

LYDIA CHELALA, MD

Department of Internal Medicine,
Staten Island University Hospital,
Staten Island, NY

CHRISTOPHER S. KOVACS, MD

Department of Infectious Disease, Cleveland
Clinic; Clinical Instructor, Cleveland Clinic
Lerner College of Medicine of Case Western
Reserve University, Cleveland, OH

ALAN J. TAEGE, MD*

Department of Infectious Disease,
Cleveland Clinic; Assistant Professor,
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University,
Cleveland, OH

IBRAHIM A. HANOUNEH, MD

Department of Gastroenterology and
Hepatology, Cleveland Clinic; Assistant
Professor, Cleveland Clinic Lerner College
of Medicine of Case Western Reserve
University, Cleveland, OH

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
- Reoperation⁸
- Hepatic artery thrombosis
- Roux-en-Y choledochojejunostomy anastomosis.⁹

*Dr. Taege has disclosed teaching, speaking, and membership on advisory committee or review panels for Gilead, and independent contracting (including contracted research) for Pfizer.

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
<i>Pneumocystis jirovecii</i>	Increased immunosuppression
<i>Mycobacterium tuberculosis</i>	Prior infection Increased immunosuppression Anti-T-lymphocyte agents Diabetes mellitus Coinfection with cytomegalovirus, fungi, <i>P jirovecii</i> , or <i>Nocardia</i>

Signs that may indicate intra-abdominal infection include fever, abdominal pain, leukocytosis, and elevated liver enzymes. But be-

cause 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 Itraconazole 200 mg twice daily Caspofungin (<i>Aspergillus</i> spp and <i>Candida</i> spp); other echinocandins (<i>Candida</i> spp) Liposomal amphotericin Optimal duration undetermined	Consider prophylaxis in high-risk patients Hepatotoxicity and drug-drug interactions more common with itraconazole vs fluconazole Consider liposomal amphotericin in high-risk patients (extended postoperative stay in intensive care unit, renal dysfunction, high degree of immunosuppression)
<i>Pneumocystis jirovecii</i>	Trimethoprim-sulfamethoxazole (single-strength daily or double-strength 3 times per week) Or dapsone 100 mg daily Or atovaquone 1,500 mg daily Minimal duration of 6–12 months	Widespread prophylaxis Lifelong prophylaxis in human immunodeficiency virus patients
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.

Transplant recipients may not readily manifest fever, owing to immunosuppression

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.

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.

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,

Intra-abdominal infections are often polymicrobial

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 <i>Staphylococcus aureus</i> , vancomycin-resistant enterococci, <i>Candida</i> species)	Herpes viruses (cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella-zoster virus)	Community-acquired pathogens (<i>S pneumoniae</i> , enteric gram-negative agents, respiratory viruses)
Consider possibility of endemic mycosis	Fungi (<i>Aspergillus</i> , <i>Cryptococcus</i>)	Fungi (<i>Aspergillus</i> , <i>Mucor</i> , atypical molds)
Recipient-derived infections (<i>Aspergillus</i> , <i>Pseudomonas</i>)	Atypical bacteria (<i>Nocardia</i> , <i>Listeria</i> , <i>Mycobacteria</i>)	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)	<i>Pneumocystis</i> Community-acquired pathogens (<i>Streptococcus pneumoniae</i> , 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.

■ 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 co-infections (**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 anti-tuberculosis therapy. Drug-drug interactions may also be responsible for marked reductions

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

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, discontinua-

tion 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 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

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

30% in genotype 1.⁸⁸

Treatment with the newer agents, especially protease inhibitors, in genotype 1 (peg-interferon, 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 health-care 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.

