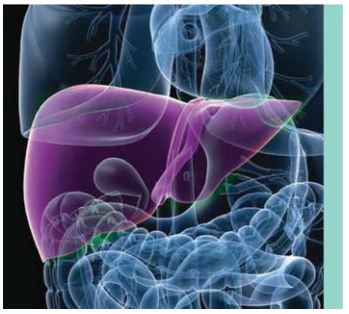

Transplanting Patients With Active Bacterial Infection

Elizabeth C. Verna, M.D., M.Sc., and Marcus R. Pereira, M.D., M.P.H.†*

Liver transplant (LT) candidates and recipients are at increased risk for bacterial infection and associated morbidity and mortality. Significant infection occurs in up to 80% of patients in the first year post-LT.[1] Infection is the primary reason for readmission within 30 days of LT in about 25% of patients, leading to increased mortality, morbidity, and cost.[2-4] Thus, strategies to identify patients at greatest risk for significant post-LT infection are key to improving outcomes, and known active bacterial infection has generally been viewed as a contraindication to LT. However, because infection is a major cause of pretransplant hospitalization and may precipitate an increase in the Model for End-Stage Liver Disease (MELD) score that enhances access to transplant, balancing the risks of surgery and immunosuppression in the setting of active infection with the loss of the opportunity to be transplanted creates a conundrum that LT clinicians frequently face. Unfortunately, few data exist to guide clinical decisions in this scenario.

TRANSPLANTING PATIENTS WITH ACTIVE BACTERIAL INFECTION

Patients with cirrhosis are at increased risk for bacterial infections for a number of reasons including compromised immune system function, high rates of instrumentation, and frequent and prolonged hospitalizations.[5,6] Clinical risk factors for infection in pre- and post-LT patients are summarized in Table 1. Although about 35% of hospitalized patients with cirrhosis have bacterial infection, very little is known about the impact of active bacterial infection at the time of LT. The American Association for the Study of Liver Diseases guidelines state, ''Active infection needs to be adequately treated before LT can be

Abbreviations: COPD, chronic obstructive pulmonary disease; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CTP, Child-Turcotte-Pugh; HCV, hepatitis C virus; ICU, intensive care unit; LT, liver transplant; MDR, multidrug-resistant; MELD, Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

From the *Center for Liver Disease and Transplantation, Columbia University Medical Center, and †Division of Infectious Diseases, Department of Medicine, Columbia University Medical Center, 622 West 168th Street New York, NY, 10032.

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TABLE 1. RISK FACTORS FOR BACTERIAL INFECTIONS PRE-LT AND EARLY (<30 DAYS) POST-LT[1,6,12-16]

Pre-LT	Early Post-LT
Age	Recipient age
Low serum albumin level	Recipient comorbidities, e.g., malnutrition, diabetes, obesity, COPD, renal failure, and dialysis
CTP score	Prolonged hospital stay and catheters before LT
HIV and HCV coinfection	Acute liver failure
Gastrointestinal bleeding	MELD score >30 at LT
ICU admission	Previous immunosuppression (autoimmune hepatitis; retransplantation)
Instrumentation (e.g., endoscopy, paracentesis)	Pre-LT infection, including sepsis
Colonization with MDR organisms	HIV and HCV coinfection
Prior SBP	Colonization with MDR organisms
For SBP: gene polymorphism involved in the innate antimicrobial defense, such as NOD2, TLR2, and MCP-1	Indwelling catheters, intravenous lines
For UTI: female sex, urinary catheter use and duration	Cold ischemia time
For pneumonia: low serum complement levels, use and length of endotracheal intubation	Infected preservation fluid
For aspiration pneumonia: encephalopathy	Infection in donor
For skin and soft tissue infections: edema, walking barefoot, use of peripheral and central intravenous lines	Quality of the liver graft (e.g., marginal graft)
For *C. difficile* infection: use of antibiotics (in particular clindamycin, third generation cephalosporins and fluoroquinolones) and PPI	Amount of intraoperative blood transfusion
	Operative time
	Type of biliary drainage (Roux-en-Y, T-tube)
	Surgical complications (e.g., primary nonfunction, hepatic artery thrombosis, necrosis, biliary strictures, bile leak)
	Reoperation including retransplantation
	Prolonged post-LT ICU stay, dialysis, prolonged ventilation
	Level and type of immunosuppression, additional immunosuppression for early rejection

Abbreviations: COPD, chronic obstructive pulmonary disease; CTP, Child-Turcotte-Pugh; HCV, hepatitis C virus; ICU, intensive care unit; MCP-1, Monocyte chemotactic protein-1; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PPI, Proton pump inhibitor; TLR2, Toll-like receptor 2. UTI, urinary tract infection.

attempted.''[7] However, more detailed recommendations are lacking due to a paucity of data. There are patients with primary sclerosing cholangitis who undergo LT in the setting of cholangitis, controlled on antibiotics, but in this case the infectious source is removed with the transplant and would not be otherwise cured.

For other infections, no guidance exists on whether to proceed to transplant when an infection with known antibiotic sensitivities is being adequately, but not yet fully, treated. What constitutes active infection in this setting is difficult to define. Furthermore, when an infection has been adequately treated, there are no data regarding a safe interval between treatment and transplant, although some experts recommend a minimum of 2 weeks.[8]

PERITONITIS

Peritonitis is the most common bacterial infection in patients with cirrhosis and may be of particular importance because intra-abdominal infection is the most common site of post-LT bacterial infection. Spontaneous bacterial peritonitis (SBP) is difficult to diagnose given the often complete lack of symptoms and negative cultures, and antibiotic selection is usually empiric. Furthermore, theoretical concern exists about increased operative difficulty in these patients who may have advanced portal

hypertension and possible abdominal adhesions related to infection.

