Clinical Aspects of Liver Diseases

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A number of bacterial infections may affect the liver to varying degrees of intensity. The frequently observed liver involvement is attributed to a number of causes: (1) size of this visceral parenchymatous organ, (2) multiplicity and activity of the hepatic RES as a filtering system, (3) double (portal and arterial) blood supply with transport of bacteria or their toxins, and (4) lymphogenous spread of pathogenic organisms.

1 Pathogenesis

The pathogenesis of liver involvement in bacterial infections often remains unresolved. In this respect, four pathomechanisms, either alone or in combination, are assumed to play a role. (s. tab. 24.1)

1. Direct effects of pathogens
   - direct haematogenic spread
   - direct lymphogenous spread
2. Indirect effects of pathogens
   - toxins
   - endotoxins
3. Reactions due to the basic disease
   - hypoxaemia
   - fever, exsiccosis, acidosis
   - electrolyte imbalance, etc.
4. Therapy-induced liver damage

Tab. 24.1: Pathomechanisms of liver involvement in bacterial diseases

| \hline 1. Residual previous liver damage & 2. Coexistent previous liver damage |
|----------------------------------|----------------------------------|
| 1. Parenchymal changes           |                                  |
|   - cytoplasmic lesions          |                                  |
|   - cell necroses                |                                  |
|   - nuclear changes              |                                  |
| 2. Mesenchymal reactions         |                                  |
|   - portal inflammation          |                                  |
|   - endothelial cell reaction    |                                  |
|   - bile duct proliferation      |                                  |
|   - fibrosis                     |                                  |

1. Non-specific reactive hepatitis
2. Retothelial nodules
3. Bacterial peliosis hepatitis
4. Granulomas
5. Giant-cell hepatitis
6. Abscess formation

Tab. 24.2: Morphological reaction types in liver involvement following bacterial infections

2 Types of lesion

Liver involvement may occur in both extrahepatically localized and generalized bacterial infections. Various morphological reactions appear depending on (1.) severity of infection, (2.) type of pathogen, (3.) respective morphological reaction of the liver, and (4.) possible previous liver damage – similar reactions also appear in viral hepatitis. Combined with the potential coexistence of scarred/fibrotic and chronic inflammatory liver changes, these additional acute infections may lead to morphological pictures that are difficult to interpret. The diversity of the morphological reaction types may also be influenced by individual factors. (s. tab. 24.2)

3 Bacterial pathogens

The principal pathogenic agents causing liver damage are pyogenic cocci, gonococci, enteric bacteria, myco-

<table>
<thead>
<tr>
<th>\hline 1. Pyogenic cocci</th>
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<tbody>
<tr>
<td>1. Neisseria gonorrhoea</td>
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<tr>
<td>2. Escherichia coli</td>
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<tr>
<td>3. Salmonella species</td>
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<tr>
<td>4. Vibrio cholerae</td>
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<tr>
<td>5. Mycobacteria</td>
</tr>
<tr>
<td>6. Leptospira species</td>
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<tr>
<td>7. Borrelia species</td>
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<tr>
<td>8. Brucella species</td>
</tr>
<tr>
<td>9. Rickettsia species</td>
</tr>
<tr>
<td>10. Chlamydia psittaci</td>
</tr>
<tr>
<td>11. Clostridium species</td>
</tr>
<tr>
<td>12. Campylobacter jejuni</td>
</tr>
<tr>
<td>13. Actinomyces israelii</td>
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</tbody>
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Tab. 24.3: Major bacterial organisms causing liver damage. In Germany, obligation for notification is given in cases of suspicion (S), disease (D), exitus (E), or perinatal infection (P). This can, however, vary from country to country. If in doubt: contact the Public Health Department!
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bacteria, spirochaetes, listeriae, brucellae, rickettsiae, chlamydiae and clostridiae. (s. tab. 24.3)

