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Infectious Diseases and the Liver

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The liver contains approximately one-third of the reticuloendothelial system mass in humans. As the recipient of both the portal and systemic circulation, the liver plays an important role in host defense against invasive microorganisms. The impact of microbial pathogens on the liver can vary greatly, presenting with a wide variety of manifestations from asymptomatic elevations in aminotransaminases, acute liver failure, hepatic fibrosis, and cirrhosis. This article will review involvement of the liver during systemic infections with organisms that are not considered to be primarily hepatotropic.

(Table 1)

VIRUSES

Epstein Barr Virus (EBV)

EBV is a member of the herpes virus group and up to 95% of the adult population is seropositive for EBV. The virus typically causes an infectious mononucleosis syndrome (fever, sore throat and lymphadenopathy) in adolescents and young adults who have not had prior exposure. A minority of patients (2–15%) will have gastrointestinal complaints such as nausea and abdominal pain, and less than 5% will have jaundice. On exam up to 14% of patients have hepatomegaly and one-half have splenomegaly. [1] Severe, fulminant hepatitis

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occurs very rarely and usually in immunosuppressed patients. Despite the infrequency of liver-related complaints and findings observed clinically, most patients with EBV–associated mononucleosis have abnormal liver function tests. Upwards of 90% of patients will have mild elevations of aminotrransferases (two to three times the upper limit of normal), which typically manifest in the second week of the illness and resolve by week six. Mild elevations in alkaline phosphatase (60% of patients) and bilirubin (45%) are also observed, with cholestasis occurring in less than 5% of cases. [1–3] EBV replicates primarily in nasopharyngeal epithelial cells and B lymphocytes. However, infection of hepatocytes by EBV has been demonstrated in patients with post-transplant lymphoproliferative disease .[4] The mechanism of liver damage has not been well defined, but likely involves the host immune responses to EBV antigens.[5,6]

The diagnosis of EBV infection usually relies on serology or a positive heterophile antibody. Typically, patients with EBV infections will have a positive IgM antibody. Liver biopsy findings vary, but typically include a sinusoidal infiltrate of mononuclear cells in a single file, the so-called Indian bead or Indian file pattern, mixed portal tract inflammatory infiltrate, and mild hepatocyte ballooning and vacuolization. Epitheliod granuloma formation and steatosis have also been described .[7] More specific adjunctive molecular testing including in situ hybridization and polymerase chain reaction (PCR) testing have been successfully used in both transplant and native liver specimens. Conflicting results have been reported on the utility of immunohistochemical staining of EBV antigens in liver biopsy specimens. [7–9].

The treatment of EBV associated hepatitis is generally supportive, however there are case reports of successful treatment with severe EBV hepatitis in both immunocompetent [5] and post liver transplant patients.[10]

Cytomegalovirus

Like EBV, cytomegalovirus (CMV) is a member of the herpes virus family with high (60–100%) seroprevalence rates in adults.[11] CMV also causes an infectious mononucleosis syndrome with concomitant hepatitis. The mononucleosis syndrome caused by CMV in immunocompetent hosts is very similar to EBV associated illness except splenomegaly is less frequent. Aminotransferase elevations are also common with abnormal AST levels in up to 91% of immunocompetent patients; only 2.8% had a total billirubin level greater than 2.0. [12] The characteristics of liver biopsies among immunocompetent patients are a sinusoidal and portal lymphocytic infiltrate and granulomas.[12–14] Owl’s eye nuclear inclusion bodies may also be found in hepatocytes and bile duct epithelium. [12,13].

Diagnosis of an acute CMV syndrome is confirmed by the presence of IgM antibodies. However, the disease course and diagnostics work up are quite different among immunocompromised hosts, including liver transplant recipients. Clinical features, prevalence, diagnosis, and management of systemic CMV infection, and possible association with rejection post liver transplant are well described elsewhere.[15] The incidence of CMV hepatitis following liver transplantation varies from 2–34%.[16,17] Factors including immunosuppressive regimen, use of antiviral prophylaxis, and donor and recipient serostatus likely contribute to this variability in incidence. A large retrospective study of over 1146 liver transplant recipients between 1988 and 2000 found CMV hepatitis in 24 (2%) patients.[17] Of those cases, 18 occurred in seronegative patients, five in seropositive patients, and one had an unknown serostatus. The majority of the cases occurred between week 4–8 post transplant and, interestingly, only three cases were noted after 1996 (after which roughly half of the patients positive for the CMV matrix protein pp65, a protein which can be detected prior to symptoms of disease, received oral ganciclovir preemptively). Twenty-two of the 24 patients had isolated hepatitis with two

having disseminated disease; all of these patients had lower graft survival rates comparable to those without CMV hepatitis. A multivariate analysis indicated that the significant risk factors for the development of CMV hepatitis included donor positive/recipient negative serostatus, OKT3 treatment and HLA-DR matches. Diagnosis is aided by molecular techniques including quantitative CMV DNA PCR from blood, and special staining for viral antigens. The histopathological findings of CMV hepatitis post liver transplant may include viral inclusion bodies. However, this is not consistent,[18] and microabscesses have also been found to be more prevalent in the transplant setting. Treatment of immunocompetent patients is generally supportive, whereas ganciclovir and valganciclovir are generally used in immunocompromised patients, including transplant recipients.[15]

