# Diagnosis and Treatment of Chronic Liver and Biliary Diseases

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# 1 Foreword

Liver diseases are common ailments that can lead to severe impairment of liver function, and from there to other organs such as the kidneys or brain in many cases. These complications frequently result in disability and reduced life expectancy.

Advances in basic research in biochemistry, cell biology, molecular biology, genetics, immunology and virology have driven major advances in the diagnosis and targeted treatment of these conditions. Progression of liver disease can be significantly delayed or even prevented entirely by timely diagnosis and initiation of treatment.

These developments reinforce the importance of recognizing liver diseases and elucidating their specific etiology.

# 2 Chronic liver diseases: symptoms and findings

Liver diseases can be classified into acute and chronic disorders. Conditions which resolve within 6 months are termed acute disease, whereas those which persist longer are termed chronic liver disease.

Some disorders may present as either an acute or a chronic liver disease, including hepatitis virus infections, acute Wilson's disease, autoimmune hepatitis, drug-induced liver injury, alcoholic liver disease, and porphyrias. In contrast, hereditary hemochromatosis, alpha-1 antitrypsin deficiency, and primary biliary cholangitis are always chronic liver diseases.

The symptoms of chronic liver diseases – fatigue, exhaustion, weakness, loss of appetite, weight loss, upper abdominal discomfort, bloating, flatulence, fever, joint pain, and, rarely, itching – are non-specific and do not allow differentiation by themselves. These symptoms are accompanied by jaundice at advanced stages of disease. Patients' urine may be dark, and stool may be discolored.

Important topics in the patient's medical history include family history, alcohol consumption, medications (including complementary and alternative products and teas), travel abroad, liver diseases among other household members or colleagues, surgery or transfusion, and exposure to organic solvents on the job or at home.

Clinical examination may reveal that the liver has a normal size, is enlarged, or is small, depending on the disease and stage. The spleen may be enlarged in some cases. Skin abnormalities caused by liver disease may be present, including spider angioma, white nails, palmar erythema,

angular cheilitis, xanthelasma, jaundice, purpura, parotid gland enlargement, edema and male gynecomastia, as well as scars from scratching, which may indicate itching.

The etiology of the liver disease must be investigated using chemical, serological, and immunological laboratory tests. These tests should also be performed even if transaminases are only marginally elevated. Ultrasound, duplex ultrasound, and other examinations such as histology, endoscopy, or X-ray- and magnetic resonance imaging (MRI) may be useful in clarifying the etiology or determining the stage of a liver disease.

A patient may have multiple liver diseases concurrently, for example a combination of alcoholic liver disease and hepatitis C virus infection or hereditary hemochromatosis, or alternatively an overlap syndrome between e.g. PBC and AIH. A complete diagnosis is mandatory, especially in patients below the age of 50.

# 3 Pathophysiology, diagnosis, and treatment of selected conditions

## 3.1 Viral hepatitis

Five different hepatitis viruses are currently known (table 1, see p. 14). Hepatitis A virus (HAV) and hepatitis E virus (HEV) are transmitted by the fecal/oral route and cause only acute hepatitis, whereas hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) can also lead to chronic liver inflammation. HBV, HCV, and HDV are transmitted by blood and blood products, while HBV can also be transmitted by sexual contact. HBV and HCV are responsible for the majority of virus-related chronic liver diseases in Western Europe. HDV infection only occurs in combination with an active hepatitis B infection, with a co-infection rate of about 5% among HBV-positive patients.

Neither hepatitis B nor C viruses cause direct injury to hepatocytes.

### *Pathophysiology*

It is currently thought that the cellular immune response to hepatitis virus infection results in the death of infected hepatocytes. These infected cells present fragments of the virus on their surface, which are then recognized by several different types of immune cells and represent a signal that the infected cell should be destroyed. Fewer than 10% of individuals infected with HBV develop chronic hepatitis, compared with 80–95% of those infected with hepatitis C virus. Cirrhosis develops in fewer than 1% of HBV patients but in 5–30% of HCV patients.

### *Diagnosis and treatment*

#### *Hepatitis A*

Hepatitis A is diagnosed by the detection of IgM class antibodies targeting hepatitis A virus **(anti-HAV, IgM)**. A positive result confirms the diagnosis of acute hepatitis A. This test is recommended for young patients, for patients returning from travel abroad, and for patients with contact to individuals infected with hepatitis A virus. Antibody testing for HAV without class-specific differentiation (i.e. IgG plus IgM) is not recommended since a positive result provides no indication of how recently the infection occurred.

There is no direct therapy for hepatitis A virus, rather, treatment of hepatitis A comprises supportive care.

Vaccination with inactivated hepatitis A virus is available and is effective. Two injections of 1 ml each are administered at a 6-month interval and is approved for children from age 1 and above. The vaccine confers nearly 100% protection for many years after a complete course. Passive immunization using immunoglobulin should only be administered in exceptional cases, for example if travel to a high-risk area is scheduled to begin in less than 1 week.

#### *Hepatitis B*

Active hepatitis B virus infection is detected by a positive hepatitis B surface antigen **(HBsAg)** in serum. This antigen represents a component of the viral envelope (fig. 1). A positive HBsAg is sufficient to confirm an initial diagnosis of hepatitis B. A positive hepatitis B e antigen **(HBeAg)** detected by additional testing indicates robust replication of the virus. It is not necessary to test for anti-HBc or HBV DNA in order to diagnose an actively-replicating HBV infection.

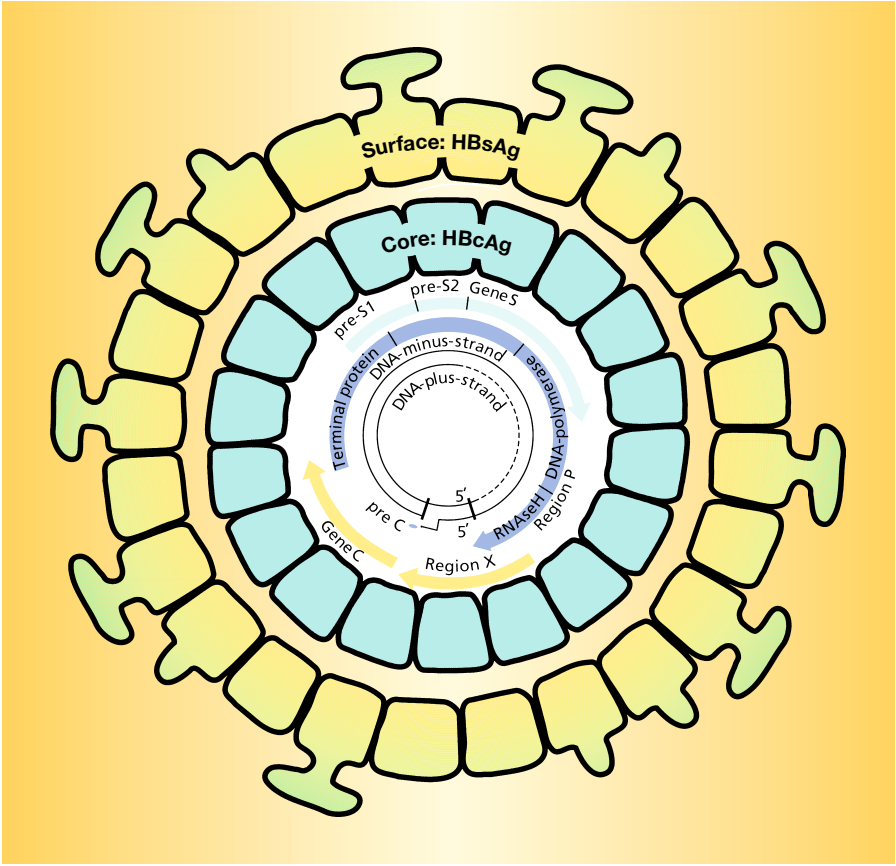


**Figure 1**
Model of hepatitis B virus

If treatment with interferon or nucleoside or nucleotide analogs is considered, HBV DNA, HBeAg and anti-HBe should be measured as these parameters may impact the effectiveness of treatment.

***Treatment***

Treatment with pegylated interferon is an option in HBeAg-positive patients with an HBV DNA level over 2,000 IU/ml (approx. 10,000 copies/ml) and no contra-indications, especially for younger patients. Following 52 weeks of this therapy, approximately 35% of patients are HBeAg-negative, with a seroconversion rate of 29% and undetectable HBV DNA (< 80 IU/ml) in 7% of patients. Alternatively, nucleoside or nucleotide analogues can be administered. These drugs are indicated in patients with the appropriate HBV DNA level (> 2,000 IU/ml in HBeAg-positive patients, > 2,000 IU/ml in HBeAg-negative patients), elevated ALT levels, and positive histology and/or Fibroscan. Six drugs have been developed to treat chronic hepatitis B: adefovir (10 mg/day), entecavir (0.5 mg or 1.0 mg/day), lamivudine (100 mg/day), telbivudine (600 mg/day; withdrawn from sale) and tenofovir disoproxil (245 mg/day) or tenofovir alafenamide (25 mg/day). Treatment is continued for at least 1 year and usually requires several years for most nucleoside analogs. Lamivudine results in HBeAg seroconversion in 17%, 27%, 40%, 47%, and 50% of patients after 1, 2, 3, 4, and 5 years, respectively. Mutations occur with increasing frequency as treatment is continued (15–20% after 1 year; 40% after 2 years; 67% after 4 years; and 70% after 5 years). Adefovir (10 mg/day) results in an absence of detectable HBV DNA (< 80 IU/ml) in 51% of HBeAg-negative patients and 21% of HBeAg-positive patients after 48 weeks of treatment. Resistance to adefovir emerges in up to 29% of patients after 5 years of treatment. HBV DNA can no longer be detected in 60% of HBeAg-positive patients and in 88% of HBeAg-negative patients following 52 weeks of treatment with telbivudine (600 mg/day). Resistance is

observed in 2–5% of patients after 1 year and in approximately 11% after 2 years. Entecavir (0.5 mg/day) results in an absence of detectable serum HBV DNA in 68% of HBeAg-positive patients and 90% of HBeAg-negative patients after 52 weeks of treatment. Resistance to entecavir is rare during the first 5 years of treatment in patients without prior treatment (< 1.5%), while HBV infection recurs within 4 years in 39% of patients previously treated with lamivudine. After 48 weeks of tenofovir disoproxil therapy (245 mg/day), HBV DNA can no longer be detected in 76% of HBeAg-positive patients and in 93% of HBeAg-negative patients. Resistance to tenofovir only occurs in exceptional cases. Entecavir, tenofovir disoproxil and tenofovir alafenamide are the preferred options due to their high efficacy and low rates of resistance. The sale of telbivudine has been discontinued.