3.1 Pyogenic cocci

Streptococcus pneumoniae: Infection with Streptococcus pneumoniae may cause both toxic liver damage and pneumococcal hepatitis with focal necroses, leading to the corresponding laboratory findings. In lobar pneumonia, jaundice (= biliary pneumonia) frequently occurs in the so-called grey hepatization stage. In addition to predominantly bacterial haemolytic jaundice, increased transaminases (20%) and cholestasis (10%) are found. The condition always regresses completely. A liver abscess induced by pneumococci is a rare event. (3–5, 9)

Staphylococci, streptococci: In sepsis, toxic liver damage and portal granulocytic infiltration may be observed. Septic bacterial invasion of the liver mainly entails periportal, circumscribed and non-suppurative septic foci (s. fig. 24.1), and occasionally multiple microabscesses as well. (10) Cholestasis usually suggests a severe course of disease; likewise, prolonged jaundice points to a poor prognosis as far as the underlying disease is concerned. (1, 2, 4–6)

3.2 Neisseria gonorrhoea

Gonococcal infection may lead to toxic liver damage or concomitant hepatitis, especially in the presence of gonococcal sepsis. Diagnosis of gonorrhoea is established by direct demonstration of pathogens (vaginal smear, liver tissue, liver capsule) or serologically by means of CFR (positive from 3rd week). Perihepatitis acuta gonorrhoea: Of special relevance is a fibrinous inflammation of the subphrenic space without abscess formation, occurring as a sequel of gonorrhoeal adnexitis in women. It is also called the Fitz-Hugh-Curtis syndrome (A. H. Curtis, 1932; T. Fitz-Hugh, 1934), although it was first described by C. Stajano in Montevideo in 1920. Only two cases of this syndrome have so far been reported in men. Symptoms include severe epigastric pain (nearly always dextral), local peritonitis (dependent on respiration and movement), shoulder pain due to irritation of the phrenic nerve, and occasional friction rub. There are no other major subjective complaints or clinical findings. • In the meantime, it has been demonstrated that, in addition to Neisseria gonorrhoea, Chlamydiae and even Coxsackie virus B5 may also be responsible for this condition. (s. pp 467, 481) • A typical feature of the syndrome are the fine violin string-like adhesions between the liver surface and the abdominal wall, which are easily identified by means of laparoscopy. The syndrome can also be diagnosed retrospectively by laparoscopy through the detection of such lesions. (11–15)

In the one case that we observed, the patient was suffering from severe recurrent epigastric pain and had pathological, inflammation-related laboratory parameters. Following unsuccessful diagnostic efforts during an 8-month course, we were finally able to obtain a diagnosis by laparoscopy at once and confirm gonorrhoea as being the cause of the disease. (s. fig. 24.2)

3.3 Enterobacteriaceae

Escherichia coli: In the case of sepsis, the occasionally massive endotoxaemia may lead to major liver cell damage, accompanied by jaundice. Histologically, focal liver cell necrosis, giant-cell transformation, inflammatory infiltrations and signs of cholestasis are detectable. Escherichia coli is the most frequent causative agent of liver abscesses, followed by Friedländer’s bacillus and Yersinia enterocolitica. In the case of bacteraemia, a toxic shock syndrome can develop with a so-called cholangiolitis lenta (M. Våberg et al., 1984).
**Ehrlichiosis:** Ehrlichia chaffeensis is an infection which is transmitted by the bite of a tick. It results in fever, myalgias and pancytopenia. Transaminases are increased in 80–90% of cases. Histologically, it is possible to detect scattered lobular lymphohistiocytic foci, various diffuse infiltrations and Kupffer-cell hyperplasia with intense phagocytosis. Occasional injuries to the bile duct epithelium may also cause elevated AP activity. Laboratory findings and histology (which often vary in severity) suggest that host inflammatory or immune responses contribute to the liver injury. (29)

