World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i20.6211

World J Gastroenterol 2014 May 28; 20(20): 6211-6220
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (7): Liver transplant

Bacterial infection after liver transplantation

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Received: October 27, 2013 Revised: January 10, 2014
Accepted: February 17, 2014
Published online: May 28, 2014

Abstract

Infectious complications are major causes of morbidity and mortality after liver transplantation, despite recent advances in the transplant field. Bacteria, fungi, viruses and parasites can cause infection before and after transplantation. Among them, bacterial infections are predominant during the first two months post-transplantation and affect patient and graft survival. They might cause surgical site infections, including deep intra-abdominal infections, bacteremia, pneumonia, catheter-related infections and urinary tract infections. The risk factors for bacterial infections differ between the periods after transplant, and between centers. Recently, the emergence of multi-drug resistant bacteria is great concern in liver transplant (LT) patients. The instructive data about effects of infections with extended-spectrum beta lactamase producing bacteria, carbapenem-resistant gram-negative bacteria, and glycopeptide-resistant gram-positive bacteria were reported on a center-by-center basis. To prevent post-transplant bacterial infections, proper strategies need to be established based upon center-specific data and evidence from well-controlled studies. This article reviewed the recent epidemiological data, risk factors for each type of infections and important clinical issues in bacterial infection after LT.

Key words: Liver transplantation; Bacterial infection; Intraabdominal infections; Resistant bacteria

Core tip: Bacterial infections are major causes of morbidity and mortality after liver transplantation. To prevent post-transplant infectious complications, epidemiology, risk factors and clinical characteristics of bacterial infections should be monitored and controlled. Currently, novel threats are arising from multi-drug resistant bacteria and recipients with higher risk for infection are increasing. Despite improved surgical techniques and post-transplant care systems, early diagnosis and appropriate treatment of bacterial infections are vital for successful liver transplantation.

Kim SI. Bacterial infection after liver transplantation. *World J Gastroenterol* 2014; 20(20): 6211-6220 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i20/6211.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i20.6211

INTRODUCTION

Infectious complications are major causes of morbidity and mortality after liver transplantation, despite advances in surgical technique, post-transplant care, hospital environments, immunosuppression, infectious disease treatment, infection prevention and prophylaxis in liver transplant (LT) recipients[1]. LT recipients are more likely to develop bacterial infections than other transplant recipients because of the complexity of the surgical procedure, which includes penetration of the hepatobiliary system[2]. After LT, bacterial infections comprise the most frequent type of infection, followed by fungal, viral and protozoal infections[2-5]. Nosocomial pathogens, including gram-negative bacteria and gram-positive bacteria, are major causative organisms consequent to epidemiological exposure[6]. The intensity and timing of the exposure, and the virulence of the organism, affect morbidity and mortality.

The "Net State of Immunosuppression" as described by Fishman and Rubin[7] is a complex interaction among multiple factors, such as immunosuppressive drugs, underlying medical condition, extent and amount of barrier breakage, neutropenia, metabolic issues, and immunomodulatory viral infections, such as cytomegalovirus, Epstein-Barr virus, herpesviridae and viral hepatitis[7].

Bacterial infection patterns change along the post-transplantation time course[1,3,7]. During the first post-transplantation month, most infections are related to the surgical procedure with medical complications[1,7]. Surgical site infections (SSIs), including deep intra-abdominal infections, pneumonia, bacteremia, urinary tract infections and catheter-related infections, are common[8-11]. The patterns and characteristics of these infections are somewhat similar to those in other surgical patients, especially patients who underwent hepatobiliary surgery; however, the underlying diseases, immunosuppressive medications and procedural complexity of transplantation lead to a higher incidence of infection. In LT recipients, 4.4 episodes of bacterial infection during the first post-transplantation month were reported per patient per year[3]. Most of the infections during this time period are caused by nosocomial organisms or the patient's normal flora; however, infection can also be transmitted from the donor. A high degree of vigilance should be maintained to prevent and treat donor derived infections in a timely manner. Donor-derived pathogens are extensively monitored and reviewed to prevent unexpected infections[12,13].

During the next post-surgical period, which comprises the second to sixth months after LT, opportunistic infections might occur, depending on patients' risk factors and the intensity of immunosuppression[1]. Although viral infections are predominant during this period, unusual bacteria, such as *Listeria monocytogenes* and *Nocardia* species, can cause infections. The reactivation of latent infections, including those caused by *Mycobacterium* species and other fungi and protozoa, might be observed during this time period.

