Infections After Orthotopic Liver Transplantation

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Opportunistic infections are a leading cause of morbidity and mortality after orthotopic liver transplantation. Systemic immunosuppression renders the liver recipient susceptible to *de novo* infection with bacteria, viruses and fungi post-transplantation as well to reactivation of pre-existing, latent disease. Pathogens are also transmissible via the donor organ. The time from transplantation and degree of immunosuppression may guide the differential diagnosis of potential infectious agents. However, typical systemic signs and symptoms of infection are often absent or blunted after transplant and a high index of suspicion is needed. Invasive procedures are often required to procure tissue for culture and guide antimicrobial therapy. Antimicrobial prophylaxis reduces the incidence of opportunistic infections and is routinely employed in the care of patients after liver transplant. In this review, we survey common bacterial, fungal, and viral infections after orthotopic liver transplantation and highlight recent developments in their diagnosis and management. (J CLIN EXP HEPATOL 2014;4:347–360)

Infection after orthotopic liver transplantation (OLT) is a major cause of morbidity and mortality. Infection is estimated to occur in upto 80% of organ recipients. Bacterial infections are most frequent (70%), followed by viral (20%) and fungal infections (8%).^{1,2,3} In addition to direct effects of infection and end-organ inflammation, pathogens may have a number of indirect effects that result in allograft injury, rejection and opportunistic superinfection.

The risk of infection in liver transplant recipients is determined by the intensity of exposure to infectious agents and the overall level of immunosuppression.⁴ In addition, conditions attendant to end-stage liver disease in the immediate perioperative period may render a recipient vulnerable to infection and include: neutropenia, def-

icits in mucocutaneous barrier integrity, presence of necrotic tissue, ischemia, diabetes mellitus, immunomodulating viruses, uremia, and protein-calorie malnutrition.⁵ Infectious exposures come from many sources post liver transplant including: *de novo* (acquired acute) in the recipient, reactivation in the recipient, the donor organ, and nosocomial and time from transplant may provide clues to etiology (Figure 1). The overall level of immunosuppression is dependent upon the dose, duration, and choice of immunosuppression as well as underlying immune deficiencies.⁶ Inflammatory responses to invading pathogens are often blunted by immunosuppressive therapy, and as a result, the classic signs or symptoms of infection may be absent. A high index of suspicion is need in the liver recipient, and a low threshold to perform invasive diagnostic procedures is often required. It is critical to identify clinical factors that predispose recipients to infection and much interest centers on identifying risk factors for infection after liver transplant.

GENETIC POLYMORPHISMS IN THE INNATE IMMUNE SYSTEM

In addition to clinical factors that promote infection, studies have been performed to identify factors that may predispose recipients to pathogens.^{7,8} Of particular interest is the recipient's innate immune system. After orthotopic liver transplantation, the adaptive immune response is blunted with use of systemic immunosuppression; as such, the recipient becomes heavily dependent on the innate immune system to control infectious pathogens. The innate system involves a number of important molecules that initiate and prime defense mechanisms against pathogens such as bacteria

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Abbreviations: OLT: orthotopic liver transplantation; SNP: single nucleotide polymorphism; TLR: toll-like receptor; CMV: cytomegalovirus; HCV: hepatitis C virus; MBL: mannan-binding lectin; FCN2: ficolin-2; MASP2: MBL-associated serine protease; HAT: hepatic artery thrombosis; NAS: non-anastomotic stricture; MELD: model for end-stage liver disease; U: unit; BAL: bronchoalveolar lavage; MDR: multi-drug resistant; LDLT: live donor liver transplantation; PPD: purified protein derivative; GM: galactomannan; ELISA: enzym linked immunosorbent assay; EBV: Epstein-Barr virus; PTLT: post-transplant lymphoproliferative disorder; HHV: human herpesvirus; HBV: hepatitis B virus; HBIG: hepatitis B immune globulin

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Figure 1 Timeline of infection after liver transplant: Characteristic pathogens cause morbidity and mortality at various times after transplant. Immediately post transplant nosocomial bacterial infections predominate. Between 1 and 6 months viruses and fungi may predominate under the influence of intense maintenance immunosuppression. As time progresses community acquired pathogens may predominate depending upon clinical course and degree of immunosuppression.

and include: toll-like receptors and the lectin pathway of complement activation.⁹ Single nucleotide polymorphisms (SNPs) or variations in the genes of these aforementioned components may influence the host's (transplant recipient's) ability to combat and control infection after OLT.

Toll-like receptor 2 (TLR2) is a receptor for gram-positive bacterial cell wall elements such as peptidoglycan. The common R753Q SNP in the TLR2 gene results in defective intracellular signaling and impaired cytokine secretion in response to bacterial component activation. The mutation has been associated with an increased frequency of bacterial and viral infections and was found to influence the risk for and outcome of cytomegalovirus (CMV) and hepatitis C (HCV) infection after OLT.¹⁰⁻¹²

The lectin pathway of complement activation is another primordial defense against microorganisms.¹³ It includes mannan-binding lectin (MBL), ficolin-2 (FCN2) and MBL-associated serine protease 2 (MASP2) which are proteins almost exclusively expressed in the liver and function as crucial effectors of the innate immune system.⁹ Polymorphisms in the lectin pathway of complement activation may serve as important risk factors for bacterial infection post-OLT.^{14,15} In an investigation, transplantation of an MBL deficient donor liver into an MBL sufficient recipient resulted in rapid decreases in MBL blood levels, while the MBL2 SNP in the donor

that resulted in low blood levels was also associated with bacterial infections after OLT.¹⁶ Genetic profiling of innate immune components in the donor and recipient may stratify patients into varying levels of infection risk and serve as the basis for tailored antimicrobial prophylactic regimens in the future.

