# Hepatobiliary Tract Infections

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## Introduction

Patients undergoing solid-organ and hematopoietic stem cell transplantation are at risk for numerous infections involving the hepatobiliary tract. Hepatobiliary tract infections contribute significantly to increased morbidity and mortality among recipients of solid-organ allografts, particularly in patients undergoing liver transplantation. Bacteria and less frequently yeast within the gastrointestinal tract may colonize a dysfunctional biliary system resulting in increased susceptibility for ascending cholangitis. Additionally, opportunistic viral infections such as varicella zoster virus, cytomegalovirus, and Epstein-Barr virus may trigger life-threatening acute illnesses or perpetuate malignancies during the posttransplant period. Fungal and protozoal infections may also find refuge within the biliary tract of immunosuppressed host and requiring multifaceted treatment approach. A thoughtful balance between utilization and adjustment of immunosuppressive medications, which are essential for graft preservation, while limiting the risk for opportunistic bacterial, fungal, viral, and parasitic disease, is pivotal in developing a fastidious approch towards patients undergoing allograft transplantation.

Strategies for infection prevention play an important role in mitigating the risk for infections during the posttransplant period. A thorough pretransplant assessment includes (1) surveillance of active and latent infections, (2) early institution of appropriate antimicrobial drug prophylaxis, and (3) appropriate active and passive immunization. A high level of suspicion for biliary tract and infections involving the liver along with improved new-generation diagnostic tests for early diagnosis, and prompt initiation of effective antimicrobial therapy, as expected, are deemed critical in improved patient outcomes. Lowering drug-induced immune suppression, when possible, remains pivotal in addressing management of infections in this high-risk group. Here were present a comprehensive review of important infections in transplant population involving the hepatobiliary tract.

## Bacterial Infections

### Pretransplant Cholangitis

Acute cholangitis is a common bacterial infection affecting patients undergoing liver transplantation with advanced liver and/or biliary tract disease. The disease process typically involves an ascending bacterial infection originating in the duodenum that migrates into the lower biliary tract. If untreated, the disease can progress resulting in life-threatening systemic dissemination such as bloodstream invasion, sepsis, severe sepsis, multiorgan dysfunction and death. In the pretransplant setting, cholangitis can develop as a complication of cirrhosis due to any etiology as well as be the first manifestation of chronic liver disease. Cirrhotic patients are prone to cholangitis due to altered biliary motility and anatomic aberrancy involving the biliary tract. In patients with chronic liver disease being considered for liver

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transplantation, underlying biliary disease increases the risk for cholangitis; these include patients with primary or secondary cholangitis and less commonly, other causes of primary biliary tract disease. Following transplantation, such infections may result from technical complications arising from vascular insufficiency and/or compromised biliary duct anastomoses.

In the normally functioning biliary system, the sphincter of Oddi and the constant forward flow of bile prevents retrograde spread of bacteria from the duodenum into the biliary tract. With the frequent clearing of bacteriostatic bile salts, bacterial multiplication is kept in check. These protective systems, however, are less effective in patients with chronic liver and/or biliary tract disease. Inflammatory damage to the hepatocyte and epithelial cells in the bile ducts distort the normal hepatic architecture and bile flow, predisposing to biliary stasis and gallstone formation. The presence of gallstones in turn serves as a nidus that promotes the risk for ascending cholangitis. Bile aspirated from individuals without gallstone disease is usually sterile. However, nearly 32% of bile cultures taken from cancer patients with gallstones demonstrate bacterial colonization [1].

Primary sclerosing cholangitis (PSC) is characterized by chronic inflammatory damage of the intrahepatic and extrahepatic bile ducts, the resulting fibrosis leads to strictures throughout the biliary tract. Although the precise etiology of this disease is not known, due its co-occurrence with inflammatory bowel disease, especially ulcerative colitis, autoimmune damage is presently the favored hypothesis for this progressive and devastating illness. Chronic inflammation impedes normal excretion of bile due to stricture formation and anatomic distortion of bile duct system, resulting in frequent episodes of cholangitis. Patients with PSC are also at a higher risk for gallstone formation. Endoscopic treatment to dilate or place stents in the region of severe bile duct narrowing is often undertaken to alleviate bile stasis and to reduce the risk for recurrent infections.

Secondary sclerosing cholangitis (SSC) is radiographically and clinically similar to PSC. Recurring injury to the bile ducts seen in patients with chronic gallstone disease, recurrent pancreatitis, surgical trauma to the biliary system, treatment with antineoplastic drugs, eosinophilic cholangitis, recurrent bacterial cholangitis, and HIV cholangiopathy are some of the common causes [2]. Injury to the bile duct results in anatomic damage and aberration in bile excretion predisposing to ascending bacterial colonization and infections. Finally, cholangitis may be associated with congenital diseases such Caroli disease and Caroli syndrome. Caroli disease involves the cystic dilation of intrahepatic bile ducts, and Caroli syndrome involves bile duct dilatation as well as congenital hepatic fibrosis [3]. These patients are prone to recurrent acute cholangitis, which manifest as the presenting sign in nearly two-thirds of the patients [4]. The true incidence of cholangitis is likely underestimated, as biliary strictures likely lead to frequent, and conceivably transient bacterial infection.

Acute cholangitis characteristically presents with jaundice, fever, and right upper quadrant abdominal pain. Because patients with chronic liver or biliary tract disease may be chronically jaundiced and have abdominal pain and fever from other causes such as spontaneous bacterial peritonitis, the diagnosis may not be readily perceived. In addition, intrahepatic fibrosis may prevent the development of intrahepatic biliary dilatation [5]. Among patients with hepatic cirrhosis, the diagnostic approach with ultrasound, CT scan, MRCP, and ERCP is the same as for the non-cirrhotic patient. However, ERCP carries significant risk for complications in patients with cirrhosis due to (1) the adverse effects of sedation in preexisting hepatic encephalopathy, (2) risk of uncontrolled bleeding due to coagulopathy, and (3) procedure-associated pancreatitis. ERCP-associated pancreatitis is a serious complication, especially in patients with end-stage liver disease. However, diagnosis and relief from bile duct obstruction is crucial in preventing future infections and other complications.

The causative organisms of acute cholangitis are of intestinal origin and similar to those associated with cholecystitis. Aerobic Gram-negative bacteria (GNB) such as *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp.; occasionally, Gram-positive bacteria (GPB) such as *Enterococcus* spp. are isolated. Anaerobes such as *Bacteroides fragilis* or *Clostridium perfringens* are uncommon pathogens [6]. In patients with PSC, *Candida* species are increasingly isolated from the bile cultures [7]. Concurrent yeast and bacterial polymicrobial infection may result in a more severe form of cholangitis. Systemic antifungals should be considered early in the course of therapy for acute cholangitis, especially in patients with known biliary tract yeast colonization, in whom initial empiric antibacterial therapy has failed.

