Infections in Liver Transplant Recipients

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Abstract

Liver transplant is a life-saving procedure for many end-stage liver diseases. 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 transplant. This article reviews major infectious concerns after liver transplant.

Key words: Infectious complications, Bacteremia, Candidemia, Cytomegalovirus, Aspergillosis

Introduction

Liver transplant has been established as an accepted therapy for end-stage liver diseases for nearly 30 years. Infectious complications remain a major problem despite advances in liver transplant. Up to 80% of patients have infectious complications resulting in considerable morbidity and mortality after liver transplant. A major cause of mortality and morbidity after liver transplant is infection, which occurs in up to 80% of the patients.1

Risk Factors for Infection

Identifying risk factors for infection before transplant permits optimal use of strategies for preventing infections in the posttransplant setting. The known major risk factors for infection after liver transplant can be grouped into 3 periods.2,3

Before transplant, latent or unrecognized infections can occur in either the donor or the recipient. These include herpes virus group, tuberculosis, hepatitis B and C (HBV, HCV), human immunodeficiency virus, rabies, and West Nile virus infections. Before transplant, colonization of the patient with multidrug-resistant bacteria such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, multidrug-resistant enterobacteriaceae.

During transplant, infections may occur through surgical complications, prolonged operative time (> 12 hours), reoperation, in patients who had undergone Roux-en-Y biliary anastomosis, and in patients who had multiple abdominal surgeries. After transplant, there may be cytomegalovirus (CMV) infection, rejection, poor graft function, or renal failure.

Time Course of Infections

Common patterns of infection are observed after solid-organ transplant based on epidemiologic exposures and the “net state of immunosuppression.” Although infections may occur at any time after transplant, the risks and types of infections vary based upon the timing after transplant.2,4 The timeline is altered based on the immunosuppressive regimen and prophylactic medications. For liver recipients, most infections can be grouped into 3 periods: the first month, 1 to 6 months, and after 6 months.4

During the first month, infections occurring immediately after transplant are generally similar to those seen in immunocompetent hosts after a similar surgical process. Nosocomial bacterial infections going to a nosocomial source such as central vascular access sites, indwelling stents, external drainage catheters, foreign bodies, necrotic tissue, or
prolonged endobronchial intubation are the most common infections during this period.5 Candida also is an important pathogen during the first month after transplant. The bloodstream, surgical wounds, and the urinary tract are common sites for primary infection, which may then disseminate.3 Except for the herpes simplex virus (HSV) and unusual situations like donor-transmitted viral illnesses (eg, owing to West Nile virus and rabies), viral infections are uncommon during the first month after transplant.6,7

Between 1 and 6 months, activation of latent infections and opportunistic infections may occur after transplant going to the cumulative effect of immunosuppression. Herpes group viruses (particularly CMV and Epstein-Barr virus), Clostridium difficile, Listeria, Nocardia, Mycobacterium tuberculosis, Pneumocystis jiroveci, and Aspergillus spp. are the major opportunistic pathogens that can cause severe infections in liver recipients. Reactivation of HBV and HCV infections also are a major concern during this time.2,4

After 6 months, liver recipients with good graft function usually develop similar types of community-acquired infections seen in the general population, although at an increased rate. Opportunistic infections are uncommon for this group. Conversely, patients with impaired graft function or those receiving higher levels of immunosuppressive medications are at risk for the similar opportunistic infections seen 1 to 6 months after transplant.

Chronic or recurrent viral infections including those caused by Epstein-Barr virus, CMV, HBV, HCV also can lead to complications in the late posttransplant period. Chronic viral infections also can produce damage to the liver allograft (HBV and HCV) or cause secondary tumors during this time, including posttransplant lymphoproliferative disease caused by Epstein-Barr virus and hepatocellular carcinoma caused by HBV or HCV.2,4

Types of Infection

Bacterial Infections

Bacterial pathogens are the most common causes of infection after liver transplant. Most of these infections occur during the first month. These infections predominantly involve the surgical site, the abdominal cavity, bloodstream, urinary system, and the respiratory tract.8-11 Pathogens isolated from the majority of the bacterial infections are enterococci, viridans streptococci, Staphylococcus aureus, and members of the Enterobacteriaceae family.2

Viral Infections

Liver recipients are commonly chronically infected with HBV and HCV, often with an accelerated clinical course.12 Respiratory and gastrointestinal viruses may cause diseases throughout the postliver transplant period, with seasonal variations such as influenza, rota, adenovirus infections.13-15

Among the opportunistic viral pathogens, HSV-1 and HSV-2, varicella-zoster virus (VZV), and CMV can be significant pathogens after transplant. Without prophylaxis, approximately 50% of patients with HSV will have a recurrence.16,17 Cytomegalovirus is the most important member of this group in liver recipients in terms of its direct and indirect effects on liver transplant outcome.

