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Review

Bacterial Infections after Liver Transplantation: Updates in Post-Surgical Infections, Vancomycin-Resistant Enterococcus, and Multi-Drug Resistant Enterobacteriaceae

Masayuki Nigo *, Rodrigo Hasbun, Karen J Vigil

Division of Infectious Diseases, Department of Internal Medicine, UTHealth McGovern Medical School, Houston, Texas, USA; E-Mails: Masayuki.Nigo@uth.tmc.edu; Rodrigo.Hasbun@uth.tmc.edu; Karen.J.Vigil@uth.tmc.edu

* **Correspondence:** Masayuki Nigo; E-Mail: Masayuki.Nigo@uth.tmc.edu

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Abstract

Liver transplantation is a life-saving procedure available worldwide. Despite advances in its surgical and immunosuppressive strategies, infectious complications carry significant morbidity and mortality. Bacterial infections are the most common infective etiologies, and the majority are seen during the first four weeks post liver transplantation. Infectious complications are often intra-abdominal in origin, such as biliary complications and abdominal abscesses. Infections due to multi-drug resistant organisms are emerging threats in this population. This article summarizes bacterial infections with special emphasis on post-surgical infections, including biliary tract infections and liver abscesses, and multi-drug resistant pathogens frequently problematic in liver transplant recipients, such as vancomycin-resistant enterococci and multi-drug resistant Enterobacteriaceae.

Keywords

Bacterial infection; multi-drug resistant organisms; liver transplantation

1. Introduction

Since 1963, when the first liver transplantation was successfully performed, this life-saving procedure has been widely available in many countries [1]. Despite its advances in technique and immunosuppressive strategies, post-liver transplant Infectious complications pose high morbidity and mortality [2-4]. Due to the complexity of its unique procedure and long operative time, immunocompromised status, metabolic abnormalities, and patient's poor nutrition status and coagulopathy, liver transplant (LT) recipients have higher rates of infectious complications compared to heart and renal transplant recipients [5]. The rate of infectious complications reaches up to 83%, being the vast majority of bacterial infections followed by fungal and viral infections [6-10]. The use of prophylaxis against cytomegalovirus and fungal infections has also contributed to the increase in the proportion of bacterial infections compared to other infectious etiologies [6, 11].

The majority of infectious complications occur within four weeks after LT and are usually nosocomial or originate from the patient's own flora [10]. Donor-derived infections may also occur during this period [12]. During the next post-LT period, which comprises the second to sixth months after the transplant, opportunistic infections might occur, depending on the patients' risk and the intensity of immunosuppression. Six months after LT, bacterial infections are usually related to environmental exposures and late biliary complications [13].

There have been several review articles discussing bacterial infections in LT recipients [14-19]. In order to avoid redundancy, we will review bacterial infections with special emphasis on post-surgical infections, (e.g. biliary tract infections and liver abscesses), and multi-drug resistant pathogens frequently problematic in LT recipients, such as vancomycin-resistant *Enterococcus* (VRE) and multi-drug resistant (MDR) Enterobacteriaceae.

2. Post-Surgical Infections among Liver Transplant Recipients

During the first four weeks post-LT period, the most common infectious complications are related to post-surgical infections, including superficial infections, hepatobiliary tract infections, peritonitis, and liver/extra-hepatic abscesses [7, 8, 20-22]. These severe infections often lead to bloodstream infections resulting in high mortality in this vulnerable population [23, 24]. Moreno et al evaluated a total of 3926 solid organ and hematopoietic stem cell transplant recipients in Spain and revealed that LT patients with bloodstream infections (BSIs) carried approximately three-fold higher mortality risk compared to kidney/heart transplant recipients with BSIs. The common source of bacteremia among overall transplant recipients was catheter-related, followed by intra-abdominal origin, which was almost exclusively seen in LT recipients [3].

Many studies have explored the risk factors for postsurgical infections among LT patients. Table 1 summarizes the risk factors from selected studies. Most of the studies have significant limitations due to the retrospective study design, small sample size, and the failure to effectively control all possible confounding factors in this complicated population [25-29]. A Brazilian study gathering 561 LT patients over a 9-year period (2002-2011) revealed that re-transplantation, the transfusion of more than two units of blood during the operation, hemodialysis, long cold

