Infections of the Liver

15

Uzma Shah

Introduction

The portal vein carries blood from the gastrointestinal tract to the liver and in so doing carries microbes as well. The liver may therefore be involved in infections with a myriad number of microbial organisms. While some of these infections most commonly occur in the immunocompromised host, others affect the immune competence. Hepatic infections may be primary in nature or secondary, as part of systemic or contagious disease. The purpose of this chapter is to provide a brief overview of the various infections of the liver in the pediatric patient.

Bacterial Infection Involving the Liver

Gram-Positive and Gram-Negative Infections

There are several gram-positive and gram-negative bacterial infections that may lead to hepatic compromise. This includes infections with *Staphylococcus aureus* or the group A streptococcal species [1]. Common risk factors for

U. Shah, MD
Pediatric Hepatobiliary and Pancreas,
Pediatric Liver Transplant,
Massachusetts General Hospital for Children,
Harvard Medical School, Boston, MA, USA
e-mail: ushah@partners.org

Staphylococcus aureus infections include surgical wounds and the use of tampons in adolescents. Complications such as hypotensive shock may ensue. Hepatic manifestations of disease include elevation of serum transaminases and the appearance of jaundice. Progression of disease may lead to extensive hepatic necrosis and liver failure. On histology the liver may be punctuated with microabscesses and granuloma formation. Treatment of infection with clindamycin is recommended and antibiotics such as vancomycin or linezolid may be required for methicillin-resistant infections.

In a study in cirrhotic patients from Spain, extended-spectrum β-lactamase-producing *Enterobacteriaceae* were the main organism identified in sepsis, followed by bacteria such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and *Enterococcus faecium*. Septic shock (26 % vs. 10 %; $P < 0.0001$) and mortality rate (25 % vs. 12 %; $P = 0.001$) were significantly higher in infections caused by multiresistant strains. Third-generation cephalosporins were found to be clinically ineffective for treatment in these patients [2].

Clostridium perfringens has also been associated with hepatic disease. Clostridial infections in children may occur in the newborn period in the setting of necrotizing enterocolitis as well as in children receiving chemotherapy or following infections of puncture wounds. The development of gas gangrene is associated with a high mortality rate. Jaundice may develop in about 20 % of these patients and hepatic disease includes

abscess formation and the appearance of gas in the portal vein [3, 4]. Surgical debridement of the affected tissue and treatment with penicillin and clindamycin is warranted.

Listeria monocytogenes

Infections with *Listeria* in the neonatal period are described as severe, infrequent, and often associated with hepatic abscess formation. Predisposing factors include prematurity and in older children immunosuppression, diabetes mellitus, and cirrhosis. Treatment of infection is with ampicillin and gentamicin while a vaccine against the organism is being developed for use in immunocompromised hosts [5].

Salmonella and Shigella

In the developing world, *Salmonella* and *Shigella* infections are common. Typhoid fever in particular leads to systemic disease that frequently involves the liver. *Salmonella typhi* infection is acquired through contaminated food/water and presents with high fever and abdominal pain. While the serum transaminases rise, the bilirubin in contrast is minimally elevated. Cholecystitis and liver abscess formation may occur. The bacterial endotoxin-mediated hepatic compromise is treated with ciprofloxacin and ceftriaxone as first-line agents [6–8]. Blood cultures, enzyme immunoassays, and bone marrow cultures assist in diagnosis. Hepatitis may also occur with *Salmonella paratyphi A* and *B*, related paratyphoid fever. Treatment is recommended with cephalosporins or fluoroquinolones.

Shigella infections lead to dysentery or an acute diarrheal illness and are acquired from contaminated food and water. The infection is common in developing countries and hepatic manifestations include a cholestatic hepatitis [9, 10].

Yersinia

Yersinia enterocolitica infection in children presents with diarrhea, abdominal discomfort, and often a terminal ileitis that mimics Crohn disease. Hepatic involvement may occur with infections in the immunocompromised host such as those with cirrhosis or diabetes. It may manifest as multiple hepatic abscess formation. The mortality in such instances is as high as 50 % and treatment with fluoroquinolones is indicated [11].

Actinomyces

Pediatric infections with *Actinomyces israelii* occur in the immunocompromised host and include cranial, thoracic, and abdominal disease. It is a gram-positive anaerobic bacterium that leads to hepatic infection in 15 % of abdominal actinomycosis cases and often spreads from other contiguous abdominal sites. The disease process is usually indolent with nonspecific elevation of inflammatory markers and leukocytosis. The liver may be dotted with multiple abscesses and treatment includes intravenous penicillin or oral tetracycline. Surgical resection may be required for large abscesses [12, 13].

Legionella

Legionnaire disease, caused by infections with *Legionella pneumophila*, manifests as pneumonia and hepatitis. Characteristically, jaundice is minimal and hepatic steatosis and necrosis may be demonstrated on biopsy. Treatment of infection is with fluoroquinolones or azithromycin [14].

Gonococci

Gonococcal infections as seen in the Fitz-Hugh–Curtis syndrome present with perihepatitis and the associated right upper quadrant pain and fever. Patients frequently have a history of pelvic inflammatory disease with gonococci demonstrated on vaginal culture. Ceftriaxone is used in treatment of infection with resolution of the perihepatitis with treatment [15].

Brucellosis

There are multiple species of *Brucella* that may cause human disease. Acquired from contaminated sheep, pigs, cattle, and goat, clinical manifestations comprise an acute onset of fever, abdominal discomfort, and jaundice. Noncaseating hepatic granulomas are identified on biopsy. Surgical drainage of the abscesses

may be required and a combination of streptomycin and doxycycline is used for treatment [16–18].

Coxiella burnetii

Infections with the organism lead to Q fever, which is characterized by relapsing fevers, pneumonitis, endocarditis, and hepatitis. Characteristically, the serum alkaline phosphatase is elevated disproportionately to the mild rise in serum bilirubin and transaminases. Fibrin ring granulomas are seen on liver biopsy and treatment is with doxycycline [19, 20].

Bartonella

Bartonella henselae infection, as in "cat scratch disease," is associated with hepatosplenic necrotizing granulomas. Peliosis hepatis or blood-filled cysts are seen in infections in patients with concomitant AIDS. A papular dermatitis and pulmonary and neurological symptoms may also occur. The bacillary angiomatosis is treated with erythromycin, while doxycycline may be considered for treatment of visceral disease [21].

Other Gram-Negative Infections

Chlamydia trachomatis infections have been described in perihepatitis (Fitz-Hugh–Curtis syndrome) similar to that seen with gonococcal disease. The liver function tests are usually normal and azithromycin and doxycycline are used for treatment of the infection.

Rocky Mountain spotted fever is a tick-borne rickettsial infection which is characterized by the development of a maculopapular rash, fever, and hepatic disease. The latter consists of portal inflammation and vasculitis. Jaundice and increased liver enzymes are seen with disease. Hemolysis may lead to hyperbilirubinemia and biliary obstruction. In contrast, Ehrlichia (another tick-borne intracellular bacteria) infections are associated with liver injury due to proliferation within the hepatocyte and a concomitant immune response. Focal necrosis, fibrin ring granulomas, and cholestasis are seen. Treatment with doxycycline is indicated.

Spirochetes

Leptospirosis

Leptospirosis is carried by a variety of domestic and wild animals with human infection on exposure to urine or contaminated soil and water. Anicteric leptospirosis occurs in more than 90 % of cases. There is usually a biphasic illness, with the first phase characterized by fever and conjunctival injection. The second phase is associated with myalgias, nausea, vomiting, and abdominal pain. It is at this time that aseptic meningitis may occur and an increase in serum liver enzymes and jaundice is seen.

Weil disease is the icteric form of the infection and occurs in 5–10 % of patients. It too has a biphasic illness with an earlier phase that is marked by jaundice. High fever and renal manifestations with acute tubular necrosis develop in the second phase and often lead to renal failure. There is a high mortality. Hemorrhagic complications are frequent and follow immune complex deposition leading to capillary injury. Serological tests and cultures help in diagnosis. Doxycycline is usually used for treatment [22, 23].

Lyme Disease

Lyme infection occurs in various parts of the USA on exposure to ticks. It is caused by a tick-borne spirochete, *Borrelia burgdorferi*. Hepatic disease manifests with anorexia, nausea, vomiting, weight loss, and right upper quadrant pain. There is an increase in liver enzymes and the appearance of a rash called erythema migrans. The diagnosis of Lyme disease is confirmed by serology and the typical clinical history. Treatment is with oral doxycycline or azithromycin [24–27].

Tuberculosis

In developing countries where tuberculosis is endemic, hepatic disease is often seen. Granulomas with central caseation necrosis are

found on liver biopsy in 25 % of patients with pulmonary tuberculosis and in about 80 % of those with extrapulmonary disease. Similar granulomas may be found in immunocompromised individuals who have been vaccinated with the Bacillus Calmette–Guérin vaccine. Diagnosis is based on the identification of the acid-fast bacilli and treatment is with 4-drug therapy. Jaundice and an increase in serum alkaline phosphatase may also occur when there is miliary disease [28].

Syphilis

Infrequently seen in children, hepatic involvement may occur in secondary syphilis. Cholestatic hepatitis with congenital syphilis has been described. The frequency of hepatitis then ranges from 1 to 50 %. In addition to nonspecific symptoms such as anorexia and weight loss, a characteristic maculopapular rash involving the palms and soles is seen. Jaundice as well as hepatomegaly and right upper quadrant pain is described. Histological examination of the liver reveals hepatitis with spirochetes demonstrated on silver stain. Treatment of the infection is with penicillin [29].

Liver Abscess

Liver abscess formation usually follows an underlying problem such as immunocompromise, diabetes mellitus, surgery, or malignancy. Pyogenic abscesses may follow an episode of appendicitis, perforated bowel, or inflammatory bowel disease. A pyogenic liver abscess may also be the initial manifestation of hepatic malignancy.

Most abscesses are due to infections with *Escherichia coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, and *Streptococcus*. Anaerobic infections with *Bacteroides* may also occur. Additionally, *Clostridium*, *Actinomyces*, *Yersinia*, *Haemophilus influenzae*, *Listeria*, and *Staphylococcus* may lead to liver abscess formation. Disseminated fungal infections may lead to micro- or macro-abscess formation in an immunocompromised host. The patient typically presents with abdominal discomfort, severe right upper abdominal pain, and high fever. Physical examination identifies the tender hepatomegaly.

Ultrasound and CT scans are the initial imaging modalities of choice and allow small abscesses up to 1 cm in diameter to be identified. A CT scan identifies localization of the abscess and defines whether there is gas in the abscess. It allows for aspiration for culture or insertion of a drain when necessary. The treatment of pyogenic liver abscess is by drainage of the pus and initiation of appropriate antibiotic treatment. An indwelling catheter may be placed in the abscess cavity when the abscess is larger than 5 cm in size. Intermittent needle aspiration may be attempted. With multiple abscesses, it is only the large ones that need to be aspirated. Small abscesses are treated by antibiotic therapy alone.

The initial antibiotic treatment before culture results are available should be broadened to cover a number of organisms. It is usually with amoxicillin and an aminoglycoside as well as a third-generation cephalosporin. Anaerobic coverage may also be required with metronidazole. Treatment is intravenously for at least 2 weeks and then orally for up to 6 weeks. For streptococcal infection high-dose oral antibiotics may be required for 6 months. The mortality rate despite treatment is high and complications of delayed diagnoses include shock, pleural effusion with sepsis, and multiorgan dysfunction [30–37].

Parasitic Infections of the Liver

Protozoa

Malaria
Malaria is an infection by the protozoan species, *Plasmodia*. It is estimated that about 300–500,000,000 people are infected globally with these parasites every year. The major species differ in their life cycle as well as presence or absence of a hepatic phase. *Plasmodium falciparum* and *Plasmodium malariae* are not associated with a hepatic cycle, while *Plasmodium vivax* and *ovale* do have a persistent exoerythrocytic phase in the liver. The extent of hepatic

injury relates to the species and the severity of infection. Active hemolysis leads to an increase in the unconjugated fraction of bilirubin. However, once hepatocellular dysfunction sets in, the conjugated fraction of bilirubin begins to rise as well. Liver failure leads to liver synthetic function impairment and a decrease in serum albumin and prolonged prothrombin time. Hyperglycemia and lactic acidosis are late complications. There is a high mortality with disease. Congenital malaria, although rare, may also lead to severe and even fulminant liver disease in the newborn infant. The diagnosis of malaria requires history, physical examination, and the identification of the parasite on blood smear. Rapid antigen detection assays are now available. Treatment depends on the species of *Plasmodium*. Chloroquine may be effective, but in many parts for the world chloroquine resistance is increasingly seen, and in these areas treatment requires mefloquine and quinine. Pyrimethamine-sulfadoxine and proguanil are also used for treatment [38, 39].

