CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will be vigilant for infections in liver transplant recipients

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Common infectious complications of liver transplant

ABSTRACT

Major improvements in the care of liver transplant recipients have mitigated but not eliminated the risk of potentially life-threatening infectious complications. This review provides general information about risk factors, prophylactic strategies, diagnostic workup, and therapy for some of the most commonly encountered infections after liver transplant.

KEY POINTS

After liver transplant, the risk of infection and the likely causal organisms vary with the patient's state of immunosuppression and the time of infection.

Recurrent or newly acquired infections may jeopardize the survival of the graft and the recipient.

Because infections with viruses, fungi, and atypical pathogens can alter the prognosis, they need to be prevented and carefully managed.

An ongoing assessment of each patient's risk of infection allows the clinician to constantly and efficiently adapt immunosuppressive, prophylactic, and therapeutic strategies.

The immunosuppressed state of liver transplant recipients makes them vulnerable to infections after surgery.[1] These infections are directly correlated with the net state of immunosuppression. Higher levels of immunosuppression mean a higher risk of infection, with rates of infection typically highest in the early posttransplant period.

Common infections during this period include operative and perioperative nosocomial bacterial and fungal infections, reactivation of latent infections, and invasive fungal infections such as candidiasis, aspergillosis, and pneumocystosis. Donor-derived infections also must be considered. As time passes and the level of immunosuppression is reduced, liver recipients are less prone to infection.[1]

The risk of infection can be minimized by appropriate antimicrobial prophylaxis, strategies for safe living after transplant,[2] vaccination,[3] careful balancing of immunosuppressive therapy,[4] and thoughtful donor selection.[5] Drug-drug interactions are common and must be carefully considered to minimize the risk.

This review highlights common infectious complications encountered after liver transplant.

INTRA-ABDOMINAL INFECTIONS

Intra-abdominal infections are common in the early postoperative period.[6,7]

Risk factors include:

- Pretransplant ascites
- Posttransplant dialysis
- Wound infection
- Reoperation[8]
- Hepatic artery thrombosis
- Roux-en-Y choledochojejunostomy anastomosis.[9]

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doi:10.3949/ccjm.82a.14118

TABLE 1

Risk factors for common invasive infections in liver transplant recipients

Organism	Risk factors
Cytomegalovirus	Serostatus of donor and recipient (donor-positive, recipient-negative)
	Increased immunosuppression
	Antilymphocyte antibodies or high-dose mycophenolate
	Allograft rejection
	Coinfection with other herpesviruses
Epstein-Barr virus	Primary Epstein-Barr virus infection
	Cytomegalovirus donor-recipient mismatch
	Cytomegalovirus disease
	Increased immunosuppression
	Antilymphocyte antibodies
Fungal infections	Perioperative colonization
	Massive transfusion (> 40 units of blood products), choledochojejunostomy
	Retransplantation
	Hepatic iron overload
	Renal replacement therapy
	Extended intervals of intensive care before liver transplant
Pneumocystis jirovecii	Increased immunosuppression
Mycobacterium tuberculosis	Prior infection
	Increased immunosuppression
	Anti–T-lymphocyte agents
	Diabetes mellitus
	Coinfection with cytomegalovirus, fungi, *P jirovecii*, or *Nocardia*

Signs that may indicate intra-abdominal infection include fever, abdominal pain, leukocytosis, and elevated liver enzymes. But because of their immunosuppressed state, transplant recipients may not manifest fever as readily as the general population. They should be evaluated for cholangitis, peritonitis, biloma, and intra-abdominal abscess.

Organisms. Intra-abdominal infections are often polymicrobial. Enterococci, *Staphylococcus aureus*, gram-negative species including *Pseudomonas*, *Klebsiella*, and *Acinetobacter*, and *Candida* species are the most common pathogens. Strains are often resistant to multiple drugs, especially in patients who received antibiotics in the weeks before transplant.[8,10]

Liver transplant recipients are also particularly susceptible to *Clostridium difficile*-associated colitis as a result of immunosuppression and frequent use of antibiotics perioperatively and postoperatively.[11] The spectrum of *C difficile* infection ranges from mild diarrhea to life-threatening colitis, and the course in liver transplant patients tends to be more complicated than in immunocompetent patients.[12]

Diagnosis. Intra-abdominal infections should be looked for and treated promptly, as they are associated with a higher mortality rate, a greater risk of graft loss, and a higher incidence of retransplant.[6,10] Abdominal ultrasonography or computed tomography (CT) can confirm the presence of fluid collections.

