Diagnosis and therapy of chronic liver and biliary diseases

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1 Preface

Liver diseases are common. In many patients they cause not only a severe reduction of liver function but also a reduced function of other organs, such as kidney and brain. This often leads to invalidity and premature death.

Advances in basic research in biochemistry, cell biology, molecular biology, genetics, immunology, and virology have allowed better diagnosis and specific treatment of the underlying disease. Early diagnosis and therapy can slow down progression of liver disease considerably or even prevent it altogether.

It is therefore mandatory to identify patients with liver disease and to specify its etiology.

2 Symptoms and clinical findings of chronic liver diseases

Liver diseases are divided into acute and chronic. If the disease resolves within six months it is classified acute, if it is ongoing it is described as chronic.

Hepatitis viral infections, autoimmune hepatitis, Wilson's disease, drug and alcohol related liver damage and porphyrias may present as acute and/or chronic liver disease, whereas hemochromatosis, α_1-antitrypsin deficiency and primary biliary cirrhosis occur as chronic disease.

Chronic liver disease may present with non-specific symptoms which allow no further differentiation: fatigue, lassitude, decrease of activity, loss of appetite, loss of weight, upper abdominal discomfort, meteorism, flatulence, fever, joint pain, and less commonly pruritus. In the more advanced stages they are accompanied by jaundice. Urine may become dark and the stool acholic.

While obtaining a patient's history it is important to ask for diseases within the family, alcohol consumption, medications, also over the counter medication, herbal or alternative medicines and teas, time spent in foreign countries, liver diseases among roommates or colleagues, previous surgery or transfusions and exposure to organic solvents either at work or during leisure activities.

On physical examination, the size of the liver may be normal, enlarged or small depending on the underlying disease and its stage. In some patients the spleen is enlarged. Cutaneous manifestations may be present – like

spider naevi, white nails, palmar erythema, xanthelasma, icterus, purpura, swelling of the parotid glands, gynecomastia and scratches because of pruritus, and edema.

Clinical-chemical laboratory, serological and immunological investigations should also be performed in the presence of only minimally elevated transaminases. Ultrasonography, duplex sonography und other examinations like histology, endoscopy or X-ray examinations may be necessary to determine the etiology and the stage of the disease.

Combinations of liver diseases may occur, for example alcoholic liver disease and hepatitis C virus infection or hemochromatosis as well as overlap syndromes, e.g. between PBC and AIH. Therefore, a complete diagnostic assessment is essential, especially in patients below the age of 50 years.

3 Pathophysiology, diagnosis, and therapy of selected clinical diseases

3.1 Viral hepatitis

Today, five different hepatitis viruses have been identified (Tab. 1, see page 13). Hepatitis A (HAV) and hepatitis E virus (HEV), which are transmitted by the fecal-oral route, cause only acute hepatitis. Hepatitis B (HBV), hepatitis C (HCV) and hepatitis D (HDV) virus can also induce chronic liver inflammation. HBV, HCV and HDV are transmitted by blood and blood products, HBV by sexual intercourse as well. Worldwide the majority of virus-related chronic liver diseases are caused by HBV and HCV. Hepatitis D virus only occurs in association with active hepatitis B, about 5% of chronic hepatitis B patients are co-infected with HDV.

Hepatitis B and hepatitis C virus probably do not directly damage liver cells.

Pathophysiology

According to our present knowledge, liver cells infected with hepatitis viruses are destroyed by the cellular immune response. The infected liver cells present fragments of the respective virus on their surface which are recognized by various cell types of the immune system and which are signals for the destruction of these cells. Less than 10% of patients infected with HBV develop chronic hepatitis, compared to 80–95% with hepatitis C. Cirrhosis occurs in less than 1% of HBV infected patients, but in 5–30% of those infected with HCV.

Diagnosis and therapy

Hepatitis A

Hepatitis A is diagnosed by the detection of antibodies of the IgM class **(Anti-HAV, IgM)**. Positive tests establish the diagnosis of acute hepatitis A. The IgM test is relevant in young patients, after a stay abroad or in contacts of a patient with hepatitis A. Undifferentiated testing of the antibodies (i. e. IgG plus IgM) for HAV is not helpful since a positive result doesn't differentiate between acute and resolved HAV infection.

Specific therapy does not exist. The patients receive supportive therapy.

Active vaccination with inactivated hepatitis A virus is available and is effective. Injections of 1 ml each are applied in time intervals of 6–12 months, in children and adolescents at 0, 1 and 6–12 months. Protection after completion of vaccination is almost 100%. Passive vaccination with immunoglobulins should only be carried out when the start of a trip is in less than a week.

Hepatitis B

Active hepatitis B virus infection is detected by a positive hepatitis B surface antigen **(HBsAg)** in the serum. This antigen corresponds to the virus envelope (Fig. 1). Determination of HBsAg is therefore sufficient to confirm a diagnosis of hepatitis B. If hepatitis B e antigen **(HBeAg)** is also positive, it is diagnostic for active replication. Testing for Anti-HBc as well as of HBV-DNA is not necessary for diagnosis of active replicating HBV infection.

If therapy with interferon or nucleos(t)ide analogues is considered, HBV-DNA and HBeAg should be measured because both factors have an impact on the therapy.

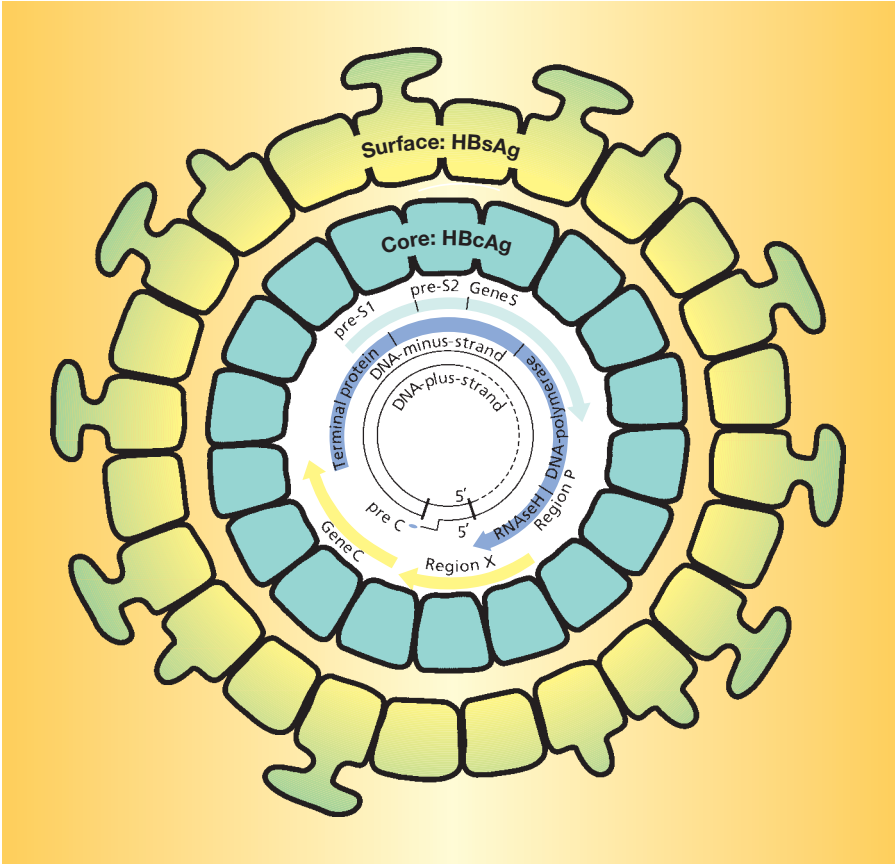

Figure 1
Model of hepatitis B virus

Therapy

In the presence of HBeAg and/or HBV-DNA with a titer of > 20,000 IU/ml (~100,000 copies/ml) and the exclusion of contraindications therapy with pegylated interferon can be instituted, especially in young patients. After 52 weeks of therapy HBeAg negativity can be achieved in 35% of the patients with a seroconversion rate of 29%. In 7%

HBV-DNA is undetectable (< 80 IU/ml). Alternatively, oral nucleosides or nucleotides can be used. Five different agents – adefovir (10 mg/day), entecavir (0.5 mg/1.0 mg/day), lamivudine (100 mg/day), telbivudine (600 mg/day) and tenofovir (245 mg/day) – have been approved in most countries. Treatment duration lasts 1 year, in most cases treatment for several years seems necessary. Lamivudine leads to seroconversion for HBeAg in 17%, 27%, 40%, 47% and 50% after 1, 2, 3, 4 and 5 years, respectively. YMDD mutants develop with treatment duration (15–20% after 1 year, 40% after 2 years, 67% after 4 years and 70% after 5 years). In 51% of the HBeAg-negative and 21% of the HBeAg-positive patients HBV-DNA is undetectable (< 80 IU/ml) after 48 weeks of therapy with adefovir. Resistant strains against adefovir are observed in 29% of the patients after 5 years. In 60% of HBeAg-positive patients HBV-DNA is undetectable after 52 weeks of telbivudine as well as in 88% of HBeAg-negative patients. After 1 year resistant strains are found in 2–5% of the patients and after 2 years in 11%. Entecavir leads to undetectable HBV-DNA in 68% of HBeAg-positive patients after 52 weeks and in 90% of HBeAg-negative patients. Resistance against entecavir is seldom observed in treatment-naive patients during the first 5 years of treatment (< 1.5%), however, in lamivudine-pretreated patients relapse is found in 39% within 4 years. 48 weeks of tenofovir (245 mg/day) leads to undetectable HBV-DNA in 76% of the HBeAg-positive and 93% of the HBeAg-negative patients with almost no resistance during therapy. Because of the low rate of resistance entecavir and tenofovir are recommended. In case of a decrease of renal function the therapy can be switched to telbivudine. With this drug creatine kinase has to be controlled in regular intervals because of the possibility of myopathy.