**Salmonellosis:** Infection with Salmonella paratyphi A, B or C may occasionally cause suppurrative cholangitis with cholangiohepatitis. In contrast, Salmonella enteritidis mainly gives rise to toxic hepatitis. • In typhus abdominalis, hepatomegaly (20–30%) as well as an increase in transaminase and alkaline phosphatase activities are invariably observed from the 2nd to 3rd week of disease. Hyperbilirubinaemia is frequent, whereas manifest jaundice is rarely witnessed. Histology may demonstrate signs of non-specific reactive hepatitis. In some cases, submiliary nodules or granulomas (so-called typhomas) are verifiable. Here, mainly intrasinusoidal proliferations of large plasma-rich cells with very small nuclei (so-called beef-like cells or typhoid cells) are found. These epithelioid cell clusters originating from reticular cells often contain multinucleate giant cells in their periphery. The toxic submiliary typhoid nodules (s. fig. 24.3), however, exhibit centroacinar necroses, proliferations of sinus endothelial cells and granulocytes with signs of regeneration. Apart from that, liver abscesses have also been identified. (16, 17, 19, 20, 22, 24–27, 30)

**Yersinia enterocolitica:** Infection with Y. enterocolitica or Y. pseudotuberculosis, together with haematogenous spread, may lead to a septic-typhoid course with hepatic and splenic abscess formation. Especially ulcerative colitis was frequently found to favour the formation of multiple liver abscesses. A genetic disposition is assumed in the presence of the HLA-B 27 gene. Patients with hepatic overload of iron are at special risk of Yersinia infection, since iron plays a major role in the metabolism of Yersinia. (18, 23, 28, 31, 32)

### 3.4 Mycobacteria

**3.4.1 Mycobacterium tuberculosis**

Tuberculous hepatic infections are transmitted pre-/perinatally via the umbilical vein or the amniotic fluid; maternal placenta tuberculosa is a precondition for both infections. • The hepatic artery and the portal vein as well as the hepatopetal lymph vessels serve as postnatal infection routes.

1. The **tuberculous primary complex** in the liver with caseation of the associated hepatic hilar lymph nodes may become the source of spread causing early systemic generalization. Given the clinical picture of a coarse-nodular or a miliary tuberculosis, this may result in the death of the newborn child.

2. **Miliary tuberculosis** generally results in an attack on the liver by a number of clustered miliary tubercles. They are distinctly recognizable on the liver surface by means of laparoscopy. (35, 39, 50, 54) GPT, GOT and GDH as well as alkaline phosphatase are moderately increased. Clinical manifestations include severe malaise, hepatospleno-megaly and fever — the cause of the latter often remaining unresolved for a long time. The haematogenous spread, occurring as intermittent episodes, also provokes a number of small tuberculous liver foci. As a rule, they show central caseation and fibrinoid necrosis. In the periphery, a corona of epithelioid cells of variable diameter is found, in which Langhans’ giant cells are embedded. (s. fig. 24.4)
These granulomatous tubercles are surrounded by a loose rim of lymphocytes. Massive miliary spread to the liver may also cause acute liver failure as well as septic shock with multiorgan failure.

3. **Tuberculomas** may develop through enlargement and subsequent confluence of the miliary foci or tubercles as well as through nodular development of tuberculous foci in the tertiary stage. These appear as nodules with a diameter of 1–4 cm. Embedded calcifications are typical features of tuberculomas. They may penetrate bile ducts and cause *tuberculous cholangitis* with bile-duct stricture. Diagnosis of a liver abscess therefore includes differentiation from tuberculosis. Differential diagnosis from pseudotumorous liver tuberculosis is very difficult, even when using imaging techniques.

In the course of healing, miliary tuberculosis or small diffuse disseminated foci give rise to scarred transformation with the morphological picture of *tuberculous pseudocirrhosis* as a result of vascularization, fibroblasts and histiocytic connective tissue. As a rule, however, no major hepatic dysfunction results from the cicatrization of the healing process, which no longer (or barely) exhibits the specific character of granulation tissue.

4. Non-specific toxic liver damage may be evident; in this connection, possible tuberculostatic toxic effects must also be considered. With severe courses of tuberculosis, *peliosis hepatis* is often observed. Frequently, *rētōthēliāl nōddulēs* are detectable, as demonstrated for the first time in tuberculosis patients by H. Hamperl in 1953. In the course of chronic pulmonary tuberculosis, *fatty infiltration of liver cells* was noted, as reported in several publications. It was attributed to toxic effects and/or undernourishment or malnutrition. Secondary hepatic amyloidosis, developing in the course of chronic lung tuberculosis, has also been postulated. A restriction of hepatic function in chronic tuberculosis, which was first observed by E. Liuret et al. in 1922, has been described in a number of publications. Depending on the severity and duration of the disease as well as the tuberculostatic pretreatment, we found pathological laboratory parameters in 15–20% and 25–40% of cases respectively.

