Infectious Complications After Liver Transplantation

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Abstract: Orthotopic liver transplantation (OLT) is the standard of care for patients with decompensated cirrhosis and for patients with hepatocellular carcinoma. More than 6000 liver transplants are performed annually in the United States. High patient and graft survival rates have been achieved in great part due to the availability of potent immunosuppressive agents. Systemic immunosuppression has rendered the liver recipient susceptible to de novo infections as well as reactivation of preexisting latent infections. Infections occurring during the first month post-OLT are usually nosocomial, donor-derived, or the result of a perioperative complication. The development of opportunistic infections (OIs) such as *Aspergillus* and the reactivation of latent infections such as *Mycobacterium tuberculosis* are more frequent 1 to 6 months posttransplant, when the net state of immunosuppression is the highest. Immunosuppressive therapy is tapered 6 to 12 months post-OLT; therefore, infections occurring during that time period and afterward generally resemble those of the general population. Screening strategies applied to determine the risk of an infection after transplantation and the use of prophylactic antimicrobial therapy have reduced the incidence of OIs after OLT. This article will review the various causes of infection post-OLT and the therapies used to manage complications.

The increased potency of current immunosuppressive agents has improved graft and patient survival after orthotopic liver transplantation (OLT) but has also increased the incidence of opportunistic infections (OIs), which are the leading cause of morbidity and mortality post-OLT.[1] Post-OLT infections are estimated to occur in more than 50% of OLT recipients.[2] Bacterial infections account for most posttransplant infections (up to 70%), followed by viral and fungal infections.[2,3] Fortunately, due to intensive screening practices to detect latent infections in liver transplant candidates, and with the implementation of appropriate prophylactic therapy, mortality associated with post-OLT infections is low (<10%).[1,2] The

Table 1. Infectious Disease Workup for Orthotopic Liver Transplantation Candidates

Serologic testing	HBV, HAV, HCV, CMV, EBV, VZV, HIV, HTLV-1, RPR
Interferon gamma release assay	Tuberculosis (via the QuantiFERON-TB Gold In-Tube test or the T-SPOT TB test)
Testing in select cases	Parasitic infections (eg, strongyloidiasis, Chagas disease, schistosomiasis), endemic mycoses (eg, coccidioidomycosis, histoplasmosis), and viral infections (eg, WNV)

CMV, *Cytomegalovirus*; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV-1, human T-lymphotropic virus type 1; RPR, rapid plasma reagin; VZV, varicella zoster virus; WNV, West Nile virus.

risk of infection after OLT is strongly influenced by the net state of immunosuppression.[2] Other factors known to increase the risk of infections after OLT include a pretransplant Model for End-Stage Liver Disease (MELD) score greater than 30, need for a second operation after OLT, posttransplant renal replacement therapy (RRT), and an intensive care unit (ICU) stay longer than 48 hours.[3] It is standard of care to obtain a good patient history, perform a thorough physical examination, and order a comprehensive infectious disease workup (Table 1) in all solid organ transplant (SOT) candidates.[3,4] These steps allow the clinician to identify active infections that would require therapy prior to transplantation, latent infections that can reactivate after transplantation, and the need for vaccinations to reduce the risk of de novo infections after transplant.[3,4] Extended screening for specific infections such as endemic mycoses, West Nile virus (WNV), Chagas disease, and strongyloidiasis is recommended in areas where the organisms that cause these infections are endemic (Table 1).[3-5]

Due to hepatocellular dysfunction, cirrhotic patients are at increased risk of infections, including spontaneous bacterial peritonitis (SBP), cholangitis, pneumonias, urinary tract infections (UTIs), and catheter-related bloodstream infections.[5] Increased hospitalization rates among patients with decompensated liver disease also predispose patients to nosocomial infections, including *Clostridium difficile* infection (CDI).[5] According to guidelines from the American Association for the Study of Liver Diseases (AASLD), only uncontrolled sepsis and AIDS in the organ recipient preclude OLT. However, HIV-infected patients who have a CD4 count greater than 100/μL and a viral load that is expected to be completely suppressed at the time of OLT have been considered eligible for transplant.[4] According to the American Society of Transplantation (AST), mycobacterial and invasive fungal infections, as well as strongyloidiasis, are associated with high mortality after SOT. Therefore, it is recommended that these infections be treated prior to transplant.[5] The detection of an infection in the donor does not necessarily preclude organ donation; the decision is based on the urgent need for transplantation and the availability of effective therapies to control the infection after transplant.[6-9] Organ donation has been precluded if the donor has HIV infection (although donation of an HIV-infected organ to HIV+ recipients is being considered) and remains contraindicated if infections such as rabies, WNV, or lymphocytic choriomeningitis are suspected.[5,10]

The timing of a specific infection post-OLT is largely influenced by the net state of immunosuppression, environmental exposure to a specific organism, and development of surgical complications (eg, bile leak, hepatic artery stenosis, biliary strictures). Infections differ during 3 different time periods after liver transplant (<1 month, 1-6 months, and >6 months post-OLT).[2,11] OIs are generally absent during the first month after transplantation because the full effect of immunosuppression is not yet present. The most common infections in this period are nosocomial infections, surgery-related infections (eg, wound infections, cholangitis, peritonitis), donor-derived infections, or recipient-derived infections from being colonized with pathogens such as *Pseudomonas aeruginosa*.[2,11,12] During the period from 1 to 6 months post-OLT, SOT recipients can develop OIs such as aspergillosis, cryptococcosis, or toxoplasmosis. Infections due to *Pneumocystis jirovecii* or herpesviruses (*Cytomegalovirus* [CMV], Epstein-Barr virus [EBV], herpes simplex virus, and varicella zoster virus [VZV]) are less likely to appear in transplant patients receiving prophylaxis. Viral pathogens and allograft rejection cause the majority of febrile episodes during this period.[9] The late posttransplant period (after 6 months) is typically associated with a reduced frequency of infections. OIs are almost exclusively seen in patients with ongoing rejection that require intensification of immunosuppressive therapy. For patients with stable disease post-OLT, infections resemble those seen in the general population. The recurrence of chronic infections such as EBV, hepatitis C virus (HCV), and hepatitis B virus (HBV) is also seen during this time period.[1-4]