Effective treatment consists of a multifaceted approach including systemic antimicrobials, biliary tract drainage, and supportive care. Current recommendations are to cover broadly for aerobic GNB, GPB, and anaerobes. More than 50% of cases respond well to conservative antimicrobial treatment alone, given for 7–10 days [8]. If patients' clinical status declines or infection fails to improve within the first 24 h after treatment with antibiotics has commenced, emergent drainage of the biliary tract is recommended. Patient with cirrhosis experience high frequency of complications following ERCP and sphincterotomy. Approximately 3–8% of cirrhotic patients will experience bleeding, and 4–5% may develop acute pancreatitis following sphincterotomy [9, 10]. Other complications such as secondary cholangitis, cholecystitis, stent occlusion, stent migration, and bile leak are also more frequent in patients with cirrhosis of liver [10]. Cholangitis in patients with PSC commonly requires dilation and/or stenting of bile duct strictures. Placement of a foreign object act as an additional nidus, that

increases the risk for future infections; recurrent cholangitis was more common after stent placement compared with PSC patients, in whom only balloon dilation was performed [10]. Finally, percutaneous transhepatic cholangiography (PTC) can be employed in cases in which ERCP is not possible due to prior surgery; however, PTC carries an increased risk for bacteremia, hemorrhage, hemobilia, and creation of vascular-biliary fistula. This technique cannot be employed in patients with significant ascites as the ascitic fluid prevents maturation of the cutaneobiliary tract [11].

For patients with frequent, recurrent cholangitis associated with surgical alterations of the biliary tract such as hepaticojejunostomy and sphincteroplasty, the use of long-term antibiotic prophylaxis with rotating antibiotic regimens including amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, or ciprofloxacin are proposed to reduce recurrences of cholangitis episodes [12, 13]. As with all long-term antibiotic prophylaxis, colonization and infection due to drug-resistant organisms remain a serious concern.

Finally, potential liver transplant recipients with PSC, during the episodes of recurrent cholangitis, have an increased risk of death; however, it is considerably lower during the intervals without such infection episodes. To account for this additional risk of death, patients who have two or more serious episodes of cholangitis requiring hospitalization and intravenous antibiotic therapy within a 6-month period are eligible to receive MELD exception points to prioritize their prospect for hepatic allograft transplantation [14].

## Posttransplantation Cholangitis

Cholangitis that occurs after transplantation procedure can be classified into conditions associated with anatomic alterations in liver transplant recipients and those associated with anti-rejection drug regimen-induced immune suppression. With the first category, bacterial pathogens are most common. In the subsequent category, polymicrobial infections associated with high level of drug-induced, cumulative immune suppression become more prominent. Temporal-relationship, and other associated features such as source of the hepatic allograft, transplantation procedure, and the underlying etiology of end-stage liver disease are important features in assessing patients with cholangitis after transplantation.

## Bacterial Cholangitis

Acute cholangitis is the most common infectious complication in liver transplant recipients and may arise at any time after undergoing transplantation. Alterations in the normal biliary anatomy predisposes to infections resulting from choledochojejunostomy anastomosis. Most surgical complications involve the biliary system; 15–30% of transplant recipients will experience a complication involving the biliary tract [15]. Surgical complications such as bile leakage, wound dehiscence, and bile duct strictures are commonly associated with the risk of cholangitis. Recurrence of primary disease in patients with PSC is a well-known risk for acute cholangitis. Finally, viral infections may involve the liver and confer a greater risk of cholangitis by promoting bile stasis.

The causes and risks associated with the infection can roughly be grouped according to two main time periods: within 30 days and after 1st month following transplantation [16]. The incidence of acute cholangitis begins to decrease after the 1st year following transplantation. This is presumably due to a decline in the risk factors for cholangitis that usually manifest early after transplant surgery.

During the first several weeks immediately following liver transplantation, surgical complications are the main cause of acute cholangitis. Acute cholangitis in the first 30 days following transplant is commonly related to biliary anastomotic leaks. Bile leaks usually manifest within the first 30 days after transplant surgery, with a mean time for presentation being 17 days [17]. Subsequently, acute cholangitis as a direct result of surgical complication becomes much less common. Placement of biliary T-tube in the duct-o-duct anastomosis increases the overall risk for complications, including the risk for cholangitis [18].

After the first month, strictures in the biliary tract become the leading cause of cholangitis. Strictures can be classified as either anastomotic or non-anastomotic strictures and typically present around 6 months after transplantation [19]. Anastomotic strictures are short, limited to the surgical anastomosis site, resulting from fibrotic scar tissue formation. Non-anastomotic strictures are typically multiple, long, and proximal to the site of anastomosis involving within the transplanted hepatic allograft. They are divided into three main groups based on causative etiology: macroangiopathic, microangiopathic, and immunogenic. Macroangiopathic strictures are related to vascular events, the most common being hepatic artery thrombosis and hepatic artery stenosis, with an incidence of 1–3% [20]. Non-anastomotic strictures due to microangiopathic complications are related to ischemic events that occur during perioperative period involving donor liver or surgical and postsurgical complications in the recipients such as inadequate tissue perfusion or the need for systemic vasopressor support. Bile duct complications are more frequent in patients undergoing living donor transplantation (LDT) due to the complex biliary and vascular grafting techniques; bile leaks and strictures may occur in up to 12.6 and 5.8% of LDT cases, respectively [21]. Finally, recurrence of primary sclerosing cholangitis can cause immunogenic strictures. Of all the causes of biliary strictures, immunogenic strictures present furthest from the transplant procedure.

The most such complications will present within the first 18 months after transplant; however, they may be encountered years after transplantation [22, 23]. Approximately 10–20% of patients undergoing transplantation for PSC will develop disease recurrence with a median presentation time of 68 months [23, 24]. These cases are associated with HLA subtype, presence of acute cellular rejection, and necessity for chronic systemic corticosteroid therapy for ulcerative colitis [24].

Transplant recipients may or may not present with typical symptoms suggestive of acute cholangitis, and comparable clinical presentation of other conditions may initially obscure the diagnosis. Abdominal pain is not uncommon after liver transplant surgery. Liver biochemistries may be abnormal due for a variety of reasons. As a result, it is often difficult to diagnose an acute episode of cholangitis based on classic physical and laboratory findings. In addition, biliary dilatation is frequently absent in patients with cholangitis due to local edema, blood clots, and sludge in the bile ducts that obscure accurate visualization of the biliary tract. Abdominal ultrasound has low diagnostic sensitivity of 38–68% [25]. As a result, diagnostic MRCP is recommended in all appropriate clinical settings.