ischemia time (more than 400 minutes) and CMV infection were independent risk factors for 60 days surgical site infections. No information regarding the site of infection was provided in this study [20]. LT often requires multiple doses of surgical antibiotics prophylaxis for the prolonged operative time [30]. Pre-existing coagulopathy often leads to heavy intraoperative bleeding which necessitates a large number of transfusions and may result in intra-abdominal hematomas susceptible to bacterial seeding. In addition, living donor liver transplant (LDLT) differs from deceased LT due to the unique procedure, which increases the risk for post-operative infections. The small-for-size donor grafts may lead to postoperative liver dysfunction with prolonged cholestasis and coagulopathy (known as smaller for size liver syndrome). Biliary leakage from the cut surface of the graft may subsequently lead to biloma formation and secondary infections. The surgical procedure for LDLT is technically more challenging and contributes to the higher incidence of complications such as biliary strictures [10, 31, 32]. Human immunodeficiency virus (HIV)-infected patients recently became considered as LT candidates. Several studies revealed LT recipients with HIV has similar overall mortality and graft loss especially in a modern era of potent antiretroviral treatment, compared to non-HIV infected recipients [33, 34]. Of note, co-infection with hepatitis C has higher mortality and poor graft survival in this population [35]. Among 109 consecutive HIV infected LT recipients between 1999 and 2010, forty patients (37%) experienced at least one infection during the first year post-transplant, and the majority were bacterial infections [36]. Only four patients developed HIV related opportunistic infections with two candida esophagitis, one tuberculous lymphadenopathy, and one disseminated *Mycobacterium avium* infection.

Table 1 Larger Studies of Risk Factors for Infection after Liver Transplant

Type of study, Periods, and country	Risk factors	Comments	Ref.
Retrospective Jan 2002 to Dec 2011 Brazil	Retransplantation Transfusion>2 units of blood during the procedure Hemodialysis Cold ischemia for > 400 minutes CMV	543 patients were included. No detail information of SSI was provided.	[20]
Prospective Aug 2003 to Sep 2005 Spain	Choledochojejunal or hepatojejunal Reconstruction Previous history of liver/kidney transplant More than four RBC transfusions	1222 patients from the Spain Registry. Only 8.8 % SSI; lower than other studies.	[30]
Retrospective Jan, 1999 to Dec, 2008 United States	MELD score >30 ICU stay >48 h prior to transplant Intraoperative transfusion ≥15 units Retransplantation Post-transplant dialysis Reoperation.	227 consecutive LT patients. Small number of biliary tract infections (1.7 %) and intra-abdominal infections (2.5%). Majority were bacteremia (7%), and pneumonia (3%).	[37]

SSI, Surgical site infection, RBC, Red blood cell, ICU, Intensive care units

2.1 Biliary Tract Infections and Cholangitis

The biliary tract is the "Achilles' heel" of liver transplantation [38, 39]. Despite the improvement in surgical techniques, biliary complications following LT remain a major cause of infection with an overall incidence of 5 – 25% [40-42]. Those complications are related to biliary strictures, leaks, stones or debris, and sphincter of Oddi dysfunction.

The type of biliary anastomosis during transplant is a well-known important factor associated with biliary complications. Two major types of anastomosis have been widely used; anastomosis of the biliary duct to a Roux-en-Y loop of the jejunum (choledochojejunostomy) and duct-to-duct anastomosis (choledochocholedochostomy). Choledochojejunostomy is generally recommended in patients with pre-existing biliary diseases, such as primary sclerosing cholangitis, prior biliary manipulation or surgeries, and for size mismatch between donor and recipient ducts [10, 43]. However, choledochojejunostomy is associated with more intra-abdominal infections, especially fungal infections, compared to choledochocholedochostomy [5]. Opening the jejunum increases the chance of contamination of the surgical field due to enteric organisms with a resultant increased risk of infection [30]. In a previous study, intraoperative surveillance cultures from the peritoneum, fascia, explant, donor liver bile, and jejunal lumen were collected in 77 LT patients. Choledochojejunostomy, previous liver transplantation, and previous hepatobiliary surgery were significantly associated with detection of bacteria from the cultures [44]. Interestingly, four out of 11 patients with positive surveillance cultures developed post-surgical infections within the first two weeks, and none of the patients with negative cultures developed infectious complications. Furthermore, three of the four patients had identical pathogens to the ones found in intraoperative cultures during the transplantation (Enterococci, *Citrobacter*, *Enterobacter*, and *Pseudomonas*). The late postoperative infections, more than three weeks after surgery, differed from the identified pathogen during operation [44]. Moreover, Bubak et al described that five out of six patients who developed sepsis after liver biopsy had choledochojejunostomy for LT [45].