EARLY INFECTIONS

Bacterial infection is the most frequent and dangerous complication among orthotopic liver transplantation patients and generally occur within 2 months of transplantation.⁵ Bacterial infections can occur anywhere in the recipient but most frequently occur in the abdomen, blood stream, and lungs.^{17,18}

Factors directly related to the OLT procedure contributing to the risk of infection can be either surgical technical issues, but can also be due ischemia-reperfusion injury or issues with the graft (e.g. steatosis). The amount of blood transfusions given intraoperatively is directly correlated with the risk of infection immediately after OLT, both in the abdomen and other sources.¹⁹ Primary non function and or initial poor graft function carries an increased infection risk. Hepatic artery thrombosis (HAT) can lead to bile duct injury with subsequent bacterial cholangitis.²⁰ HAT may lead to hepatic necrosis, abscesses, and

perihepatic abdominal fluid collections that can become infected after OLT and affect outcomes.²¹ Both anastomotic and non-anastomotic biliary strictures (NAS) that may from after biliary reconstruction increase the risk of cholangitis.²²

In a study of nosocomial infections after OLT, 367 adult recipients were analyzed. The overall incidence of infection was approximately 37%: with common sources being the abdomen, surgical site, blood stream, lung, and urine. Significant risk factors for infection within the first 30 days included: deceased donor, Model for End-Stage Liver Disease (MELD) >20, albumin level >2.8 g/dL, intraoperative erythrocyte transfusion >6 U, intraoperative fresh frozen plasma >12 U, bilioenteric anastomosis, postoperative intensive care unit stay >6 days, and postoperative length of stay >21 days. Significant risk factors detected within the first 90 days included: MELD >20, preoperative length of stay >7 days, reoperation, postoperative length of intensive care unit stay >6 days, and postoperative length of stay >21 days.²³

Early bacterial or fungal infections in the first three months following OLT among 151 consecutive adult recipients were evaluated over a six year period. Samples included blood, bile, urine, and bronchoalveolar lavage (BAL) specimens. Etiologic agents revealed: gram-negative rods (49.8%), gram-positive cocci (43.8%), and *Candida* species (6.1%).²⁴

Frequent use of antibiotics prior to surgery for varying indications (e.g. infection and SBP prophylaxis) render liver transplant recipients vulnerable to multi-drug resistant strains of bacteria. In one study evaluating microbiological data from liver recipients with urinary tract infections after transplant, an increased proportion of multi-drug resistant (MDR) bacterial and fungal strains were seen: extended spectrum beta-lactamase strains 38.5%; high level aminoglycoside enterococci 80.4%; vancomycin resistant enterococci 17.6%; methicillin resistant staphylococcus aureus/methicillin resistant coagulante negative staphylococcal 100% and non-albicans *Candida* spp.²⁵ In addition to MDR infections, frequent antibiotic use and systemic immunosuppression facilitate frequent clostridium difficile (estimated at 3–7% incidence) after OLT.²⁶

INFECTIOUS COMPLICATIONS IN LIVING DONOR TRANSPLANT RECIPIENTS

Living donor liver transplantation (LDLT) has been performed with increasing frequency to make transplantation available to an increasing number of patients worldwide.²⁷ The differences in the spectra of infectious complications between living donor and deceased donors are not yet well understood. Several small studies have examined the incidence of infectious complications in the immediate post transplant period. A retrospective case study from Ko-

rea found the overall infectious complications to be similar between deceased donor (67.7) and LDLT (67.0%) ($p = 0.9$); however, subgroup analysis found intra-abdominal infections to be more frequent in the LDLT group than the deceased donor group.²⁷ This was also seen in a recent retrospective case study from the Centers for Disease Control and Prevention that demonstrated having a living donor versus a deceased donor liver transplant was a risk factor for having a bacterial infection within 90 days (OR 2.45, $p = 0.049$). The subgroup driving this was having a surgical site (23% versus 51%, $p = 0.009$) after liver transplant.²³ In contrast, Saner et al concluded that LDLT recipients had a significant higher rate of pulmonary infections and a trend toward higher rate of blood stream infections.²⁸ Long term infectious complications after LDLT have been even less well investigated. Notably, one multicenter case study from the United States demonstrated similar outcomes for patients with hepatitis C regardless of whether they underwent LDLT or deceased donor liver transplantation based on 90 day and 3 year graft survival if each procedure was done by an experienced surgeon.²⁹

TUBERCULOSIS

Tuberculosis after solid organ transplantation can occur and its incidence rate is largely affected by the geographic location of the transplant program and the background of the recipient (ranges from less than 5% in the United States and Europe and upto 15% elsewhere in areas of endemicity).^{30,31} Post-OLT, the likely mechanism of infection is reactivation of a dormant infection, although rare cases of nosocomial and donor transmission have been documented.³²

The onset of tuberculosis can occur within 2 weeks to years after solid organ transplantation.³³ Most patients with tuberculosis (51–64%) have pulmonary infection, although extrapulmonary infection are also common.³⁴ The most common site of extrapulmonary involvement is the gastrointestinal tract. Tuberculosis involvement of the gut can involve the ileocecal area with abscesses presenting as abdominal pain, gastrointestinal tract bleeding, bowel perforation (similar to Crohn's disease).³⁵ Among liver transplant recipients with tuberculosis, hepatic inflammation is common and other sites can be involved: muscle, joints, skin, and central nervous system, and lymph nodes.^{36,37} Fever, night sweats, and weight loss are frequent constitutional symptoms. Findings on chest radio graphs vary and include focal, miliary, or nodular patterns as well as cavitations.