REFERENCES

1. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; 357:2601–2614.
2. Avery RK, Michaels MG; AST Infectious Diseases Community of Practice. Strategies for safe living after solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):304–310.
3. Danziger-Isakov L, Kumar D; AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):311–317.
4. San Juan R, Aguado JM, Lumberras C, et al; RESITRA Network, Spain. Incidence, clinical characteristics and risk factors of late infection in solid organ transplant recipients: data from the RESITRA study group. *Am J Transplant* 2007; 7:964–971.
5. Ison MG, Grossi P; AST Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):22–30.
6. Kim YJ, Kim SI, Wie SH, et al. Infectious complications in living-donor liver transplant recipients: a 9-year single-center experience. *Transpl Infect Dis* 2008; 10:316–324.
7. Arnou PM. Infections following orthotopic liver transplantation. *HPB Surg* 1991; 3:221–233.
8. Reid GE, Grim SA, Sankary H, Benedetti E, Oberholzer J, Clark NM. Early intra-abdominal infections associated with orthotopic liver transplantation. *Transplantation* 2009; 87:1706–1711.
9. Said A, Safdar N, Lucey MR, et al. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. *Am J Transplant* 2004; 4:574–582.
10. Safdar N, Said A, Lucey MR, et al. Infected bilomas in liver transplant recipients: clinical features, optimal management, and risk factors for mortality. *Clin Infect Dis* 2004; 39:517–525.
11. Niemczyk M, Leszczynski P, Wyzga J, Paczek L, Krawczyk M, Luczak M. Infections caused by *Clostridium difficile* in kidney or liver graft recipients. *Ann Transplant* 2005; 10:70–74.
12. Albright JB, Bonatti H, Mendez J, et al. Early and late onset *Clostridium difficile*-associated colitis following liver transplantation. *Transpl Int* 2007; 20:856–866.
13. Lee SO, Razonable RR. Current concepts on cytomegalovirus infection after liver transplantation. *World J Hepatol* 2010; 2:325–336.
14. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002; 34:1094–1097.
15. Beam E, Razonable RR. Cytomegalovirus in solid organ transplantation: epidemiology, prevention, and treatment. *Curr Infect Dis Rep* 2012; 14:633–641.
16. Bodro M, Sabé N, Lladó L, et al. Prophylaxis versus preemptive therapy for cytomegalovirus disease in high-risk liver transplant recipients. *Liver Transpl* 2012; 18:1093–1099.
17. Weigand K, Schnitzler P, Schmidt J, et al. Cytomegalovirus infection after liver transplantation incidence, risks, and benefits of prophylaxis. *Transplant Proc* 2010; 42:2634–2641.
18. Razonable RR, Humar A; AST Infectious Diseases Community of