Babesiosis

Babesia is transmitted by the deer tick *Ixodes scapularis*. Infection manifests as fever, anemia, and hepatosplenomegaly. Infected individuals typically have anemia, hemoglobinuria, and hemophagocytosis on bone marrow examination. Treatment is with azithromycin and atovaquone or clindamycin and quinine. In complicated cases exchange transfusions may be required.

Leishmaniasis

Leishmaniasis, caused by *Leishmania donovani*, is transmitted by the sand fly and is endemic in the Mediterranean, Central Asian, and South Asian regions as well as Africa, South America, and New Guinea. A papular or ulcerative lesion occurs at the bite site and is followed over a period of time, ranging from months to years, with fever, weight loss, diarrhea, and massive hepatosplenomegaly. Hepatocyte necrosis is followed by cirrhosis and complications of chronic liver disease. The diagnosis is based on characteristic clinical features, history, and the identification of the parasite on Wright, Giemsa, Leishman, or Jenner staining of buffy-coat preparations of peripheral blood or aspirates from marrow, spleen, liver, lymph nodes, or skin lesions spread on a slide to make a thin smear. Pancytopenia and an increased predisposition to secondary bacterial infections such as pneumococcal infections and tuberculosis may occur. Cutaneous pigmentation may also be seen. Treatment of infection is with the pentavalent antimonials. Alternative parenteral agents include liposomal amphotericin B and paromomycin. Miltefosine, a phosphocholine analogue, has also been used for treatment [40–45].

Toxoplasmosis

Toxoplasma gondii infection may be acquired congenitally or by the ingestion of oocytes from contaminated meat, soil, and water. Hepatic involvement may occur with severe disseminated infection. Patients typically present with fever, headache, lymphadenopathy, and hepatosplenomegaly. Myocarditis and encephalitis may also occur. The diagnosis is made by the identification of specific antibody on enzyme immune assay, and treatment is with a combination of pyrimethamine, sulfadiazine, and folinic acid [46–49].

Entamoeba

Amoebic Liver Abscess

Amoebic infections of the liver occur commonly in the developing world. Patients present with abdominal pain and an enlarged liver. There may be a history of a preceding diarrhea. Pulmonary features as well as pericardial involvement and peritonitis may occur but are very rare. The diagnosis of amoebic liver abscess is based on a good history, clinical exam, imaging, and serological analysis. However, it is important to note that serological testing may need to be interpreted with caution as antibodies may remain elevated for several years after treatment. Aspiration may be attempted when the diagnosis is unclear. There is a characteristic reddish-brown anchovy paste on aspiration. Treatment includes antibiotics such as metronidazole for a month or if necessary intravenously for 7–10 days. Tinidazole or

chloroquine may be used [50–53]. An oral luminal amebacide, such as diloxanide furoate or iodoquinol, is used following the course of metronidazole for an additional 7–10 days.

Helminths

Although liver infections with helminthes occur infrequently in developed countries, in contrast, hepatic disease with nematodes is seen often in the developing world.

Nematodes

Toxocariasis

Toxocara canis and *cati* infect dogs and cats, respectively, and may ultimately lead to human disease. Visceral larva migrans is seen commonly in children with a history of pica ingestion. It presents with fever, hepatomegaly, urticaria, and an increased eosinophil count. The infection leads to cholestatic hepatitis and liver abscess formation. Pulmonary disease with asthma and pneumonia may be seen and neurological involvement with seizures and encephalopathy may also occur. Migration into the eyes is associated with visual loss. A liver biopsy may be necessary and enzyme immunoassays confirm diagnosis. Treatment of infection is with mebendazole or albendazole [54, 55].

Ascariasis

Ascaris lumbricoides affects at least one million people in the developing world. Infection is through ingestion of contaminated fruits and vegetables. There may be respiratory symptoms with cough and wheezing and occasional hepatomegaly. Infection of the biliary tree leads to calculus formation. Obstructive jaundice, cholangitis, and liver abscesses may be seen. Treatment is with mebendazole, albendazole, or pyrantel pamoate. Endoscopic or surgical interventions may be required for intestinal or biliary obstruction [56].

Strongyloidiasis

Strongyloides stercoralis is prevalent mostly in the tropics. The larvae penetrate the skin, are carried to the lungs, and then are swallowed to reach the intestine where maturation occurs. Symptoms of acute infection include pruritus, abdominal discomfort, and diarrhea. Hepatic infection leads to jaundice and cholestasis. Periportal inflammation and eosinophilic granulomas are seen on biopsy. Diagnosis is achieved by serological tests or the identification of the larvae in the stool or intestinal biopsy specimens. The treatment for acute infection is ivermectin or albendazole.

Trichinosis

Trichinella spiralis is acquired through the ingestion of contaminated raw pork. The larvae may be found in the liver and gallbladder. The clinical manifestations include diarrhea fever, marked eosinophilia, and obstructive jaundice. Diagnosis is suggested by the characteristic history and serological analysis. A muscle biopsy may help confirm the diagnosis. Treatment is with antihelminthics such as albendazole or mebendazole [57, 58].

Trematodes

Schistosomiasis

Schistosoma infection is found in various parts of the world, most commonly in areas of Africa and the Middle East. *Schistosoma intercalatum* in particular causes liver disease. The cercariae penetrate skin and proceed to the lungs and in the liver. The adult fluke may also migrate to the mesenteric vasculature. The eggs induce a granulomatous response. Clinical features of schistosomiasis include headache, fever, cough, a tender liver, and diarrhea. Chronic liver disease is described with portal hypertension, gastroesophageal varices, ascites, and splenomegaly. Chronic infection may be associated with an increased susceptibility to Salmonella infections

and frequently coexist with hepatitis B and C viral infections in endemic areas. This leads to progression of liver disease and an increased predisposition to hepatocellular carcinoma. Stool tests and serological analysis aid in diagnosis. A liver biopsy demonstrates periportal fibrosis. The infection is treated with praziquantel.

Fascioliasis

Fasciola hepatica is caused by a liver fluke and leads to acute, chronic, or obstructive hepatic disease. Clinical features are marked by fever, right upper quadrant pain, and eosinophilia. An enlarged liver is appreciated on exam. The chronic obstructive phase is characterized by intrahepatic and extrahepatic bile duct inflammation. This leads to cholangitis, stone formation, and obstruction. The diagnosis is by antibody detection or the identification of the eggs in stool, duodenal aspirate, or bile. Treatment is with triclabendazole.

Clonorchiasis

Clonorchis sinensis infection is acquired by the ingestion of contaminated seafood. The clinical features are those of fever, abdominal pain, and diarrhea. On physical exam a tender hepatomegaly is appreciated. Biliary obstruction and stone formation may also occur. There may be recurrent pyogenic cholangitis and cholangiocarcinoma may arise. The diagnosis is by the detection of characteristic eggs in the stool or the identification of the flukes in the bile ducts or gallbladder. Treatment is with praziquantel [59–64].

Cestodes

Echinococcosis

Echinococcus granulosus is also found in many areas of the world. Infection occurs through the ingestion of contaminated food. The liver is most commonly involved followed by the lungs,

kidney, spleen, and brain. Cysts in the liver are called hydatid cysts. The cyst has characteristic layers on imaging with most patients being asymptomatic. However, as the cyst increases in size, it may lead to abdominal pain and a tender enlarged liver. The cyst may rupture into the lungs or may induce a life-threatening anaphylactic reaction. It may also rupture into the biliary tree and may induce cholangitis or obstruction. Rare complications include pancreatitis, portal hypertension, and the Budd–Chiari syndrome. Infection of the bile ducts may lead to liver abscess formation as well. Diagnosis requires the identification of ring-like hepatic calcifications on plain X-ray and further imaging with an ultrasound or computed tomography (CT) scan for confirmation of diagnosis. Percutaneous aspiration of the cyst may be associated with anaphylactic reactions and therefore was traditionally discouraged. However, aspiration may be attempted under carefully controlled circumstances. Treatment has included surgical cystectomy, marsupialization, and in advanced cases hepatic resection. Calcified cysts do not need to be removed. Percutaneous drainage may be attempted for complicated cysts. Administration of albendazole for 8 weeks is recommended [65].

Fungal Infections of the Liver

Candidiasis

Candida albicans is an infection that is frequently seen in severely immunocompromised individuals. It may lead to hepatic abscess formation and multiorgan disease with dissemination. Seeding of the portal vein leads to the formation of small abscesses in the liver. A CT scan of the abdomen is the most useful test to identify these tiny abscesses. Clinical features include fever, abdominal discomfort, and tender hepatomegaly. The serum aminotransferases, bilirubin, and alkaline phosphatase levels are elevated. There is a very high mortality rate. Treatment of infection is with intravenous amphotericin B [66, 67]. Alternative treatment includes fluconazole, liposomal amphotericin, caspofungin, micafungin, and anidulafungin.

Histoplasmosis

Histoplasma capsulatum infection is acquired via the respiratory tract in patients with immunodeficiency and may manifest with fever, hepatosplenomegaly, and lymphadenopathy. A liver biopsy can be done to identify yeast in areas of caseation necrosis or granulomas. Treatment is amphotericin B or fluconazole [68, 69].

Viral Infections of the Liver

Hepatitis A

Hepatitis A virus (HAV) is an enterovirus belonging to the *Picornaviridae* family. It has an icosahedral shape and lacks an envelope. The virion measures 27–28 nm in diameter and there is only one known serotype. The HAV genome consists of a positive sense RNA that is 7.48 kb long, single stranded, and linear. HAV RNA has a long open reading frame consisting of 6,681 nucleotides [70].

Numerous strains of the virus exist with considerable sequence variability. Human HAV is grouped into genotypes 1, 2, 3, and 7. Simian strains belong to genotypes 4, 5, and 6. The antigenic structure of human HAV is highly conserved [71]. Differences in the genome may play a role in the development of fulminant hepatic failure [72].

The incidence of hepatitis A virus infection has declined in the USA since 1995. Since some infections are asymptomatic, the true number of infections may be underreported. Most infections occur among children aged 5–14 years. In the USA the epidemiology of infection in 2006 was unknown in about 65 % of patients; 15 % was attributed to international travel, 12 % contact with the patient who had hepatitis, 10 % men having sex with men, 9 % from contaminated food water, 7 % children or employee in a day-care center, 4 % contact with a day-care child or employee, and 2 % with injection drug use [73]. In the developing world where there are poor hygiene conditions, children are infected early in life. It has been shown that almost 100 % of children in these countries have immunity by about 5 years of age. It has also been shown that symptomatic infection is more common in older children [74–77].

The primary transmission is fecal–oral, by person-to-person contact, or through ingestion of contaminated food/water. Parenteral transmission has been described but is rare. The risk of perinatal transmission is very small and transmission of the infection during the neonatal period is also rare. However, it has been described in neonatal intensive care units attributed to transfusion of contaminated blood or plasma and horizontal spread from infected persons [78, 79].

The virus infects the liver and the pathogenesis of injury is not yet well defined. Immunologically mediated injury to hepatocytes seems to be the likely mechanism.

HAV hepatitis is an acute infection and does not develop into chronic disease. There may be a prolonged or relapsing course with significant cholestasis. A relapsing course, occurring over a 6–10 week period, is observed in approximately 10 % of patients with acute hepatitis. Rarely acute hepatic failure may occur. The incubation period is short from 2 to 4 weeks. In previously healthy children, the morbidity and mortality are low but are higher in older children and adults. Younger children are usually asymptomatic and jaundice may develop in only 20 % of these patients. Icterus is seen more often in children older than 5 years of age. HAV infection is not associated with a higher mortality in pregnant woman.

The clinical features are those of anorexia, nausea, vomiting, and abdominal pain. Myalgias and diarrhea may also occur. Dark urine precedes other symptoms in approximately 90 % of infected people. The symptoms of abdominal discomfort last from a few days to several weeks and usually decline as jaundice becomes manifest. Complete clinical recovery is achieved in about 60 % of patients within 2 months. The overall prognosis is excellent although a few infections may be associated with fatal complications. Acute hepatic failure is seen rarely in children. The case fatality rate in individuals older than 49 years is 1.8 % compared to an overall rate

of 0.3 % in persons of all ages. The fulminant failure usually becomes obvious in the first week of illness in the majority of patients. There is an increase morbidity and high risk of liver failure in the elderly and those with chronic liver disease and HIV [80–85].

