

Infections in liver transplant recipients

Fabian A Romero, Raymund R Razonable

Fabian A Romero, Raymund R Razonable, Division of Infectious Diseases and the William J von Liebig Transplant Center, Mayo Clinic, Rochester, MN 55905, United States

Author contributions: Romero FA and Razonable RR contributed equally to this review.

Correspondence to: Raymund R Razonable, MD, Division of Infectious Diseases Marian Hall 5, Mayo Clinic, 200 First Street SW, Rochester, MN 55905,

United States. razonable.raymund@mayo.edu

Telephone: +1-507-2843747 Fax: +1-507-2557767

Received: October 20, 2010 Revised: December 6, 2010

Accepted: December 13, 2010

Published online: April 27, 2011

© 2011 Baishideng. All rights reserved.

Key words: Bacteremia; Candidemia; Cytomegalovirus; Aspergillosis; Transplant

Peer reviewer: Paolo Feltracco, MD, Assistant Professor of Anaesthesia and Intensive Care, Istituto di Anestesiologia e Rianimazione, Università di Padova, Via Cesare Battisti 267, Padova 35100, Italy

Romero FA, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; 3(4): 83-92 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v3/i4/83.htm> DOI: <http://dx.doi.org/10.4254/wjh.v3.i4.83>

Abstract

Liver transplantation is a standard life-saving procedure for the treatment of many end-stage liver diseases. The success of this procedure may be limited by infectious complications. In this article, we review the contemporary state of infectious complications during the post-operative period, with particular emphasis on those that occur most commonly during the first 6 mo after liver transplantation. Bacteria, and less commonly *Candida* infections, remain the predominant pathogens during the immediate post-operative period, especially during the first month, and infections caused by drug-resistant strains are emerging. Infections caused by cytomegalovirus and *Aspergillus* sp. present clinically during the "opportunistic" period characterized by intense immunosuppression. As newer potent immunosuppressive therapies with the major aim of reducing allograft rejection are developed, one potential adverse effect is an increase in certain infections. Hence, it is essential for liver transplant centers to have an effective approach to prevention that is based on predicted infection risk, local antimicrobial resistance patterns, and surveillance. A better understanding of the common and most important infectious complications is anticipated to lead to improvements in quality of life and survival of liver transplant recipients.

INTRODUCTION

Liver transplantation is a life-saving procedure for many end-stage liver diseases. According to the United Network for Organ Sharing (UNOS), a total of 6331 liver transplantations were performed in the United States during 2008-2009, with a survival rate of 85% at one year^[1-3]. Survival after liver transplantation has improved over the years, partly due to advances in surgical techniques, and a reduction in allograft rejection. However, there remain multiple preventable conditions that contribute to the poor prognosis of liver transplant recipients. Understanding these complications may optimize management strategies, and further improve the quality of life, and survival rate of patients.

Despite measures such as the use of protective barriers, antimicrobial prophylaxis, and vaccination, infections still represent a major cause of morbidity and mortality after liver transplantation^[1,2,4-13]. It is estimated that up to 80% of liver recipients will develop at least one infection during the first year after transplantation, and, while most are successfully treated, some will result in death^[14]. Indeed, opportunistic infections are a leading cause of death during the first three years after liver transplantation^[4,9]. Often, the diagnosis of these infections is delayed

Table 1 Selected infections after liver transplantation

Time period after liver transplantation		
1st mo	Between 1st and 6th mo	Beyond 6th mo
General risks: surgical procedure, prolonged hospitalization, prior colonization, mechanical ventilation, indwelling vascular and urinary catheterization, donor-transmitted diseases, among others	General risks: over-immunosuppression, D+/R- mismatch status for viruses, allograft rejection, donor-transmitted diseases, repeated biliary tract manipulations, re-transplantation	General risks: variable High-risk patients include those with recurrent rejection and allograft dysfunction that would require intense immunosuppression
Bacterial infections including resistant pathogens - bloodstream infections, pneumonia, surgical site infections, intra-abdominal infections, abscesses, urosepsis, <i>Clostridium difficile</i> associated colitis	Bacterial infections continue to occur in some patients - bloodstream infections, pneumonia, abdominal infections, <i>C difficile</i> associated colitis	Minimal immunosuppression - usual community acquired infections and zoster
Herpes simplex virus infection - herpes labialis or genitalis with potential for disseminated disease	Opportunistic pathogens: cytomegalovirus, Epstein-Barr virus, human herpesvirus 6 and 7, <i>Aspergillus</i> species, <i>Pneumocystis jirovecii</i> , during the opportunistic period (see middle column)	Intense immunosuppression due to allograft rejection and dysfunction - infections occurring
<i>Candida</i> sp. infections - fungemia, abscesses, urosepsis	<i>Nocardia</i> species, <i>Mycobacterium tuberculosis</i> , column)	continue to occur; course of chronic endemic mycoses, <i>Toxoplasma gondii</i> , among others

because, as part of allograft-conserving strategies, immunosuppressive therapy diminishes inflammatory responses, and the clinical signs of infection may be blunted or absent, leading to delayed diagnosis and treatment^[15].

There are three consecutive and often overlapping periods after liver transplantation that are associated with specific types of infections (Table 1). This article reviews the contemporary state of infections after liver transplantation, with special emphasis on bacterial infections (surgical site, intra-abdominal, and bloodstream infections) and selected viral [cytomegalovirus (CMV)] and fungal (*Candida* species and *Aspergillus* species) opportunistic pathogens.

BACTERIAL INFECTIONS

Bacterial pathogens are the most common causes of infection after liver transplantation. The highest incidence occurs during the first month after liver transplantation, and these infections predominantly involve the surgical site, the abdominal cavity, bloodstream, urinary system, and/or the respiratory tract^[2,4,5,8,9,12,14,16-20]. Risk factors include biliary tract manipulation, prolonged hospitalization, and the necessity for surgical and other invasive procedures (Table 1)^[14,16-18,21,22].

Virtually any bacteria can cause disease after liver transplantation, although the vast majority is caused by enterococcus, viridans streptococcus, *Staphylococcus aureus*, and members of the Enterobacteriaceae family^[23-26]. There is an increasing trend towards antimicrobial resistance patterns among bacteria, although variations in prevalence rates among geographic regions and centers^[23,26] have been found. In some centers, the prevalence rate of methicillin-resistant *S. aureus* (MRSA) colonization may exceed 80%^[23,26], while vancomycin-resistant enterococcus (VRE) colonization may reach up to 55%^[25]. There have been reported outbreaks of infections due to extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* or *Escherichia coli*^[27] and linezolid-resistant VRE^[24]. Risk factors for resistant bacterial pathogens are prior antibiotic

use, recurrent hospitalizations, the use of invasive interventions such as mechanical ventilation and indwelling devices, and severe underlying diseases^[26].