The association between bile leak, cholangitis and T-tube stents for biliary anastomosis is still controversial. Between 15-30% of cadaveric LT recipients with T-tube develop significant biliary complications. However, biliary stenosis frequently develops in patients without T-tube group [46-48]. The recent randomized trial from Spain suggested the selective use of T-tube based on the high incidence of biliary stricture in the patients with the biliary diameter less than 7mm without T-tube as well as the T-tube inherit complications after the removal [48]. In addition to T-tube biliary reconstruction and Roux-en-Y anastomosis, ischemia/reperfusion injury, hepatic artery thrombosis (HAT), CMV infection and primary sclerosing cholangitis are also implicated risk factors for biliary complications [49].

2.2 Bile Leaks and Infected Biloma

Bile leaks have an incidence of 2 – 25% in post-LT, which is especially emphasized in living donor liver transplantation [43, 50]. Those are divided into two categories, early (within 4 weeks transplant) and late [51]. Early postoperative bile leaks are often due to ischemia from hepatic artery anastomosis, bleeding from the cut end of the bile ducts, and excessive tension on the ductal anastomosis. Late bile leaks are often related to elective or inadvertent removal of the T-tube.

Bilomas arise when bile ducts rupture into the intrahepatic parenchyma or free abdominal cavity due to bile duct necrosis, stricture or leaks, and result in intrahepatic or peri-hepatic bilious fluid collections. Most bilomas encountered in LT are outside the liver and usually in the perihepatic spaces [51]. In a study evaluating 492 orthotropic liver transplants (OLT) recipients between 1994 and 2001, a total of 57 patients (11.5%) developed bilomas. Patients presented with fever (44%) and abdominal pain (40%). 28% of patients were diagnosed with bilomas within four weeks after transplantation. However, 14% were detected more than one year after transplantation. Risk factors were evaluated among 51 (12%) patients with infected bilomas; HAT (Odds ratio: OR 91), hepatic artery stenosis (OR 13), and Roux-en Y reconstruction (OR 6) were found to be independently associated [52]. Safdar et al also described their experience of infected bilomas in 57 patients in Wisconsin. The most common pathogens were enterococci (37%) with a high incidence of vancomycin-resistant enterococci (VRE) (48% of enterococci cases), followed by coagulase-negative *Staphylococcus* (26%) and *Candida* species (26%). Furthermore, one or more new "superinfecting" pathogens were later detected in 95% of cases. There was complete resolution in 35 (61%) patients, 12 (21%) patients required re-transplantation and 20 (35 %) patients died. All patients underwent early diagnostic percutaneous aspiration and received more than four weeks of antimicrobial therapy [52]. In the absence of re-transplantation, the optimal duration of antimicrobial therapy is unknown, but a prolonged antibiotic duration is almost often required [51].

2.3 Liver Abscess

Liver abscesses post-LT are a rare but life-threatening complication [53]. It often occurs four weeks after transplantation and is frequently associated with the HAT [54, 55]. In a retrospective study of 2,175 SOT patients from 1990 to 2000, 12 episodes of liver abscesses occurred in 10 (2.2%) out of 459 LT patients [55]. Of note, eight out of 12 episodes were accompanied with HAT (overall cases of HAT were 13), which was preceded by hepatic abscesses in four cases [55]. Stange et al. evaluated 30 patients (2.5%) who developed HAT among 1,250 LT recipients in Germany. One-third of HAT patients developed a liver abscess, and 50% of patients required re-transplantation [56]. In an Iranian study of five cases of liver abscess among 560 LT recipients; three out of five patients had a bile duct anastomosis stricture (60%). Solitary abscess was seen in 60% of cases and was exclusively located in the right lobe [53]. The management of abscesses includes both surgical interventions to correct the underlying process as well as antimicrobial therapy. The patient often requires multiple drainages and prolonged antimicrobial therapy. "Superinfection" is a common complication [55].

3. Multi-Drug Resistant Organisms (MDROs)

Prolonged waiting time and repeated and unavoidable exposures to both healthcare facility and antibiotics contribute increased risk for both colonization and infections due to MDROs. The rate of MDR bacteria and its species depend on the geographical locations or even facilities. For instance, in Spain, there is a higher rate of MDR gram-negative pathogens (*Acinetobacter* 8/11, *Pseudomonas* 26/35), but less MDR rate in gram positives (MRSA 5/13 and VRE 0/16) [57, 58]. A trend shifting from gram-positive bacteria towards gram-negative pathogens has been observed in the U.S. study over several decades, after a previous global surge of *S. aureus* infections in the

1990s [11, 15, 59]. Routine prophylaxis for spontaneous bacterial peritonitis with quinolones might have contributed to this trend. More recently, MDROs are an emerging threat among the LT population. Carbapenem-resistant organisms have been reported in pre and post LT population [24]. A prospective study from Brazil demonstrated that 18% of patients were colonized with carbapenem-resistant Enterobacteriaceae (CRE), and those patients had a higher incidence of CRE infections after transplant [60].

