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TOPIC HIGHLIGHT

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Multidrug-resistant bacterial infections after liver transplantation: An ever-growing challenge

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Abstract

Bacterial infections are a leading cause of morbidity and mortality among solid organ transplant recipients. Over the last two decades, various multidrug-resistant (MDR) pathogens have emerged as relevant causes of infection in this population. Although this fact reflects the spread of MDR pathogens in health care facilities worldwide, several factors relating to the care of transplant donor candidates and recipients render these patients particularly prone to the acquisition of MDR bacteria and increase the likelihood of MDR infectious outbreaks in transplant units. The awareness of this high vulnerability of transplant recipients to infection leads to the more frequent use of broad-spectrum empiric antibiotic therapy, which further contributes to the selection of drug resistance. This vicious cycle is difficult to avoid and leads to a scenario of increased complexity and narrowed therapeutic options. Infection by MDR pathogens is more frequently associated with a failure to start appropriate empiric antimicrobial therapy. The lack of appropriate treatment may contribute to the high mortality occurring in transplant recipients with MDR infections. Furthermore, high therapeutic failure rates have been observed in patients infected with extensively-resistant pathogens, such as carbapenem-resistant *Enterobacteriaceae*, for which optimal treatment remains undefined. In such a context, the careful implementation of preventive strategies is of utmost importance to minimize the negative impact that MDR infections may have on the outcome of liver transplant recipients. This article reviews the current literature regarding the incidence and outcome of MDR infections in liver transplant recipients, and summarizes current preventive and therapeutic recommendations.

Key words: Multidrug resistance; Bacterial infections; Organ transplantation; Methicillin-resistant *Staphylococcus aureus*; Liver transplantation

Core tip: Infections caused by multidrug-resistant bacteria have been a growing cause of concern for those involved in the care of solid organ transplant recipients all over the world. The emergence of various pathogens with extensive antibiotic resistance creates a challenging scenario. This article presents an overview of the available epidemiological and clinical data on the most common multidrug-resistant bacterial infections among liver transplant recipients. Currently recommended therapeutic and preventive interventions are also summarized.

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INTRODUCTION

Bacterial infections are a leading cause of morbidity and mortality in patients receiving solid organ transplants (SOT)[1-3]. Although infections can occur at any time after transplantation[4], their incidence is highest in the first postoperative month[2,3] due to factors such as clinical severity of the underlying illness at the time of transplantation, breaches in the muco-cutaneous barrier resulting from surgery and the use of different invasive devices, technical complications of the surgery and immunosuppression. Studies specifically addressing the risk after liver transplantation have associated the incidence of bacterial infections with age, length of preoperative hospital stay, duration of surgery, retransplantation, volume of transfused blood products, bilioenteric anastomosis, technical complications such as biliary leakage and hepatic artery thrombosis, reoperation, length of intensive care unit (ICU) stay, hyperglycemia, preoperative Child-Pugh and model for end-stage liver disease (MELD) scores, dialysis, graft dysfunction and cytomegalovirus infection[2,5-13].

Over the last two decades, a succession of various multidrug-resistant (MDR) pathogens causing relevant morbidity and mortality among transplant recipients has emerged[14-23]. This fact reflects the emergence and spread of MDR bacteria in health care facilities all over the world, especially among patients admitted to the ICU. Nevertheless, several studies have suggested that SOT recipients are particularly prone to MDR bacterial infections[20,24-30]. The early postoperative care of transplant recipients is associated with the frequent manipulation of the patients and use of invasive devices, factors which increase the probability for cross-transmission of MDR pathogens[26,28,29,31-37]. Additionally, the awareness of this high vulnerability leads to the frequent use of empiric broad-spectrum antibiotic therapy[14,19,38], which further contributes to the selection of drug-resistant pathogens. This vicious cycle is difficult to avoid and leads to a scenario of increased complexity and narrowed therapeutic options.

