must be individually adjusted to avoid both deficiencies as well as hyperalimentation. In addition, the adaptation and absorption capacity of the intestine should be promoted to the maximum (Pironi 2023). In most cases, an individual formulation (compounded) will be required as part of a long-term PE. Lipid intake has been focused on as a critical nutrient parameter in studies, with lipid emulsions containing fish oil being attributed a protective effect (Koletzko 2010). However, few basic rules can be derived from these studies. Accordingly, for the prevention of PE-associated liver damage in both children and adults, mixed lipid emulsions, which may contain omega-3 fatty acids in addition to MCT, oleic acid, should be used rather than pure soybean oil emulsions (Pironi 2023). If PNALD is suspected, the lipid emulsion should be changed to a reduced ratio of omega-6/omega-3 fatty acids (Lapillonne 2018).

- Parenteral nutrition may cause liver disease (PNALD).
- PNALD may manifest as a cholestatic or steatotic liver disease.
- Omega-3 fatty acids may be used to treat PNALD.

References

Addeo P, Cesaretti M, Anty R, Iannelli A. Liver transplantation for bariatric surgery-related liver failure: a systematic review of a rare condition. Surg Obes Relat Dis 2019;15:1394-1401.

Anlamlert W, Sermsappasuk P. Pomegranate Juice does not Affect the Bioavailability of Cyclosporine in Healthy Thai Volunteers. Curr Clin Pharmacol 2020;15:145-151.

Behrendt P, Steinmann E, Manns MP, Wedemeyer H. The impact of hepatitis E in the liver transplant setting. J Hepatol 2014;61:1418-1429.

Bischoff SC, Bernal W, Dasarathy S, et al. ESPEN practical guideline: Clinical nutrition in liver disease. Clin Nutr 2020;39:3533-3562.

Bitetto D, Fabris C, Falleti E, et al. Vitamin D and the risk of acute allograft rejection following human liver transplantation. Liver Int 2010;30:417-444.

Boulhosa RSSB, Lourenço RP, Côrtes DM, Oliveira LPM, Lyra AC, de Jesus RP. Comparison between criteria for diagnosing malnutrition in patients with advanced chronic liver disease: GLIM group proposal versus different nutritional screening tools. J Hum Nutr Diet 2020;33:862-868.

Buchman AL, Naini BV, Spilker B. The Differentiation of Intestinal-Failure-Associated Liver Disease from Nonalcoholic Fatty Liver and Nonalcoholic Steatohepatitis. Semin Liver Dis 2017;37:33-44.

Campos-Murguia A, Guetzlaff L, Bosselmann E, et al. Overweight Impacts Histological Disease Activity of De Novo Metabolic Dysfunction-Associated Steatotic Liver Disease After Liver Transplantation. Clin Transplant 2024;38:e70039.

Carey EJ, Lai JC, Wang CW, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl 2017;23:625-633.

Chan LN. Drug-nutrient interactions in transplant recipients. JPEN J Parenter Enteral Nutr 2001;25:132-141.

Chang S, Jiang J. Association of Body Mass Index and the Risk of New-Onset Diabetes After Kidney Transplantation: A Meta-analysis. Transplant Proc 2018;50:1316-1325.

Dam G, Aamann L, Vistrup H, Gluud LL. The role of Branched Chain Amino Acids in the treatment of hepatic Encephalopathy. J Clin Exp Hepatol 2018;8:448-451.

EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019;70:172-193.

Elke G, Hartl WH, Kreymann KG, et al. Clinical Nutrition in Critical Care Medicine - Guideline of the German Society for Nutritional Medicine (DGEM). Clin Nutr ESPEN 2019;33:220-275.

Fagiuoli S, Colli A, Bruno R, et al. Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. J Hepatol 2014;60:1075-1089.

Fujita T, Kawase A, Niwa T, et al. Comparative evaluation of 12 immature citrus fruit extracts for the inhibition of cytochrome P450 isoform activities. Biol Pharm Bull 2008;31:925-930.

Galvin Z, Rajakumar R, Chen E, et al. Predictors of De Novo Nonalcoholic Fatty Liver Disease After Liver Transplantation and Associated Fibrosis. Liver Transpl 2019;25:56-67.

Georgiou A, Papatheodoridis GV, Alexopoulou A, et al. Validation of cutoffs for skeletal muscle mass index based on computed tomography analysis against dual energy X-ray absorptiometry in patients with cirrhosis: the KIRRHOS study. Ann Gastroenterol 2020;33:80-86.

Grenier J, Fradette C, Morelli G, Merritt GJ, Vranderick M, Ducharme MP. Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. Clin Pharmacol Ther 2006;79:255-262.

Hammad A, Kaido T, Aliyev V, Mandato C, Uemoto S. Nutritional Therapy in Liver Transplantation. Nutrients 2017;9:1126.

Hammad A, Kaido T, Hamaguchi Y, et al. Impact of sarcopenic overweight on the outcomes after living donor liver transplantation. Hepatobiliary Surg Nutr 2017;6:367-378.

Hammad A, Kaido T, Uemoto S. Perioperative nutritional therapy in liver transplantation. Surg Today 2015;45:271-283.