Treatment of acute cholangitis in the transplant population is similar to treatment approach for patients with acute cholangitis during pretransplant period; prompt initiation of empiric antibiotic coverage for GNB and GPB is recommended. Concomitant fungal infection may be present in 1–12% among such infections, typically *Candida* spp., rarely *Aspergillus* spp., and it is exceedingly rare to find extrapulmonary *Pneumocystis* as a concurrent fungal pathogen [16, 26]. Antifungal coverage should also be considered in patients receiving intensified antirejection regimen. Invasive fungal disease of the biliary tract is often rapidly fatal unless effective systemic treatment is given empirically and high level of suspicion plays an important role in such decision making [27]. Finally, ERCP-assisted biliary decompression with drainage and placement of stents may be needed.

## Cholangitis Associated with Immunosuppression

Immunosuppression used to prevent or treat liver graft rejection predisposes the patients to infection with a variety of viruses and fungi which are normally harmless in individuals with intact immune function. In patients with CMV hepatitis, viral infection may extend to involve the biliary tract; fungal infections primarily *Candida* spp. and less commonly *Aspergillus* spp. may occur, especially in highly susceptible population with (1) documented fungal infection prior to transplantation; (2) advanced renal disease; (3) patients after prolonged transplant operative time; and (4) those with a choledochojejunostomy.

## Cholecystitis

Cholelithiasis and cholecystitis are prevalent in the general population, nearly 500,000 cholecystectomies are performed annually in the United States [28]. Detection and treatment of the disease among otherwise healthy individuals is generally successful without significant morbidity and mortality. However, gallbladder disease and surgery in the cirrhotic patient carries significant risk. Development of gallstones and progression to cholecystitis is common in patients with hepatic cirrhosis, this is ascribed to high levels of estrogen, unconjugated bilirubin, and increased risk for hemolysis. In patients with cirrhosis of liver, gallstones may develop at a frequency of 38% higher compared with general population [29, 30]. The prevalence of gallstones increases with disease severity, and recent studies have suggested chronic hepatitis C viral infection as an independent risk factor for gallstone disease in patients with cirrhosis [31, 32].

Clinical presentation of cholecystitis in patients with cirrhosis may be similar to that observed in the general population; however, presence of abdominal distension and abdominal pain from ascites, preexisting liver test abnormalities may obscure the diagnosis. The bacteriology of acute cholecystitis in cirrhosis is similar to that of cholecystitis in otherwise healthy patient, namely, the normal intestinal flora. Gram-negative bacilli such as *E.coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Enterobacter* spp. and anaerobes such as *Bacteroides* and *Fusobacterium* spp. are frequently isolated. Due to higher frequency of exposure to the healcare environment including hospitalization and frequent antibiotic use including antimicrobials given for prevention of spontaneous bacterial peritonitis in patients with end-stage cirrhosis; the probability of infections due to multidrug-resistant organisms (MDROs) is a concern. Colonization of the gastrointestinal tract with MDROs and unusual pathogens resulting from altered hosts' microbiota is regarded as an important contributor in the changing spectrum of the causative agents for acute cholecystitis [33, 34]. Additionally, cirrhotic patients are at increased risk for renal failure due to impairments in normal renal circulation [35]. Predictive factors for renal failure in this population include, higher baseline MELD score of greater than 27 and severity of infection; therefore, administration of albumin with antibiotics has been proposed to improve outcomes in high-risk individuals [36].

Curative therapy for cholecystitis involves surgical removal of the gallbladder, however, patients with cirrhosis are poor surgical candidates. Derangements in fluid dynamics due to portal hypertension, dysregulation in coagulation cascade, and overall poor functional performance status in patients with end-stage liver disease are some of the salient factors contributing to the significant risk associated with surgery. Cirrhosis follows cardiovascular disease such as congestive heart failure in predicting complications during and after surgery. Prior to the

advent of laparoscopic cholecystectomy, advanced cirrhosis was considered as a contraindication for cholecystectomy due to high mortality rates approaching 25–83%. Such patients were managed conservatively with systemic antibiotics and supportive care [37, 38]. Surgical complications included intra-abdominal hemorrhage, variceal bleed, development or worsening of ascites, superimposed infection(s), and cardiovascular compromise. With laparoscopy advanced cholecystectomy techniques, favorable outcomes have improved substantially [39] and should be attempted as the initial approach for a select group of patients [40]. Laparoscopic surgery is associated with shorter hospital stay, earlier resumption of enteral feeding, earlier ambulation, less blood loss, and reduced pain during the postoperative period [41]. Additionally, postoperative ascites is less common after laparoscopic procedure; probably a reflection on reduced disruption of hepatic and biliary lymphatic circulation and lower risk of bleeding in the peritoneal cavity [42]. In cases where laparoscopic total cholecystectomy is not possible due to extensive fibrosis and/or severe local inflammation, subtotal cholecystectomy procedure that leaves the posterior wall of the gallbladder intact along the liver allows symptomatic relief and clinical resolution of the infection, while mitigating the aforementioned risk of complications associated with a more invasive surgical dissection needed during total cholecystectomy procedure [42–44].

Operation risk was initially assessed with Child-Turcotte-Pugh classification. Individuals with Child-Pugh A or B score were considered safe to undergo surgical procedure, whereas those with Child-Pugh C were managed with conservative therapy alone [45, 46]. More recently, the MELD (model for end-stage liver disease) scoring system, which also includes serum bilirubin, INR, and serum creatinine levels, has shown to be a more accurate predictor of postoperative survival. In a retrospective study between 1995 and 2009, complications following surgery significantly increased in patients with MELD scores greater than 13 [47]. Postoperative complications including hemorrhage, abdominal fluid collection, wound infection, and pulmonary infection increased from 11.6% in those with a MELD score of <13 to as high as 45.8% in patients with a MELD score higher than 13 [48, 49]. Many of the surgical complications were a result of portal hypertension, which increases the risk for hemorrhage, formation of ascites, and renal failure during and after surgery. Placement of transjugular intrahepatic portosystemic shunt (TIPS) is now routinely used to lower portal circulation pressure in patients with end-stage liver disease with refractory ascites and/or recurrent, or severe varecieal bleed. This procedure has made liver and intra-abdominal surgery possible in patients, in whom such procedures otherwise would have been differed [50–53]. Patients with advanced cirrhosis are still considered high-risk candidates for laparoscopic cholecystectomy, despite best medical optimization efforts. For appropriate patients, liver transplantation is the only feasible approach. As a provi-