Unlike hepatitis B virus infection, arthralgias, rashes, vasculitis, and glomerular nephritis are uncommon with acute hepatitis A. Extrahepatic manifestations include myocarditis, renal failure, optic neuritis, transverse myelitis, polyneuritis, and cholecystitis. Aplastic anemia and red cell aplasia may occur. Autoimmune hepatitis has also been described following infection with this virus.

Diagnosis

The diagnosis of infection is by the detection of specific antibodies in serum. An elevation of anti-HAV IgM indicates an acute infection and is detectable in the serum with the onset of symptoms and may remain positive for approximately 4 months. Some patients may have low levels of IgM antibody for almost a year after the initial infection. IgG antibody remains present for life and indicates previous infection or vaccination. Testing for the RNA is limited to research. The RNA can be detected in body fluid such as serum, stool, and liver tissue.

Vaccination against the infection is now licensed for use after 12 months of age. Universal childhood vaccination was adopted in 2006 with the hope of eliminating transmission in the USA. This led to a decline in incidence rates among children in high-risk population for the virus. In the USA, greatest risk is to healthy individuals traveling to endemic areas, men who have sex with men, patients who are positive for HIV, and patients with underlying chronic liver disease or drug use. There are no specific medications to treat acute hepatitis A.

Administration of serum immunoglobulins have been the mainstay in preventing infection. The availability of the vaccine has rendered the use of immunoglobulin for preexposure prophylaxis relatively unnecessary. The vaccine has also been used for post-exposure prophylaxis since the early 2000s. The Advisory Committee on Immunization Practices suggests that those who have recently been exposed to the virus and have not been vaccinated previously be given a single dose of the vaccine or immunoglobulin as soon as possible ideally within 2 weeks of exposure. Since immunoglobulin preparations are derived from blood products, there is concern with their use. Post-exposure prophylaxis with immunoglobulin can be administered at the same time as the initiation of active immunization with the vaccine. Patients who have concomitant chronic liver disease particularly need to be protected against HAV and the vaccine is recommended for these individuals [86–89].

Hepatitis E

The hepatitis E (HEV) virus is a small RNA virus that is 32–34 nm in diameter. It is a non-enveloped, icosahedral particle that belongs to the family Hepeviridae. It contains three open reading frames (ORF). The open reading frame [ORF] 1 includes nonstructural proteins. ORF2 encodes the virus capsid protein and ORF3 encodes a protein of unknown function. Details of replication in the liver cells and release from infected cells remain unknown. They are four different genotypes. Genotype 1 is found in Asia and genotype 2 from Mexico and Western Africa. The USA has genotype 1, 2, and 3 infections. Genotype 3 has also been reported in several European countries and genotype 4 from China, Taiwan, Japan, and Vietnam. All genotypes belong to a single serotype [90–93].

There have been several epidemics of the virus in the Indian subcontinent as well as Central Asia, Middle East, and Africa. The overall attack rates ranges from 1 to 15 % and is higher for adults than for children. In children attack rates are from 0.2 to 10 %. There is a high mortality among pregnant women. In endemic areas hepatitis E accounts for 50–70 % of cases of sporadic acute hepatitis. In those countries that are non-endemic, the infection is related to travel to

endemic areas. A few patients are asymptomatic and are not jaundiced although most patients are icteric [94].

The virus is transmitted through the ingestion of contaminated food and water. The outbreaks frequently follow the monsoon season. Secondary attack rates among household contacts range from 0.7 to 2.2 %. It is thought that contamination of water sources, subclinical infection, animal reservoirs, and prolonged fecal shedding lead to persistence of the virus in communities.

In countries such as India, antibodies to the hepatitis A virus are almost universally detectable by early childhood or adolescence. However, antibody development to hepatitis E in contrast remains uncommon.

The infection has an incubation period of about 4–5 weeks. The virus can be detected in the stool approximately 1 week before the onset of illness and for up to 2 weeks after that. Fecal shedding continues for about 4 weeks from the onset of illness. Histopathologic features of the infection are similar to those of other forms of acute hepatitis. Massive necrosis is seen rarely. Chronic HEV viremia with the genotype 3 virus has been reported in some kidney and liver transplant patients in Europe, and it has been suggested that such infection may potentially lead to chronic liver disease [94].

The symptoms of hepatitis include fever, abdominal pain, anorexia, nausea, and vomiting. There is a period of cholestasis where the stools are clay colored and the urine is dark. Pruritus and a transient macular rash may be seen. Physical exam demonstrates jaundice and an enlarged tender liver. Serum transaminases are elevated and there is a conjugated hyperbilirubinemia. Ultrasound demonstrates a mildly enlarged liver.

Viral infection with HEV is self-limited and case fatality rates of 0.5–4 % have been described. Pregnant women particularly those in the second and third trimester are affected more frequently and have a worse outcome. The mortality in these patients is from 5 to 25 %. In an epidemic in India, clinical hepatitis developed in 17.3 % of pregnant women. Fulminant hepatic failure was seen in approximately 22 % of the infected pregnant women with an increased frequency of complications.

The diagnosis requires the detection of the virus in stool and serum. PCR is done to look for HEV RNA. Enzyme immune assays for the detection of IgM and IgG antibody have been developed. The presence in serum of IgM antibody indicates acute infection, and the presence of IgG indicates past disease.

Treatment is supportive with no specific medication. Prevention of hepatitis E in endemic areas comprises of improved hygiene. The antibody is not fully protective as seen with the occurrence of large epidemics among adults living in endemic areas. Candidate vaccines have been developed and are being currently studied in Nepal. An IgG antibody was observed after the third vaccine dose although only 56 % of the volunteers had a high antibody titer by the end of the study [95]. The vaccine may potentially be useful for travelers to endemic areas.

Hepatitis B

Hepatitis B virus (HBV) infection is a worldwide health problem, which can cause acute liver failure, acute hepatitis, chronic hepatitis, cirrhosis, and liver cancer. It is most prevalent in Asia, Africa, southern Europe, and Latin America, where the hepatitis B surface antigen (HBsAg) positive rate in the general population ranges from 2 to 20 %. Approximately two billion people in the world have been infected by HBV and more than 350 million are chronic HBsAg carriers. In endemic areas, HBV infection occurs mainly during infancy and early childhood. Mother-to-infant transmission accounts for approximately half of the chronic HBV infections. In contrast to infection in adults, HBV infection during early childhood results in a much higher rate of persistent infection and long-term serious sequelae such as liver cirrhosis and hepatocellular carcinoma (HCC). HBV carriers have a lifetime risk of developing HCC in up to 25 % and an incidence of cirrhosis of 2–3 %/year [96, 97].

Hepatitis B virus is an enveloped DNA virus that is a member of the Hepadnaviridae family. It has several important structures that include the surface antigen, the core antigen, and e antigen. Various tests have been developed to these different structures to help make a diagnosis of hepatitis B. Ten genotypes (A to J) and several subtypes have been described. Genotype A is prevalent in North America and Europe. The virus is transmitted predominantly by the parenteral route, sexual contact, and perinatal exposure [98].

Acute illness may have varying manifestations, and while the majority developed antibodies to the infection and immunity, 10–15 % go on to develop chronic disease and approximately 1 % will have fulminant failure. After exposure, the risk of developing chronic infection is indeed higher for newborns (90 %) than for infants and children <5 years of age (25–30 %) or adolescents and adults (<5 %) [99]. To reduce mother-to-child transmission, the World Health Organization recommends the administration of both the vaccine and hepatitis B immunoglobulins (HBIG) to newborns of HBsAg-positive mothers within 24 h from birth (90–98 % protection rate) [100, 101]. HBsAg and HBV DNA can be detected in breast milk of chronic carriers, but no increased risk of transmission to a breast-fed infant has been shown and breastfeeding is currently recommended after proper infant immunization [102].

Neonates with the infection rarely show any signs of disease. There may be a transient mild acute hepatitis or chronic persistent hepatitis. There is no specific therapy for acute infection for neonates.

Three phases of chronic hepatitis B have been identified: the immune-tolerant phase, the immune-active phase, and the inactive phase. Most children with chronic HBV infection are immune tolerant, with high viral replication, positive hepatitis B envelope antigen (HBeAg), high HBV deoxyribonucleic acid (DNA) levels, and normal levels of aminotransferases [103]. This pattern is mainly seen in children infected at birth. The immune-tolerant phase may last long into adulthood; however, some children go into the immune-active phase. This phase is marked by active inflammation and elevated aminotransferases and may develop into fibrosis over time.

Most individuals with sudden elevations of aminotransferases undergo spontaneous HBeAg/anti-HBe seroconversion. After HBeAg clearance, aminotransferase levels gradually return to normal limits, with anti-HBe developing spontaneously. The majority of individuals who demonstrate this clearance enter an "inactive carrier" state with normalization of aminotransferases, a reduction in HBV DNA levels, and improvement in hepatic inflammation. A fraction of patients retain hepatic inflammation with elevated aminotransferases and HBV DNA and remain in the immune-active state. There is a greater risk for the development of cirrhosis and HCC. Risk factors that have been associated with progressive hepatic inflammation and subsequent complications include HBV genotype, persistent viremia, and specific mutations in the HBV genome. The optimal goal of antiviral therapy for chronic HBV infection is to eradicate HBV and to prevent its related liver complication by shortening the duration of liver inflammation. However, due to the limited effect of available therapies in viral eradication, the goal of current antiviral therapy for hepatitis B is to reduce viral replication, minimize the liver injury, and reduce infectivity [104] (Table 15.1).

The guidelines for treatment are represented in Fig. 15.1.

Treatment Options
Interferon-Alpha
IFN-alpha is delivered by subcutaneous injection and was the first of the approved therapies for HBV. Predictors of IFN responsiveness include active hepatitis, low HBV DNA levels (<1,000 pg/mL), high serum alanine aminotransferase ALT(>2× ULN), short duration of disease, non-Asian ethnic origin, and horizontal transmission. On the basis of European experience, consensus recommendations for the use of IFN-alpha for HBV infected children were developed. The main goals of therapy, according to these recommendations, were to accelerate HBeAg clearance in children with HBeAg and HBV DNA positivity, with low-intermediate HBV DNA levels and

Table 15.1 Phases of chronic hepatitis B infection

Phase	Laboratory results and histology	Note
Immune tolerant	HBsAg and HBeAg detectable	Biopsy not indicated
	HBV DNA >20,000 IU/mL (>105 copies/mL)	Antiviral therapies generally ineffective
	ALT normal	Risk of drug resistance if treated with nucleos(t)ide analogs
	Absent or minimal liver inflammation and fibrosis	Continued monitoring
HBeAg+immune active	HBsAg and HBeAg remain detectable	Most asymptomatic
	HBV DNA >20,000 IU/mL (>105 copies/mL)	Biopsy
	ALT persistently elevated	Rule out other liver diseases
Inactive HBsAg	HBsAg present	Age at serconversion influenced by HBV genotype
	HBeAg undetectable, anti-HBe present	Risk of developing cirrhosis declines
	HBV DNA <2,000 IU/mL (>104 copies/mL) or undetectable	Risk of developing HCC
	ALT normal	Biopsy generally not indicated
	Absent or minimal liver inflammation, fibrosis regresses over time	Continued monitoring
Reactivation of HBeAg-negative, immune active	HAsAg present	Occurs in 20–30 % of patients
	HBeAg remains negative and anti-HBe positive	"e-antigen-negative" hepatitis B
	HBV DNA levels >2,000 IU/mL (>104 copies/mL)	Liver biopsy indicated, especially if ALT raised
	ALT normal or elevated	Treatment should be considered if moderate/severe inflammation of fibrosis present
	Active liver inflammation ± fibrosis	

Modified from Jonas et al. [104]

abnormal aminotransferase enzymes, ages 2 years or older. IFN therapy is less likely to be of benefit in children with perinatally acquired infection who have normal or minimally elevated aminotransferases. The recommended treatment regimen for IFN-alpha is five to ten million units per square meter thrice weekly by subcutaneous injection for 4 to 6 months. The response rates are variable, depending on route of acquisition, ethnic origin, disease activity, and treatment regime. Adult data suggest that HBeAg-negative chronic disease should be treated for 12 months, whereas others demonstrate that longer durations of treatment of 24 months increased sustained response rates [105]. Pretreatment with corticosteroids ("priming") and their withdrawal before commencing IFN-alpha may exacerbate the host immune response, facilitating seroconversion. The benefit, however, remains unproven and is associated with the risk of precipitating fulminant liver failure. IFNα is thought to simply accelerate seroconversion, as many patients who do not respond to treatment may still seroconvert to anti-HBe later in life [106]. In a series, 74 children were followed for 7 years. In treated patients with elevated baseline ALT levels HBsAg clearance was observed in 4–15 % of children treated with IFN (15–25 % of responders), compared to 0–10 % of controls [106].