Bacterial infections that occur more than 6 mo after LT are related to environmental exposure, late biliary complications, graft function and combined viral hepatitis[14]. At 12 mo after LT, urinary tract infections, intra-abdominal infections, sepsis of unknown etiology, and pneumonia are the major types of infection in solid organ transplant recipients[14].

Shifts in nosocomial pathogenic patterns, increasing antibiotic resistance, potent immunosuppression, improved diagnostic methods, grafts from marginal donors and broader epidemiologic exposure, influence the risk and outcomes of bacterial infections[15]. In this article, the current status, epidemiology, characteristics and prevention of bacterial infections after LT will be reviewed.

INCIDENCE AND RISK FACTOR

Bacterial infection trends have changed as a result of bacterial epidemiology, perioperative prophylactic antibiotics, surgical techniques, immunosuppressive agents and post-transplant care[16]. In reports from the 1980s and 1990s, 33%-68% of LT recipients contracted at least one bacterial infection after transplantation[4]. During that period, major transplant centers in the United States reported a bacterial infection incidence range of 53%-56%[3,17,18]. In a report of a Swiss cohort in the 2000s, 47% of the patients contracted bacterial infections[19]. Kim *et al*[20] reported rate of 30.2% during the first month and 67.9% during the total follow-up period (mean, 672 d). Others reported rates of 14.1%[21] in the first 3-mo, and 75% and 42.9%[22] in deceased and living-donor LT recipients, respectively. The bacterial infection incidence rates differ between centers, according to follow-up duration, study design and different microbiological environments, even though the centers use a relatively standardized definition of infection. As observed in current reports, nearly half of all bacterial infections occur within the first 2 mo after transplantation[3,8,18]. The important infection sites are the abdomen, including the biliary tract, surgical wound, respiratory tract, and blood stream with or without catheter-related infections. Enteric gram-negative bacteria (GNB) and gram-positive bacteria (GPB) comprise a major portion of the causative organisms, although the predominant pathogens differ between the centers and between geographical areas[9,10,17,19,23,24].

Risk factors for overall bacterial infections are shown in Table 1. Some factors in studies from the 1990s[3,18,25-28] were not significant factors in studied from the 2000s[14,21,29,30]. Singh *et al*[31] reported that sources and risk factors differ for early versus late bacterial infections. In addition to risk factors, lack of classical signs and symptoms, such as fever, caused by immunosuppressives and steroids lead to delay in diagnosis of infections and, hence, one should monitor carefully and maintain a high index of suspicion for infection.

TYPES OF INFECTION

In LT recipients, SSIs, including deep intra-abdominal infections, bacteremia, pneumonia, catheter-related infections and urinary tract infection are common[3,8,20]. The types of infection are similar to those observed decades ago, because the main surgical procedures still include the penetration and manipulation of the hepatobiliary system; however, the incidence and risk factors of each type of infection differ between centers.

SURGICAL SITE AND INTRA-ABDOMINAL INFECTIONS

SSIs are among the most common bacterial infections[2]. Patients with SSIs have higher rates of graft loss, longer hospital stays and increased medical costs. Despite advances in post-transplant care, prophylactic strategies and improved immunosuppression, the prevalence of SSIs has changed little[32-34]. Although the Centers for Disease Control and Prevention defined the SSIs into superficial incisional, deep incisional, and organ/space SSIs[35], the

Table 1 Risk factors for bacterial infection in liver transplant recipients

1990s	2000s
Pre-transplantation plasma creatinine value greater than 1.58 mg/dL	Long-term renal replace therapy (> 30 d)
Prolonged surgical time more than 12 h	Increased serum ferritin level
increased number of abdominal operations	Early
Use of Roux-en-Y choledocho-jejunostomy	Portal vein thrombosis
Acute rejection	Age older than 45 yr
CMV infection	Preoperative hyponatremia
Prolonged hospitalization	ICU satay longer than 9 d
Increased operative transfusion requirement	Postoperative bile leakage
Retransplantation	Severe hyperglycemia
Elevated bilirubin levels	Late
	Recurrent hepatitis C
	Age
	Female gender
	Anti-hepatitis C virus positive serostatus
	Chronic allograft dysfunction
	Early CMV disease
	Early bacterial infection

ICU: Intensive care unit; CMV: Cytomegalovirus.