3.1 Vancomycin-Resistant Enterococcus (VRE)

Since VRE was first recognized in the 1980s after the introduction of cephalosporins, the prevalence has steadily increased. In the last 10 years, the prevalence of VRE among enterococcal bloodstream isolates in the United States was 27.8% [61, 62]. Although *Enterococcus faecium* comprises only 10-20% of overall enterococcal infections, it is frequently identified as vancomycin-resistant; moreover, 80.7% of all bloodstream E. faecium isolates in the US were resistant to vancomycin in 2010 [62]. VRE colonization often persists for months to years, and precede its invasive infections [63-65]. A meta-analysis estimated the prevalence of VRE colonization to be 15.6% among LT population in the U.S. and the colonized recipients carried 6.7 times higher risk of VRE infections in post-LT [66]. VRE infections among LT recipients increase mortality up to nearly 60% [67, 68]. Due to its intrinsic resistance and tolerance against antimicrobials, the therapeutic options are significantly limited and left significant challenges in its treatment.

Daptomycin (DAP) is a cyclic antimicrobial lipopeptide targeting the cell membrane in a calcium-dependent fashion. It is one of the few antibiotics exhibiting in vitro bactericidal activity against VRE. However, recent studies suggested that enterococci harboring higher DAP MIC (3-4 mcg/mL, CLSI breakpoint for susceptible is 4 mcg/mL) may already have a single mutation which abolishes its bactericidal activity [69]. This finding is further supported by another retrospective study where DAP MICs of 3-4 mcg/mL, and immunosuppression were associated with microbiologic failure [70]. An in vitro study comparing DAP (6, 8, 10, and 12 mg/kg/day) against VRE in a pharmacokinetic model demonstrated that 12mg/kg/day was required to sustain bactericidal activity and prevent the emergence of DAP-nonsusceptible strains [71]. In order to overcome these problems, two strategies have often used. First is the use of a higher dose of DAP of 8 – 12 mg/kg/day, as opposed to the FDA, approved dosage of DAP (6 mg/kg for skin soft tissue infections). The efficacy of high-dose DAP therapy against VRE bacteremia was supported by several retrospective studies, and no significant safety concerns, such as CPK elevation, was observed [72, 73]. The second approach to enhance its efficacy is to use combination therapy with ampicillin or ceftaroline [74]. Despite the above strategies, DAP non-susceptible VRE has been an emerging issue, and a recent retrospective study in 14 LT recipients infected with DAP-nonsusceptible enterococci showed 71% of mortality with this recalcitrant pathogen [75].

The oxazolidinones class has two commercially available compounds, linezolid, and tedizolid. Both agents have intravenous and oral formulations. The oral formulations demonstrate great bioavailability in patients tolerating enteral nutrition. Linezolid is a bacteriostatic agent inhibiting protein synthesis by interacting with the A site of bacterial ribosomes. Linezolid is considered to be a valuable antibacterial agent for the treatment of VRE infections [61]. Linezolid has been used as salvage therapy for bacteremic patients with VRE in a small, open-label study with a reported clinical cure rate of 78% [76]. Another study of the compassionate use of linezolid for solid organ

transplant recipients, including 50 liver transplant, showed 63% survival rates in this futile population [77]. It also has good penetration to the biliary tract in post-transplant patients, which has potential benefit in biliary tract infections [78, 79]. Hematologic and neurologic toxicities and lactic acidosis are the major side effects of linezolid as well as serotonin syndrome due to drug interactions. The former toxicities are considered due to mitochondrial toxicity. In LT recipients, a small study of 46 cases did not show significant adverse events related to linezolid, however, the median duration was only 11 days [80]. Tedizolid was FDA approved in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Several favorable advantages over linezolid are (i) its less mitochondrial toxicity that leads to myelosuppression and neuropathy [81], and (ii) its bactericidal profile against enterococci in non-immunocompromised models. However, in Phase III studies (ESTABLISH-1/2) for ABSSSIs, [82, 83] this drug was used only for 6 days; thus, the toxicity of its prolonged use is questioned due to the paucity of clinical data. The efficacy of tedizolid in other sources of infections, such as bacteremia, is scarce [84]. In ten linezolid-resistant *Enterococcus* isolates, tedizolid retained its in vitro activity with an average 4-8 fold lower MICs compared to linezolid [85]. However, in vivo data is lacking.