Surveillance for resistant bacteria (MRSA and VRE) in liver recipients may guide prevention strategies. Since MRSA colonization has been associated with risk of later infection^[28-32], infection control strategies should be an integral component of liver transplant programs in order to reduce its incidence and transmission. With surveillance, cohorting, contact isolation, and nasal decolonization, the incidence of MRSA after liver transplant has been reduced^[30,31]. MRSA decolonization is often achieved with the use of 2% intranasal mupirocin and chlorhexidine baths. The benefits of decolonization with oral antibiotics are debatable, due to concerns about further enhancing drug resistance^[23]. Active surveillance for VRE is also performed to prevent healthcare-associated transmission, however, there are no solid data to support antimicrobials to eradicate VRE carrier state^[25].

Surgical site infections

One of the most common bacterial infections found to manifest itself early after liver transplantation, is surgical site infection, which has been estimated to occur in about 10% of patients^[2]. This is most often manifested as erythema, induration, tenderness, and drainage at the surgical site. In some cases, leukocytosis and fever may occur. Surgical site infection occurs more commonly in liver recipients who require a large number of blood transfusions, thus implying a more complex nature and prolonged duration of the surgical procedure. Notably, centers that perform fewer transplant procedures per year (e.g. < 50) have a higher rate of surgical site infections^[2].

Surgical site infections are most commonly caused by Gram-positive cocci such as *S. aureus* and enterococcus, although Gram-negative pathogens like *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, and fungal pathogens such as *Candida* spp may be involved^[1,9,14,22]. It is not uncommon for multiple pathogens to cause surgical site infections after liver transplantation, hen-

ce it is important to obtain samples for culture so that optimal therapy can be administered.

While surgical site infections are common causes of morbidity during the early period after liver transplantation, they may not be associated with a significant increase in overall mortality^[22]. Treatment of surgical site infections consists of a combination of surgical debridement and pathogen-directed antimicrobial therapy.

Intra-abdominal infections

Intra-abdominal infections account for 27%-47% of early bacterial infections after liver transplantation^[1,11,17,33]. Intra-abdominal abscesses, peritonitis, and cholangitis commonly present during the first few weeks after liver transplant as fever, leukocytosis, and abdominal pain, although clinically asymptomatic cases which are mainly manifested with elevated liver enzymes are not uncommon. The offending pathogens of intra-abdominal infections are often polymicrobial and, at present, often include multi-drug-resistant isolates. Some of the important bacteria causing intra-abdominal infections are enterococci, including VRE, *S. aureus* including MRSA, *Candida* species, and Gram-negative bacilli such as *Pseudomonas* sp., *Klebsiella* sp., *Acinetobacter* sp., and *Enterobacter* sp.^[17,20].

Intra-abdominal infections are significantly associated with higher all-cause mortality (they double the risk), graft loss (39% *vs* 7%), and re-transplantation^[17]. Predisposing factors are Roux-en-Y choledochojejunostomy, hepatic artery thrombosis, or arterial stenosis^[34]. Once clinically suspected, the test to document the presence of fluid collections is radiographic imaging, either through CT scan or ultrasound. Treatment of infected collections consists of percutaneous or open surgical drainage combined with prolonged antimicrobial therapy, guided by susceptibility testing.

Bloodstream infections

Bloodstream infections may occur any time after liver transplantation, although the majority occur during the first post-operative month. Clinical manifestations most often include fever and rigors, accompanied by leukocytosis and organ-specific or localizing symptoms related to the potential source of the bloodstream infection, such as erythema and drainage at vascular catheter sites (catheter-related blood stream infections), cough and dyspnea (pneumonia), and dysuria and suprapubic and flank pain (urosepsis). Risk factors include intra-abdominal infection, the need for re-operation, prolonged use of indwelling vascular catheters, and acute allograft rejection^[5,21]. The gastrointestinal tract is usually the most common source of bloodstream infections in liver transplant recipients, and thus they are most commonly due to enterococcus, viridans streptococcus, Gram-negative bacilli, or may even be polymicrobial^[5,35]. Other less common sources of bloodstream infection after liver transplantation include the urinary tract (urosepsis), pulmonary system (pneumonia), or infections emanating from infected indwelling vascular catheters. Interestingly, when compared to other solid organ trans-

plant recipients, there is a higher incidence of mortality due to Gram-negative bloodstream infection among liver transplant recipients^[5,35].

Bacteria causing bloodstream infection after liver transplant are predominately Gram-positive cocci such as enterococcus, viridans streptococcus and *Staphylococcus* sp., however, there has been an increasing trend towards Gram-negative bacteria, particularly when the source is the gastrointestinal tract^[5,35,36]. Today, there is an increasing prevalence of multi-drug resistant bacteria such as MRSA, which may be the cause of as much as 50% of bloodstream infections in some centers^[5]. Transplant candidates who are carriers of MRSA have a higher risk of bloodstream infection, and may thus benefit from decolonization prior to transplantation^[30]. Likewise, VRE-colonized transplant recipients have a higher risk of infection, postoperative stay in the intensive care unit, and death^[37,38]. VRE colonization may also serve as an indicator of a more severe illness, an increased incidence of biliary complications, and multiple previous abdominal surgeries^[37,38].

E. coli is the most common Gram-negative bacilli causing bloodstream infection after liver transplantation, followed by *K. pneumoniae* and *P. aeruginosa*^[35]. There is increasing resistance among these Gram-negative pathogens. The prevalence of ESBL-producing Gram-negative bacilli is now close to 13% in some centers^[2,4,8,14], while 44% of *E. coli* isolates have developed resistance to quinolones^[35], potentially due to common use of ciprofloxacin and norfloxacin as prophylaxis for spontaneous bacterial peritonitis, or levofloxacin as empiric therapy for community-acquired respiratory and urinary infections. Likewise, multidrug-resistant strains have been reported in as high as 62.5% of *A. baumannii*, 54.2% of *Stenotrophomonas maltophilia*, and 51.5% of *Pseudomonas* sp. isolates^[19,21]. Outbreaks of carbapenem-resistant *Klebsiella spp.* bloodstream infections have occurred, with fatal outcomes^[39].

Treatment of bloodstream infections should be directed towards the elimination of the predisposing factor, combined with pathogen-directed antimicrobial therapy that is guided by antimicrobial susceptibility testing. For persistent bloodstream infections, endocarditis should be evaluated by means of a transesophageal echocardiogram. Indwelling vascular and urinary catheters should be removed, intra-abdominal abscesses should be drained, and other potential nidus of infection should be surgically corrected, if feasible.