To reduce the risk of infections among OLT recipients, the AASLD recommends that all liver transplant candidates receive vaccination to avoid preventable diseases such as hepatitis A virus, HBV, measles, mumps, rubella, and VZV. Live virus vaccines are not recommended following transplantation; if indicated, they should be administered no earlier than 4 weeks prior to SOT.[4] The AASLD also recommends the administration of vaccines for diphtheria, tetanus, and pertussis; influenza; and pneumococcus prior to OLT.[4] Other measures aimed at reducing the risk of infections after OLT include antimicrobial prophylaxis, which is described in detail in the next section.

Table 2. Risk Factors Associated With Bacterial Infections After Orthotopic Liver Transplantation

Older age
Length of preoperative stay
CMV infection
Duration of surgery
Retransplantation
Volume of transfused blood products
Preoperative MELD and CTP scores
Bilioenteric anastomosis
Technical complications (eg, biliary leak, HAT)
Renal replacement therapy
Hyperglycemia

CMV, *Cytomegalovirus*; CTP, Child-Turcotte-Pugh; HAT, hepatic artery thrombosis; MELD, Model for End-Stage Liver Disease.

Adapted from Sun HY et al[3] and Kim SI.[13]

Bacterial Infections

Bacterial organisms are the leading cause of infection post-OLT, with an incidence that ranges from 53% to 70%.[2,13] Although infections can occur at any time after liver transplant, their incidence is highest during the first postoperative month due to factors such as alteration of the mucocutaneous barrier and the use of invasive devices and immunosuppression.[2,12,13] It is believed that OLT recipients are more susceptible to bacterial infections than any other SOT recipients, in part due to the complexity of the surgical procedure involved.[13] Antimicrobial agents that provide coverage for skin flora, *Enterococcus* species, anaerobic organisms, and Enterobacteriaceae are routinely used as prophylactic treatments in the immediate postoperative period. The effect of pretransplant infections on the incidence and severity of posttransplant infections has been investigated and has shown conflicting results.[14,15] It is well known that SBP is the most common infection among patients awaiting liver transplantation, followed by bloodstream infections, cellulitis, pneumonia, and UTIs.[16,17] However, pretransplant infections are not associated with a reduced patient or graft survival post-OLT.[18] The most common risk factors for bacterial infections post-OLT are listed in Table 2.[3,13]

Bacterial colonization during the perioperative period results in same-pathogen infections among some OLT recipients. Factors directly associated with liver transplantation that contribute to the risk of infection include the development of ischemia-reperfusion injury or issues directly related to the graft (eg, steatosis).[1,2,4,17,18] The amount of blood transfused intraoperatively is directly correlated with the risk of infection immediately after OLT. Postsurgical complications such as hepatic artery thrombosis and biliary strictures increase the risk of cholangitis.[17,19-21]

Over the past 15 years, there has been an increased incidence of infections caused by multidrug-resistant organisms (MDROs).[22-32] These infections are common and cause high mortality rates among OLT recipients.[13,22-24] Extended use of preoperative broad-spectrum antibiotics, preoperative fecal carriage, surgical reexploration, and a MELD score greater than 25 are known to increase the risk of posttransplant infections with MDROs.[22,23]

Chronic use of quinolones for SBP prophylaxis has led to a decrease in infections caused by enteric gram-negative bacteria, but an increase in *Staphylococcus aureus* colonization and subsequent methicillin-resistant *S aureus* (MRSA) infections after OLT.[24-27] A high prevalence of MRSA infections among OLT recipients has been documented.[24,26,27] Nearly one-third of all MRSA infections occur within 14 days of transplantation. MRSA infections appear to increase the mortality risk after OLT.[24,27] Mortality rates have been reported as high as 86% among patients with MRSA bacteremia and MRSA-related abdominal infections.[27] Parallel to an increase in MRSA, the emergence of vancomycin-resistant enterococci (VRE) has been widely documented as an important pathogen in OLT recipients.[25,31] Several studies have also reported a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae infections in SOT recipients.[26,30] The most commonly isolated ESBL-producing species are *Klebsiella pneumoniae* and *Escherichia coli*. The reported incidence of post-OLT ESBL infections is 5.5% to 7%.[26]

Colonization with *K pneumoniae* carbapenemase (KPC)-producing bacteria after OLT has been reported with increased frequency.[28,32] More than 50% of patients colonized with KPC will present with bacteremia. Reported mortality rates associated with KPC infections are as high as 89%.[28] The most common therapeutic options for patients with KPC infection are colistin (polymyxin E), a known nephrotoxic agent, and tigecycline, which is usually not effective for bacteremia.[28]