If laboratory tests and imaging techniques have proved unsuccessful, it is only possible to obtain a reliable diagnosis and differentiation of the multiple manifestations of liver tuberculosis by means of laparoscopy and targeted biopsy. Treatment consists of a fourfold combination: isoniazid (5 mg/kg BW/day), rifampicin (10 mg/kg BW/day), pyrazinamide (25 mg/kg BW/day), ethambutol (20 mg/kg BW/day), generally for 2–4 months, subsequently isoniazid + rifampicin for 6–12 months.

### 3.4.2 Mycobacterium scrofulaceum

Mycobacterium scrofulaceum may cause granulomatous hepatitis. Clinical findings include a clear increase in alkaline phosphatase as well as fever and general malaise. Diagnosis is confirmed by positive culture of the pathogen in liver biopsy specimens. Other atypical mycobacteria may also cause liver damage, possibly in the form of granulomatous hepatitis, especially in AIDS.

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**Fig. 24.5:** Small nodular hepatic tuberculosis: foci, the size of a millet seed up to that of a lentil, in the right lobe of liver

**Fig. 24.6:** Old intrahepatic tuberculoma. Encapsulated eosinophilic necrosis with marked caseation (HE)
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3.4.3 Mycobacterium leprae

In lepromatous leprosy with a high germ count, the liver is affected in 50–90% of cases. Glisson’s capsule is thickened and whitish. The number of lepra granulomas in the liver, which appear in the form of yellowish nodules, may be high enough to justify the term granulomatous hepatitis. Initially, these granulomas consist of histiocytic and lymphocytic infiltrates, which contain lepra bacteria in approximately 75% of cases. The lepra bacteria can be identified above all in Kupffer cells. Eventually, the characteristic bacteria-phagocytizing leprotic cells are formed (so-called foam cells or Virchow cells). These large-cell lepra granulomas are localized predominantly in the portal tract and show a tendency to central caseation. (s. fig. 24.8)

The treatment regimen consists of diphenylsulphone, clofazimine and rifampicin in combination for 6 to 24 months or longer (depending on the course of the disease). Thalidomide has also proved effective. • BCG vaccination is an effective prophylactic measure against infection induced by Mycobacterium leprae. (66–68)

3.5 Spirochaetes

3.5.1 Leptospirosis

In 1886 A. Wen reported 4 patients with an acute, highly febrile, infectious disease, accompanied by icterus and a high mortality rate. This disease was termed icterus infectious Weil. In 1915 R. Isada et al. in Japan and P. U. Born et al. in Germany discovered virtually at the same time that the Leptospira interrogens (or L. icterohaemorrhagiae) were pathogenic agents (S. interrogans). So far, about 180 serotypes have been identified, all of which are generally pathogenic for humans and may provoke Weil’s disease.

Reservoir hosts include especially rats, mice, hedgehogs, hamsters and various domesticated animals. Leptospirosis is therefore a globally distributed zoonosis. Transmission to humans occurs via the oral or percutaneous route with small skin or mucosal lesions serving as portals of entry for the pathogens, which are excreted in the urine of infected animals.