- Practice. Cytomegalovirus in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):93–106.
19. Meije Y, Fortún J, Len Ó, et al; Spanish Network for Research on Infection in Transplantation (RESITRA) and the Spanish Network for Research on Infectious Diseases (REIPI). Prevention strategies for cytomegalovirus disease and long-term outcomes in the high-risk transplant patient (D+/R-): experience from the RESITRA-REIPI cohort. *Transpl Infect Dis* 2014; 16:387–396.
 20. Durand CM, Marr KA, Arnold CA, et al. Detection of cytomegalovirus DNA in plasma as an adjunct diagnostic for gastrointestinal tract disease in kidney and liver transplant recipients. *Clin Infect Dis* 2013; 57:1550–1559.
 21. Levitsky J, Singh N, Wagener MM, Stosor V, Abecassis M, Ison MG. A survey of CMV prevention strategies after liver transplantation. *Am J Transplant* 2008; 8:158–161.
 22. Marcelin JR, Beam E, Razonable RR. Cytomegalovirus infection in liver transplant recipients: updates on clinical management. *World J Gastroenterol* 2014; 20:10658–10667.
 23. Kalil AC, Freifeld AG, Lyden ER, Stoner JA. Valganciclovir for cytomegalovirus prevention in solid organ transplant patients: an evidence-based reassessment of safety and efficacy. *PLoS One* 2009; 4:e5512.
 24. Kalil AC, Mindru C, Botha JF, et al. Risk of cytomegalovirus disease in high-risk liver transplant recipients on valganciclovir prophylaxis: a systematic review and meta-analysis. *Liver Transpl* 2012; 18:1440–1447.
 25. Eid AJ, Arthurs SK, Deziel PJ, Wilhelm MP, Razonable RR. Emergence of drug-resistant cytomegalovirus in the era of valganciclovir prophylaxis: therapeutic implications and outcomes. *Clin Transplant* 2008; 22:162–170.
 26. Kumar D, Humar A. Cytomegalovirus prophylaxis: how long is enough? *Nat Rev Nephrol* 2010; 6:13–14.
 27. Lurain NS, Chou S. Antiviral drug resistance of human cytomegalovirus. *Clin Microbiol Rev* 2010; 23:689–712.
 28. Torres-Madriz G, Boucher HW. Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients. *Clin Infect Dis* 2008; 47:702–711.
 29. Burra P, Buda A, Livi U, et al. Occurrence of post-transplant lymphoproliferative disorders among over thousand adult recipients: any role for hepatitis C infection? *Eur J Gastroenterol Hepatol* 2006; 18:1065–1070.
 30. Jain A, Nalesnik M, Reyes J, et al. Posttransplant lymphoproliferative disorders in liver transplantation: a 20-year experience. *Ann Surg* 2002; 236:429–437.
 31. Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):107–120.
 32. Allen U, Preiksaitis J; AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. *Am J Transplant* 2009; 9(suppl 4):S87–S96.
 33. Perrine SP, Hermine O, Small T, et al. A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. *Blood* 2007; 109:2571–2578.
 34. Jagadeesh D, Woda BA, Draper J, Evans AM. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol* 2012; 13:122–136.
 35. Opelz G, Daniel V, Naujokat C, Fickenscher H, Döhler B. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis. *Lancet Oncol* 2007; 8:212–218.
 36. Nowalk AJ, Green M. Epstein-Barr virus-associated posttransplant lymphoproliferative disorder: strategies for prevention and cure. *Liver Transpl* 2010; 16(suppl S2):S54–S59.
 37. Pappas PG, Silveira FP; AST Infectious Diseases Community of Practice. *Candida* in solid organ transplant recipients. *Am J Transplant* 2009; 9(suppl 4):S173–S179.