Despite the increased incidence of infections caused by MDROs after OLT, the use of broad-spectrum prophylactic antimicrobial agents with activity against MRSA and other MDROs varies by transplant center.[17,21] Selective bowel decontamination remains a controversial approach to the prevention of infections in critically ill patients awaiting OLT. A meta-analysis of OLT recipients showed that while selective bowel decontamination did not lead to a reduction in the overall incidence of infections, it significantly reduced gram-negative bacterial infections.[33] There has been an increased interest on the effect of chronic rifaximin (Xifaxan, Salix) therapy and the incidence of infections after OLT. A retrospective study

performed in 2012 showed that pretransplant rifaximin use appeared to reduce early infections post-OLT among patients with severe liver disease (MELD score >30).[34]

Finally, CDI is a major problem in SOT recipients. Fulminant colitis is more frequent in SOT recipients than in the general population (13% vs 8%, respectively).[35] The incidence of CDI is estimated to be 3% to 19% in OLT recipients (incidence <1% in the general population).[35] The incidence of CDI in SOT recipients is higher during the first 3 months after transplant, which is explained by the increased antimicrobial exposure, intense immunosuppression, and more frequent hospitalizations. Exposure to antimicrobial agents has continued to be the most important risk factor associated with the development of CDI.[35] Selection of the antimicrobial agent to treat CDI is largely based on the severity of the infection.[35] For patients with mild to moderate infection, oral metronidazole is the drug of choice. Patients with severe CDI are recommended to receive oral vancomycin 125 mg every 6 hours. In cases of severe CDI complicated with reduced gastrointestinal motility, an increased dose of vancomycin (up to 500 mg every 6 hours), the addition of intravenous (IV) metronidazole, or the use of vancomycin rectal enemas are frequently used to increase chances for response.

Reducing Bacterial Infections After Liver Transplantation

Prophylactic antimicrobial therapy is universally used in the immediate posttransplant period to reduce the incidence of bacterial infections. The selection of an appropriate antimicrobial agent is typically guided by the local epidemiology. Transplant prophylactic antibiotics should not be used beyond 48 hours posttransplantation. Prolonged use of broad-spectrum antibiotics without evidence of an active infection is always discouraged.[13-15] The use of broad-spectrum antimicrobials suppresses normal gastrointestinal flora and increases stool concentration of VRE, which increases the susceptibility for VRE acquisition and subsequent infection. Moreover, the use of broad-spectrum antimicrobial agents increases the risk of MRSA colonization and CDI.[22,23,26] Other preventive measures recommended to reduce the risk of infections post-OLT include the implementation of a strict hand hygiene regimen among all medical personnel. Isolation and contact precautions are recommended for all patients with a history of colonization or infection of MDROs. Gloves and gowns should be worn at all times when entering the patient's room.[22-26,32,35] Other interventions aimed at reducing the risk of posttransplant bacterial infections include limiting invasive devices such as urinary catheters for a minimum period of time[22,23] and decolonization of patients colonized with MRSA, which can decrease the incidence of postoperative *S aureus* infections.[24]

Fungal Infections

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality among OLT recipients,[2,36] although the overall incidence of IFIs after SOT has decreased in recent years. The annual cumulative incidence of IFIs is 1.9% among SOT recipients.[37-39] IFIs occur in 5% to 42% of OLT recipients and are associated with an increased mortality rate. Candidiasis (60%-80%) and aspergillosis (1%-8%) are the most common mycoses, with associated mortality rates of 30% to 50% and 65% to 90%, respectively.[2,37-40] IFIs are more common in OLT recipients who require surgical reexploration or retransplantation and in those who receive transfusions of large amounts of blood products. Retransplantation confers a 30-fold increased risk of IFIs.[41-43] Other factors associated with the development of IFIs include the preoperative use of broad-spectrum antibiotics, pretransplant diagnosis of fulminant hepatic failure, CMV or HCV infection, creatinine level greater than 3 mg/dL, long ICU stay, and surgical time greater than 11 hours.[40-43]

The increased mortality associated with IFIs is in part attributed to delayed diagnosis and historically limited therapeutic options.[40-43] Diagnosis relies on the identification of suggestive signs and symptoms, as well as on laboratory isolation of the causative microorganism. Laboratory identification of a fungal pathogen is difficult because some fungi have slow growth, and others can be colonizers in the absence of disease (eg, *Candida*).[43-49] An overall reduction in the incidence of IFIs after OLT is believed to be the result of improved surgical methods and techniques as well as advances in immunosuppressive therapy that has led to the limited use of corticosteroids after transplant.[40-45] Furthermore, the rapid initiation of antifungal therapy when IFIs are suspected has also reduced mortality rates among patients with fungal infections.[45,46]

Antifungal Prophylaxis

Antifungal prophylaxis in SOT recipients remains a complex and controversial issue. A targeted prophylactic strategy is used to prevent fungal infections.[43-46] Fluconazole and echinocandins are both used for targeted prophylaxis, but the latter have become the leading choice as they have fungicidal activity, prevent against fluconazole-resistant *Candida* species, and have no interaction with calcineurin inhibitors (CNIs).[37] Candidates for targeted antifungal prophylaxis include patients with a prolonged and complicated liver transplant surgery, patients who received multiple blood products, and patients with renal insufficiency requiring RRT.[2,36] In high-risk patients, antifungal prophylaxis is recommended for 7 to 14 days after SOT.[47] The use of antifungal prophylaxis in high-risk patients has reduced the incidence of fungal infections, but has

not led to improvement in overall mortality in most series.[37-39] In a meta-analysis of 10 trials of antifungal prophylaxis that included 1106 OLT recipients, fluconazole prophylaxis decreased IFIs by 75%, but did not reduce mortality.[45] Echinocandins appear to have an acceptable safety profile[44] and prevent IFIs in more than 90% of OLT recipients. In the absence of any form of antifungal prophylaxis, invasive mycoses typically occur in 36% to 50% of high-risk OLT recipients.[44-49]