Active vaccination against hepatitis B is recommended. The patients receive 10 µg or 20 µg of a genetically synthesized vaccine with injections 4 weeks and 6 months

after the initial injection. Passive vaccination using hyper-immunoglobulins should only be carried out after an injury with a needle and in newborns in combination with active vaccination if the mother is HBsAg-positive.

Hepatitis C

Hepatitis C virus infection is diagnosed by detection of specific antibodies **(Anti-HCV)**. In most patients these antibodies can be identified as early as two or three weeks *post infectionem* by enzyme-linked immunosorbent assay (ELISA) of the third generation, which are very reliable.

The recombinant immunoblot assay (RIBA) is using almost the same antigens as the ELISAs, which can be read separately. It is not necessary any more as confirmation test. HCV infection is confirmed by the existence of HCV-RNA in the blood with the polymerase chain reaction with preceding reverse transcription (RT-PCR). This test has become more reliable during the last years. These methods allow quantification also. Sensitivity of qualitative tests should be at least 15 IU/ml. Genotyping is performed by RT-PCR.

Diagnosis of hepatitis C can be made if:
1. Anti-HCV and HCV-RNA are positive,
2. transaminases are elevated and
3. other severe liver diseases are excluded.

Treatment of chronic hepatitis is indicated if the following prerequisites are met:
1. elevated transaminases,
2. HCV-RNA positive in serum, and
3. liver histology consistent with inflammation and fibrosis or elevated values in the transient elastography are measured.

Severe concomitant diseases must be excluded.
To determine the combination of the different drugs and the length of the therapy HCV genotype and virus titer are determined.

Hepatitis	**A**	**B**	**C**	**D**	**E**
Virus family	Picorna	Hepadna	Flavi	Viroid	Calici
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Incubation period (days)	14–45	30–180	14–180	?	21–60
Transmission – fecal-oral – blood – vertical – sexual	 yes no[1] no[1] no[2]	 no yes yes yes	 no yes yes yes[2]	 no yes yes yes	 yes no no no
Antigens	HAAg	**HBsAg**, HBeAg	–	HDAg	HEAg
Antibodies	Anti-HAV **Anti-HAV**, **IgM**	Anti-HBs Anti-HBe Anti-HBc Anti-HBc, IgM	**Anti-HCV** Anti-HCV, IgM	Anti-HDV, **Anti-HDV**, **IgM**	**Anti-HEV**
Acute resolving hepatitis	> 99%	> 90%	5–15%	50–80%	> 95%
Chronic active hepatitis	0%	< 10%	80–95%	20–50%	(< 5%) ?
Liver cirrhosis	< 0.1%	1–3%	5–30%	(10%) ?	?
(The tests relevant for diagnosis are printed in bold type)					

Table 1
Hepatitis viruses

[1] Parenteral infection is rare because donor blood contains HAV only during a very short period of time during the prodromal time.
[2] Infection by sexual intercourse has not been proven, but cannot be excluded, because of the higher prevalence in partners of hepatitis A or C infected index patients in comparison to controls.

Therapy

Patients receive combinations of different direct-acting antivirals (DAAs).

At the moment NS3/4 protease inhibitors (simeprevir 1 x 150 mg/day, paritaprevir 1 x 150 mg/day), NS5A inhibitors (ledipasvir 1 x 90 mg/day, ombitasvir 1 x 25 mg/day,

daclatasvir 1 x 60 mg/day) and NS5B inhibitors (sofosbuvir 1 x 400 mg/day, dasabuvir 2 x 250 mg/day) are available and used in different combinations, in part with ribavirin (1000 mg/day [< 75 kg body weight], 1200 mg/day [≥ 75 kg body weight]) either for 12 or 24 weeks depending on genotype and fibrosis stage and previous therapy.

The success rate (sustained virological response, SVR) is exceeding 90%, independent of the previous therapy and the absence or presence of liver cirrhosis. Only for genotype 5 no data with DAAs exist. Fortunately, these combination therapies have only minor side effects. For some of these substances drug interactions have to be taken into account. Dose reductions have to be applied for some patients with renal impairment. Previous therapies with interferon and ribavirin have no influence on the SVR. If HCV-RNA is negative 12 weeks after therapy has been stopped it can be considered as being a SVR.

Hepatitis D

Hepatitis D only occurs in combination with a replicating hepatitis B infection, since this infectious agent uses the surface proteins of the latter for synthesis of its own envelope. It is diagnosed by detection of antibodies to the virus **(Anti-HDV)**. Determination of the antigen is not possible, but the HDV-RNA can be amplified by means of the reverse transcription/polymerase chain reaction. For routine diagnosis, identification of specific antibodies is sufficient.

Therapy with pegylated interferon for 48 weeks leads to undetectable HDV-RNA in a quarter of the patients with a SVR after 6 months of follow-up.
Despite the unfavorable results long-term therapy with pegylated interferon may be indicated in some patients with rapidly progressive liver disease to delay the development of liver cirrhosis. Combination of pegylated

	Drugs	Duration	Drugs	Duration	Drugs	Duration	Drugs	Duration
Genotype 1a without cirrhosis	ledipasvir + sofosbuvir	12 weeks	paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin	12 weeks	sofosbuvir + simeprevir ± ribavirin	12 weeks	daclatasvir + sofosbuvir	12 weeks
with cirrhosis	ledipasvir + sofosbuvir	12 weeks	paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin	24 weeks	sofosbuvir + simeprevir ± ribavirin	24 weeks	daclatasvir + sofosbuvir + ribavirin	12 weeks
Genotype 1b without cirrhosis	ledipasvir + sofosbuvir	12 weeks	paritaprevir + ritonavir + ombitasvir + dasabuvir +	12 weeks	sofosbuvir + simeprevir	12 weeks	daclatasvir + sofosbuvir	12 weeks
with cirrhosis	ledipasvir + sofosbuvir	12 weeks	paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin	12 weeks	sofosbuvir + simeprevir ± ribavirin	24 weeks	daclatasvir + sofosbuvir + ribavirin	12 weeks
Genotype 2	sofosbuvir + ribavirin	12 weeks					daclatasvir + sofosbuvir	12 weeks
Genotype 3 without cirrhosis	sofosbuvir + ribavirin	24 weeks					daclatasvir + sofosbuvir	12 weeks
with cirrhosis	sofosbuvir + ribavirin	24 weeks					daclatasvir + sofosbuvir + ribavirin	24 weeks
Genotype 4 without cirrhosis	ledipasvir + sofosbuvir	12 weeks	paritaprevir + ritonavir + ombitasvir + ribavirin	12 weeks	sofosbuvir + simeprevir	12 weeks	daclatasvir + sofosbuvir	12 weeks
with cirrhosis	ledipasvir + sofosbuvir + ribavirin	12 weeks	paritaprevir + ritonavir + ombitasvir + ribavirin	24 weeks	sofosbuvir + simeprevir + ribavirin – ribavirin	12 weeks 24 weeks	daclatasvir + sofosbuvir + ribavirin	12 weeks
Genotype 5 or **Genotype 6**	ledipasvir + sofosbuvir (+ ribavirin in cirrhosis)	12 weeks					daclatasvir + sofosbuvir (+ ribavirin in cirrhosis)	12 weeks

simeprevir 1 x 150 mg/day, paritaprevir 1 x 150 mg/day, ledipasvir 1 x 90 mg/day, ombitasvir 1 x 25 mg/day, daclatasvir 1 x 60 mg/day, sofosbuvir 1 x 400 mg/day, dasabuvir 2 x 250 mg/day, ribavirin 1000 mg/day (< 75 kg), 1200 mg/day (≥ 75 kg)

Table 2
Therapy of chronic hepatitis C with combinations of direct-acting antivirals (DAAs) in treatment-naive patients with and without cirrhosis of the liver

interferon with tenofovir doesn't seem to improve the success rate. In HIV-positive patients tenofovir monotherapy might be beneficial.

There is no active vaccination specifically against HDV, but vaccination against HBV indirectly protects against HDV infection. Passive vaccination is not successful.

Hepatitis E

Like HAV, hepatitis E virus is transmitted via the fecal-oral route. Up to now most infections have been reported from Third World countries. Mortality rate ranges between 0.5 and 4%. In Germany it occurs predominantly after travels to endemic areas. Specific antibodies can be detected shortly after the infection. Hepatitis E virus infection is diagnosed by detection of specific antibodies **(Anti-HEV)**.

There is no specific therapy. In transplant immunesuppressed patients ribavirin might be beneficial. Active vaccination is under development with a success rate of 95% in volunteers.