VIRAL INFECTIONS

Liver recipients are somewhat unique among transplant recipients because they are commonly chronically infected with hepatitis B or C viruses, often with an accelerated clinical course^[40]. Respiratory and gastrointestinal viruses may occur throughout the post-liver transplant period, with seasonal variations for some viruses such as influenza and parainfluenza^[41-43]. A list of selected viruses that affect liver transplant recipients is listed in Table 1. Among the opportunistic viral pathogens, the most commonly oc-

curing are members of the herpes virus group^[44-47], of which CMV is most important in terms of its direct and indirect impact on liver transplant outcome.

Cytomegalovirus

CMV seroprevalence rates in humans ranges from 45% to 100%^[48,49]. Its ability to establish latency inside cells leads to a high infection rate in transplant recipients^[50,51]. While immunocompetent hosts are usually infected without symptoms, liver recipients often present with more severe clinical presentation, including tissue invasion. Liver recipients at highest risk of CMV infection and disease are those who have never had CMV infection until they receive a latently infected organ from a CMV-seropositive donor (CMV D+/R- mismatch). The risk of progression into CMV disease is magnified by the intense immunosuppression required to avoid or to treat allograft rejection.

The clinical impact of CMV disease after liver transplantation can be classified into: (1) an acute infection with clinical signs known as direct effects (fever, mononucleosis, and invasive organ disease); and (2) a broad range of immunomodulatory and vascular effects, referred to as indirect effects. The most common presentation of CMV disease consists of fever and bone marrow suppression (CMV syndrome). A more aggressive form includes tissue invasion, commonly affecting the gastrointestinal tract, and presenting as gastritis or colitis. This is most often manifests itself as abdominal pain and diarrhea. Endoscopic findings include mucosal erosions and ulcerations, but mild hyperemia or even normal mucosa may also be present^[52]. A second clinical presentation that is fairly prevalent in liver recipients is CMV hepatitis, which usually presents with abnormal liver function tests in a cholestatic pattern^[53]. CMV hepatitis can be confirmed by means of biopsy, where inclusion bodies with clusters of polymorphonuclear cells is the hallmark^[12,53]. A tissue sample is often necessary to rule out the alternative diagnosis of allograft rejection. Other organs such as the central nervous system and the lungs may be infected, and present themselves through headache, delirium, changes in mental function, and cough and dyspnea, respectively. Current practice relies on biologic markers (CMV pp65 antigenemia or CMV DNA by polymerase chain reaction) as the earliest indicators of infection^[12,53].

It is proposed that the indirect effects of CMV result from its immunomodulatory property^[54-58]. Excessive production of interleukin 10, which is an important inhibitor of the immune response^[54], could potentially be one of the mechanisms for the higher incidence of bacteremia, fungal and other viral infections [human herpesvirus 6 (HHV-6), HHV-7, Epstein-Barr virus (EBV) associated post-transplant lymphoproliferative disorder (PTLD), and accelerated HCV course] in CMV-infected individuals. Infection of vascular networks supplying the transplanted organ may cause functional impairment, leading to the loss of the allograft^[58].

Because of its negative impact on overall outcome, prevention of CMV disease is a key management strategy after liver transplantation. One major strategy is antiviral prophylaxis, wherein antiviral drugs such as valganciclovir or oral ganciclovir are given to patients for at least 3 mo after liver transplantation. However, antiviral prophylaxis is associated with delayed-onset CMV disease, which typically occurs soon after completion of prophylaxis. Delayed onset CMV disease is significantly associated with increased mortality and graft failure after liver transplantation^[59-61]. Risk factors for delayed onset CMV disease are CMV D+/R- mismatch status, acute allograft rejection, and the corresponding increase in immunosuppression, especially with anti-lymphocyte antibodies^[59,62]. The second strategy for CMV disease prevention is pre-emptive therapy, which relies on a close virologic follow-up through serial blood markers (such as viral load or pp65 antigenemia) as the trigger for antiviral therapy, usually with intravenous ganciclovir or valganciclovir^[63]. A recent systematic review^[64] showed a low incidence (2.6%) of CMV disease in patients who had received pre-emptive valganciclovir therapy, and no case of delayed onset CMV disease was observed. Pre-emptive strategy, which allows short-term low level CMV replication, may prime the immune system to develop CMV-specific immunity, thus preventing late-occurring CMV disease. On the other hand, patients receiving universal prophylaxis had a higher incidence of late onset CMV disease (9.9% at one year). Nonetheless, systematic reviews and meta-analysis have demonstrated the similar reduction in CMV disease for both prophylaxis and pre-emptive therapy strategies, but all-cause mortality appears to be reduced by prophylaxis but not by pre-emptive therapy^[63]. There remains a concern for the rapidly replicating virus in CMV D+/R- transplant recipients, so that in this high-risk population, the recommendation is to use antiviral prophylaxis. For lower risk recipients (D+/R+ and D-/R+), universal prophylaxis or pre-emptive therapy regimens may be effectively used (Table 2)^[63].

Treatment of CMV disease is with intravenous ganciclovir (5 mg/kg every 12 h) or oral valganciclovir (900 mg orally twice daily) (Table 2), combined with reduction in immunosuppression. Severe cases warrant the initial use of intravenous ganciclovir, while treatment of mild to moderate cases may be initiated upfront with oral valganciclovir. For severe cases, the addition of CMV-hyperimmune globulin as adjunct treatment may be considered. The efficacy of treatment should be guided by clinical and virologic assessments, often with serial weekly monitoring of viral load or antigenemia levels. The vast majority of CMV disease cases after liver transplantation, even those occurring at delayed onset, remain susceptible to ganciclovir. Non-responders should be tested for drug-resistant virus, with UL97 and UL54 gene sequencing. Therapy for drug-resistant CMV is tailored, based on the results of genotyping. Foscarnet and cidofovir are often used for treatment of ganciclovir-resistant UL97-mutant CMV strains, but they have a high risk of nephrotoxicity.