incidence of SSIs has been rarely determined according to a standardized definition, especially in LT recipients[36]. In previous well-organized studies, the incidence of SSIs ranged from 9% to 21.5% as wound infection, from 6% to 18% as cholangitis, from 6.3% to 9% as peritonitis, and from 4% to 12.9% as abscess[3,18]. Currently, the overall incidence of SSI ranges from 18% to 37%, and on average, up to 2.4 SSIs per patient[32,33,36,37]. In a large multicenter study, 11.6% of the total patients had organ/space, 4.9% had superficial, and 1.4% had deep SSIs[36]. In a subgroup analysis, the organ/space SSIs were found to be significantly associated with death, graft loss, and death without prior graft loss[36]. LT recipients differ from other transplant recipients with regard to underlying poor nutrition, bleeding tendencies, difficulties and longer surgical durations. Although the medical condition of the patient pre-transplant affects the occurrence of post-transplant SSIs, recent data showed that SSIs were more closely related to intraoperative conditions and post-transplant events[33]. The biliary tract is often a source of intra-abdominal infections, as well as cholangitis and abscess, when the patient has a biliary stricture, with or without hepatic artery occlusion[2,3]. A longer cold ischemia time (7.9 ± 2.6 h *vs* 5.5 ± 2.8 h) was associated with the presence of non-anastomotic biliary strictures in patients with hepatic artery stenoses[38]. Anastomosis of the biliary duct using Roux-en-Y loop has been associated with a higher rate of infection[2,3]; however, recently, making a Roux-en-Y loop is not a routine process. Additional risk factors include; retransplantation, dialysis, transfusion ⩾ 2 units of blood during LT, cold ischemia for > 400 min, and cytomegalovirus (CMV) infection in one study[33]; donor liver mass-to-recipient body mass ratio of ⩽ 0.01, and an increased surgical duration in another study[36]. Causative pathogens included gram-positive cocci [*Staphylococcus aureus* (*S. aureus*), *Enterococcus* species, and coagulase-negative staphylococci and streptococci)], gram-negative bacilli [Enterobacteriaceae, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter baumannii* (*A. baumannii*), and *Stenotrophomonas maltophilia*], anaerobes and fungi[3,17,32,36,37].

BACTEREMIA

Bacteremia has been a main cause of morbidity and mortality in LT recipients[39]. Bacteremia, as a proportion of all infections, increased because of a decline in infections caused by other pathogens, such as viruses and fungi[5]. Most bacterial infections occur within the first month after transplantation, with a range of 19%-33%[3,18,20,26,40,41]. The prevalence of specific pathogens varies between transplant centers. Traditionally, gram-positive cocci were considered common causative agents of early post-transplant bloodstream infections[17,24], whereas, decades later, there had been a increment of bacteremia due to GNB[5,41-44]. One of the largest transplant centers reported that the proportion of GNB increased from 25% during the period 1989-1993 to 51.8% during the period of 1998-2003, whereas the GPB decreased from 75% to 48.2% during the same period[5]. However, the center-specific epidemiology and post-transplant management reflect the continued high prevalence of bacteremia caused by GPB[40,45-47]. In one study, the common sites of entry were the gastrointestinal and biliary tract in 27% of the cases, pneumonia in 10%, intravenous site in 6%, and unknown in 41%[24]. Others study reported that 52.8% of bacteremia cases entered through the gastrointestinal tract, followed by unknown (22.6%), urinary tract (17%) and catheter (3.8%)[42]. However, an indwelling central catheter was one of major sources of bacteremia (30%) and the duration of catheterization ($P < 0.0001$) was a significant risk factor[40]. The mortality rate in bacteremic LT recipients has been reported to range from 24% to 36%[5,18,40]. After the onset of bacteremia, the 14-d mortality rate was 24%[24], and the 30-d rate was 27.8%[5].