The incubation period for leptospirosis (Weil’s disease) is 7 to 14 days. Subsequently, the septicaemic phase sets in with fever, chills, myalgia, arthralgia, headaches, haemorrhagic conjunctivitis, abdominal pain, vomiting and renal involvement (erythrocyturia, proteinuria). Histologically, interstitial nephritis with tubular necrosis is demonstrable. • In just a few days, icterus, hepatomegaly, an increase in transaminase activity and haemorrhagic diathesis occur, especially in severe cases. Histology reveals focal cirrhotic lesions (acidophilic degeneration, turbid swelling) and lymphocytic infiltration of the portal tract, stellate cell proliferation and bile thrombi in the canaliculi as well as active hepatocyte mitosis. The histological picture corresponds to that of cholestatic hepatitis (cholestasis is usually not verifiable by laboratory tests). • Identification of pathogens is successfully performed in blood and CSF (1st week) and in the urine (2nd week); increasing antibody titres (up to four times the norm) are detectable in the serum as from the 2nd week. Proof of specific IgM is also possible. • As the disease advances, a typical iridocyclitis as well as meningitis or encephalomyelitis with brain oedema can appear. Convalescence may take a long time in some cases; this phase is characterized by adynamia and loss of hair. Mortality can range from 4–50%, depending on the course — anicteric or icteric — and is mostly due to renal insufficiency. The recommended therapy consists of penicillin (10–20 million U/day) or doxycycline (2 × 100 mg/day). (69–73)

▶ We observed a lethal case (treatment with doxycycline was unsuccessful) showing massive amounts of leptospirae in the serum and in the centrifuged urine under dark-field examination. Maximum values were: GPT 4,200 U/l, GOT 2,290 U/l, GDH 1,080 U/l, serum bilirubin 11 mg/dl and Quick’s value 17%, but with normal AP (1); such pathological levels have repeatedly been reported in the literature. Autopsy revealed severe interstitial nephritis, tubular necrosis (laboratory findings corresponding to severe renal insufficiency), brain oedema (680 g), severe

Fig. 24.7: Acid-fast bazilli of mycobacterium tuberculosis in the liver of an AIDS patient (Fite staining)

Fig. 24.8: Lepra: granuloma-like, lymphohistiocytic infiltration in the liver parenchyma (HE)
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Hepatic dystrophy with marked centrolobular necroses and diffuse small-droplet fatty degeneration of the liver cells as well as haemorrhagic organ lesions. (s. fig. 24.9)

Fig. 24.9: Enlargement of hepatocytes with large nucleoli (arrow), distinct icterus with (green) bile thrombi in the biliary capillaries and hepatocytes. Multivacuolar steatosis of isolated liver cells. Groups of histiocytes (far left of picture) with phagocytized nuclear material and lipofuscin. Clinical diagnosis: Weil’s disease

3.5.2 Syphilis

The coexistence of jaundice and syphilis was described by Paracelsus as early as 1585. In all stages of syphilis, congenital or acquired, liver involvement is possible. The pathogen (anaerobic, gram-negative) is very sensitive to environmental factors and perishes rapidly. The period of cellular fission is 36 hours. Treponema pallidum is occasionally verifiable in histological preparations as corkscrew-shaped structures, 6–10 µm in length and 0.2 µm in diameter. (s. fig. 24.11)

Lues connata (congenital syphilis) is a form of syphilis transmitted to the foetus after the 4th month of pregnancy. If neither foetal death nor abortion occurs (approx. 30%), hepatosplenomegaly, “capillaritis” and interstitial syphilitic hepatitis develop. Splitting of the liver cell plates into small epithelial groups takes place. Subsequent swift interstitial fibrosis leads to the picture of microgranular intralobular cirrhosis. Focal cell necrosis in the liver of the neonate causes the formation of miliary syphilomas, which contain giant cells, epithelioid cells, lymphocytes and macrophages. (s. fig. 24.10)

Fig. 24.10: Lues connata: Severe inflammatory infiltration (especially left of picture); sinusoidal fibrosis; irregular liver cell plates (far right of picture). So-called “interstitial syphilitic hepatitis” (HE)

Fig. 24.11: Syphilis, secondary stage: hepatitis syphilitica. In the liver parenchyma, massive amounts of corkscrew-shaped syphilis pathogens, 6–10 µm in length, are visible (treponema pallidum) (silver impregnation)

Lues acquisita progresses as (1) early syphilis throughout the primary and secondary stages, lues latens seropositiva (= early latent form) and as (2) late syphilis in the tertiary stage, lues latens seronegativa (= late latent form), and stage IV. From the primary complex, haematogenous dissemination of the pathogen throughout the body takes place, with development of the early stage of syphilis (primary and secondary stages). Syphilitic hepatitis is found in 10% of cases, with focal liver cell necrosis, infiltrates of lymphocytes, eosinophils and granulocytes, focal activation of the stellate cells and portal infiltrations. The portal bile ducts are narrowed by infiltrations, resulting in pronounced cholestasis. The portal vessels show signs of vasculitis. Hepatomegaly of hard consistency is present. About 50% of patients exhibit elevated transaminases. Usually, the antimitochondrial antibody M1 is positive. Healing is accompanied by fibrosis. Cirrhosis may also develop.