IFNα is contraindicated in children with decompensated cirrhosis, cytopenias, and autoimmune disease. Side effects of IFNα treatment included fever and flu-like symptoms, behavioral disorders, gastrointestinal disorders, and
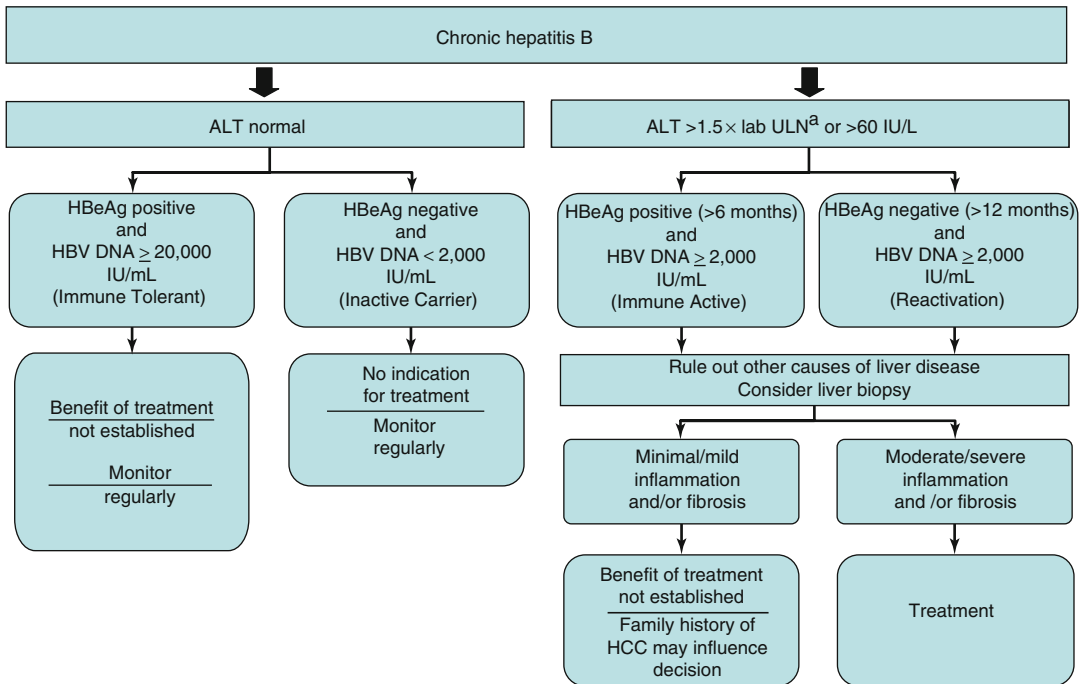
Fig. 15.1 HBV antiviral treatment in children (Modified from Jonas et al. [104])

neutropenia. Furthermore, IFNα was shown to temporarily affect growth. Pegylated interferon-alpha (PegIFN) has not yet been approved for the treatment of chronic hepatitis B in children.

Lamivudine

Lamivudine is an orally administered pyrimidine nucleoside analogue. It prevents replication of HBV in infected hepatocytes, is incorporated into viral DNA leading to chain termination, and competitively inhibits viral reverse transcriptase. Viral response was achieved by 23 % of children receiving lamivudine after 1-year treatment (compared to 13 % in the control group). The response increased to 35 % in children with ALT levels of at least twice the ULN [107]. At the end of 2–3 years of treatment, the response rate was 56 % for children receiving lamivudine in the absence of resistant mutations. Resistance rates increased over time (24 % after 1 year of treatment, 49 % at 2 years, and 64 % at 3 years) [108].

The recommended treatment dose is 3 mg/kg/day (maximum 100 mg/day), administered orally once daily. Longer treatment leads to higher resistance rates and it is therefore recommended that lamivudine be discontinued after 6 months for lack of complete viral suppression or if YMDD mutants emerge. Alternative therapy should be considered with severe and protracted transaminitis.

Combination therapy with lamivudine/IFNa (either concurrent or sequential) proved to be more effective than single drugs alone in adult patients with elevated ALT levels [109]. Three studies in children investigated therapy in treatment-naïve children with elevated ALT levels. Although no difference was found between different combination strategies, the children reached 30–60 % seroconversion to anti-HBe and 9–17 % to anti-HBs [110]. As no large clinical trials have been conducted so far, advantages of combination therapy over monotherapy in children are still unclear.

Adefovir

Adefovir dipivoxil is a purine analogue approved to treat children with chronic hepatitis B aged 12 years and older. 23 % of patients

aged 12–17 years achieved viral response after a 48-week treatment with adefovir (compared to 0 % of placebo-treated subjects). The efficacy on HBV DNA suppression and ALT normalization was less significant in younger children (15 % vs. 3 %) [111]. While mutations are rare in children, adefovir-resistant mutations are reported in more than 20 % of HBeAg-positive adults after a 5-year treatment [112]. A proximal renal tubular toxicity is a side effect of adefovir, which has been rarely reported in adults, but not in children. Patients with HBeAg-positive chronic HBV infection should continue on treatment for at least 6 months after seroconversion with discontinuation of treatment if there is incomplete viral suppression after 24 weeks.

Entecavir
Entecavir is a carbocyclic analogue of 20-deoxyguanosine that has proved to be effective in adult patients [113]. Resistance is rare, even after 5 years of treatment [114]. It has been approved by the FDA for treatment of adolescents aged 16 years or older. The recommended dose is 0.5 mg once daily for nucleoside-naïve patients and 1 mg/day for lamivudine-resistant patients. A phase III clinical trial in children as young as 2 years old is underway.

New Drugs
Telbivudine is an L-nucleoside analogue with a potent antiviral activity and a safety profile similar to lamivudine (although myopathy and peripheral neuropathy were reported in adults). Resistance rate is lower than lamivudine but higher than adefovir. Therefore, telbivudine is only used in combination with other antiviral drugs. A phase I clinical trial is ongoing on children 2–18 years of age [115].

Tenofovir disoproxil fumarate is a nucleoside analogue originally licensed for treatment for HIV infection. The dose for tenofovir in adults is higher than that of adefovir (300 mg/day) and has a greater antiviral activity than adefovir in clinical trials (undetectable HBV DNA in 76 % of patients vs. 13 % of adefovir-receiving subjects after 48 weeks of treatment) [116]. No genotypic resistance to tenofovir has yet been confirmed. A phase III trial is ongoing on 12–17-year-old patients [117] (Table 15.2).

Hepatitis D

Hepatitis delta virus (HDV) is closely associated with hepatitis B virus (HBV) infection. The simultaneous presence of HBV is required for complete virion assembly and secretion. HBV replication is suppressed in most HDV-infected individuals. The HDV genome is a small RNA molecule and expresses the HDV antigen.

Coinfection of HBV and HDV results in acute hepatitis that is usually transient and self-limited. However, a high incidence of liver failure has been reported among drug users [118].

HDV superinfection of a chronic HBsAg carrier may present as severe acute hepatitis in a previously unrecognized HBV carrier or as an exacerbation of preexisting chronic hepatitis B. Progression to chronic HDV infection occurs, while HBV replication is usually suppressed [119].

In the Western world, where the predominant HDV genotype is genotype 1 [120], acute hepatitis D has an increased risk of a fulminant disease. Chronic HDV infection exacerbates the preexisting liver disease in patients with hepatitis B with rapidly progressive cirrhosis [121]. In the Far East, where the predominant genotype is genotype 2, there is a less frequent fulminant hepatitis with acute HDV infection and rapidly progressive liver disease with chronic HDV. Severe outbreaks of acute hepatitis D with a high incidence of liver failure have been reported in South America with genotype 3.

Treatment
Interferon
The only drug approved at present for treatment of chronic hepatitis D is IFNα. In the largest multicenter trial, 61 Italian patients with chronic hepatitis D were randomly assigned to receive IFNα in doses of 5 MU/m^2 three times weekly for 4 months, followed by 3 MU/m^2 three times weekly for an additional 8 months or placebo [122]. They were followed for another 12 months.

Table 15.2 Available treatments for chronic hepatitis B in children

Treatment	Licensing	Dose	Duration	Advantages	Disadvantages
IFNa	≥12 months	5–10 M units/m² SC 3×/week	6 months	No resistance Usable in young children	Side effects Parenteral administration Not for use in decompensated cirrhosis or transplantation
Lamivudine	≥3 years	3 mg/kg po once daily (max 100 mg/day)	≥1 year	Few side effects Usable in young children Oral administration	High resistance rate
Adefovir	≥12 years	10 mg po once daily	≥1 year (+6 months after HBeAG seroconversion)	Partially effective in lamivudine resistant patients Oral administration	
Entecavir	≥16 years + Phase III (2–17 years)	0.5 mg/day once Daily (1 mg/day for Lamivudine-resistant pts)	≥1 year (+6 months after HBeAG seroconversion)	Partially effective in lamivudine resistant patients Oral administration	Not approved for children < 12 years resistant mutations
PegIFN	Phase III (2–18 years)	180 ug/week	6 months	No resistance Once weekly administration	Side effects Parenteral administration
Telbivudine	Phase 1 (2–18 years)	600 mg/day once daily	≥1 year	Few side effects Oral administration	High resistance
Tenofovir	Phase III (12–17 years)	300 mg/day once daily	≥1 year	High response rate No resistance identified Few side effects Oral administration	No available preparation for young children Reduced mineral density

Modified from Paganelli et al. [98]

Twenty-five percent of the 31 treated patients had normal serum transaminases versus none of the 30 controls at the end of the study. All but one of the responders had biochemical relapse after discontinuation of treatment.

Pegylated Interferon

There is little data with pegylated interferon in the treatment of chronic hepatitis D. The largest published study included 38 patients who were treated with pegylated IFN alfa-2b (1.5 MU/kg/week) alone or in combination with ribavirin for 48 weeks [123]. Patients were maintained on pegylated IFN for an additional 24 weeks and then followed for 24 weeks. At the end of follow-up, HDV RNA was not detectable in 21 %. The response rate was similar in the monotherapy and combination therapy groups suggesting that ribavirin had no effect on viral clearance. A higher virologic response rate (43 %) was found in another study with 12 months of pegylated IFN [120].

Combination therapies with nucleoside and nucleotide analogues have not been encouraging and there are currently no standard recommendations for the treatment of pediatric HDV infection. The mainstay of prevention of HDV infection is vaccination against its helper virus, HBV.

Hepatitis C

HCV is an RNA virus that affects >180 million individuals worldwide. In the USA, antibodies to HCV are present in approximately 0.2 % of children ages 6–12 and 0.4 % of those ages 12–19. Overall, approximately 28,000 new HCV infections occur in the USA each year, although the specific incidence in children is unknown [124]. Chronic HCV infection is estimated to affect 0.1–2 % of children in the USA.

Perinatal transmission is a common source of infection in children. Adolescents may be exposed through intravenous or intranasal drug use and use of shared tattoo needles. The incidence of HCV vertical transmission is approximately 2–5 % in HCV RNA positive mothers, with the highest risk in mothers with high HCV viral load. The risk also is increased fourfold for mothers with a concomitant HIV coinfection [125–130].

Six major genotypes of HCV have been defined with greater than 50 subtypes. Genotype 1 is most common (60–70 %) in the USA and Europe; genotypes 2 and 3 are less common in these areas, while genotypes 4, 5, and 6 are rare. Genotype 3 is most common in India, the Far East, and Australia. Genotype 4 is most common in Africa and the Middle East and genotype 5 is most common in South Africa. Genotype 6 is common in Hong Kong, Vietnam, and Australia. The most common subtypes are 1a, 1b, 2a, and 2b.

Viral genotypes affect the response to interferon therapy. The sustained virologic response to pegylated interferon plus ribavirin ranges from about 40 to 50 percent with genotype 1 (including 1a and 1b) to as high as 70–80 % with genotypes 2 and 3 [131–136].

Infections acquired during infancy are more likely to resolve on their own. Spontaneous clearance rates ranging from 20 to 45 % have been described [137–143]. In follow-up of perinatally acquired HCV in 266 children, approximately 20 % cleared the infection, while 80 % had chronic disease [144]. The disease progresses slowly and therefore advanced liver disease is uncommon in children. However, progression to advanced fibrosis and cirrhosis during childhood has been reported.