Quinupristin/dalfopristin (Q/D) is a combination of quinupristin (streptogramin B) and dalfopristin (streptogramin A) that has in vitro bactericidal activity against *E. faecium* through the inhibition of protein synthesis. Importantly, Q/D has no activity against *E. faecalis* (due to intrinsic resistance). The data for its clinical use among LT patients are limited to case series of pediatric LT recipients and 12 adult cases among the case series of VRE infections with a success rate of 74% and 48%, respectively [86, 87]. Additionally, Q/D has three important limitations: (i) its safety and tolerability profile with a high frequency of secondary effects (e.g., phlebitis, arthralgia, and myalgia) often resulting in treatment interruptions; (ii) many *E. faecium* carry the *erm* gene (B) which eliminates the bactericidal activity of Q/D [88]. (iii) In cirrhotic patients, the mean values of the area under the curve of Q/D were approximately 2.8 and 1.5 times higher than in healthy volunteer [89]. In addition, patients with hyperbilirubinemia had significantly higher exposure to quinupristin metabolites (up to a four-fold increase in AUC) due to the delayed elimination of the drug [89]. Liver diseases were found to be a possible associated risk factor in 25 out of 50 patients who received Q/D and experienced significant arthralgia [90, 91].

Tigecycline, a glycylcycline derivated from minocycline, but with a functional group substitution, has broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including VRE. It is FDA approved for the treatment of complicated intra-abdominal infection, complicated skin and soft tissue infections and community-acquired pneumonia. However, there is a significant concern of its serum concentration and its bacteriostatic activity, which is a plausible explanation of high mortality among septic patients, resulting in a black-box warning by the FDA [92]. In addition, phase 3 randomized clinical trials (RCT) comparing tigecycline and imipenem/cilastatin for hospital-acquired pneumonia demonstrated inferiority in tigecycline, mainly driven by the ventilator-associated pneumonia group [93]. In order to achieve higher tissue/serum concentration of tigecycline, a higher dose (200mg IV loading followed by 100 mg every 12 hours) was investigated with improved outcome in VAP, but with higher side effects, especially gastrointestinal [94]. On the other hand, tigecycline achieves high penetration in the biliary tract, making it an ideal option for the treatment of biliary tract infections [95]. However, a recent small study of abdominal transplant recipients (LT:63%, Kidney: 22%) complicated with intra-abdominal

infection (VRE was seen in 70% of cases) had higher mortality in the tigecycline group than the other comparators [96].

Oritavancin is a glycopeptide semisynthetic derivative of chloroeremomycin with the interesting property that it retains activity against VRE. This agent was FDA approved in 2014 for ABSSSIs after SOLO I/II studies demonstrated its non-inferiority to comparators [97, 98]. This compound has in vitro activity against VRE isolates with an additional mechanism against secondary binding sites [99]. This compound could be a theoretical option for the treatment of VRE infections; however, the suitable dosing and clinical data against this pathogen are undetermined.

3.2 Multi-Drug Resistant (MDR) Enterobacteriaceae

The prevalence of MDR gram-negative bacteria infections, including Enterobacteriaceae, has been increasing throughout the world. MDR Enterobacteriaceae infections have been recognized as major threats in the LT population, often leading to inappropriate initial empirical antimicrobial therapy, and carrying a high mortality rate, especially with bloodstream infections (BSIs) [57, 60, 100, 101]. Additionally, LT recipients, compared to kidney and heart transplantation, have a higher incidence of MDR bacteremia [57]. The emergence of carbapenem-resistant Enterobacteriaceae (CRE) infections are becoming a serious health care problem, and, indeed, solid organ transplantation (SOT) was one of the independent risk factors for CRE infection in New York City [102]. The incidence in LT recipients varies widely among transplant centers, ranging from 3% to 23% with an increasing rate in recent studies [60, 100, 103]. Carriage of carbapenem-resistant *Klebsiella* at any point either pre-/post- LT seems the highest risk factor for the infection [104]. Freire et al recently reported 36.8% of LT recipients who were infected or colonized with CRE prior to transplantation developed CRE infections in the post-transplant period [60]. Carbapenem resistance can arise through the production of metallo-beta-lactamase or other mechanisms, such as KPCs or OXA-type carbapenemases. Alternatively, strains may express extended-spectrum beta-lactamases (ESBLs) or AmpC beta-lactamases in conjunction with loss or decreased expression of outer membrane porins. *K. pneumoniae* is one of the major pathogens producing carbapenemase and has spread throughout the world, especially sequence type 258 (ST258). A study from Pittsburg University identified 17 carbapenem-resistant *K. pneumoniae* bacteremic patients, and 80% of them were associated with liver or intestinal transplantation with frequent association with intra-abdominal abscesses. All but one strain of carbapenem-resistant *Klebsiella* spp. were ST258, KPC-2 producing strains [105]. Infections with carbapenem-resistant *Klebsiella* infection or CRE are significant treatment challenges and often lead to a poor outcome, compared to carbapenem susceptible infections [29, 100, 106].