Risk factors for bacteremia include old age, a longer catheterization time, United Network of Organ Sharing (UNOS) class I or ⅡA status, diabetes, pre- and post-transplant renal dysfunction, and hypoalbuminemia[40,48]. In a study by Iida *et al*[45], a multivariate analysis showed that Child-Pugh class C status, preoperative hepatic hydrothorax or ascites requiring drainage, CMV infection, ABO incompatibility, and older donor age were independent risk factors for bacteremia within 3 mo after living-donor LT[45]. In that study, a longer intensive care unit (ICU) stay, intravenous catheterization, renal failure, hemodialysis, and diabetes mellitus were not significant risk factors for post-transplant bacteremia. The risk of mortality was related to the severity of underlying disease, source of bacteremia and choice of antimicrobial agents[24]. When timing of the onset of bacteremia was considered, the one-year mortality rate was significantly associated with early episodes, but not with late episodes[24,43]. However, a recent study by Lee *et al*[46] demonstrated that no significant differences were observed in the 30- and 60-d all-cause mortality rate of patients with

early- and late-onset bacteremia, although the microbiological spectra differed. Enterobacteriaceae such as *Escherichia coli* (*E. coli*), *Klebsiella pneumonia, Enterobacter* species, and *Klebsiella* species, as well as enterococci, were common pathogens in bacteremias that originated from the hepatobiliary and gastrointestinal tract[5,17,24,40-43,45,49]. Multidrug resistant (MDR) gram-negative bacilli that produce extended-spectrum beta-lactamase (ESBL) and carbapenemase are increasing[42,50-55]. MDR GNB induced bloodstream infections that have significantly worse prognoses than those caused by susceptible isolates[44,52]. Among the glucose non-fermenting GNB, *P. aeruginosa* and *A. baumannii* were notable pathogens, which were related to an increased fatality rate (37%-50%)[24,44,56]. Gram-positive cocci can also cause of bacteremia in patients with SSIs, pneumonia, catheter-related infections and urinary tract infections. Methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *S. aureus*, coagulase-negative staphylococci, enterococci, and streptococci are commonly reported pathogens[21,24,40,43,57-59].

PNEUMONIA

LT recipients are vulnerable to respiratory infections because of the long surgical duration, frequent use of post-transplant mechanical ventilation, immunosuppression, massive transfusions, frequent edema with fluid overload, difficulty coughing after surgery and underlying malnutrition[60,61]. Bacterial pneumonia occurs in 11%-28% of LT recipients; nosocomial pneumonia in 50%-75%, and community-acquired pneumonia in 25%-50%[8]. Although bacterial pneumonias occur less frequently than other types of bacterial infections, they can cause morbidity and mortality[8,60-62]. In a previous report, of the changes in immunosuppressive agents from cyclosporine to tacrolimus, the causative organisms included bacteria (58%), fungi (37%), and protozoa (5%), with controlled reductions in *Pneumocystis jirovecii* pneumonia and CMV infections because of prophylactic use of trimethoprim/sulfamethoxazole (TMP/SMZ) and ganciclovir[63]. Currently, when comparing the pattern of pneumonia to the time course, during the first month after LT, bacterial pneumonia was the most common infection, followed by fungal pneumonia[64]. *Pneumocystis* pneumonia is presented as a late-onset complication[65]. Other *Aspergillus* and MDR pathogen infections occur on a center-specific basis[15]. In a study by Ikegami *et al*[61], GNB were the predominant pathogens, causing up to 84% of bacterial pneumonia, and the short-term mortality rate was 42%. *P. aeruginosa*, *Klebsiella*, *Enterobacter*, *Haemophilus influenzae,* (*H. influenzae*) and *S. maltophilia, Serratia marcescens,* and methicillin-susceptible or methicillin-resistant *S. aureus* were also reported as pathogens[60,62,64]. In living-donor LT recipients, significant risk factors were diabetes, UNOS class I or ⅡA status, and operative blood loss > 10 L[61]. Additional factors were post-operative prolonged mechanical ventilation for more than 2 or 3 d, ICU stay ⩾ 7 d, tracheostomy, primary graft dysfunction, the use of mycophenolate mofetil, lactatemia, vasopressor requirements, high Simplified Acute Physiology Score Ⅱ score and the need for renal replacement therapy[60,61]. Pathogen-specific antimicrobial therapy is crucial for the treatment of bacterial pneumonia, with or without reduction of immunosuppressive agents. After the immediate period, opportunistic bacterial pneumonia may occur less frequently. Beyond 6 mo after LT, in patients with good graft function and immunologically stability, the presenting pattern of bacterial pneumonia is similar to that of non-LT patients[65].