Screening

Patients suspected of having chronic hepatitis C virus (HCV) infection or with risk factors for HCV should be tested for HCV antibodies. HCV RNA testing should be performed in those with a positive antibody test to confirm infection and in those with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised. HCV RNA quantitation (viral load) should be obtained in patients being considered for treatment. Quantitative and qualitative tests are used during treatment to assess response. HCV genotype should be determined in all infected persons prior to treatment to determine

Table 15.3 Screening for HCV infection

Group	Screening
Injected illicit drug use	Antibody
Persons with conditions associated with a high prevalence of HCV infection including:	Antibody or RNA
HIV infection	
On hemodialysis	
Unexplained abnormal amionotransferases	
Earlier recipients of transfusions or organ transplants before July 1992 including:	Antibody or RNA
Children born to HCV-infected mothers	Antibody after 18 months of age. RNA for younger ages
Health care, emergency medical, and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood	Antibody or RNA
Present sexual partners of HCV-infected persons	Antibody
Children from a region with high prevalence of HCV infection	Antibody

Modified from Mack et al. [146]

Table 15.4 Investigational therapy for hepatitis C infection

Direct acting antiviral therapy
Ns3/4a protease inhibitors
Boceprevir/Telaprevir
BI201335
Danoprevir
TMC 435
Asunaprevir
NS5B polymerase inhibitors
GS7977
NS5A inhibitors
Daclatasvir
Combinations without peginterferon
Treatment targeting host encoded factors
HCV vaccine
Complementary medicine

the duration of therapy, dose of ribavirin, and the likelihood of response (Table 15.3).

The NASPGHAN guidelines recommend testing for anti-HCV antibodies in the infant after 18 months of age and confirmation by PCR if positive. If the parents desire, HCV RNA may be tested in the first year of life; however, the infant must be older than 2 months of age at testing [145, 146].

Chronic infection with HCV has been associated with hepatocellular carcinoma (HCC), in those with cirrhosis [147]. As a result, HCC is rare among children infected with HCV but appears to be more common in children who developed HCV after treatment for childhood leukemia.

Treatment

Children with hepatitis C with persistently elevated serum aminotransferases or those with fibrosis on liver histology should be considered for treatment. Presently available treatments are IFNα or PEG-IFNα and ribavirin. AASLD and NASPGHAN recommend the FDA-approved combination of PEG-IFNα with ribavirin as first-line treatment for children ages 3–17 years [148–153].

Triple Therapy

As of May 2011, two protease inhibitors, boceprevir and telaprevir, are licensed in the USA for use in combination with pegylated interferon and ribavirin in adults with chronic HCV genotype 1. This therapy is associated with a significantly higher rate of sustained virologic response as compared with the combination of pegylated interferon and ribavirin. A pediatric trial of combination therapy with boceprevir is underway and a trial of telaprevir is being planned.

Practice recommendations for children with chronic HCV are similar to those for adults [154]. However, because of limited data in the pediatric age group, treatment decisions may vary with the child's age and individual disease characteristics. Combination treatment with pegylated interferon plus ribavirin is considered for children with chronic HCV infection who are older than 3 years and who appear to have progressive disease or advanced histological features. For these children, the course of action depends on the HCV genotype.

Newer potential treatments include direct acting antivirals and possible options that may minimize the use of injectable therapy (Table 15.4).

Hepatitis G

Hepatitis G virus (HGV) was discovered incidentally and was named after a 35-year-old surgeon who developed jaundice. His serum led to the identification of GBV-A, GBV-B, and GBV-C. Subsequent studies have not identified any association between infections with GBV or acute hepatitis. Therefore, the term hepatitis G virus has been questioned. It is a positive-strand RNA virus belonging to the Flaviviridae family and GB V-C shares 27 % homology with HCV [155].

The virus is found worldwide with five different genotypes. The development of antibodies correlates with loss of viremia and suggests past exposure and clearance of the infection [156]. About 16 % of healthy blood donors are positive for antibodies with much lower rate of active viremia. The rate of natural clearance of the virus is higher than that for hepatitis C. Although GBV-C is detected in many patients with chronic hepatitis of unclear etiology, it does not appear to cause any liver disease [157–159]. The duration of infection depends on the immune status and the age of the patient. No association has been found with malignancy or aplastic anemia [160]. Antibodies can be checked to document past infection and PCR analysis may be done.

TT Virus

This virus was first identified in 1977 and is also known as the transfusion transmitted virus. It is a non-enveloped single-stranded DNA virus that is believed to be hepatotropic. It is found worldwide and is common. It has been found in 1–40 % of healthy blood donors and is transmitted by parenteral routes [161]. Although it was associated with hepatitis in the first patient in whom it was identified, studies have not supported a relationship between liver disease and the virus [162].

Several similar viruses, Sanban, Yonban and Sen viruses, have also been identified. Their clinical significance remains controversial.

Epstein–Barr Virus

Infection with this virus has myriad clinical presentations. While most infants and young children are asymptomatic or have nonspecific complaints, adolescents may have fever, lymphadenopathy, and pharyngitis. Subclinical liver disease may occur and overt disease ranges from mild transaminitis to hepatic necrosis with fulminant failure. Serum lactic dehydrogenase may be elevated to three times ULN. Alkaline phosphatase is elevated and hyperbilirubinemia is also seen in about 45 % of patients. The laboratory abnormalities are slow to resolve. Cholestatic jaundice with pruritus may occur in women with EBV hepatitis taking the oral contraceptive pill. Fatal fulminant hepatitis has been described in both immunocompromised patients as well as the immunocompetent. Fever, hepatosplenomegaly, liver failure, and bone marrow suppression with hyperferritinemia may develop in the hemophagocytic syndrome associated with EBV infection [163].

The diagnosis of EBV hepatitis is based on clinical features as well as the tests that support the diagnosis. There are predominant lymphocytosis, monocytosis, and thrombocytopenia [164]. The monospot test may be positive and IgM antibodies are seen early in disease with IgG antibodies indicating possible past infection. It is important to note that the monospot test however may be falsely negative. An abdominal ultrasound frequently demonstrates hepatosplenomegaly, lymphadenopathy, and gallbladder thickening. A liver biopsy is rarely necessary for diagnosis. There is no specific therapy for EBV hepatitis. Acyclovir inhibits replication of EBV but has no effect on clinical symptoms or outcome [165]. Improvement in acute and chronic EBV hepatitis has been reported with ganciclovir treatment, but this is not yet well studied [166]. Liver transplantation has been performed for fulminant hepatitis caused by EBV.

Cytomegalovirus

Cytomegalovirus or CMV is a member of the herpes family and persists for life in a

non-replicative state. Clinically disease may occur as a primary infection or reactivation in immunocompromised patients. In those who are immunocompetent, primary infection is usually subclinical or may mimic infection with EBV. Hepatic disease is characterized by an increase in liver enzymes and alkaline phosphatase with or without organomegaly. The clinical course is usually mild; however, occasionally there may be hepatic necrosis. In congenital infections with CMV, jaundice, hepatosplenomegaly, thrombocytopenic purpura, and severe neurological impairment have been described [167]. Portal vein thrombosis may occur [168]. Disseminated disease can occur in the immunocompromised host and may manifest as hepatitis, pancreatitis, and rarely gangrenous cholecystitis. CMV has been described in AIDS-associated cholangiopathy and primary sclerosing cholangitis [169, 170]. CMV hepatitis may be difficult to distinguish from graft rejection in liver transplant patients, but the differentiation is crucial to appropriate management. Diagnosis requires serological analysis and liver biopsy. IgM antibodies demonstrate acute infection and PCR is used for confirmation particularly in immunocompromised patients. Multinucleated giant cells and mononuclear portal infiltrate are seen on liver biopsy. There are characteristics intranuclear inclusions that are called "owl's eye" inclusions. Ganciclovir is used for treatment, and alternative agents include foscarnet and cidofovir.

Herpes Simplex Virus

HSV hepatitis is seen in immunocompromised individuals and neonates. The infection may be rapidly progressive and life threatening. The neonate may be exposed to infected maternal secretions at the time of delivery. In pregnant women the hepatitis may be fulminant. There is therefore a high maternal and perinatal mortality of approximately 40 %. Prompt diagnosis and treatment is extremely important [171, 172].

A liver biopsy is required for diagnosis. Extensive hemorrhagic necrosis may be seen on biopsy with intranuclear inclusions (Cowdry A bodies). The hepatocytes may have a ground glass appearance [173]. Treatment is with acyclovir but liver transplantation may be indicated for severe disease.

Varicella-Zoster Virus

Children infected with the virus may demonstrate hepatitis with an increase in liver enzymes, albeit rarely. Dissemination of infection leading to visceral involvement has been described before the onset of cutaneous features in patients who have received solid organ transplantation and other forms of immunodeficiency. If visceral involvement is suspected, high-dose intravenous acyclovir is required [174].

Infectious Complications in Liver Transplantation

In transplant patients, morbidity and mortality due to infections remains a persistent problem. Infections include those with bacterial, viral, or fungal pathogens. It is important to note that in solid organ transplant recipient, the signs and symptoms of infection are often blunted in the setting of immune suppression. In addition, antibiotics or antimicrobials used may have interactions with immunosuppressive medications. An important risk factor is the presence of latent infections in either the transplant recipient or donor. All potential transplant donors are screened for infection with cytomegalovirus, herpes virus, tuberculosis, hepatitis B and C, syphilis, and the human immunodeficiency virus. Pretransplant infections with methicillin-resistant Staphylococcus aureus or MRSA or vancomycin-resistant enterococcus VRE lead to posttransplant infections [175, 176]. However, colonization with these pathogens is not a contraindication to transplantation [177].

An additional risk factor includes surgical complications at transplant. For example, the risk of bacterial infections is increased in those who undergo a Roux-en-Y biliary anastomosis and in

those with multiple abdominal surgeries [178–180]. Those patients who develop rejection or have poor graft function are also at increased risk of infection because of the aggressive immunosuppression required.

Minimizing infections includes strategies for appropriate vaccination prior to transplantation. Particularly since antirejection immunosuppressive medications prevent the development of an optimal response to vaccines, certain vaccines such as the pneumococcal and influenza vaccines may need to be repeated after transplantation. Live vaccines are to be avoided in transplant recipients due to potential risk of disseminated disease.

There is a higher chance of developing surgical site infections in liver transplant recipient compared to other solid organ transplants. Treatment with trimethoprim sulfamethoxazole is generally used after liver transplantation for 3–12 months to reduce the risk of Pneumocystis but also to prevent infections with Listeria, Nocardia, Toxoplasma, and many other common infections [181–183]. The dose is a single-strength tablet taken daily or double-strength tablets taken thrice a week. The most common adverse effect is allergy and myelosuppression. It is also important to note that higher doses may increase the nephrotoxicity associated with cyclosporin or tacrolimus.

Although cytomegalovirus remains an important viral infection posttransplant, other viruses such as HSV I and 2 and VZV are significant pathogens. Ganciclovir and valganciclovir are used for posttransplant viral prophylaxis [184]. CMV-negative transplant recipients who receive an organ from a CMV seropositive donor are at increased risk to develop CMV reactivation posttransplant. CMV seropositive recipients have a lower risk and CMV donor/recipient negative patients the least risk of CMV activation [185, 186]. Infection with the CMV virus increases risk for bacterial and fungal infections and leads to an almost fourfold increased risk of death by a year posttransplant [187–191].

Fungal infections are also problematic in the posttransplant setting. *Candida albicans* is the most commonly seen fungal pathogen although infections with non-albicans Candida may occur [192]. The role of antifungal treatment for prophylaxis is not well studied; however, fluconazole or liposomal amphotericin B for 14–27 days is used for postoperative antifungal prophylaxis for high-risk liver transplant recipients such as those with renal failure, fulminant hepatic failure, prolonged hospitalization, prolonged antibiotic use, or large transfusion requirements [193, 194].
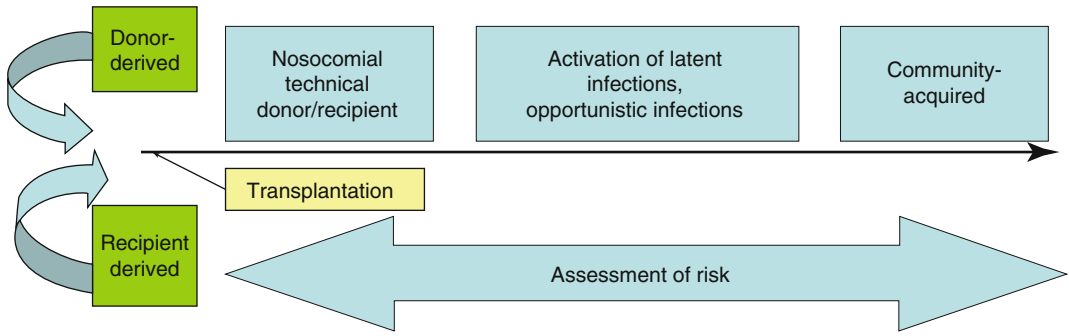
Patients with liver transplantation remain at increased risk for the development of active *Mycobacterium tuberculosis* infection. Although it is optimal to treat latent TB prior to transplantation, it can be very difficult to do because of the significant hepatotoxicity of isoniazid. Treatment can sometimes be attempted after transplantation [195].