Treatment. Infected collections can be treated with percutaneous or surgical drainage and antimicrobial therapy. In the case of biliary tract complications, retransplant or surgical correction of biliary leakage or stenosis decreases the risk of death.[6]

Suspicion should be high for *C difficile*-associated colitis in cases of posttransplant diarrhea. *C difficile* toxin stool assays help confirm the diagnosis.[12] Oral metronidazole is recommended in mild to moderate *C difficile* infection, with oral vancomycin and intravenous metronidazole reserved for severe cases. Colectomy may be necessary in patients with toxic megacolon.

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus is an important opportunistic pathogen in liver transplant recipients.[13] It causes a range of manifestations, from infection (viremia with or without symptoms) to cytomegalovirus syndrome (fever, malaise,

TABLE 2

Prophylaxis against common organisms in liver transplant recipients

Organism	Prophylactic strategy	Notes
Cytomegalovirus		No need for routine screening if patient is receiving prophylaxis
Donor positive	Oral valganciclovir 900 mg/day or intravenous ganciclovir 5 mg/kg/day for 3–6 months	
Recipient positive	Oral valganciclovir 900 mg/day or intravenous ganciclovir 5 mg/kg/day for 3 months	*Or* weekly cytomegalovirus viral load monitoring and initiation of therapy if viremia is noted
Fungi	Fluconazole 100–400 mg daily	Consider prophylaxis in high-risk patients
	Itraconazole 200 mg twice daily	Hepatotoxicity and drug-drug interactions more common with itraconazole vs fluconazole
	Caspofungin (*Aspergillus* spp and *Candida* spp); other echinocandins (*Candida* spp)	
	Liposomal amphotericin	Consider liposomal amphotericin in high-risk patients (extended postoperative stay in intensive care unit, renal dysfunction, high degree of immunosuppression)
	Optimal duration undetermined	
Pneumocystis jirovecii	Trimethoprim-sulfamethoxazole (single-strength daily or double-strength 3 times per week)	Widespread prophylaxis
	Or dapsone 100 mg daily	Lifelong prophylaxis in human immunodeficiency virus patients
	Or atovaquone 1,500 mg daily	
	Minimal duration of 6–12 months	
Latent tuberculosis	Isoniazid 300 mg daily for 9 months	Monitor liver function tests, ie, aminotransferases, alkaline phosphatase, and bilirubin

and cell-line cytopenias) to tissue-invasive disease with end-organ disease.[14] Without preventive measures and treatment, cytomegalovirus disease can increase the risk of morbidity, allograft loss and death.[15,16]

Risk factors for cytomegalovirus infection (**Table 1**) include:

- Discordant serostatus of the donor and recipient (the risk is highest in seronegative recipients of organs from seropositive donors)
- Higher levels of immunosuppression, especially when antilymphocyte antibodies are used
- Treatment of graft rejection
- Coinfection with other human herpesviruses, such as Epstein-Barr virus.[4,17]

Preventing cytomegalovirus infection

The strategy to prevent cytomegalovirus infection depends on the serologic status of the donor and recipient and may include antiviral prophylaxis or preemptive treatment (**Table 2**).[18]

Prophylaxis involves giving antiviral drugs during the early high-risk period, with the goal of preventing the development of cytomegalovirus viremia. The alternative preemptive strategy emphasizes serial testing for cytomegalovirus viremia, with the goal of intervening with antiviral medications while viremia is at a low level, thus avoiding potential progression to cytomegalovirus disease. Both strategies have pros and cons that should be considered by each transplant center when setting institutional policy.