Herpes Simplex Virus (HSV) and other Herpes Viruses

HSV-1 typically causes orolabial infections and has an estimated seroprevalence of 62%. HSV-2 causes genital disease and has an estimated seroprevalence in the United States of 17% among adolescents and young adults.[19] Hepatic involvement during infections with HSV 1 and HSV 2 is rare, and most cases in the medical literature have had acute liver failure. Thus, the full spectrum of liver involvement during disseminated HSV is not well characterized and may be biased toward the more severe hepatitis cases. Of the approximately 100 cases described in the literature, less than 10 were described in immunocompetent patients. The remainder of cases had varying degrees of impaired immunity, including neonates, malnourished children, pregnant women, and patients receiving immunosuppressive medications.[20] Clinical presentation [21] includes fever (82%), severe abdominal pain (33%), concomitant lesions suggestive of HSV (57%), and hepatomegaly (45%). Jaundice was uncommon. Laboratory findings typically include abnormal liver tests (71%), WBC count of less than 5,000/mm^3 (43%) and thrombocytopenia (45%). Other reviews describe very high elevations of transaminases (up to 100 times the upper limit of normal) [22] with only minor elevations in bilirubin.[20] Liver biopsy typically reveals extensive necrosis with hemorrhage, minimal inflammatory cells and hepatocytes with intranuclear inclusions. The diagnosis of HSV-associated hepatitis is often difficult, with only 12 of the 52 cases having a correct diagnosis established prior to death in one case series.[21] The finding of acute liver failure with fever, leucopenia, and thrombocytopenia without jaundice, even in the absence of suspicious mucocutaneous lesions, should arouse suspicion for HSV hepatitis. Adjunctive immunohistochemical staining for HSV may help in establishing the diagnosis. Hepatitis associated with other herpes viruses including HHV-6 and HHV-7 in immunocompromised patients and disseminated varicella zoster infections have also been reported.

The pathogenesis of HSV hepatitis remains speculative and proposed mechanisms include a large inoculum of HSV, an impaired immune response including possible hypersensitivity reactions, enhanced virulence of certain HSV strains and directly viral cytopathy.[21]

Early treatment with acyclovir appears to be associated with improved survival, reinforcing the need to establish the diagnosis promptly.[21,23] In one review of treated cases, 13 of 21 patients survived.[24] Given the severity of this syndrome, some authors recommend treatment with acyclovir at a dose of 10mg/kg IV every 8 hours.

Yellow Fever

Yellow fever is an arthropod-borne viral hemorrhagic fever syndrome caused by the yellow fever virus. A member of the Flavivirus genus, yellow fever virus is unique among the viral hemorrhagic fevers in its capacity to cause hepatitis and jaundice. Ninety percent of the estimated 200,000 annual cases occur in Africa and the other 10% occur in South America. [25] The incidence of infection appears to fluctuate, in many instances occurring in

epidemics (with infection incidences that may be as high as 20%) which are either seasonal, or caused by war and other events that interrupt health care delivery. As expected, more cases are reported in regions with low yellow fever vaccine coverage. Still, the scope of infection, especially in more remote areas of Africa and South America is unknown due to lack of disease reporting, limited healthcare resources for diagnosis and presence of asymptomatic or mild cases. Between 1970–2002, there were 9 reported cases (8 fatal) of yellow fever among unvaccinated travelers from the United States and Europe.[25]

The virus is spread by the *Aedes* species mosquitoes in Africa and the *Haemoagogus* species in South America. Person to person transmission does not occur. The clinical spectrum of yellow fever ranges from asymptomatic infection (5–50%) to a febrile multisystem hemorrhagic illness.[26] The incubation period is 3–6 days after acquisition of infection via bite by an infected mosquito, after which time peak viral levels are maintained, usually between 10^5 to 10^6 viral particles milliliter of blood. Most of the understanding of the clinical course of disease is descriptive, given its occurrence in areas with limited resources. The disease is described in three phases. The first phase, or “period of infection,” occurs when virus levels peak and is characterized by an acute onset of fevers, chills, myalgias, nausea and vomiting. Patients appear acutely ill and may have conjunctival injection, and temperature-pulse dissociation (Faget’s sign). This phase lasts 3–6 days. Other findings during this phase include modest elevation of transaminases, leukopenia and lack of jaundice. The second phase is a brief (less than 24 hours) recovery phase (“period of remission”) at which times symptoms and fever abate. Patients may recover from this phase and develop lifelong immunity. Fifteen to twenty-five percent progress to the 3rd phase, “the period of intoxication” which lasts from 3–8 days. During this phase, patients may have fever, emesis, abdominal pain, jaundice, coagulopathy with bleeding diathesis, and renal failure. Transaminase levels peak and are directly proportional to the severity of disease. In one study, average AST and ALT levels among fatal cases were 2766 IU/L and 660IU/L and were 929 IU/L and 351IU/L among survivors with jaundice. AST levels are higher than ALT levels due to myocardial and skeletal muscle injury. Liver pathology typically reveals mid-zonal hepatocyte necrosis and injury often with sparing of the central vein and portal tracts, minimal inflammatory cell infiltrates, and preserved reticulin framework. Infected hepatocytes undergo apoptosis with characteristic eosinophilic condensed nuclear chromatin called Councilman bodies.[27] Among patients who develop jaundice, mortality is estimated at 20–50%, usually 7–10 days afterward. The pathogenesis of severe disease is not fully understood. Proposed mechanisms include undetermined host genetic factors that confer susceptibility to infection, direct viral cytopathic effect and host cytokine dysregulation. Direct viral infection of hepatocytes and ischemia contribute to liver injury observed in yellow fever.