In the first 3 months immediately following transplantation, bacterial infections predominate. They usually have a nosocomial source such as indwelling catheters and drains. Prolonged intubation increases risk of infections. Abdominal abscesses, cholangitis, wound infections, and nosocomial pneumonias are common. Clostridium difficile colitis may also occur [196, 197] (Fig. 15.2).

If bacterial infection is suspected in the transplant recipient, empiric broad-spectrum antibiotics are used, until sensitivities are identified. Aminoglycosides are usually avoided due to their nephrotoxicity particularly if calcineurin inhibitors are being used for immunosuppression. Common organisms isolated in bacteremic patients are methicillin-resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Beyond the immediate posttransplant period, other infections with cytomegalovirus, VZV, Epstein–Barr virus, respiratory syncytial virus, human herpesvirus 6, influenza virus, and adenovirus may occur [198]. Infections with EBV are very important because of the potential to induce posttransplant lymphoproliferative disease.

Invasive aspergillosis is associated with a very high mortality [199]. Opportunistic infections become uncommon beyond the first 6 months after transplant. However, since these patients are immunocompromised, they are at increased risk for infections with pathogens such as *Cryptococcus neoformans*, Legionella, and also

Fig. 15.2 Common patterns of opportunistic infection. Abbreviations: *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HSV* herpes simplex virus, *MRSA* methicillin-resistant Staphylococcus aureus, *SARS* severe acute respiratory syndrome, *VRE* vancomycin-resistant enterococcus, *VZV* varicella-zoster virus (Modified from Fishman and AST Infectious Diseases Community of Practice [202]. Copyright © 2009 American Society of Transplantation and the American Society of Transplant Surgeons)

West Nile virus. Respiratory infections due to pathogens such as *Streptococcus pneumonia* and *Haemophilus influenza* may be life threatening if not promptly treated. Recurrent infections with EBV, CMV, and herpesvirus 6 and 7 may occur and may be devastating. Fungal infections with *Histoplasma*, *Coccidioides*, and *Blastomyces* may be seen in the late posttransplant period. Listeria infection may manifest as hepatitis, bacteremia, and meningitis [200, 201].

References

1. Stevens DL. Group A streptococcal sepsis. Curr Infect Dis Rep. 2003;5:379–86.
2. Fernández J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective. Hepatology. 2012;55(5):1551–61.
3. Bryant AE, Chen RY, Nagata Y, et al. Clostridial gas gangrene. I. Cellular and molecular mechanisms of microvascular dysfunction induced by exotoxins of Clostridium perfringens. J Infect Dis. 2000;182:799–807.
4. Chen YM, Lee HC, Chang CM, et al. Clostridium bacteremia: emphasis on the poor prognosis in cirrhotic patients. J Microbiol Immunol Infect. 2001;34:113–8.
5. Le DT, Brockstedt DG, Nir-Paz R, Hampl J, Mathur S, Nemunaitis J, Sterman DH, Hassan R, Lutz E, Moyer B, Giedlin M, Louis JL, Sugar EA, Pons A, Cox AL, Levine J, Murphy AL, Illei P, Dubensky Jr TW, Eiden JE, Jaffee EM, Laheru DA. A live-attenuated Listeria vaccine (ANZ-100) and a live-attenuated Listeria vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction. Clin Cancer Res. 2012;18(3):858–68.
6. El-Newihi HM, Alamy ME, Reynolds TB. Salmonella hepatitis: analysis of 27 cases and

comparison with acute viral hepatitis. Hepatology. 1996;24:516–9.

7. Chaudhry R, Mahajan RK, Diwan A, et al. Unusual presentation of enteric fever: three cases of splenic and liver abscesses due to Salmonella typhi and Salmonella paratyphi a. Trop Gastroenterol. 2003;24:198–9.

8. Kamath PS, Jalihal A, Chakraborty A. Differentiation of typhoid fever from fulminant hepatic failure in patients presenting with jaundice and encephalopathy. Mayo Clin Proc. 2000;75:462–6.

9. Hsueh PR, Kao JH, Chen YC, et al. Paratyphoid hepatitis: an emerging clinical entity. Am J Med. 2002;113:257–8.

10. Rajagopal A, Ramasamy R, Mahendran G, Thomas M. Hepatic abscess complicating paratyphoid infection. Trop Gastroenterol. 2002;23:181–2.

11. Bergmann TK, Vinding K, Hey H. Multiple hepatic abscesses due to Yersinia enterocolitica infection secondary to primary haemochromatosis. Scand J Gastroenterol. 2001;36:891–5.

12. Wong JJ, Kinney TB, Miller FJ, Rivera-Sanfeliz G. Hepatic actinomycotic abscesses: diagnosis and management. AJR Am J Roentgenol. 2006;186:174–6.

13. Uehara Y, Takahashi T, Yagoshi M, Shimoguchi K, Yanai M, Kumasaka K, Kikuchi K. Liver abscess of Actinomyces israelii in a hemodialysis patient: case report and review of the literature. Intern Med. 2010;49(18):2017–20. Review.

14. Pedro-Botet ML, Sabria M. Legionellosis. Semin Respir Crit Care Med. 2005;26:625–34.

15. Holmes KK, Counts GW, Beaty HN. Disseminated gonococcal infection. Ann Intern Med. 1971;74:979–93.

16. Akritidis N, Tzivras M, Delladetsima I, et al. The liver in brucellosis. Clin Gastroenterol Hepatol. 2007;5:1109–12.

17. Colmenero Jde D, Queipo-Ortuno MI, Maria Reguera J, et al. Chronic hepatosplenic abscesses in brucellosis. Clinico-therapeutic features and molecular diagnostic approach. Diagn Microbiol Infect Dis. 2002;42:159–67.

18. Ariza J, Pigrau C, Canas C, et al. Current understanding and management of chronic hepatosplenic suppurative brucellosis. Clin Infect Dis. 2001;32:1024–33.

19. Zaidi SA, Singer C. Gastrointestinal and hepatic manifestations of tickborne diseases in the United States. Clin Infect Dis. 2002;34:1206–12.

20. Tissot-Dupont H, Raoult D. Q fever. Infect Dis Clin North Am. 2008;22:505–14.

21. VanderHeyden TR, Yong SL, Breitschwerdt EB, Maggi RG, Mihalik AR, Parada JP, Fimmel CJ. Granulomatous hepatitis due to Bartonella henselae infection in an immunocompetent patient. BMC Infect Dis. 2012;12:17.

22. Palaniappan RU, Ramanujam S, Chang YF. Leptospirosis: pathogenesis, immunity, and diagnosis. Curr Opin Infect Dis. 2007;20:284–92.

23. Feigin RD, Anderson DC. Human leptospirosis. CRC Crit Rev Clin Lab Sci. 1975;5:413–67.

24. Steere AC. Lyme disease. N Engl J Med. 2001;345:115–25.

25. Nadelman RB, Wormser GP. Lyme borreliosis. Lancet. 1998;352:557–65.

26. Goellner MH, Agger WA, Burgess JH, Duray PH. Hepatitis due to recurrent Lyme disease. Ann Intern Med. 1988;108:707–8.

27. Horowitz HW, Dworkin B, Forseter G, et al. Liver function in early Lyme disease. Hepatology. 1996;23:1412–7.

28. Alvarez SZ. Hepatobiliary tuberculosis. J Gastroenterol Hepatol. 1998;13:833–9.

29. Peeters L, Van Vaerenbergh W, Van der Perre C, et al. Tertiary syphilis presenting as hepatic bull's eye lesions. Acta Gastroenterol Belg. 2005;68:435–9.

30. Yu SC, Ho SS, Lau WY, et al. Treatment of pyogenic liver abscess: prospective randomized comparison of catheter drainage and needle aspiration. Hepatology. 2004;39:932–8.

31. Zerem E, Hadzic A. Sonographically guided percutaneous catheter drainage versus needle aspiration in the management of pyogenic liver abscess. AJR Am J Roentgenol. 2007;189:W138–42.

32. Lee KT, Wong SR, Sheen PC. Pyogenic liver abscess: an audit of 10 years' experience and analysis of risk factors. Dig Surg. 2001;18:459–65.

33. Alvarez JA, Gonzalez JJ, Baldonedo RF, et al. Single and multiple pyogenic liver abscesses: etiology, clinical course, and outcome. Dig Surg. 2001;18:283–8.

34. Alvarez Perez JA, Gonzalez JJ, Baldonedo RF, et al. Clinical course, treatment, and multivariate analysis of risk factors for pyogenic liver abscess. Am J Surg. 2001;181:177–86.

35. Wong WM, Wong BC, Hui CK, et al. Pyogenic liver abscess: retrospective analysis of 80 cases over a 10-year period. J Gastroenterol Hepatol. 2002;17:1001–7.

36. Chemaly RF, Hall GS, Keys TF, Procop GW. Microbiology of liver abscesses and the predictive value of abscess gram stain and associated blood cultures. Diagn Microbiol Infect Dis. 2003;46:245–8.

37. Serste T, Bourgeois N, Vanden Eynden F, et al. Endoscopic drainage of pyogenic liver abscesses with suspected biliary origin. Am J Gastroenterol. 2007;102:1209–15.

38. Kochar DK, Agarwal P, Kochar SK, et al. Hepatocyte dysfunction and hepatic encephalopathy in plasmodium falciparum malaria. QJM. 2003;96:505–12.

39. Devarbhavi H, Alvares JF, Kumar KS. Severe falciparum malaria simulating fulminant hepatic failure. Mayo Clin Proc. 2005;80:355–8.

40. Artan R, Yilmaz A, Akcam M, Aksoy NH. Liver biopsy in the diagnosis of visceral leishmaniasis. J Gastroenterol Hepatol. 2006;21:299–302.

41. Moreno A, Marazuela M, Yebra M, et al. Hepatic fibrin-ring granulomas in visceral leishmaniasis. Gastroenterology. 1988;95:1123–6.

42. Sundar S, Jha TK, Thakur CP, et al. Injectable paromomycin for visceral leishmaniasis in India. N Engl J Med. 2007;356:2571–81.

43. Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. Trans R Soc Trop Med Hyg. 2006;100 Suppl 1:S17–20.

44. Bhattacharya SK, Sinha PK, Sundar S, et al. Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis. J Infect Dis. 2007;196:591–8.

45. Myles O, Wortmann GW, Cummings JF, et al. Visceral leishmaniasis: clinical observations in 4 U.S. Army soldiers deployed to Afghanistan or Iraq, 2002-2004. Arch Intern Med. 2007;167:1899–901.

46. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. Toxoplasma gondii infection in the United States, 1999 2004, decline from the prior decade. Am J Trop Med Hyg. 2007;77:405–10.

47. Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet. 2004;363:1965–76.

48. Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. Am J Med. 2007;120: 911.e1-8.

49. Remington JS, Thulliez P, Montoya JG. Recent developments for diagnosis of toxoplasmosis. J Clin Microbiol. 2004;42:941–5.

50. Botterel F, Ichai P, Feray C, et al. Disseminated toxoplasmosis, resulting from infection of allograft, after orthotopic liver transplantation: usefulness of quantitative PCR. J Clin Microbiol. 2002;40:1648–50.

51. Stanley Jr SL. Amoebiasis. Lancet. 2003;361: 1025–34.

52. Soentjens P, Ostyn B, Clerinx J, et al. A case of multiple amoebic liver abscesses: clinical improvement after percutaneous aspiration. Acta Clin Belg. 2005;60:28–32.

53. Salles JM, Salles MJ, Moraes LA, Silva MC. Invasive amebiasis: an update on diagnosis and management. Expert Rev Anti Infect Ther. 2007;5:893–901.

54. Leone N, Baronio M, Todros L, et al. Hepatic involvement in larva migrans of Toxocara canis: report of a case with pathological and radiological findings. Dig Liver Dis. 2006;38:511–4.

55. Kaplan KJ, Goodman ZD, Ishak KG. Eosinophilic granuloma of the liver: a characteristic lesion with relationship to visceral larva migrans. Am J Surg Pathol. 2001;25:1316–21.

56. Shah OJ, Zargar SA, Robbani I. Biliary ascariasis: a review. World J Surg. 2006;30:1500–6.

57. Hurtado RM, Sahani DV, Kradin RL. Case records of the Massachusetts General Hospital. Case 9-2006. A 35-year-old woman with recurrent right-upper-quadrant pain. N Engl J Med. 2006;354:1295–303.