Criteria for the treatment of chronic hepatitis B:

- HBeAg-positive and HBeAg-negative patients with HBV DNA > 2,000 IU/ml, elevated ALT levels and fibrosis and/or inflammation on histology
- Patients with compensated or decompensated cirrhosis regardless of ALT levels and with detectable HBV DNA
- Patients with HBV DNA levels > 2,000 IU/ml and ALT > 2-fold upper limit of normal regardless of degree of fibrosis
- Patients older than 30 years of age with HBeAg-positive, chronic HBV infection with normal ALT levels and high HBV DNA levels, regardless of liver histology
- Treatment can also be initiated for patients with a family history of cirrhosis, hepatocellular carcinoma, or extrahepatic complications.

A vaccine against hepatitis B virus is available: Patients are administered 10 µg or 20 µg of a recombinant vaccine as a first dose, then again after 4 weeks and 6 months. Passive immunization with hyperimmune globulin is only

recommended within 12 (24) hours after a needlestick injury or following childbirth from a hepatitis B virus-positive mother in combination with active vaccination.

*Hepatitis C*

Infection with hepatitis C virus is diagnosed by detection of specific antibodies **(anti-HCV)**. Third-generation enzyme-linked immunosorbent assays (ELISA) are very reliable and can even detect specific antibodies 2–3 weeks post-infection in most cases.

Most recombinant immunoblot assays (RIBA) use the same antigens as the ELISA tests and allow independent evaluation of the reaction with these antigens. However, they are now obsolete as confirmatory tests.
HCV infection is currently confirmed by detection of HCV RNA using reverse transcription-polymerase chain reaction (RT-PCR). This method has become much more reliable in recent years and also allows infection to be quantified. Qualitative tests should have a limit of quantification of less than 15 IU/ml. RT-PCR is also used for genotyping.

The diagnosis of hepatitis C requires
1. positive anti-HCV test and detectable HCV RNA, and
2. elevated transaminase levels.

The criteria for treatment of chronic hepatitis C are
1. elevated transaminase levels,
2. detectable HCV RNA in serum, and
3. fibrosis by histology or elevated levels in transient elastography.

The HCV genotype and RNA levels should be determined in order to select the proper drug combination and determine the optimal duration of treatment.

| **Hepatitis** | **A** | **B** | **C** | **D** | **E** |
|---|---|---|---|---|---|
| Virus family | Picorna | Hepadna | Flavi | Viroid | Calici |
| Genome | RNA | DNA | RNA | RNA | RNA |
| Incubation period (days) | 14–45 | 30–180 | 14–180 | ? | 21–60 |
| Transmission<br>– fecal/oral<br>– blood<br>– vertical<br>– sexual | <br>yes<br>no[1]<br>no[1]<br>no[2] | <br>no<br>yes<br>yes<br>yes | <br>no<br>yes<br>yes<br>yes[2] | <br>no<br>yes<br>yes<br>yes | <br>yes<br>no<br>no<br>no |
| Antigens | HAAg | **HBsAg**, HBeAg | – | HDAg | HEAg |
| Antibodies | anti-HAV<br>**anti-HAV**, **IgM** | anti-HBs<br>anti-HBe<br>anti-HBc<br>anti-HBc, IgM | **anti-HCV**<br>anti-HCV, IgM | anti-HDV,<br>**anti-HDV**, **IgM** | **anti-HEV, anti-HEV, IgM** |
| Resolving acute hepatitis | > 99% | > 90% | 5–15% | 50–80% | > 95% |
| Chronic hepatitis | 0% | < 10% | 80–95% | 20–50% | (< 5%) ? |
| Cirrhosis | < 0.1% | 1–3% | 5–30% | (10%) ? | ? |
| (The key diagnostic tests are shown in boldface) | | | | | |

**Table 1**
Hepatitis viruses

[1] Parenteral transmission is very rare since donor blood only contains HAV for a very short period during the prodromal phase.
[2] Sexual transmission has not been reported to date, but cannot be ruled out due to the high prevalence among partners of hepatitis A and hepatitis C patients.

***Treatment***

Patients are prescribed a combination regimen consisting of several different oral direct-acting antivirals (DAAs).

The drugs currently available include NS3/4 protease inhibitors (grazoprevir 1 x 100 mg/day, voxilaprevir 1 x 100 mg/day, glecaprevir 1 x 100 mg/day), NS5A inhibitors (pibrentasvir 1 x 40 mg/day, velpatasvir 1 x 100 mg/day, elbasvir 1 x 50 mg/day) and one NS5B inhibitor (sofosbuvir 1 x 400 mg/day), which can be prescribed for between 8–12 (16) weeks in various combinations (see table 2) depending on HCV genotype, fibrosis grade, and prior treatment. The combination regimen of grazoprevir/elbasvir for 12 weeks is also approved for genotype 1b, and the combination of sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg for 12 weeks is available for infections with resistant mutants.

In most studies, these combination therapies have success rates of over 95%, both for patients with and without prior treatment and/or cirrhosis. Fortunately, these oral antiviral combination regimens have only few adverse effects. For some of the drugs, interactions with other medications must be taken into account. Some drugs require dose reduction in patients with renal impairment. Prior treatment with pegylated interferon and ribavirin has no major impact on the outcome of treatment. HCV RNA negativity 12 weeks after the end of treatment is classified as sustained virological response.

*Hepatitis D*

Hepatitis D infection only occurs in patients with a concurrent, replicating hepatitis B infection, since the former pathogen uses the latter's surface proteins to synthesize its own envelope. This infection is diagnosed by detection of antibodies targeting the virus **(anti-HDV)**; it is not

| Treatment | Genotype | Cirrhosis | Prior treatment | Sofosbuvir/ velpatasvir | Glecaprevir/ pibrentasvir |
|---|---|---|---|---|---|
| Simplified, pan-genotype treatment | All genotypes | No | ± | 12 weeks | 8 weeks |
| | | Compensated cirrhosis | – | | |
| | | | + | | 12 weeks |

**Table 2**
Simplified, pan-genotype antiviral treatment for patients with and without cirrhosis and with or without prior treatment with interferon and ribavirin or sofosbuvir ± ribavirin

possible to detect the viral antigens directly. HDV RNA can be amplified by RT-PCR. The detection of specific antibodies is sufficient for routine diagnosis.

Treatment with pegylated interferon for 48 weeks results in an absence of detectable HDV RNA in blood in about one-quarter of patients; viral RNA remains undetectable 24 weeks after the end of treatment in these patients as well.
Despite these disappointing success rates, long-term treatment with pegylated interferon is nonetheless a realistic option for patients with rapidly progressing disease in order to slow the rapid progression to cirrhosis. Furthermore, the risk of hepatocellular carcinoma is 9-fold greater with HDV co-infection than with HBV infection alone. The combination regimen consisting of pegylated interferon plus tenofovir appears to confer no major added benefit. Tenofovir therapy may have a positive effect for patients with HIV co-infection.
Recently, bulevirtide – a virion entry inhibitor – has been approved by the European Medicines Agency (EMA) in a dose of 2 mg/day s.c. for a longtime therapy.

While there is no specific vaccination against HDV, vaccination against HBV indirectly protects against HDV infection. Passive immunization is not feasible.

*Hepatitis E*

Hepatitis E virus is transmitted by the fecal/oral route (like HAV) as well as by eating undercooked pork meat. To date, most infections have been reported from developing countries, although HEV is also now detected more frequently than HAV in many Western European countries. Extrahepatic manifestations such as acute pancreatitis, thrombosis, aplastic anemia, autoimmune thyroiditis, myositis, cryoglobulinemia with exanthema, and glomerulonephritis have been reported, as well as neurological complications such as encephalitis, Bell's palsy, brachial neuritis, Guillain-Barré syndrome, and peripheral neuropathy.
Specific antibodies against the virus can be detected soon after infection, and the infection is diagnosed by detecting these specific antibodies (**anti-HEV**, IgA, IgM, and IgG).

There is no specific treatment for hepatitis E. Ribavirin may have positive effects in immunocompromised transplant patients. A vaccine is in development and has been shown to be effective in 95% of subjects tested. Prevention consists of strict adherence to proper hygiene while in endemic countries. Pork should always be cooked well before consumption.

## 3.2 Hereditary hemochromatosis

Hereditary hemochromatosis is an autosomal-recessive disease that represents one of the most common congenital metabolic disorders. Among Northern Europeans, 6% are heterozygous and about 0.3–0.5% are homozygous for the condition, with a prevalence between 1 in 200 to 1 in 400. Approximately 90% of hereditary hemochromatosis patients harbor a homozygous cysteine-to-tyrosine mutation at position 282 in the HLA-H gene (HFE) located on the short arm of chromosome 6 (type 1). A smaller percentage of patients harbor an aspartate instead of histidine at position 63, or a cysteine instead of serine at position 65. Hemochromatosis can also develop when patients harbor separate heterozygous mutations at these positions on the different alleles (called compound heterozygotes). Mutations can also occur in other genes, but these are rarer (hemojuvelin [type 2A], hepcidin [type 2B] transferrin receptor-2 [type 3], ferroportin 1 [type 4], H-ferritin, L-ferritin). Although the disease manifests at a younger age in men than women, only 10–33% of men homozygous for C282Y develop clinically manifest disease. The disorders present with tan skin color at an advanced stage. Patients may also suffer from diabetes mellitus, hepatomegaly, cardiac arrhythmia, or cardiomyopathy, and frequently report joint pain. Hypogonadism may develop at early stages of the disease. Hemochromatosis patients are also at high risk for hepatocellular carcinoma.

### *Pathophysiology*

The homeostasis of iron ions is very delicate in the cells. Although many enzymes require iron ions, they also represent a potent cellular toxin if present at excessive amounts. This can interfere with certain enzymes in the electron transport chain and lead to the production of free radicals, which are themselves highly toxic.