As reactivation of latent infection is predominant mechanism, it is of paramount importance to identify persons with latent infection and consider prophylaxis. Efficacy of chemoprophylaxis has not been well established, but case series shown promise.³⁸ In this context, isoniazid has proven valuable with minimal hepatotoxicity reported.

Classically, the purified protein derivative (PPD) skin test has been used to screen patients for latent tuberculosis, noting that for patients with positive results, active tuberculosis must be ruled out, and for patients with negative results, anergy must be considered.³⁹ Some of the practical difficulties of PPD testing may be ameliorated with interferon- γ release assays (such as the QuantiFERON-TB Gold assay, Cellestis). The concordance rate between positive PPD and assay results has been reported as being as high as 80% in a recent single center study of patients with solid organ transplants in an endemic area, with the assay being the more sensitive test.⁴⁰

Treatment of active TB often includes the initiation of a 4-drug regimen using isoniazid, rifampin, pyrazinamide, and ethambutol with adjustments in accordance with culture results/sensitivities. Because of the risk of marked reduction in levels with rifampin co-administration, doses of calcineurin inhibitors (cyclosporine or tacrolimus) need to be increased 2- to 5-fold.³⁹ Alternatively, rifabutin may be considered, as it is a weaker inducer of the cytochrome P450 enzymes, but data on the use of this drug in transplant recipients remains limited.³⁹

MYCOBACTERIAL INFECTIONS

Nontuberculous mycobacterial infections are unusual in liver transplant recipients; however, their incidence is increasing. Infections from *Mycobacterium avium* intracellular, *Mycobacterium chelonae*, *Mycobacterium mucogenicum*, *Mycobacterium triplex*, and *Mycobacterium xenopi* have been reported in liver transplant recipients.⁴¹ Pulmonary and multifocal cutaneous infections are more common presentations.⁴² Treatment decisions are guided by susceptibility tests and may be complicated by medication interactions with immunosuppressive regimens. Control of infection may require reduction in immunosuppression.

FUNGI

Candida

Candidiasis is the most frequent fungal infection encountered after orthotopic liver transplantation and the leading cause of invasive fungal infection. *Candida albicans* is the most common isolated species followed by *Candida glabrata* and *Candida tropicalis*.^{43,44} The gastrointestinal tract is often colonized with candidal species and those with advanced liver disease/cirrhosis may be predisposed to supercolonization. One study of potential orthotopic liver transplant recipients identified colonization with candida species in all subjects at varying locations in the alimentary canal.⁴⁵ Infection is theorized to occur through potential overgrowth and translocation to extraluminal locations or as a consequence of spillage that may occur through anastomosis creation with segments of the bowel.

Candidal seeding of extraluminal sites may allow for the formation of intrabdominal abscesses and/or peritonitis and subsequent hematogenous dissemination to distant sources to affect other organs.^{46–48}

Risk factors for invasive candidiasis include the use of prophylactic antibiotics to prevent spontaneous bacterial peritonitis, the need for renal replacement therapy (hemodialysis) postoperatively, and retransplantation.⁴⁴ Other potential risk factors include technically complicated and lengthy transplantation operative procedures, intraoperative transfusion, prolonged ICU admission, repeated intra-abdominal surgery after transplantation, *Candida* colonization, and cytomegalovirus disease.⁴⁸

CMV disease is a clear risk factor for all types of invasive candidal infections, and effective prophylaxis of patients at high risk for CMV disease, such as those who are CMV D+/R– (donor positive, recipient negative), has been shown to significantly decrease the incidence of invasive *Candida* infection in the absence of specific anti-*Candida* prophylaxis.⁴⁹

It is now routine that transplant centers use routine antifungal prophylaxis with the majority of studies have showing clear reduction in rates of colonization, incidence fungal infections, and mortality (attributable to fungal infection).^{50–52} Such practices with fluconazole has resulted in a shift in epidemiology resulting in a shift in infections toward non-*C. albicans* species (e.g., *Candida glabrata* and *Candida krusei*).^{53,54}

Aspergillus

Aspergillus spp are the second most common fungal infection after orthotopic liver transplantation and account for approximately one quarter of invasive fungal infections after transplant.⁵³ Inhalation of spores (ubiquitous in the environment) can lead to pulmonary infection which is often characterized by angioinvasion and subsequent tissue infarcts. Extrapulmonary dissemination is common leading to infection in the central nervous system and other organs and occurs frequently (50–60%).^{55,56}

Diagnosis of invasive aspergillosis can be difficult and often require invasive procedures (e.g. bronchoscopy with bronchioalveolar lavage). Even with invasive diagnostics the diagnosis may be missed, as one study found 79% culture positive washes in *Aspergillus* pneumonia.⁵⁷ Detection may require a number of diagnostic modalities. High-resolution computed tomography (CT) may be helpful as invasive pulmonary aspergillosis can manifest early as a nodular opacity with surrounding attenuation, or 'halo sign'.⁵⁸ In late invasive aspergillosis, parenchymal nodularity, diffuse pulmonary infiltrates, consolidation, or ground-glass opacities can be seen. Given the difficulty of isolation of spp. with bronchoscopy and variable radiologic features, much interest has focused on molecular tools for the diagnosis.