Hasse JM, Blue LS, Liepa GU, et al. Early enteral nutrition support in patients undergoing liver transplantation. JPEN J Parenter Enteral Nutr 1995;19:437-443.

Heit JJ, Apelqvist AA, Gu X, et al. Calcineurin/NFAT signalling regulates pancreatic beta-cell growth and function. Nature 2006;443:345-349.

Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. J Cachexia Sarcopenia Muscle 2017;8:113-121.

Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. PLoS One 2017;12:e0186990.

Koletzko B, Goulet O. Fish oil containing intravenous lipid emulsions in parenteral nutrition-associated cholestatic liver disease. Curr Opin Clin Nutr Metab Care 2010;13:321-326.

Lai JC, Tandon P, Bernal W, et al. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74:1611-1644.

Lapillonne A, Fidler Mis N, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids. Clin Nutr 2018;37:2324-2336.

Levine JA, Harris MM, Morgan MY. Energy expenditure in chronic alcohol abuse. Eur J Clin Invest 2000;30:779-786.

Limon-Miro AT, Jackson CD, Eslamparast T, et al. Predicted estimates of resting energy expenditure have limited clinical utility in patients with cirrhosis. J Hepatol 2022;77:98-107.

Llibre-Nieto G, Lira A, Vergara M, et al. Micronutrient Deficiencies in Patients with Decompensated Liver Cirrhosis. Nutrients 2021;13:1249.

Mannel M. Drug interactions with St John's wort: mechanisms and clinical implications. Drug Saf 2004;27:773-797.

Mansoor K, Bardees R, Alkhawaja B, et al. Impact of Pomegranate Juice on the Pharmacokinetics of CYP3A4- and CYP2C9-Mediated Drugs Metabolism: A Preclinical and Clinical Review. Molecules 2023;28:2117.

Moctezuma-Velazquez C, Márquez-Guillén E, Torre A. Obesity in the Liver Transplant Setting. Nutrients 2019;11:2552.

Müller MJ, Böttcher J, Selberg O, et al. Hypermetabolism in clinically stable patients with liver cirrhosis. Am J Clin Nutr 1999;69:1194-1201.

Nardelli S, Gioia S, Faccioli J, Riggio O, Ridola L. Sarcopenia and cognitive impairment in liver cirrhosis: A viewpoint on the clinical impact of minimal hepatic encephalopathy. World J Gastroenterol 2019;25:5257-5265.

Noppe G, van den Akker EL, de Rijke YB, Koper JW, Jaddoe VW, van Rossum EF. Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body-fat distribution. Int J Obes (Lond) 2016;40:1503-1509.

Perito ER, Lustig RH, Rosenthal P. Prediabetes in Pediatric Recipients of Liver Transplant: Mechanism and Risk Factors. J Pediatr 2017;182:223-231.e3.

Pironi L, Cuerda C, Jeppesen PB, et al. ESPEN guideline on chronic intestinal failure in adults - Update 2023. Clin Nutr 2023;42:1940-2021.

Plank LD, McCall JL, Gane EJ, et al. Pre- and postoperative immunonutrition in patients undergoing liver transplantation: a pilot study of safety and efficacy. Clin Nutr 2005;24:288-296.

Plauth M, Bechmann L, Grajecki D, et al. S2k guideline Clinical nutrition in Hepatology on behalf of the German Society for Nutritional Medicine (DGEM). Aktuel Ernahrungsmed 2024;49:256-317.

Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr 2019;38:485-521.

Plauth M, Schütz T. Branched-chain amino acids in liver disease: new aspects of long known phenomena. Curr Opin Clin Nutr Metab Care 2011;14:61-66.

Rayes N, Seehofer D, Hansen S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. Transplantation 2002;74:123-127.

Rosen E, Bakshi N, Watters A, Rosen HR, Mehler PS. Hepatic Complications of Anorexia Nervosa. Dig Dis Sci 2017;62:2977-2981.

Ruiz-Margáin A, Xie JJ, Román-Calleja BM, et al. Phase Angle From Bioelectrical Impedance for the Assessment of Sarcopenia in Cirrhosis With or Without Ascites. Clin Gastroenterol Hepatol 2021;19:1941-1949.e2.

Sprinzl MF, Weinmann A, Lohse N, et al. Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation. Transpl Int 2013;26:67-74.

Sugawara G, Nagino M, Nishio H, et al. Perioperative synbiotic treatment to prevent postoperative infectious complications in biliary cancer surgery: a randomized controlled trial. Ann Surg 2006;244:706-714.

Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007;7:1506-1514.

Walsh TS, Wigmore SJ, Hopton P, Richardson R, Lee A. Energy expenditure in acetaminophen-induced fulminant hepatic failure. Crit Care Med 2000;28:649-654.

Żalikowska-Gardocka M, Przybyłkowski A. Review of parenteral nutrition-associated liver disease. Clin Exp Hepatol 2020;6:65-73.

HEPATOLOGY

A clinical textbook

Wedemeyer, Mauss, Berg, Keitel, Rockstroh, Sarrazin

11th Edition **2024–2025**

The evelenth edition of ***Hepatology – A clinical textbook*** offers an update of all relevant areas and is a source of information for physicians, residents and advanced medical students seeking a broader understanding of liver disease.

www.hepatologytextbook.com