Preoperative factors also influence the risk of post-transplantation MDR infections. Pre-transplant colonization with MDR bacteria occurs with variable frequency in liver transplant candidates and contributes to a higher risk of postoperative infection[39-42]. Pre-transplant colonization likely results from frequent hospital admissions and antibiotic usage in patients with high pre-transplant clinical severity, factors that have also been associated with increased incidence of post-transplant MDR infections[39,43-45]. The colonized transplant candidate may thus become the dissemination source of MDR pathogens for other patients, a fact that must be considered when designing routines for the control of MDR bacterial infections in transplant units[25].

Occasionally, the source of transmitted MDR organisms is the transplanted graft[46-48]. Published data indicate that the transmission of bacterial infection from donor to recipient is an uncommon event provided that the recipient receives appropriate antibiotic prophylaxis. However, the emergence and dissemination of extensively drug-resistant or pandrug-resistant bacteria, for which the optimal therapy has not been established or is not available, may increase the risk for donor-transmitted bacterial infections and may negatively affect graft and recipient survival.

Infections with MDR bacteria have been associated with high mortality rates among transplant recipients[15,16,49-54]. In general, the outcome of bacterial infections in these patients is influenced by the net state of immunosuppression and the clinical severity at the time of infection. Additional factors may also negatively impact the outcome of MDR infections. Failure to start appropriate empiric antimicrobial therapy occurs more frequently in these cases and may contribute to the higher mortality rate[52,54]. Furthermore, high therapeutic failure rates have also been observed in patients with infections caused by extensively resistant pathogens[55], such as carbapenem-resistant *Acinetobacter baumannii* and *Enterobacteriaceae*, for which optimal treatment is still undefined[15,16].

MAIN MDR INFECTIONS AFTER LIVER TRANSPLANTATION

Methicillin-resistant Staphylococcus aureus

Numerous studies from various centers have demonstrated a high prevalence of methicillin resistance in *Staphylococcus aureus* (*S. aureus*) isolates from infections of liver transplant recipients[2,21,22,41,56]. The most common sources of infections are catheter-related bloodstream infections, surgical wounds, the intra-abdominal space and lungs[22,57]. Most methicillin-resistant *Staphylococcus aureus* (MRSA) infections are diagnosed within 30 d after liver transplantation[21], with preoperative colonization as the most consistently reported risk factor[21,40-42,58]. Postoperative colonization has been found to occur in 6.7%-22% of recipients[40,59,60] and is associated with subsequent infection[61]. Other risk factors include a long operation time (> 16 h), preoperative use of antibiotics and postoperative apheresis[21], cytomegalovirus primary infection or seronegativity[22], recent surgery (within the previous two weeks)[56], alcoholic cirrhosis and a decreased prothrombin ratio[41]. Studies assessing the impact of methicillin resistance in liver transplant patients showed no significant association with survival[40,45,57]. However, there were trends for shorter survival in patients with MRSA in two of these studies in which the lack of significant association may have resulted from inadequate statistical power[45,57].

Vancomycin is the primary treatment for severe MRSA infections[62]. Teicoplanin is another glycopeptide with a similar spectrum of activity. Results of a meta-analysis of 24 clinical trials suggest that while teicoplanin and vancomycin have comparable efficacies, teicoplanin is associated with a lower incidence of adverse events, such as nephrotoxicity[63]. Nevertheless, among patients with endocarditis, a higher rate of therapeutic failure was reported with teicoplanin, despite adequate plasma