sional measure for patients in urgent need for biliary tract decompression, percutaneous drainage via transhepatic route by placement of cholecystostomy tube or immediate gallbladder aspiration may be considered. Numerous studies have examined this technique versus laparoscopic cholecystectomy among high-risk patients such as elderly and those with multiple comorbidities; favorable results accompanied by reduced complication rates make this as a first-line approach for a select group of high-risk individuals. Treatment success rates approach 83–85% with 30-day mortality rates between 12 and 15% among otherwise inoperable patients [54, 55]. Similar studies involving patients with severe cirrhosis have shown similar favorable outcomes [56]. Finally, placement of stents in the cystic duct during ERCP has also been evaluated. A case series involving 13 nonsurgical candidates with advanced cirrhosis and symptomatic gallbladder disease reported successful stent placement from gallbladder into the duodenum with complete resolution of symptoms and absence of major complications with the procedure [57].

## Hepatic Abscess

Hepatic abscesses are a rare, albeit a life-threatening complication in patients undergoing allograft transplantation [58]. As with other serious infections, a high index of suspicion, prompt diagnosis, and institution of appropriate therapy are the essential components for better outcome [58]. Risk factors include diabetes mellitus, hepatic artery thrombosis, and strictures involving the bile duct anastomosis site. Most liver abscesses develop within the first 3 months following transplantation surgery; liver ultrasonography remains the quickest and safest diagnostic test [58, 59]. Enteric Gram-negative bacilli are common causative organisms, including enteric organims with hyperproduction of capsular polysaccharide or those exhibiting hypermucoviscosity, such monomicrobial infections can lead to large, multiloculated intrahepatic collections. Polymicrobial infections, mixed aerobic, ananerobic bacteria and less frequently *Candida* spp. infection may occur. Treatment involves surgical or intervention radiology-assisted abscess drainage, and broad-spectrum intravenous antibiotics.

## Viral Infections

### Cytomegalovirus

Cytomegalovirus (CMV) is a member of the β-herpesvirus group and is endemic around the world with seroprevalence rates ranging from 45 to 100% [60, 61]. In immunocompetent hosts, primary CMV infection most commonly presents without symptoms or as a self-limiting mononucleosis-like

syndrome. Infected individuals harbor the virus for life in a latent phase. However, reaction of the virus in immunocompromised individuals following allograft transplantation is common and associated with significant morbidity and death [62].

Primary CMV infection in the general population presents as asymptomatic infection, and in 10% as mild self-limiting illness; whereas, life-threatening viral disease may rarely lead to severe cholestatic hepatitis and fulminant hepatic failure (FHH) [63–67]. CMV may involve any internal organ; in abdominal organ transplant recipients, gastrointestinal viral disease is most frequently encountered. In one report, FHH due to CMV infection was successfully treated with an emergency living-donor liver transplantation and ganciclovir therapy continued during the posttransplant period. Following liver transplantation, CMV is the most common viral pathogen that affects the overall outcome after transplantation. The clinical impact of CMV infection can be categorized as direct or an indirect viral effect. Direct effects of CMV can manifest as either CMV syndrome with fever, viral myelosuppression, or tissue-invasive end-organ viral disease [68]. CMV may involve any organ resulting in hepatitis, esophagitis, gastritis, enteritis, colitis, meningioencephalitis, retinitis, and pneumonitis to name a few. Transplanted liver allografts are more susceptible to tissue-invasive CMV disease compared with the risk of viral disease involving the native organ. Reactivation of latent CMV infection in CMV seropositive recipient or allograft-transmitted primary CMV infection in CMV naive liver transplant recipient are well-established risk factor for poor allograft function and patient survival [62, 69, 70]. CMV has the ability to upregulate alloantigen presentation thereby promoting the risk of both, acute and chronic allograft rejection; CMV-induced immune dysregulation included stunted hosts' cellular immune response increases the risk for infection due to other opportunistic pathogens; and its adverse impact on accelerated HCV recurrence after liver transplantation are all important issues [71]. CMV infection has been linked to the vanishing bile duct syndrome, chronic rejection noticeable by ductopenia, and extrahepatic bile duct strictures resulting in chronic cholestasis and eventual allograft failure [72–74].

## Epstein-Barr Virus Infection

Epstein-Barr virus (EBV), a member of the herpes virus family, is a nearly ubiquitous infection in humans. According to the World Health Organization (WHO), nearly 95% of the world's population by the age of 35–40 years has latent EBV infection [75]. The virus is transmitted via oropharyngeal secretions and consists of a linear DNA genome, nucleocapsid, and viral envelope. Infection is usually transmitted in early adolescence, and most primary infections are asymptomatic with only 30% presenting as acute viral illness [75]. Primary clinical EBV infection, known as infectious mononucleosis, causes a flu-like illness, patients may have fever, pharyngitis, generalized lymphadenopathy, splenomegaly, atypical lymphocytosis, and elevations in transaminase levels. Acute infection is usually a self-limiting illness and managed with supportive care; most infections resolve in 4–6 weeks. Less than 5% of patients present with jaundice [76]. In very rare instances, acute EBV infection leads to fulminant hepatic failure with jaundice, aminotransferase levels elevated to 10,000–20,000 international units; hepatic encephalopathy, coagulopathy, and thrombocytopenia are other common features. In some, an alarming progression of disease may result in nearly 90% mortality [77]. Although fulminant hepatic failure is more common in immunocompromised patients [78], this has been reported in individuals with competent immune function, both adults and children are at risk for this rare complication [79, 80]. Serologic testing confirms acute EBV primary infection; blood EBV quantitative PCR is better to assess severity of infection. Low levels of free EBV DNA are usually present in acute infection, whereas high viral DNA levels are noted in severe life-threatening cases; patients with fatal EBV infection tend to have 100× higher EBV DNA level in blood [81]. Liver transplantation is the only curative treatment once disease has progressed to fulminant hepatic failure. Although there is no expert consensus or ongoing trials to assess pharmacotherapy, high-dose steroids, antiviral agents; plasmapheresis is recommended while awaiting liver transplantation. Finally, there is limited information regarding the risk for EBV recurrence after transplantation in patients with EBV-induced liver failure. A single case report noted prevention of EBV recurrence up to 2 years after hepatic allograft transplantation with a regimen of acyclovir, low-dose antirejection immune suppression, and anti-EBV gamma globulin therapy; however, this has not been replicated in other reports [77]. In the posttransplant period, acute EBV infection can either be the result of a primary infection or more commonly reactivation of remotely acquired latent viral infection. EBV has been implicated in a number of diseases that may occur in this population, such as posttransplant lymphoproliferative disorder, lymphoma, nasopharyngeal carcinoma, Burkett's lymphoma, and Hodgkin's disease and are discussed in detail elsewhere [82–86].