Patients with hemochromatosis and advanced liver disease may have more than 25 g of iron in their entire body, compared with only 3–4 g in healthy individuals. This iron overload in the body results from excessive absorption of iron from the gastrointestinal tract, approximately 2–5 mg/day versus 1 mg in healthy individuals. Hence the primary defect in this disorder is not found in the liver, but in the enterocytes of the gut mucosa.
In addition to mutations in the HFE gene, the disease is also influenced by other factors including sex, alcohol consumption, viral hepatitis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), infections, hepatic porphyria, and thalassemia.
The disease begins with only elevated serum iron concentration and increased transferrin saturation, followed later by elevated tissue iron concentration and elevated ferritin levels, and finally to extremely high ferritin levels (> 1,000 µg/l) with organ damage.

### *Diagnosis*

Hemochromatosis is diagnosed by measuring serum ferritin levels (normal: 10–200 µg/l; hemochromatosis: 900–6,000 µg/l). However, elevated ferritin levels may also be caused by inflammation, diabetes mellitus, alcohol consumption, and liver tissue necrosis. If the result of this test lies in the pathological range, the next step is to measure transferrin saturation (normal: 22–46%; hemochromatosis: 50–100%); alternatively, transferrin saturation can be measured first followed by genetic testing for mutations at positions 282, 63, and 65 in the HFE gene.

If no mutations are detected at these positions, a quantitative test for iron levels in liver tissue is performed (normal: 300–1,400 µg/g dry weight; hemochromatosis: 6,000–18,000 µg/g) and is used to calculate the hepatic iron index (µg Fe/g dry liver weight/56/age; normal: < 1.0; hemochromatosis: > 2) (table 3). Alternatively, T2-weighted magnetic resonance imaging (MRI) may be performed.

| Test | Normal level | Hemochromatosis, symptomatic | Hemochromatosis, asymptomatic, homozygous | Hemochromatosis, heterozygous | Alcoholic liver disease |
|---|---|---|---|---|---|
| Serum iron (µg% [µmol/l]) | 50–150 [9–27] | 180–300 [32–54] | Elevated | Normal to elevated | Elevated |
| Transferrin saturation (%) | 22–46 | 50–100 | 50–100 | Normal to elevated | 27–60 |
| Serum ferritin (µg/l) | 10–200 | 900–6,000 | 200–500 | Typically < 500 | 10–500 |
| Hepatic iron concentration (µg/g dry weight) | 300–1,400 | 6,000–18,000 | 2,000–4,000 | 300–3,000 | 300–2,000 |
| Hepatic iron index µg/g dry weight/ 56/patient age | < 1.0 | > 2 | Typically > 2 | < 2 | < 2 |

**Table 3**
Laboratory tests for hemochromatosis

Echocardiography and Holter ECG should be carried out for patients with known hemochromatosis. When present, joint pain typically affects the joints of the fingers and should be further investigated by radiographic imaging. The differential diagnoses of diabetes mellitus, hypothyroidism, and hypogonadism must all be ruled out. The patient's relatives should also be screened for cases of undiagnosed hemochromatosis.

### *Treatment*

The objective of treating hemochromatosis is to reduce the iron overload in the body. This goal can be most effectively accomplished by therapeutic phlebotomy, which must be performed every 1–2 weeks for the first 1–2 years, and less frequently thereafter, until the ferritin concentration drops below 50 µg/l and transferrin saturation drops below 30%. 500 ml of blood are withdrawn per venesection, equivalent to 200–250 mg of iron; hence, over 100 venesections are required in total. Once these have been performed, transferrin saturation should be maintained below 50% and ferritin concentration below 100 µg/l. Should phlebotomy be contraindicated due to anemia, subcutaneous or intravenous deferoxamine therapy (20–60 mg/kg BW/day for 8–24 hours, 5–7x/week) is a further option, albeit with the potential adverse effects of retinopathy and hearing loss.

With comprehensive and consistent treatment, life expectancy can be significantly improved. Alcohol consumption should always be avoided since it increases the risk of cirrhosis by 10-fold. One-third of patients with known cirrhosis develop hepatocellular carcinoma even with adequate treatment, and accordingly such patients require regular follow-up (every 6–12 months) with ultrasound examination and measurement of alpha-fetoprotein (AFP).

## 3.3 Wilson's disease

Wilson's disease is an autosomal-recessive disorder of copper accumulation with a prevalence of 1:30,000 individuals. Patients may initially present with a liver disease (42%), or with neurological (34%), psychiatric (10%), or hematologic (12%) symptoms.
Although the symptoms are typically consistent with a chronic liver disease, acute and even fulminant forms may also occur. Neurological presentations differ according to the region(s) of the brain in which copper is deposited, and may include tremor (which may resemble Parkinson's), akinesia, rigidity, ataxia, gait abnormalities, dysarthria, pseudobulbar palsy, dysdiadochokinesia, bradykinesia, hypomimia, dystonia, and autonomic dysfunctions including increased sweating, hypersalivation, headache, or orthostatic symptoms. Approximately half of all patients with neurological symptoms also have a behavioral disorder with mood swings, impulsivity, irritability, and asocial behavior. Cognitive disorders, depression, neurosis, and psychosis are also observed.

Further examination reveals a greenish or brownish ring around the cornea of the eyes (Kayser-Fleischer rings) – which may be only visible by slit lamp in some cases – in 98% of patients with neurological symptoms and 50% of patients with liver disease. Sunflower cataract is a common complication. Both of these complications are reversible with successful pharmacological treatment or liver transplant.
Hemolysis may occur in acute forms, which is triggered by the release of copper from the liver.

### *Pathophysiology*

The pathological gene has been identified as ATP7B, in which more than 700 different mutations have been reported. This intracellular copper transport protein harbors a defect resulting in the accumulation of copper

in various organs, of which depositions in the liver and brain are of particular clinical significance. Fulminant liver failure is observed in 5% of patients. Wilson's patients suffer from coagulation disorders, encephalopathy, Coombs test-negative hemolytic anemia, and kidney failure. They also have elevated concentrations of copper in serum and urine. Most patients already have known cirrhosis at the time of their diagnosis.
Hepatocellular carcinoma is rare with Wilson's disease. Lesions can be detected by MRI in the putamen, globus pallidus, thalamus, midbrain, pons, and cerebellum. Cortical atrophy of white matter may also occur.
The Kayser-Fleischer rings are caused by fine deposits of copper in Descemet's membrane.

### *Diagnosis*

Wilson's disease is diagnosed by measuring serum levels of ceruloplasmin (normal: > 25 mg/dl; Wilson's: < 20 mg/dl). Up to 95% of homozygous patients and 20% of asymptomatic heterozygous patients have a serum ceruloplasmin level of less than 20 mg/dl. According to several studies, 5% of homozygous patients and up to 50% of patients with decompensated cirrhosis have normal ceruloplasmin concentrations. Levels of 24-hour urinary copper excretion are elevated (normal: 20–50 µg/day), with values greater than 40 µg per 24 hours indicative of Wilson's disease. Excretion can be increased by administering 500 mg D-penicillamine at the start of 24-hour testing and after 12 hours. Copper excretion greater than 600 µg/24 h under these conditions is indicative of Wilson's disease. The diagnosis is confirmed by quantitative measurement of the copper concentration in liver tissue (normal: < 40 µg/g dry weight; Wilson's disease: > 250 µg/g dry weight). The Leipzig score can also be used to diagnose Wilson's disease. This score incorporates the presence of Kayser-Fleischer rings, neurological symptoms, serum ceruloplasmin, Coombs-negative hemolytic anemia, 24-hour urinary copper, liver copper, and molecular analysis of ATP/B.

Patients with acute liver failure typically have AST and ALT levels < 2,000 IU/ml, normal or low alkaline phosphatase levels, coagulation disorders refractory to vitamin K, and hemolysis. In a small fraction of these patients, ceruloplasmin levels are not decreased.

### *Treatment*

Treatment comprises D-penicillamine (1.0–1.5 g/day), a chelating agent that binds copper increasing excretion in urine. Patients are also prescribed vitamin $B_6$ to reduce the side effects of D-penicillamine. Tests for anti-nuclear antibodies, urinary protein excretion, and hematuria must be performed regularly over the course of life-long treatment. An alternative pharmacological option is another chelating agent, trientine (1.2–1.8 g/day initially, then 0.9–1.2 g/day). Trientine should not be taken together with iron products as they form toxic complexes. Zinc (150 mg/day or 3 mg/kg BW) can be prescribed following decoppering using D-penicillamine or trientine. Zinc and chelating agents should be taken with a time interval. Copper excretion should be monitored during therapy with chelating agents. Excretion of 200–500 µg confirms that therapy is adequate. Dosage should start low and be increased gradually for patients with neurological symptoms, keeping copper excretion below 1,000 µg. Patients should avoid eating copper-rich foods such as liver, kidney, mussels, nuts, chocolate, dried fruits, beans, peas, and mushrooms at the start of treatment. With comprehensive and consistent treatment, liver function can be fully restored, and a normal life expectancy can be achieved with an early diagnosis.

## 3.4 Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin deficiency is a hereditary metabolic disorder which is inherited in an autosomal co-dominant pattern. Approximately 1 in 2,000 individuals harbors a variant of the SERPINA1 (serpin peptidase inhibitor, clade A, member 1) gene (e.g. ZZ, Znull, SS, SZ, MZ, Mnull or null/null). Alpha-1 antitrypsin is an inhibitor of the elastase protease. Patients with the disease may have alpha-1 antitrypsin levels which are normal, low (< 35% of normal), or not detectable. There is also a group of patients with normal levels of non-functional alpha-1 antitrypsin. The normal concentration of alpha-1 antitrypsin is 20–53 µmol/l (150–350 mg/dl). The majority of patients with clinically apparent disease have alpha-1 antitrypsin concentrations of 5–6 µmol/l. Some patients may have a childhood history of cholestasis. While concurrent pulmonary disorders are common, cutaneous disorders are observed less frequently. There are reports of patients with ANCA-associated vasculitis. Approximately 10% of newborns with alpha-1 antitrypsin deficiency develop liver disease presenting as hepatitis with cholestasis, and approximately 3% eventually develop cirrhosis. The risk for hepatocellular carcinoma is significantly elevated. Liver diseases are observed in patients with the Z and M alleles.