Candida

Candidiasis is the most frequent fungal infection encountered post-OLT and is the leading cause of IFIs. *Candida albicans* is the most common isolated species, followed by *Candida glabrata* and *Candida tropicalis*. Risk factors for invasive candidiasis include the use of prophylactic antibiotics to prevent SBP, the need for RRT postoperatively, and retransplantation. CMV infection is a clear risk factor for all types of invasive candidal infections, and effective CMV prophylaxis among high-risk patients has been shown to significantly decrease the incidence of invasive *Candida* infection. Routine use of fluconazole prophylaxis is associated with an increased occurrence of infections with *Candida* species other than *C albicans* (eg, *C glabrata* and *Candida krusei*).[42-46] Treatment of invasive *Candida* infections in OLT recipients should reflect the type and severity of *Candida* infection and its susceptibilities, as well as the comorbid conditions of the patient.[42]

Fluconazole remains an appropriate treatment choice for mild to moderate candidemia. All azoles show significant drug-drug interactions, especially with CNIs. Careful monitoring of the levels of CNIs is recommended while patients are on azoles. Echinocandins have proven to be effective and safe when used to treat IFIs among OLT recipients. Echinocandins are the agents of choice for severe candidemia or infections caused by azole-resistant *Candida* species.[42,44] Other interventions recommended in patients with candidemia include the removal of all central venous catheters and the administration of a fundoscopic eye examination to exclude endophthalmitis.[44] Therapy is recommended for 2 weeks after the first negative blood culture. The extension of therapy is recommended when candidemia is complicated by endocarditis or endophthalmitis.[44]

Aspergillus

Aspergillus is the second most common fungal infection observed post-OLT, accounting for approximately one-fourth of IFIs.[47-49] According to reports, infection occurs at a median of 17 days posttransplantation. *Aspergillus* infection is characterized by angioinvasion, resulting in tissue infarcts that limit the eradication of infection with antifungal therapy. Disease is caused by the inhalation of airborne spores that result in pulmonary infection, with extrapulmonary dissemination to the central nervous system and virtually any other organ.[47] Extrapulmonary dissemination is common, appearing in 50% to 60% of cases of *Aspergillus* infection. Isolation of *Aspergillus* from the respiratory secretions of patients who are not immunosuppressed usually indicates colonization, but its presence in transplant recipients should not be ignored unless invasive disease can be excluded.[48,49] The diagnosis of aspergillosis can be difficult. When *Aspergillus* infection is suspected, a computed tomography scan of the chest can help in the diagnosis, as invasive pulmonary aspergillosis can manifest early as a nodular opacity with surrounding attenuation (halo sign).[48,49] Molecules that have been used as diagnostic markers of *Aspergillus* infection include galactomannan and beta-D-glucan.[47-49] The galactomannan test is an enzyme-linked immunosorbent assay that detects galactomannan, an antigen released from hyphae upon host tissue invasion.[47-49] Beta-D-glucan is another surrogate marker of IFIs. Glucan is the most important and abundant polysaccharide component of the fungal cell wall.[47-49]

Aspergillus infection is seen more frequently among patients who experience retransplantation and patients who require RRT.[48,49] A study conducted at a large transplant center showed that 25% of patients with invasive aspergillosis had undergone liver retransplantation, 82% of whom required hemodialysis at the onset of infection. Infection with CMV is also known to increase the risk of invasive aspergillosis.[47-49] The risk of invasive aspergillosis is highest during the first 30 days following retransplantation; 53% of all *Aspergillus* infections occur within this time period. Therefore, some transplant centers recommend beginning antifungal prophylaxis during this high-risk period.[47-49] The mortality risk associated with *Aspergillus* infection has been reported to be as high as 92%. Due to high mortality rates associated with this infection, it is recommended that empiric antifungal therapy be initiated with any clinical suspicion of aspergillosis.[47-49] Voriconazole is the recommended drug of choice because it has been shown to lead to better responses, improved survival, and fewer severe side effects when compared to amphotericin B.[50]

Combination therapy with voriconazole and echinocandins is reserved for refractory aspergillosis.[47-49]

Cryptococcus

Cryptococcus infection is not commonly seen post-OLT.[2] Symptoms caused by cryptococcal infection develop at a mean of 30 months after transplant. Posttransplant cryptococcal infection can manifest as pneumonia (46%), isolated meningitis (36%), disseminated disease (11%), and, less frequently, involvement of another single organ

(eg, lymph node; 7%). The mortality rate associated with this infection is reported to be as high as 25% among transplant recipients. Cryptococcal infection can be diagnosed by isolation of the fungus in blood. Detection of the serum cryptococcal antigen is helpful for the diagnosis of meningitis or disseminated disease, but lacks sensitivity in the diagnosis of cryptococcal pneumonia.[51] Patients without overt central nervous system symptoms should undergo lumbar puncture because of the possibility of subclinical meningitis.[51] Cryptococcal meningitis is treated with a combination of amphotericin B and flucytosine for 2 weeks, followed by fluconazole 400 to 800 mg/day for 8 weeks, and fluconazole 200 to 400 mg/day for 6 to 12 months.[51] Maintenance treatment can be extended in some patients based on their net status of immunosuppression.[51]