3.2 Hemochromatosis

Hemochromatosis is one of the most frequent inborn errors of metabolism in Europe. The inheritance is autosomal recessive. 6% of the population are heterozygous for the disease and about 0.3–0.5% are homozygous. It is an autosomal recessive disorder. About 90% of hemochromatosis patients exhibit a mutation in the HLA H gene located on the short arm of chromosome 6 (type I), where tyrosine instead of cysteine is found in position 282. In a small part of hemochromatosis patients in position 63 histidine is substituted by aspartate and in others serine substituted for cysteine in position 65. In rare cases concomitant heterozygous mutations are found in the above mentioned positions called compound heterozygosis. Even rarer are mutations in other genes like hemojuvelin (type IIA), hepcidin (type IIB), transferrin receptor 2 (type III), ferroportin 1 (type IV) or H-ferritin and L-ferritin. In males the disease becomes apparent earlier in life than in females but only 10–33% of the C282Y homozygous males develop symptoms.
In advanced stages of the disease the skin has a brownish color. Patients may also have insulin-dependent diabetes mellitus ("bronze diabetes"), hepatomegaly, cardiac arrhythmias, cardiomyopathy, and arthralgia. Patients with hemochromatosis have a high risk to develop hepatocellular carcinoma. Hypogonadism may occur already in an early stage of the disease.

Pathophysiology

In cells a very delicate balance for iron ions exists. Iron is required by many enzymes, but in excess iron ions are a potent poison which disturbs the function of several enzymes of the respiratory chain and causes the formation of free oxygen radicals, which are very toxic.

In patients with hemochromatosis and advanced liver disease the total body iron is higher than 25 g, in com-

parison to 3–4 g in healthy subjects. This iron overload in the body is due to excessive iron uptake from the gastrointestinal tract amounting to 2–5 mg per day compared with 1 mg in healthy people. The primary defect is thus not in the liver but in the enterocytes of the mucosa of the gastrointestinal tract.
Other factors such as gender, alcohol consumption, viral hepatitis, non-alcoholic fatty liver disease (NAFLD) and hepatitis (NASH), infections, hepatic porphyria and thalassemia are also important for the expression of the disease.
Stepwise progression with elevated plasma iron concentration and elevated transferrin saturation to elevated iron tissue contents and serum ferritin and finally serum ferritin concentrations exceeding 1000 µg/l and tissue damage is observed.

Diagnosis

For screening ferritin concentration in the serum is determined (standard value for ferritin 10–200 µg/l; hemochromatosis 900–6000 µg/l). If these tests show pathological results, transferrin saturation is measured (standard value 22–46%; hemochromatosis: 50–100%). Alternatively, transferrin saturation iron can be used for screening already. If the result is pathologic HFE gene mutations in position 282, 63, and 65 are tested.

In the absence of HFE gene mutations the iron content in the liver tissue is measured (standard value 300–1400 µg/g dry weight; hemochromatosis 6000–18,000 µg/g) and the liver iron index is calculated (µg Fe/g liver dry weight/age × 56; standard value < 1.0; hemochromatosis > 2; Tab. 3). Alternatively, T2 and R2 (FerriScan) measurements by MRI can be performed.

After the diagnosis of hemochromatosis an echocardiography and a 24-h ECG monitoring should be performed. Joint pain, which involves the fingers in most patients,

Test	Standard value	Hemochromatosis, symptomatic	Hemochromatosis, asymptomatic, homozygous	Hemochromatosis, heterozygous	Alcoholic liver disease
Serum iron (µg%[µmol/l])	50–150 [9–27]	180–300 [32–54]	raised	normal to raised	raised
Transferrin saturation (%)	22–46	50–100	50–100	normal to raised	27–60
Serum ferritin (µg/l)	10–200	900–6000	200–500	mostly < 500	10–500
Liver iron content (µg/g dry weight)	300–1400	6000–18,000	2000–4000	300–3000	300–2000
Transferrin index µg/g dry weight / 56 × age of patient	< 1.0	> 2	mostly > 2	< 2	< 2

Table 3
Laboratory tests in hemochromatosis

should be examined by X-ray. Diabetes mellitus should be excluded, as well as hypothyreosis and hypogonadism. Screening of the family for hemochromatosis is mandatory.

Therapy

The aim of the treatment is to reduce the excess of iron of the body. The most efficient method is phlebotomy, which is done once per week or every other week for 1–2 years until the ferritin concentration is below 50 µg/l and the transferrin saturation below 30%. Each 500 ml of blood removes 200–250 mg of iron, therefore, more

than 100 phlebotomies are necessary. Afterwards iron saturation should be kept below 50% and ferritin concentration below 100 µg/l.

Uncompromising therapy leads to a significant improvement of life expectancy. Alcohol consumption should be avoided as it increases the risk for cirrhosis 10-fold. If hepatic cirrhosis is already present, hepatocellular carcinoma will ensue in one third of the patients in spite of appropriate treatment. Ultrasonography controls and α-fetoprotein (AFP) determinations at regular intervals of 6–12 months are therefore mandatory.

3.3 Wilson's disease

Wilson's disease is a copper-storing disease which affects about one in 30,000 of the population. Initially, patients may have symptoms of liver disease (42%) or may have neurological (34%), mental (10%) or hematological (12%) symptoms.
The symptoms are those of a chronic liver disease, but acute and even fulminant courses of the disease may be observed. Since copper is deposited in distinct regions of the brain, it may also lead to a variety of neurological symptoms like tremor, akinesia, rigidity, choreiform movements, parkinsonism, gait disturbances, dysarthria, pseudobulbar palsy, rigid dystonia, seizures, migraine headaches, insomnia. About half of the patients with neurological symptoms also have mental disturbances like depression, neuroses, impulsiveness, changes of mood, antisocial behavior, cognitive disturbances, personality changes and psychosis.

On examination, 98% of the patients with neurological symptoms as well as 50% of the patients with liver disease have a green or brown ring at the periphery of the cornea (Kayser-Fleischer ring) and are visible only by slit-lamp examination. Sunflower cataracts occur frequently. Both findings are reversible with medical therapy or after liver transplantation.
In patients with acute Wilson's disease hemolysis may be present, due to release of large quantities of copper from liver cells.

Pathophysiology

The gene responsible for the development of Wilson's disease (ATP7B gene) has been identified. Up to date more than 250 different mutations have been described. The intracellular copper transport protein is defective, leading to an accumulation of copper in various organs. Storage in liver and brain has the greatest impact for the

patient. Fulminant hepatic failure is observed in about 5% of the patients and is characterized by coagulopathy and encephalopathy with an associated Coombs-negative hemolytic anemia and renal failure. Serum and urinary concentrations of copper are increased. Most of these patients have liver cirrhosis already.
A significant part of patients with Wilson's disease present already with cirrhosis. Hepatocellular carcinoma is rarely associated with Wilson's disease. Structural brain MRI has shown lesions in the putamen, globus pallidus, thalamus, midbrain, pons, and cerebellum as well as cortical atrophy and white matter changes.
Kayser-Fleischer rings are caused by the granular deposition of copper on the inner surface of the cornea in Descemet's membrane.

Diagnosis

The diagnosis is established by the analysis of ceruloplasmin in the blood (normal value > 25 mg%; Wilson's disease < 20 mg%). Up to 95% of homozygotes and 20% of asymptomatic heterozygotes have serum ceruloplasmin values less than 20 mg%. Five percent of homozygotes, and in some studies up to 50% of affected individuals with severe decompensated liver disease have normal ceruloplasmin concentrations. The 24-h urinary copper excretion (normally 20–50 µg/day) is increased and an amount of more than 40 µg per 24 h is suggestive for Wilson's disease. Urinary copper excretion with penicillamine administration can also be a used. A dose of 500 mg of D-penicillamine is given orally at the beginning and 12 h later during 24-h urine collection. Copper excretion greater than 600 µg/24 h is suggestive for Wilson's disease.
Diagnosis is confirmed by quantitative copper analysis in the liver tissue (standard value < 40 µg/g dry weight; Wilson's disease > 250 µg/g dry weight).
Patients with acute liver failure have ALT and AST values < 2000 IU/ml, normal or subnormal alkaline phosphatase,

coagulopathy that doesn't respond to vitamin K substitution and hemolysis. In a small number of patients the ceruloplasmin concentration is not decreased in this situation.

Therapy

D-penicillamine (1.0–1.5 g/day) is the treatment of choice. It is a chelating agent, which binds copper. To reduce adverse events vitamin B_6 must be given. Anti-nuclear antibodies, urinary total protein excretion and erythrocytes must be controlled regularly during lifetime therapy. Trientene, another chelating agent may also be used (1.2–1.8 g/day initially and for maintenance 0.9–1.2 g/day). Coadministration of iron should be avoided since the trientene iron complex is toxic. Zinc (150 mg/day or 3 mg/kg body weight) can be used once the excess copper has been removed. A time interval of several hours should be taken into account if zinc and chelating agents are applied concomitantly. During chelation therapy, 24-h urinary copper excretion is measured and an output of 200–500 µg confirms adequate treatment. In patients with neurological symptoms therapy should be started cautiously, copper excretion should be below 1000 µg/day. Patients with Wilson's disease should avoid copper-rich food such as liver, kidney, shellfish, nuts, dried fruits or beans, peas, chocolate and mushrooms. Consequent therapy leads to normalization of liver function and if diagnosed early also to a normal life expectancy.