OTHERS

Donor-derived infection

Transplanted organs facilitate transmission of bacterial, viral, fungal and parasitic infections[1]. Recently, estimated donor-derived infections (DDIs) in the United States occur in less than 1% of all transplant procedures[12]. Although the incidence of DDI is low, when a transmission does occur, significant morbidity and mortality can result[12]. Outcomes of DDIs are variable, and the definitive incidences of death and graft loss are difficult to determine[66]. Although several cases of DDIs were reported, patients having bacterial infections without evidence of multiorgan failure can be candidates for LT donor weighing risk benefit of transplantation[67]. In some recent reports, LT recipients who had donor-derived bacterial infections did not die after the use of appropriate antibiotic therapies[68-70]. Lumbreras *et al*[71] reported unrecognized bacteremic donors did not affect the outcome of LT recipients. However, Nery *et al*[72] reported a primary non-functioning graft after an LT from a donor with unsuspected bacterial infection. Factors for transmission of infection by grafts are virulence, tissue tropism of the bacteria, recipient's immune status, graft condition, clinical experience, laboratory technical support and extent of donor exposures[73].

Urinary tract infection

In a multicenter large cohort study, urinary tract infection (UTI) was the third ranked type of infection in the early period and the second most common infection in late period among solid organ transplant recipients[74]. Another cohort data revealed that UTI was the most prevalent primary source of bacterial infection over 6 mo after solid organ transplantation[14]. In LT recipients, the incidence of UTIs, excluding non-complicated cystitis and asymptomatic bacteriuria, was 0.06 episodes per 1000 transplant-days overall[75], and 0.03 during late period[74].

Pathogens are *E. coli, Enterococcus faecium, Klebsiella* species, *S. aureus, Enterobacter* species, and *Enterococcus faecalis*[18,75]. UTIs are common sources of antibiotic resistant bacterias, such as ESBL producing Enterobacteriaceae, vancomycin-resistant enterococci, and methicillin-resistant staphylococci[51,53]. Risk factors for UTI are age (OR per decade = 1.79, 95%CI: 1.09-3.48), female sex (OR = 1.7, 95%CI: 1.43-2.49) and diabetes (OR = 1.02, 95%CI: 1.001-1.040)[75]. Long-term use of a urinary indwelling catheter is one of common risk factors for UTI;

however, data are scarce focusing on LT recipients. In clinical settings, many centers introduce prophylactic use of TMP/SMZ for the prevention of *Pneumocystis jirovecii* pneumonia as well as UTIs; however, UITs are considered less preventable because of the increasing rate of TMP/SMZ resistance[76].

Clostridium difficile associated colitis

Diarrhea is a common symptom after LT, with an approximated incidence of 10%-43%[77]. The most common causes were *Clostridium difficile* (*C. difficile*) and CMV as infectious etiologies, particularly during the first 2 mo after LT[78]. Other non-infectious causes of diarrhea are ulcerative colitis and medications[78]. In a nationwide analysis, *C. difficile* infection (CDI) was more prevalent in LT patients than in non-LT population (2.7% *vs* 0.9%, $P < 0.001$) and CDI was associated with a higher mortality rate (5.5% *vs* 3.2%, adjusted OR = 1.70, 95%CI: 1.29-2.25)[79]. Early onset (≤ 28 d post-LT) CDIs were significantly more likely to have variables of redo LT ($P = 0.013$), higher model for end-stage liver disease (MELD) score ($P = 0.007$), presence of major intra-abdominal bleeding ($P < 0.0001$), biliary complications ($P = 0.034$), bile leaks ($P = 0.026$) and systemic infection ($P < 0.001$)[80]. The incidence of CDI in living donor LT recipients was 5%, and the independent risk factors were male sex (OR = 4.56) and serum creatinine (> or = 1.5 mg/dL, OR = 16.0)[81]. Recently, in study by Boutros *et al*[82], 15.8% of CDI in solid organ transplant recipients developed complicated *C. difficile*-associated colitis resulting in graft loss, total colectomy or death. In this study, surgical intervention was strongly recommended, especially for those who had independent risk factors for complicated CDI, such as white blood cell count ⩾ 25000/μL (HR = 1.08, 95%CI: 1.025-1.15) and evidence of pancolitis on computed tomography (CT) scan (HR = 2.52, 95%CI: 1.195-5.35)[82]. When the LT recipient presents with pathological diarrhea, an early serological test, sigmoidoscopic examination, and/or CT scan for differential diagnosis and proper management is crucial.

PATHOGENS

Bacterial pathogens differ between the post-transplant period[1]. Most bacterial infections occur within 2 mo of transplantation[8]. Although the predominant pathogens differ between centers and between geographic areas, enteric GNB and GPC are the major causative organisms[9,10,17,19,23,24].