## Herpes Simplex

Herpes simplex virus (HSV) is a common, double-stranded DNA virus with two subtypes HSV-1 and HSV-2; in the developed world prevalence of HSV-1 is around 80% and HSV-2 nearly 30% [87, 88]. Primary and recurrent HSV

infection may rarely result in a disseminated infection that may result in fulminant hepatitis. Less than 1% of acute liver failure and 2% of viral-induced acute liver failure are caused by HSV [87, 89]. HSV hepatitis most commonly affects infants who acquire the virus via vertical transmission and adults with impaired cellular immunity due to malignancy, HIV/AIDS, and treatment with immunosuppressive anti-rejection or anti-GVHD drugs [90–92]. Though commonly associated with immune deficiency, 25% of patients with HSV hepatitis are seen in patients with apparently competent immune function [87]. The development of HSV hepatitis can occur as a result of large inoculums at the time of initial infection that overwhelm natural immune defenses or secondary to dissemination from recrudescent herpetic lesion in the absence of an effective hosts' immune response. Virulence through reactivation of latent virus with superimposed infection due to a new viral strain and infection due to hepatotropic viral strain promote risk for HSV hepatitis [92–94].

Patients with HSV hepatitis most commonly present with fever (98%), coagulopathy (84%), encephalopathy (80%), and leukopenia (71%) [87]. A rise in transaminase levels in the absence of jaundice is a characteristic feature of severe HSV hepatitis [90]. The presence of a herpetic rash can be observed in 40–60% of cases [87, 92]. Diagnosis of HSV hepatitis is challenging, as most cases are diagnosed during postmortem examination [87]. Pelvic examination may be helpful as women may less evident vaginal or cervical herpetic lesions while sparing the vulva or perineum [87, 95]. Tzanck smear, or direct fluorescent antibody staining of skin lesions aid in diagnosis [87, 96]. Serologic testing has limited clinical use [87]. Detection of HSV DNA in blood by PCR and/or demonstration/isolation of the virus in liver biopsy samples is needed for establishing diagnosis [87, 97]. Gross pathologic specimens of HSV hepatitis are characterized by a mottled appearance with multiple red-yellow necrotic lesions. Histologic examination often reveals centrilobular hemorrhagic necrosis, scattered acidophilic bodies, and intranuclear ground-glass inclusions with margination of chromatin. The inflammatory response in these tissue specimens is often minimal [90, 98, 99].

Clinical suspicion alone should prompt initiation of high-dose intravenous acyclovir given as 10 mg/kg dose every 8 h adjusted to renal dysfunction, when present [94, 100]. In a review of 134 patients with HSV hepatitis, 49 were treated with acyclovir within 4 days of the symptoms onset; 51% deaths and progression to liver transplant vs. 81% in the untreated group was a significant difference in outcome [87]. Risk factors for death and liver transplantation include age > 40, male gender, coagulopathy, immunosuppression, encephalopathy, ALT >5000, platelets <75,000 U, and the absence of treatment with acyclovir. A delay in institution of antiviral therapy of 4.7 vs. 3.5 days from the onset of symptoms was significantly related with the risk for death or need for urgent liver transplantation. Three of seven patients who underwent orthotopic liver transplantation for HSV acute liver failure survived [87]. Children have a significantly better 5-year survival (74%) compare with long-term survival of 27% seen in adult liver transplant recipients with fulminant HSV hepatitis [92].

Acyclovir prophylaxis is recommended for all patients undergoing liver transplantation for HSV liver failure [98, 100]. However, several recent reports have noted recurrence of infection due to acyclovir-resistant HSV strains following transplantation, close monitoring is recommneded for possible recurrent infection due to a mutant viral strains [97, 98]. Foscarnet therapy followed by liver retransplantation in such cases demonstrated a 43% survival rate, though the degree of immune suppression in patients with severe sepsis-like syndrome should be deemed carefully [101–103].

## Fungal Infections

### Aspergillosis

*Aspergillus* is a ubiquitous, saprophytic fungus that is widely distributed in the natural environment and the second most common cause of invasive fungal disease (IFD) in patients undergoing liver transplantation [104, 105]. Nearly one quarter of all IFD is due to *Aspergillus* spp. and account for 1–8% of infections in the post-liver transplant period [106]. Risk factors of invasive aspergillosis include renal insufficiency, retransplantation, CMV infection, thrombocytopenia, leukocytopenia, recurrent bacterial infections, allograft dysfunction, fulminant hepatic failure, high requirement for blood and blood products, and treatment with anti-CD3 monoclonal antibodies [106–113]. Invasive aspergillosis historically manifest within 3 weeks after liver transplantation. However, several recent studies have noted that most cases of invasive aspergillosis are seen 100 days after transplant surgery [108, 114–116]. This late occurrence coincides with CMV infection and prophylaxis with fluconazole, when used does not provide adequate protection against filamentous molds such as *Aspergillus* spp. [106]. Hepatic *Aspergillus* spp. abscesses were described in liver and in renal transplant recipients, especially during treatment with high-dose corticosteroid therapy for acute allograft rejection [117, 118].

Invasive aspergillosis (IA) typically manifest as a sinopulmonary disease in patients undergoing allogeneic hematopoietic stem cell transplantation, and due to neurotropism, fungal brain involvement may also occur, although fungal brain abscesses are not common complications in allograft transplant patients with IA. Given its ability to invade blood vessels, fungus may be disseminated widely and patients may have clinically diverse presentations, including

involvement of the eyes, liver, spleen, heart, kidneys, bone, and brain [119]. In patients with seldom seen aspergillosis of the liver, fungal abscesses and mycotic aneurysms are notible presentations [117, 120–123]. Posttransplant mycotic abscesses carry a significant mortality of nearly 60%; it is important to note that ruptured mycotic aneurysm may be the initial presentation of IA in patients undergoing liver allograft transplants [117, 120–123]. Early diagnosis continues to pose a challenge and thought to contribute toward high mortality seen with these infections [124–126]. All liver abscesses require guided aspiration to establish correct diagnosis and early institution of appropriate therapy [117, 120–122]. Fungal stains and culture of fine-needle aspirates samples from intra- or extrahepatic collections should be performed routinely; however, to establish diagnosis of proven IFD, it is important to demonstrate tissue invasion by molds; and tissue biopsy should be pursued when possible in patients suspected for invasive aspergillosis [117, 120–122]. The role of ancillary fungal antigen assays such as beta D glucan and galactomannan for diagnosis of IA involving hepatic allograft remain uncertain.

