Bacterial, Mycobacterial, and Protozoal Infections After Liver Transplantation—Part I

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Infection is one of the leading causes of morbidity and mortality in liver transplant recipients. More than two-thirds of liver transplant recipients have infection in the first year after transplantation, and infection is the leading cause of death in these patients.[1] In addition, release of cytokines during the infection may have other indirect and negative effects, including allograft injury, opportunistic superinfection, and malignancy.[1]

The risk of infection in liver transplant recipients is determined by the intensity of exposure to infectious agents (hospital or community sources) and the overall immunosuppression level. This "net state of immunosuppression"[2] is influenced by the dose, duration, sequence, and choice of immunosuppressive medications, underlying immune deficiencies, the presence of neutropenia or lymphopenia, mucocutaneous barrier integrity, the presence of necrotic tissue, ischemia or fluid collection, metabolic conditions such as diabetes mellitus, and the activity of immunomodulating viruses.[2]

After solid organ transplantation, there are 3 time periods when specific infections are likely to occur. The patient's susceptibility to infection during these periods is strongly influenced by surgical factors, the level of immunosuppression and environmental exposure, and the dose, duration, and types of prophylaxis.[3,4] Figure 1 depicts an infection time line of typical organisms after solid organ transplantation.

During the first period, the month immediately after transplantation, most infections are related to technical or surgical issues and complications. Exposure to infectious agents through prolonged hospitalization before transplantation or during postoperative care may also result in infection. Bacterial and candidal wound infections, urinary infections, catheter-related infections, pneumonias, and *Clostridium difficile* colitis predominate during this period, and the etiologic organisms are similar to hospital-acquired infections common in other surgical patients.[4,5] Although its incidence has markedly diminished with prophylaxis, reactivated human herpesvirus 1 (herpes simplex virus) is also a common viral illness in this time frame.

The next period encompasses the second through sixth posttransplant months. During this time, infections from opportunistic organisms predominate as a result of cumulative immunosuppression. Typical infectious organisms of this period include cytomegalovirus, *Pneumocystis jiroveci,* and *Aspergillus* species. Other viruses (human herpesvirus 6, hepatitis B and C, human herpesvirus 3 [varicella-zoster virus], and others), fungi (*Cryptococcus*, *Histoplasma*, and *Coccidioides* species), and bacteria (*Nocardia* species, *Listeria* species, or *Mycobacterium tuberculosis*) may also be seen.[4]

From approximately the seventh to 12th posttransplant months and beyond, most recipients acquire infections such as influenza, urinary tract infections, and community-acquired pneumonias, which are similar to the infections acquired by patients who have not received transplants.[4,6,7] Reactivation of human herpesvirus 3 may manifest as herpes zoster, and although it is uncommon, cytomegalovirus infections can occur. Three notable scenarios may enhance patient susceptibility to opportunistic infections, including (1) acute organ rejection necessitating increased immunosuppression therapy, (2) retransplantation, which "restarts" the immunosuppression and infection time line, and (3) chronic viral infections such as human immunodeficiency virus or hepatitis B or C.[4]

Kusne et al.[8] studied 101 consecutive liver transplantation patients for 1 year or longer. The patients received antibiotics for wound prophylaxis for 5 days and nystatin for antifungal prophylaxis for 30 days. No prophylaxis was administered for pneumocystic or viral infections. Figure 2 shows the timing of all severe infections and separately profiles the rates of bacterial, fungal, viral, and protozoal infections. The majority of infections occurred within 6 months of transplantation.

Abbreviations: OLT, orthotopic liver transplantation; VRE, vancomycin-resistant enterococci.