Pneumocystis jirovecii

P jirovecii is an opportunistic pathogen that can cause a severe form of pneumonitis in SOT recipients.[1,2] The incidence of *P jirovecii* pneumonia (PJP) is reported to be as high as 10% during the first 6 months after transplantation in the absence of prophylaxis.[52] Treatment with corticosteroids, CNIs, and sirolimus may initially suppress some of the early clinical findings, including dyspnea and hypoxemia, which can lead to delay in the diagnosis of this infection.[2] The risk of PJP is higher during periods of increased immunosuppression (acute rejection). Prophylactic therapy with trimethoprim (TMP)-sulfamethoxazole (SMX) has been shown to be safe and effective against PJP in OLT recipients. It is well known that the incidence of *P jirovecii* declines after the first year in SOT patients.[52] Thus, prophylaxis beyond the first year should be targeted only at patients receiving treatment for allograft rejection. Of note, TMP-SMX may not only prevent PJP, but may also prevent infections by *Toxoplasma gondii* and *Listeria* species, as well as common respiratory, skin, urinary, and gastrointestinal pathogens.[37] If TMP-SMX cannot be used (due to intolerance or allergy), alternative treatments include pentamidine, clindamycin-primaquine, TMP-dapsone, and atovaquone.[52-54]

Endemic Mycoses

Histoplasmosis

Histoplasmosis is caused by *Histoplasma capsulatum* and is found in different areas such as South America, India, and Bangladesh.[55] Within the United States, *H capsulatum* is endemic in the Ohio and Mississippi River valleys.[55,56] Any organ can be affected by *H capsulatum*, but the most common clinical findings are pneumonia, hepatosplenomegaly, gastrointestinal involvement, and pancytopenia.[55] In OLT recipients, histoplasmosis can result from primary infection or reactivation of prior infection.[55] Transmission from an infected liver allograft has also been reported.[57] However, histoplasmosis is rare in SOT recipients.[55,58] SOT recipients with mild to moderate infection can be treated with itraconazole, and for those with moderately severe and severe infection, initial therapy with amphotericin B is recommended. Treatment is usually continued until stabilization of the infection, followed by de-escalation to itraconazole to complete a total of 12 months.[55] Itraconazole decreases the metabolism of CNIs, and mammalian target of rapamycin inhibitors and levels need to be monitored on therapy. Pretransplant screening for prior histoplasmosis infection in endemic areas is usually not recommended based on the low chances for subsequent infection.[59]

Coccidioidomycosis

Coccidioidomycosis is endemic in parts of South and Central America, as well as in the southwestern region of the United States.[55,60] Coccidioidomycosis is caused by *Coccidioides immitis* and *Coccidioides posadasii*; in OLT recipients, coccidioidomycosis can result from primary infection or reactivation of prior infection, although donor-derived coccidioidomycosis has also been reported.[55,61] SOT recipients are more likely to develop severe pneumonia and disseminated infection.[55] Cutaneous, osteoarticular, and central nervous systems are the most common extrapulmonary sites.[55] In a large study from Arizona, 4% of the OLT recipients developed coccidioidomycosis, mostly during the first year posttransplant. One-third of the patients had disseminated disease, and the mortality rate was 13%.[60] Fluconazole or itraconazole is usually used to treat mild to moderate coccidioidomycosis, amphotericin B is used to treat severe pneumonia or disseminated infection, and prophylactic antifungal therapy is recommended for all SOT recipients with a history of coccidioidomycosis or positive *Coccidioides* serologies.[55] Prophylaxis is recommended for 6 to 12 months post-OLT.[60]

Blastomycosis

Blastomycosis is caused by *Blastomyces dermatitidis*, and it is endemic in the midwestern, southeastern, and south central regions of the United States.[55] It has also been reported in Canada and Africa.[62] Blastomycosis can present as a primary infection or reactivation of prior infection.[55] Cases transmitted by donors have not been reported. SOT recipients are more likely to present with severe pulmonary or disseminated infection. Therefore, amphotericin B is considered the drug of choice. Itraconazole can be used for mild infection, but close clinical monitoring is required.[55] Blastomycosis is rare after SOT; therefore, primary or secondary antifungal prophylaxis after OLT is not recommended.[55]

Tuberculosis

It is estimated that one-third of the world's population has latent tuberculosis infection (LTBI).[63] SOT recipients are at significant risk for tuberculosis reactivation, as they are up to 74 times more likely to develop active tuberculosis as compared to the general population.[64] Therefore, screening for LTBI prior to SOT with tuberculin skin testing (TST) or the quantiFERON-TB Gold In-Tube test (Quest Diagnostics) is the standard of care.[64] A thorough clinical evaluation should be performed to rule out active tuberculosis before the initiation of LTBI treatment. Therapeutic options for LTBI include isoniazid daily for 9 months, isoniazid/rifapentine weekly for 12 weeks, and rifampin daily for 4 months.[64] Isoniazid-containing regimens are effective approximately 90% of the time.[65,66] The treatment completion rate for 9-month isoniazid therapy is low (45%-60%).[67] Therefore, the shorter regimens of rifampin and isoniazid/rifapentine are appealing; however, they should not be continued after OLT because of drug-drug interactions with CNIs. Isoniazid monotherapy for 9 months is the preferred regimen for patients who are likely to undergo a liver transplant within the next few months.[64] Isoniazid-related hepatotoxicity in patients with compensated cirrhosis is uncommon.[68] The data on isoniazid/rifapentine therapy in OLT candidates are limited to 1 small study in which treatment was completed in the majority of patients, and none developed significant transaminase elevations or clinical hepatotoxicity.[69] LTBI treatment can also begin after OLT, depending on the patient's risk for LTBI treatment-induced hepatotoxicity and for progression to active tuberculosis. OLT candidates and recipients should have their transaminases checked every 2 weeks for the first 6 weeks of treatment and then monthly.[64] LTBI treatment should be stopped with a 3-fold increase in transaminases plus signs and symptoms of hepatotoxicity, or a 5-fold elevation without symptoms and signs.[70]