Amphotericin was effective in the treatment of hepatic mycotic pseudoaneurysms [127]. Mortality rate associated with aspergillus abscesses in allograft transplant recipients was unacceptably high, despite treatment with amphotericin B [117, 120–122]. The addition of broad-spectrum triazole-based drugs such as voriconazole, posaconazole and the recent addition of isavuconazonium sulfate in the current antifungal armamentarium provided a less toxic and more effective treatment option for these life-threatening opportunistic pathogens. Similarly, echinocandins including caspofungin, micafungin, and anidulafungin also considered safe treatment option and with significantly less potential for drug-drug interaction compared with the triazole drugs. Reduced intragenic, drug-induced immune suppression is important in solid allograft transplant patients with an active invasive fungal disease, an option that is not available for patients with IFD following allogeneic HSCT. Surgical drainage, excision of necrotic tissue, or resection of the infected devitalized organ is considered as important as treatment with effective antifungal drugs [117, 119, 121, 128, 129]. However, due to various reasons, patients with IFD during posttransplant period may not be suitable candidate for surgical resection or debridement.

## Candidiasis

*Candida* is a commensal yeast normally found on skin and mucus membranes of upper respiratory, orointestinal, and genitourinary tracts [119]. Particular disease-causing species of *Candida* may lead to tissue invasive infection with a potential for widespread hematogenous systemic dissemi-

nation. Yeast colonization involving multiple body-sites, yeast overgrowth in patients with impaired milieu inflicting alterations in hosts' protective microbiota, presences of indwelling foreign devices such as intravascular catheters, and surgical drains increases the risk for invasive candidiasis in severely immunosuppressed patients undergoing transplantation. Individuals treated with extended and often multiple courses of broad-spectrum antibiotics and prolonged exposure to healthcare that includes doctors office visit, repeat hospitalizations among others, are vulnerable to these complications.

*Candida* infection plays a particularly prominent role in the development of cholangitis. In a recent retrospective study of 171 patients with PSC that were followed for 20 years, the presence of *Candida* in biliary cultures was associated with a significantly poor transplant-free survival compared to patients with sterile bile cultures [130]. Infection with *Candida* and *Enterococcus* is responsible for sclerosing cholangitis in critically ill patients, this entity represents severe biliary disease, which may rapidly progress to liver cirrhosis; distinguished from PSC by a more rapid clinical course and absence of a prior history of liver disease or injury responsible for bile duct obstruction [131].

Early diagnosis of invasive candidiasis presents a challenge as clinical features are not specific and *Candida* colonization is particularly common in such hospitalized patients; furthermore, lack of sensitivity of routine blood cultures makes diagnosis of fungemia difficult. The fungal antigen assasys like beta-D-glucan assay, which detects fungal cell wall complex sugar in blood and bronchoscopy samples, common to most clinically relevant fungi, are increasingly used to diagnose *Candida* spp. invasive disease. Several studies in renal transplant recipients have noted a diagnostic specificity of 80% and a sensitivity of 50% with this assay [132–134]. Dialysis with cellulose membranes, concomitant use of certain antibiotics, perhaps infection due to *S. pneumoniae*, use of albumin products, coagulation factors, and human plasma-derived albumin and globulin may occasionally result in false-positive detection of beta-D-glucan in sterile body fluid samples [135]. Recently, flow cytometry has been used to identify yeast colonization in patients undergoing living-donor liver transplantation [136].

Empiric antifungal therapy is recommended in organ transplant patients with persistent fever, despite treatement with broad-spectrum antibiotics [119]. Historically, amphotericin B was considered the drug of choice at a dose of 0.5–0.7 mg/kg/day [119]. Echinocandins, such as caspofungin, micafungin, or anidulafungin, have shown high degree of efficacy and excellent safety profile compared with amphotericin B in patients undergoing solid-organ and hematopoietic stem cell transplantation [137–141]. A recent case report by Goicoechea et al. has documented biliary excretion of caspofungin at levels above the $MIC_{50}$ for *C. albicans* [142].

Transient elevation of serum transaminases was observed in patients receiving caspofungin 70 mg daily along with cyclosporine; FDA has cautioned against such combination therapy [143, 144]. Fluconazole remains an alternative agent for *C. albicans* infections, although increasing resistance among the *C. glabrata* clinical isolates warrants fluconazole use as first-line agent, especially in transplant patients with invasive candidiasis, which may include anastomosis site abscesses, fungal cholangitis, with or without evidence of fungemia [145–147].

## Protozoal Infections

### Cryptosporidium

*Cryptosporidium* is a genus of protozoan parasites that causes an acute, self-limited diarrheal illness in the normal host, whereas in patients with severe immune suppression, *Cryptosporidium* may be responsible for debilitating chronic diarrheal illness. The most common species affecting humans is *Cryptosporidium parvum*, which is ubiquitous in natural water source around the world; transmission occurs via ingestion of water or food contaminated with mature oocysts. Cryptosporidiosis is an uncommon illness among transplant recipients in the United States and Europe; however, such infections are more visible in the immunosuppressed patients residing or visiting *Cryptospridium* endemic regions in the Middle East, India, South America, or Africa.

Extraintestinal manifestations are rare; biliary tract involvement has been noted in patients with advanced HIV/AIDS, those with congenital immunodeficiencies, and in patients undergoing organ allograft transplantation [148–154]. Biliary manifestations observed in patients with AIDS include acalculous cholecystitis, sclerosing cholangitis, and pancreatitis [148, 149]. Diagnosis of cryptosporidiosis is based on microscopic examination of stool with findings of oocysts similar to size and shape of yeasts [154]. Immunofluorescent assays that employ monoclonal antibodies against *Cryptosporidium* oocysts and antigen-detection assays by ELISA and immunochromatographic formats are also available and have higher sensitivity compared with stool studies using acid-fast staine. Initial management should focus on replacement of fluids and electrolytes. Treatment includes reducing the degree of drug-induced immunosuppression; antiparasitic agents active against *C. parvum* are nitazoxanide, paromomycin, or macrolide antibiotics [154]. To date, only five cases of *C. parvum*-associated sclerosing cholangitis have been reported in the transplant population [150–152]. One case was reported in an adult renal transplant recipient with a reversal of cholangiopathy secondary to *C. parvum* after reduction in immunosuppression [152]. Three other cases were in children in a series of 461 pediatric

liver transplant recipients who developed diarrhea with a diffuse cholangitis while on immunosuppression with tacrolimus and prednisone [151]. Bile duct anastomosis was revised in all three children, and one required retransplantation procedure. The fifth case was in an adult liver transplant recipient in whom the diagnosis of *C. parvum*-associated sclerosing cholangitis was made after percutaneous core biopsy of the liver showed *C. parvum* lining the bile duct epithelium [150]. In this patient, diarrhea and liver abnormalities resolved after treatment with azithromycin plus paromomycin, and follow-up liver biopsy was negative for the parasite.