Gram-negative bacteria

Enterobacteriaceae are the major pathogens in LT recipients. Many of these infections are associated with technical problems with the graft, biliary leaks or obstructions. Thrombosis of the hepatic artery results in ischemia of the allograft, which might cause liver abscesses. GNB can also cause SSIs, including deep intra-abdominal infections, bacteremia, pneumonia, urinary tract infections and catheter-related infections. Common pathogenic Enterobacteriaceae are *E. coli, Klebsiella* species, *Enterobacter* species, and *S. marcescens*[3,8,22,43]. *P. aeruginosa* and *A. baumannii* are also common causes of GNB infection. *S. maltophilia*, *Burkholderia cepacia, H. influenza*, and *Campylobacter jejuni* are also reported, but infrequently.

Recently, a high rate of drug-resistant GNB infection has become the major and global concern, including among LT recipients[83,84]. The prevalence of ESBL producing GNB, carbapenem-resistant *K. pneumonia* (CRKP), MDR *Acinetobacter* and MDR *Pseudomonas* are increasing and are related to higher rates of treatment failure[85]. In one study in China, 56% of GNB infections were caused by multi-drug resistant organisms after LT[55]. Borer *et al*[86] reported strikingly high crude mortality rate in patients with CRKP infections compared with the control group (71.9% *vs* 21.9%). In a study of LT recipients, the survival rate was significantly lower in patients with a CRKP infection than in patients without a CRKP infection (29% *vs* 86%, $P < 0.001$)[87]. Multivariate analysis showed that the only pre- and post-LT clinical variables significantly associated with death were a MELD score > 30 (HR = 3.4, $P = 0.04$) and a post-LT CRKP infection (HR = 4.9, $P = 0.007$)[87]. Also, fatal cross infection by CRKP in LT recipients was reported[88]. However, in one report, Varghese *et al*[22,89] described a low mortality rate (1 of 10 patients) associated with CRKP infection. The reasons for the differences in mortality between the centers is unknown, but might result from study designs, overall severity of the illness and underlying demographic characteristics[89].

The presence of ESBL producing GNB is worldwide; however, the prevalence of infection is quite variable[85]. One of the largest transplant centers reported six (67%) of nine LT candidates were colonized with ESBL producing GNB[90]. Others reported that ESBL producing GNB comprised 43.3% of GNB in LT and kidney transplant recipients, and the common types of MDR-GNB were TEM and CTX-M[51]. Risk factors for MDR-GNB were the extended use of pre-transplant broad-spectrum antibiotics and prolonged endotracheal intubation[55]. Additional risk factors for MDR-GNB infections include post-transplantation renal dysfunction, prolonged pre-transplantation hospitalization, antibiotic exposure, surgical complications and the need for invasive devices[55]. Infections and carriage of MDR-GNB are associated with higher rates of allograft failure and mortality[91]. The administration of inadequate antibiotic treatment is significantly related to increased mortality[56,92]. Thus, the center specificity result in different mortality rates in patients with MDR-GNB infections, early diagnosis, proper treatment, environmental infection control, and judicious use of antibiotics are crucial to improve survival.

Gram-positive bacteria

GPB are a main cause of superficial and deep SSIs, bacteremias and pneumonia, predominantly during the first 2 mo after LT[2]. Common GPB include staphylococci, streptococci and enterococci. GPB are traditionally common causes of early post-transplant SSI and bloodstream

infections; however, the reported frequencies of these infections differ between countries and between centers[8,93]. Kawecki *et al*[34] reported GPB were 78% of infection, and the percentage of methicillin-resistant coagulase negative staphylococci (MRCNS) was 42% and the high-level aminoglycoside-resistant enterococci was 24.3%[34]. Although GNB infections are increasing in some centers[5,43], the MRSA and vancomycin-resistant enterococci (VRE) remain threats in LT recipients[47,94]. The rate of VRE colonization and infection is highly variable and center-specific[95]. Gearhart *et al*[96] demonstrated that LT patients in the VRE group had lower survival than those in the non-VRE group (52% *vs* 82%, $P = 0.048$); prior antibiotic use, multiple abdominal surgeries, and biliary complications were associated with acquisition of VRE. Linezolid is used to treat VRE disease. Herrero *et al*[97] reported nosocomial spread of linezolid resistant VRE. The emergence of linezolid-resistant, vancomycin-resistant *E. faecium* is of great concern, not only in LT patients, but also in public health. Prudent use of linezolid is crucial[97].