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ency, gumma syphiliticum may be observed inter alia in the liver, where it is either solitary or multiple and mostly localized in the right lobe. Gummases are large, closely circumscribed, nodular structures with a diameter of a few millimetres up to several centimetres. They consist of central caseation, which is surrounded by vascularized granulation tissue resembling a capsule and by plasma and giant cells. (75, 78, 83) (s. fig. 24.12) The hepatic architecture is generally not affected. Usually, endarteritis develops. Treponemas are only rarely found in the guma. • In the case of multiple occurrence with associated deep grooves and scar formation, the striking picture of hepatic lobatum appears.

Fig. 24.12: Hepatic guma from syphilitic hepatic lobatum. Intrahepatic necrotic zones surrounded by a thin layer of granulation tissue

3.5.3 Borreliosis

In 1976 Lyme borreliosis was observed for the first time in Lyme (USA). It is caused by Borrelia burgdorferi and transmitted by insects and ticks. The multisystemic clinical picture initially includes erythema chronicum migrans with non-specific manifestations. During the following weeks and months, cardiac involvement, polyneuroradiculoneuritis and arthritis may be seen.

In isolated cases, pronounced Lyme hepatitis develops. The pathogen is often identifiable in liver cells and sinusoids. Treatment consists of doxycycline or erythromycin.

The epidemic (European) relapsing fever is induced by the spirochaete Borrelia recurrentis (obermeyeri), which is transmitted by lice. Following an incubation period of 3 to 15 days, there are sudden repeated (up to ten) attacks of fever separated by fever-free intervals together with parallel hepatomegaly and splenomegaly, cutaneous and mucosal bleeding (e.g. colon, nose), myalgia, arthralgia, iridocyclitis, facial paresis and meningism.

Jaundice is often observed. Histologically, signs of non-specific reactive hepatitis with spotty liver cell necrosis are generally detectable. (87–90)

3.6 Listeriosis

Listeria monocytogenes is most common in animals. Transmission to humans is effected through the secretions of infected animals or contaminated food (e.g. milk and dairy products, raw meat). An increased proneness to listeriosis is found in drug-related immunosuppression, pregnancy, liver cirrhosis, diabetes mellitus and AIDS. In connatal (displacental) transmission (= granulomatosis infantioptica), listeriosis generally leads to an abortion or premature delivery with meningocencephalitis and multiple organ abscesses, so that the neonate dies within a few days. • The disease course varies from uncharacteristic “flu-like” manifestations to (1) septic, (2) central nervous, (3) glandular or cutaneous, and (4) chronic septic forms with isolated organic affection. • Treatment: ampicillin and amoxicillin at high dosage are the remedies of choice.

Liver involvement is reflected in moderately elevated transaminases, histologically detected mononhistiocytic granulomas and miliary microabscesses (frequently with gram-positive rods) as well as occasional evidence of non-specific reactive hepatitis. (91, 93) (s. fig. 24.13)

3.7 Brucellosis

Brucellae are gram-negative, aerobic, non-motile, rod-shaped bacteria, with a natural reservoir in some mammals: B. abortus in cattle (Bang’s disease), B. melitensis (in goats and sheep, the “Malta fever” is a special form), B. suis (especially in pigs, the natural host of the Brucellae), B. ovis (in sheep) and B. canis (in dogs). The pathogens enter the host via skin lesions or mucosa (conjunctiva, respiratory tract, gastrointestinal tract).