### *Pathophysiology*

Over 120 different mutations have been identified in the alpha-1 antitrypsin gene. These mutations lead to a toxic accumulation of misfolded alpha-1 antitrypsin in hepatocytes while simultaneously resulting in a deficiency of alpha-1 antitrypsin in serum. The disease progresses more rapidly in men and obese patients of both sexes.

### *Diagnosis*

The disease is diagnosed by detection of low alpha-1 antitrypsin levels in serum (< 50 mg/dl) and confirmed by molecular analysis of the M, Z, and S phenotypes.

### *Treatment*

There is no specific treatment for alpha-1 antitrypsin deficiency, although a gene therapy is in development.

Patients with pulmonary involvement should not smoke under any circumstances; augmentation therapy with alpha-1 antitrypsin (60 mg/kg BW/week) is also a possibility for patients with impaired lung function.

In contrast, augmentation is not beneficial for patients with cirrhosis since the liver damage in the disease results from accumulation of misfolded alpha-1 antitrypsin in hepatocytes.

## 3.5 Porphyrias

Porphyrias are characterized by disorders of heme biosynthesis. Porphyrias can be subclassified into erythropoietic and hepatic porphyria as well as acute versus non-acute porphyria. These forms can be differentiated by determining the deficient enzyme responsible for the metabolic disorder.

### *Acute hepatic porphyria*

#### *Pathophysiology and clinical presentation*

The acute hepatic porphyrias (acute intermittent porphyria [AIP], variegate porphyria, hereditary coproporphyria, and aminolevulinic acid dehydratase deficiency porphyria) manifest clinically and metabolically as a result of dysregulation in the induction of porphyrin biosynthesis in the liver.
Acute symptoms can be triggered by certain medications (www.drugs-porphyria.org), toxic substances, alcohol, cigarettes, fasting, inflammation, and infections.

#### *Characteristic symptoms*

- Acute, intermittent, colic-like abdominal pain which may progress to ileus symptoms
- Back pain
- Vomiting
- Constipation
- Tachycardia and hypertension
- Neurological symptoms such as muscle weakness, paresthesia, peripheral nerve palsy, status epilepticus
- Psychiatric symptoms which may be misinterpreted as psychosis or depression

Paralysis, possibly as severe as quadriplegia, is the most frequent complication of undiagnosed and untreated porphyric crises.

### *Diagnosis*

Porphyrias are diagnosed based on detection of excessive excretion of the two porphyrin precursors, delta-aminolevulinic acid and porphobilinogen (> 10-fold), as well as total porphyrins in urine.
A single 20 ml random urine sample during an acute attack is sufficient to confirm the diagnosis.

During acute AIP, the levels of these excretion parameters are many times higher than normal levels. Additional tests of porphyrin biosynthesis parameters in stool and blood are required for a differential diagnosis between the acute porphyrias and between acute and chronic hepatic porphyrias. Genetic analyses are also now possible: Mutations can be found on chromosome 11q23.3 of patients with acute intermittent porphyria, which is inherited in an autosomal-dominant pattern. Variegate porphyria and hereditary coproporphyria are also inherited in an autosomal-dominant pattern (chromosomes 1q22 and 3q12, respectively), whereas ALA-deficient porphyria is inherited in an autosomal-recessive pattern (chromosome 9q33.1).

### *Treatment*

Heme arginate is a drug that effectively treats acute porphyrias by suppressing the induction and dysregulation of the porphyria process in the liver. This specific mode of action induces clinical remission by downregulating metabolic expression. Heme arginate should not be administered until the diagnosis of clinically active AIP or another acute hepatic porphyria has been confirmed.
In other words, administration of heme arginate is only indicated in patients with high excretion of the metabolites delta-aminolevulinic acid, porphobilinogen, and porphyrins. To obtain an objective measure of the treatment outcomes and monitoring, excretion parameters should be checked after treatment. These parameters are expected to decrease by at least one-half depending on their original pathological levels.

### *Heme arginate*

Intravenous administration of heme arginate is initiated as soon as a diagnosis of hepatic porphyria is confirmed. Heme arginate is administered at a dosage of 3 mg/kg BW/day for 4 consecutive days. Concurrently, a carbohydrate-rich and protein-rich diet should also be consumed orally or by feeding tube. Intravenous administration of 300–500 g glucose per day or 4–6 g carbohydrates/kg BW is additionally recommended for severe cases.

Other interventions address the symptoms of the disease (e.g. opiates for pain, propranolol for hypertension and tachycardia, etc.) as well as the issues which arise due to the discontinuation or avoidance of porphyrinogenic drugs, lists of which can be found in various national drug product databases and compendia or online (www.drugs-porphyria.org).

## 3.6 Autoimmune hepatitis

The term autoimmune hepatitis denotes a number of rare forms of chronic liver diseases characterized by detectable autoantibodies. It more frequently afflicts women (75%) than men (25%) and can occur at any age. The condition manifests as acute hepatitis in about 25% of patients. The typical symptoms are itching, joint pain, and jaundice. Extrahepatic symptoms such as arthralgia, arthritis, cutaneous vasculitis, and glomerulonephritis are triggered by circulating immune complexes. Many patients have non-specific symptoms such as fatigue, exhaustion, upper right abdominal pain, drowsiness, malaise, nausea, and weight loss.

### *Pathophysiology*

The etiology and pathogenesis of autoimmune hepatitis are unknown. Genetic factors appear to play a role, since certain histocompatibility haplotypes frequently associated with autoimmune disorders (HLA class I, II, and III loci: HLA-A1, Cw7, B8, TNFAB*a2b3, TNFN*S, C2*C, Bf*s, C4A*Q0, C4B*1, DRB1*03:01, DRB1*04:01, DRB1*13:01, DRB3*01:01, DQA1*05:01, DQB1*02:01, HLA-DRB1*03:01) are also observed in patients with autoimmune hepatitis. Furthermore, autoimmune hepatitis patients and/or their relatives also have higher incidences of other autoimmune diseases such as thyroiditis, rheumatoid arthritis, hemolytic anemia, ulcerative colitis, proliferative glomerulonephritis, juvenile diabetes, or Sjögren's syndrome. The cellular immune response likely plays a major role in the pathogenesis of the disease. Cytotoxic lymphocytes which target certain cellular components are presumed to cause destruction of hepatocytes. The detected autoantibodies are probably only an indicator of the liver disease but not its causal agent.

| Parameters | Threshold | Points |
|---|---|---|
| ANA or SMA* | ≥ 1:40<br>≥ 1:80 | 1<br>2 |
| Anti-LKM* | ≥ 1:40 | 2 |
| Anti-SLA/LP* | Positive titer | 2 |
| Total IgG | > upper limit of normal<br>> 1.1x upper limit of normal | 1<br>2 |
| Liver histology | Consistent with AIH<br>Typical of AIH | 1<br>2 |
| No viral hepatitis | No<br>Yes | 0<br>2 |

*Maximum score for all antibodies: 2

**Table 4**
Simplified criteria for the diagnosis of autoimmune hepatitis

### *Diagnosis*

In addition to total IgG, the concentrations of the following autoantibodies are also measured if autoimmune hepatitis is suspected: anti-nuclear antibodies (ANA, 50–60% positive), smooth muscle antibodies (SMA, 50–60% positive), liver, kidney microsomal antibodies (LKM, < 5% positive), anti-soluble liver antigen/liver pancreas antibody (SLA/LP, 10–30% positive) and antibodies targeting myeloperoxidase (MPO) in neutrophil azurophilic granules (pANCA, in 50–96% of patients with type 1 AIH, helpful in the absence of other antibodies). Patients with type 1 AIH are ANA- and/or SMA- and/or SLA/LP-positive, while type 2 AIH patients are anti-LKM-positive. It is worth noting that no antibodies can be detected in up to 10% of autoimmune hepatitis patients. IgG levels are typically elevated. Liver histology findings include lymphoplasmacytic infiltrates (CD4 cells, B lymphocytes, plasma cells) in portal tracts and the lobes of differing intensity depending on disease activity. The International Autoimmune Hepatitis Group (IAHG) has pro-

posed using IgG, ANA, SMA, LKM, SLA/LP, histology, and exclusion of viral hepatitis as diagnostic criteria (table 4). A score of ≥ 6 denotes probable AIH and a score of 7 denotes definite AIH.

### *Treatment*

The course of the disease can be markedly improved or even cured with corticosteroids (initially 50 mg/day or 1 mg/kg BW/day, then weekly reduction down to 15 mg/day, then 10 mg/day starting week 12) and azathioprine (1–1.5 mg/kg BW/day or 50–100 mg/day) starting in week 2. However, it must be kept in mind that azathioprine itself can cause liver damage. After liver function parameters have returned to normal, the drugs must still be taken continuously for at least another 2 and preferably 4 years. A liver biopsy should be performed before any decision to discontinue immunosuppressive treatment is made. For patients with no signs of inflammation on biopsy, the recurrence rate is 20–30% versus 75–90% for patients with residual signs of hepatitis on biopsy. One alternative to prednisone or prednisolone is budesonide (3 x 3 mg/day), which causes fewer systemic adverse effects.
Other immunosuppressants such as mycophenolate mofetil, cyclosporine A, and tacrolimus are enjoying increasing use.

## 3.7 Primary biliary cholangitis

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune liver disease characterized by destruction of the small and medium-size bile ducts. It was previously called primary biliary cirrhosis, which is a misnomer since the disease progresses to cirrhosis only in a subset of patients. PBC most commonly afflicts females (male:female ratio: 5:95 to 10:90) above the age of 40 and exhibits a familial pattern. The prevalence of PBC has been reported to be approximately 30 per 100,000 individuals or 80 per 100,000 women. The incidence of the disease has been continuously increasing over the past decade, which may be explained in part by more frequent and earlier diagnoses owing to improved diagnostic methods.

The initial symptoms of PBC are relatively non-specific, with patients most often reporting fatigue/exhaustion, digestion issues, hyperpigmentation, and especially itching. Joint pain is also quite common, as are dry mucosa and conjunctiva (keratoconjunctivitis). Typical liver signs such as jaundice or xanthelasma may be absent during the early stage of the disease. Over the course of the disease, patients may develop malabsorption with significant weight loss, osteoporosis, night blindness, and hematoma.