Molecules that have been employed as diagnostic markers of *Aspergillus* infection include: *Aspergillus* galactomannan (GM) and (13)- β -glucan (BG). The GM test is an enzyme-linked immunosorbent assay (ELISA) that detects galactomannan, an antigen released from hyphae upon host tissue invasion. Variable reports exist on the test's sensitivity and specificity and a potential drawback is false-positives (lower sensitivity) in patients taking mold-active drugs.^{59–61} BG, a main cell wall polysaccharide component of *Aspergillus*, can be colorimetrically detected and is useful in diagnosis, with a sensitivity ranging from 50% to 87.5 but false-positives can also occur.⁶² A combination of the GM and BG can be useful for identifying false-positive reactions.⁶³

A specific *Aspergillus* PCR assay has also been used to diagnose invasive aspergillosis (100% sensitivity and 89% specificity). Quantitative real-time PCR for diagnosing invasive aspergillosis has shown sensitivity and specificity values of 67% and 100%, respectively, and can be used to monitor response to treatment.⁵³

In a case series of 26 patients with invasive aspergillosis after orthotopic liver transplantation, infection occurred a median of approximately 2.5 weeks after transplantation with a mortality rate of 92%.⁶⁴ The identification of potential risk factors may reduce the morbidity and mortality rates of invasive aspergillosis are necessary but reports have been variable and conflicting in some instances with regards to the importance of immunosuppression.^{64–66}

Suspected risk factors for invasive aspergillosis including: renal insufficiency, the need for renal replacement therapy post-transplantation, retransplantation, CMV infection, repeated bacterial infections, preoperative ICU stay, preoperative steroid administration, fulminant hepatic failure, the presence of *Aspergillus* antigenemia, and the use of OKT3 monoclonal antibody.^{65,67,68}

Antifungal therapy should be instituted upon any clinical suspicion of aspergillosis without waiting for microbiology results. For severely immunocompromised patients after liver transplantation, a heightened level of suspicion for invasive fungal infection development is needed as is a prompt and aggressive search for etiology. Triazoles (voriconazole is the drug of choice; itraconazole and posaconazole), caspofungin, or amphotericin B can be considered for treatment.^{2,69}

Cryptococcus

Cryptococcus neoformans is the third most common fungal infection after liver transplantation and most common cause of meningitis in transplant recipients. Inhalation of fungal spores (which have been associated with bird defecation) can result in a possible symptomatic pneumonia or asymptomatic infection often with dissemination to other body sites, most commonly the central nervous system.⁴⁶ In a recent case series: infected patients

had pneumonia only (46%), meningitis only (36%), dissemination to multiple distant organs (11%), or involvement of another single organ (e.g., lymph node) (7%). Symptoms developed a mean of 30 months (range, 1–146 months) after transplantation with a mortality rate of 25%.⁷⁰

Cryptococcal pneumonia may be difficult to identify and differentiate on radiographic characteristics. In addition, diagnostic yield of bronchial wash culture can be low and the sensitivity of cryptococcal antigen in cases of pneumonia is low.⁷¹ Patients with cryptococcal CNS involvement may not display classic signs of meningitis such as nuchal rigidity, photophobia, or headache.⁷² A low threshold must be held to perform lumbar puncture.

Less is known about risk factors for cryptococcal infection post liver transplant but those with higher levels of immunosuppression seem to be linked. In addition, concomitant CMV infection is thought to increase the risk of *Cryptococcus* infection as with other mycoses. Once diagnosed, cryptococcal meningitis is treated with a combination of liposomal amphotericin B or amphotericin B lipid complex and flucytosine (5-FC) for at least 2 weeks for the induction regimen, followed by fluconazole for 8 weeks for consolidation therapy, and fluconazole for 6–12 months for maintenance treatment.⁷³

ENDEMIC MYCOSES: HISTOPLASMA AND COCCIDIOMYCOSES

Histoplasma capsulatum is an endemic, opportunistic dimorphic fungus which can exist as spore-forming mold in the environment and pathogenic budding yeast. Initial exposure may lead to a subclinical infection or mild respiratory illness in the immunocompetent host.⁷⁴ Disseminated histoplasmosis likely results from a primary or secondary exposure or reactivation of latent disease in the post liver transplant patient with systemic immunosuppression. Symptoms of dissemination may be non specific (fever, fatigue, dyspnea) but the disease can progress to multiorgan involvement and even death.⁷⁵ A histoplasma urinary antigen test is available. Coccidiomycosis is an infection caused by *Coccidioides* species, which are endemic for the Southwestern United States and parts of Central America and South America. Similar to histoplasmosis, inhalation of spores may be common and result in subclinical presentations in immunocompromised hosts. Post transplantation, *de novo* or reactivated infection can occur with systemic immunosuppression as well.⁷⁶