Table 2 Suggested prevention and treatment regimens for various infections after liver transplantation

Infection	Prevention	Treatment
Bacterial infections	According to risk factors (i.e. cephalosporins or vancomycin)	Susceptibility-guided antimicrobial treatment
Herpes simplex virus	Acyclovir 400 mg PO BID for 4 wk (if they are not receiving drugs for CMV prevention)	Acyclovir 5 mg/kg every 8 h for mucocutaneous disease or 10 mg/kg every 8 h for encephalitis
Cytomegalovirus	Valganciclovir 900 mg daily for 3-6 mo Oral ganciclovir, 1 gram TID for 3-6 mo Preemptive therapy (guided by CMV PCR or antigenemia)	Valganciclovir 1 gram PO BID for less severe disease Valganciclovir PO 900 mg BID or ganciclovir IV 5 mg/kg BID. If severe or life-threatening disease, initiate therapy with IV ganciclovir. Treatment must continue until viral eradication is achieved, but not shorter than 2 wk
Varicella zoster virus	Pre-transplant vaccination	CMV Ig may be considered for severe forms of disease like pneumonitis. Valacyclovir 1-gram PO TID or IV acyclovir 10 mg/kg every 8 h Initiate with IV acyclovir for disseminated disease such as pneumonia or encephalitis
<i>Candida</i> species	Fluconazole, echinocandin, or amphotericin B in high-risk recipients for 4 weeks	VZV immunoglobulin adds no additional benefits and not recommended Amphotericin B 3 to 5 mg/kg IV daily Fluconazole 800 mg loading dose, then 400 mg PO daily Caspofungin at an initial dose of 70 mg followed by 50 mg daily Anidulafungin initial dose of 200 mg first day followed by 100 mg daily
<i>Aspergillus</i> species	Voriconazole, echinocandin, or amphotericin B in high-risk patients	Voriconazole 6 mg/kg IV BID on day 1 followed by 4 mg/kg BID daily; transition to oral regimen when clinically stable Echinocandins (caspofungin or anidulafungin)
<i>Cryptococcus neoformans</i>	Not recommended	Amphotericin B preparations Amphotericin B (conventional or liposomal) and flucytosine (5-FC) for at least 2 wk then fluconazole as long-term maintenance (e.g. 6 mo)
<i>Pneumocystis jirovecii</i>	TMP-SMX 160/800 mg daily or three times per week Alternative: TMP-SMX 80/400 mg daily	Fluconazole 800 mg loading dose, then 400 mg PO daily for limited disease TMP-SMX preferred; 15-20 mg/kg per day of TMP component in 3-4 divided doses (keep the sulfa level above 100); transition to oral regimen when clinically stable Alternatives: Pentamidine isethionate, trimethoprim-dapsone (in patients who are not deficient in glucose-6-phosphate dehydrogenase), atovaquone, and clindamycin-primaquine.
<i>Toxoplasma gondii</i> <i>Listeria monocytogenes</i>	TMP-SMX 160/800 mg daily Not recommended but TMP-SMX for <i>Pneumocystis</i> prophylaxis may prevent some infections	Pyrimethamine in combination with sulfadiazine or clindamycin. Ampicillin 2 g IV every four hours plus Gentamicin 3 mg/kg per day IV in three divided doses Alternatives: TMP-SMX 10-20 mg/kg IV per day divided every 6 to 12 h Meropenem 2 g IV every eight hours
<i>Nocardia asteroides</i>	Not recommended but TMP-SMX for <i>Pneumocystis</i> prophylaxis may prevent some infections	TMP-SMX preferred; 8-10 mg/kg per day of TMP component in 2-4 divided doses; higher doses may be used in severe disease; transition to oral therapy when clinically stable

CMV: cytomegalovirus; VZV: Varicella zoster virus; HSV: herpes simplex virus; TMP-SMX: trimethoprim sulfamethoxazole.

FUNGAL INFECTIONS

Although various fungal species infect liver transplant recipients, by far the most common are the *Candida* species followed by the *Aspergillus* species. *Cryptococcus neoformans* occurs much less commonly in the form of meningitis, lung disease and cellulitis^[66]. Endemic mycoses due to *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis* may occur in liver recipients from endemic regions, and among these, *C. immitis* often persist and require prolonged therapy^[67]. Other less common fungi that may cause skin disease could potentially become invasive in liver transplant recipients, include *Alternaria* species, *Sporothrix schenckii*, *Trichophyton rubrum*, among others^[68]. Finally, infection due to *Pneumocystis jirovecii* occurs primarily as diffuse bilateral pneumonitis, although the use of trimethoprim sulfamethoxazole prophylaxis has remarkably reduced its incidence after liver transplantation^[69].

Candida species

Candida sp. accounts for over half of all invasive fungal infections in liver recipients^[70]. Superficial and invasive candidiasis occurs early and often during the first 1-3 mo after liver transplantation^[70]. *Candida albicans* is the single most common species, but collectively the non-*albicans* *Candida* species are now being reported more frequently from blood cultures. The distribution of the species varies among reports, including *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. guilliermondii* and *C. krusei*^[2,5,7,10,71-75]. This has implications in empiric antifungal treatment, since some of these isolates, particularly *C. glabrata* and *C. krusei*, are inherently resistant to fluconazole. The most common clinical presentation is mucosal candidiasis (e.g. oral thrush), but the much more worrisome illness, because of its impact on morbidity and mortality, is invasive candidiasis^[70-76]. Invasive candidiasis is defined as the (1) direct microscopic evidence of the candida in a specimen obtained from a normally sterile site; (2) recovery of candida by

Table 3 Risk factors of fungal infections after liver transplantation

<i>Candida</i> species	<i>Aspergillus</i> species
Renal insufficiency	Renal insufficiency
Renal insufficiency (creatinine > 3.0 mg/dL)	Renal failure
Renal replacement therapy within the first 30 days after transplant	Need for dialysis
Surgical factors	Surgical factors
Prolonged transplant operation time (> 11 h)	Retransplantation
Second surgical intervention for any reason within 5 d of the initial transplant procedure	Microbial factors
Choledochojejunostomy anastomosis.	CMV infection
Transfusion of ≥ 40 units of blood products during the surgery	Prior colonization
Microbial factors	Fulminant hepatic failure
Early fungal colonization (within 3 d after liver transplantation)	
Documented colonization (nasal, pharyngeal or rectal cultures)	
Fulminant hepatic failure	

CMV: cytomegalovirus.

culture of a sample obtained from a normally sterile site in a suspicious clinical setting; or (3) recovery of *Candida* species in one or more blood cultures (candidemia)^[77]. Disseminated candidiasis is defined as an episode of candidemia with associated target-like abscesses in the liver or the spleen, or the presence of progressive retinal exudates on ophthalmologic examination^[77].

The incidence of candidemia among transplant recipients ranges between 2%-8%^[2,75], and the overall mortality associated with invasive fungal presentation has been reported to be as high as 77%^[74]. Invasive candidiasis could be primary or secondary to infected catheters or surgical wounds^[72]. Dissemination to involve distant sites such as the eyes and the bone may occur, and should warrant evaluation in the presence of clinical symptoms such as blurring of vision and bone pains, respectively. Surgical site infection, peritonitis, liver and abdominal abscesses, endophthalmitis, esophagitis, and urinary tract or anastomotic infections are the other clinical presentations of candidiasis^[70,76].