### *Pathophysiology*

It is not clear what causes primary biliary cholangitis. The disease is presumed to have an autoimmune etiology due to both elevated IgM levels as well as the presence of anti-mitochondrial antibodies (AMA), which can be found in more than 95% of patients. PBC patients frequently suffer from other autoimmune diseases such as keratoconjunctivitis sicca (72–100%), arthritis/arthropathy (4–42%), autoimmune thyroiditis (15–20%), CREST syndrome (7%), Raynaud's disease (8%), and scleroderma (3–4%).

Viruses, bacteria, toxins, or environmental factors have all been proposed to be the underlying trigger. PBC is typically asymptomatic for 5–10 years, with its primary symptom of pruritus only manifesting gradually as the disease progresses. Mean survival is 6–7 years following onset of jaundice or 10–12 years after the initial diagnosis. Because bile acid secretion is decreased, patients develop malabsorption of fats and fat-soluble vitamins (A, D, E, and K).

### *Diagnosis*

A diagnosis of PBC should be suspected in cases with
- elevated GGT and/or alkaline phosphatase, elevated IgM and/or bilirubin (the transaminases AST and ALT are typically only slightly elevated),
- reported itching, and
- female sex.

In the early stages of PBC, laboratory test results may be fairly normal or may not display a characteristic pattern; therefore, immune serology is of key importance. Anti-mitochondrial antibodies (AMA), especially subgroup AMA-M2, are detectable in nearly 100% of patients, and other autoantibodies are also frequently observed: rheumatoid factors (70%), smooth muscle antibodies (SMA 66%), anti-thyroid antibodies (41%), and anti-nuclear antibodies (ANA 35%).
Ultrasound must be performed to rule out tumors or gallstones. Although liver biopsy is not required for diagnosis, it may be useful for staging purposes.

### *Treatment*

Primary biliary cholangitis is primarily treated with ursodeoxycholic acid (UDCA, 14 ± 2 mg/kg BW/day), which leads to improvement in liver function parameters in most patients and even to normalization in 30%, as well as improvement in liver histology in many patients. UDCA can delay disease progression and boost life expectancy,

particularly among patients in a pre-cirrhotic stage. Ursodeoxycholic acid is more effective the earlier treatment is initiated, and conversely is less effective in advanced stages of PBC. Treatment must be continued for many years or even life-long. Obeticholic acid is also approved in combination with UDCA for patients without cirrhosis (5 mg/day; maximum 10 mg/day) who don't respond to UDCA monotherapy.
Some patients also benefit from a combination regimen of ursodeoxycholic acid plus prednisone or the topical steroid budesonide (3 x 3 mg/day).
Supplementation with vitamin D and calcium is indicated for patients with osteoporosis, while vitamin A is indicated for patients with night blindness and vitamin K for patients with coagulation disorders.
Cholestyramine (4–16 g/day) can be used to treat mild or moderate itching, or mild itching which does not respond to any of the therapies listed above; however, it should not be taken in parallel with ursodeoxycholic acid. Rifampicin (2 x 150–300 mg/day) is a potential option for patients with bilirubin concentrations below 3 mg/dl as long as its adverse effects (liver, kidney, hemolysis) and potential drug interactions are taken into account. Naltrexone (1 x 50 mg/day) and sertraline (1 x 75 mg) may be effective in some patients, whereas antihistamines usually show no benefit.

Patients should take medium-chain triglycerides (MCT) to control body weight. Pancreatic enzymes should be prescribed for patients with suspected pancreatic insufficiency.

Treatment should be monitored by regular follow-ups: liver function tests every 3–6 months; TSH every 12 months; vitamins A, D, and K every 12 months if bilirubin > 2.0 mg/dl; ultrasound and AFP every 12 months in patients with cirrhosis; upper endoscopy every 1–3 years for patients with cirrhosis, and bone densitometry every 2–4 years.

## 3.8 Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic inflammation that may lead to stenosis or even occlusion of intrahepatic and/or extrahepatic bile ducts and can lead to cirrhosis and eventually bile duct cancer in 10–30% of patients. It afflicts men twice as frequently as women. The onset of initial symptoms occurs between the ages of 25 and 40. The prevalence of PSC is 1–8 per 100,000 individuals. About 80% of patients with PSC also have inflammatory bowel disease.

### *Pathophysiology*

Although the cause of PSC is not clear, it may have an autoimmune mechanism as autoantibodies can be detected in some patients (pANCA, perinuclear anti-neutrophil autoantibodies: 84%; anti-cardiolipin antibodies: 66%; anti-nuclear antibodies, ANA: 53%). It is also very frequently (> 80%) accompanied by ulcerative colitis or Crohn's disease. Conversely, 4–6% of ulcerative colitis patients also have PSC. In addition to the immunological factors, a genetic predisposition has also been proposed as a cause of the disease.

### *Diagnosis*

A diagnosis of PSC should be suspected in cases with
- elevated GGT and/or alkaline phosphatase (levels of the transaminases AST and ALT are typically only slightly elevated),
- negative AMA, positive pANCA,
- reported itching,
- known inflammatory bowel disease,
- recurring high temperature, fever, or weight loss, and
- male patients between the ages of 25 and 40.

The diagnosis is confirmed by typical features in endoscopic retrograde cholangiopancreatography (ERCP) or,

alternatively, MRI. Only the small bile ducts are afflicted in about 5–10% of patients (small-duct PSC), for whom a liver biopsy is required for diagnosis.
Ultrasound must be performed regularly to rule out tumors or gallstones.
Since patients typically suffer from osteoporosis, bone densitometry should be performed early in the disease and vitamin $D_3$ supplementation prescribed when indicated. Vitamin A deficiencies are also common in PSC. Follow-ups every 6–12 months are necessary to monitor alkaline phosphatase, CA 19-9, and MRI (or ultrasound or ERCP) in order to detect progression and bile duct cancer as early as possible. PSC patients also frequently develop liver or colon cancers.

***Treatment***

There is no treatment option that addresses the underlying cause of PSC. While treatment with ursodeoxycholic acid (15–20 mg/kg BW/day) can improve laboratory parameters, it is no longer recommended as standard therapy but can be prescribed to patients with itching. Endoscopy can be used to dilate stenoses, and thorough endoscopic dilation and antibiotics can prolong life expectancy. Liver transplant must be considered in a timely manner since PSC often leads to bile duct cancer.

## 3.9 IgG4-related sclerosing cholangitis

Immunoglobulin (Ig)G4-related sclerosing cholangitis (IgG4-SC) is a rare disease characterized by elevated serum concentrations of IgG4, infiltration of the bile duct walls by IgG4-positive plasma cells and lymphocytes, and fibrosis of the bile ducts. It is frequently associated with autoimmune pancreatitis and belongs to the family of IgG4-related diseases (IgG4-RD).

### *Pathogenesis*

The pathogenesis is unknown, and no IgG4-SC-specific autoantibodies have been identified.

### *Diagnosis*

The disease is diagnosed by elevated serum concentrations of IgG4, characteristic biliary findings in ERCP or magnetic resonance cholangiopancreatography (MRCP), the presence of other IgG4-RD, and typical histological features.

### *Treatment*

Treatment with 50 mg prednisolone/day should be attempted for 2 weeks. If patients respond, the dose should be reduced by 5 mg/day every 1–2 weeks down to a maintenance dose of 5 mg/day.

Biliary drainage using ERCP or PTD can be performed for patients with jaundice due to strictures.

## 3.10 Overlap syndromes

The term overlap syndrome refers to patients who present with characteristic features from multiple disorders simultaneously and which cannot be unambiguously classified as a single entity. For example, combinations between autoimmune hepatitis with features of PBC or PSC have been observed. Autoantibodies have also been detected in patients infected with hepatitis C. Patients with typical clinical and histological features of PBC may be AMA-negative and may experience variations in clinical symptoms and immunological parameters over the course of the disease.

### *Pathogenesis*

The pathogenesis of overlap syndromes is not known. While the autoantibodies observed in some patients – namely AMA, ANA, SMA, ANCA, and LKM-1 – are indicators of the disease, they likely play no role in its pathogenesis.

### *Diagnosis*

Diagnosis requires tests for levels of transaminases, alkaline phosphatase, gamma-glutamyltransferase (GGT), and various autoantibodies as well as liver histology. ERCP may be required for some patients.

### *Treatment*

Treatment begins by using the parameters listed above to attempt to elucidate whether the disease more closely resembles a cholestatic liver disease (PBC or PSC) or autoimmune hepatitis. If cholestasis is the primary disorder, treatment with ursodeoxycholic acid is initiated, and can be combined with the immunosuppressants used for autoimmune hepatitis in case of non-response. If the disease more closely resembles autoimmune hepatitis, immunosuppressant therapy is initiated, with the possibility of

adjunct ursodeoxycholic acid from the start. If patients do not respond to this therapy, treatment with corticosteroids plus azathioprine may be attempted. Patients with hepatitis C and detectable HCV RNA in blood should be prescribed antiviral therapy using direct-acting antivirals (DAAs).

## 3.11 Liver involvement in cystic fibrosis

Cystic fibrosis is one of the most common hereditary multisystem diseases. Approximately 5% of the Caucasian population is heterozygous for the CFTR gene. The most common polymorphism in these individuals is a three-base pair deletion (ΔF508, 70%), although more than 1,000 mutations in the CFTR gene have been reported.
The prevalence of cystic fibrosis is 1:1,600. Until recent years, only few patients survived past the age of 20. Reports of the frequency of liver involvement vary between 2% and 17% (much higher in adult patients). This difference can likely be explained by the increase in life expectancy achieved over the past 2 decades. For adult patients, the increase in liver involvement represents one of the major issues in the disease.
Liver involvement can manifest as chronic cholestasis, inflammation, fatty liver disease, fibrosis, or even cirrhosis. Disorders of the extrahepatic bile ducts are common.

### *Pathophysiology*

The causal mechanism is a disruption in the cholangiocyte transport system. The reduction in secretory capacity by the biliary epithelia is likely responsible for the decrease in bile viscosity and the increase in its alkalinity. To date, no links have been identified between specific mutations in the CFTR gene and liver involvement.

### *Diagnosis*

Cystic fibrosis is diagnosed using a sweat test. Cystic fibrosis-related liver disease should be suspected in cases with

- elevated GGT, transaminases, and alkaline phosphatase, and
- bile duct stenosis, dilation, and stiffness in MRI.