Polymyxin and colistin (polymyxin E) were originally introduced into clinical use in the 1950s. However, due to its significant side effects profile, these antimicrobials were not considered as therapeutic options for decades. As a desperate need for antimicrobial options against highly resistant organisms, the utility of these antimicrobials has been recently revisited. Although there is a little structural difference between those two compounds, a substantial difference of its pharmacokinetics exists. Polymyxin B is administered as an active antibacterial entity, whereas colistin is administered in the form of colistimethate, which requires conversion to colistin after its administration [107]. As colistimethate is mainly excreted through the kidneys and has an

unpredictable rate of conversion to an active molecule, there is a concern in attaining the optimal therapeutic serum concentration of active metabolites. In addition, the optimal dosage of those antibiotics is still undetermined. In order to attain possible synergistic effects, those compounds are often used with a second agent such as carbapenems, even when the MICs are above susceptible range against isolates. Mostardeiro et al evaluated nephrotoxicity among 92 transplant recipients that received polymixins, including eight LT recipients. Nephrotoxicity was reported in 36.2% of patients, and half of them required hemodialysis [108]. Furthermore, in the last years, even these antimicrobials are facing resistance [109, 110].

Tigecycline, as discussed above, has a broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including CRE. Mouloudi et al described case series of LT recipients infected with CRE from various sources. Most of the patients were treated with tigecycline combined with other agents, such as colistin, and high ICU mortality was observed (60%) [111]. In addition, high rate of polymicrobial infection/superinfection with Pseudomonas, intrinsically resistant against tigecycline, was observed and complicated the treatment strategy.

Fosfomycin is also considered as a salvage therapeutic option for CRE, especially in Europe as its intravenous formulation is not commercially available in many countries, including the U.S. Fosfomycin binds to the enzyme UDP-N-acetylglucosamine ennolpyruvyl transferase, inhibiting the formation of N-acetylmuramic acid, resulting in disruption of peptidoglycan assembly [112]. It is a small hydrophilic molecule that achieves high levels of tissue penetration, including the central nervous system. Clinical use of this agent in LT is limited. A single case of a colistin resistant, carbapenem-resistant *Klebsiella* invasive infection in a LT patient was successfully treated with intravenous fosfomycin with other agents [12].

Recently introduced antimicrobial armamentarium for those carbapenem/multi-drug resistant organisms is ceftazidime-avibactam and imipenem-vaborbactam. Those new beta-lactam-beta-lactamase inhibitor combinations overcome beta-lactamase-mediated resistance to beta-lactam antibiotics. Older beta-lactamase inhibitors, such as clavulanic acid, tazobactam, and sulbactam do not inhibit class A carbapenemase [113]. Avibactam has potent activity against KPC, Amp C, and Oxa-48, but not active against metallo-beta-lactamases. Ceftazidime-avibactam was approved by the U.S. FDA in February 2015 for complicated intra-abdominal infection and complicated urinary tract infections. More recently, a phase III study demonstrated its non-inferiority against meropenem in ventilator-associated pneumonia [114]. However, noteworthy is that it is unknown if CRE were included in those studies, and the clinical utility among SOT recipients is yet to be determined. A recent small study evaluating the utility of ceftazidime-avibactam in bacteremic patients with carbapenem-resistant K. pneumoniae revealed better 90 days survival rate in univariate analysis compared to other options, although 30 days mortality did not differ [115]. A study of CRE infections from Pittsburgh showed clinical successes at 30 days were 59% (22/37), and 23% (5/22) of the clinical successes had recurrent CRE infections within 90 days [116]. Furthermore, the recent multicenter prospective observational study revealed a better outcome of 65% in patients with CRE infections treated with ceftazidime-avibactam, compared to the one treated with colistin [117]. A study from MD Anderson in 2015 showed a high rate of isolates harboring metallo-beta-lactamases such as blaNDM (6/11, 55%) [118]. Metallo-beta-lactamases, Ambler Class B, are resistant against new beta-lactamase inhibitors and other beta-lactams, except for aztreonam. However, the isolates harboring MBL are often accompanied with the production of ESBL, which abolishes the activity of aztreonam. With the understanding of the