Brucellosis is the generic term for diseases induced by the various Brucella species in animals and humans. Following an incubation period of approximately 14 days, headaches, pronounced fatigue, myalgia, arthralgia, swollen lymph nodes and especially undulant fever occur. Frequently, organ manifestations (cholecystitis, endocarditis, meningoencephalitis, nephritis, prostatitis, pneumonia, etc.) are in evidence. • Hepatosplenomegaly and moderate increases in transaminases and in alkaline phosphatase are found. Histologically, histiocytic granulomas are present (in 90–95% of cases), often with central necrosis, portal and peripheral infiltration and hyperplasia of the Kupffer cells. (100, 103, 105) Up to now, 24 cases of hepatic brucellosis have been reported in the literature. (101, 102) (s. fig. 24.12) They result from the caseation of a granulomatous reaction by persistent brucellae in macrophages. The imaging methods show central calcification and peripheral necrotic areas, which
imitate malignant tumours or pyogenic liver abscesses. In many patients, fatty infiltration of liver cells, lipofuscinosis and siderosis are found. Extensive focal necrosis may occur in infections with B. melitensis and B. suis. Severe courses, possibly with acute liver failure, are rarely observed. Occasionally, ascites appears. Hepatic abscesses are seldom. Fewer than 50 cases have been described in the literature. (101, 104) • The diagnosis is confirmed by serological tests, culture of pathogens or animal experiments. As treatment, the combination of rifampicin (900 mg/day) + doxycycline (200 mg/day) for 3 months or doxycycline + gentamycin, possibly also tetracycline + streptomycin, has proved effective. In chronic brucellosis, treatment with tetracycline must be repeated.

3.8 Rickettsiosis

Rickettsiae are gram-negative pathogens living as cellular parasites in the gastrointestinal tract of arthropods (especially lice, fleas, ticks and mites). They may be transmitted to human beings and cause endemic and epidemic rickettsioses, generally showing a typhoid-like clinical picture. Major rickettsioses include 

- Q fever (R. burneti), Boutonneuse fever (R. conorii) and 
- marine endemic spotted fever (R. typhi).

Following infection, the pathogens may spread haematogenously to all organs and colonize the endothelial cells of the small arteries and capillaries, so that partial or complete vascular obstruction ensues.

Each of the 10 Rickettsia species pathogenic to humans may cause concomitant hepatitis. Clinical findings include hepatomegaly with an increase in transaminases as well as (occasionally) in alkaline phosphatase and bilirubin. Histology reveals granulomas of round cells, granulocytes, proliferated stellate cells and polymuclear giant cells as well as spotty infiltrations with single-cell necrosis and portal infiltrates. (s. fig. 24.14) Chronic Q-fever hepatitis has been reported. Fatty granulomas typical of Q fever are frequently found in the liver lobules or in the portal tracts. Treatment consists of doxycycline, chloramphenicol or tetracycline. (106–113)

3.9 Tularaemia

This clinical picture was observed for the first time in Tulare, California in 1911 (G.W. McCoy). The causative pathogen was identified as Bacterium tularense by G.W. McCoy et al. (1912) and W.B. Wannzy et al. (1914). The gram-negative, aerobic and non-motile Francisella tularensis is transmitted to humans by arthropods infected by sick rodents, directly by the rodents themselves or through contaminated water.

After a short incubation period (1 to 3 days), a clinical picture develops comprising high fever, chills, lymphadenitis and local ulceration, occasionally also meningitis, pneumonia or pulmonary abscesses and mediastinitis. • In the course of this severe disease, liver granulomas up to 2 mm in diameter may occur with central necrosis, epithelioid cells and giant cells. The portal fields show inflammatory infiltration. Liver abscesses and the clinical picture of cholangitis or obstructive jaundice have also been observed; ascites is rarely seen. There is evidence of hepatomegaly together with the corresponding pathological laboratory parameters. Diagnosis is confirmed by serology or skin tests. Treatment consists of antibiotics (e.g. tetracycline, streptomycin, gentamycin, ampicillin). (114, 115)

3.10 Psittacosis

Chlamydia psittaci is the causative pathogen of ornithosis (psittacosis or parrot disease). It is transmitted to humans by birds via their droppings. The incubation period is 4 to 28 days. In the course of the occasionally severe pneumonia, concomitant hepatitis may be in evidence. (116, 118, 119) The Fitz-Hugh-Curtis syndrome rarely develops. (117, 120) (s. fig. 24.2) Clinical findings generally include hepatomegaly and slightly increased transaminases. Diagnosis of this infectious disease is confirmed by CFR. The treatment regimen consists of tetracycline.