Risk factors for invasive candidiasis are often related to the surgical procedure (such as prolonged or repeat operations and re-transplantation), high-transfusion requirement, previous *Candida* specie colonization during the perioperative period, and renal failure after liver transplantation (Table 3)^[7,70,72,76,78]. Choleduco-jejunostomy anastomosis is especially associated with a higher risk of candidiasis when compared to choledoco-choledoco anastomosis^[7].

The American Society of Transplantation recommends antifungal prophylaxis against *Candida* to high-risk liver recipients^[70,76]. However, the duration of prophylaxis is not defined, with many centers providing it for 4 weeks. Echinocandins, azoles, and amphotericin B are the various options for antifungal prophylaxis^[78]. Clinical studies have shown that fluconazole, itraconazole, or amphotericin B prophylaxis markedly reduced the incidence of invasive candidiasis in liver recipients^[79-81]. Caspofungin also appears to be well tolerated^[78] and has been shown to result in a low rate of invasive fungal infection^[78,82]. However, a meta-analysis showed that, while antifungal prophylaxis in liver recipients significantly reduced the incidence of

superficial and invasive fungal infection, it neither impacted on the overall mortality nor the need for empirical antifungal treatment^[71]. Antifungal prophylaxis is not recommended for low-risk patients^[83] due to concerns for toxicity, and may select for resistant strains^[78,84].

Treatment of invasive candidiasis after liver transplantation is often a combination of antifungal therapy, elimination of nidus of infection, and reduction of immunosuppression. Empiric treatment of invasive candidiasis consists of the use of a broad-spectrum antifungal agent (such as caspofungin, micafungin and anidulafungin) in view of the increasing incidence of fluconazole-resistant strains due to non-*albicans* *Candida* species^[2]. Once the species and its antifungal susceptibility pattern have been confirmed, a more focused treatment should be used. The vast majority of *C. albicans* remains susceptible to fluconazole and that should be the treatment of choice. The shift from *C. albicans* to non-*albicans* species in many clinical settings has most likely resulted from the widespread use of fluconazole prophylaxis^[73]. Fluconazole resistance in invasive candidiasis should be suspected in patients who have received fluconazole during the 30 d prior to the illness. Abscesses and infected wounds need to be drained and debrided, while infected indwelling vascular and urinary catheters need to be removed. Potential sites of dissemination such as the eye (candidal retinitis and endophthalmitis) and the bones (osteomyelitis) should be examined.

Aspergillus species

After *Candida* sp., this highly aerobic mold is the second most common fungal infection in liver recipients, with invasive aspergillosis occurring in 1%-9.2%^[85]. The risk factors are listed in Table 3^[86,87]. Among the most notable risk factors are re-transplantation, which could bring about a 30-fold higher risk, and renal failure, especially with the requirement for renal replacement therapy, which could bring about a 15-25 fold increase in risk^[85]. Other risk factors that have been described are fulminant hepatic failure, CMV disease, and prolonged ICU stay^[85]. Mortality from invasive aspergillosis is high among liver recipients, so that treatment needs to be started early and aggres-

sively^[13].

Aspergillus fumigatus is the most common offending species^[85], whereas *A. niger*, *A. flavus* and *A. terreus* are less common^[88]. In a recent study of the clinical features of invasive aspergillosis from 23 US transplant centers, the most common clinical presentation (90%) was lung infection^[85]. Most infections occur during the first year, with a median time to diagnosis of 100 d. Other studies have described an earlier onset of invasive aspergillosis, such as within 30 d after liver transplantation, although others report a much more delayed onset of infection^[85]. Notably, liver recipients with invasive fungal infection had the highest mortality reported, perhaps as result of the severity of the illness and the patient's underlying compromised status^[13,88].

The possibility of invasive aspergillosis should be suspected in the presence of risk factors and suspicious clinical findings, and should be confirmed by one of the following: (1) lower respiratory tract infection symptoms, with associated risk factors and CT images showing well-circumscribed lesions with or without the halo sign, air-crescent sign or a cavity; (2) central nervous system infection with focal lesions on imaging or (3) recovery by culture of the mold^[77]. Since sensitivity of fungal cultures is relatively low, it has been suggested that measuring aspergillus antigens such as galactomannan in clinical samples such as plasma, serum, bronchoalveolar lavage fluid, or CSF could be useful for diagnosis^[85]. Special caution, however, is suggested in interpreting the galactomannan test in patients who are receiving β -lactam antibiotics (specifically piperacillin tazobactam and ampicillin) which cross-react with the assay, thereby providing false positive results^[89,90]. These antimicrobials are semisynthetic derivatives from *Penicillium* species that contain galactofuran-bearing molecules, which react with the assay^[91,92].

Antifungal prophylaxis against *Aspergillus* sp. could result in an important reduction in superficial and invasive infection, as well as mortality attributable to fungal infections^[85]. However, antifungal prophylaxis does not reduce overall mortality or the need for empirical antifungal therapy^[71]. The overall efficacy of universal antifungal prophylaxis is limited by the generally low incidence of invasive aspergillosis^[85]. Hence, providing prophylaxis only to the high-risk patients would seem to be a more rational approach^[71]. The American Society of Transplantation recommends the use of a lipid formulation of amphotericin B (3-5 mg/kg per day) or an echinocandin for liver recipients with factors that place them at high risk^[85]; the duration of antifungal prophylaxis is during the initial hospital stay or for 4 wk after liver transplantation^[85].

Prompt diagnosis and initiation of antifungal therapy, coupled with a reduction in the immunosuppressive regimen is essential for achieving optimal outcomes with invasive aspergillosis after liver transplantation^[85]. The current guideline endorses voriconazole as the first-line choice for the treatment of invasive aspergillosis (Table 2)^[88]. Antifungal therapy with amphotericin B preparations is now considered as second line therapy^[87]. Echinocandins are effective for treatment, but they have been tested mainly

as salvage therapy for invasive aspergillosis^[85]. Of the echinocandins, caspofungin is currently approved by the US FDA for the treatment of invasive aspergillosis. Combination antifungal therapy has been reported in certain situations (such as severe disseminated disease), but the efficacy of this approach remains controversial^[85]. The Infectious Disease Society of America reserves the option of combination antifungal regimens as salvage therapy for non-responsive cases of invasive aspergillosis^[85,88]. Surgical excision or debridement remains an integral part of the management of invasive aspergillosis. The optimal duration of therapy depends on the response to therapy, and the patient's underlying immune function. Generally, treatment is continued for at least 12 wk, although it should be individualized, based on clinical response.