Diagnosis is usually established on clinical grounds in persons with an appropriate travel history. Other febrile illnesses that cause jaundice include bacterial sepsis, acute HSV hepatitis, leptospirosis, severe malaria, relapsing fever from *Borrelia recurrentis* infection, dengue hemorrhagic fever, and acute hepatitis A, B, or E infection (although fever is less likely with these hepatotropic viruses). Commercially available tests include IgG and IgM ELISAs, which may cross react with other flaviviruses, while PCR testing is available in research laboratories. There are no specific antiviral therapies available for yellow fever. A 17D live-attenuated vaccine is available for travelers to endemic regions, but is contraindicated in pregnancy, and immunosuppressed persons. Reports of serious infection with the attenuated vaccine strain have been reported but are exceedingly rare and occur in less than one per a million vaccinations.

Dengue and Dengue Hemorrhagic Fever

Dengue is an acute, usually self-limited febrile zoonotic illness commonly referred to as "breakbone fever." Dengue virus is a flavivirus with 4 antigenically similar types(1–4); however, human infection with one type does not consistently or completely confer immunity to the other types. The World Health Organization estimates that Dengue virus infects 50 million people annually.[28] The virus is spread by the mosquito, *Aedes aegypti*, and the disease distribution generally occurs within the vector's distribution(largely tropical and subtropical regions of Africa, the Caribbean, the Americas, Asia, and Australia). The incubation period ranges from several days to 1–2 weeks. The symptoms and severity of disease vary with age. Infections are often asymptomatic in children. Classic Dengue presents with fever, severe myalgias, arthralgias, headache, retro-orbital pain, gastrointestinal symptoms and rash. Minor bleeding from mucosal surfaces, hemoptysis and gastrointestinal hemorrhage can occur.[29] In contrast, Dengue hemorrhagic Fever (DHF) and Dengue Shock syndrome(DSS) are characterized by increased vascular permeability, spontaneous hemorrhage, and hypotension.

Serum aminotransaminases are increased in the majority of cases (60–80%) and can be accompanied by symptoms of acute hepatitis including right upper quadrant pain, hepatomegaly, and jaundice. The enzyme elevations peak on day 9 and return to normal levels within 2–3 weeks.[30,31] Although the presence of hepatic dysfunction generally does not confer a worse prognosis, liver involvement has been reported to be more severe in DHF and DSS and fulminant hepatic failure can occur.[31–34] Dengue virus has been isolated and antigen detected in hepatocytes suggesting that hepatocytes may support viral replication.[34,35] Recently, one group has reported that liver injury in dengue is due to direct infection of Kupffer cells and hepatocytes.[33] Pathologic evaluation of the liver reveals findings similar to those seen in yellow fever and can include: centrilobular necrosis, fatty alterations, hyperplasia of the Kupffer cells, Councilman bodies, and monocyte alteration of the portal tracts.[31,36]

The differential diagnosis of dengue is very similar to that of yellow fever. There is no effective antiviral treatment at this time and treatment is supportive. Although there are vaccine candidates in development, there are currently no approved vaccines for dengue.

BACTERIA

Systemic bacterial infections can have an impact on many organ systems including the liver. The indirect impact of these infections that is seen with syndromes such as sepsis are discussed elsewhere in this issue. Formation of abscesses in the liver is a complication of many bacterial infections. Although not a focus of this review, Table 2 describes the pathogens that have been reported to cause liver abscesses. This topic has also been reviewed in depth elsewhere.[37,38] This section will focus on bacteria with specific liver manifestations.

Typhoid Fever

Salmonella enterica serotype typhi is the causative agent of typhoid fever which is an enteric fever syndrome characterized by acute onset of fever and abdominal pain. There are approximately 16 million cases of typhoid fever and 600,000 deaths annually.[39] Most of the cases reported in the United States occur either among travelers endemic areas such as Asia and Central America or during point source outbreaks.[40] Infection usually occurs one to two weeks after ingestion of the organism. In addition to fever and abdominal pain, other clinical features of typhoid fever are variable and non-specific and include headache, relative bradycardia, leukopenia, hepatomegaly, splenomegaly. Constipation may occur as frequently as diarrhea in otherwise healthy adults whereas diarrhea occurs more frequently

in children and patients infected with HIV.[41] One of the classically described features, Rose spots, which are 2–4mm erythematous papules typically observed on the abdomen and chest, are seen in 5–30% of cases.[41] Most cases go untreated or are managed in an outpatient setting. Intestinal perforation occurs in 1–3% of those admitted for typhoid fever.[42] Hepatic involvement with Salmonella occurs via both hematogenous seeding of the liver during bacteremic periods and from infection of cells of the reticuloendothelial system. Hepatic manifestations of typhoid fever include incidental findings of hepatomegaly and abnormal liver function tests which occur in 50% of cases. A severe form of disease with jaundice can occur in 0.4–26% of cases. The elevations in serum transaminases are usually 3–5 times the upper limit of normal with AST usually being higher than the ALT. Twenty-three percent of cases have elevations in serum bilirubin and alkaline phosphatase levels are normal to slightly elevated.[43] The diagnosis of typhoid fever is established by positive blood cultures, which are positive in 60–80% of cases. Bone marrow cultures have a higher yield and may remain positive even after initiation of antibiotics.[41] Treatment generally entails a 7–10 day course of a fluoroquinolone.[41] Live oral and parenteral polysaccharide vaccines are available for travelers to endemic areas and have a protective efficacy that ranges from 50 to 96%.[41]