A prophylactic approach seems very effective at preventing both infection and disease from cytomegalovirus and has been shown to reduce graft rejection and the risk of death.[18] It is preferred in cytomegalovirus-negative recipients when the donor was cytomegalovirus-positive—a high-risk situation.[19] However, these patients are also at higher risk of late-onset cytomegalovirus disease. Higher cost and potential drug toxicity, mainly neutropenia from ganciclovir-based regimens, are additional considerations.

Preemptive treatment, in contrast, reserves drug treatment for patients who are actually infected with cytomegalovirus, thus resulting in fewer adverse drug events and lower cost; but it requires regular monitoring. Preemptive methods, by definition, cannot prevent infection, and with this strategy tissue-invasive disease not associated with viremia does occasionally occur.[20] As such, patients with a clinical presentation that suggests cytomegalovirus but have negative results on blood testing should be considered for tissue biopsy with culture and immunohistochemical stain.

Transplant recipients may not readily manifest fever, owing to immunosuppression

The most commonly used regimens for antiviral prophylaxis and treatment in liver transplant recipients are intravenous ganciclovir and oral valganciclovir.[21] Although valganciclovir is the most commonly used agent in this setting because of ease of administration, it has not been approved by the US Food and Drug Administration in liver transplant patients, as it was associated with higher rates of cytomegalovirus tissue-invasive disease.[22–24] Additionally, drug-resistant cytomegalovirus strains have been associated with valganciclovir prophylaxis in cytomegalovirus-negative recipients of solid organs from cytomegalovirus-positive donors.[25]

Prophylaxis typically consists of therapy for 3 months from the time of transplant. In higher-risk patients (donor-positive, recipient-negative), longer courses of prophylaxis have been extrapolated from data in kidney transplant recipients.[26] Extension or reinstitution of prophylaxis should also be considered in liver transplant patients receiving treatment for rejection with antilymphocyte therapy.

Routine screening for cytomegalovirus is not recommended while patients are receiving prophylaxis. High-risk patients who are not receiving prophylaxis should be monitored with nucleic acid or pp65 antigenemia testing as part of the preemptive strategy protocol.

Treatment of cytomegalovirus disease

Although no specific threshold has been established, treatment is generally indicated if a patient has a consistent clinical syndrome, evidence of tissue injury, and persistent or increasing viremia.

Treatment involves giving antiviral drugs and also reducing the level of immunosuppression, if possible, until symptoms and viremia have resolved.

The choice of antiviral therapy depends on the severity of disease. Intravenous ganciclovir (5 mg/kg twice daily adjusted for renal impairment) or oral valganciclovir (900 mg twice daily, also renally dose-adjusted when necessary) can be used for mild to moderate disease if no significant gastrointestinal involvement is reported. Intravenous ganciclovir is preferred for patients with more severe disease or gastrointestinal involvement. The minimum duration of treatment is 2 weeks and may need to be prolonged until both symptoms and viremia completely resolve.[18]

Drug resistance can occur and should be considered in patients who have a history of prolonged ganciclovir or valganciclovir exposure who do not clinically improve or have persistent or rising viremia. In such cases, genotype assays are helpful, and initiation of alternative therapy should be considered. Mutations conferring resistance to ganciclovir are often associated with cross-resistance to cidofovir. Cidofovir can therefore be considered only when genotype assays demonstrate specific mutations conferring an isolated resistance to ganciclovir.[27] The addition of foscarnet to the ganciclovir regimen or substitution of foscarnet for ganciclovir are accepted approaches.

Although cytomegalovirus hyperimmunoglobulin has been used in prophylaxis and invasive disease treatment, its role in the management of ganciclovir-resistant cytomegalovirus infections remains controversial.[28]

EPSTEIN-BARR VIRUS POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE

Epstein-Barr virus-associated posttransplant lymphoproliferative disease is a spectrum of disorders ranging from an infectious mononucleosis syndrome to aggressive malignancy with the potential for death and significant morbidity after liver transplant.[29] The timeline of risk varies, but the disease is most common in the first year after transplant.