CONCLUSION

Infectious complications remain important preventable causes of morbidity and mortality among liver recipients. The vast majority of infections that occur during the immediate period after liver transplantation are often related either to surgical procedures, medical devices, or the need for prolonged hospitalization. During the highly intense period of immunosuppression, the most common opportunistic infections are cytomegalovirus and invasive fungal infections (candidiasis and less commonly aspergillosis). It is therefore essential to have in place an effective approach to prevention, based on predicted infection risk, local antimicrobial resistance patterns, and surveillance of specific risk factors. A better understanding of the common and important infectious complications is anticipated to improve quality of life and survival rate after liver transplantation.

REFERENCES

- 1 **Arnou PM.** Infections following orthotopic liver transplantation. *HPB Surg* 1991; **3**: 221-232; discussion 232-233
- 2 **Moreno A,** Cervera C, Gavaldá J, Rovira M, de la Cámara R, Jarque I, Montejo M, de la Torre-Cisneros J, Miguel Cisneros J, Fortún J, López-Medrano F, Gurguá M, Muñoz P, Ramos A, Carratalá J. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. *Am J Transplant* 2007; **7**: 2579-2586
- 3 **Watt KD,** Burak KW, Deschênes M, Lilly L, Marleau D, Marotta P, Mason A, Peltekian KM, Renner E, Yoshida EM. Survival after liver transplantation for hepatitis C is unchanged over two decades in Canada. *Can J Gastroenterol* 2008; **22**: 153-154
- 4 **Watt KD,** Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; **10**: 1420-1427
- 5 **Bert F,** Larroque B, Paugam-Burtz C, Janny S, Durand F, Dondero F, Valla DC, Belghiti J, Moreau R, Nicolas-Chanoine MH. Microbial epidemiology and outcome of bloodstream infections in liver transplant recipients: an analysis of 259 episodes. *Liver Transpl* 2010; **16**: 393-401
- 6 **Charlton M,** Ruppert K, Belle SH, Bass N, Schafer D, Wiesner RH, Detre K, Wei Y, Everhart J. Long-term results and modeling to predict outcomes in recipients with HCV infec-

- tion: results of the NIDDK liver transplantation database. *Liver Transpl* 2004; **10**: 1120-1130
- 7 **Collins LA**, Samore MH, Roberts MS, Luzzati R, Jenkins RL, Lewis WD, Karchmer AW. Risk factors for invasive fungal infections complicating orthotopic liver transplantation. *J Infect Dis* 1994; **170**: 644-652
 - 8 **del Pozo JL**. Update and actual trends on bacterial infections following liver transplantation. *World J Gastroenterol* 2008; **14**: 4977-4983
 - 9 **Fishman JA**. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; **357**: 2601-2614
 - 10 **Horn DL**, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA, Pfaller MA, Chang CH, Webster KM. Epidemiology and outcome of invasive fungal infections in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin Infect Dis* 2009; **48**: 1695-1703
 - 11 **Kim YJ**, Kim SI, Wie SH, Kim YR, Hur JA, Choi JY, Yoon SK, Moon IS, Kim DG, Lee MD, Kang MW. Infectious complications in living-donor liver transplant recipients: a 9-year single-center experience. *Transpl Infect Dis* 2008; **10**: 316-324
 - 12 **Linden PK**. Approach to the immunocompromised host with infection in the intensive care unit. *Infect Dis Clin North Am* 2009; **23**: 535-556
 - 13 **Neofytos D**, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, Pfaller M, Steinbach WJ, Webster KM, Marr KA. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis* 2010; **12**: 220-229
 - 14 **Kawecki D**, Chmura A, Pacholczyk M, Lagiewska B, Adadynski L, Wasiaak D, Czerwinski J, Malkowski P, Sawicka-Grzelak A, Kot K, Wroblewska M, Rowinski W, Durlik M, Paczek L, Luczak M. Bacterial infections in the early period after liver transplantation: etiological agents and their susceptibility. *Med Sci Monit* 2009; **15**: CR628-CR637
 - 15 **Moon DB**, Lee SG. Liver transplantation. *Gut Liver* 2009; **3**: 145-165
 - 16 **Tenza E**, Bernardo CG, Escudero D, Otero J, Quindós B, Miyar A, Vázquez L, Taboada F, Rodríguez M, González-Diéguez L, González-Pinto I, Barneo L. Liver transplantation complications in the intensive care unit and at 6 months. *Transplant Proc* 2009; **41**: 1050-1053
 - 17 **Safdar N**, Said A, Lucey MR, Knechtle SJ, D'Alessandro A, Musat A, Pirsch J, McDermott J, Kalayoglu M, Maki DG. Infected bilomas in liver transplant recipients: clinical features, optimal management, and risk factors for mortality. *Clin Infect Dis* 2004; **39**: 517-525
 - 18 **Kim SI**, Kim YJ, Jun YH, Wie SH, Kim YR, Choi JY, Yoon SK, Moon IS, Kim DG, Lee MD, Kang MW. Epidemiology and risk factors for bacteremia in 144 consecutive living-donor liver transplant recipients. *Yonsei Med J* 2009; **50**: 112-121
 - 19 **Linares L**, García-Goez JF, Cervera C, Almela M, Sanclemente G, Cofán F, Ricart MJ, Navasa M, Moreno A. Early bacteremia after solid organ transplantation. *Transplant Proc* 2009; **41**: 2262-2264
 - 20 **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
 - 21 **Shi SH**, Kong HS, Xu J, Zhang WJ, Jia CK, Wang WL, Shen Y, Zhang M, Zheng SS. Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 405-412
 - 22 **Asensio A**, Ramos A, Cuervas-Mons V, Cordero E, Sánchez-Turrión V, Blanes M, Cervera C, Gavalda J, Aguado JM, Torre-Cisneros J. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. *Liver Transpl* 2008; **14**: 799-805
 - 23 **Garzoni C**. Multiply resistant gram-positive bacteria methicillin-resistant, vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* (MRSA, VISA, VRSA) in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S41-S49
 - 24 **Herrero IA**, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant *Enterococcus faecium*. *N Engl J Med* 2002; **346**: 867-869
 - 25 **Muñoz P**. Multiply resistant gram-positive bacteria: vancomycin-resistant enterococcus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S50-S56
 - 26 **van Delden C**, Blumberg EA. Multidrug resistant gram-negative bacteria in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S27-S34
 - 27 **Paterson DL**, Singh N, Rihs JD, Squier C, Rihs BL, Muder RR. Control of an outbreak of infection due to extended-spectrum beta-lactamase--producing *Escherichia coli* in a liver transplantation unit. *Clin Infect Dis* 2001; **33**: 126-128
 - 28 **Bert F**, Galdbart JO, Zarrouk V, Le Mée J, Durand F, Mentré F, Belghiti J, Lambert-Zechovsky N, Fantin B. Association between nasal carriage of *Staphylococcus aureus* and infection in liver transplant recipients. *Clin Infect Dis* 2000; **31**: 1295-1299
 - 29 **Desai D**, Desai N, Nightingale P, Elliott T, Neuberger J. Carriage of methicillin-resistant *Staphylococcus aureus* is associated with an increased risk of infection after liver transplantation. *Liver Transpl* 2003; **9**: 754-759
 - 30 **Russell DL**, Flood A, Zaroda TE, Acosta C, Riley MM, Busuttill RW, Pegues DA. Outcomes of colonization with MRSA and VRE among liver transplant candidates and recipients. *Am J Transplant* 2008; **8**: 1737-1743
 - 31 **Singh N**, Paterson DL, Chang FY, Gayowski T, Squier C, Wagener MM, Marino IR. Methicillin-resistant *Staphylococcus aureus*: the other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis* 2000; **30**: 322-327
 - 32 **Wertheim HF**, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis* 2005; **5**: 751-762
 - 33 **Akin K**, Ozturk A, Guvenc Z, Isiklar I, Haberal M. Localized fluid collections after liver transplantation. *Transplant Proc* 2006; **38**: 627-630
 - 34 **Said A**, Safdar N, Lucey MR, Knechtle SJ, D'Alessandro A, Musat A, Pirsch J, Kalayoglu M, Maki DG. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. *Am J Transplant* 2004; **4**: 574-582
 - 35 **Al-Hasan MN**, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of Gram-negative bloodstream infection in solid organ transplant recipients. *Am J Transplant* 2009; **9**: 835-843
 - 36 **Singh N**, Wagener MM, Obman A, Cacciarelli TV, de Vera ME, Gayowski T. Bacteremias in liver transplant recipients: shift toward gram-negative bacteria as predominant pathogens. *Liver Transpl* 2004; **10**: 844-849
 - 37 **McNeil SA**, Malani PN, Chenoweth CE, Fontana RJ, Magee JC, Punch JD, Mackin ML, Kauffman CA. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. *Clin Infect Dis* 2006; **42**: 195-203
 - 38 **Gearhart M**, Martin J, Rudich S, Thomas M, Wetzel D, Solomkin J, Hanaway MJ, Aranda-Michel J, Weber F, Trumbull L, Bass M, Zavala E, Steve Woodle E, Buell JF. Consequences of vancomycin-resistant *Enterococcus* in liver transplant recipients: a matched control study. *Clin Transplant* 2005; **19**: 711-716
 - 39 **Mathers AJ**, Cox HL, Bonatti H, Kitchel B, Brassinga AK, Wispelwey B, Sawyer RG, Pruett TL, Hazen KC, Patel JB, Sifri CD. Fatal cross infection by carbapenem-resistant *Klebsiella* in two liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 257-265
 - 40 **Levitsky J**, Doucette K. Viral hepatitis in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S116-S130