Active tuberculosis in SOT recipients is usually the result of LTBI reactivation, which typically occurs during the first year after SOT.[64] Donor-derived active tuberculosis has also been reported; however, it accounts for less than 5% of cases.[64] A study from Spain reported an active tuberculosis incidence of 512 cases per 100,000 patients per year among SOT recipients.[71] This incidence is suspected to be higher in countries where tuberculosis is endemic. Compared with the general population, OLT recipients have an 18-fold increase in the prevalence of active tuberculosis.[72] The clinical picture of active tuberculosis can be different in SOT, as 33% to 50% of all active tuberculosis cases after transplantation are disseminated or extrapulmonary, compared with approximately 15% of cases in immunocompetent patients.[73] Sixty-seven percent of OLT recipients had extrapulmonary involvement in 1 study.[74] The standard treatment recommended for active tuberculosis is a 4-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid and rifampin for an additional 4 months. Ethambutol can be discontinued if the *M tuberculosis* isolate is susceptible to isoniazid, rifampin, and pyrazinamide. Fluoroquinolones are useful antituberculosis agents in OLT recipients with poor hepatic function. Despite known drug-drug interactions with CNIs, a rifamycin-containing regimen is strongly preferred given its potent sterilizing activity.[64] Rifampin is usually replaced by rifabutin, which is associated with fewer drug-drug interactions. The treatment duration should be longer than 6 months for bone and joint disease, central nervous system disease, severe disseminated disease, and for patients with cavitary lesions in whom sputum cultures are still positive at the completion of 2 months of treatment.[64] OLT recipients should be monitored closely, as 50% of them may develop drug-induced hepatotoxicity during treatment for active tuberculosis.[74] Compared with the general population, OLT recipients with active tuberculosis have a 4-fold increase in the case-fatality rate.[74] In terms of prevention, all SOT candidates should be evaluated for LTBI and treated if testing is positive.[64] Organs from potential donors with active tuberculosis disease should not be used. Living donors should also be tested for LTBI. Treating living donors for LTBI prior to organ donation should be considered, especially for recent TST or interferon gamma release assay converters.[64]

Nontuberculous Mycobacteria

Most nontuberculous mycobacteria (NTM) are ubiquitous free-living saprophytic organisms.[75] The number of NTM species has significantly increased over time.[76] Infections develop following exposure in the environment, although nosocomial infections of water-contaminated medical devices have also been reported.[75] Because NTM infections are not reportable, the real incidence of NTM infections is uncertain, although it was estimated to be 0.04% in OLT recipients.[77] In a case series of 34 SOT recipients, including 4 OLT patients, the median time to NTM disease was 8 months posttransplant. The most common pathogens were *Mycobacterium abscessus* and *Mycobacterium avium* complex, and pleuropulmonary disease was the most common presentation, followed by disseminated disease.[78] Also reported in the literature are skin, soft tissue, musculoskeletal, catheter-associated, and lymphadenitis infection sites.[79,80] A multidrug regimen is recommended for 3 months to 2 years (depending on the type of infection) to treat NTM infections. Two-drug therapy can be used; however, 3 agents are

recommended when the illness is life-threatening, the burden of organisms is high, or the patient has a rapidly growing mycobacteria whose identification and susceptibilities are not yet known.[77] Surgery may be required to treat localized infections because NTM infections may persist despite antimycobacterial therapy.[77] Secondary prophylaxis after completion of NTM treatment is sometimes used. However, it is not recommended by the AST due to the lack of data.[77]

Viral Infections

Cytomegalovirus

CMV is the most common viral infection that influences outcomes after OLT.[81] The risk of infection is strongly dependent on the serologic status of both the organ donor and the recipient. In the study by Singh and colleagues,[82] CMV infection resulted in 85% of donor-positive/recipient-negative OLT patients, 33% of donor-positive or -negative/recipient-positive OLT patients, and 4% of donor-negative/recipient-negative OLT patients. CMV usually occurs during the first 3 months after OLT.[83] The incidence of CMV infection for OLT (donor-positive/recipient-negative) decreases to approximately 30% and 15% with 3 months and 6 months of CMV prophylactic treatment, respectively.[84] CMV syndrome accounts for over 60% of CMV diseases after OLT, and it is usually manifested by fever, malaise, and bone marrow suppression.[84] Less frequently, CMV may manifest as a tissue-invasive disease (eg, colitis, enteritis, esophagitis, gastritis, hepatitis, pneumonitis, encephalitis, retinitis).[84] CMV can also cause indirect effects, such as allograft rejection, vanishing bile duct syndrome, chronic ductopenic rejection, HCV recurrence, and allograft hepatitis. In addition, CMV has immunomodulatory effects, which can make patients more susceptible to developing OIs.[84] The reduction of immunosuppression should be considered in SOT patients with moderate to severe CMV disease.[85] IV ganciclovir is preferred in patients with severe or life-threatening disease. Valganciclovir is frequently used as a step-down treatment when clinical symptoms have resolved after an initial course with IV ganciclovir.[84] The duration of treatment for induction has varied from 2 to 4 weeks based on clinical and virologic response.[86] After completion of induction treatment, 1 to 3 months of maintenance treatment is recommended to prevent relapse.[85] In terms of prevention, antiviral prophylaxis for 3 to 6 months is recommended for donor-positive/recipient-negative patients after OLT. Antiviral prophylaxis for 3 months or preemptive therapy are both accepted for recipient-positive OLT recipients.[84] Valganciclovir and oral and IV ganciclovir can be used for antiviral prophylaxis.[84] Preemptive therapy consists of checking CMV polymerase chain reaction or phosphoprotein 65 antigen every week for 12 weeks after OLT, and if a positive result is obtained, treatment with valganciclovir or IV ganciclovir is indicated.[85] In the event of treatment for allograft rejection with antilymphocyte therapy or high-dose corticosteroids, the reinitiation of antiviral prophylaxis is recommended.