underlying mechanism of resistance, the intriguing combination of ceftazidime/avibactam and aztreonam has been proposed [119]. The combination of ceftazidime/avibactam with aztreonam demonstrated a synergistic effect against metallo-beta-lactamase producing gram-negative pathogens, and successful use in a few cases [120, 121]. Emerging resistance against avibactam has been reported [122]. A single point mutation in SHV-1 and KPC-2 or various blaKPC-3 mutations conferred avibactam resistance [123, 124]. Vaborbactam is the first boronic acid beta-lactamase inhibitor approved for by FDA in 11/2017. Boronates have a high affinity to serine proteases resulting in a covalent association between the catalytic serine and the boronate moiety. This is a novel mechanism compared to other clinically available beta-lactamase inhibitors [125]. The combination remained its activity in 131/133 (98.5%) clinical KPC-producing Enterobacteriaceae strains from New York City [126].

Plazomicin was newly approved by FDA in 6/2018. This is a semisynthetic aminoglycoside which is designed to avoid enzymatic inactivation by common aminoglycoside-modifying enzymes [127]. This antimicrobial compound has In vitro activity against gram-negative rods and some gram-positive cocci [128]. The data of EPIC trial comparing plazomicin to meropenem in the patients with complicated UTIs due to drug-resistant Enterobacteriaceae revealed its non-inferiority and rapid clearance of bacteria than meropenem [129]. Furthermore, plazomicin was associated with improved survival rates compared to colistin in the patients with carbapenem-resistant Enterobacteriaceae [130]. No specific data are available in liver transplant populations.

Lastly, the management of MDROs is becoming more complex, in which infectious diseases specialists are of an utmost important role in this complicated group of patients. (Table 2 summarize the selected antibiotics for MDROs.) Early infectious diseases consultation has been shown to reduce all-cause mortality [131,132].

4. Conclusion

Bacterial infections have significant morbidity and mortality among the LT population, despite advances in technique and immunosuppressive strategy. Intra-abdominal infections are the main source of post-operative infections, which often requires surgical intervention and prolong antimicrobial therapy. BSIs in LT recipient lead three times higher mortality compared to the ones in other types of transplantation. Due to underlying morbidity and antimicrobial exposures pre and post LT, LT recipients carry a high risk for MDRO infections. VRE and MDR Enterobacteriaceae are often problematic in this population. Despite several new antibiotic armamentaria against those recalcitrant pathogens, better therapeutic options and strategies are still warranted.

Author Contributions

M.N. wrote the manuscript. R.H and K.V. critically reviewed the manuscripts.

Competing Interests

The authors have declared that no competing interests exist.

Table 2 Potential Antimicrobial Options for Multi-Drug Resistant Bacteria

	Antibiotics	**Class**	**Mechanisms of action**	**S/C**	**Spectrum of activity**	**FDA approved indication**	**Key Side effects**	**Biliary penetration**	**Available data in liver transplants**
Gram-Positive Agents	**Daptomycin (DAP)**	Cyclic lipopeptide	Targeting the cell membrane in a calcium-dependent fashion	C	Most of the GPCs, including VRE	- cSSSIs - *S. aureus* BSIs including those with right-sided IE	- Elevation of CPK - Rhabdomyolysis - Acute eosinophilic pneumonia	No specific data for biliary concentration Excreted primarily by the kidneys.	- A case report MRSA endocarditis. [133] - High mortality in infections with DAP nonsusceptible enterococci. [75]
	Linezolid	Oxazolidinones	Binding to the 50S ribosome	S	Most of the GPCs, including VRE	- VREF infections, including BSI - Nosocomial pneumonia - cSSSIs - uSSSIs - CAP	- Neuropathy - Optic neuropathy - Myelosuppression - Thrombocytopenia - Lactic acidosis	The ratio of biliary/serum concentration: 1.3-1.9 [78,79]	- 63% survival rate in multicenter compassionate use for VRE infection.[77] - No adverse events were observed in 46 LT patients. [80]

	Tedizolid		Additional target site: the peptidyl transferase binding region of 23S rRNA in the 50S[83]	C/S[1]	Most of the GPCs, including VRE	- ABSSSI	The same side effects of linezolid But less frequent	Considered biliary excretion, but no specific data for the biliary concentration. [134]	No data
	Q/D	Streptogramins	Dalfopristin: Binding free arms of the peptidyl transferase site in 50S ribosomal subunits Quinupristin: Binding 50S ribosomal subunit	C	Most of the GPCs, except for ***E. faecalis***	- cSSSIs - Serious or life-threatening infections associated with VREF bacteremia	- Dose-dependent infusion-related reaction - Arthralgia/myalgia - Asymptomatic hyperbilirubinemia	Considered biliary excretion, but no specific data for the biliary concentration. [135]	- Pediatric LT cases [86] - Twelve LT cases in a case series.[87]
	Oritavancin	Glycopeptide	Binding to the carboxyl-terminal D-Ala D-Ala as well as depsipeptides, including D-Ala D-Lac residues	C	GPCs, including VRE (in vitro)	- ABSSSI	- Potential concerns for side effects related to glycopeptide. The study showed well tolerance compared to vancomycin.	No specific data for biliary concentration	No data