Mycobacterium tuberculosis

There are a variety of clinical manifestations of hepatic tuberculosis prompting some investigators [44] to further classify the various forms as miliary, granulomatous, and localized hepatic tuberoculosis. Miliary or disseminated tuberculosis accounts for 50–80% of cases. [45] Granulomatous disease refers to cases of caseating granulomatous hepatitis and fever that respond to empiric antitubercular therapy. Localized hepatic tuberculosis may occur either with or without biliary involvement. This last form, includes hepatic tuberculous abscesses and tuberculomas, but occurs in less than 1% of tuberculosis in various case series [46,47]. Yet, localized hepatic tuberculosis accounts for the majority of case series and reports of “hepatic tuberculosis” cited in the literature and, thus, will be the focus of this review. Clinical features of hepatic tuberculosis noted in a review of 4 case series (over 400 total patients) included fever in 60–90% of cases, weight loss in 55–75%, hepatomegaly in 80–95%, splenomegaly in 25–57%, and jaundice in 11–35%. Another review of 14 cases noted a median time from the onset of symptoms to presentation for medical evaluations of over 40 days.[47] Diagnostic tests showed modest elevations of transaminases (35–70%), abnormal chest radiographs (65–78%), and hepatic calcifications of plain abdominal films (50%). On computed tomography, both solitary and multiple lesions were found, and were often difficult to distinguish from malignancy, amebic or pyogenic abscesses. Caseating granulomas were observed in 51–83% of cases. In some instances, the tuberculous lesions were described as having a “hard gritty sensation” during liver biopsy [44]. Chalky hepatic and bile duct calcifications have also been described.[48] Caseating granulomas may be observed in other infections such as coccidiomycosis [49] , brucellosis[50] and Hodgkin’s disease.[51] Non-caseating granulomas have also been observed. The yield of acid fast bacillus smear and culture are low, ranging from 0–45% and 10–60% respectively.[52,53] Tissue PCR for Mycobacterium tuberculosis may have a higher sensitivity and specificity and allow for more rapid diagnosis.[52,54–56] Treatment entails standard four-drug antitubercular therapy for at least 1 year. The role of adjunctive drainage is debated and instances of biliary involvement may necessitate ERCP and stent placement.

Brucellosis

Brucellosis is a systemic febrile illness caused by zoonotic infection with Brucella species, which are small, intracellular gram negative diplococci. The four species responsible for disease in humans and their main domestic animal hosts include *B. melitensis* (sheep, goat),

B. abortus (cows), *B. canis* (dogs), and *B. suis* (pigs, boar). The majority of human infections are caused by B. melitensis. Exposure to domestic animals is the usual mode of transmission. Infection can occur through direct contact with infected animal hides and carcasses, inhalation of aerosols and ingestion of contaminated milk or milk products. The incubation period is variable and may be up to several months. Apart from fevers, chills and constitutional symptoms, clinical manifestations of brucellosis can vary widely as multiple organ systems may be involved. One of the most common findings is hepatomegaly, which occurs in 20–40% of patients.[57] A review of 530 cases of *B. melitensis* infection found hepatomegaly as the most common physical finding, occurring in 38% of cases.[58] The next most common physical finding from the same review was osteoarticular involvement, which was seen in 23% of cases. Elevations in aminotransferase levels occur in 25% of cases (range 5–40%). Jaundice is a rare finding and in a large study 5/432 had jaundice. In one series of 14 brucellosis patients with known hepatic involvement, the average ALT was 152 IU/mL (51–460) and AST was 106 IU/ML (46–240).[57] The extent of liver involvement in Brucellosis varies, and may even be species dependent. Hepatitis associated with brucella appears to be mild, with no reports of acute liver failure. In its more severe form, brucella can cause hepatic abscesses, traditionally associated with *B. suis. A* correlation with cirrhosis has been observed but is not definitive. Histopathology also varies, with the most common finding being hepatic granulomas, inflammatory cell infiltrates and mild, localized parenchymal necrosis.[57]

Diagnosing brucellosis is challenging, Serological assays are the most common diagnostic test used to make the diagnosis. The most commonly available assay is the serum agglutination assay; a titer >1:160 in the presence of a compatible illness is considered diagnostic. Titers generally remain high for prolonged periods. However this test does not detect *B. suis* infections and is not specific, as other organisms may cross-react with the test. ELISA may offer improved sensitivity and specificity, and PCR from blood and tissue specimens is promising but not yet widely available. Blood cultures have a sensitivity of 15 to 70%. Modern blood culture systems appear to have a higher yield. Bone marrow cultures have a higher yield of organisms. In both cases, laboratory personnel should be alerted to the suspicion of brucellosis.

The WHO recommends treatment with doxycycline 200mg daily for 6 weeks combined with either rifampin 600–900 mg daily for 6 weeks or IM streptomycin 1 gm daily for 2 weeks. [59]

Q fever

Q fever is a worldwide zoonotic infection caused by *Coxiella burnetii*, an intracellular gram-negative coccobacillus formerly classified as a rickettsiae. Many animals are reservoirs of infection with cattle, goats and sheep being the most frequent sources of human infection. The organism is shed in animals' urine, feces and milk and is found in very high concentrations in placental tissue. Infection typically arises after inhalation of aerosolized infectious particles, usually from parturient livestock or carcasses, although animal contact is notably absent in some cases.[60] Consumption of unpasteurized milk may also lead to infection.