Epstein-Barr Virus

Primary EBV infection is uncommon in the general adult population in the United States, as more than 80% of individuals at age 19 are seropositive.[87] Therefore, the majority of OLT recipients have already been infected at the time of transplantation. EBV can also be transmitted to OLT recipients from seropositive donors and blood transfusions when nonleukoreduced blood products are used.[88] EBV infection can lead to posttransplant lymphoproliferative disease (PTLD) in SOT recipients.[88] The most common risk factors for PTLD after OLT are EBV-seronegativity in the recipient age 18 years or older, the degree of immunosuppression, and the first year posttransplant. PTLD can occur in up to 3% of adults and 15% of pediatric OLT recipients.[89] Some of the prognostic factors for poor PTLD are high-grade, monoclonal, multisite, EBV-negativity; graft or central nervous system involvement; coinfection with HBV or HCV; and poor performance status.[87-89] Mortality has been reported to be as high as 50%.[89] Treatment options are immunosuppression reduction, rituximab (Rituxan, Genentech) for CD20-positive PTLD cases, and chemotherapy.[90] Local control (surgical resection and radiotherapy) can be useful for localized liver PTLD.[89] Antiviral medications such as ganciclovir and acyclovir have been used as part of the treatment for early PTLD.[88] SOT recipients at high risk for PTLD should be monitored carefully for symptoms and signs of PTLD such as fever, lymphadenopathy, diarrhea, allograft dysfunction, weight loss, and splenomegaly.[88] PTLD can be prevented by reducing immunosuppression in patients with a high EBV viral load; in 1 study, the incidence of PTLD decreased from 16% to 2% in pediatric OLT recipients.[91]

Varicella Zoster Virus

VZV infection can present as chickenpox or herpes zoster (HZ). VZV infection has a low likelihood for organ dissemination among OLT recipients.[92-96] OLT recipients with chickenpox, disseminated HZ, organ-invasive disease, HZ ophthalmicus, or Ramsay-Hunt syndrome should be treated with IV acyclovir, and localized nonsevere dermatomal HZ can be treated with valacyclovir or famciclovir in an outpatient setting.[97] Acyclovir, valacyclovir, and famciclovir can be used for short-term treatment after OLT to prevent VZV reactivation in patients who are not receiving CMV prophylaxis.[97]

Herpes Simplex Virus

Herpes simplex virus hepatitis has been reported in OLT recipients. It appears to occur very early in the posttransplant course (20±12 days), suggesting early reactivation of the virus because of immunosuppressive drugs or donor-acquired primary infection.[96] The clinical presentations are usually nonspecific (eg, fever, highly abnormal liver function test results without jaundice, right superior quadrant abdominal pain, leukopenia), and mucocutaneous lesions are seen in less than one-third of OLT patients. Early diagnosis and treatment are essential to improve survival.[98] Prophylaxis with acyclovir is recommended for the first 3 months after OLT in patients not receiving CMV prophylaxis.

Human Herpesvirus 6

Primary infection with *human herpesvirus 6* (HHV-6) usually occurs during the first 2 years of life; most patients are asymptomatic or might present with fever followed by a maculopapular rash (exanthema subitum).[99] HHV-6 infection after OLT is usually caused by viral reactivation, transmission from the transplanted allograft or blood products, or through natural transmission in children who have never been exposed.[99] HHV-6 infections typically occur during the first 2 to 8 weeks after OLT, when the level of immunosuppression is most intense.[99] OLT recipients with HHV-6 can present with a febrile illness (sometimes associated with rash), myelosuppression, pneumonitis, neurologic diseases, and hepatitis.[99-101] HHV-6 can predispose OLT recipients to certain infections such as CMV.[99] HHV-6 hepatitis is commonly associated with acute rejection.[100] Ganciclovir, cidofovir, and foscarnet have been used for the treatment of HHV-6–associated diseases.[99]

Adenovirus

In immunocompetent patients, adenovirus is usually associated with self-limited respiratory, gastrointestinal, or conjunctival disease; however, in immunocompromised patients, adenovirus can cause severe and disseminated infections.[102] Adenovirus infections can be acquired de novo, through reactivation of a latent infection, or from the transplanted organ.[103] In 1 study, the incidence of adenovirus infection in adult OLT recipients was 6%.[104] Four patients (36%) were asymptomatic, 3 patients (27%) had UTIs, 3 patients (27%) had pneumonia and disseminated disease, and 1 patient (9%) had fulminant hepatitis.[104] The mean time to the initial detection of adenovirus was 2.2 months posttransplantation.[104] The most important component of therapy is supportive care and a decrease in immunosuppression. IV cidofovir is considered the drug of choice for the treatment of severe, progressive, or disseminated adenovirus.[103]

Parvovirus B19

Parvovirus B19 (PVB19) infection is a common illness of childhood.[105] PVB19 is usually transmitted via respiratory secretions, but it can also be transmitted through transplantation. In immunocompetent patients, PVB19 can cause erythema infectiosum in children and acute symmetric polyarthropathy in adults. Anemia is present in 99% of immunocompromised patients with PVB19 infection.[105] In 1 study, pure red cell anemia was reported in 8 OLT recipients, all of whom improved with intravenous immunoglobulin (IVIG).[106] PVB19 should be suspected in OLT recipients with erythropoietin-resistant anemia. PVB19 can also cause pancytopenia, hepatitis, myocarditis, pneumonitis, neurologic disease, or vasculitis.[105] IVIG is recommended for treatment, although the optimal dosing and duration have not been established.