The incidence of MRSA is continuously increasing and still causes a significant proportion of bloodstream infections. A multicenter study in Spain reported that MRSA bacteremia was an independent risk factor for mortality among bacteremia patients[47]. However, Malinis *et al*[98] reported that solid organ transplant recipients had an unusually lower *S. aureus* bacteremia incidence rate and mortality rate than non-transplant patients; this difference might result from early antibiotic treatment, the involvement of infectious disease physicians and the effects of immunomodulatory therapies. There has been great concern about community-acquired MRSA (CA-MRSA)[99]. The incidence is not clear in transplant recipients, but there was a report of fatal CA-MRSA infection by transmission from a donor[100]. The prevalence of vancomycin-intermediate *S. aureus* (VISA) and heterogeneous or heteroresistant VISA (hVISA) is reported to be increasing worldwide, with regional differences[99]. In one study in France, Bert *et al*[101] reported that 13 (27%) of the 48 LT recipients had heterogeneous glycopeptide-intermediate *S. aureus* over a 5-year period. Only two of 13 patients had history of previous glycopeptide therapy and the prevalence was considered the effect of clonal spread of a multiresistant strain[101].

PROPHYLAXIS AND PREVENTION

Certain bacterial infections are preventable with appropriate prevention strategies, which can be divided into three phases; pre-transplant, intra-operative and post-transplant. During the pre-transplant period, pre-existing infections in the recipients should be controlled before transplantation. Sepsis and pneumonia are considered absolute contraindications for liver transplantation[102]. Emergent situations may arise in which it may not be possible to clear the infection before a life-saving transplant. However, no consensus has been reached on the recommended optimal therapy duration or interval between the infection resolution and transplantation[13]. Donor-derived infections have been widely discussed, and there have been reports about bacterial transmission via transplantation. Bacterial infection screening should be performed in both living and deceased donors[103]. However, there are limitations on the evaluations and elapsed time between the test and results in cases of emergency surgeries with deceased donors. Communication between surgeons and the organ procurement organization is vital when evaluating the risk of infection. Perioperative antibiotics use within 48 h is a widely adopted protocol for preventing bacterial infection. Prophylactic antibiotic regimens can yield different bacterial infection rates[8]. Selective bowel decontamination regimens with non-absorbable antibiotics have been studied. Some reported reduced infection[104,105], whereas others showed no benefit[106]. Selective decontamination was associated with gastrointestinal intolerance and patient noncompliance[105]. A randomized trial that compared fiber and lactobacillus supplementation with selective bowel decontamination showed a reduced rate of infections in patients who received supplementation[107]. Rifaximin, a poorly absorbable form of rifamycin, was studied to determine whether it could reduce early post-transplant enteric GNB infections in severely ill recipients[108]. A significantly lower incidence of infection within 90 d after transplant was observed[108]. However, many interventions, such as selective bowel decontamination, active lactobacillus with fibers, inactivated lactobacillus with fibers or different doses of granulocyte-colony stimulating factor, did not provide significant benefits in the reduction of bacterial infections and wound complications in meta-analysis[109].

It is certain that elimination of known risk factors, such as early removal of unnecessary central venous catheter, is crucial. During the intra-operative and post-transplant periods, aforementioned controllable risk factors should be minimized to prevent infections. Perioperative antibiotics need to be selected according to institutional antimicrobial susceptibility patterns. No clear data are available regarding benefits of modifying perioperative antibiotics to donor cultures in liver transplantation.

CONCLUSION

Bacterial infections are the major targets to overcome during the first 2 mo after transplantation. In this period, controllable factors such as renal function preservation, minimizing biliary complications, glucose control, preserving renal function, adequate management of portal vein thrombosis, preventing acute rejection, effective respiratory toilet and early removal of unnecessary catheters should be applied. Patients need to be monitored closely to detect any subtle signs and symptoms of infection, as the markers of infection, such as fever, may be lacking in LT recipients because of underlying liver disease and immunosuppression. Transplant surgeons and physicians should communicate with infectious disease specialists, microbiologists, intensive care specialists, infection control specialists and epidemiologists who are members of the transplant team. Individualized center-

specific strategies for the prevention and treatment of bacterial infections in LT must be implemented, based on patient's risk factors, operative factors, nosocomial environments, local microbiologic epidemiology, center specific antimicrobial sensitivity and evidence-based medicine.

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