3.4 α_1-Antitrypsin deficiency

α_1-Antitrypsin deficiency is a congenital metabolic disease which is inherited by autosomal co-dominant transmission. About one person in every 2000 is homozygous for mutations of the SERPINA1 (serpin peptidase inhibitor, clade A, member 1) gene (ZZ, Z0, SS, SZ, MZ, M0 or 00 phenotype). α_1-Antitrypsin is a protease inhibitor of elastase. α_1-Antitrypsin concentration can be either normal, diminished (< 35% of normal) or undetectable. In addition, patients with normal concentrations but no protease activity are found. The normal α_1-antitrypsin concentration is 20–53 µmol/l (150–350 mg%). Most of the symptomatic patients have α_1-antitrypsin concentrations of 5–6 µmol/l. Patients may have had cholestasis in childhood. They frequently have a concurrent lung disease. Skin involvement is rare. About 10% of all neonates with an α_1-antitrypsin deficiency develop liver disease (hepatitis with cholestasis), and about 3% overall progress to liver cirrhosis. The risk for hepatocellular carcinoma is significantly increased. Liver disease can be observed in patients with Z and M alleles.

Pathophysiology

More than 120 different mutations have been found in the α_1-antitrypsin gene. They cause accumulation of abnormally folded α_1-antitrypsin in hepatocytes with consecutive damage and a decreased α_1-antitrypsin concentration in the serum. In males and obese patients progression of disease is faster.

Diagnosis

The diagnosis is established by detection of a low α_1-antitrypsin level in the serum (< 50 mg%). M, Z, and S phenotypes are analyzed in order to confirm the diagnosis.

Therapy

There is no specific treatment for this disease. Gene therapy to replace the diseased gene is being developed.

In patients with lung disease cessation of smoking is mandatory. Weekly intravenous augmentation therapy with α_1-antitrypsin (60 mg/kg body weight) may be useful in patients with severe pulmonary disease.

In patients with liver cirrhosis α_1-antitrypsin substitution is not indicated, as liver damage is due to accumulation of abnormally folded α_1-antitrypsin in liver cells.

3.5 Porphyrias

Porphyrias are characterized by disturbance of hem biosynthesis and can be divided into erythropoietic and hepatic types as well as acute and non-acute. Differentiation between the different types of porphyria is made by analysis of the defective enzyme causing the metabolic disorder.

Acute hepatic porphyrias

Pathophysiology and clinical manifestation

The acute hepatic porphyrias (acute intermittent porphyrias [AIP], porphyria variegata, hereditary coproporphyria and Doss porphyria) become metabolically and clinically manifest as the result of a dysregulation which induces porphyrine biosynthesis in the liver. Acute symptoms may be triggered by a variety of drugs (www.drugs-porphyria.org), toxic substances, ethanol, cigarettes, fasting, inflammation and infections.

Characteristic symptoms

- Acute, intermittent, colicky abdominal pain that may even present as ileus
- Backache
- Vomiting
- Constipation
- Tachycardia and hypertension
- Neurological symptoms, such as myasthenia, paresthesia and peripheral paralyses, epileptiforme convulsions
- Psychological disorders that may be misinterpreted as psychosis or depression

The most frequent complications of an unidentified and untreated porphyria crisis are paralysis or even tetraparesis.

Diagnosis

Diagnosis is based on detecting excessively increased urinary excretion of the two porphyrine precursors δ-aminolevulinic acid and porphobilinogen (> 10-fold), as well as of total porphyrines.
An aliquot of 20 ml of urine is sufficient for the tests during the acute episode.

Excretion of these metabolites is increased several fold in AIP as compared to controls. Additional examinations of the porphyrine biosynthesis parameters in stool and blood are required to establish the type of acute and chronic hepatic porphyrias. Genetic analysis is possible. In acute intermittent porphyria which is autosomal dominant, mutations are found on chromosome 11q23.3. Porphyria variegata and hereditary coproporphyria are also autosomal dominant (chromosome 1q22 and 3q12, respectively) whereas ALA deficiency porphyria is autosomal recessive (chromosome 9q33.1).

Therapy

An effective drug, hemarginate, is available for the treatment of acute porphyrias. It suppresses induction and dysregulation of porphyrine metabolism in the liver. This effective treatment leads to clinical remission via a decrease of metabolic expression. Hemarginate should be administered only after confirmed diagnosis of clinically active AIP or other acute hepatic porphyrias. Hemarginate is indicated if elimination rate of the metabolites δ-aminolevulinic acid, porphobilinogen and porphyrines is elevated. Excretion is controlled after treatment for the assessment of effective therapy. Depending on the degree of initial pathology a drop of the values by at least 50% is mandatory.

Application of hemarginate

As soon as the diagnosis of hepatic porphyria is confirmed, intravenous treatment with hemarginate should be initiated. Hemarginate is administered in a dosage of 3 mg/kg body weight per day on four consecutive days. Food rich in carbohydrates and proteins should be given at the same time either orally or via a nasogastric tube. If this therapy is not sufficient, intravenous administration of 300–500 g/day of glucose or 4–6 g carbohydrates per kg/body weight is recommended.

Symptomatic therapy, e. g. opiates for pain, propranolol for hypertension and tachycardia, etc. should be institutive whenever necessary. Porphyrinogenic drugs are indexed in the "red list" appendix under "medicinal agents for the treatment of acute hepatic porphyrias" or can be checked in the internet (www.drugs-porphyria.org) must be discontinued and avoided in the future.

3.6 Autoimmune hepatitis

Autoimmune hepatitis can be classified into at least two types which are characterized by a variety of distinct autoantibodies. About 75% of the patients are female. The disease may occur at any age. Typical symptoms are itching, joint pain and jaundice. Extrahepatic symptoms like arthralgia, arthritis, cutaneous vasculitis and glomerulonephritis are caused by circulating immune complexes.

Pathophysiology

Etiology and pathogenesis of these diseases are not clear. Genetic factors may play a role as a number of histocompatibility haplotypes, which are associated with autoimmune diseases (HLA-B1, -B8, -DR3 and -DR4) are also frequently observed in patients with autoimmune hepatitis. In addition other autoimmune diseases like thyroiditis, rheumatoid arthritis, hemolytic anemia, ulcerative colitis, proliferative glomerulonephritis, juvenile diabetes mellitus and Sjögren's syndrome are often found in these patients or their relatives. Cellular immune response probably plays a major role. Cytotoxic lymphocytes, which are directed against specific cell antigens are supposed to lead to cell damage and ultimately cell death. The autoantibodies are probably only the result of the liver disease rather than its cause.

Diagnosis

If autoimmune hepatitis is suspected, autoantibodies should be tested: antibodies to cell nucleus constituents (ANA = antinuclear antibodies, positive in 50–60%), to smooth muscle (SMA = smooth muscle antibodies, positive in 50–60%), to microsomes in liver and kidney (LKM = liver/kidney microsomal antibodies, positive in < 5%), to soluble liver antigen (SLA/LP = anti-soluble liver antigen/liver pancreas antibody, positive in 10–30%)

and to cytoplasmic myeloperoxidase (pANCA = perinuclear antineutrophil cytoplasmic antibody, positive in 50–96% AIH 1). In patients with type 1 autoimmune hepatitis ANA and/or SMA are positive, whereas in type 2 AIH Anti-LKM1 and/or SLA/LP are observed. In about 10% of the patients none of the above mentioned antibodies are present. Elevated IgG is a surrogate marker for autoimmune hepatitis. Histology frequently supports the diagnosis with lymphoplasmacellular infiltrates (CD4 cells, B lymphocytes, plasma cells) of the portal area or the lobules which are more or less pronounced, depending on the disease activity. Proposals of the International Autoimmune Hepatitis Group (IAHG) include IgG (> 16 g/l 1 point, > 18,5 g/l 2 points), ANA, SMA, LKM (> 1:40 1 point, > 1:80 2 points), SLA/LP positive (2 points), histology (compatible with AIH 1 point, typical for AIH 2 points), absence of viral hepatitis (2 points). With a score of ≥ 6 AIH is probable, with 7 points definite.

Therapy

Medication with corticosteroids (initially 70 mg/day or 1 mg/kg body weight/day, weekly reduction, maintenance dose 5–10 mg/day) and azathioprine (1–1.5 mg/kg body weight/day or 50–100 mg/day) starting at week 2 may lead to a significant improvement of symptoms and liver tests and even healing. However, azathioprine itself can cause liver damage which needs to be taken into account. The drugs must be taken continuously for at least 2, preferentially 4 years after normalization of liver values. Before cessation of the therapy liver biopsy is recommended. Relapse rate is 20–30% without signs of hepatitis in comparison to 75–90% in the presence of inflammation. Budesonide (2–3 × 3 mg/day), which causes less systemic side effects, may be an alternative to prednisone or prednisolone.
Other immunosuppressive agents like mycophenolate mofetil, cyclosporine A and tacrolimus are evaluated.