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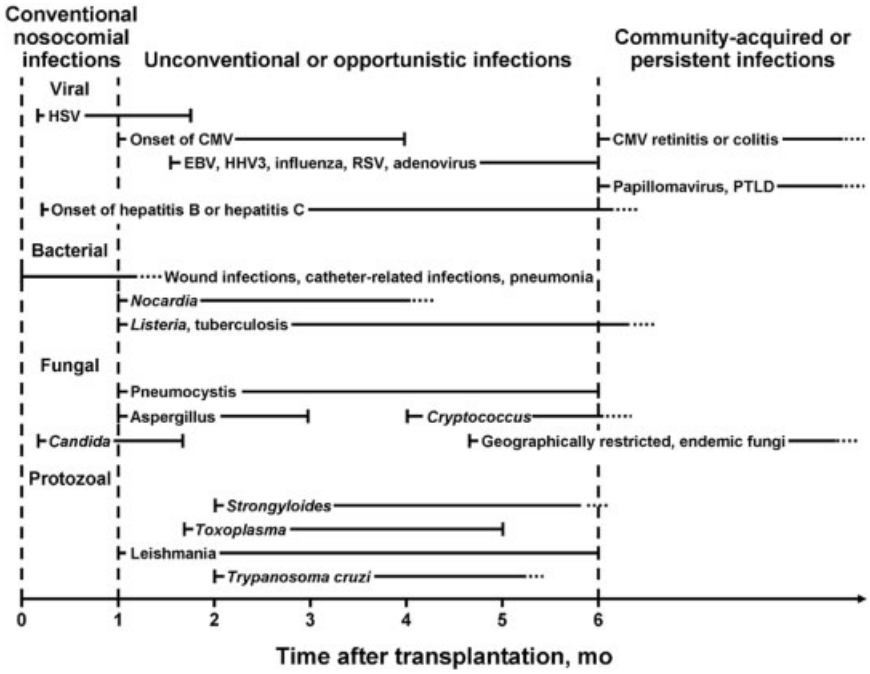

Figure 1. Usual sequence of infections after organ transplantation. Zero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted lines and arrows indicate periods of continued risk at reduced level. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV3, human herpesvirus 3; HSV, herpes simplex virus; PTLD, posttransplantation lymphoproliferative disease; RSV, respiratory syncytial virus. (From Rubin RH, Wolfson JS, Cosimi JS, Tolkoff-Rubin NE. Infection in the renal transplant recipient. Am J Med. 1981;70:405-411. Used with permission.)

Bacterial Infections

Bacterial infection is one of the most frequent and serious complications among orthotopic liver transplantation (OLT) patients.[5,9,10] The majority of bacterial infections occur within 2 months of transplantation,[5,9,10] and they typically occur in the abdomen (e.g., intrahepatic or extra-

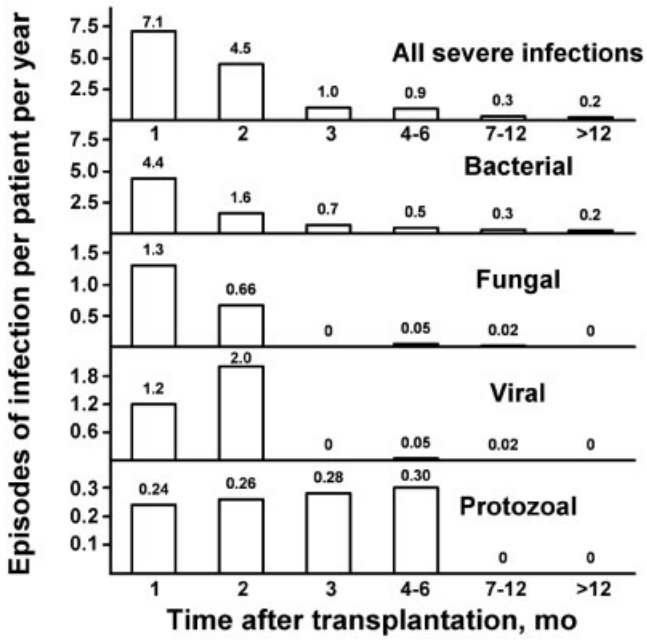

Figure 2. Incidence in episodes of infections per patient per year and time of occurrence after liver transplantation. (From Kusne et al.[8] Used with permission.)