The clinical spectrum of illness caused by this pathogen varies from asymptomatic infection to acute and chronic Q fever. Acute Q fever may manifest as a flu–like illness, hepatitis, and pneumonia. Illness is characterized by the acute onset of high fever, headache, and myalgias. Pneumonia, when present is usually mild without characteristic chest X-ray findings. Hepatitis typically manifests as fever and mild asymptomatic elevations (2–3 xULN) of transaminases.[61] Other gastrointestinal symptoms including nausea, vomiting and abdominal pain are uncommon. Chronic Q fever may also present as endocarditis,

osteomyelitis , arteritis with aneurysm formation and hepatitis. [62] Q fever hepatitis is seen in younger patients [63] and may even vary geographically as it appears to be more common among cases reported in Spain. In a retrospective review of over 1000 cases of Q fever in France, 40% presented with hepatitis, and only 8 total patients were suspected of having chronic hepatitis. [63] One patient had acute jaundice and liver failure necessitating transplant. Jaundice is reportedly rarely in other case series, usually less than 1% of cases. It may be difficult to distinguish Q fever hepatitis from other cases of acute hepatitis save for the presence of severe headache and fever. As with other self-limited illnesses with abnormal liver function, biopsy may not be performed, but it can prove quite useful. Liver pathology reveals minimal hepatic necrosis [64], a granulomatous hepatitis and the presence of a characteristic fibrin-ring or “doughnut-like” granulomas which are fibrin rings surrounding a lipid vacuole. Fibrin-ring granulomas have also been observed with CMV, EBV, mycobacterial infections, typhoid fever and lymphomas.[65] The pathogenesis of liver disease is felt to arise from Kupffer cells, and not direct hepatocyte infection, with ensuing granulomatous inflammatory response.[66]

The diagnosis of Q fever is usually established by positive serology, usually indirect immunofluorescent assays.[62] Treatment of symptomatic acute fever is doxycycline for 14 days whereas much longer (18–36 months) courses with the addition of hydroxychloroquine are required for chronic Q fever, especially endocarditis.

Leptospirosis

Leptospirosis, caused by spirochetes of the genus Leptospira., is one of the most widespread zoonotic infections in the world. Human infection is usually acquired through contact with urine from infected animals, most commonly rodents and other small mammals. Infections usually peak during late summer/early fall in temperate regions and the rainy season in the tropics. The clinical presentation of the disease is variable. Subclinical infection occurs in a majority of cases, which, in general, do not seek medical attention. Symptomatic disease generally consists of biphasic illness which can occur in 2 forms: anicteric and icteric (Weil’s Disease).Anicteric disease, generally a self-limited illness, occurs in approximately 90% of infections and presents with an abrupt onset of high fever, chills, rigors, headache, and malaise. Conjunctival suffusion occurs in 30–99% of cases, and is an important diagnostic sign. The acute phase can last 5–7 days and then is followed a brief period of improvement. A second (or immune) phase is characterized by recurrence of the symptoms and signs seen in the acute phase and may last from 4–30 days. Notably, the headache may be severe and throbbing . Other symptoms and signs include: nausea, vomiting, abdominal pain and diarrhea. Aseptic meningitis has been reported in up to 80% of cases and rash may occur in 2–30%.[67,68] Elevated transaminases and bilirubin are relatively uncommon in this phase, but hepatomegaly can occur.

Icteric disease(Weil’s Disease) is a severe form of the disease that develops in 5–10% of cases. In this form, jaundice may occur in the acute phase and last for weeks. The immune phase follows without the period of brief improvement. This phase presents with high fever, hepatic failure, and renal failure. Hemorrhagic complications, likely a result of immune complex mediated capillary injury, are common and thrombocytopenia may occur in the absence of disseminated intravascular coagulation.[69] Although conjugated bilirubin levels may rise to 80 mg/dL, transaminase elevations are usually mild to moderate(< 200 U/L). Hepatic histology is usually non-specific but may reveal intrahepatic cholestasis, hypertrophy of Kupffer cells, and, in severe cases, erythrophagocytosis.[70] Hepatocyte necrosis is usually not seen.

The disease is diagnosed by blood or urine cultures and serologies are used for confirmation of the diagnosis. Doxycycline is effective in mild disease or when utilized as disease prophylaxis. Penicillin or ceftriaxone are generally utilized in more severe disease.[71]

Other Spirochetes (Syphilis, Borrelia)

Hepatic involvement during the various stages of syphilis is a rare event in the postantibiotic era. Mild elevations in serum aminotransferase levels occur in about 10% of cases of secondary syphilis [72] whereas in a large series of over 30,000 patients, the incidence of acute syphilitic hepatitis was 0.24%.[73] Liver pathology is variable and may include evidence of gummas, caseating and non-caseating granulomas , and focal necrosis around the central vein. Hepatic architecture remains intact with cirrhosis occurring very rarely. [74,75]

Lyme disease, caused by *Borrelia burgdorferi* may also be accompanied by hepatitis, usually manifesting as incidental, asymptomatic elevations in aminotransferases. This has been reported in 20–50% of patients with erythema migrans, the initial stage of Lyme's disease. [76] Patients presenting with hepatitis as the primary manifestation of Lyme's disease are exceedingly rare and, in these instances, diagnosis requires a very high index of suspicion. There are 2 cases reported in the literature of granulomatous hepatitis presumably caused by Lyme's Disease. [77,78]

PARASITES

Evaluation of parasitic infections requires a careful clinical history including travel and exposures in order to direct further work-up. Many parasitic infections may cause liver pathology as outlined in Table 3. Schistosoma and malaria are two of the most common parasitic infections globally and will be discussed in more detail in this section.