Risk factors for this disease (**Table 1**) are:

- Primary Epstein-Barr virus infection
- Cytomegalovirus donor-recipient mismatch
- Cytomegalovirus disease
- Higher levels of immunosuppression, especially with antilymphocyte antibodies.[30]

The likelihood of Epstein-Barr virus playing a contributing role is lower in later-onset posttransplant lymphoproliferative disease. Patients who are older at the time of transplant, who receive highly immunogenic allografts including a liver as a component of a multivisceral transplant, and who receive increased immunosuppression to treat rejection are at even greater risk of late posttransplant lymphoproliferative disease.[31] This is in contrast to early posttransplant lymphoproliferative disease, which is seen more commonly in children as a result of primary Epstein-Barr virus infection.

Recognition and diagnosis. Heightened suspicion is required when considering posttransplant lymphoproliferative disease, and careful evaluation of consistent symptoms and allograft dysfunction are required.

Clinically, posttransplant lymphoproliferative disease should be suspected if a liver transplant recipient develops unexplained fever, weight loss, lymphadenopathy, or cell-line cytopenias.[30,32] Other signs and symptoms may be related to the organ involved and may include evidence of hepatitis, pneumonitis, and gastrointestinal disease.[31]

Adjunctive diagnostic testing includes donor and recipient serology to characterize overall risk before transplantation and quantification of Epstein-Barr viral load, but confirmation relies on tissue histopathology.

Treatment focuses on reducing immunosuppression.[30,32] Adding antiviral agents does not seem to improve outcome in all cases.[33] Depending on clinical response and histologic classification, additional therapies such as anti-CD20 humanized chimeric monoclonal antibodies, surgery, radiation, and conventional chemotherapy may be required.[34]

Preventive approaches remain controversial. Chemoprophylaxis with an antiviral such as ganciclovir is occasionally used but has not been shown to consistently decrease rates of posttransplant lymphoproliferative disease. These agents may act in an indirect manner, leading to decreased rates of cytomegalovirus infection, a major cofactor for posttransplant lymphoproliferative disease.[24]

Passive immunoprophylaxis with immunoglobulin targeting cytomegalovirus has shown to decrease rates of non-Hodgkin lymphoma from posttransplant lymphoproliferative disease in renal transplant recipients in the first year after transplant,[35] but data are lacking regarding its use in liver transplant recipients. Monitoring of the viral load and subsequent reduction of immunosuppression remain the most efficient measures to date.[36]

FUNGAL INFECTIONS

Candida species account for more than half of fungal infections in liver transplant recipients.[37] However, a change has been noted in the past 20 years, with a decrease in *Candida* infections accompanied by an increase in *Aspergillus* infections.[38] Endemic mycoses such as coccidioidomycosis, blastomycosis, and histoplasmosis should be considered with the appropriate epidemiologic history or if disease develops early after transplant and the donor came from a highly endemic region.[39] *Cryptococcus* may also be encountered.

Intra-abdominal infections are often polymicrobial

Diagnosis. One of the most challenging aspects of fungal infection in liver transplant recipients is timely diagnosis. Heightened suspicion and early biopsy for pathological and microbiological confirmation are necessary. Although available noninvasive diagnostic tools often lack specificity, early detection of fungal markers may be of great use in guiding further diagnostic workup or empiric treatment in the critically ill.

Noninvasive tests include galactomannan, cryptococcal antigen, histoplasma antigen,

TABLE 3

Common infections after liver transplant

Time after transplant		
< 3 Months	**3–6 Months**	**> 6 Months**
Nosocomial infections	Highest level of immunosuppression, highest infectious risk	Reduced immunosuppression, reduced infectious risk
Consider possibility of resistant strains (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Candida* species)	Herpes viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus)	Community-acquired pathogens (*S pneumoniae*, enteric gram-negative agents, respiratory viruses)
Consider possibility of endemic mycosis	Fungi (*Aspergillus, Cryptococcus*)	Fungi (*Aspergillus, Mucor*, atypical molds)
Recipient-derived infections (*Aspergillus, Pseudomonas*)	Atypical bacteria (*Nocardia, Listeria, Mycobacteria*)	Late viral infections (cytomegalovirus colitis and retinitis, hepatitis B virus, hepatitis C virus, herpes simplex viral encephalitis)
Donor-derived infections are less common (eg, herpes simplex virus, human immunodeficiency virus, lymphocytic choriomeningitis virus)	*Pneumocystis*	
	Community-acquired pathogens (*Streptococcus pneumoniae*, enteric gram-negative agents, respiratory viruses)	

Ongoing assessment of the patient's infection risk and adjustment of prophylaxis and immunosuppressive therapy are necessary.