hepatic abscesses, cholangitis, or peritonitis),[5,9,10] bloodstream,[5,9] surgical site,[9] and lungs.[5] Risk factors for bacterial infection include acute rejection,[11] prolonged hospitalization,[11] a history of acute liver failure,[11] and elevated serum bilirubin levels.[9] Prolonged intraoperative time may also be associated with bacterial infections.[9-11] Shorter stays in the intensive care unit have been associated with fewer septic complications.[12] Although most studies of infection after transplantation have focused on recipients of deceased donor liver transplants, recipients of living donor liver transplants also commonly experience wound and deep surgical-site infections related to technical surgical issues.[13]

Gastrointestinal bacterial and fungal organisms greatly affect postoperative morbidity and mortality in liver transplant recipients. Selective bowel decontamination regimens with nonabsorbable antibiotics have been examined to measure their effect on the number of colonizing organisms and postoperative infections. The results of these studies are inconclusive. Some showed decreased infection rates[14,15] or mortality rates (in patients with sterile feces[16]), whereas others showed no benefit.[17-19] Selective decontamination was associated with gastrointestinal intolerance,[14] patient noncompliance,[14] and increased patient costs.[18] A randomized trial comparing fiber and lactobacillus supplementation to selective bowel decontamination showed a reduced rate of infections in patients with supplementation[20]; this finding may warrant further study.

Bacteremia

Bacteremia frequently follows OLT.[11,21]; one center reported higher rates of bloodstream infections in liver transplant recipients when compared with patients undergoing kidney, heart, or heart-lung transplantation.[22] Gram-positive bacteria such as *Staphylococcus aureus* and *Enterococcus* species are responsible for a high proportion of these infections.[11,23] However, causative organisms may vary with prophylaxis regimens.[10] Bacteremia due to *S. aureus*,[24] *Pseudomonas aeruginosa* and *Enterobacter* species are associated with high mortality.[22] Indwelling vascular catheters[5,21] and infection at another site[5,10] are also important sources of bacteremia. Diabetes mellitus, low serum albumin, and cytomegalovirus seropositivity are all risk factors for bacteremia.[21,25]

Surgical-Site and Intra-Abdominal Infections

Surgical-site infections are common among liver transplant recipients; 1 study reported an infection rate of 32%.[26] The spectrum of surgical-site infections in OLT recipients includes incision infections, peritonitis, cholangitis, liver abscesses, and infections of intra-abdominal structures adjacent to the transplanted liver.[9,26] These infections are associated with longer hospital stays and higher patient charges when compared with OLT recipients without surgical-site infections.[26,27]

In general, surgical-site infections have not been associated with decreased patient survival or graft survival.[26,27] Risk factors include biliary anastomotic leaks, elevated preoperative white blood cell count, prolonged intraoperative time, human leukocyte antigen mismatches, low serum albumin levels, ascites, increased transfusion requirements, severe obesity, and receipt of OKT3 monoclonal antibodies within 7 days of transplantation.[9,26,27] Evidence of intra-abdominal pathogenic bacteria during transplantation was associated with early postoperative infections, and the same bacteria were often isolated from the infection and the preoperative cultures.[28] Infections were more likely to occur when colonizing bacteria were resistant to the perioperative antibiotic regimen.[28]

Hepatic artery thrombosis occurs in approximately 7% of adult liver recipients and may be associated with cholangitis, hepatic abscesses, and graft loss.[29-32] Broad-spectrum antibiotics and percutaneous drainage of hepatic abscesses have varying degrees of success[29,31,32]; retransplantation is often required and may be associated with high death rates.[29] One center reported successful nonsurgical management of patients with a single hepatic abscess.[31]

A range of organisms, including coagulase-negative and coagulase-positive staphylococci, enterococci, anaerobes, and gram-negative bacteria such as *Escherichia coli*, *Enterobacter* species, and *P. aeruginosa* are common in surgical-site infections.[9] Unusual organisms such as *Mycoplasma hominis*,[33,34] *Aspergillus* species,[35] or *Clostridium* species[36] have also been described. In addition to treatment with appropriate antibiotics, infections may require drainage, débridement, or, in serious cases of graft sepsis, retransplantation.