Both	**Tigecycline**	Glycylcyclines	Binding to bacterial 30S ribosomal subunits	S	GPCs, including VRE, GNRs, and Anaerobes[2]	- cSSSIs - cIAI - CAP	- Nausea/vomiting - Hyperbilirubinemia	The ratio of biliary/serum concentration: 600 – 2000 [95]	- High ICU mortality was observed in a single study. [111]
Gram-Negative Antibiotics	**Polymyxin B**	Polymyxins	Interact electrostatically with phospholipids in the membrane, and disrupt the membranes. Binds to the lipid A portion of cell wall endotoxin or LPS	C	Most of the GNRs, except for ***Proteus* spp**.[3]	- Serious infections caused by *P. aeruginosa*, *H. influenzae*, *E. coli*, *E. aerogenes*, *K pneumoniae*	- Dose-related nephrotoxicity - Reversible neurotoxicity - Paresthesias - Peripheral neuropathy	Possible biliary excretion, but no specific data for the biliary concentration [136]	- A few successful cases in case series. [103]
	Colistin					- Acute or chronic infections due to sensitive strains of certain GNR		No biliary excretion [137]	- A few successful cases. [138]

	Fosfomycin	Fosfomycin	Inhibiting the synthesis of peptidoglycans	C	GPCs & GNRs[4]	Uncomplicated cystitis	Generally, well tolerated GI: diarrhea, and nausea	Less than 0.5% is eliminated by the biliary route.[139]	- A single case report [12]
	Ceftazidime-Avibactam	Beta-lactam plus Non-beta-lactam beta-lactamase inhibitor	Inhibiting KPC, Oxa-48, ESBL, and some AmpC[5]	C	GNRs, including CRE	- cIAI - cUTI	Generally well tolerated	Both antibiotics are mainly excreted by kidneys[140]	- A single case in a case series [116]
	Meropenem-Vaborbactam	Beta-lactam plus Boronic acid beta-lactamase inhibitor	Inhibiting KPC and ESBL[6]	U[7]	GNRs, including CRE	- cUTI	Generally well tolerated	Both antibiotics are mainly excreted by kidneys [141]	No data
	Plazomicin	Aminoglycosides	Binding to the bacterial ribosome	C	GNRs, including CRE	- cUTI	Nephrotoxicity Ototoxicity Neuromuscular toxicity	97.5% of the dose was recovered from Urine [142]	No data

1. Some animal models suggest bactericidal activity in vivo. [143]
2. Less active against P. aeruginosa, Proteus spp., Providencia spp., and Morganella spp.
3. Poor activities against Serratia spp., Providencia spp., and Morganella spp.
4. Less active against Pseudomonas spp., Morganella morganii, Acinetobacter spp. Enterobacter spp. Proteus vulgaris, Providencia spp. and Serratia spp.
5. Avibactam is a potent inhibitor of class A carbapenemase (e.g. KPC), class C and some class D beta-lactamases (e.g. Oxa-48). [144, 145] However, class B carbapenemases are not inhibited.
6. Vaborbactam is a potent inhibitor of class A carbapenemase (e.g. KPC) and other class A (CTX-M, SHV, TEM) and class C beta-lactamases. However, class B and D carbapenemases are not inhibited. [146]
7. Meropenem exhibits bactericidal activity against susceptible isolates. [147] However, no data were found with the combination, especially against meropenem resistant strains.

C, Bactericidal, S, Bacteriostatic, U, Unknown, cSSSIs, Complicated skin and skin structure infections, uSSSIs, Uncomplicated skin and skin structure infections, BSIs, Bloodstream infections, cIAI, Complicated intra-abdominal infection, IE, Infective endocarditis, cUTI, Complicated UTI, Vancomycin-resistant Enterococcus faecium (VREF), CAP, Community-acquired pneumonia, CRE, Carbapenem-resistant Enterobacteriaceae, D-Ala D-Ala ,D-acyl-d-alanyl-d-alanine, D-Ala D-Lac, d-alanyl-d-lactate residues, Q/D, Quinupristin/dalfopristin

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