3.7 Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune chronic progressive liver disease which is accompanied by destruction of the cholangioles and the medium-sized bile ducts. The term cirrhosis is misleading, because only a small number of patients has developed cirrhosis at the time of diagnosis today (renaming as "primary biliary cholangitis" is under discussion). PBC occurs frequently among members of the same family, and especially in women (male:female ratio 5:95–10:90) above the age of 40 years. Its prevalence is about 30 cases per 100,000 inhabitants or 80/100,000 women. Frequency of the disease has been steadily increasing during the last decades but this might also be explained that PBC is diagnosed earlier and more frequently.

Early symptoms are non-specific. Patients most frequently complain of fatigue/exhaustion, indigestion, hyperpigmentation and typically itching. Joint pain is common. Dry mucosa and conjunctiva (keratoconjunctivitis) are reported. Indicators of liver disease, such as jaundice or xanthelasma may be absent in the early stage of the disease. In the course of the disease malabsorption worsens with significant weight loss, osteoporosis, night blindness and hematomas.

Pathophysiology

The cause of primary biliary cirrhosis is not clear. The raised IgM levels as well as the presence of antimitochondrial antibodies (AMA), which are detected in more than 95% of patients are indicators for an autoimmune disorder. PBC frequently occurs in combination with other autoimmune diseases like keratoconjunctivitis sicca (72–100%), arthritis/arthropathy (4–42%), autoimmune thyroiditis (15–20%), CREST-syndrome (7%), Raynaud's phenomenon (8%) und scleroderma (3–4%).

Viral, bacterial as well as toxic factors and environmental influences have been discussed as causative agents. In most patients, PBC takes an asymptomatic course during the first 5–10 years. The leading symptom of PBC is the sometimes unbearable itching, which is typical in the more advanced stages of the disease. The average survival period is 6–7 years once the patient is jaundiced or 10–12 years after the diagnosis has been established. Bile acid secretion is reduced which leads to malabsorption of fat and fat-soluble vitamins.

Diagnosis

Diagnosis of PBC is suspected if

- γ-GT and/or alkaline phosphatase (AP), IgM and/or bilirubin are elevated (the transaminases AST or ALT are only slightly increased in most patients),
- the patient complains of itching, and
- the patient is female.

Immunological tests are especially important, since in the early stages laboratory tests may be almost unchanged and non-characteristic. Antimitochondrial antibodies (AMA), particularly subgroup AMA-M2 are detectable in almost 100% of affected patients. Additional autoantibodies are also observed: rheumatoid factors (70%), smooth muscle antibodies (SMA 66%), antithyroid peroxidase (Anti-TPO 41%) and antinuclear antibodies (ANA 35%).
Ultrasonography should be carried out to exclude tumors or gallstones. Liver biopsy is not necessary for diagnosis but helpful in staging of liver disease.

Therapy

In most patients with primary biliary cirrhosis, treatment with ursodeoxycholic acid (UDCA, 14 ± 2 mg/kg body weight/day) leads to an improvement of clinical and laboratory status. In 30% of patients liver tests return to normal.

In a significant portion of patients improvement is also observed in the histology. It has also been shown that in the pre-cirrhotic stage this therapy retards the progression of the disease and increases life expectancy. The earlier ursodeoxycholic acid therapy is started the more effective it is. In advanced stages of PBC this treatment is less effective.

Therapy must be continued for several years if not lifelong.

Some patients may benefit from a combination therapy with ursodeoxycholic acid and prednisone or the topical corticosteroid budesonide (3 × 3 mg/day). Substitution with vitamin D and calcium is indicated in patients with osteoporosis. Night blindness is treated with vitamin A, and decreased prothrombin time with vitamin K.

Mild or moderate to severe pruritus, or mild pruritus that does not respond to the above measures may be treated with colestyramine (4–16 g/day) with a time interval to ursodeoxycholic acid. Rifampicin (2 × 150–300 mg/day) may be effective in patients with a bilirubin concentration < 3 mg%, but adverse events (liver, kidney, hemolysis) and drug-drug interactions have to be considered. Naltrexone (1 × 50 mg/day) and sertraline (1 × 75 mg/day) may reduce pruritus. Antihistamines seldom relieve pruritus.

Medium-chain triglycerides (MCTs) should be added if caloric supplementation is required to maintain body weight. If pancreatic insufficiency is suspected pancreatic enzyme should be given. Regular controls are indicated: liver function tests every 3–6 months, TSH, vitamin A, D and K every 12 months if bilirubin is > 2 mg%. In patients with cirrhosis ultrasonography and AFP should be performed every year as well as esophagogastroduodenoscopy every 1–3 years, and bone density measurement every 2–4 years.

3.8 Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic obstructive inflammation of the intra- and extrahepatic bile ducts complicated by cirrhosis and cholangiocarcinoma in 10–30%. Men are affected twice as often as women. Manifestation is between the ages of 25 and 40 years in most patients. Prevalence is in 1–8 of 100,000 inhabitants. In more than 80% of the patients PSC is accompanied by inflammatory bowel disease.

Pathophysiology

The etiology of PSC has not been clarified, but an autoimmune disorder has been proposed. Autoantibodies are observed in some patients (perinuclear antineutrophil cytoplasmic antibodies, pANCA, 84%; anticardiolipin antibodies 66%; antinuclear antibodies, ANA 53%). A striking association (> 80%) with ulcerative colitis and Crohn's disease is observed. Conversely, PSC is present in 4–6% of patients with ulcerative colitis. In addition to immunologic etiology, a genetic predisposition is possible.

Diagnosis

Diagnosis is made if

- γ-GT and/or alkaline phosphatase (AP) are elevated (AST or ALT are only slightly increased in most patients),
- AMA negative, pANCA positive,
- the patient complains of itching,
- inflammatory bowel disease is known,
- recurrent elevated temperature, fever or loss of weight,
- the patient is male and his age between 25 and 40 years.

Diagnosis is made by endoscopic retrograde cholangiopancreaticography (ERCP) which shows typical alterations. Magnetic resonance cholangiopancreatography (MRCP) may be used alternatively. In about 5% of the patients with PSC only the small ducts are involved (small duct PSC) which can be diagnosed by histology. Ultrasonography should be carried out to exclude tumors or gallstones.
Osteoporosis is a common complication, therefore, bone density measurement should be performed and vitamin D_3 should be substituted if necessary. Vitamin A deficiency is also observed frequently.
Periodic controls of alkaline phosphatase, CA 19-9 and MRI for assessment of progression and early diagnosis of cholangiocarcinoma are mandatory. Hepatocellular carcinoma and colon carcinoma are more frequent also.

Therapy

Causal therapy does not exist. Ursodeoxycholic acid (15–20 mg/kg body weight/day) improves the clinical chemical laboratory values in some patients but is not recommended any more as routine therapy. In some patients it may lead to a decrease of pruritus, however. Stenosis can be dilated endoscopically. Consequently performed endoscopic dilatations and early institution of antibiotic therapy prolongs survival. Liver transplantation has to be considered in time as cholangiocarcinoma is frequently observed in PSC.

3.9 Overlap syndromes

Overlap syndromes are characterized by the coexistence of typical features from different diseases which hamper the classification to one or the other disease. Combinations of autoimmune hepatitis with features of PBC or PSC are observed.
In patients infected with hepatitis C, autoantibodies may prevail. Patients with typical symptoms and histology for PBC may be negative for AMA. During the course of the disease, symptoms or immunological results may change.

Pathogenesis

The pathogenesis of the overlap syndromes is not established. Different autoantibodies are observed in a proportion of patients and are indicators for the disease, but they probably play no role in the pathogenesis. Autoantibodies which may be found are AMA, ANA, SMA, ANCA und LKM-1.

Diagnosis

Determination of transaminases, alkaline phosphatase, γ-glutamyltranspeptidase and of autoantibodies is essential, as well as liver histology. In some patients ERCP is necessary.

Therapy

In accordance with the tests mentioned above efforts should be made to clarify whether the prominent features of the disease are that of cholestatic liver disease – such as PBC or PSC – or that of autoimmune hepatitis. If cholestasis prevails treatment is started with ursodeoxycholic acid. In case of non-response immunosuppressive agents are added like in autoimmune hepatitis. If the disease has predominant features of autoimmune hepatitis immunosuppressive therapy is initiated eventually combined with ursodeoxycholic acid. In patients with

hepatitis C infection and positive HCV-RNA in the serum therapy with pegylated interferon-α in combination with ribavirin is recommended. If this therapy fails corticosteroids and azathioprine may be tried.

3.10 Liver disease in cystic fibrosis

Cystic fibrosis (CF) is one of the most frequent inherited multisystemic disorders. About 5% of the white population is heterozygous for the cystic fibrosis gene (CFTR). A 3-base-pair-deletion (ΔF08) is the most frequently observed mutation (70%), although up to date more than 1000 mutations of CFTR gene have been reported. The prevalence of the disease is 1:1600. Until some years ago only a few patients survived the second decade. Data concerning accompanying liver disease vary between 2 and 17% (in adults significantly more). These differences are probably due to the improved life expectancy during the last two decades.
In adults cumulative liver disease is one of the leading causes of morbidity. It is characterized by chronic cholestasis, inflammation, fatty liver, fibrosis and even cirrhosis. Extrahepatic disease of the bile ducts is common.

Pathophysiology

The primary defect affects the cholangiocyte transport system. The impaired secretory function of the biliary epithelium is considered responsible for reduced bile fluidity and alkalinity. A specific association with one of the CFTR gene mutations and liver disease has not been identified.

