Multidrug-Resistant Bacterial Infections in Solid Organ Transplant Candidates and Recipients

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KEYWORDS

- Multidrug-resistant pathogens • Solid organ transplantation
- Extended-spectrum β-lactamase-producing enterobacteriaceae
- Carbapenem-resistant gram-negative bacilli
- Methicillin-resistant *Staphylococcus aureus* • Vancomycin-resistant enterococci
- Donor-derived infections

KEY POINTS

- The magnitude of the challenge of multidrug-resistant pathogens is huge; this problem affects several aspects of the management of transplant candidates and recipients.
- Areas of uncertainty are predominant in this field concerning selection of candidates, infection prevention, infection control policies, and treatment.
- In addition, continually updated recommendations are needed to face the ever-present and evolving epidemiology of bacterial infection in this setting.

INTRODUCTION

The advancements in surgical techniques, immunosuppressive therapies, and infection control and prophylaxis, along with significant changes in the policy of graft recruitment and allocation altered dramatically the characteristics of patients undergoing solid organ transplantation (SOT) in recent years. In fact, an increasing rate of patients being transplanted in critical condition, directly transferred from intensive care units (ICUs), often receiving marginal organs, is commonly observed.

As a whole, these variations have increased the graft availability and improved the accessibility to organ transplantation; however, they have also changed, and

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increased, the infectious risk. In the current era, ruled by an alarming evolution of antimicrobial resistances, SOT recipients seem one of the patient categories most prone to develop infection caused by multidrug-resistant (MDR) pathogens.[1–3] Not surprisingly, infections caused by MDR pathogens are found more frequently in SOT recipients than in the non-SOT population.[4]

The current major challenges of MDR pathogens are the following. First, MDR infections in transplant recipients are frequently associated with graft complication, and their treatment is often hampered by an ominous lack of effective drugs, resulting in an overall poor outcome. Second, MDR pathogens are frequently associated with outbreaks. This factor is related to the ability of these pathogens, especially Gram-negative bacilli, to spread among a frail population. Third, donor-derived infections (DDI) caused by MDR pathogens are increasingly reported with significant impact on recipients' outcomes.[5]

In light of a clear need of updating the body of knowledge of the infectious risk in the transplanted populations, the current review emphasizes the epidemiologic trends, old and new risk factors, and pretransplant and posttransplant clinical management of MDR-related infection in SOT recipients. We focus on infections owing to methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), extended spectrum β-lactamase (ESBL)-producing, and carbapenem-resistant Enterobacteriaceae (CRE), MDR *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* (CR-AB).

EPIDEMIOLOGY OF MULTIDRUG-RESISTANT PATHOGENS AMONG SOLID ORGAN TRANSPLANT RECIPIENTS

The prevalence, risk factors, and mortality of infection caused by MDR pathogens in the setting of organ transplant are summarized in **Table 1**. Significant differences are present between different pathogens. Furthermore, the prevalence and incidence of infections may vary among different centers located in different countries and between American and European centers.

Methicillin-Resistant Staphylococcus aureus

S aureus is a major cause of invasive infection in the general population, being the second most common bacterial species after *Escherichia coli*.[6] Among all *S aureus* infections, those owing to MRSA represent 21% to 24% of cases in Europe and 31% to 39% in the United States.[7,8] However, in recent years, the incidence of MRSA infection has had a significant downward trend observed in both the United States and Europe, owing to the widespread use of specific infection prevention and control measures.[7,9] In SOT recipients, a similar decrease in MRSA infection may be hypothesized when comparing recent epidemiologic studies with older reports.[10–12]

Overall, the incidence of MRSA infection seems to be higher in lung and liver transplant recipients (0.2–5.7 cases per 100 transplant-years for the former, 0.1 cases per 100 transplant-years the latter) with respect to other kinds of transplants. Most MRSA infections occur in the early posttransplant period, after a median of 7 to 29 days after liver and lung transplantation.[12–14] A longer time frame between transplant and infection is reported among kidney transplant recipients in a recent study.[15] The most frequent sources of infection are pneumonia, bloodstream infection (BSI), vascular catheters, and the surgical site itself, with surgical site infections (SSIs) found mostly in heart and lung transplant recipients. Risk factors for infection found in previous studies are pretransplant and posttransplant nasal colonization, ICU stay, mechanical ventilation for more than 5 days, and cytomegalovirus primary infection in

Table 1
Summary of prevalence, risk factors, and outcome of infection caused by MDR pathogens in solid organ transplant recipients