 38. Singh N, Wagener MM, Marino IR, Gayowski T. Trends in invasive fungal infections in liver transplant recipients: correlation with evolution in transplantation practices. *Transplantation* 2002; 73:63–67.
 39. Miller R, Assi M; AST Infectious Diseases Community of Practice. Endemic fungal infections in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):250–261.
 40. Fontana C, Gaziano R, Favaro M, Casalnuovo IA, Pistoia E, Di Francesco P. (1-3)-beta-D-glucan vs galactomannan antigen in diagnosing invasive fungal infections (IFIs). *Open Microbiol J* 2012; 6:70–73.
 41. Aydogan S, Kustimur S, Kalkanç A. Comparison of glucan and galactomannan tests with real-time PCR for diagnosis of invasive aspergillosis in a neutropenic rat model [Turkish]. *Mikrobiyol Bul* 2010; 44:441–452.
 42. Hadley S, Huckabee C, Pappas PG, et al. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. *Transpl Infect Dis* 2009; 11:40–48.
 43. Pappas PG, Kauffman CA, Andes D, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:503–535.
 44. Person AK, Kontoyiannis DP, Alexander BD. Fungal infections in transplant and oncology patients. *Infect Dis Clin North Am* 2010; 24:439–459.
 45. Van Hal SJ, Marriott DJE, Chen SCA, et al; Australian Candidaemia Study. Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience. *Transpl Infect Dis* 2009; 11:122–127.
 46. Singh N. Fungal infections in the recipients of solid organ transplantation. *Infect Dis Clin North Am* 2003; 17:113–134.
 47. Liu X, Ling Z, Li L, Ruan B. Invasive fungal infections in liver transplantation. *Int J Infect Dis* 2011; 15:e298–e304.
 48. Raghuram A, Restrepo A, Safadjou S, et al. Invasive fungal infections following liver transplantation: incidence, risk factors, survival, and impact of fluconazole-resistant *Candida parapsilosis* (2003–2007). *Liver Transpl* 2012; 18:1100–1109.
 49. De Pauw B, Walsh TJ, Donnelly JP, et al; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; 46:1813–1821.
 50. Moreno A, Cervera C, Gavalda J, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *Am J Transplant* 2007; 7:2579–2586.
 51. Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. *Liver Transpl* 2006; 12:850–858.
 52. Singh N, Husain S; AST Infectious Diseases Community of Practice. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant* 2009; 9(suppl 4):S180–S191.
 53. Fortún J, Martín-Dávila P, Alvarez ME, et al. False-positive results of *Aspergillus galactomannan* antigenemia in liver transplant recipients. *Transplantation* 2009; 87:256–260.
 54. Cherian T, Giakoustidis A, Yokoyama S, et al. Treatment of refractory cerebral aspergillosis in a liver transplant recipient with voriconazole: case report and review of the literature. *Exp Clin Transplant* 2012; 10:482–486.
 55. Luong ML, Hosseini-Moghaddam SM, Singer LG, et al. Risk factors for voriconazole hepatotoxicity at 12 weeks in lung transplant recipients. *Am J Transplant* 2012; 12:1929–1935.
 56. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* 2010; 12:220–229.
 57. Martin SI, Fishman JA; AST Infectious Diseases Community of Practice. *Pneumocystis pneumonia* in solid organ transplant recipients. *Am J Transplant* 2009; 9(suppl 4):S227–S233.
 58. Levine SJ, Masur H, Gill VJ, et al. Effect of aerosolized pentamidine