### Entamoeba Histolytica

*Entamoeba histolytica* is transmitted via oral-fecal contamination; such infections are common in the developing countries and areas of poor water sanitation. Disease initially involves the intestinal mucosa, the amoeba subsequently penetrates hepatic tissue forming multiple cysts or liver abscesses throughout the organ, although most patients present with a single prominent liver lesion and other smaller cysts scattered throughtout the organ. Patients present with vague abdominal discomfort or pain and a history of prolonged diarrheal illness. Laboratory evaluation may reveal leukocytosis, but liver tests are usually unremarkable. Diagnosis includes a high index of suspicion along with fecal antigen and/or serum antigen tests. Radiographic imaging show multiple cysts in the liver. Paromomycin is recommended for treatment due to limited cyst penetration by metronidazole. Surgical drainage is generally not required.

There is no clear consensus as to increased risk for amebic liver disease in patients with hepatic cirrhosis. A report in the 1980s suggested a reduced prevalence of hepatic amebiasis in patients with cirrhosis; which was hypothesized to reflect reduced number of viable hepatocytes susceptible to amoebic invasion and severely altered hepatic architecture [155]. More recent reports, however, suggest contrary to be the case. A decade-long review of liver abscesses among cirrhotic patients in a high-incidence region of Thailand reported that 36% were due to amoebiasis [156].

Treatment is usually effective against protozoal infections; however, in nearly 7% of successfully treated individuals, residual hepatic lesions may persist on ultrasound; these are vestiges of previously treated infection and do not require further antiparasitic therapy [157]. For unclear reasons, the residual lesions can persist for years at the site of prior infection, and as long as patients are not symptomatic, this does not warrant further therapy. This holds true for individuals being considered for organ transplantation. A recent report described a patient who had residual abscess cavity after receiving treatment for amoebic liver disease; patient

underwent successful renal transplantation without infection recurrence during posttransplant follow up [158].

## Mycobacterial Infection

Tuberculosis is the most common mycobacterial infection worldwide. In the developed world, incidence of active tuberculosis infection after allograft transplantation is less than 1%. Whereas, in the developing world, active tuberculosis may be encountered in as high as 15% of transplant recipients [159, 160]. Predisposing factors for acute tuberculosis include coinfection with HCV and/or HIV and severe drug-induced cellular immune suppression [161–163]. Most cases are reactivation of latent tuberculosis rather than newly acquired, primary infection. In 63%, infection is confined to the lungs. Extrapulmonary foci of infection may be seen in 12% of the cases with active tuberculosis infection. Disseminated tuberculosis may occur in upto 25% of transplant patients and involves various extrapulmonary sites. Gastrointestinal tract is the most common non-pulmonary infection site; nearly half of such patients (48%) will demonstrate tuberculous hepatitis.

Following transplantation, diagnosis of tuberculous hepatitis may be challenging as common presenting symptoms are non-specific, which may include recurring fever, along with other constitutional symptoms, and a vague right upper quadrant discomfort. Most patients with active tuberculosis will present within first year after transplantation [160, 164]. Common laboratory findings are elevated liver enzymes, including high alkaline phosphatase levels and coagulation abnormalities. Elevated alkaline phosphatase is the most common finding seen in 75–87% of patients, whereas elevated serum transaminase levels are noted in 35–75% of patients [165, 166]. Isolated cases of tuberculous hepatitis may occur, although it is rare to see tuberculosis confined to the liver as most patients will have concurrent pulmonary disease [166, 167].

Demonstration of acid-fast bacilli and/or a positive *M. tuberculosis* cultures in liver biopsy samples confirms the diagnosis of active tuberculosis infection. In contrast to the general population, presence of granuloma in the hepatic parenchyma in itself is not diagnostic for active tuberculosis infection, especially in allograft transplant recipients as granulomas may occur with other conditions such as acute cellular allograft rejection, recurrence of PBC, infections due to nontuberculous mycobacteria; hepatosplenic candidiasis, nocardiosis, and endemic mycoses among others. In a retrospective analysis, in patients after liver transplantation, less than 3% of granulomas were attributed to active *M. tuberculous* infection [168].

The common nontuberculous mycobacterial infections in patients undergoing allogeneic HSCT or SOT, are as follows: *Mycobacterium avium complex*, *Mycobacterium haemophilum*, *Mycobacterium kansasii*, *Mycobacterium abscessus*, and *Mycobacterium chelonae*. These insidious infections may present months to years after transplantation; a variety of organ systems may be involved [169]. It is not uncommon for hepatic *M. kansasii* infection to present with a protracted febrile illness accompanied by abdominal pain; multiple liver abscesses may be seen on imaging [170]. Granulomatous liver disease due to MAC may present as portal hypertension and ascites [171]. Elevated alkaline phosphatase serum levels may be the only finding, transaminase and bilirubin levels are often within the normal range. Treatment of mycobacterial infection is presented in Chapter 56.

## Schistosomiasis

*Schistosoma* is an infection of trematode fluke that affect nearly 200 million people in the endemic regions worldwide [172]. Transmission occurs through infectious cercariae that emerge and released from freshwater snails into the local water reservoirs such as lakes, ponds, and rivers. The cercariae penetrate human skin and transform into immature worms [173]. Worms mature over 6 weeks and hone to target vessels in the mesentery and bladder, producing eggs that erode into the walls of the intestine and urinary bladder [173]. Three major *Schistosoma* species are known to cause disease. *Schistosoma mansoni* is prominent in Africa and South America, whereas *Schistosoma japonicum* intestinal and hepatic schistosomiasis is prevalent in Asia. Hepatic schistosomiasis results from entrapment of eggs lodged in the portal venules, initiating an inflammatory cascade that ultimately leads to portal fibrosis and venous congestion [173]. *Schistosoma haematobium* is associated with urinary bladder infestation; post-obstructive nephropathy is the consequence of chronic bladder and ureteral inflammation among patients in Africa and the Middle East [174, 175].