Diagnosis

The diagnosis of liver disease in CF is made if
- γ-GT,- transaminases and alkaline phosphatase are elevated,
- magnetic resonance imaging demonstrate bile duct stenosis, dilatation and rigidity.

Therapy

If high grade stenosis of the biliary tract is visualized treatment by dilatation is recommended. If cholangitis is present antibiotics are given. Ursodeoxycholic acid (20 mg/kg body weight/day) leads to an improvement of liver function tests and transaminases, more pronounced with higher doses (up to 30 mg/kg body weight/day), although the number of patients included in these studies has been small.

3.11 Liver disease in celiac sprue

Celiac sprue is characterized by abnormal small-bowel mucosa anatomy and malabsorption caused by gluten (gluten-induced enteropathy). The villi are absent or short and broad leading to a flattened mucosal surface, hyperplasia of the crypts and inflammation is observed. The prevalence of celiac sprue is about 1%. Up to 40% of the patients with the diagnosis of celiac sprue have elevated liver values. Up to 5% of patients with unexplained elevated transaminases have IgA and/or IgG antigliadin antibodies as well as antiendomysial antibodies.

Pathophysiology

Pathophysiology of liver disease in patients with celiac sprue is unresolved. Antiendomysial antibodies and antitissue transglutaminase antibodies are found in patients with celiac sprue.

Diagnosis

Diagnosis of liver involvement in celiac sprue is made if:
- γ-GT, ALT, AST and alkaline phosphatase are elevated,
- steatosis or inflammation are observed in the liver biopsy without any other cause.

Therapy

Gluten-free diet leads to a normalization of liver values in about 90% of the patients. Untreated celiac sprue may lead to liver cirrhosis.

3.12 Drug-induced liver injury
(see: www.livertox.nih.gov)

Clinically significant liver damage due to drugs (DILI) is rare if the total amount of all pharmaceuticals is taken into account. Less than 5% of acute liver damage and icteric patients are caused by drugs, in chronic liver disease the proportion is even lower. In acute liver disease paracetamol is the most frequent cause of DILI in a dose-dependent manner. In elderly patients drug-induced liver damage is more frequent than in younger patients.
Slight increases of the transaminases, γ-glutamyltranspeptidase (γ-GT) and alkaline phosphatase are somewhat more frequent, for instance with some of the tuberculostatic drugs. The changes are usually reversible. In some patients, the responsible drug may or must be continued despite liver damage. Drugs may cause liver diseases by different mechanisms. Except from a very small number of drugs almost every pharmaceutical can lead to liver damage.
A large number of chemicals, e. g. organic solvents, potentially lead to severe liver damage.

Pathophysiology

Hypothetically toxic – that means dose-dependent, predictable liver damage may be differentiated from idiosyncratic, unpredictable (dose-independent) hypersensitivity reactions.
Most drugs undergo a chemical reaction that allows them to be coupled to endogenous compounds in subsequent steps, so that they can be excreted by the kidneys and the bile. These reactions may be very complex and involve reaction steps with the cytochrome P450 system. The toxic liver damage is dose-dependent and is observed in all people, whereas hypersensitivity reactions occur only in some people, either because of altered metabolism or allergic immunological reactions.

Hepatocellular (hepatitis-like) injury is more frequent (~75%) than cholestatic (~20%) or mixed injury. Patients with cholestatic DILI have the worst prognosis.
Chemical compounds may lead to different patterns of damage: micro- or macrovesicular fatty liver, mitochondrial damage, cell death, cholestasis (in this case, bile accumulation in the liver cells), increased formation of fibrous tissue, inflammatory reactions, vascular changes and in rare cases the formation of tumors.

Diagnosis

Diagnosis is suspected by the patient's history which may reveal an exposure to drugs or chemicals that have the potential to cause liver damage. Drugs that may lead to DILI are chlorpromazine, amoxicillin-clavulanate, flucloxacillin, diclofenac metoclopramid, tetracyclines, macrolides, sulfasalazine, antiepileptics, sulfamethoxazole-trimethoprim, anti-tuberculosis agents, valproic acid, phenytoin, antidepressant agents, troglitazone, antiretroviral drugs, azathioprine, 6-mercatopurine and methotrexate.
Nowadays, alternative medications like herbal preparations have to be taken into account, as they may also lead to liver damage (see Tab. 4).
Histological examination might substantiate the suspicion and the diagnosis is confirmed when stopping of the drug or of the exposure to chemicals improves symptoms and pathological liver values.

Name	Common use	Hepatotoxicity	Toxic ingredient
Aloe vera [Aloe barbadensis]	Laxative	Portal/lobular inflammation	Unknown
Copalchi [Hintonia latiflora]	Diabetes, antipyretic	Centrolobular necrosis	Furanoterpenoids
Germander/ Gamander [Teucrium]	Weight loss	Acute/chronic hepatitis with icterus	Epoxids; hepatocellular apoptosis induced by N-nitroso-diterpenoids
Green tea [Camellia sinensis]	Many positive effects for health, diabetes, obesity, Alzheimer's disease	Cholestasis, occasional steatosis and necrosis	Catechins and their gallates. Negative effects only after consumption of > 10 cups/day
Carline thistle [Carlina gummifera]	Antipyretic, antiemetic, diuretic	Diffuse hepatic necrosis	Inhibition of gluconeo-genesis, apoptosis due to damage of mito-chondria
Skullcaps [Scutellaria]	Anti-inflammatory, sedative	Inflammatory infiltrates, bridging fibrosis, cirrhosis	Flavonoids, alkylating substances
Kava kava extracts [Piper methysticum]	Anxiety, depressive symptoms	Acute/fulminant hepatitis	Unknown; CYP2D6 polymorphism?
Creosote bush [Larrea tridentata]	Rheumatic pain, bronchitis, diabetes	Cholestatic hepatitis, biliary changes, cirrhosis, massive necrosis	Nordihydroguaiaretic acid (estrogen-like effects); inhibition of cyclooxygenase
Greater celandine [Chelidonium majus]	Dyspepsia	Cholestatic hepatitis, with autoimmune antibodies	Unknown
Ox-Eye Daisy [Callilepis laureola]	Stomach problems, cough, (impotence)	Acute liver failure, several fatal casualties	Atractyloside
Black cohosh [Cimicifuga racemosa]	Menopausal symptoms	Acute/fulminant hepatitis; autoimmune features	Apoptosis due to damage of mitochondria

Table 4
Plants/extracts with hepatotoxic potential (selection)

Therapy

Specific treatment is not possible, apart from stopping the drug and avoiding exposure to the causative agents, except in patients with paracetamol intoxication in whom N-acetylcysteine therapy is given within the first 8 hours after ingestion over a time period of 72 hours, which leads to a dramatic reduction of mortality. Rechallenge with the suspected drug should be avoided because acute liver failure has been reported.

3.13 Alcoholic liver damage

Alcohol is the most frequent cause of chronic liver disease in Europe. Three alcohol related conditions can be differentiated: 1) fatty liver, 2) alcoholic hepatitis and 3) liver cirrhosis. The following amounts of alcohol can cause liver damage if consumed regularly for more than 10 years: 20 g per day for women and 50 g per day for men. It is difficult to distinguish between the three different disease conditions.

In fatty liver the most prominent feature is the enlarged liver. The patient often complains of a feeling of pressure in the upper abdomen. Liver function is usually normal. Fatty liver hepatitis is of greater clinical importance, because it is associated with liver cell damage, cell death and functional loss. This condition may be life-threatening. Both conditions are usually reversible with complete abstinence from alcohol. On the basis of symptoms and clinical features alcoholic liver cirrhosis cannot be differentiated from cirrhosis due to other causes.

Pathophysiology

Alcohol leads to a variety of metabolic changes. Chronically increased alcohol consumption can cause disorders of the redox potential. A significant role in liver cell damage and connective tissue formation is attributed to acetaldehyde, the first metabolite of ethanol. Other factors contributing to liver damage are hepatic antioxidant deficiency, structural and functional disorganization of mitochondria and other cell organelles, disturbance of intracellular signaling, imbalance of cytokines and eicosanoids. Endotoxins are suspected as exogenous factors for inflammation.

In lipid metabolism, an increased formation and a reduced breakdown of lipids is observed which leads to fat accumulation in liver cells. In addition, protein synthesis is

altered. The breakdown of drugs is frequently delayed, potentiating and prolonging their actions. Chronic alcohol consumption and alcoholism are often associated with malnutrition, and this may lead to vitamin and trace element deficiency.

Diagnosis

History is important in patients with alcoholic liver disease, especially the kind of drinks, the length of alcohol use, the amount (drinks) consumed and it is useful to question the family.
Alcoholic fatty liver is enlarged on physical examination. It has a typical appearance on ultrasound, while laboratory tests do not show any significant functional abnormalities. Specific tests for the diagnosis of alcoholic liver disease don't exist. AST/ALT ratio is typically above 2 in alcoholic liver disease. γ-GT is often significantly elevated, as well as the erythrocyte volume. In the differential diagnosis of fatty liver diabetes mellitus, overweight and drugs should be considered (Tab. 5).