Microorganism or Group	Organ Transplanted	Prevalence	Risk Factors	Mortality
All MDR pathogens[21,64,131–134]	Liver	15%	Abdominal infection episodes, reoperation, acute rejection, use of pretransplant broad-spectrum antibiotics and prolonged (≧72 h) endotracheal intubation	6-mo mortality 39%
	Kidney	14%	Age >50 y, HCV infection, double kidney-pancreas transplantation, posttransplant RRT, surgical reoperation, nephrostomy	19%
	Lung	37%–51%[a]	ICU stay >14 d, presence of a tracheostomy, previous exposure to broad-spectrum antibiotics	14%
	Heart	25%	NA	NA
MRSA[10,12,14,16–19]	Liver	1.4%–23%	ICU stay, CMV primary coinfection	30-d mortality 21%–25%
	Kidney	0.8%–2%	NA	In-hospital mortality 0%–10%
	Lung	10%–60%	Mechanical ventilation >5 d MRSA nasal carriage MRSA in recipient sterile cultures	30-d mortality 17%
	Heart	30%	NA	NA
VRE[24,26]	Liver Kidney	2%–11% 0%[b]	Biliary leak, reoperation	In hospital 9%–48% 1-y mortality 56%–80%
ESBL[41,44,135]	Liver	7%	Pretransplant ESBL fecal carriage, MELD >25, reoperation	30-d mortality 15%–26%
	Kidney	3%–11%	Double kidney/pancreas transplantation, previous use of antibiotics, posttransplant dialysis requirement, posttransplant urinary obstruction	30-d mortality 14%
	Lung	2%	NA	30-d mortality 17%
	Heart	5%	NA	30-d mortality 14%

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Table 1
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Microorganism or Group	Organ Transplanted	Prevalence	Risk Factors	Mortality
CRE[47,48,51,53,136,137]	Liver	5%–19%	RRT; mechanical ventilation >48 h; HCV recurrence, colonization at any time with CR-KP	In-hospital mortality 18%
	Kidney	2%–26%	Multiorgan transplantation, the use of a ureteral stent	In-hospital mortality 33%–41%
	Lung	0.4%–20.0%	NA	30-d mortality 26% 1-y mortality 53%
	Heart	5%–17%	NA	50%
Carbapenem-resistant *Acinetobacter baumannii*[55–57]	Liver	8%–29%	Prolonged cold ischemia, post-LT dialysis, LT owing to fulminant hepatitis	60-d mortality 42%
	Kidney	3%	NA	30-d mortality 39%
	Lung	21%	NA	30-d mortality 62%
	Heart	7%	NA	NA
MDR-*Pseudomonas aeruginosa*[60–62,131,132]	Liver	4%	Previous transplantation	37%–38%
	Kidney	6%–9%	Hospital-acquired BSI	NA
	Lung	14%	ICU admission in the previous year	1-y mortality 27%
	Heart	19%	Septic shock	NA

Abbreviations: BSI, bloodstream infection; CMV, cytomegalovirus; CRE, carbapenem-resistant Enterobacteriaceae; CR-KP, carbapenem-resistant *Klebsiella penumoniae*; ESBL-E, extended spectrum β-lactamase-producing Enterobacteriaceae; HCV, hepatitis C virus; ICU, intensive care unit; LT, liver transplantation; MDR, multidrug-resistant; MELD, model for end-stage liver disease; MRSA, methicillin resistant *Staphylococcus aureus*; NA, not available; RRT, renal replacement therapy; VRE, vancomycin-resistant Enterobacteriaceae.

[a] Study on MDR organisms in lung transplant patients evaluated mostly airway colonization and respiratory tract infection rather than other types of infection.

[b] One study evaluated 38 kidney transplanted patients colonized with VRE. No one developed VRE-related infection.[86]

cytomegalovirus-seronegative recipients. The mortality for infection caused by MRSA ranges between 14% and 36%.[10,12,14,16–19]

Vancomycin-Resistant Enterococci

Enterococcus spp infection is common after abdominal SOT. The prevalence of *Enterococcus* spp infection is reported in up to 15% of SOT recipients, mainly liver transplant recipients.[20] *Enterococcus* spp is the causative pathogen of 6% to 15% of BSIs in SOT recipients. This rate can reach 20% in hospital-acquired BSI.[21–23] Among all enterococcal infections, the impact of VRE is extremely variable between countries. Centers in North America reported a prevalence of 2% to 11% of VRE infection in liver transplant recipients,[24–26] whereas nearly no infections were reported in studies conducted in Europe.[20,21] This marked disparity may be related to the differing use of vancomycin between American and European hospitals.[27]