### *Treatment*

Dilation is recommended for major stenosis of the biliary system. Antibiotic therapy is mandatory in cases with cholangitis. Ursodeoxycholic acid (20 mg/kg BW/day) improves liver function parameters and can be prescribed if transaminases are significantly elevated. While there are reports that higher doses (up to 30 mg/kg BW/day) may be even more effective, the number of such studies remains low.

## 3.12 Liver involvement in celiac disease

Celiac disease is a disorder of the small intestine resulting from gluten intolerance, and is characterized by villous atrophy, crypt hyperplasia, and inflammation of the small intestinal mucosa. The prevalence of celiac disease is 1%. About 40% of patients with known celiac disease have elevated liver enzyme levels. Conversely, up to 5% of patients with elevated transaminases of unknown origin have antibodies against gliadin and/or tissue transglutaminase.

### *Pathophysiology*

While the pathogenesis of liver disease in celiac disease is not known, anti-tissue transglutaminase (tTG) and anti-endomysial antibodies are frequently detected.

### *Diagnosis*

Celiac disease is diagnosed based on elevated levels of anti-transglutaminase IgA antibodies (tTG IgA Ab) and/or anti-endomysial IgA antibodies (EMA IgA Ab). If these antibodies are not elevated, the serum IgA concentration should be determined. If this parameter is very low, levels of anti-transglutaminase IgG antibodies should be measured. The diagnosis of celiac disease should be confirmed by small intestine biopsy, which should reveal partial or total villous atrophy, crypt hyperplasia, increased mitosis in crypts, increased intraepithelial lymphocytes, increased mitosis in intraepithelial lymphocytes, and large infiltrates consisting of plasma cells, lymphocytes, eosinophils, and basophils in the lamina propria.
Liver involvement in celiac disease is diagnosed in cases with

- elevated GGT, transaminases, and alkaline phosphatase, and
- detectable steatosis or progressive hepatitis in histology with no other known cause.

### *Treatment*

A gluten-free diet leads to normalization of liver function parameters in about 90% of patients. Celiac disease can progress to cirrhosis if left untreated.

## 3.13 Drug-induced liver injury

(see: livertox.nih.gov)

Clinically-relevant drug-induced liver injuries are relatively rare in light of the large number of medications taken. Fewer than 5% of cases of acute liver injury and jaundice are caused by medications, and even fewer cases of chronic liver diseases. The most common pharmacological cause of acute liver injury is acetaminophen (paracetamol), which is toxic in a dose-dependent manner. Drug-induced liver injury occurs more often in elderly patients. It must also be remembered that drug interactions can slow their metabolism and thereby enhance drug toxicity. Slight elevations in transaminases, gamma-glutamyltransferase (GGT), and alkaline phosphatase are more common, for example with some tuberculosis drugs. These elevations are usually reversible. In many cases, the drug causing the toxicity must be continued despite the minor liver injury. Drugs can cause liver disease by many different mechanisms, and nearly every drug can cause liver damage with few exceptions.
A large number of chemicals can also cause severe liver damage, primarily organic solvents.

### *Pathophysiology*

It is not possible to formally distinguish predictable, toxic (i.e. dose-dependent) liver injury from idiosyncratic, unpredictable (not dose-dependent) hypersensitivity reactions.
Most drugs initially undergo a chemical reaction in the body that allows them to be coupled with endogenous compounds in later steps, which in turn facilitates elimination of the drug via the kidneys or biliary system. These reactions can be very complex and involve catalytic steps by the cytochrome P450 system. In the toxic form of drug-induced injury, patients experience toxicity in a dose-dependent manner, whereas hypersensitivity reactions only affect a certain subset of individuals who have

either altered metabolic pathways or an allergic immune reaction. Liver injury has also been observed with the use of checkpoint inhibitors, requiring discontinuation of therapy in some patients depending on the severity. Hepatocellular (hepatitis-like) injury is more common (75%) than cholestatic (20%) or mixed forms. The prognosis is least favorable for patients with cholestatic liver injury.
Different drugs can cause different patterns of injury: microvesicular or macrovesicular steatosis, nodular regenerative hyperplasia, ductopenia (vanishing bile duct syndrome), drug-induced autoimmune hepatitis, acute steatohepatitis, mitochondrial damage, apoptosis, cholestasis due to bile accumulation in hepatocytes, secondary sclerosing cholangitis, fibrotic scarring, inflammation, vascular pathologies and, in rare cases, cancer.

### *Diagnosis*

The diagnosis of drug-induced liver injury is guided by a patient's medical history and exposure to drugs or substances known to be (potentially) toxic to the liver. Drugs which can cause liver damage include the following: chlorpromazine, amoxicillin/clavulanic acid, flucloxacillin, diclofenac, metoclopramide, tetracyclines, macrolides, sulfasalazine, antiepileptics, sulfamethoxazole/trimethoprim, antituberculosis drugs, valproic acid, phenytoin, antidepressants, thiazolidinediones, antiretroviral drugs, azathioprine, 6-mercaptopurine, methotrexate, and checkpoint inhibitors.
In modern times, patients must also be asked specifically about "alternative" medications such as medicinal herbs, including traditional Chinese medical drugs, since some of these may also be hepatotoxic (see table 5).
Histological examination can solidify suspicion of drug-induced liver injury, which is proven by resolution of symptoms and of pathological liver function parameters after discontinuation of the medication or cessation of the chemical exposure.

### *Treatment*

No specific treatment exists other than discontinuing the medication or avoiding the causal chemical exposure. The one exception is acetaminophen intoxication, for which N-acetylcysteine is administered within the first 8 hours and every 8 hours thereafter for 72 hours. This intervention drastically reduces mortality. Patients should not be re-exposed to the suspected medication since fulminant liver failure has been described in this situation.

| Name | Indication/ application | Hepatotoxicity | Toxic agent |
|---|---|---|---|
| **Aloe vera** [*Aloe barbadensis*] | Laxative | Portal/lobular inflammation | Not known |
| **Copalchi** [*Hintonia latiflora*] | Diabetes, antipyretic | Centrilobular necrosis | Furanterpenoids |
| **Germander** [*Teucrium*] | Weight loss | Acute/chronic hepatitis with jaundice | Epoxies; hepatocellular apoptosis by N-nitroso-diterpenoids |
| **Green tea** [*Camellia sinensis*] | Many beneficial effects, diabetes, obesity, Alzheimer's | Cholestasis, occasionally steatosis and necrosis | Catechins and their gallates. Potentially toxic effects start at > 10 cups/day |
| **Chamaeleon gummifer** [*Carlina gummifera*] | Antipyretic, antiemetic, diuretic | Diffuse hepatic necrosis | Inhibits gluconeogenesis, apoptosis due to mitochondrial damage |
| **Chinese skullcap** [*Scutellaria*] | Anti-inflammatory, sedative | Inflammatory infiltrates, bridging fibrosis, cirrhosis | Flavonoids, alkylating agents |
| **Kava extracts** [*Piper methysticum*] | Anxiety disorders, agitation | Acute/fulminant hepatitis | Unknown; CYP2D6 polymorphism? |
| **Creosote bush** [*Larrea tridentata*] | Rheumatoid arthritis therapy, bronchitis, diabetes | Cholestatic hepatitis, biliary pathology, cirrhosis, massive necrosis | Nordihydroguaiaretic acid (exerts estrogen-like effects); inhibits cyclooxygenase |
| **Greater celandine** [*Chelidonium majus*] | Dyspepsia | Cholestatic hepatitis, possibly with autoantibodies | Not known |
| **Ox-eye daisy** [*Callilepis laureola*] | Stomach issues, coughing, (impotence) | Acute liver failure, multiple deaths | Atractyloside |
| **Black cohosh** [*Actaea racemosa*] | Postmenopausal symptoms | Acute/fulminant hepatitis; autoimmune phenomena | Apoptosis due to mitochondrial damage |

**Table 5**
Plants/extracts with hepatotoxic potential (selection)

## 3.14 Alcoholic liver disease

Alcohol is the most frequent cause of chronic liver diseases in Europe. Alcohol-related liver disease can be subdivided into three conditions: 1. fatty liver disease, 2. alcoholic hepatitis, and 3. cirrhosis. The quantity of regular alcohol consumption that can lead to liver injury within 10 years is 20 g/day for women and 50 g/day for men. The three stages of the disease can overlap.

In fatty liver disease, the greatly enlarged liver is the primary pathology and is frequently reported as a sensation of pressure in the upper abdomen. Liver function is usually not impaired. Of greater clinical relevance is steatohepatitis, which is associated with hepatocyte injury, apoptosis, and loss of hepatic function and may manifest in life-threatening forms. Both conditions are typically reversible following complete cessation of alcohol consumption. The symptoms and findings of alcoholic cirrhosis do not differ from those of cirrhosis due to other causes, and cirrhosis is also reversible – at least partially – following complete abstinence from alcohol.

### *Pathophysiology*

Alcohol can alter metabolism in many ways. Chronic, heavy alcohol consumption may trigger redox homeostasis disorders. The initial degradation product of alcohol, acetaldehyde, is thought to play a major role in hepatocyte toxicity and connective tissue growth.
Other factors that play a role in liver injury are hepatic antioxidant deficiency, structural and functional disorganization of the mitochondria and other cellular organelles, impaired intracellular signal transduction, and cytokine and eicosanoid imbalances. Endotoxins are thought to be important exogenous factors for inflammation.

Fat metabolism is altered, leading to increased production and decreased breakdown of fats, which results in fatty

deposits in the liver. Protein synthesis is also disrupted. Drug metabolism is frequently slowed, prolonging and enhancing the effects of any medications taken. Chronic alcohol consumption is frequently associated with malnutrition, resulting in deficiencies in vitamins and trace elements.

### *Diagnosis*

A patient's medical history is important for alcoholic liver disease. It is crucial to determine the duration of alcohol consumption, the quantity consumed, and the type of beverage, and it can also be helpful to interview the patient's relatives.

Fatty liver is palpable. These patients appear normal in ultrasound and laboratory liver function tests reveal no major impairment. There are no specific tests to diagnose alcoholic liver disease. The AST:ALT ratio is usually greater than 2, and GGT and mean corpuscular volume are frequently elevated to a varying degree. The differential diagnoses of diabetes mellitus, obesity, or drug toxicity must be ruled out for fatty liver (table 6).