MUCORMYCOSES

Mucormycoses are filamentous fungi that can cause local infections with direct extension and rarely angioinvasive or disseminated infections. These infections are more common in patients after stem cell transplantation or during diabetic ketoacidosis, but can be seen in liver transplant

recipients as well. The incidence of infection in liver transplant recipients ranges from 0% to 1.6%.⁷⁷ Patients with iron overload syndromes, either from transfusion or hemochromatosis, have increased risk of mucormycosis, particularly if they are treated with deferoxamine (though deferasirox and deferiprone do not increase risk in this way).⁷⁷ A matched, case-controlled study of solid organ transplant recipients found renal failure, diabetes mellitus, and prior voriconazole and/or caspofungin use to be associated with a higher risk of zygomycosis. In contrast, tacrolimus was associated with a lower risk. Liver transplant recipients were more likely to have disseminated disease and develop mucormycosis earlier than did recipients of other organs.⁷⁸ These disseminated infections spread hematogenously, but are infrequently associated positive blood cultures.⁷⁹ A metastatic skin lesion may be an important clue to diagnosis as symptoms will vary based on the location and degree of angioinvasion and infarction in the infected organ. The treatment of mucormycosis involves surgical debridement of infarcted tissue when feasible, and amphotericin B or liposomal amphotericin B. Posaconazole may have a role in salvage therapy, but is not currently recommended as primary therapy.⁸⁰ Even with appropriate treatment, mortality rate among patients with solid organ transplants ranges from 49% to 71%.⁷⁸

PNEUMOCYSTIS JIROVECI

Pneumocystis jiroveci is a well established opportunistic pathogen whose incidence is recognized in both immunodeficient states (human immunodeficiency virus) and in immunosuppressed patients after solid organ transplant.⁸¹ Patient with pneumocystis infection may present with fever, shortness of breath, and nonproductive cough. Classically, bilateral interstitial infiltrates are seen in chest X-ray. If the microbial burden is high, pneumocystis organisms may be identified from bronchoalveolar lavage fluid by direct immunofluorescence using a fluorescein-conjugated monoclonal antibody or by staining with toluidine blue O.⁸² Patients should be treated with trimethoprim-sulfamethoxazole unless a strong contraindication (intolerance, allergy) is identified. Alternative treatments include aerosolized pentamidine isethionate, trimethoprim-dapsone (in patients who are not deficient in glucose-6-phosphate dehydrogenase), atovaquone, and clindamycin-primaquine.⁸³

VIRAL

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the human herpesvirus (HHV) group and is a common cause of morbidity after liver transplant.⁸⁴ Cytomegalovirus 'CMV infection' is defined as isolation of the CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue spec-

imen.⁸⁵ The minimum conditions for determination of 'CMV disease' are fever ($>38^{\circ}\text{C}$, for at least 2 days within a 4-day period), neutropenia or thrombocytopenia, and the detection of CMV in blood.⁸⁶ End-organ disease, e.g., pneumonia, retinitis, nephritis, or central nervous disease is common and requires detection of CMV in tissue examination. CMV pneumonia remains a life-threatening syndrome, which is usually complicated by other pathogens, such as fungal or bacterial co-pathogens.⁸⁴ In liver transplantation, a common end-organ disease is CMV hepatitis.⁸⁷

The risk of acquiring CMV infection or disease after transplantation can be stratified by the serologic status of the donor and the recipient.⁴⁶ The highest risk of developing CMV infection occurs in the seronegative recipient (R) of an organ from a seropositive donor (D) (referred to as D+/R-). CMV infection will eventually develop in most recipients in this category and a high percentage of them will become symptomatic.⁸⁸ Endogenous CMV can be reactivated in seropositive recipients, or they can sometimes become superinfected with an exogenous *de novo* virus from the donor organ (D+/R+). Seronegative recipients who receive an organ from a seronegative donor (D-/R-) are considered at low risk, although CMV infection can still develop (unscreened blood transfusion).⁸⁹ Other risk factors for CMV infection include specific post-transplantation immunosuppressive medications: including prednisone, calcineurin inhibitor and antithymocyte globulin (thymoglobulin).^{90,91}

In addition to clinical disease, awareness of indirect effects of CMV, such as increased risk of acute or chronic allograft rejection and the development of other infections, has increased.^{92,93} CMV is thought to be a risk factor for invasive fungal and bacterial infections in liver recipients as aforementioned.^{44,94,95} CMV can also interact with other viruses and may accelerate hepatitis C virus pathogenesis.⁹⁶ In addition, the activation of the other herpesviruses human herpesvirus-6 and Epstein-Barr virus has been reported with CMV.⁹⁷⁻⁹⁹

Cytomegalovirus is also suggested to be involved in liver rejection—including an association with chronic rejection.^{100,101} CMV triggers inflammation in the graft by upregulation of cytokines, MHC antigens and adhesion molecules, and induces various chemokines and growth factors.^{86,102} After liver transplantation, CMV increases inflammation in the graft and the expression of class II molecules adhesion molecules critical for T-cell activation.¹⁰³⁻¹⁰⁵ Despite adequate treatment to resolve viremia, CMV DNA may persist in hepatocytes and bile duct epithelium.¹⁰⁶ As such, successful antiviral treatment of CMV infection does not exclude the persistence of the virus and the risk of chronic rejection.¹⁰⁷

Prevention of CMV infection is based on two strategies (Figure 2). The first entails administration of an antiviral agent to all transplant recipients immediately after

Figure 2 CMV management after liver transplant. Preventative approaches to CMV infection post-OLT include universal antiviral prophylaxis for those at risk *(CMV D+/R+ and D+/R-) or preemptive based (initiation of antiviral therapy after first detectable CMV DNA PCR). Symptomatic CMV disease mandates treatment with valgancyclovir or alternative agent.