Schistosomiasis

Schistosomiasis is a parasitic infection caused by trematode blood flukes referred to as schistosomes. The four main species capable of producing hepatic complications during human infection include *S. mansoni, S. japonicum, S, mekongi*, and *S. intercalatum*. The fifth major species, *S. haematobium* is classically associated with genitourinary complications and only rarely affects the liver.[79] There are over 200 million people worldwide with schistosomiasis, about 60% with symptomatic disease. Approximately, 20 million suffer from more severe disease which causes an estimated 100,000 deaths annually. [80,81] The geographic distribution of schistosomiasis varies by species and endemic locales are present across tropical and subtropical regions of Africa, Asia, South America, and the Caribbean. Schistosomes have a complicated life cycle with snails as an intermediate host and humans as the definitive host. Infected humans excrete eggs of the parasite in feces and urine, which can contaminate fresh, warm water, especially in areas with poor sanitation. The eggs hatch, releasing miracidia which infect susceptible snails, reproduce asexually and emerge as cercariae. The cercariae then penetrate through the human skin and transform into schistosomula. The schistosomula traverse through blood and lymph making their way to the left side of the heart and eventually into mesenteric and portal vessels where the maturing worms take up residence about 3–6 weeks after initial infection. The subsequent sexual reproduction with egg deposition in various organs elicits an immune response responsible for tissue damage and disease.[80, 82–83]

Clinical syndromes from schistosomiasis include asymptomatic infection, a self-limited cercarial dermatitis (swimmer's itch), acute schistosomiasis , and chronic schistosomiasis. Most infections occur in inhabitants of endemic regions and the severity of infection is generally proportional to the organism burden. Infections in travelers to endemic regions

with brief freshwater exposures have been reported. Most patients with the chronic form will have eosinophilia. Acute schistosomiasis may manifest as “Katayama fever” a serum-sickness like illness characterized by acute onset of fever, chills, headache, arthralgias, myalgias, diarrhea, and abdominal pain, sometimes accompanied by hepatomegaly . Chronic schistosomiasis can present with as intestinal or hepatosplenic disease. Hepatic disease is usually caused by *S. mansoni, S, japonicum*, or *S. mekongi*. The spectrum and severity of liver disease seen in schistosomiasis varies according to duration of infection and organism load. Early in the disease, egg deposition in portal vein tributaries elicits an immune response with granuloma formation, hepatomegaly and splenomegaly. This inflammatory hepatic form of schistosomiasis is usually seen in children. Five-ten percent of infected young and middle aged adults who have been infected for a number of years develop periportal or Symmers pipestem fibrosis as a consequence of the chronic inflammation. Hepatic parenchymal perfusion is usually preserved, thus hepatocyte dysfunction is generally not observed, and lobular architecture remains intact.[82,83] Liver chemistries may be normal. Nonetheless, the fibrosis can progress leading to clinical sequelae of portal hypertension including splenomegaly , bleeding esophageal varices and, with decompensated disease, encephalopathy and ascites. Stigmata of chronic liver disease are noticeably absent.[83] Patients with concomitant liver disease such as alcoholic hepatitis B or C may have an accelerated disease course.[82]

Diagnosis is based on clinical findings in patients with appropriate exposure history and microscopic examination of feces or urine for eggs. Eosinophilia is present in 33–66% of patients.[84,85] Serological assays, including ELISAs for the various schistosome species, have variable sensitivities, and cannot distinguish acute from chronic infection.[83] Praziquantel 40–60mg/kg divided into 1–3 doses for one day is the treatment of choice [82,86],.

Malaria

Malaria is caused by one of four species of the protozoan parasite, Plasmodium: Plasmodium falciparum, Plasmodim vivax, Plasmodium malariae and Plasmodium ovale. The WHO estimates that there were 246 million cases of malaria in 2006 which led to close to one million deaths.[87] It is transmitted through the bite of an infected anopheline mosquito and commonly occurs in areas where this mosquito flourishes, primarily underdeveloped tropical countries. The life cycle of all of the Plasmodium species is composed of 2 phases. The bite of the anopheline mosquito introduces sporozoites into the bloodstream which after circulating for a short period of time invade hepatocytes in the liver. The sporozoites then mature into tissue schizonts, a hepatocyte infected by a sporozoite, which can each produce thousands of merozoites. When the hepatocyte ruptures to release the merozoites, each merozoite can invade a human erythrocyte and produce an additional 20–30 merozoites through asexual replication. Infected erythrocytes then rupture to release the merozoites which are able to repeat this cycle which is termed erythrocytic schizogony. In Plasmodium vivax and ovale, which can cause relapsing malaria, sporozoites also can become dormant hypnozoites when they invade hepatocytes. These hypnozoites may remain dormant for months after an initial infection, without any symptoms of disease, before they mature to tissue schizonts and produce symptomatic infection.