Parasitic Infections

Strongyloidiasis

Approximately 100 million people worldwide have strongyloidiasis.[107] SOT patients with latent infection are at risk for hyperinfection syndrome and disseminated disease, both of which are associated with high mortality.[108,109] Donor-derived infections have also been reported.[110] Strongyloidiasis can present with acute and severe abdominal disease, bloody diarrhea, intestinal obstruction, gastrointestinal hemorrhage, pulmonary involvement, bacterial sepsis, or bacterial meningitis due to gram-negative rods or *Enterococcus* species, and it is most likely to occur in the initial months after SOT when immunosuppression is higher.[108] Ivermectin is the drug of choice, as it has an efficacy greater than 90%.[111] The administration of 2 doses of ivermectin given 2 weeks apart is recommended by the AST for uncomplicated strongyloidiasis; for hyperinfection syndrome and disseminated disease, daily doses of ivermectin should be administered until parasitic clearance, and then for 7 to 14 days afterward to prevent relapse.[108]

Toxoplasmosis

It is estimated that 30% to 50% of the world population is infected with *T gondii*.[112] Its prevalence in the United States is 10% to 20%.[113] The majority of infected patients have latent toxoplasmosis.[112] Toxoplasmosis in OLT recipients can occur through contaminated food, cat exposure, infected allograft, or reactivation of latent infection.[108] In a matched case-control study by Fernàndez-Sabé and colleagues, the most common manifestations of toxoplasmosis for OLT recipients were pneumonitis, myocarditis, and brain abscesses.[114] The time to diagnosis was approximately 3 months posttransplantation, and the crude mortality rate was 14%.[114] The recommended

treatment for active toxoplasmosis in SOT patients is pyrimethamine/leucovorin and sulfadiazine for at least 6 weeks followed by chronic suppressive therapy.[108] Universal screening for OLT candidates is recommended only in high-prevalence areas.[108] The recommended duration of prophylactic treatment with TMP/SMX is uncertain for OLT recipients.[108]

Chagas Disease

Chagas disease is endemic in most Latin American countries, as approximately 9 million people are currently infected with this disease.[108] OLT recipients can become infected with *Trypanosoma cruzi* from contaminated feces of a triatomine insect vector, or by receiving blood or organs from *T cruzi*–infected donors.[108,115] The transmission rate from seropositive donors to seronegative OLT recipients is approximately 20%.[115] Chagas cardiomyopathy should also be considered in the differential diagnosis of patients who develop cardiac complications after liver transplantation when there is positive epidemiology for Chagas disease.[116] Patients who are not treated for acute Chagas disease may become chronically infected, and one-third will become symptomatic (2/3 with chagasic cardiomyopathy and 1/3 with megacolon and megaesophagus).[117] Liver transplant programs are allowed to use livers from *T cruzi*–infected donors with informed consent from recipients, although it is recommend to monitor recipients and plan for immediate antitrypanosomal treatment if recipient infection is found.[118] Monitoring recipients with chronic *T cruzi* infection is also recommended, and treatment should be given if reactivation is detected.[108] Monitoring should be performed by checking serum for *T cruzi* DNA and peripheral blood for parasitemia weekly for 2 months posttransplant, every 2 weeks for the third month, and then monthly afterward for at least 6 months.[118] Benznidazole (5-7 mg/kg/day in 2 divided doses) for 60 days is the treatment of choice, and nifurtimox (8-10 mg/kg/day in 3 divided doses) for 90 days is the alternative treatment due to the former being better tolerated and having fewer drug interactions.[118] Chagas disease can be prevented by screening donors and recipients from Latin America and in low-prevalence countries such as the United States; thus, targeted screening of all high-risk populations is recommended.[118]

Echinococcosis

Echinococcosis is caused by *Echinococcus granulosus* or *Echinococcus multilocularis*. *E granulosus* causes cystic hydatidosis (CH), whereas *E multilocularis* causes alveolar echinococcosis (AE).[108] Patients with CH are usually asymptomatic, but symptoms can occur from the mass effect of the enlarging cyst or from leakage, rupture, or bacterial superinfection of the cyst.[108] Patients with AE are typically symptomatic, with the most common symptoms being malaise, weight loss, and right upper quadrant discomfort.[108] OLT is usually considered for patients with AE who have hilar involvement, recurrent biliary infections, secondary biliary cirrhosis, or lesions that invade the hepatic veins and the inferior vena cava. AE has been reported in parts of central Europe, central Asia, China, the northwestern portion of Canada, and western Alaska.[119] AE is difficult to treat post-OLT, as only approximately half of the patients who receive antiparasitic treatment for residual AE have favorable responses.[120] OLT candidates can receive livers with CH as long as the livers have a single and calcified cyst with no biliary tree involvement that is amenable for resection without damaging the main vascular and biliary structures.[121]

Summary

Comprehensive pretransplant infectious diseases workup, immunizations, and perioperative and prophylactic antimicrobials are vital to decrease the rate of infections after OLT. Early diagnosis and treatment of infections are usually associated with improved outcomes.

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