transplantation (i.e., universal prophylaxis). The second preventive strategy is preemptive therapy in which transplant recipients are carefully monitored for early evidence of viral replication by use of a CMV DNA PCR and antiviral therapy is initiated at the first positive result.¹⁰⁸⁻¹¹⁰ No specific quantitative threshold value as an indication for initiation of antiviral medication exists in seropositive transplant recipients, but generally treatment is initiated in seronegative recipients whenever DNA becomes detectable. Both universal and preemptive approaches have their drawbacks. The disadvantages of universal prophylaxis include prolonged drug exposure, the development of resistance and perhaps most importantly, the development of delayed and late-onset CMV disease.¹¹¹⁻¹¹³ Prophylaxis does not prevent the development of primary CMV infection; it only delays the onset of viral replication, and primary CMV infections are relatively common after the cessation of prophylaxis. Preemptive therapy is time and cost intensive, requiring repeated and vigilant blood testing. When disease does occur, valgancyclovir (with relatively convenient oral dosing) has emerged as the preferred treatment over gancyclovir as well as foscarnet and cidofovir (nephrotoxicity).¹¹⁴

Epstein-Barr Virus

Epstein-Barr Virus (EBV) infection can present a variety of ways after liver transplantation. Acute infection is characterized by fever and malaise in conjunction with leukopenia, atypical lymphocytosis, or thrombocytopenia. Primary EBV infections predominately occur in children and it is estimated that as many as 90% of adults are

EBV seropositive (often from a previous subclinical infection). As such, reactivation is presumed to be the predominant pathophysiologic process in adults post liver transplantation with active EBV infection.¹¹⁵

While acute illness is generally self-limited and resolves with supportive care, EBV infection can lead to post transplant lymphoproliferative disease (PTLD) in the liver recipient. EBV-associated PTLD is an uncommon but serious complication of LT with an incidence in adults of less than 3%.^{116,117} Risk factors for development include a primary EBV infection, CMV donor-recipient mismatch; presence of CMV disease, and augmentation immunosuppression.¹¹⁸ The association of PTLD with EBV infection is variable in adult LT recipients; later onset PTLD is less likely to be EBV-associated.^{119,120} PTLD include lymphadenopathy, cytopenias, unexplained fever, and disturbances of the gastrointestinal tract, lungs, spleen, and central nervous system.

Radiographic studies can identify sites of involvement, especially when pulmonary or intra-abdominal sites are involved.¹²¹ The detection of EBV viremia with nucleic acid testing is not diagnostic of EBV-associated PTLD. Initial treatment of PTLD is a reduction of immunosuppression.^{120,122} If there is no clinical response within 2-4 weeks, additional therapies, including anti-CD20 humanized chimeric monoclonal antibodies (rituximab radiation therapy, and cytotoxic chemotherapy may be required).

Herpes Simplex Virus and Varicella Zoster Virus

Herpes Simplex Virus (HSV 1 and 2) and Varicella Zoster virus are relatively rare occurrences after orthotopic liver transplantation. HSV infection typically manifests with

oral or genital mucositis. HSV can lead to organ specific disease with hepatic, gastrointestinal, and pulmonary disease.¹²³

Varicella Zoster Virus, the etiologic agent for “chickenpox” is often primarily acquired in childhood. Once primary infection has passed, VZV may remain latent in neural tissues for years—reactivating in the context of systemic immunosuppression. Zoster virus can present with a painful, bullous eruption in a dermatomal pattern. With the routine use of antiviral prophylaxis, the incidence of this primary HSV and VZV infection has declined substantially. Susceptible transplant recipients who are exposed to VZV are usually given post contact prophylaxis with varicella zoster immunoglobulin. Varicella vaccine is an attenuated live virus, so it can be administered to susceptible transplant candidates prior to but not after transplantation.¹²⁴

Human Herpes Virus-6

Human Herpes Virus-6 (HHV-6) is another member of the herpesviridae family as CMV and is believed to have immunomodulatory properties and synergistic effects with other acquired/latent viruses.¹²⁵ HHV-6 is a frequent cause of infection in childhood, and it is the cause of roseola infantum. It frequently causes subclinical infection and a majority of the population is seropositive by adolescence.⁴⁶ Of the two recognized variants of HHV-6 (A and B), variant B is believed to be the cause of most infections in transplant recipients, principally by reactivation of the virus 2–8 weeks after transplantation. HHV-6 incidence in liver transplant recipients varies from 14 to 82%.¹²⁵ Symptoms and signs attributed to HHV-6 include fever, rash, cytopenia, interstitial pneumonitis, hepatitis but a definite cause-and-effect relationship with HHV-6 is often lacking.^{126,127,128} The virus may have immunosuppressive effects through interaction with CMV or by affecting the immune system directly. An association between invasive fungal infections and HHV-6 has been suggested.¹²⁹

The diagnosis of HHV-6 infection requires shell-vial culture. Currently available serologic tests available are of limited value because of high seroprevalence in the general population and also because transplant recipients receiving immunosuppressive medication may not mount a serologic response.¹²⁸ Sensitive polymerase chain reaction-based detection of HHV-6 may detect latent virus and overestimate the presence of infection. Antiviral agents active against CMV are also active against HHV-6, including ganciclovir, foscarnet, and cidofovir.