The classic presentation of malaria is cyclic fever occurring every 48 to 72 hours. Shaking chills usually precede the high fever. Fever coincides with schizont rupture and can be accompanied by cough, headache, nausea, vomiting, abdominal pain, diarrhea, backache, and tachycardia. After several hours, the febrile phase is followed by severe diaphoresis and fatigue. Severe cases of Plasmodium falciparum can also present with hypotension, altered consciousness and CNS complications, hypoglycemia, renal failure, pulmonary edema and, occasionally, hepatic failure. Although the exact pathogenesis of all of these complications

is not clear, obstruction of the microvasculature related to cytoadherence of falciparum to vessel endothelia, binding of infected erythrocytes to noninfected erythrocytes, reduced erythrocyte deformability and platelet-mediated clumping of infected erythrocytes of parasitized erythrocytes are thought to be the central process. [88]

Approximately 60 percent of patients with Plasmodium falciparum or vivax may have hepatomegaly and/or splenomegaly.[89] The reports of jaundice seen with malaria vary greatly, from 2.58–5.3% of patients with falciparum malaria; however, jaundice has been reported in 11–62% of patients during epidemics.[90–92] Jaundice has been reported more commonly in falciparum compared to vivax malaria.[92] Both unconjugated and conjugated hyperbilirubinemia have been reported.[91] Causes of jaundice in malaria include: hepatocellular dysfunction, intravascular hemolysis of parasitized RBC, septicemic hepatitis, microangiopathic hemolysis associated with DIC, G6PD-related hemolysis, anti-malarial-drug induced, coexisting acute viral hepatitis, and underlying chronic hepatitis.[92]. Moderate elevations of serum aminotransferase levels are commonly seen in malaria. However, severe falciparum malaria may mimic hepatic failure with marked transaminase elevations usually accompanied by multi-organ dysfunction.[92] Liver biopsy demonstrates Kupffer cell hyperplasia with pigment deposition due to phagocytosis of erythrocytes (parasitized and unparasitized). Hepatocyte necrosis, portal inflammation, steatosis and cholestasis may also be observed especially in fatal cases.[93]

Peripheral blood smears(thick and thin) can be diagnostic for malaria however, in many cases, the number of organisms may be very low, especially in mild cases. Evaluation by an experienced examiner is recommended in these situations. Clinical history and physical examination are also important in making the diagnosis of malaria. Treatment for malaria depends on the species and the prevalence of antimalarial drug resistance in the region malaria was acquired. For chloroquine sensitive malaria, the treatment is usually chloroquine 600 mg base initially followed by 300 mg base at 6, 24 and 48 hours. Other agents utilized in the treatment of uncomplicated malaria include: mefloquine, quinine plus doxycycline, atovaquone-proguanil, and artemether plus lumefantine. For patients infected with Plasmodium vivax or ovale, chloroquine treatment is followed by 14 days of primaquine to eradicate hypnozoites. Note that primaquine is contraindicated in patients with G6PD deficiency.

FUNGI

Candida

Liver infection with Candida species usually manifests as hepatosplenic candidiasis, a complication of disseminated candida infection that is usually seen among patients with hematologic malignancies who are recovering from a prolonged severe neutropenia. Prior to the more widespread use of antifungal chemoprophylaxis among high risk patients with hematologic malignancies, the incidence of disseminated hepatosplenic candidiasis in various case series varied from 3–7%.[94,95] The incidence appears to be decreasing with the more widespread use of antifungal prophylaxis among high-risk patients.[96,97] The pathogenesis of disease is felt to arise from seeding of fungal organisms into liver and spleen after chemotherapy-induced damage to intestinal mucosa. Clinically, the classic symptom of hepatosplenic candidiasis is prolonged fever despite broad spectrum antibiotics in a patient with recovering neutropenia. The patients may also have abdominal pain and 50% will have hepatomegaly or splenomegaly, or both. Laboratory abnormalities are notable for a substantially elevated serum alkaline phosphatase level (3–5 times times upper limit of normal) in 86% [98]) and either normal or modest elevations in serum aminotransferases. Imaging is the mainstay of diagnosis with multiple, small, round lesions noted on either CT or MRI in close to 90% of patients. The characteristic “bull’s eye” appearance, or target

lesions, is one pattern well described in hepatosplenic candidiasis. Diagnosis is usually made on clinical grounds, precluding the need for more invasive measures. When performed, liver biopsy may reveal granulomatous inflammation with characteristic fungal elements demonstrated with special staining techniques. The treatment of hepatosplenic candidiasis is usually an induction course of liposomal amphotericin B, as the deoxycholate preparation does not penetrate well into liver tissue[96] and has been associated with treatment failure and relapse. [99] After induction, therapy usually consists of a prolonged course of oral fluconazole in doses of 400–800mg and serial monitoring of imaging (usually CT scans). [96,100] Optimal duration is unknown but is at least several months and most patients respond by 6 months. [99]