VRE infections occur mainly in liver transplant recipients, probably as a consequence of the high prevalence of colonized or infected patients before transplantation.[28,29] In a case-control study, liver transplantation was found to be an independent risk factor for VRE BSI.[30] Infections occur within an average of 29 to 48 days after transplantation. The main types of infection are bacteremia, peritonitis, SSI, and urinary and biliary tract infections.[28,31,32] In an epidemiologic study focused on SSI after liver transplantation, VRE accounted for 23% of all culture-positive superficial and deep SSI. Risk factors for deep VRE SSI were pretransplant VRE colonization, renal failure requiring hemodialysis, bile leak, and male gender.[33] Other kinds of infections, such as endocarditis and mediastinitis, have been reported.[34] Last, VRE in heart transplant recipients have been described mostly in patients with a VRE left ventricular assist device infection in the pretransplant period.[35] Overall, crude mortality for VRE infection represents 9% to 48% of cases, but can reach 56% to 80% during the 1-year of follow-up period.[25,26,31,32]

Extended Spectrum β-Lactamase–Producing Enterobacteriaceae

ESBL production in gram-negative bacteria, especially Enterobacteriaceae, has emerged in past decade and became a global health concern in the general patient population. Despite being initially found mainly during outbreaks in hospitalized patients, throughout the years ESBL-producing strains have become common in the community.[36,37]

Similarly, the prevalence of ESBL-producing strains among transplant patients has increased dramatically in recent years. A study analyzing the etiology of BSI occurring among transplant recipients in a center in Spain in the first year posttransplant, an increasing rate of ESBL-producing strains was found, principally *Klebsiella pneumoniae,* from 7% in 2007 to 2008 to 34% in 2015 to 2016.[38] Another study performed in China evaluating 350 consecutive liver and kidney transplants found a prevalence of 12% of infection caused by ESBL-producing Enterobacteriaceae.[39]

Most infections in patients receiving liver, lung, and heart allografts occur early in the posttransplant period.[40–42] However, longer delays between transplantation and infection have been observed in kidney transplant recipients (28–864 days).[40,43] Urinary tract infections (UTI) are a type of infection commonly associated with ESBL isolation as well as BSI, intraabdominal infection, and pneumonia with differences among different kinds of transplants. More specifically, ESBL-producing Enterobacteriaceae cause mostly UTI in kidney transplant recipients and pneumonia in lung transplant recipients. Mortality associated with infection owing to ESBL-producing strains may vary from 8% to 26% of cases.[40,41] In addition, a significant rate of

recurrent infection has been observed (21%–41% of cases). In particular, recurrent UTI in kidney transplant recipients are frequently reported.[41,43,44]

Carbapenem-Resistant Enterobacteriaceae

Nowadays the global emergence of CRE is a major health challenge. The SOT population seems particularly at risk to develop CRE infections. SOT recipients are characterized by a high propensity to develop bacterial infections in the initial posttransplant period. Consequently, the antimicrobial pressure owing to both antibiotic treatment and prophylaxis is very high in this setting. Thus, in studies analyzing CRE BSI episodes in the general patient population, SOT patients are involved in 14% to 37% of cases.[45,46] In addition, a multicenter study conducted in SOT recipients in Italy shows that the prevalence of carbapenem resistance was 26% among all isolated Enterobacteriaceae and 49% among all isolated *Klebsiella* spp.[47]

Overall, in endemic areas, the incidence of CRE infection after SOT is approximately 5%; CRE infection commonly occurs in the initial posttransplant period (on average 11–36 days).[48–50] Infections associated with CRE are usually BSI, including catheter-related BSI, pneumonia, UTI, intraabdominal infections, and SSIs. Posttransplant renal replacement therapy, CRE rectal colonization, HCV recurrence in liver transplant recipients, bile leak, and prolonged mechanical ventilation are risk factors for CRE during the early posttransplant period.[37,48] The CRE-associated crude mortality rates vary from 25% to 71%, with differences reported between *K pneumoniae* carbapenemase (KPC)-producing CRE and KPC-negative CRE.[50–54]