Human Herpes Virus-8

HHV-8, also called KS-associated herpesvirus (KSHV), is the etiologic agent of Kaposi's sarcoma (KS) along with Castleman disease. KS is characterized by purplish, nodular skin lesions but also may occur in visceral organs

and has been reported to occur in liver transplant recipients.¹³⁰ A presentation similar to that of patients with PTLTD has been reported in liver transplant recipients who have persistent HHV-8 viremia prior to diagnosis of visceral KS.¹³¹

The precise route of transmission of HHV-8 is unknown. It is presumed to occur by direct contact with bodily fluids, but transmission can also occur through organ transplantation or transfusion of blood products.¹³² A study from the University of Pittsburgh Medical Center identified increased HHV-8 seropositivity with organ transplantation from 5.3% before transplantation to 15.8%. Many of the patients who had seroconversion had received organs from seronegative donors, which suggests that HHV-8 may have been acquired from another source (e.g., blood products).¹³³

KS lesions may regress with reduction or discontinuation of immunosuppressant medications. For patients with visceral KS, chemotherapy agents such as bleomycin sulfate, doxorubicin hydrochloride liposome, and vincristine sulfate have been used with some success.¹³⁴ HHV-8 is sensitive in vitro to ganciclovir, foscarnet, and cidofovir.

Hepatitis E Virus

Acute hepatitis E virus (HEV) may generally cause subclinical or self-limiting illness in immunocompetent patients. HEV genotype 1 and 2, waterborne genotypes found in developing countries can cause illness and rarely progress to liver failure (possible in pregnant women or those with pre-existing liver disease). HEV infections in industrialized nations have been associated with zoonotic (pig) transmission of genotypes 3 and 4.¹³⁵

Chronic HEV infection has been recently reported in immunocompromised patients, occasionally leading to significant hepatic injury or advanced fibrosis and cirrhosis.¹³⁶ In a study population of kidney, kidney-pancreas, and liver transplant recipients with unexplained short-term elevations of liver function tests in France (271 organ recipients), 6% were found to harbor HEV RNA in their serum. Six of 14 patients had normalization of their liver function tests within 6 months without specific therapy. Six of the remaining 8 patients underwent liver biopsies, and all biopsies showed chronic hepatitis.¹³⁷ In Germany, 4% of OLT recipients (226 patients) were positive for HEV antibodies compared with 3% of patients with chronic liver diseases and 1% of healthy controls. One third of these patients previously exposed OLT recipients were viremic, and 1 had advanced fibrosis on histology. Notably, anti-HEVs were detected several months after the detection of HEV RNA.¹³⁸

HEV infection can lead to chronic hepatitis in OLT recipients, which can progress into a spectrum of hepatic injury, including graft loss. Evaluation for chronic HEV infection should be considered in liver recipients with

unexplained abnormalities of aminotransferases.¹³⁹ Assessment of HEV RNA may be necessary due to diminished/delayed seroconversion due to systemic immunosuppression. A recent retrospective, multicenter study showed that ribavirin monotherapy (600 mg daily) for 3 months may be effective in the treatment of chronic HEV infection.¹⁴⁰

Hepatitis B Core Antibody Positive Donors

Worldwide, many transplant programs routinely utilize liver grafts from hepatitis-B core antibody (HBcAb)-positive and hepatitis-B surface antigen (HBsAg)-negative donors. With this practice, there is a risk for the development of *de novo* hepatitis B in recipients. In a recent systemic analysis of liver recipients who were HBV naïve (as well as those recipients with isolated HBsAb positivity) a significantly reduced incidence of infection was observed with HBV prophylaxis after transplantation with a HBcAb-positive graft.¹⁴¹ Although the ideal prophylactic regimen for prevention of *de novo* HBV infection in this scenario is unclear, many centers employ hepatitis B immunoglobulin (HBIG) post-OLT along with initiation of an antiviral. The availability of potent antivirals (entecavir and tenofovir) with high genetic barrier to resistance and minimal side effects may allow for HBIG-free prophylactic regimens in selected patients after transplant.¹⁴²

Issues on Transmission

Transmission of diseases is an undesirable, but seemingly inevitable outcome of orthotopic liver transplantation.¹⁴³ In this context, infection source is the donor organ – separate from nosocomial infections that may develop in the recipient. The precise risk of infection associated with liver transplantation is unknown but is related to multiple factors including: epidemiology of donor specific infectious exposures, potential high risk (for acquisition of infection) donor behaviors, hepatotropism of the specific infectious agent, and transmissibility of agent through the operative procedure.¹⁴⁴

In an attempt to prevent donor-derived infections in transplantation, organ and tissue donors are evaluated to identify those that might be more likely to harbor transmissible pathogens. Many centers performing liver transplantation perform thorough chart histories to screen potential donors and test for the occurrence of communicable disease. Donor testing includes the donor's microbial culture data (e.g., blood, urine, sputum), serologic assay results (e.g., antibodies against HIV, hepatitis B virus [HBV], and hepatitis C virus [HCV]) and specific PCRs for nucleic acids when applicable. Less common but important viruses can be transmitted via liver transplant, including West Nile Virus (WNV).^{145–147}

Recognizing emerging infectious diseases in liver transplantation is challenging because of nonstandardization of donor evaluations and data collection as well as surveil-

lance of the recipient. Quantifying risk is further complicated by the absence of data regarding the factors affecting disease transmission. Gaps in systematic identification and characterization of the scope and magnitude of donor-derived infectious disease transmissions through organ and tissue transplantation remain a major hurdle to improvements in assessing risk and in developing more effective donor screening and testing strategies.¹⁴⁸ This biovigilance must be pursued and balanced with potential wait times on the transplant list.¹⁴⁹

Prevention and Prophylaxis

Prompt identification and directed antimicrobial treatment can often control infection after orthotopic liver transplantation. An assessment for infections following orthotopic liver transplantation should take into account: the timing of presentation in relation to surgery, the intensity and recent changes to systemic immunosuppression, and a review of both potential donor and recipient related exposures. Furthermore, a review of any potential latent infections in and immunization history of the recipient should be reviewed.