Although oral valganciclovir is used more than intravenous ganciclovir, it is not approved for liver transplant patients

(1-3)-beta-D-glucan assay and various antibody tests. Galactomannan testing has been widely used to aid in the diagnosis of invasive aspergillosis. Similarly, the (1-3)-beta-D-glucan assay is a non–culture-based tool for diagnosing and monitoring the treatment of invasive fungal infections. However, a definite diagnosis cannot be made on the basis of a positive test alone.[40] The complementary diagnostic characteristics of combining noninvasive assays have yet to be fully elucidated.[41] Cultures and tissue histopathology are also used when possible.

Treatment is based on targeted specific antifungal drug therapy and reduction of immunosuppressive therapy, when possible. The choice of antifungal agent varies with the pathogen, the site of involvement, and the severity of the disease. A focus on potential drug interactions, their management, and therapeutic drug monitoring when using antifungal medications is essential in the posttransplant period. Combination therapy can be considered in some situations to enhance synergy. The following sections discuss in greater detail *Candida* species, *Aspergillus* species, and *Pneumocystis jirovecii* infections.

Candida infections

Candidiasis after liver transplant is typically nosocomial, especially when diagnosed during the first 3 months (**Table 3**).[37]

Risk factors for invasive candidiasis include perioperative colonization, prolonged operative time, retransplant, greater transfusion requirements, and postoperative renal failure.[37,42,43] Invasive candidiasis is of concern for its effects on morbidity, mortality, and cost of care.[43–46]

Organisms. The frequency of implicated species, in particular those with a natural resistance to fluconazole, differs in various reports.[37,45,46] *Candida albicans* remains the most commonly isolated pathogen; however, non-albicans species including those resistant to fluconazole have been reported more frequently and include *Candida glabrata* and *Candida krusei*.[47,48]

Signs and diagnosis. Invasive candidiasis in liver transplant recipients generally manifests itself in catheter-related blood stream infections, urinary tract infections, or intra-abdominal infections. Diagnosis can be made by isolating *Candida* from blood cultures, recovering organisms in culture of a normally sterile

site, or finding direct microscopic evidence of the fungus on tissue specimens.[49]

Disseminated candidiasis refers to the involvement of distant anatomic sites. Clinical manifestations may cause vision changes, abdominal pain or skin nodules with findings of candidemia, hepatosplenic abscesses, or retinal exudates on funduscopy.[49]

Treatment of invasive candidiasis in liver recipients often involves antifungal therapy and reduction of immunosuppression. Broad-spectrum antifungals are initially advocated in an empirical approach to cover fluconazole-resistant strains of the non-albicans subgroups.[50] Depending on antifungal susceptibility, treatment can later be adjusted.

Fluconazole remains the agent of choice in most *C albicans* infections.[47] However, attention should be paid to the possibility of resistance in patients who have received fluconazole prophylaxis within the past 30 days. Additional agents used in treatment may include echinocandins, amphotericin, and additional azoles.

Antifungal prophylaxis is recommended in high-risk liver transplant patients, although its optimal duration remains undetermined.[44] Antifungal prophylaxis has been associated with decreased incidence of both superficial and invasive candidiasis.[51]

Aspergillus infection

Aspergillus, the second most common fungal pathogen, has become a more common concern in liver transplant recipients. *Aspergillus fumigatus* is the most frequently encountered species.[38,52]

Risk factors. These infections typically occur in the first year, during intense immunosuppression. Retransplant, renal failure, and fulminant hepatic failure are major risk factors.[52] In the presence of risk factors and a suggestive clinical setting, invasive aspergillosis should be considered and the diagnosis pursued.