levels[64]. Due to the higher risk of therapeutic failure, an alternative antimicrobial therapy should be used when the minimum inhibitory concentration (MIC) is ⩾ 1.5 μg/mL for vancomycin, or ⩾ 2.0 μg/mL for teicoplanin[65-67]. Daptomycin is a bactericidal drug that has been approved for the treatment of MRSA bacteremia, right-sided endocarditis and complicated skin and soft tissue infections[62], though it is not recommended for the treatment of pneumonia as it is inactivated by the lung surfactant. Linezolid, a synthetic oxazolidinone that has bacteriostatic activity against *S. aureus*, has also been recommended for skin and soft tissue infections and pneumonia caused by MRSA[62]. Results of a clinical trial suggest that linezolid may have a higher efficacy than vancomycin for the treatment of MRSA pneumonia[68]. Quinupristin-dalfopristin, a combination of two streptogramins, has been recommended for the treatment of complicated skin and soft tissue infections. Its use has been limited by the frequent occurrence of adverse events such as severe arthralgia, myalgia, nausea and infusion related reactions. Other therapeutic options that may be used in patients with skin and soft tissue infections caused by MRSA include tigecycline, doxycycline, minocycline, telavancin, clindamycin and co-trimoxazole. The latter two agents may be also used for the treatment of osteoarticular infections. Rifampicin can be used in combination with other anti-staphylococcal agents for the treatment of infections associated with prosthetic devices. Interaction of rifampicin with calcineurin inhibitors and sirolimus results in reduction of the serum concentrations of these immunosuppressive drugs, necessitating close monitoring of blood levels[69].

Vancomycin-resistant enterococci

The incidence of vancomycin-resistant enterococci (VRE) infections varies widely among centers. Most infections occur within two months of a liver transplantation and the predominant sites of VRE isolation are the blood, peritoneal fluid, bile and urine[49]. Similar to what has been described for MRSA, patients colonized with VRE are at a high risk for infection[70]. The prevalence of preoperative VRE colonization in liver transplant candidates ranges from 0% to 18%[70-73], with postoperative colonization rates as high as 14%-44%[40,70,73]. Once acquired, colonization may persist for months to years[74,75]. The factors most consistently associated with VRE infections include complications or procedures related to the biliary tract[49-51,76], as well as surgical re-exploration, longer hospital stays and prior antibiotic use[23,49,76].

There are limited therapeutic options for VRE infection. High doses of ampicillin should be used in cases with documented *in vitro* susceptibility. Although ampicillin susceptibility is an uncommon feature for *Enterococcus faecium* (*E. faecium*), it is frequently found in vancomycin-resistant *Enterococcus faecalis* (*E. faecalis*) isolates. Linezolid, which has bacteriostatic activity against *E. faecalis* and *E. faecium*, can be used to treat infections caused by vancomycin-resistant strains of both species. However, resistance to linezolid has been described in up to 20% of VRE isolates[77]. Daptomycin has *in vitro* bactericidal activity against enterococci, though its clinical effectiveness has not been established. In two retrospective studies, daptomycin and linezolid had comparable clinical and microbiological cure rates[78,79]. Quinupristin-dalfopristin has bacteriostatic activity restricted to *E. faecium* isolates and thus, cannot be used to treat infections caused by other enterococcal species. Interactions of these streptogramins with calcineurin inhibitors and mTOR inhibitors can result in increased levels in the blood. Tigecycline may be an option for the treatment of clinically stable, non-bacteremic patients with abdominal and skin and soft tissue infections. VRE infection has been associated with higher mortality of liver transplant recipients[49-51]. This finding may possibly reflect the lower effectiveness of the therapeutic options used in older studies. Nevertheless, in a case series of organ transplant recipients treated with linezolid, mortality associated with VRE infection was still approximately 40%[80].

Extended-spectrum beta-lactamase-producing Enterobacteriaceae

Several studies have reported a high prevalence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLE) isolates in infections from SOT recipients[81-83]. In such cases, the most commonly isolated ESBL-producing species are *Klebsiella pneumoniae* and *Escherichia coli*. The incidence of ESBLE infection is higher in renal transplant recipients in whom they are important etiologic agents for urinary tract infection[83]. Nevertheless, ESBLE infection is not unusual among liver transplant recipients, with reported incidences of 5.5%-7%[39,83]. In addition, preoperative fecal carriage, reoperation and a MELD score > 25 have been associated with a higher risk for infection with these MDR organisms[39].