58. Rana SS, Bhasin DK, Nanda M, Singh K. Parasitic infestations of the biliary tract. Curr Gastroenterol Rep. 2007;9:156–64.

59. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet. 2006;368:1106–18.

60. Manzella A, Ohtomo K, Monzawa S, Lim JH. Schistosomiasis of the liver. Abdom Imaging. 2008;33:144–50.

61. Bottieau E, Clerinx J, de Vega MR, et al. Imported Katayama fever: clinical and biological features at presentation and during treatment. J Infect. 2006;52:339–45.

62. Maclean JD, Cross J, Mahanty S. Liver, lung, and intestinal fluke infections. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical infectious diseases: principles, pathogens, and practice. 2nd ed. Philadelphia: Churchill Livingstone; 2006. p. 1349.

63. Sezgin O, Altintas E, Disibeyaz S, et al. Hepatobiliary fascioliasis: clinical and radiologic features and endoscopic management. J Clin Gastroenterol. 2004;38:285–91.

64. Marcos LA, Tagle M, Terashima A, et al. Natural history, clinicoradiologic correlates, and response to triclabendazole in acute massive fascioliasis. Am J Trop Med Hyg. 2008;78:222–7.

65. Choi D, Lim JH, Lee KT, et al. Cholangiocarcinoma and Clonorchis sinensis infection: a case-control study in Korea. J Hepatol. 2006;44:1066–73.

66. Paksoy Y, Odev K, Sahin M, et al. Percutaneous treatment of liver hydatid cysts: comparison of direct injection of albendazole and hypertonic saline solution. AJR Am J Roentgenol. 2005;185:727–34.

67. Sora F, Chiusolo P, Piccirillo N, et al. Successful treatment with caspofungin of hepatosplenic candidiasis resistant to liposomal amphotericin B. Clin Infect Dis. 2002;35:1135–6.

68. Kontoyiannis DP, Luna MA, Samuels BI, Bodey GP. Hepatosplenic candidiasis. A manifestation of chronic disseminated candidiasis. Infect Dis Clin North Am. 2000;14:721–39.

69. Assi MA, Sandid MS, Baddour LM, et al. Systemic histoplasmosis: a 15-year retrospective institutional review of 111 patients. Medicine (Baltimore). 2007;86:162–9.

70. Kauffman CA. Diagnosis of histoplasmosis in immunosuppressed patients. Curr Opin Infect Dis. 2008;21:421–5.

71. Robertson BH, Jansen RW, Khanna B, et al. Genetic relatedness of hepatitis A virus strains recovered from different geographic regions. J Gen Virol. 1992;73:1365–77.

72. Mathiesen LR, Feinstone SM, Purcell RH, Wagner JA. Detection of hepatitis A antigen by immunofluorescence. Infect Immun. 1977;18:524–30.

73. Centers for Disease Control and Prevention. Surveillance for acute viral hepatitis, United States-2006. MMWR. 2008;57(SS02).

74. Emerson SU, Huang YK, Nguyen H, et al. Identification of VP1/2A and 2C as a virulence genes of hepatitis A virus and demonstration of genetic instability of 2C. J Virol. 2002;76:8551–9.

75. Gust ID. Epidemiological patterns of hepatitis A in different parts of the world. Vaccine. 1992;10:S56–8.

76. Gandolfo GM, Ferri GM, Conti L, et al. Prevalence of infections by hepatitis A, B, C and E viruses in two different socio-economic groups of children from Santa Cruz, Bolivia. Med Clin (Barc). 2003;120:725–7.

77. Prevention of hepatitis A through active or passive immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1996;45(RR-15):1.

78. Coulepis AG, Locarnini SA, Lehmann NI, Gust ID. Detection of HAV in feces. J Infect Dis. 1980;141: 151–6.

79. Rosenblum LS, Villarino ME, Nainan OV, et al. Hepatitis A outbreak in a neonatal intensive care unit: risk factors for transmission and evidence of prolonged viral excretion among preterm infants. J Infect Dis. 1991;164:476–82.

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

81. Schiødt FV, Atillasoy E, Shakill AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg. 1999;5:29–34.

82. Tagle Arrospide M, Leon Barua R. Viral hepatitis A as a triggering agent of autoimmune hepatitis report of a case and review of literature. Rev Gastroenterol Peru. 2003;23:134–7.

83. Rezende G, Roque-Alsonso M, Samuel D, et al. Viral and clinical factors associated with fulminant course of hepatitis A infection. Hepatology. 2003;38:613–8.

84. Fujiwara K, Yokosuka O, Imazeki F, et al. Analysis of the genotype-determining region of hepatitis A viral RNA in relation to disease severities. Hepatol Res. 2003;25:124–34.

85. Shah U, Habib Z, Kleinman RE. Liver failure due to hepatitis A virus infection in a developing country. Pediatrics. 2000;105(2):436–8.

86. American Academy of Pediatrics. Committee on infectious disease: hepatitis A vaccine recommendations. Pediatrics. 2007;120:189–99.

87. Center of Disease Control and Prevention. Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. MMWR. 2007;56:1080–4.

88. Victor JC, Monto AS, Surdina TY, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med. 2007;357:1685–94.

89. Diaz-Mitoma F, Law B, Subramanya A, Hoet B. Long-term antibody persistence induced by a combined hepatitis A and B vaccine in children and adolescents. Vaccine. 2008;26:1759–63.

90. Yamashita T, Mori Y, Miyazaki N, et al. Biological and immunological characteristics of hepatitis E-like particles based on the crystal structure. Proc Natl Acad Sci U S A. 2009;106:12986–91.

91. Guu TS, Liu Z, Ye Q, et al. Structure of the hepatitis E virus-like particle suggests mechanism for virus assembly and receptor binding. Proc Natl Acad Sci U S A. 2009;106:12992–7.

92. Berke T, Matson DO. Reclassification of the Caliciviridae into distinct genera and exclusion of hepatitis E virus from the family on the basis of comparative phylogenetic analysis. Arch Virol. 2000; 145:1421–36.

93. Arankalle VA, Chobe LP, Joshi MV, et al. Human and swine hepatitis E viruses from Western India belong to different genotypes. J Hepatol. 2002;36:417–25.

94. Aggarwal R, Krawczynski K, Hepatitis E. Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. Boston: Saunders Elsevier; 2010. p. 1337–42.

95. Shrestha MP, Scott RM, Joshi DM, et al. Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med. 2007;356:895–903.

96. Shah U, Kelly D, Chang MH, Fujisawa T, Heller S, González-Peralta RP, Jara P, Mieli-Vergani G, Mohan N, Murray KF. Management of chronic hepatitis B in children. J Pediatr Gastroenterol Nutr. 2009;48(4):399–404.

97. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology. 2009;49:S45–55.

98. Paganelli M, Stephenne X, Sokal EM. Chronic hepatitis B in children and adolescents. J Hepatol. 2012;57(4):885–96.

99. McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis. 1985;151:599–603.

100. World Health Organization. Hepatitis B vaccines – WHO position paper. Weekly epidemiological record. 2009;89:405–20.

101. Chen H-L, Lin L-H, Hu F-C, Lee J-T, Lin W-T, Yang Y-J, et al. Effects of maternal screening and universal immunization to prevent mother-to infant transmission of HBV. Gastroenterology. 2012;142(4):773–81.e2.

102. Shi Z, Yang Y, Wang H, Ma L, Schreiber A, Li X, et al. Breastfeeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review. Arch Pediatr Adolesc Med. 2011;165:837–46.

103. Chang MH, Hsu HY, Hsu HC, et al. The significance of spontaneous HBeAg seroconversion in childhood: with special emphasis on the clearance of HBeAg before three years of age. Hepatology. 1995;22:1387–92.

104. Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, Narkewicz MR, Rosenthal P, Schwarz KB, McMahon BJ. Hepatitis B foundation treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. Hepatology. 2010;52(6):2192–205. doi:10.1002/hep.23934. Epub 2010 Oct 1.

105. Lampertico P, Del Ninno E, Vigano M, et al. Long term suppression of HBeAg negative chronic hepatitis B by 24 months interferon therapy. Hepatology. 2003;37:756–63.

106. Vo Thi Diem H, Bourgois A, Bontems P, Goyens P, Buts J-P, Nackers F, et al. Chronic hepatitis B infection: long-term comparison of children receiving interferon alpha and untreated controls. J Pediatr Gastroenterol Nutr. 2005;40:141–5.

107. Jonas MM, Kelly DA, Mizerski J, Badia IB, Areias JA, Schwarz KB, et al. Clinical trial of lamivudine in children with chronic hepatitis B. N Engl J Med. 2002;346:1706–13.

108. Sokal EM, Kelly DA, Mizerski J, Badia IB, Areias JA, Schwarz KB, et al. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. Hepatology. 2006;43:225–32.

109. Sarin SK, Kumar M, Kumar R, Kazim SN, Guptan RC, Sakhuja P, et al. Higher efficacy of sequential

therapy with interferon-alpha and lamivudine combination compared to lamivudine monotherapy in HBeAg positive chronic hepatitis B patients. Am J Gastroenterol. 2005;100:2463–71.

110. Akman SA, Okcu SC, Halicioglu O, Sutcuoglu S, Anil M, Kizilgunesler A, et al. Therapeutic efficacy of sequential and simultaneous treatments with interferon-alpha and lamivudine in children with chronic hepatitis B. Pediatr Int. 2007;49:848–52.

111. Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. Hepatology. 2008;47:1863–71.

112. Marcellin P, Chang T-T, Lim SGL, Sievert W, Tong M, Arterburn S, et al. Long term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. Hepatology. 2008;48:750–8.

113. Leung N, Peng C-Y, Hann H-W, Sollano J, Lao-Tan J, Hsu C-W, et al. Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: a randomized international study of entecavir versus adefovir. Hepatology. 2009;49:72–9.

114. Sherman M, Yurdaydin C, Simsek H, Silva M, Liaw Y-F, Rustgi VK, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology. 2008;48:99–108.

115. Novartis Pharmaceuticals. Pharmacokinetics and safety of single-dose telbivudine in children and adolescents with chronic hepatitis B. In: ClinicalTrials. gov [Internet]. Bethesda: National Library of Medicine (US); 2000 – [cited 18.09.11]. Available from: http://clinicaltrials.gov/show/NCT00907894. NLM Identifier: NCT00907894.

116. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359:2442–55.

117. Gilead Sciences. Evaluation of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B infection. In: ClinicalTrials.gov. Bethesda: National Library of Medicine (US); 2000. [cited 18.09.11]. http://clinicaltrials.gov/show/NCT00734162. NLM Identifier: NCT00734162.

118. Lau JY, King R, Tibbs CJ, et al. Loss of HBsAg with interferon-alpha therapy in chronic hepatitis D virus infection. J Med Virol. 1993;39:292.

119. Battegay M, Simpson LH, Hoofnagle JH, et al. Elimination of hepatitis delta virus infection after loss of hepatitis B surface antigen in patients with chronic delta hepatitis. J Med Virol. 1994;44:389.

120. Castelnau C, Le Gal F, Ripault MP, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. Hepatology. 2006;44:728.

121. Ferenci P, Formann E, Romeo R. Successful treatment of chronic hepatitis D with a short course of peginterferon alfa-2a. Am J Gastroenterol. 2005;100:1626.

122. Rosina F, Pintus C, Meschievitz C, Rizzetto M. A randomized controlled trial of a 12-month course of recombinant human interferon-alpha in chronic delta (type D) hepatitis: a multicenter Italian study. Hepatology. 1991;13:1052.

123. Niro GA, Ciancio A, Gaeta GB, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. Hepatology. 2006;44:713.

124. Alter MJ. Epidemiology of hepatitis C. Hepatology. 1997;26(3 Suppl 1):62S–5.

125. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. The vertical transmission of hepatitis C virus collaborative study group. N Engl J Med. 1994;330:744–50.

126. Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. Pediatr Infect Dis J. 2001;20:10–4.

127. Steininger C, Kundi M, Jatzko G, et al. Increased risk of mother-to infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. J Infect Dis. 2003;187:345–51.

128. Minola E, Maccabruni A, Pacati I, et al. Amniocentesis as a possible risk factor for mother-to-infant transmission of hepatitis C virus. Hepatology. 2001;33:1341–2.

129. Ducarme G, Ceccaldi PF, Bernuau J, et al. Amniocentesis and viral risk (hepatitis B, C virus and HIV). J Gynecol Obstet Biol Reprod (Paris). 2009;38:469–73.

130. Ferrero S, Lungaro P, Bruzzone BM, et al. Prospective study of mother-to-infant transmission of hepatitis C virus: a 10-year survey (1990–2000). Acta Obstet Gynecol Scand. 2003;82:229–34.