Diagnosis is suggested by positive findings on CT accompanied by lower respiratory tract symptoms, focal lesions on neuroimaging, or demonstration of the fungus on cultures.[49] However, *Aspergillus* is rarely grown in blood culture. The galactomannan antigen is a noninvasive test that can provide supporting evidence for the diagnosis.[41,52] False-positive results do occur in the setting of certain antibiotics and cross-reacting fungi.[53]

Treatment consists of antifungal therapy and immunosuppression reduction.[52]

Voriconazole is the first-line agent for invasive aspergillosis. Monitoring for potential drug-drug interactions and side effects is required.[54,55] Amphotericin B is considered a second-line choice due to toxicity and lack of an oral formulation. In refractory cases, combined antifungal therapy could be considered.[52] The duration of treatment is generally a minimum of 12 weeks.

Prophylaxis. Specific prophylaxis against invasive aspergillosis is not currently recommended; however, some authors suggest a prophylactic approach using echinocandins or liposomal amphotericin B in high-risk patients.[51,52] Aspergillosis is associated with a considerable increase in mortality in liver transplant recipients, which highlights the importance of timely management.[52,56]

Pneumocystis jirovecii

P jirovecii remains a common opportunistic pathogen in people with impaired immunity, including transplant and human immunodeficiency virus patients.

Prophylaxis. Widespread adoption of antimicrobial prophylaxis by transplant centers has decreased the rates of *P jirovecii* infection in liver transplant recipients.[57,58] Commonly used prophylactic regimens after liver transplantation include a single-strength trimethoprim-sulfamethoxazole tablet daily or a double-strength tablet three times per week for a minimum of 6 to 12 months after transplant. Atovaquone and dapsone can be used as alternatives in cases of intolerance to trimethoprim-sulfamethoxazole (**Table 2**).

Inhaled pentamidine is clearly inferior and should be used only when the other medications are contraindicated.[59]

Signs and diagnosis. *P jirovecii* pneumonia is characterized by fever, cough, dyspnea, and chest pain. Insidious hypoxemia, abnormal chest examination, and bilateral interstitial pneumonia on chest radiography are common.

CT may be more sensitive than chest radiography.[57] Findings suggestive of *P jirovecii* pneumonia on chest CT are extensive bilater-

***Candida* accounts for more than half of fungal infections in liver transplant recipients, but *Aspergillus* is gaining**

al and symmetrical ground-glass attenuations. Other less-characteristic findings include upper lobar parenchymal opacities and spontaneous pneumothorax.[57,60]

The serum (1,3)-beta-D-glucan assay derived from major cell-wall components of *P jirovecii* might be helpful. Studies report a sensitivity for *P jirovecii* pneumonia as high as 96% and a negative predictive value of 99.8%.[61,62]

Definitive diagnosis requires identification of the pathogen. Routine expectorated sputum sampling is generally associated with a poor diagnostic yield. Bronchoscopy and bronchoalveolar lavage with silver or fluorescent antibody staining of samples, polymerase chain reaction testing, or both significantly improves diagnosis. Transbronchial or open lung biopsy are often unnecessary.[57]

Treatment. Trimethoprim-sulfamethoxazole is the first-line agent for treating *P jirovecii* pneumonia.[57] The minimum duration of treatment is 14 days, with extended courses for severe infection.

Intravenous pentamidine or clindamycin plus primaquine are alternatives for patients who cannot tolerate trimethoprim-sulfamethoxazole. The major concern with intravenous pentamidine is renal dysfunction. Hypoglycemia or hyperglycemia, neutropenia, thrombocytopenia, nausea, dysgeusia, and pancreatitis may also occur.[63]

Atovaquone might also be beneficial in mild to moderate *P jirovecii* pneumonia. The main side effects include skin rashes, gastrointestinal intolerance, and elevation of transaminases.[64]

A corticosteroid (40–60 mg of prednisone or its equivalent) may be beneficial in conjunction with antimicrobial therapy in patients with significant hypoxia (partial pressure of arterial oxygen < 70 mm Hg on room air) in decreasing the risk of respiratory failure and need for intubation.