SBP experienced at any time in the pre-LT setting has not been associated with diminished post-LT patient survival in single-center experiences, although in the largest series available, pre-LT SBP was found to increase the risk for post-LT reoperation and death caused by sepsis.[9] In a smaller series of 100 patients with SBP in the more immediate pre-LT setting (within 30 days), SBP was not predictive of post-LT episodes of sepsis if 4 or more days of appropriate antibiotics have been administered.[10] However, this was a small single-center study, and additional outcomes including abdominal infections, readmissions, and death were not evaluated.

In a more recent study, of 434 asymptomatic patients who underwent screening for peritonitis at the time of LT, 19 (4.8%) patients met diagnostic criteria for SBP.[11] Of these 19 patients, 16 went through with LT, and the overall 30-day post-LT survival was similar between those with and without peritonitis. Thus, no data currently support the clinical utility of SBP screening at the time of LT in asymptomatic patients. However, this study cannot be used as evidence that LT is safe in a symptomatic or severe case of SBP. It is advisable that for patients with SBP, especially those with negative cultures, assurance of response to antibiotics (including response in ascites absolute neutrophil count to <250 cells/mm^3 and/or at least a 50% decline from the initial count) should be required before LT.

BACTEREMIA AND SEPSIS

Bloodstream infections are common in cirrhotics and LT recipients, and are associated with increased post-LT mortality.[12] Most post-LT bloodstream infections occur in the first month, highlighting the risks in this period.[12] It is perhaps intuitive that pre-LT patients with bacteremia complicated by severe sepsis or with concomitant critical illness may be at the greatest risk for adverse outcomes post-LT. In a large, retrospective series of patients who underwent LT with MELD >40, septic shock within 1 month before LT was one of four factors associated with a futile outcome (3-month or in-hospital mortality).[13] However, not every episode of bacteremia is associated with sepsis. Although it has not been studied, experts recommend against LT in the setting of active bacteremia. Whether scenarios exist in which adequate antibiotic coverage and clinical stability may mitigate these risks is not known.

MULTIDRUG-RESISTANT INFECTIONS

Antibiotic susceptibilities should be known and the team must feel confident that the infection can be adequately treated to consider transplant in close proximity to bacterial infection. An increasing proportion of infections in patients with cirrhosis and solid organ transplants are with multidrug-resistant (MDR) organisms.[14-16] For example, post-LT infection with a highly resistant organism such as carbapenem-resistant *Klebsiella pneumoniae* (CRKP) may be among the strongest clinical predictors of post-LT mortality, with an adjusted hazard ratio of 6.92 in the largest series to date.[17] Similarly, pre-LT infections with carbapenem-resistant *Acinetobacter baumannii* (CRAB) are associated with post-LT infections with the same organism, which are in turn associated with poor outcomes.[18] There is a growing literature on the use of active screening for MDR colonization to guide prophylaxis and also debate whether patients colonized with these microbes should be considered eligible for LT.[19] LT during active MDR infection, especially CRKP and CRAB, which require the most toxic antibiotic regimens, may not be advisable in our opinion.

CLOSTRIDIUM DIFFICILE INFECTION

Patients with cirrhosis are also at increased risk for *Clostridium difficile* infection (CDI), with a rising incidence that has run in parallel to the general population over the last two decades. CDI significantly impacts patient outcomes, including increased length of stay and decreased survival among patients with cirrhosis.[20] A recent retrospective study of CDI among LT recipients showed that a large proportion of CDI occurred within 1 week post-LT and was associated with lower overall survival.[21] This risk highlights the role of hospitalization and antibiotic exposures in the pathogenesis of CDI, and it is uncertain whether these patients could have had early disease at the time of LT. Although there are no data on active CDI at the time of transplant, most experts would recommend against LT in the acute setting because of the potential for operative complications and the risk for development of fulminant colitis on high-dose immunosuppression postoperatively.

CONCLUSIONS

There is a dearth of information to guide recommendations about the safety of LT at the time of active infection. Because infection in the early posttransplant period is a major cause of morbidity and mortality, and the use of high-dose immunosuppression may limit the ability to control even sensitive infections, the general consensus is that fully treating an infection before transplant is the optimal approach when possible. Conversely, infection in patients with cirrhosis awaiting LT commonly precipitates an increase in MELD score that may represent a precious opportunity for access to life-saving transplantation. In that setting, clinicians must carefully assess the risks and benefits of withholding versus proceeding with LT. It is possible that in well-selected cases, overall mortality without LT in the acute setting will be higher than proceeding with LT on antibiotics. At this time it is difficult to risk-stratify patients for this approach. Assessment of the severity of infection is key, because patients with sepsis and clinical instability are likely at the greatest risk and cannot be recommended for urgent LT. The rapid increase in MDR infections in this population and the profound impact of MDR infections on post-LT mortality also highlight the importance of knowing drug susceptibility and confirming clinical response to treatment before LT. Providers should proceed with caution when considering LT in the setting of active highly resistant infection. Additional studies are urgently needed to assess the safety of transplant in the setting of mild or partially treated infection because it is possible that there are populations in which the benefits of immediate LT outweigh the risks.

CORRESPONDENCE

Elizabeth C. Verna, M.D., M.Sc., Assistant Professor of Medicine, Director of Clinical Research, Transplant Initiative, Center for Liver Disease and Transplantation, Division of Digestive and Liver Diseases, Columbia University, New York, NY. E-mail: ev77@cumc.columbia.edu

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