- prophylaxis on the diagnosis of *Pneumocystis carinii* pneumonia by induced sputum examination in patients infected with the human immunodeficiency virus. *Am Rev Respir Dis* 1991; 144:760–764.
59. **Rodriguez M, Sifri CD, Fishman JA.** Failure of low-dose atovaquone prophylaxis against *Pneumocystis jiroveci* infection in transplant recipients. *Clin Infect Dis* 2004; 38:e76–e78.
60. **Crans CA Jr, Boisselle PM.** Imaging features of *Pneumocystis carinii* pneumonia. *Crit Rev Diagn Imaging* 1999; 40:251–284.
61. **Onishi A, Sugiyama D, Kogata Y, et al.** Diagnostic accuracy of serum 1,3-beta-D-glucan for *Pneumocystis jiroveci* pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. *J Clin Microbiol* 2012; 50:7–15.
62. **Held J, Koch MS, Reischl U, Danner T, Serr A.** Serum (1→3)-β-D-glucan measurement as an early indicator of *Pneumocystis jirovecii* pneumonia and evaluation of its prognostic value. *Clin Microbiol Infect* 2011; 17:595–602.
63. **Fishman JA.** Prevention of infection caused by *Pneumocystis carinii* in transplant recipients. *Clin Infect Dis* 2001; 33:1397–1405.
64. **Colby C, McAfee S, Sackstein R, Finkelstein D, Fishman J, Spitzer T.** A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as *Pneumocystis carinii* pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; 24:897–902.
65. **Subramanian A, Dorman S; AST Infectious Diseases Community of Practice.** *Mycobacterium tuberculosis* in solid organ transplant recipients. *Am J Transplant* 2009; 9(suppl 4):S57–S62.
66. **Subramanian AK, Morris MI; AST Infectious Diseases Community of Practice.** *Mycobacterium tuberculosis* infections in solid organ transplantation. *Am J Transplant* 2013; 13(suppl 4):68–76.
67. **Horne DJ, Narita M, Spitters CL, Parimi S, Dodson S, Limaye AP.** Challenging issues in tuberculosis in solid organ transplantation. *Clin Infect Dis* 2013; 57:1473–1482.
68. **Holty JE, Gould MK, Meinke L, Keefe EB, Ruoss SJ.** Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. *Liver Transpl* 2009; 15:894–906.
69. **Jafri SM, Singal AG, Kaul D, Fontana RJ.** Detection and management of latent tuberculosis in liver transplant patients. *Liver Transpl* 2011; 17:306–314.
70. **Fábrega E, Sampedro B, Cabezas J, et al.** Chemoprophylaxis with isoniazid in liver transplant recipients. *Liver Transpl* 2012; 18:1110–1117.
71. **Aguado JM, Torre-Cisneros J, Fortún J, et al.** Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis* 2009; 48:1276–1284.
72. **Yehia BR, Blumberg EA.** *Mycobacterium tuberculosis* infection in liver transplantation. *Liver Transpl* 2010; 16:1129–1135.
73. **Katz LH, Paul M, Guy DG, Tur-Kaspa R.** Prevention of recurrent hepatitis B virus infection after liver transplantation: hepatitis B immunoglobulin, antiviral drugs, or both? Systematic review and meta-analysis. *Transpl Infect Dis* 2010; 12:292–308.
74. **Jiang L, Jiang LS, Cheng NS, Yan LN.** Current prophylactic strategies against hepatitis B virus recurrence after liver transplantation. *World J Gastroenterol* 2009; 15:2489–2499.
75. **Riediger C, Berberat PO, Sauer P, et al.** Prophylaxis and treatment of recurrent viral hepatitis after liver transplantation. *Nephrol Dial Transplant* 2007; 22(suppl 8):viii37–viii46.
76. **Cholongitas E, Vasiliadis T, Antoniadis N, Goulis I, Papanikolaou V, Akriviadis E.** Hepatitis B prophylaxis post liver transplantation with newer nucleos(t)ide analogues after hepatitis B immunoglobulin discontinuation. *Transpl Infect Dis* 2012; 14:479–487.
77. **Fox AN, Terrault NA.** Individualizing hepatitis B infection prophylaxis in liver transplant recipients. *J Hepatol* 2011; 55:507–509.
78. **Fox AN, Terrault NA.** The option of HBIG-free prophylaxis against recurrent HBV. *J Hepatol* 2012; 56:1189–1197.
79. **Wesdorp DJ, Knoester M, Braat AE, et al.** Nucleoside plus nucleotide analogs and cessation of hepatitis B immunoglobulin after liver transplantation in chronic hepatitis B is safe and effective. *J Clin Virol* 2013; 58:67–73.
80. **Terrault NA, Berenguer M.** Treating hepatitis C infection in liver transplant recipients. *Liver Transpl* 2006; 12:1192–1204.
81. **Ciria R, Pleguezuelo M, Khorsandi SE, et al.** Strategies to reduce hepatitis C virus recurrence after liver transplantation. *World J Hepatol* 2013; 5:237–250.
82. **Issa NC, Fishman JA.** Infectious complications of antilymphocyte therapies in solid organ transplantation. *Clin Infect Dis* 2009; 48:772–786.
83. **Kalambokis G, Manousou P, Samonakis D, et al.** Clinical outcome of HCV-related graft cirrhosis and prognostic value of hepatic venous pressure gradient. *Transpl Int* 2009; 22:172–181.
84. **Neumann UP, Berg T, Bahra M, et al.** Long-term outcome of liver transplants for chronic hepatitis C: a 10-year follow-up. *Transplantation* 2004; 77:226–231.
85. **Wiesner RH, Sorrell M, Villamil F; International Liver Transplantation Society Expert Panel.** Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003; 9:S1–S9.
86. **Dinges S, Morard I, Heim M, et al; Swiss Association for the Study of the Liver (SASL 17).** Pegylated interferon-alpha2a/ribavirin treatment of recurrent hepatitis C after liver transplantation. *Transpl Infect Dis* 2009; 11:33–39.
87. **Veldt BJ, Poterucha JJ, Watt KD, et al.** Impact of pegylated interferon and ribavirin treatment on graft survival in liver transplant patients with recurrent hepatitis C infection. *Am J Transplant* 2008; 8:2426–2433.
88. **Faisal N, Yoshida EM, Bilodeau M, et al.** Protease inhibitor-based triple therapy is highly effective for hepatitis C recurrence after liver transplant: a multicenter experience. *Ann Hepatol* 2014; 13:525–532.
89. **Mariño Z, van Bömmel F, Forns X, Berg T.** New concepts of sofosbuvir-based treatment regimens in patients with hepatitis C. *Gut* 2014; 63:207–215.
90. **Coilly A, Roche B, Dumortier J, et al.** Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: a multicenter experience. *J Hepatol* 2014; 60:78–86.
91. **Lucey MR, Terrault N, Ojo L, et al.** Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl* 2013; 19:3–26.

ADDRESS: Ibrahim A. Hanouneh, MD, Department of Gastroenterology and Hepatology, A30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: Hanouni2@ccf.org