Alcoholic fatty liver hepatitis is characterized by an increased leukocyte count, elevated serum bilirubin and liver enzyme values in the blood, indicating severe liver damage. Synthesis is also decreased, e. g. decreased prothrombin time (Quick value).

Therapy

The most important treatment for all types of alcoholic liver disease is absolute and continuous abstinence from alcohol. In life-threatening liver failure due to alcoholic hepatitis corticosteroid therapy may be beneficial. In the initial phase, supplementary measures include vitamins and trace elements.

Etiology	Pathogenesis	Fat distribution	Localization of the nucleus	Other characteristics
Alcohol	oxidation of fatty acids toxic	diffuse	peripheral	neutrophilic infiltrates Mallory bodies
Type I diabetes mellitus	lipolysis	diffuse	peripheral	unspecific
Type II diabetes mellitus	lipogenesis			
Obesity	dietary fat	centrolobular diffuse	peripheral	unspecific
Toxic drugs (e. g. tetra-cyclines)	secretion of VLDL	diffuse	central	unspecific

Table 5
Clinical symptoms and findings in alcoholic hepatitis and other liver diseases involving fatty degeneration of the liver

3.14 Non-alcoholic fatty liver disease (NAFLD); non-alcoholic steato-hepatitis (NASH)

These liver diseases are characterized by an increased fat deposition in the liver (NAFLD) which might be accompanied by elevated transaminases (NASH). Today terminology is still inconsistent. Before the diagnosis is made, other causes, especially alcoholic liver disease must be ruled out. Increased fat deposition in the liver without elevated transaminases is found in obese patients.
NASH with elevated transaminases may develop in these patients without known causes. Fibrosis is observed in 15–50% of these patients and cirrhosis in 7–16%.
In patients with NASH other factors such as insulin resistance, diabetes mellitus, hyperlipidemia or rapid weight loss may also play an important role. NASH is also found in patients who underwent extensive small bowel resection or procedures for weight loss such as gastropexia or jejuno-ileal bypass.
NAFLD and NASH are part of the metabolic syndrome which is characterized by abdominal obesity (waist circumference > 102 cm in males, > 88 cm in females), dyslipoproteinemia (serum triglycerides > 150 mg/dL, HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women), diabetes mellitus, insulin resistance, and hypertension (RR > 140/90 mmHg).

Pathophysiology

A unifying pathogenesis doesn't exist. There is a close relationship between NAFLD and NASH with the metabolic syndrome. Today it is assumed that NASH has several causes in a given patient. Amino acid imbalance, hyperglycemia, elevated insulin concentrations, reduced leptin concentrations and endotoxins may be important factors. Lipogenesis is elevated by these factors. NASH and alcoholic liver disease share some common features like activation of microsomal enzymes, elevated endotoxin

concentrations in the blood, elevated TNF-α concentrations, and reduced ATP contents of the liver. Adipocytokines like leptin, adipsin, resistin, adiponectin and visfatin probably play a role in liver injury. Some drugs like tamoxifen induce a NASH-like hepatic injury.

Diagnosis

Patients with NASH have low to medium elevations of transaminases, γ-glutamyltranspeptidase is also increased in some. Hyperglycemia, caused by insulin resistance, hypercholesterolemia, and hypertrigylceridemia are found in 25–75% of the patients. Signs of marked hepatic steatosis with homogenously increased structural changes are found in ultrasonography. Diagnosis is made by liver biopsy which shows macrovesicular steatosis, cytologic ballooning, Mallory's hyaline, and focal necroinflammation. Perivenular and sinusoidal fibrosis are observed which may progress to cirrhosis. Other causes of liver injury must be excluded, especially ethanol.

Therapy

A specific therapy doesn't exist. A cautious weight loss by reduced caloric intake and increased physical activity, as well as a meticulously controlled blood glucose level in diabetics and treatment of hyperlipemia, if present is recommended.
Bariatric surgery shows some benefit in NASH patients. Small studies with insulin sensitizers, vitamin E, pentoxifylline, losartan, betaine, S-adenosyl methionine, polyunsaturated fatty acids, fibrates and statins have shown no long-term benefits.
If drugs may play a concomitant role they should be stopped if possible.

3.15 Liver cirrhosis

Liver cirrhosis is the final stage of many liver diseases. It is defined by a transformation of liver architecture with destruction of the regular structure which is necessary for its function and a reduction of the total blood vessel diameter. This has effects on blood flow, metabolism and detoxification in the liver.

The disturbed hepatic blood flow leads to an elevated portal pressure, resulting in formation of esophageal and gastric varices, portal hypertensive gastropathy, ulcers of the stomach or the duodenum, and angiodysplasias, which may bleed. A further consequence is the formation of fluid retention in the abdomen (ascites).

The decreased metabolism leads to a reduction of protein synthesis, which may affect clotting factors, enzymes and albumin.
The disturbed metabolism of substances, regardless whether it affects endogenous compounds, nutritional components or drugs, causes a reduction in their excretion from the body. This may lead to disorders of other organs, such as the brain, kidneys and heart. Jaundice is the visible sign of the reduced detoxification.

Symptoms

The patients show unspecific symptoms of chronic liver disease. They often report of chronic fatigue, a recently occurring tendency to bleed, of dark urine, strong flatulence, edemas or have difficulties in concentration (hepatic encephalopathy).

Clinical aspects

On examination, the general state of health is often reduced, there is jaundice, so-called spider naevi (small superficial blood vessels with spider-like vessels), scarlet

tongue, fissures in the corners of the mouth (rhagades), reduced pubic hair, abdominal baldness and white nails. Bruises (hematomas) are observed frequently. Some patients are locally and temporally disoriented and have a tremor.

Diagnosis

The diagnosis is made by:
1. physical examination, the organ is solid,
2. ultrasonography und duplex examination with typical features,
3. clinico-chemical changes of reduced parameters of synthesis, prolonged prothrombin time (INR, International Normalized Ratio), reduced albumin and reduced cholinesterase activity, abnormally high enzyme values (AST, ALT, possibly γ-GT and alkaline phosphatase) and increased bilirubin,
4. histology.

The clinical course of hepatic cirrhosis is routinely assessed by means of the Child-Pugh classification (Tab. 6). The MELD (Model for End-Stage Liver Disease, http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=9) score may be used as an alternative. Age, bilirubin, creatinine and prothombin time are included in this scoring system. It is used for patients listed for transplantation.

Therapy

Therapy (see also Fig. 2) is directed towards relief of symptoms and complications. Salt intake must often be reduced. Reduction of protein intake is not useful for hepatic encephalopathy, but protein selection should be considered.

Score/ parameter	1	2	3
Bilirubin (mg%)	< 2.0	2.0 to < 3.0	> 3.0
µmol/l	< 35	35 to < 50	> 50
Albumin (g%)	> 3.5	2.8 to < 3.5	< 2.8
Prothrombin time (Quick%)	> 60	40 to < 60	< 40
INR	< 1.7	1.7–2.3	> 2.3
Ascites	no	controlled	refractory
Hepatic encephalopathy	no	stages I and II	stages III and IV

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

Table 6
Child-Pugh classification

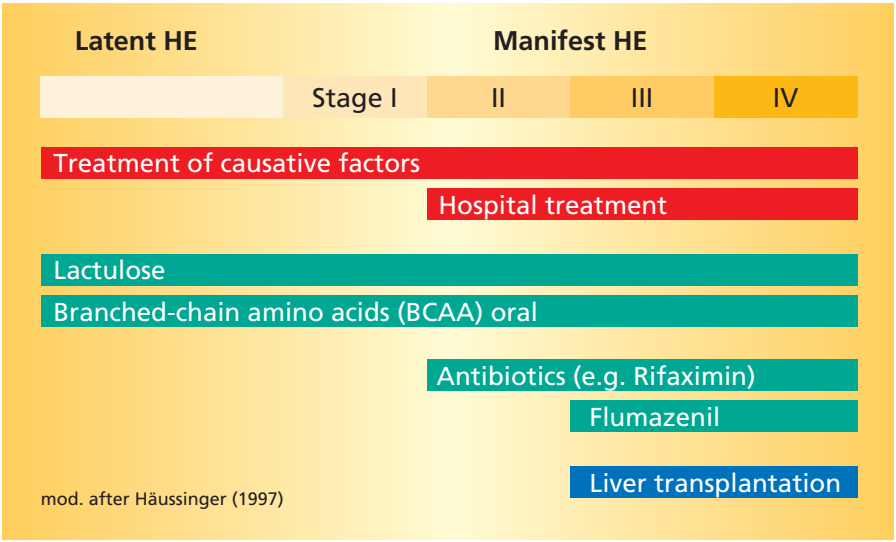

Figure 2
Scheme for treatment of hepatic encephalopathy (HE) (mod. after Häussinger [1997])

In patients with ascites and edema, different diuretic medications, like spironolactone and/or furosemide are given and the amount of liquid intake should be restricted. To prevent and treat neurological symptoms lactulose administration is instituted to reduce absorption of toxic substances from the intestine. L-ornithine-L-aspartate and non-absorbable antibiotics like rifaximin may be given also to treat hepatic encephalopathy. Branched-chain amino acids are sometimes beneficial.