131. Simmonds P, Alberti A, Alter HJ, Bonino F, Bradley DW, Brechot C, Brouwer JT, Chan SW, Chayama K, Chen DS, et al. A proposed system for the nomenclature of hepatitis C viral genotypes. Hepatology. 1994;19(5):1321–4.

132. Simmonds P, Bukh J, Combet C, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology. 2005; 42:962.

133. Lau JY, Davis GL, Prescott LE, et al. Distribution of hepatitis C virus genotypes determined by line probe assay in patients with chronic hepatitis C seen at tertiary referral centers in the United States. Hepatitis interventional therapy group. Ann Intern Med. 1996;124:868.

134. Dusheiko G, Schmilovitz-Weiss H, Brown D, et al. Hepatitis C virus genotypes: an investigation of type-specific differences in geographic origin and disease. Hepatology. 1994;19:13.

135. Davis GL, Lau JY. Factors predictive of a beneficial response to therapy of hepatitis C. Hepatology. 1997;26:122S.

136. Martinot-Peignoux M, Marcellin P, Pouteau M, et al. Pretreatment serum hepatitis C virus RNA levels and

hepatitis C virus genotype are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic hepatitis C. Hepatology. 1995;22:1050.

137. Minola E, Prati D, Suter F, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood. 2002;99:4588.

138. Casiraghi MA, De Paschale M, Romanò L, et al. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. Hepatology. 2004;39:90.

139. Matsuoka S, Tatara K, Hayabuchi Y, et al. Serologic, virologic, and histologic characteristics of chronic phase hepatitis C virus disease in children infected by transfusion. Pediatrics. 1994;94:919.

140. Vogt M, Lang T, Frösner G, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med. 1999;341:866.

141. Tovo PA, Pembrey LJ, Newell ML. Persistence rate and progression of vertically acquired hepatitis C infection. European paediatric hepatitis C virus infection. J Infect Dis. 2000;181:419.

142. Mohan P, Colvin C, Glymph C, et al. Clinical spectrum and histopathologic features of chronic hepatitis C infection in children. J Pediatr. 2007;150:168.

143. Matsuoka S, Tatara K, Hayabuchi Y, et al. Post-transfusion chronic hepatitis C in children. J Paediatr Child Health. 1994;30:544.

144. European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. Clin Infect Dis. 2005;41:45.

145. Indolfi G, Resti M. Perinatal transmission of hepatitis C virus infection. J Med Virol. 2009;81:836.

146. Mack C, Gonzales-Peralta RP, Gupta N, Leund D, et al. NASPGHAN practice guidelines. Diagnosis and management of hepatitis C infection in infants, children and adolescents. J Pediatr Gastroenterol Nutr. 2012;54:838–55.

147. González-Peralta RP, Langham Jr MR, Andres JM, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2009;48:630.

148. Gonzalez-Peralta RP, Kelly DA, Haber B, et al. International Pediatric Hepatitis C Therapy Group Interferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: efficacy, safety, and pharmacokinetics. Hepatology. 2005;42:1010–8.

149. Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology. 2011;140:450–8.

150. Wirth S, Lang T, Gehring S, et al. Recombinant alfa-interferon plus ribavirin therapy in children and adolescents with chronic hepatitis C. Hepatology. 2002; 36:1280–4.

151. Wirth S, Pieper-Boustani H, Lang T, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology. 2005;41:1013–8.

152. Wirth S, Ribes-Koninckx C, Calzado MA, et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. J Hepatol. 2010;52:501–7.

153. Christensson B, Wiebe T, Akesson A, et al. Interferon-alpha and ribavirin treatment of hepatitis C in children with malignancy in remission. Clin Infect Dis. 2000;30:585–6.

154. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49:1335.

155. Muerhoff AS, Leary TP, Sathar MA, et al. African origin of GB virus C determined by phylogenetic analysis of a complete genotype 5 genome from South Africa. J Gen Virol. 2005;86(Pt 6):1729–35.

156. Schaluder GG, Dawson GJ, Simons JN, et al. Molecular and serologic analysis in the transmission of the GB hepatitis agents. J Med Virol. 1995;46: 81–90.

157. Tan D, Matsumoto A, Conry-Cantilena C, et al. Analysis of hepatitis G virus (HGV) RNA, antibody to HGV envelope protein, and risk factors for blood donors coinfected with HGV and hepatitis C virus. J Infect Dis. 1999;179:1055–61.

158. Alter MJ, Gallagher M, Morris TT, et al. Acute non-A-E hepatitis in the United States and the role of hepatitis G virus infection. Sentinel counties viral hepatitis study team. N Engl J Med. 1997;336: 741–6.

159. Tanaka E, Alter HJ, Nakatsuji Y, et al. Effect of hepatitis G virus infection on chronic hepatitis C. Ann Intern Med. 1996;125:740–3.

160. Kanda T, Yokosuka O, Imazeki F, et al. GB virus-C RNA in Japanese patients with hepatocellular carcinoma and cirrhosis. J Hepatol. 1997;27:464–9.

161. Simmonds P, Davidson F, Lycett C, et al. Detection of a novel DNA virus (TTV) in blood donors and blood products. Lancet. 1998;352:191–5.

162. Gimenez-Barcons M, Forns X, Ampurdanes S, et al. Infection with a novel human DNA virus (TTV) has no pathogenic significance in patients with liver diseases. J Hepatol. 1999;30:1028–34.

163. Rouphael NG, Talati NJ, Vaughan C, et al. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007;7:814–22.

164. Edwards JM, Vandervelde EM, Cohen BJ, McSwiggan DA. Laboratory diagnosis of EB virus infection in some cases presenting as hepatitis. J Clin Pathol. 1978;31:179–82.

165. van der Horst C, Joncas J, Ahronheim G, et al. Lack of effect of peroral acyclovir for the treatment of acute infectious mononucleosis. J Infect Dis. 1991;164:788–92.

166. Adams LA, Deboer B, Jeffrey G, et al. Ganciclovir and the treatment of Epstein-Barr virus hepatitis. J Gastroenterol Hepatol. 2006;21:1758–60.

167. Domiati-Saad R, Dawson DB, Margraf LR, et al. Cytomegalovirus and human herpesvirus 6, but not human papillomavirus, are present in neonatal giant cell hepatitis and extrahepatic biliary atresia. Pediatr Dev Pathol. 2000;3:367–73.

168. Squizzato A, Ageno W, Cattaneo A, Brumana N. A case report and literature review of portal vein thrombosis associated with cytomegalovirus infection in immunocompetent patients. Clin Infect Dis. 2007;44:e13–6.

169. Benhamou Y, Caumes E, Gerosa Y, et al. AIDS-related cholangiopathy. Critical analysis of a prospective series of 26 patients. Dig Dis Sci. 1993;38:1113–8.

170. Mahajani RV, Uzer MF. Cholangiopathy in HIV-infected patients. Clin Liver Dis. 1999;3:669–84.

171. Chatelain S, Neumann DE, Alexander SM. Fatal herpetic hepatitis in pregnancy. Infect Dis Obstet Gynecol. 1994;1:246–8.

172. Bissig KD, Zimmermann A, Bernasch D, et al. Herpes simplex virus hepatitis 4 years after liver transplantation. J Gastroenterol. 2003;38:1005–8.

173. Fink CG, Read SJ, Hopkin J, et al. Acute herpes hepatitis in pregnancy. J Clin Pathol. 1993;46:968–71.

174. Fehr T, Bossart W, Wahl C, Binswanger U. Disseminated varicella infection in adult renal allograft recipients: four cases and a review of the literature. Transplantation. 2002;73:608–11.

175. McNeil SA, Malani PN, Chenoweth CE, et al. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. Clin Infect Dis. 2006;42:195.

176. Russell DL, Flood A, Zaroda TE, et al. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. Am J Transplant. 2008;8:1737.

177. Avery RK. Recipient screening prior to solid-organ transplantation. Clin Infect Dis. 2002;35:1513.

178. Collins LA, Samore MH, Roberts MS, et al. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. J Infect Dis. 1994;170:644.

179. Castaldo P, Stratta RJ, Wood RP, et al. Clinical spectrum of fungal infections after orthotopic liver transplantation. Arch Surg. 1991;126:149.

180. Gladdy RA, Richardson SE, Davies HD, Superina RA. Candida infection in pediatric liver transplant recipients. Liver Transpl Surg. 1999;5:16.

181. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med. 1998;338:1741.

182. Fishman JA. Pneumocystis carinii and parasitic infections in transplantation. Infect Dis Clin North Am. 1995;9:1005.

183. Martin SI, Fishman JA, AST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplant recipients. Am J Transplant. 2009;9 Suppl 4:S227.

184. Park JM, Lake KD, Arenas JD, Fontana RJ. Efficacy and safety of low-dose valganciclovir in the prevention of cytomegalovirus disease in adult liver transplant recipients. Liver Transpl. 2006;12:112.

185. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2004;4:611.

186. Singh N, Dummer JS, Kusne S, et al. Infections with cytomegalovirus and other herpesviruses in 121 liver transplant recipients: transmission by donated organ and the effect of OKT3 antibodies. J Infect Dis. 1988;158:124.

187. Razonable RR. Cytomegalovirus infection after liver transplantation. Liver Transpl. 2010;16:S45.

188. Munoz-Price LS, Slifkin M, Ruthazer R, et al. The clinical impact of ganciclovir prophylaxis on the occurrence of bacteremia in orthotopic liver transplant recipients. Clin Infect Dis. 2004;39:1293.

189. George MJ, Snydman DR, Werner BG, et al. The independent role of cytomegalovirus as a risk factor for invasive fungal disease in orthotopic liver transplant recipients. Boston Center for Liver Transplantation CMVIG-Study Group. Cytogam, MedImmune, Inc. Gaithersburg, Maryland. Am J Med. 1997;103:106.

190. Falagas ME, Snydman DR, Griffith J, et al. Effect of cytomegalovirus infection status on first-year mortality rates among orthotopic liver transplant recipients. The Boston Center for Liver Transplantation CMVIG Study Group. Ann Intern Med. 1997;126: 275.

191. Singh N, Paterson DL, Gayowski T, et al. Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus I.V. ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, controlled trial. Transplantation. 2000;70:717.

192. Husain S, Tollemar J, Dominguez EA, et al. Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: prospective, multicenter, case-controlled study. Transplantation. 2003;75:2023.

193. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503.

194. Reed A, Herndon JB, Ersoz N, et al. Effect of prophylaxis on fungal infection and costs for high-risk liver transplant recipients. Liver Transpl. 2007;13: 1743.

195. Singh N, Wagener MM, Gayowski T. Safety and efficacy of isoniazid chemoprophylaxis administered during liver transplant candidacy for the prevention of posttransplant tuberculosis. Transplantation. 2002;74:892.

196. Albright JB, Bonatti H, Mendez J, et al. Early and late onset Clostridium difficile-associated colitis following liver transplantation. Transpl Int. 2007;20:856.

197. Riddle DJ, Dubberke ER. Clostridium difficile infection in solid organ transplant recipients. Curr Opin Organ Transplant. 2008;13:592.

198. Arthurs SK, Eid AJ, Pedersen RA, et al. Delayed-onset primary cytomegalovirus disease after liver transplantation. Liver Transpl. 2007;13:1703.

199. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. Clin Infect Dis. 2003;36:46.

200. Freifeld AG, Iwen PC, Lesiak BL, et al. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. Transpl Infect Dis. 2005;7:109.

201. Peetermans WE, Endtz HP, Janssens AR, van den Broek PJ. Recurrent Listeria monocytogenes bacteraemia in a liver transplant patient. Infection. 1990;18:107.

202. Fishman JA, AST Infectious Diseases Community of Practice. Introduction: infection in solid organ transplant recipients. Am J Transplant. 2009;9 Suppl 4:S3.

Key References

Aggarwal R, Krawcyznski K. Sleisenger and Fordtran's gastrointestinal and liver disease, pathophysiology/diagnosis/management. 2013;1337–42.

Feld JJ, Heathcote EJ. Hepatitis caused by other viruses. Sleisenger and Fordtran's gastrointestinal and liver disease, pathophysiology/diagnosis/management. 2013;1343–50.

Kim AY, Chung RT. Bacterial, parasitic and fungal infections of the liver, including liver abscess. Sleisenger and Fordtran's gastrointestinal and liver disease, pathophysiology/diagnosis/management. 2013;1351–69.

Sjogren MH, Cheatham JG, Hepatitis A. Sleisenger and Fordtran's gastrointestinal and liver disease, pathophysiology/diagnosis/management. 2013;1279–85.