3.11 Clostridium welchii

In the course of the rare systemic gas gangrene caused by Clostridium perfringens (gram-positive, anaerobic bacterium), severe clostridial hepatitis may ensue. Necrotic foci, abscesses and aerogenesis develop. The pathogens can be cultivated from biopsy material. A major harmful factor is the respective exotoxin, which sometimes causes pronounced haemolytic icterus. (121)

3.12 Tropheryma whippeli

Whipple’s disease (G.H. Whipple, 1907) with feverish, sprue-like symptoms is generally accompanied by polyadenopathy, arthritis, polyserositis and endocarditis or pericarditis. • Liver involvement occurs in the form of granulomas, in which macrophages loaded with bacteria are present. The gram-positive-positive Tropheryma whippeli has been identified as the causative pathogen. It is assigned to the group of Actinomycetes. (122, 123)

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3.13 Campylobacter colitits

The intestinal disease with fever and arthralgia caused by Campylobacter colitis may show findings corresponding to non-specific reactive hepatitis in terms of laboratory parameters and histology. (124, 125)

3.14 Rochalimaea

The Rochalimaea species (R. quintana, R. henselae, R. vinsonii, R. bacilliformis) are responsible for four clinical syndromes: (1.) cat-scratch disease, (2.) bacterial angiomatosis, (3.) bacterial peliosis hepatitis, and (4.) relapsing fever with bacteremia (so-called trench fever). • The cat-scratch disease (R. derm & et al., 1950) was first attributed to a new pathogen, named Afipia felis; more recent studies point to a species of Rochalimaea (Bartonella henselae) as the causative pathogen. The incubation period ranges from 3 to 20 days. Thereafter, feverish lymphadenitis with a molliform rash appears. Painful hepatomegaly is experienced. Transaminases are elevated. Diagnosis involves specific serological tests, PCR or liver biopsy. • Liver involvement is manifested by granulomas with occasional central star-shaped microabscesses, in which pathogens can be demonstrated, and by focal infiltrates, possibly also with single-cell necrosis. (126–130)

3.15 Actinomycosis

The abdominal form of the so-called ray-fungus disease (actinomycosis) is a non-contagious, mostly chronic infectious disease induced through the gram-positive, anaerobic rod-shaped bacterium Actinomyces israelii. It is a pseudomycosis. Under favourable conditions, this human saprophyte can cause enterococci.

Pronounced formation of granulomas or microabscesses and major (hyperdense) liver abscesses with cauliflower-like druses may be due to haematogenous spread of the pathogen to the liver (portal vein, systemic circulation) or, occasionally, to direct encroachment on the liver. The abscess pus contains the typical so-called sulphur granules. Treatment consists of penicillin G (e.g. 2 × 10 million U/day i.v. for approximately 4 weeks), ampicillin, tetracycline, clindamycin or metronidazole. (131–141)

3.16 Burkholderia pseudomallei

Meliodosis, which is caused by pathogens, is endemic in the different subtropical and tropical countries. Patients with diabetes mellitus are particularly susceptible to infection. Acute meliodosis displays large numbers of both localized and disseminated necrotic foci, which produce confluent abscesses, sometimes with a diameter of 2–3 mm. The presence of pathogens can be confirmed using Giemsa staining. Chronic meliodosis is characterized by epithelioid cell granuloma with giant cells and central necrosis. Pathogens (previously known as pseudomonas) are only rarely found in the foci themselves. (142)

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Rickettsiosis

Hepatitis B

Hepatitis C

Rheumatic Fever

Acute Hepatitis

Acute Hepatitis of Unknown Etiology

Acute Hepatitis C

Acute Hepatitis B
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