3.16 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most frequent cancer worldwide, particularly in Asia. Risk factors include infections with hepatitis B and C, hemochromatosis, α_1-antitrypsin deficiency, non-alcoholic steatohepatitis (NASH) and alcoholism. A sudden rapid deterioration of the health status of patients with liver cirrhosis may signify this carcinoma. α-Fetoprotein concentration (AFP) and ultrasonography should be controlled yearly in all patients with cirrhosis. In patients with elevated AFP contrast-enhanced computed tomography or ultrasonography should be performed.

Partial liver resection is possible in a small number of patients. Liver transplantation may be an alternative in selected patients with encouraging results if the tumor is smaller than 3 or 5 cm in diameter and no further tumors are present.

Therapeutical alternatives are alcohol injection directly into the tumor (percutaneous ethanol injection, PEI), transcutaneous arterial chemoembolization (TACE), radiofrequency thermo-ablation (RFTA), and selective intra-arterial radionuclide therapy (SIRT). Patients with Child-Pugh stage A cirrhosis with advanced stages of HCC may be treated with sorafenib (2×400 mg/day) leading to a prolongation of survival of 3 months.

3.17 Gallstones

Since the introduction of ultrasound, gallstones are more often discovered accidentally. In the Western industrialized countries 10–15% of the population have gallstones, women are more often affected than men. Besides gender other risk factors include age, overweight, diabetes mellitus and disturbances of lipid metabolism. Long-term use of some drugs, such as estrogens and some lipid-lowering drugs may also lead to formation of gallstones.

Only a small portion of patients (approx. 20%) complain of symptoms, such as right upper abdominal pain, biliary colic (possibly triggered by diet), fat intolerance, stool decoloration and dark urine. Four therapeutic procedures are currently available for the treatment of gallstones:

- cholecystectomy (open or laparoscopic surgery)
- oral litholysis using bile acids (ursodeoxycholic acid/ chenodeoxycholic acid)
- extracorporeal shock-wave lithotripsy (ESWL) with adjuvant bile acid therapy (only few cases)
- direct percutaneous transhepatic litholysis (PTL) with methyl-tert-butyl ether (MTBE) (only experimental).

Only patients with symptomatic gallstones should be treated. Today laparoscopic cholecystectomy is the treatment of choice. Gallstones without symptoms, so-called silent gallstones, should only be treated in exceptional circumstances.

Before any of the three non-surgical types of treatment is considered a radiological stone classification should be made, since only cholesterol stones can be treated successfully with these methods.

A decision which of the three types of therapy, which leave the gallbladder intact should be used, will depend both on the symptoms and the size, type and number of stones. (Fig. 3).

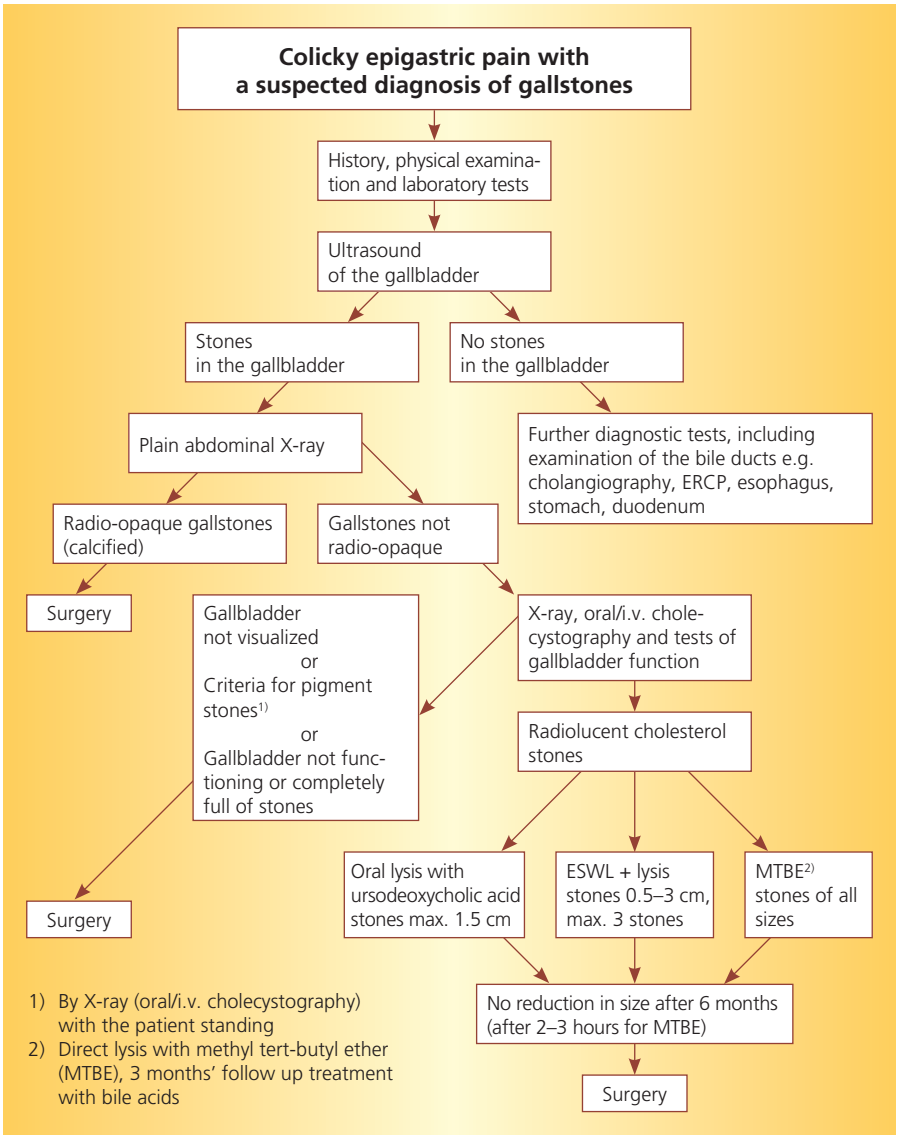
Colicky epigastric pain with a suspected diagnosis of gallstones
History, physical examination and laboratory tests
Ultrasound of the gallbladder
Stones in the gallbladder
No stones in the gallbladder
Plain abdominal X-ray
Further diagnostic tests, including examination of the bile ducts e.g. cholangiography, ERCP, esophagus, stomach, duodenum
Radio-opaque gallstones (calcified)
Gallstones not radio-opaque
Surgery
Gallbladder not visualized or Criteria for pigment stones1) or Gallbladder not functioning or completely full of stones
X-ray, oral/i.v. cholecystography and tests of gallbladder function
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) stones of all sizes
No reduction in size after 6 months (after 2–3 hours for MTBE)
Surgery
1) By X-ray (oral/i.v. cholecystography) with the patient standing
2) Direct lysis with methyl tert-butyl ether (MTBE), 3 months' follow up treatment with bile acids

Figure 3

3.18 Functional disorders of the extra-hepatic biliary tract

Postcholecystectomy syndrome

Up to 40% of patients report symptoms of gallstone disease after cholecystectomy. Symptoms may resemble those before surgery or may present differently. Consequent use of diagnostic procedures such as ultrasound, ERCP (endoscopic retrograde cholangiopancreaticography) and magnetic resonance cholangiopancreatography (MRCP) leads to a diagnosis in most patients. The etiology of the symptoms remains unsolved in only a small number of patients.

4 Diagnostic approach

4.1 Diagnosis of liver damage

Cell Damage	Cholestasis	Excretion and Conjugation
AST (aspartate aminotransferase)	**AP (alkaline phosphatase)**	**Bilirubin**
ALT (alanine aminotransferase)	**γ-GT (γ-glutamyl-transpeptidase)**	
GLDH (glutamate-dehydrogenase)	5′-nucleotidase	**Hint:** The tests that are not highlighted yellow can usually be omitted, since they are of no use, neither for diagnosis nor for clarifying the etiology
LDH (lactate-dehydrogenase)	LAP (leucine-aminopeptidase)	
IDH (isosorbide-dehydrogenase)		
SDH (sorbitol-dehydrogenase)		

4.2 Clarification of etiology of chronic liver damage

1st step	2nd step	3rd step
Viral cause:	**Metabolic cause:**	**Metabolic cause:**
HBsAg (hepatitis B), Anti-HCV (hepatitis C)	Transferrin saturation and/or ferritin	Ceruloplasmin, urinary copper excretion per 24 hours
	Autoimmune hepatitis/ PBC/PSC:	α_1-Antitrypsin
	AMA, ANA	δ-Aminolevulinic acid, if symptomatic
		Porphobilinogen, if symptomatic
		Uroporphyrin/coproporphyrin in the urine, if symptomatic
		Autoimmune hepatitis:
		SMA, Anti-LKM, [Anti-SLA]

4.3 Follow-up for chronic liver disease

General tests: AST, ALT

Parameters for specific diseases:
HBeAg with patients during interferon or nucleos(t)ide therapy
HBV-DNA during therapy
HCV-RNA with patients with hepatitis C during combination therapy
Ferritin and iron for hemochromatosis
Copper in urine in patients with Wilson's disease
α-Fetoprotein and ultrasound (once a year) for hemochromatosis, untreated hepatitis B, C, D

Parameters for liver cirrhosis: Bilirubin, albumin, prothrombin time, creatinine, α-fetoprotein and ultrasound (once a year)

Table 7
Diagnostic approach of liver disease

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