Alcoholic steatohepatitis is characterized by elevated WBC counts in blood, elevated serum bilirubin, and elevated liver enzymes in blood, which reflect severe liver injury. The liver's synthetic capacity is also reduced, which is indicated by an increased prothrombin time.

For patients with alcohol-related cirrhosis under consideration for liver transplant, tests for carbohydrate-deficient transferrin (CDT) in serum or ethyl glucuronide (EtG) in urine, serum, or hair can be performed to determine whether the patient is still consuming alcohol. EtG can be detected for about 36 hours in serum, for several days in urine, and for several weeks in hair depending on the dose of alcohol consumed.

| Etiology | Pathogenesis | Fat pattern | Location of cell nucleus | Other features |
|---|---|---|---|---|
| Alcohol | Toxic oxidation of fatty acids | Diffuse | Peripheral | Neutrophil infiltrates Mallory bodies |
| Type 1 diabetes | Lipolysis | Diffuse | Peripheral | Non-specific |
| Type 2 diabetes | Lipogenesis | | | |
| Obesity | Dietary fat | Centrilobular Diffuse | Peripheral | Non-specific |
| Drug toxicity (e.g. tetracyclines) | Secretion of VLDL | Diffuse | Central | Non-specific |

**Table 6**
Clinical symptoms and findings in patients with alcoholic hepatitis and other fatty liver diseases

### *Treatment*

The primary goal for all forms of treatment of alcoholic liver disease is complete and permanent abstinence from alcohol. Corticosteroid therapy may be beneficial for severe cases of acute alcoholic hepatitis. Vitamins and trace elements can be prescribed as an adjunct measure during the initial phase of treatment; in particular, vitamin $B_1$ supplementation should be prescribed in order to prevent Wernicke-Korsakoff syndrome. The need for liver transplant must be determined in a timely manner for patients with advanced cirrhosis.

## 3.15 Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

These liver diseases are characterized by an increase in fatty deposits in the liver (NAFLD) which may be associated with elevated transaminase levels (NASH). The terminology for these conditions remains inconsistent. Other causes must be excluded first, particularly excessive alcohol consumption. Overweight individuals often have a fatty liver, defined as increased fatty deposits in the liver without elevated transaminase levels. For unknown reasons, this condition can develop into non-alcoholic steatohepatitis with elevated transaminase levels, which leads to fibrosis (in 15–50% of cases) or cirrhosis (7–16%).
Obesity as well as insulin resistance, diabetes, hyperlipidemia, and possibly rapid weight loss are thought to play a role in NASH. NASH has also been observed following extensive small bowel resection and bariatric surgery, such as sleeve surgery, gastric or jejunoileal bypass.
Non-alcoholic fatty liver disease usually occurs in patients with metabolic syndrome (overweight with abdominal obesity [waist circumference > 102 cm for men, > 88 cm for women], dyslipoproteinemia [serum triglycerides > 150 mg/dl; HDL cholesterol < 40 mg/dl for men, < 50 mg/dl for women], diabetes/insulin resistance, or hypertension [BP > 140/90 mmHg]).

### *Pathophysiology*

There is no single etiology for these conditions. NAFLD and NASH are both closely linked to metabolic syndrome. NASH is currently thought to be a multifactorial disease. Imbalances in amino acid metabolism, hyperglycemia, elevated insulin levels, decreased leptin, and endotoxins are thought to play a role in its pathogenesis by increasing lipogenesis. NASH and alcoholic liver disease share several common features including the activation of microsomal enzymes, elevated endotoxin concentrations in blood,

elevated TNF-α and decreased ATP levels in liver tissue. Adipocytokines such as leptin, adipsin, resistin, adiponectin, and visfatin are thought to play a role in liver injury. Several drugs may trigger NASH-like features, for example tamoxifen.

### *Diagnosis*

Patients with NASH typically have slightly to moderately elevated transaminase levels, and gamma-glutamyltransferase is also frequently elevated. Between 25–75% of patients have an elevated glucose concentration caused by insulin resistance, as well as hypercholesterolemia, and hypertriglyceridemia. Signs of fatty deposits with homogeneous echogenicity are observed in the liver on ultrasound. Liver histology is key to diagnosis, with the classical features being fatty deposits with large drops and less frequently small drops, focal necrosis, inflammatory infiltrates, and also occasionally Mallory bodies. Fibrosis and later cirrhosis develop as the disease progresses. Other potential causes must be excluded, particularly excessive alcohol consumption.

### *Treatment*

There is no specific treatment for NAFLD or NASH. The recommended measures are (slow) normalization of body weight, optimal glycemic control for diabetics, and treating hyperlipidemia if present. Weight reduction surgery may have a positive impact on NASH.
Small studies on insulin sensitizers, vitamin E, pentoxifylline, losartan, betaine, S-adenosyl methionine, polyunsaturated fatty acids, fibrates, and statins all revealed no statistically significant long-term effects.
If drugs are suspected to be the cause of a patient's disease, they should be discontinued whenever possible.

## 3.16 Cirrhosis

Cirrhosis represents the end stage of many liver diseases. In cirrhosis, the liver architecture is remodeled, and the ordered and required structure of the liver required for its proper function is destroyed combined with the reduction of the total cross section of blood vessels. This can impact the blood flow, metabolism, and detoxification functions of the liver.

The reduced perfusion of the liver leads to blockage of the portal vein upstream of the liver, resulting in varicose veins in the esophagus (esophageal varices), gastric varices, portal hypertensive gastropathy, gastric ulcers, duodenal ulcers, or angiodysplasia, which may cause severe bleeding. Another consequence of cirrhosis is the accumulation of water in the abdomen (ascites).

Protein synthesis is reduced due to impaired metabolism, which may impact coagulation factors, enzymes, and albumin. The abnormal metabolism of substances, regardless of whether they are endogenous compounds, food molecules, or medications, results in reduced elimination of these substances. This in turn can lead to disorders in other organs such as the brain, kidneys, or heart. One obvious sign of this defective detoxification function is the typical finding of jaundice.

### *Symptoms*

Patients have the non-specific symptoms of a chronic liver disease. They report rapid fatigability, new onset bleeding propensity, dark urine, intense bloating, water accumulation in the legs (edema), or difficulty concentrating (hepatic encephalitis).

### *Examination findings*

A clinical examination often reveals reduced overall condition as well as signs such as jaundice, web-like red spots (spider angioma), bright red tongue (smooth tongue), cracks at the edge of the mouth (angular cheilitis), decreased pubic hair, absence of hair on belly, and white nails. Bruises (hematomas) are frequently observed. Some patients are disoriented to time and place and display tremor.

### *Diagnosis*

Diagnosis of cirrhosis is based on

1. palpation findings: The organ is compact or not palpable because it is shrunken.
2. typical features in ultrasound, Fibroscan, and duplex ultrasound,
3. changes in laboratory tests with reductions in biosynthesis parameters: longer prothrombin time or increased INR (international normalized ratio), decreased albumin, and reduced cholinesterase activity; pathologically elevated enzyme levels (AST, ALT, GGT, and alkaline phosphatase), and elevated bilirubin levels, as well as
4. histology results.

The clinical course of cirrhosis can be easily evaluated using the Child-Pugh classification system (table 7). Another option is the MELD classification (Model for End-stage Liver Disease, http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=9), which incorporates bilirubin, creatinine, and prothrombin time (PT ratio). It is used for patients scheduled to receive liver transplant.

| Points/ Parameters | 1 | 2 | 3 |
|---|---|---|---|
| Bilirubin (mg/dl) | < 2.0 | 2.0 to < 3.0 | > 3.0 |
| µmol/l | < 35 | 35 to < 50 | > 50 |
| Albumin (g/dl) | > 3.5 | 2.8 to < 3.5 | < 2.8 |
| Prothrombin time (PT ratio %) | > 60 | 40 to < 60 | < 40 |
| INR | < 1.7 | 1.7–2.3 | > 2.3 |
| Ascites | No | Controlled | Refractory |
| Hepatic encephalopathy | No | Grades I and II | Grades III and IV |

Child-Pugh A: 5–6 points, B: 7–9 points, C: 10–15 points.

**Table 7**
Child-Pugh classification

### *Treatment*

Treatment (see also fig. 2) is guided by the individual patient's symptoms and complications. It is often necessary to reduce salt intake (< 5 g salt/day) in the diet. While reducing protein intake does not improve hepatic encephalitis, eliminating certain types of proteins may be beneficial.

Certain diuretic medications such as spironolactone and/or torasemide are prescribed for patients with water retention, and fluid intake must also be reduced. In order to prevent and treat neurological symptoms, the uptake of toxic substances from the gut can be reduced by drugs including lactulose. L-ornithine L-aspartate and non-absorbable antibiotics such as rifaximin are other options for treating hepatic encephalopathy, and branched-chain amino acids are effective in some patients.

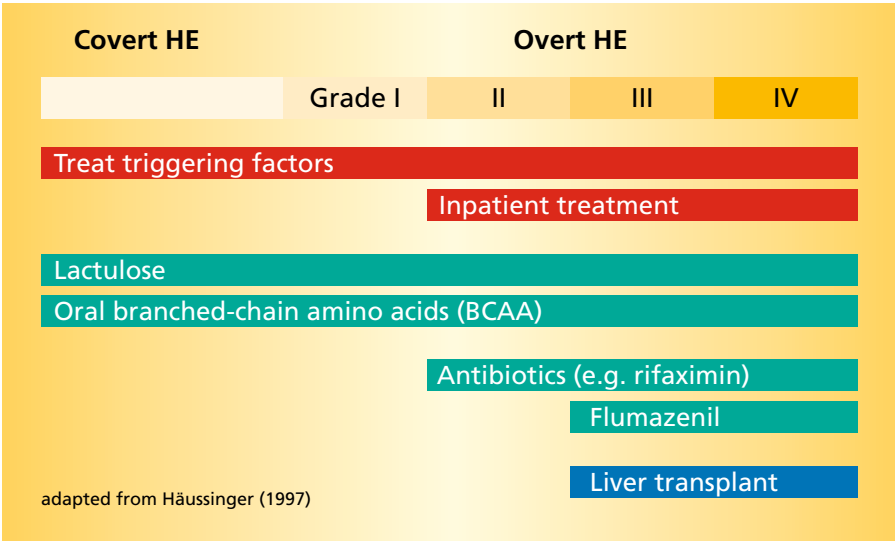


**Figure 2**
Treatment algorithm for hepatic encephalopathy (HE) (adapted from Häussinger, 1997)

## 3.17 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common cancer globally, especially in Asia. Risk factors for HCC are hepatitis B and hepatitis C infection, hemochromatosis, alpha-1 antitrypsin deficiency, non-alcoholic steatohepatitis, and alcoholic liver disease. A sudden, rapid deterioration in patients with known cirrhosis may be an indication of HCC. Serum alpha-fetoprotein (AFP) levels should be measured regularly, and ultrasound should be performed at least once per year in patients with cirrhosis. Contrast-enhanced CT and/or MRI and/or contrast-enhanced ultrasound are indicated for patients with elevated AFP levels.
Partial resection of the liver may be possible in some patients. Outcomes following liver transplant are encouraging if the diameter of the tumor is less than 3–5 cm and multiple tumors are not present.
Other treatment options include direct injection of alcohol into the tumor (percutaneous ethanol injection, PEI), radiofrequency ablation (RFA), selective internal radiation therapy (SIRT), stereotactic body radiation therapy (SBRT), transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), ablation by high-intensity focused ultrasound (HIFU), microwave ablation (MWA), irreversible electroporation (IRE), and laser-induced thermotherapy (LITT).