With appropriate and timely antimicrobial prophylaxis, cases of *P jirovecii* pneumonia should continue to decrease.

Widespread adoption of prophylaxis has decreased the rate of *P jirovecii* infection in liver transplant recipients

TUBERCULOSIS

Development of tuberculosis after transplantation is a catastrophic complication, with mortality rates of up to 30%.[65] Most cases of posttransplant tuberculosis represent reactivation of latent disease.[66] Screening with tuberculin skin tests or interferon-gamma-release assays is recommended in all liver transplant candidates. Chest radiography before transplant is necessary when assessing a positive screening test.[67]

The optimal management of latent tuberculosis in these cases remains controversial. Patients at high risk or those with positive screening results on chest radiography warrant treatment for latent tuberculosis infection with isoniazid unless contraindicated.[67,68]

The ideal time to initiate prophylactic isoniazid therapy is unclear. Some authors suggest delaying it, as it might be associated with poor tolerance and hepatotoxicity.[69] Others have found that early isoniazid use was not associated with negative outcomes.[70]

Risk factors for symptomatic tuberculosis after liver transplant include previous infection with tuberculosis, intensified immunosuppression (especially anti-T-lymphocyte therapies), diabetes mellitus, and other coinfections (**Table 1**).[71]

The increased incidence of atypical presentations in recent years makes the diagnosis of active tuberculosis among liver transplant recipients challenging. Sputum smears can be negative due to low mycobacterial burdens, and tuberculin skin testing and interferon-gamma-release assays may be falsely negative due to immunosuppression.[67]

Treatment of active tuberculosis consists initially of a four-drug regimen using isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months. Adjustments are made in accordance with culture and sensitivity results. Treatment can then be tapered to two drugs (isoniazid and rifampin) for a minimum of 4 additional months. Prolonged treatment may be required in instances of extrapulmonary or disseminated disease.[65,72]

Tuberculosis treatment can be complicated by hepatotoxicity in liver transplant recipients because of direct drug effects and drug-drug interactions with immunosuppressive agents. Close monitoring for rejection and hepatotoxicity is therefore imperative while liver transplant recipients are receiving antituberculosis therapy. Drug-drug interactions may also be responsible for marked reductions

in immunosuppression levels, especially with regimens containing rifampin.[71] Substitution of rifabutin for rifampin reduces the effect of drug interactions.[66]

VIRAL HEPATITIS

Hepatitis B virus

Hepatitis B virus-related end-stage liver disease and hepatocellular carcinoma are common indications for liver transplant in Asia. It is less common in the United States and Europe, accounting for less than 10% of all liver transplant cases. Prognosis is favorable in recipients undergoing liver transplant for hepatitis B virus, with excellent survival rates. Prevention of reinfection is crucial in these patients.

Treatment with combination antiviral agents and hepatitis B immunoglobulin (HBIG) is effective.[73] Lamivudine was the first nucleoside analogue found to be effective against hepatitis B virus. Its low cost and relative safety are strong arguments in favor of its continued use in liver transplant recipients.[74] In patients without evidence of hepatitis B viral replication at the time of transplant, monotherapy with lamivudine has led to low recurrence rates, and adefovir can be added to control resistant viral strains.[75]

The frequent emergence of resistance with lamivudine favors newer agents such as entecavir or tenofovir. These nucleoside and nucleotide analogues have a higher barrier to resistance, and thus resistance to them is rare. They are also more efficient, potentially allowing use of an HBIG-sparing protocol.[76] However, they are associated with a higher risk of nephrotoxicity and require dose adjustments in renal insufficiency. Data directly comparing entecavir and tenofovir are scarce.

Prophylaxis. Most studies support an individualized approach for prevention of hepatitis B virus reinfection. High-risk patients, ie, those positive for HBe antigen or with high viral loads (> 100,000 copies/mL) are generally treated with both HBIG and antiviral agents.[77] Low-risk patients are those with a negative HBe antigen, low hepatitis B virus DNA levels, hepatitis B virus-related acute liver failure, and cirrhosis resulting from coinfection with both hepatitis B and hepatitis D virus.[75] In low-risk patients, discontinuation of HBIG after 1 to 2 years of treatment is appropriate, and long-term prophylaxis with antiviral agents alone is an option. However, levels of hepatitis B DNA should be monitored closely.[78,79]

Hepatitis C virus

Recurrence of hepatitis C virus infection is the rule among patients who are viremic at the time of liver transplant.[80,81] Most of these patients will show histologic evidence of recurrent hepatitis within the first year after liver transplant. It is often difficult to distinguish between the histopathological appearance of a recurrent hepatitis C virus infection and acute cellular rejection.