Pneumonia

Although pneumonia occurs less frequently than other bacterial infections, it can cause morbidity and mortality in liver transplant recipients.[37-39] The majority of pneumonias after OLT are caused by bacteria (58-63%),[37,39,40] although pneumocystic, fungal,[37] viral,[37] and mycobacterial infections are also common. Bacteria and *Aspergillus* species[38,41] are the most com-

mon organisms causing pneumonia in the first month after transplantation, whereas infections from opportunistic organisms are more likely to occur thereafter.[40] Liver transplantation with simultaneous splenectomy increases the risk for opportunistic pneumonia.[42]

The etiology of pneumonia is unknown in up to half the patients.[40] Gram-negative bacilli such as *P. aeruginosa,*[38] *Enterobacter* species, and *Serratia marcescens*[38] and methicillin-susceptible or methicillin-resistant gram-positive *S. aureus*[38] are common bacterial agents. Pneumonia can be difficult to diagnose, and telescoping catheter cultures,[41] bronchoalveolar lavage,[40-45] and biopsies[41,43] can help identify the infectious agent. In addition, these tests can determine if the patient has a noninfectious pneumonia-mimicking illness such as bronchiolitis obliterans with organizing pneumonia.[46-49]

Legionella species, especially *L. pneumophila*, may be acquired from community or hospital sources; *L. pneumophila* is common in institutions with environmental colonization of water supplies.[39,50] The source may not be readily identified without the use of specific media[51] and urine antigen tests during the routine work-up of patients with pneumonia.[39] Increased *Legionella*-related mortality is associated with nosocomial acquisition, intubation, and pulmonary complications such as empyema, abscess, or cavitary disease.[52]

S. aureus and Methicillin Resistance

S. aureus is a major cause of bacterial infection in liver transplant recipients; it is associated with bacteremia, surgical-site infections, and pneumonia. Multiply-resistant strains of *S. aureus* are commonplace, and methicillin-resistant strains are frequently seen among liver transplant patients.[53] Bacteremic infection with methicillin-susceptible[24] or methicillin-resistant[54] *S. aureus* is associated with high mortality rates (range, 20%-86%).

Nasal carriage of methicillin-resistant *S. aureus* is associated with higher Model for End-Stage Liver Disease scores. After transplantation, nasal carriers (especially those with concurrent rectal carriage[55]) have higher rates of methicillin-resistant *S. aureus* infections.[53,56,57] Methicillin-resistant *S. aureus* infections occur early in the posttransplantation period (mean, 16 days) and are attributable to endogenously colonizing strains rather than to a new infection.[53] Mupirocin can be used to eliminate *S. aureus,* but 1 study showed recolonization was common, and mupirocin did not prevent future *S. aureus* infections.[58]

Enterococci and Vancomycin Resistance

Enterococci are frequent pathogens in liver transplant recipients, and infections with vancomycin-resistant enterococci (VRE) have become a troublesome complication. Risk factors for vancomycin-susceptible enterococcal bacteremia include Roux-en-Y choledochojejunostomy or biliary strictures, prolonged intraoperative time, and cytomegalovirus infection.[59] Enterococcal bacteremias are frequently polymicrobial.[60] The frequency of VRE colonization and infection among liver transplant centers is variable.[61,62]

VRE can cause recurrent bacteremia and refractory infection, and the organism can persist at the primary site of infection.[60] High death rates in earlier studies[60,63-66] were probably at least partly attributable to inadequate antibiotics.[60] Despite the noted clinical differences between vancomycin-susceptible and vancomycin-resistant strains, a recent study of enterococcal infections did not find any differences in intensive care unit costs, length of stay in the intensive care unit, or mortality.[67]

Risk factors for VRE acquisition include the use of any antibiotics, especially broad-spectrum antibiotics such as cephalosporins, or vancomycin.[63-66] Prolonged antimicrobial use,[66] recent infection with vancomycin-susceptible enterococci,[65] and other concurrent infection,[64] including any fungal infections or intra-abdominal infections by any organism,[65] are additional risk factors for VRE acquisition. Biliary complications,[61,64,65] surgical reexploration,[64,66] renal failure,[65] or prolonged postoperative care were also noted risk factors.[66]