- 41 **Ison MG**, Green M. Adenovirus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S161-S165
- 42 **Ison MG**, Michaels MG. RNA respiratory viral infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S166-S172
- 43 **Kumar D**, Morris MI, Kotton CN, Fischer SA, Michaels MG, Allen U, Blumberg EA, Green M, Humar A, Ison MG. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. *Am J Transplant* 2010; **10**: 18-25
- 44 **Humar A**, Snyderman D. Cytomegalovirus in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S78-S86
- 45 **Razonable RR**, Zerr DM. HHV-6, HHV-7 and HHV-8 in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S97-S100
- 46 **Pergam SA**, Limaye AP. Varicella zoster virus (VZV) in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S108-S115
- 47 **Zuckerman R**, Wald A. Herpes simplex virus infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S104-S107
- 48 **Bate SL**, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. *Clin Infect Dis* 2010; **50**: 1439-1447
- 49 **Cannon MJ**, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol* 2010; **20**: 202-213
- 50 **Boin ID**, Boteon YL, Stucchi RS, Pereira MI, Portugal TC, Udo EY. Serological profile of pretransplantation liver patients. *Transplant Proc* 2010; **42**: 491-493
- 51 **Dahiya D**, Lee CF, Chan KM, Wu TJ, Chou HS, Cheng SS, Lee WC. A short-term preemptive treatment for cytomegalovirus infection in seropositive patients after liver transplantation. *J Hepatobiliary Pancreat Sci* 2011; **18**: 32-38
- 52 **Eid AJ**, Arthurs SK, Deziel PJ, Wilhelm MP, Razonable RR. Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2010; **10**: 157-161
- 53 **Koffron A**, Stein JA. Liver transplantation: indications, pre-transplant evaluation, surgery, and posttransplant complications. *Med Clin North Am* 2008; **92**: 861-888, ix
- 54 **van de Berg PJ**, Heutink KM, Raabe R, Minnee RC, Young SL, van Donselaar-van der Pant KA, Bemelman FJ, van Lier RA, ten Berge IJ. Human cytomegalovirus induces systemic immune activation characterized by a type 1 cytokine signature. *J Infect Dis* 2010; **202**: 690-699
- 55 **Razonable RR**, Emery VC. Management of CMV infection and disease in transplant patients. 27-29 February 2004. *Herpes* 2004; **11**: 77-86
- 56 **Razonable RR**, Paya CV. Herpesvirus infections in transplant recipients: current challenges in the clinical management of cytomegalovirus and Epstein-Barr virus infections. *Herpes* 2003; **10**: 60-65
- 57 **Razonable RR**, Paya CV. Infections and allograft rejection - intertwined complications of organ transplantation. *Swiss Med Wkly* 2005; **135**: 571-573
- 58 **Baron C**, Forconi C, Lebranchu Y. Revisiting the effects of CMV on long-term transplant outcome. *Curr Opin Organ Transplant* 2010; **15**: 492-498
- 59 **Kim JM**, Kim SJ, Joh JW, Kwon CH, Shin M, Kim EY, Moon JI, Jung GO, Choi GS, Lee SK. Early and delayed onset cytomegalovirus infection of liver transplant recipients in endemic areas. *Transplant Proc* 2010; **42**: 884-889
- 60 **Husain S**, Pietrangeli CE, Zeevi A. Delayed onset CMV disease in solid organ transplant recipients. *Transpl Immunol* 2009; **21**: 1-9
- 61 **Arthurs SK**, Eid AJ, Pedersen RA, Kremers WK, Cosio FG, Patel R, Razonable RR. Delayed-onset primary cytomegalovirus disease and the risk of allograft failure and mortality after kidney transplantation. *Clin Infect Dis* 2008; **46**: 840-846
- 62 **Razonable RR**, Rivero A, Rodriguez A, Wilson J, Daniels J, Jenkins G, Larson T, Hellinger WC, Spivey JR, Paya CV. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *J Infect Dis* 2001; **184**: 1461-1464
- 63 **Eid AJ**, Razonable RR. New developments in the management of cytomegalovirus infection after solid organ transplantation. *Drugs* 2010; **70**: 965-981
- 64 **Sun HY**, Wagener MM, Singh N. Prevention of posttransplant cytomegalovirus disease and related outcomes with valganciclovir: a systematic review. *Am J Transplant* 2008; **8**: 2111-2118
- 65 **Kotton CN**, Kumar D, Caliendo AM, Asberg A, Chou S, Snyderman DR, Allen U, Humar A. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 2010; **89**: 779-795
- 66 **Singh N**, Forrest G. Cryptococcosis in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S192-S198
- 67 **Proia L**, Miller R. Endemic fungal infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S199-S207
- 68 **Kubak BM**, Huprikar SS. Emerging & rare fungal infections in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S208-S226
- 69 **Martin SJ**, Fishman JA. Pneumocystis pneumonia in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S227-S233
- 70 **Pappas PG**, Silveira FP. Candida in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S173-S179
- 71 **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
- 72 **Hadley S**, Huckabee C, Pappas PG, Daly J, Rabkin J, Kauffman CA, Merion RM, Karchmer AW. Outcomes of antifungal prophylaxis in high-risk liver transplant recipients. *Transpl Infect Dis* 2009; **11**: 40-48
- 73 **Person AK**, Kontoyiannis DP, Alexander BD. Fungal infections in transplant and oncology patients. *Infect Dis Clin North Am* 2010; **24**: 439-459
- 74 **Singh N**. Fungal infections in the recipients of solid organ transplantation. *Infect Dis Clin North Am* 2003; **17**: 113-134, viii
- 75 **van Hal SJ**, Marriott DJ, Chen SC, Nguyen Q, Sorrell TC, Ellis DH, Slavin MA. Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience. *Transpl Infect Dis* 2009; **11**: 122-127
- 76 **Pappas PG**, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503-535
- 77 **De Pauw B**, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhne M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE. 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
- 78 **Fortún J**, Martín-Dávila P, Montejo M, Muñoz P, Cisneros JM, Ramos A, Aragón C, Blanes M, San Juan R, Gavaldá J, Linares P. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. *Transplantation* 2009; **87**: 424-435