Many steps can be taken to potentially mitigate the risk of infection. In the immediate postoperative infection (especially in recipients remaining in the ICU) meticulous attention to and serial assessment of the need for invasive catheters and drains should be performed. Efforts can be made to wean sedation and mechanical ventilation to prevent ventilator acquired pneumonia. Incentive spirometry and early mobilization may potentially combat atelectasis and pneumonia or aspiration pneumonitis. The implementation of prophylactic antimicrobials, the avoidance of high risk exposures, and the minimization of immunosuppression may further reduce the occurrence of both nosocomial and opportunistic infections.

Transplant centers generally develop institution protocols with regards to prophylaxis. While specific agents and duration may among programs, almost uniformly, centers do take prophylactic measures to prevent CMV, PJP, and fungal infections. The following recommendations represent our center's approach to opportunistic infection prophylaxis:

High risk recipients (CMV-seronegative recipients of CMV-seropositive donor organs) receive prophylaxis with ganciclovir or valganciclovir for a minimum of 3 months after transplantation. Beyond three months post-transplant, prophylaxis against CMV is reinstituted whenever recipients receive anti-lymphocyte therapy for the treatment of rejection and continued for 3 months after the treatment of rejection. All OLT recipients receive prophylaxis against *P. jiroveci* with trimethoprim-sulphamethoxazole (single strength daily or double strength 3 times per week) for a minimum of 6–12 months after transplantation. Dapsone or inhaled pentamidine are the preferred alternatives for

Table 1 Interactions Between Antimicrobials and Immunosuppressants. Various Antimicrobials may Alter Levels of Calcineurin Inhibitors (CNI): Tacrolimus and Cyclosporine and Sirolimus (SRL).

Drug class	Example	CNI level/effect	SRL-level
Macrolides	Erythromycin Clarithromycin	Increase	Increase
Anti TB	Rifampin	Decrease	
Aminoglycoside	Gentamicin Tobramycin	Renal	
Antifungals	Ketoconazole Itraconazole Voriconazole	Increase	Increase
Antivirals	Foscarnet Telaprevir Boceprevir	Renal Increase	

patients who are intolerant of trimethoprim-sulfamethoxazole. Patients transplanted at our center are given 6 months of fluconazole for fungal prophylaxis (area of endemicity for *Coccidiomycoses*).

In addition to prophylaxis regimens, attention should be paid to previous immunization history. In the post transplant patient, we routinely recommend annual inactivated influenza vaccination. In addition the pneumococcal vaccine is offered when not previously given, and is reoffered at 5 years. This the aforementioned take on heightened importance in those who may have undergone splenectomy—conferring an increased risk to encapsulated bacteria.

A critical issue with respect to prophylaxis or treatment of infectious diseases after orthotopic liver transplantation is monitoring for any potential drug-drug interactions (Table 1). The cornerstones of immunosuppression after orthotopic liver transplantation include the Calcineurin inhibitors cyclosporine and tacrolimus and the m-TOR inhibitor rapamycin. Cyclosporine, tacrolimus, and rapamycin are extensively metabolized by cytochrome P450 3A4 enzymes in the intestine and liver. Drugs that inhibit cytochrome P450 3A4 (e.g., erythromycin) may decrease the metabolism of these agents and cause increased plasma concentrations.¹⁵⁰

The azole antifungals also inhibit p-glycoprotein (voriconazole > ketoconazole > itraconazole > fluconazole).⁶ Conversely, the metabolism of cyclosporine and tacrolimus is up-regulated by drugs such as rifampin, isoniazid, and nafcillin. This results in lower blood levels with a given dose of the immunosuppressive agent and an increased risk of rejection. Important drug interactions with azathioprine and mycophenolate mofetil include increased neutropenia with trimethoprim/sulfamethoxazole, dapsone, other sulfonamides, pentamidine, pyrimethamine, chloramphenicol, allopurinol, cytozan, and ganciclovir.⁶

CONCLUSION

Infection after orthotopic liver transplantation is common cause of morbidity and mortality. When possible, comprehensive evaluation is performed to screen and test donor organs for communicable disease. An evaluation of the presenting symptoms and timing from operation, coupled with comprehensive (and often invasive) diagnostics may lead to prompt identification and treatment. Evaluation of common nosocomial infection and avoidance of unnecessary indwelling catheters can prevent early morbidity. Prophylaxis for common infections (CMV and PJP) in high risk patients improves outcomes in the first year after transplant. Despite survival benefit, universal prophylaxis likely promotes pathogen resistance and in some instances, delayed onset of infection. Further study is needed to further evaluate perioperative factors that predispose to infection.

CONFLICTS OF INTEREST

All authors have none to declare.

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