VRE colonization can persist for months or years, and VRE infection ensues in about 10% of patients in whom colonization has occurred.[68] High rates of colonization among hospitalized liver transplant recipients may be caused by multiple strains or a single clonal outbreak.[63] Adherence to infection control measures may limit the spread of VRE to other persons.[63] Susceptible strains of VRE can be treated with linezolid or the combination of quinupristin and dalfopristin.

Multiply-Resistant Gram-Negative Bacilli

A high proportion of infections from multiply-resistant gram-negative bacilli in OLT recipients was recently reported.[69] Unlike methicillin-resistant *S. aureus* or VRE, multiply-resistant gram-negative bacilli did not increase in incidence of infection over the decade studied (1990-1999). Nevertheless, the high proportion of *Pseudomonas* and Enterobacteriaceae resistant to piperacillin or ceftazidime suggested that these bacteria had

acquired an extended-spectrum β-lactamase.[69] An outbreak of infection caused by extended-spectrum β-lactamase-producing *E. coli* was abruptly curtailed with a multipronged intervention that included contact isolation, improved healthcare worker hand hygiene, and gut decontamination with orally administered fluoroquinolone.[70]

Mycobacterial Infections

Tuberculosis

Tuberculosis after solid organ transplantation is unusual, but the incidence is variable; it ranges from less than 1% to 6% in the developed world and up to 15% elsewhere.[71,72] The incidence rate is affected by the endemic area of the transplant recipients and program. Tuberculosis is associated with extensive morbidity and mortality (up to 40%).[71] The probable mechanism of infection is reactivation of a dormant infection in the transplant recipient, although rare cases of nosocomial and donor transmission have been documented.[73,74]

The onset of tuberculosis can occur within 15 days to several years of solid organ transplantation[71] (mean, 9 months).[74] Most patients with tuberculosis (51-64%) have pulmonary infection, although 1 or more sites of extrapulmonary infection are also common[71,74] Fever, night sweats, and weight loss are frequent constitutional symptoms. Cough, dyspnea, and pleuritic pain are associated with lung infections. Findings on chest radiographs vary and include focal, miliary, or nodular patterns. Cavitary tuberculosis, commonly seen in nonimmunocompromised persons, is observed in 4% of published cases.[74]

Extrapulmonary and disseminated infections are commonplace among transplant recipients who develop tuberculosis; the most common sites of involvement are the gastrointestinal tract[74] and the genitourinary tract.[71] Tuberculosis in the gastrointestinal tract involves the ileocecum, with ileitis, colitis, abscesses manifesting as abdominal pain, gastrointestinal tract bleeding, or perforation of viscus. Among liver transplant recipients with tuberculosis, tubercular hepatitis was present in 48% of patients.[74] Other sites included skin, muscle, bones or joints, central nervous system (meningitis or brain abscesses[75]), and lymph nodes.[74]

The goals of antituberculosis chemotherapy are to kill tubercle bacilli rapidly, prevent the emergence of drug resistance, and eliminate persistent bacilli from host tissues to prevent relapse.[76] The treatment of tuberculosis combines at least 3 or 4 medications such as isoniazid, rifampin, pyrazinamide, ethambutol hydrochloride, and others. Medication-induced hepatotoxicity can be detected by identifying rising levels of liver aminotransferases. Patients receiving 3 or fewer antituberculosis medications have less hepatotoxicity than those receiving 4 or more medications. In addition to hepatotoxicity, rifampin decreases cyclosporine levels in the serum, which may be associated with acute organ rejection.[71]

Because many cases of tuberculosis arise through reactivation of latent infection, it is important to identify persons with latent infection and ensure prophylaxis. Efficacy of chemoprophylaxis has not been demonstrated in controlled trials, but case series have demonstrated its value. Isoniazid was well tolerated in liver transplant candidates when compared with control patients[72]; following transplantation, isoniazid hepatotoxicity was observed in 25 to 41% of patients. Hepatotoxicity rates increased when patients with active tuberculosis received an isoniazid-based combination treatment.