Other Fungi

Other fungi may involve the liver and do so in a similar manner to candida, i.e during disseminated infection in immunocompromised hosts. There do not appear to be fungi with a peculiar proclivity for liver tissue, perhaps accounting for the rarity of hepatic fungal infections in the absence of disseminated disease. Candida species normally inhabit the gastrointestinal tract , explaining the frequency with which hepatosplenic candidiasis is seen. Other fungal infections, such as those with endemic mycoses like Histoplasma capsulatum, are acquired exogenously and typically disseminate in immunocompromised hosts , most commonly those with AIDS. Disseminated histoplasmosis is a rare event after acute infection, occurring in about 1 in 2000 cases.[101–102] However, the liver is involved in up to 90% of cases of disseminated histoplasmosis. [103] The pattern of liver involvement is not well characterized and, in one review of 36 cases with hepatic infection, liver involvement was characterized by hepatomegaly and a more diffuse infiltrative infection; focal lesions were only seen in 17% of cases. When present, the focal lesions were small nodules ranging from 0.2 to 1.0 cm. In this series, the yield of visualizing organisms through special fungal stains, such as methenamine silver staining, was high. Presumably, this occurs through liver seeding during dissemination of infection due to the organisms' affinity for the reticuloendothelial system. Liver biopsy findings are variable and include sinusoidal Kupffer cell hyperplasia and granulomatous changes in 19% of cases.[104] Diagnosis [105] and treatment of disseminated histoplasmosis [106] are reviewed elsewhere. As hepatic involvement by fungi occurs almost exclusively in the context of disseminated infection in immunocompromised hosts, the diagnosis of hepatic fungal infections (with the exception of hepatosplenic candidiasis) is usually established by positive cultures or antigen tests in blood or other extrahepatic sites. Liver biopsy with fungal stains may be a useful diagnostic adjunct in difficult or atypical cases.

Summary

Due to its role as a filter, the liver is exposed to many systemic infectious pathogens. As has been noted in this review, these pathogens may directly or indirectly affect the liver depending on the characteristics of the pathogen. Liver disease in this setting may frequently be multifactorial with the pathogen, other pathogens and disease states and drug treatments all contributing. In evaluating the liver manifestations of a potential infectious pathogen, diagnosis of some of the less common infectious pathogens is dependent on a high level of suspicion and recognition of some of the key diagnostic clues. Successful diagnosis can only be accomplished through a careful history, including travel and exposures, physical examination and appropriate microbiologic studies.

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Table 1

Summary Table of Pathogens Reviewed

Viruses	**Bacteria and Mycobacteria**	**Parasites**	**Fungi**
Epstein Barr Virus (EBV]	Salmonella enterica serotype typhi	Schistosoma species (Schistosomiasis)	Candida species
Cytomegalovirus (CMV)	Mycobacterium tuberculosis	Plasmodium species (malaria)	Histoplasma capsulatum
Herpes Simplex Virus (HSV) and other Herpes Viruses	Brucella species		
Yellow Fever Virus	Coxiella bunerii (Q fever)		
Dengue Virus	Leptospira and other Spirochetes		

Table 2

Infectious Pathogens Isolated from Cystic or Mass Lesions of the Liver

Bacteria						
Aerobes		Anaerobes		Other	Parasites	Fungi
Gram-negative	Gram-positive	Gram-negative	Gram-positive			
Eschericha coli	Streptococcus species	Bacteroides species	Streptococcus species	Mycobacterium species	Entamoeba histolytica	Candida species
Klebsiella pneumoniae and other Klebsiella species	Viridans streptococcus (facultatively anaerobic)	Fusobacterium species	Peptococcus species	Chlamydia species	Echinococcus	Cryptococcus
Pseudomonas aeruginosa	Streptococcus pyogenes	Prevotella	Peptostreptococcus species			
Enterobacter species	Streptococcus pneumoniae	Eikenella	Clostridium species			
Proteus species	Staphylococcus species	Brucella species	Lactobacillus species			
Citrobacter species	Staphylococcus aureus	Veillonella species	Eubacterium			
Morganella species	Staphylococcus epidermidis	Yersinia species	Actinomyces			
Providencia species	Enterococcus species		Propionibacterium acnes			
Salmonella species	Diphtheroid species					
Hemophilus species	Listeria monocytogenes					
Serratia species	Bacillus cereus					
Legionella pneumophila						
Yersinia species						
Burkholderia						
Capnocytophaga canimorsus (facultatively anaerobic)						
Pasteurella species						
Acaligenes xylosoxidans						

Table 3

Parasitic Infections of the Liver

Parasitic Disease	Liver Pathology associated with infection
Ascariasis	Biliary hyperplasia
Babesiosis	Kupffer cell hyperplasia or infection
Capillariasis	Granulomatous hepatitis
Clonorchiasis	Cholangitis, biliary hyperplasia and obstruction, cholangiocarcinoma
Cryptosporidiosis	Biliary strictures, cholangitis
Echinococcosis	Cystic lesions
Entamoeba histolytica	Hepatic abscess
Fascioliasis	Hepatic fibrosis and necrosis, cholangitis, biliary obstruction, biliary cirrhosis
Opisthorchiasis	Cholangitis, biliary hyperplasia and obstruction, cholangiocarcinoma
Plasmodium species (malaria)	Kupffer cell hyperplasia, rarely hepatic necrosis
Schistosomiasis	Portal fibrosis, portal hypertension
Strongyloidiasis	Periportal inflammation, granulomatous hepatitis
Toxocariasis	Granulomatous hepatitis
Toxoplasmosis	Hepatitis, hepatocyte necrosis
Trypanosoma cruzi	Kupffer cell infection, fatty degeneration, fibrosis
Visceral Leishmaniasis	Kupffer cell infection, rare noncaseating granulomas