- 79 **Lumbreras C**, Cuervas-Mons V, Jara P, del Palacio A, Turrión VS, Barrios C, Moreno E, Noriega AR, Paya CV. Randomized trial of fluconazole versus nystatin for the prophylaxis of *Candida* infection following liver transplantation. *J Infect Dis* 1996; **174**: 583-588
- 80 **Sharpe MD**, Ghent C, Grant D, Horbay GL, McDougal J, David Colby W. Efficacy and safety of itraconazole prophylaxis for fungal infections after orthotopic liver transplantation: a prospective, randomized, double-blind study. *Transplantation* 2003; **76**: 977-983
- 81 **Winston DJ**, Pakrasi A, Busuttill RW. Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **131**: 729-737
- 82 **Winkler M**, Pratschke J, Schulz U, Zheng S, Zhang M, Li W, Lu M, Sgarabotto D, Sganga G, Kaskel P, Chandwani S, Ma L, Petrovic J, Shivaprakash M. Caspofungin for post solid organ transplant invasive fungal disease: results of a retrospective observational study. *Transpl Infect Dis* 2010; **12**: 230-237
- 83 **Pappas PG**, Andes D, Schuster M, Hadley S, Rabkin J, Merion RM, Kauffman CA, Huckabee C, Cloud GA, Dismukes WE, Karchmer AW. Invasive fungal infections in low-risk liver transplant recipients: a multi-center prospective observational study. *Am J Transplant* 2006; **6**: 386-391
- 84 **Singh N**. Antifungal prophylaxis in solid-organ transplant recipients: considerations for clinical trial design. *Clin Infect Dis* 2004; **39** Suppl 4: S200-S206
- 85 **Singh N**, Husain S. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S180-S191
- 86 **Rosenhagen M**, Feldhues R, Schmidt J, Hoppe-Tichy T, Geiss HK. A risk profile for invasive aspergillosis in liver transplant recipients. *Infection* 2009; **37**: 313-319
- 87 **Baddley JW**, Andes DR, Marr KA, Kontoyiannis DP, Alexander BD, Kauffman CA, Oster RA, Anaissie EJ, Walsh TJ, Schuster MG, Wingard JR, Patterson TF, Ito JI, Williams OD, Chiller T, Pappas PG. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis* 2010; **50**: 1559-1567
- 88 **Singh N**, Pruett TL, Houston S, Muñoz P, Cacciarelli TV, Wagener MM, Husain S. Invasive aspergillosis in the recipients of liver retransplantation. *Liver Transpl* 2006; **12**: 1205-1209
- 89 **Fortún J**, Martín-Dávila P, Alvarez ME, Norman F, Sánchez-Sousa A, Gajate L, Bárcena R, Nuño SJ, Moreno S. False-positive results of *Aspergillus* galactomannan antigenemia in liver transplant recipients. *Transplantation* 2009; **87**: 256-260
- 90 **Viscoli C**, Machetti M, Cappellano P, Bucci B, Bruzzi P, Van Lint MT, Bacigalupo A. False-positive galactomannan platelia *Aspergillus* test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis* 2004; **38**: 913-916
- 91 **Metan G**, Ağkuş C, Buldu H, Koç AN. The interaction between piperacillin/tazobactam and assays for *Aspergillus* galactomannan and 1,3-beta-D-glucan in patients without risk factors for invasive fungal infections. *Infection* 2010; **38**: 217-221
- 92 **Xavier MO**, Pasqualotto AC, Aquino VR, Sukiennik TC, Severo LC. Galactomannan detection from piperacillin-tazobactam brands available in the Brazilian market. *Braz J Infect Dis* 2009; **13**: 353-355

S- Editor Zhang HN L- Editor Herholdt A E- Editor Liu N