Nontuberculous Mycobacterial Infections

Nontuberculous mycobacterial infections are unusual in liver transplant recipients. However, the incidence of these infections after solid organ transplantation may be increasing because of improved patient survival and diagnostic capabilities.[77] Infections from *Mycobacterium avium* intracellulare, *M. chelonae*, *M. mucogenicum*, *M. triplex*, and *M. xenopi* have been reported in liver transplant recipients.[77] *M. kansasii, M. haemophilum, M. fortuitum, M. terrae,* and *M. gordonae* have been observed in recipients of other organ transplants.[77] Pulmonary and pleuropulmonary infections and unifocal and multifocal cutaneous infections are more common than infections of the bones and joints, lymph nodes, intravascular catheters, surgical site, ileum and colon, and urinary tract. Allograft infections have rarely been observed.[77] Treatment decisions are guided by susceptibility tests and may be complicated by medication interactions with immunosuppressive regimens. Control of infection may require decreased doses of immunosuppressive drugs.[77]

Protozoal Infections

Pneumocystis Infections

Pneumocystis carinii, originally classified as a protozoon, has been renamed *P. jiroveci* and reclassified as a fungus.[78] Before the routine institution of anti-*Pneumocystis* prophylaxis, infections due to *P. jiroveci* were observed in 5 to 10% of organ transplant recipients, usually between 1 and

6 months after transplantation.[78] With routine prophylaxis, pneumocystic infections have virtually been eliminated. Nevertheless, transplant recipients requiring augmented immunosuppression for chronic or recurrent rejection are at risk for contracting pneumocystic infections even a year after transplantation.[79]

Most patients with *Pneumocystis* infections manifest an indolent fever, shortness of breath, and nonproductive cough. Bilateral interstitial infiltrates are seen in chest radiographs, and patients may have considerable hypoxemia. If the microbial burden is sufficiently 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. Patients should be treated with trimethoprim-sulfamethoxazole unless a strong contraindication (intolerance, allergy) is identified.[80] Effective but not fail-proof alternative treatments include aerosolized pentamidine isethionate, trimetrexate, trimethoprim-dapsone (in patients who are not deficient in glucose-6-phosphate dehydrogenase), atovaquone, and clindamycin-primaquine.[78-80] If standard therapies fail, a patient may have a concurrent infection or a secondary, noninfectious process.[78]

Toxoplasmosis

Infection with *Toxoplasma gondii*, or toxoplasmosis, is infrequent after solid organ transplantation, except in seronegative heart transplant recipients acquiring an allograft from an infected donor. Widespread use of trimethoprim-sulfamethoxazole prophylaxis for *P. jiroveci* has markedly reduced the frequency of toxoplasmosis in transplant recipients. Although it is unusual in liver allograft recipients, toxoplasmosis can manifest as a reactivated disease[81,82] and may cause pneumonia.[81] A cytologic evaluation of bronchoalveolar lavage fluid with confirmation by direct immunofluorescence and polymerase chain reaction analysis is required to identify *Toxoplasma* organisms.[81] One study reported detection of *Toxoplasma* organisms by their growth on cell culture media normally used for fibroblasts.[82] *T. gondii* rarely causes encephalitis, chorioretinitis, or hepatitis in solid organ recipients.[79] Optimal treatment includes pyrimethamine in combination with sulfadiazine or clindamycin.

Conclusion

Infections greatly influence morbidity and mortality in liver transplant recipients. After liver transplantation, patient susceptibility to infection is affected by surgical factors, immunosuppression, environment, and prophylaxis. Infections often occur intra-abdominally or at the surgical site, but bacteremia and pneumonia are also common. Infections with bacteria, fungi, viruses, and pneumocystis routinely occur. Less frequently, liver allograft recipients develop infections with mycobacteria or toxoplasmosis.

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