The direct effects of CMV reactivation after transplant can cause clinical presentations such as isolated fever or mononucleosis syndrome (fever and bone marrow suppression) and/or invasive organ diseases such as gastritis, colitis, hepatitis, central nervous system involvement, pneumonitis, retinitis.2,18

The indirect effects of CMV infection result from the immunomodulatory property of the virus. It also has numerous indirect effects because of its ability to modulate the immune system. Cytomegalovirus has been associated with other infections such as bacteremia, invasive fungal disease, and Epstein-Barr virus-associated posttransplant lymphoproliferative disease.18 Cytomegalovirus infection is an important contributor to acute and chronic allograft injury. Cytomegalovirus reactivation causes in almost 4-fold increase in the risk of death within 1 year of transplant.19,20

Fungal Infections

Although various fungal species cause infection in liver recipients, the most common are the Candida species followed by Aspergillus spp.

Candida infections usually occur during the first month after transplant. The bloodstream, surgical wounds, and the urinary tract are common sites for primary infection. Candida infections also may
manifest as esophagitis, oral cavity infections, and superficial skin infections.\textsuperscript{21}

The incidence of candidemia among transplant recipients ranges between 2\% and 8\%. Because the overall mortality associated with invasive fungal infections has been reported to be as high as 77\%, candidemia should be treated aggressively. In addition, more invasive \textit{Candida} infections among liver transplant recipients in recent years have been caused by nonalbicans \textit{Candida} spp., which may have significant effects on outcome and treatment.\textsuperscript{21}

The second most common fungal infection in liver recipients is Aspergillosis with an incidence of 1\% to 9\%.\textsuperscript{22} The most common clinical presentation of aspergillosis is lung infection (90\%) followed by central nervous system. Although most infections occur during the first year (median time to diagnosis, 100 d) for high-risk patients (renal impairment or retransplant), infection may occur in the first month after transplant. Recent studies have reported improved outcomes with mortality rates ranging from 33.3\% to 65\% for transplant recipients. Mortality, however, remains high in liver recipients.\textsuperscript{22}

\section*{Prevention}

Because infectious complications are a major concern for liver recipients, prevention strategies are essential for this group of patients. In addition to screening potential liver donors and recipients for infectious causes, there are three general approaches for preventing infections in liver transplant patients: vaccination, administration of prophylactic antimicrobials, and preemptive therapy.\textsuperscript{2-4}

Transplant candidates and recipients are at an increased risk of infectious complications of vaccine-preventable diseases. Because the response to many vaccines is diminished in organ failure, transplant candidates should be immunized early in the course of their diseases. As a general rule, live vaccines should be avoided in transplant recipients after transplant because of the risk of disseminated disease.

Trimethoprim/sulfamethoxazole is generally administered after a liver transplant for 3 to 12 months, primarily to reduce the risk of \textit{Pneumocystis jirovecii} (carinii) pneumonia, but it also helps to prevent infections with \textit{Listeria monocytogenes}, \textit{Nocardia asteroides}, \textit{Toxoplasma gondii}, and some of the common urinary, respiratory, and gastrointestinal bacterial pathogens.

\textit{Cytomegalovirus} remains the most important viral infection in liver transplant recipients. Ganciclovir and valganciclovir are first-choice agents to prevent CMV disease in patients at risk of CMV reactivation. These agents may be used in prophylactic or preemptive approaches.

Other \textit{herpesviridae} including HSV 1 and 2 and VZV may cause reactivation after transplant. Approximately 50\% of patients with HSV will have a recurrence without prophylaxis. Antiviral agents used to prevent CMV infection also have activity against HSV and VZV.

The role of prophylaxis for fungal infections in liver transplant has not been well studied, although it is used commonly. It is generally recommended for the patients at high risk of invasive fungal infection.\textsuperscript{2,3} In conclusion, infectious complications remain a major concern for liver recipients, and lifelong monitoring of patients with infectious diseases will be essential.

\section*{References}