Several studies examining the outcome of ESBLE infection among SOT recipients report mortality rates ranging from 5% to 20%[28,83,84]. However, these studies included a large proportion of non-bacteremic patients with urinary tract infections. A preliminary analysis carried out at our center (unpublished data) has shown that the 30-d mortality rate of liver transplant recipients with bacteremia caused by ESBLE was 41%, similar to what has been described in other groups of patients[85,86].

Carbapenems are the most reliable class of drugs for the treatment of ESBLE infections. Of this class, imipenem and meropenem are the most clinically utilized[87]. Limited clinical data suggest that the efficacy of doripenem is similar to that observed with the former two drugs[88]. Accordingly, the results of a few studies suggest that ertapenem, in cases with proven susceptibility, has comparable effectiveness[89,90]. However, as a considerable proportion of ESBLE show resistance to ertapenem[91], it is not considered a reliable first-line therapeutic option for patients who present with severe sepsis. Cefepime and piperacillin-tazobactam are associated with a higher probability for clinical failure even when *in vitro* susceptibility is documented[87,92]. Thus, these drugs should be

considered as an alternative treatment only to patients who are not severely ill, especially when the primary site of infection is the urinary tract[93]. There are few reports of the effectiveness of other drugs, such as aminoglycosides and quinolones, for the treatment of ESBLE infections.

MDR Pseudomonas aeruginosa

A reported 18% of nosocomial pneumonia cases following liver transplantation are caused by *MDR Pseudomonas aeruginosa* (*P. aeruginosa*)[94]. Furthermore, MDR *P. aeruginosa* has been isolated in up to 9% of bloodstream infections in liver transplant patients[14,43]. Studies on specific risk factors for MDR *P. aeruginosa* among liver transplant recipients are not available. Bloodstream MDR *P. aeruginosa* infections were found to be more frequent in subjects who had hospital-acquired bacteremia or who had been admitted to an ICU in the previous year in a study population in which half of the analyzed SOT recipients had received a liver graft[20].

Optimal treatment for MDR *P. aeruginosa* is not established. In a recent review on this issue[93], it was pointed out that most experts caring for transplant patients generally recommend the use of a combination of two or three drugs from different classes. Antimicrobial drug classes that are usually combined in these regimens include beta-lactams, aminoglycosides, polymyxins and a quinolone[93,95]. There is also data to suggest that the combination of aerosolized antibiotics with intravenous antimicrobial therapy may be beneficial for patients with nosocomial pneumonia due to *P. aeruginosa* and other multidrug-resistant Gram-negative pathogens[96].

Carbapenemase-producing Enterobacteriaceae

Carbapenemase-producing *Enterobacteriaceae* (CRE) infections are associated with a high mortality of SOT recipients[15,97,98]. In a study of liver transplant recipients, the survival rate of subjects with CRE infection was 29%, compared to an 86% survival rate in those without[15]. This study also found that CRE infection and a preoperative MELD score > 30 were independently associated with mortality. The impact of preoperative colonization on the rates of CRE infection and mortality after liver transplantation remains undefined. Nonetheless, a study including other groups of critically ill patients demonstrated a high incidence of CRE infection among colonized individuals[99].

The high mortality observed with these infections reflects the very limited therapeutic options currently available. Furthermore, the failure of currently used automated systems to detect carbapenem resistance may delay the start of appropriate antibiotic therapy and contribute to the increased mortality of these infections[36]. Most CRE isolates have *in vitro* susceptibility to polymyxins, tigecycline and fosfomycin, and a considerable proportion retain susceptibility to aminoglycosides. Data from a few studies carried out in non-transplant patients suggest that combination therapy may improve survival[100-102]. The use of a carbapenem in these combination antimicrobial regimens may be beneficial if the MIC to these drugs is $\leqslant$ 4 mg/L[103]. Aminoglycoside monotherapy is effective for the treatment of urinary tract infections, with higher microbiological clearance as compared with monotherapy with polymyxin B or tigecycline[104]. Control of the source of infection (removal of intravascular catheters, drainage of abscesses) is of essential importance and is associated with lower mortality[105].