Advanced HCC or locally untreatable tumors can be treated pharmacologically, with first-line therapy consisting of anti-PD-L1 antibody (atezolizumab) and anti-VEGF antibody (bevacizumab) and other options being the tyrosine kinase inhibitors sorafenib or lenvatinib. The patient's Child-Pugh class is crucial when prescribing pharmacological therapy, as it is not recommended for class C patients.

## 3.18 Gallstone disorders

Since the advent of ultrasound examination, gallstones are a frequent (incidental) finding. Approximately 10–15% of the populations of developed countries have gallstones, with a much higher prevalence in women than men. Other risk factors for gallstones are age, obesity, diabetes, and metabolic disorders. Long-term use of some medications can also lead to gallstone formation, including estrogens or some lipid-lowering agents.

Symptoms are only reported by a small fraction of patients (about 20%) in the form of discomfort in the upper-right abdomen, colic (possibly food-dependent), intolerance of fatty foods, discolored stools, and dark urine. Four procedures are presently used to treat symptomatic gallstones:

- Cholecystectomy (open or laparoscopic surgery)
- Gallstone dissolution with oral drugs (ursodeoxycholic acid/chenodeoxycholic acid)
- Extracorporeal shock-wave lithotripsy (ESWL) with adjunct bile acid therapy (currently only rarely used)
- Direct percutaneous transhepatic litholysis (PTL) using methyl tert-butyl ether (MTBE) (experimental)

The procedures listed above should only be performed on patients with symptomatic gallstones. Laparoscopic cholecystectomy represents the first-line option. Silent gallstones – i.e., gallstones which do not cause any symptoms – should only be treated in exceptional situations.

It is crucial that gallstones be further classified using radiographic imaging before performing any of the three non-surgical treatment options, since these interventions are only effective against cholesterol gallstones.

The selection of the most suitable of the three gallbladder-sparing treatment options depends on the patient's symptoms and the type, size, and number of stones (fig. 3). Laparoscopic cholecystectomy is the recommended method, since all other procedures are associated with higher rates of recurrence.

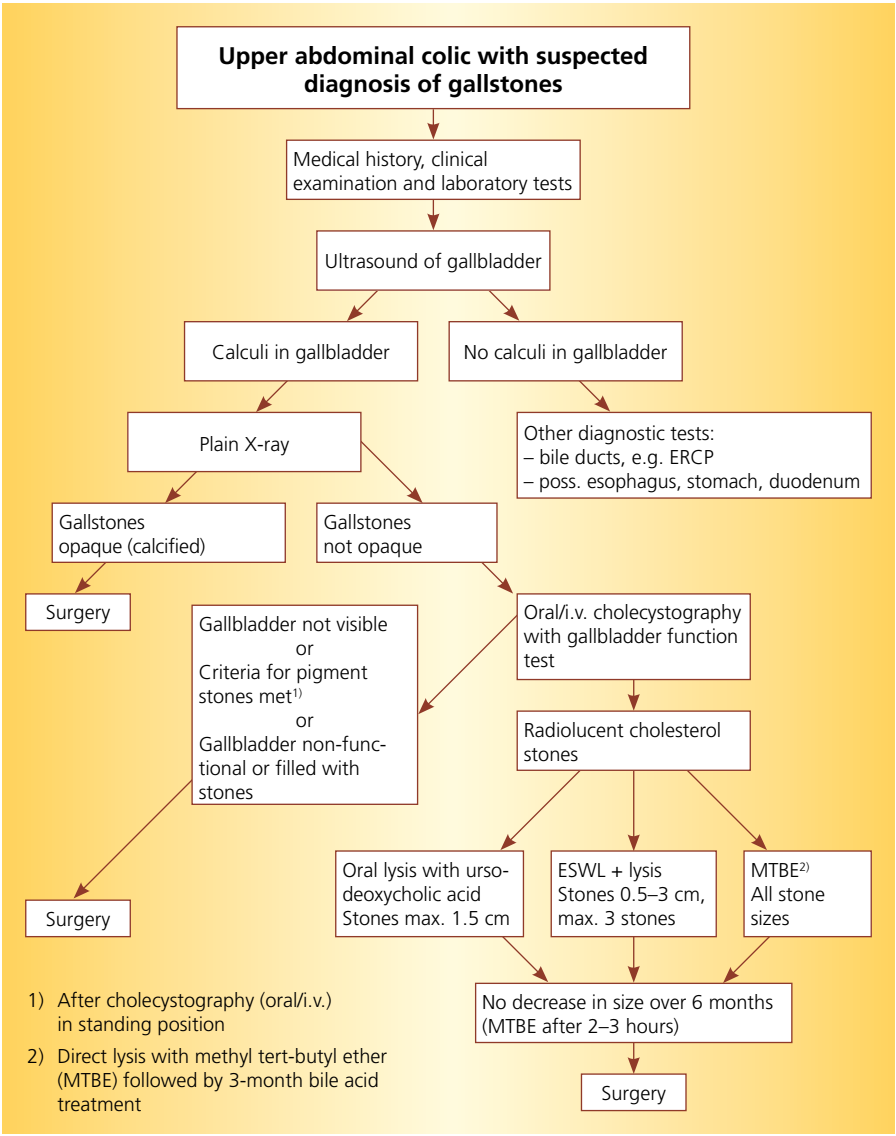
Upper abdominal colic with suspected diagnosis of gallstones
Medical history, clinical examination and laboratory tests
Ultrasound of gallbladder
Calculi in gallbladder
No calculi in gallbladder
Plain X-ray
Other diagnostic tests:
– bile ducts, e.g. ERCP
– poss. esophagus, stomach, duodenum
Gallstones opaque (calcified)
Gallstones not opaque
Surgery
Gallbladder not visible
or
Criteria for pigment stones met1)
or
Gallbladder non-functional or filled with stones
Oral/i.v. cholecystography with gallbladder function test
Radiolucent cholesterol stones
Surgery
Oral lysis with ursodeoxycholic acid Stones max. 1.5 cm
ESWL + lysis Stones 0.5–3 cm, max. 3 stones
MTBE2) All stone sizes
No decrease in size over 6 months (MTBE after 2–3 hours)
Surgery
1) After cholecystography (oral/i.v.) in standing position
2) Direct lysis with methyl tert-butyl ether (MTBE) followed by 3-month bile acid treatment

**Figure 3**

## 3.19 Functional disorders of the extrahepatic bile ducts

### *Postcholecystectomy syndrome*

Following cholecystectomy, abdominal symptoms persist in up to 40% of patients. These symptoms may resemble those experienced before surgery or may have a new quality. The symptoms can usually be explained with comprehensive diagnosis using procedures such as ultrasound, MRCP, and ERCP. Following these tests, the cause of the symptoms remains unknown only for a small percentage of patients.

# 4 Diagnostic algorithms

## 4.1 Investigation of liver injury

| Hepatocellular damage | Cholestasis | Excretion and conjugation |
|---|---|---|
| **AST (aspartate aminotransferase)** | **AP (alkaline phosphatase)** | **Bilirubin** |
| **ALT (alanine aminotransferase)** | **GGT (gamma-glutamyltransferase)** | **Note:** The tests which are not highlighted in yellow are typically not required, since they are not useful for either diagnosis or clarification of etiology. |
| GLDH (glutamate dehydrogenase) | 5'-Nucleotidase | |
| LDH (lactate dehydrogenase) | LAP (leucine aminopeptidase) | |
| IDH (isocitrate dehydrogenase) | | |
| SDH (sorbitol dehydrogenase) | | |

## 4.2 Investigation of etiology of chronic liver injury

| Step 1 | Step 2 | Step 3 |
|---|---|---|
| **Viral etiology:** | **Metabolic etiology:** | **Metabolic etiology:** |
| HBsAg (Hepatitis B) | Transferrin saturation and/or ferritin | Ceruloplasmin, 24-hour urinary copper excretion |
| Anti-HCV (Hepatitis C) | **Autoimmune hepatitis/ PBC/PSC:** | Alpha-1 antitrypsin |
| | AMA, ANA | Delta-aminolevulinic acid (if symptomatic) |
| | | Porphobilinogen (if symptomatic) |
| | | Uroporphyrin/ coproporphyrin in urine (if symptomatic) |
| | | **Autoimmune hepatitis:** |
| | | SMA, anti-LKM, possibly anti-SLA |

## 4.3 Monitoring of chronic liver diseases

**General tests:** AST, ALT

**Monitoring parameters for specific diseases:**
HBeAg for patients with hepatitis B treated on interferon or nucleoside/nucleotide therapy
HBV DNA during treatment
HCV RNA for patients with hepatitis C after combination therapy
Ferritin and transferrin saturation in patients with hemochromatosis
24-hour urinary copper for patients with Wilson's disease
Alpha-fetoprotein and ultrasound (1x per year) in patients with hemochromatosis, untreated chronic hepatitis B, C, and D

**Monitoring parameters for cirrhosis:** Bilirubin, albumin, prothrombin time or INR, creatinine, alpha-fetoprotein, and ultrasound (1x per year)

**Table 8**
Diagnostic algorithm for liver diseases

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