Progression to fibrosis and subsequently cirrhosis and decompensation is highly variable in hepatitis C virus-infected liver transplant recipients. Diabetes, insulin resistance, and possibly hepatitis steatosis have been associated with a rapid progression to advanced fibrosis. The contribution of immunosuppression to the progression of hepatitis C virus remains an area of active study. Some studies point to antilymphocyte immunosuppressive agents as a potential cause.[82] Liver biopsy is a useful tool in this situation. It allows monitoring of disease severity and progression and may distinguish recurrent hepatitis C virus disease from other causes of liver enzyme elevation.

The major concern with hepatitis C recurrence after liver transplant is allograft loss

The major concern with the recurrence of hepatitis C virus infection after liver transplant is allograft loss. Rates of patient and graft survival are reduced in infected patients compared with hepatitis C virus-negative patients.[83,84] Prophylactic antiviral therapy has no current role in the management of hepatitis C virus disease. Those manifesting moderate to severe necroinflammation or mild to moderate fibrosis indicative of progressive disease should be treated.[81,85]

Sustained viral clearance with antiviral agents confers a graft survival benefit.

The combination of peg-interferon and weight-based ribavirin has been the standard of treatment but may be associated with increased rates of rejection.[86,87] The sustained virologic response rates for hepatitis C virus range from 60% in genotypes 4, 5, and 6 after 48 weeks of treatment to 60% to 80% in genotypes 2 and 3 after 24 weeks, but only about

30% in genotype 1.[88]

Treatment with the newer agents, especially protease inhibitors, in genotype 1 (peginterferon, ribavirin, and either telaprevir or boceprevir) has been evaluated. Success rates reaching 70% have been achieved.[89] Adverse effects can be a major setback. Serious complications include severe anemia, renal dysfunction, increased risk of infection, and death.

Triple therapy should be carefully considered in liver transplant patients with genotype 1 hepatitis C virus.[90] Significant drug-drug interactions are reported between hepatitis C virus protease inhibitors and immunosuppression regimens. Additional new oral direct-acting antivirals have been investigated. They bring promising advances in hepatitis C virus treatment and pave the way for interferon-free regimens with pangenotypic activity.

IMMUNIZATION

Immunization can decrease the risk of infectious complications in liver transplant recipients, as well as in close contacts and healthcare professionals.[3]

Influenza. Pretransplant influenza vaccine and posttransplant annual influenza vaccines are necessary.

Pneumococcal immunization should additionally be provided prior to transplant and repeated every 3 to 5 years thereafter.[3,91]

A number of other vaccinations should also be completed before transplant, including the **hepatitis A and B** vaccines and the **tetanus/diphtheria/acellular pertussis** vaccines. However, these vaccinations have not been shown to be detrimental to patients after transplant.[91]

Varicella and zoster vaccines should be given before liver transplant—zoster in patients over age 60, and varicella in patients with no immunity. Live vaccines, including varicella and zoster vaccines, are contraindicated after liver transplant.[3]

Human papillomavirus. The bivalent human papillomavirus vaccine can be given before transplant in females ages 9 to 26; the quadrivalent vaccine is beneficial in those ages 9 to 26 and in women under age 45.[3,91]

IMMUNOSUPPRESSION CARRIES RISK OF INFECTION

Most liver transplant patients require prolonged immunosuppressive therapy. This comes with an increased risk of new or recurrent infections, potentially causing death and significant morbidity.

Evaluation of existing risk factors, appropriate prophylaxis and immunization, timely diagnosis, and treatment of such infections are therefore essential steps for the successful management of liver transplant recipients.

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