Acute schistosomiasis infection is asymptomatic although patients may experience fever, headache, myalgia, abdominal pain, or a systemic serum sickness-like reaction known as Katayama fever, which results from immune responses to parasitic invasion and migration [173]. Liver abscesses may occur in persons with early schistosome infections due to the sequestration of encapsulated bacteria in the integument of the adult worms [176]. Chronic schistosomiasis may occur in 60% of infected individuals, leading to extensive liver disease in 4–8% of cases [172, 177]. Patients with hepatic schistosomiasis may present with variceal bleeding and splenomegaly due to portal congestion; synthetic liver function indices are often normal, and histologically, tissue infiltration with inflammatory cells is routinely noted. Advanced fibrosis in patients with long-standing schistosomal infection

**Table 17.1** A summary of hepatobiliary tract infections in patients undergoing liver trnasplantation, along with clinical features, diagnosis and treatment

| Infection | Pathogens | Clinical features | Diagnosis | Treatment |
|---|---|---|---|---|
| Cholangitis | *E.coli*, *Klebsiella*, *Enterobacter*, *Enterococcus* (plus fungal following transplantation) | Jaundice, fever, RUQ pain | Ultrasound, CT, MRCP (avoid ERCP in cirrhotics) | 7–10 days antimicrobials, emergent drainage if no response within 24 h |
| Cholecystitis | *E.coli*, *Klebsiella*, *Enterobacter*, *Bacteroides* | RUQ pain | Ultrasound | Cholecystectomy, percutaneous drainage with abx if surgery contraindicated |
| Viral | CMV | Hepatitis, biliary stasis | Serum PCR, viral ctx, liver biopsy | Ganciclovir, transplant for FHH |
| | EBV | Jaundice, FHH | Serum PCR | Transplant for FHH (bridge w/ steroids, antivirals, plasmapheresis) |
| | HSV | Fever, coagulopathy, encephalopathy, leukopenia | Serum PCR, liver biopsy | IV acyclovir |
| Fungal | *Aspergillus* | Variable, usually always pulmonary involvement | Abscess drainage with culture | Itraconazole, voriconazole, or caspofungin, consider surgical drainage |
| | *Candida* | Primarily involves biliary tract (cholangitis), usually within 1st 30d of transplant | Difficult dx; can try beta-D-glucan or flow cytometry if suspicious | Amphotericin B |
| Protozoal | *Cryptococcus* | Diarrhea with cholangitis and/or cholecystitis | Stool oocysts or antibody oocyst testing | Nitazoxanide, paromomycin, or macrolides |
| | *E. histolytica* | Vague abdominal pain with diarrhea | Fecal or serum antigen, radiographic cysts | Paromomycin |
| Mycobacterial | *M. tuberculosis* | Sweats, weight loss, almost always pulmonary involvement | Biopsy with AFB stain or positive culture | Extrapulmonary TB regimen with close LFT monitoring |
| Trematode | *Schistosome* | Fever, myalgia, abdominal pain (Katayama fever – serum sickness) | Eggs in stool or on mucosal biopsy | Praziquantel (oxamniquine if *S. mansoni*) |

resembles clay pipestems histologically and known as Symmers pipestem fibrosis [178].

Diagnosis is established by demonstrating schistosome eggs in the stool sample. The extent of fecal egg output correlates with the burden of mature worms and the extent of disease in infections due to *S. mansoni* and *S. japonicum* [173]. ELISA assays are useful for population screening, however, a + ELISA test result does not predict the activity of parasite in an individual [173]. Identification of *Schistosoma* eggs on mucosal biopsy remains the most sensitive method of diagnosis, although there are no widely accepted screening guidelines for patients undergoing allograft transplantation. It has been suggested that individuals from endemic areas, particularly the Middle East, Africa, South America, and Asia, should undergo serological and stool screening for ova and parasites during the pretransplant assessment [173, 179–181].

Effective treatment of schistosomiasis is achieved with three doses of 20 mg/kg praziquantel or oxamniquine given every 8 h for *S. mansoni* infection. Early treatment can result in total resolution of fibrosis, particularly in patients with early and mild disease [182]. Response to treatment may be followed by serial stool analysis. Epidemiological studies have demonstrated that high levels of IgE correlate with long-term resistance to schistosomal reinfection in individuals residing in the endemic regions [183].

*Schistosoma*-HCV coinfection is a leading indication for transplantation in Egypt and Saudi Arabia [184–186]. Mass treatment programs for schistosomiasis prior to 1980 utilized non-disposable syringes and needles, which significantly worsened the spread of HCV and regarded as largely responsible for the high HCV prevalence and transmission rates in the North African countries [187]. Clinical studies have demonstrated that *Schistosoma*-HCV coinfection accelerates liver injury compared with HCV-positive patients without schistosomiasis; co-infection has as been known to increases the risk for hepatocellular carcinoma [184, 187–189]. It has been suggested that TH1 response, critical for containment and resolution of acute HCV infection, is downregulated by a prominent TH2 cellular immune response garnered to tackle the invading parasites [190–192].

Recent evidence has demonstrated that patients with schistosomiasis in the absence of detectable organ damage may be viable liver and kidney donors. A study compared schistosoma-positive 20 living kidney donors with 20 uninfected donors; the investigators found no significant difference in graft survival over an average of 3.5-year follow-up [193]. Several case reports have demonstrated similar findings in recipients of liver allograft from schistosoma-seropositive donors [194–196]. Moreover, a large trial by Mahmoud et al. demonstrated no significant difference in

renal allograft function; incidence and frequency of acute vs. chronic graft rejection between patients with schistosoma infection vs. no evidence of schistosoma infection [197]. In this trial, however, immunosuppression in schistosoma-positive patients was challenging due to higher doses of cyclosporine needed to achieve target blood level, which probably reflected poor intestinal drug absorption in the presence of parasitic infestation [198].

Recurrence of schistosomiasis after liver transplant is rare, with only few case reports described in the literature, and all of such cases were successfully treated with praziquantel [179, 186]. Transplant recipients are at increased risk for reinfection particularly in endemic areas where re-exposure to parasite remains high. A study in Egypt by Sobh et al. demonstrated that 23% of allograft recipients were diagnosed with reinfection during posttransplant follow-up [199]. End-stage kidney or end-stage liver disease may be present for many decades after the initial exposure to the parasites, and it is recommended that previously infected patients be treated prophylactically before undergoing allogeneic transplantation, as adult worms can survive for several years after the initial exposure [179, 194]. Table 17.1 provides a summary of hepatobiliary tract infections in patients undergoing liver transplantation.

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