Carbapenem-resistant Acinetobacter baumannii

Carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) infections are associated with a high mortality of SOT recipients[16,52,54,106]. Although risk factors for these infections are not well defined, the outcomes of CR-Ab-infected SOT recipients are influenced by clinical severity when the infection is diagnosed, the delay to start appropriate therapy[52,54] and the therapeutic regimen used[16]. Recurrence or persistence of infection despite therapy with drugs with proven *in vitro* susceptibility has also been described[16,46,52]. Infections caused by CR-Ab strains that retain *in vitro* susceptibility to sulbactam may be treated with ampicillin-sulbactam or amoxicillin-sulbactam. However, most isolates are extensively resistant, being susceptible only to polymyxins and, with variable frequency, a drug of another antimicrobial class, such as an aminoglycoside or tigecycline. However, monotherapy with a polymyxin has been associated with the emergence of resistant strains[107]. Conflicting results have been reported regarding the effectiveness of combined colistin and rifampicin treatment in non-transplant patients with CR-Ab infections[108,109]. There are also limited data on the effectiveness of the combination colistin-tigecycline, with indications that it is associated with a high rate of treatment failure and emergence of resistance[110,111]. On the other hand, a single-center retrospective study reported a significantly higher survival rate in transplant recipients treated with the combination colistin-carbapenem (doripenem in most cases)[16].

PREVENTION

Although some components of the preventive strategy should be adapted according to the local epidemiology, several general measures can be recommended to reduce the risk of acquiring MDR bacterial pathogens. Continuous education of strict hand hygiene should be implemented concerning contact with contaminated surfaces and before and after contact with a patient. Medical equipment and patient care surfaces should be cleaned and disinfected. Contact isolation precautions must be used for patients with known pathogen colonization. Invasive devices should only be used for a minimum duration, as necessary. Moreover, to minimize the selective pressures favoring the emergence of MDR pathogens, the rational use of antibiotics must be constantly promoted through antibiotic stewardship programs.

Although the universal screening of asymptomatic transplant candidates and recipients with surveillance cultures is not generally recommended[69,93,112], it is war-

ranted during outbreaks, in high prevalence areas and for patients with known risk factors for colonization with a given MDR pathogen[39,59,113], such as patients with recent hospital admissions. In these settings, pre- or perioperative screening of high-risk transplant candidates may help with the timely implementation of contact isolation precautions and to guide empiric antibiotic selection for septic patients while the results of cultures are pending[39]. For patients colonized with MRSA who do not have open wounds, intranasal mupirocin and chlorhexidine cleansing should be attempted[114]. Cleansing with chlorhexidine may also help to limit the cross-transmission of VRE[115]. Two recent studies suggest that selective digestive decontamination with unabsorbable antibiotics may be a suitable strategy for selected groups of patients colonized with CRE[116,117]. However, in other studies, this intervention has also been associated with the rapid emergence of isolates resistant to colistin and aminoglycosides[118,119]. Several studies have shown that the implementation of a variable set of these preventive strategies in endemic settings or during outbreaks effectively curtails the transmission of MDR bacterial pathogens to transplant recipients[25,26,34,37,76,113].

While cases of unfavorable outcomes resulting from donor-derived MDR infections have been reported[46-48], there are also several reports of good short-term outcomes from SOT using organs from donors with CRE colonization or infection[120-122]. Thus, the criteria defining the eligibility of transplant organs from donors infected or colonized with extensively resistant organisms, such as CR-Ab and CRE, are not established and solely based on expert opinion. Potential donors with bloodstream infections caused by these agents should not be accepted[121]. However, for donors without bacteremia, the decision to accept organ donation should take into account the organ to be transplanted and the source of positive donor cultures, provided that there is adequate antibiotic therapy for the isolated organism[93,121].

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