Carbapenem-resistant Acinetobacter baumannii

CR-AB is commonly reported to affect 9% to 29% of SOT patients. This variability is primarily related to the distinctive propensity of CR-AB to generate outbreaks.[55–57] Epidemiologic studies of BSI in SOT patients report a rate of CR-AB of 2% to 6%.[21] Most infections occur in liver and lung transplant recipients, commonly during the ICU stay in the early posttransplant period. The most common infections are SSI, pneumonia, and BSI, with a mortality rate after 30 days of 57% to 62%.[55,56] Factors associated with poor prognosis are ICU admission, treatment with mechanical ventilation, transplantation for fulminant hepatitis, re-transplantation, prolonged cold ischemia time, and longer surgical time.[56] Despite the high reported mortality rate, the role of CR-AB in determining the prognosis in SOT recipients is under debate and some authors have raised the question whether CR-AB represents a marker of severity of illness rather than a factor associated with poor prognosis. In fact, in a study evaluating a series of 49 infections caused by *A baumannii* in liver and kidney transplant recipients, carbapenem resistance did not negatively affect the prognosis of patients.[58]

Multidrug-Resistant Pseudomonas aeruginosa

P aeruginosa is involved in 6% to 13% of BSI after SOT, being a leading pathogen in lung transplant patients[23,38,59] The prevalence of drug resistance among *P aeruginosa* strains may vary significantly between centers. Among the infections caused by *P aeruginosa*, 44% to 55% of cases were caused by an MDR strain.[59,60] Moreover, a single-center study found a worrisome rate of 63% of extensively drug-resistant (XDR) strains among all *P aeruginosa* BSI cases.[61] There are also concerns regarding *P aeruginosa* infections and colonization among lung transplant candidates, especially those affected by cystic fibrosis. Studies conducted in this population showed close to 50% of lung transplant candidates harboring pandrug-resistant *P aeruginosa* in the airways.[62] Colonization and/or infection by *P aeruginosa* after lung transplantation is

associated with a higher risk of developing bronchiolitis obliterans syndrome and death.[63] Finally, MDR *P aeruginosa* is frequently found among recurrent cases of UTI among kidney transplant recipients.[64]

Outside the lung transplantation setting, the most common sources of MDR/XDR *P aeruginosa* BSI are the urinary tract, central venous catheters and the abdomen. About one-half of infections occur during the first 90 days and one-quarter during the first 2 weeks after the transplant.[60,61] Retransplantation, nosocomial BSI, septic shock, and prior ICU admission were found to be risk factors for MDR/XDR *P aeruginosa* infection. Infection caused by MDR/XDR *P aeruginosa* are associated with a recurrence rate of 21%, and a higher rate of ICU admission and renal impairment when compared with infections caused by other pathogens, as well as a 30-day mortality rate of 38%.[61]

PRETRANSPLANT SCREENING AND MANAGEMENT OF COLONIZED PATIENTS

Infection or colonization by MDR is common in patients awaiting transplantation (**Table 2**). In fact, patients with end-stage diseases treatable with transplantation share several risk factors for infections caused by MDR, including variable levels of immune system impairment, frequent health care contacts, ICU admission, greater susceptibility to infection, and subsequently increased exposure to broad-spectrum antibiotics.

Infection is a leading cause of morbidity and mortality in patients with end-stage liver disease. About one-third of patients admitted for an episode of acute decompensation of liver disease develops a bacterial or fungal infection.[65] In addition, infection seems to accelerate the course of the disease, being the most important event triggering the acute-on-chronic liver failure syndrome.[66] Thus, it is not surprising that approximately 20% of patients undergo transplantation during the course of an infectious episode.[67] MDR in this setting causes approximately 30% to 46% of infections and is associated with inadequate empirical therapy and increased mortality.[29,68,69]

Table 2
Incidence and etiology of MDR pathogens among infectious episodes in patients with underlying transplant-treatable diseases

Disease/ Condition	Rate of MDR Pathogens Among Episodes of Infections/ Colonization	Main Isolated Pathogens	Comments/Notes
Liver cirrhosis[68,69,138]	25%–47%	MRSA 3%–7% ESBL-E 12%–15% CRE 3%–8% VRE 0%–7%	Major infections are spontaneous bacterial peritonitis, BSI, UTI, and pneumonia
End-stage renal disease[73,74]	12%–25%	MRSA 0%–14% VRE 2%–21% ESBL-E 12%–25%	Most of infections studied are hemodialysis catheter-related BSIs
Cystic fibrosis[76,139]	48%	MRSA 17%–36% MDR *Pseudomonas aeruginosa* 21%–52% ESBL-E 4%	Studies collected mostly culture (surveillance or diagnostic) samples rather than Infectious episodes

Abbreviations: BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; ESBL-E, extended spectrum β-lactamase-producing Enterobacteriaceae; MDR, multidrug-resistant; MRSA, methicillin resistant *Staphylococcus aureus*; UTI, urinary tract infection; VRE, vancomycin-resistant Enterococci.

Infectious biliary complications such as recurrent cholangitis or infected bilomas in liver transplant recipients may be an indication for retransplantation.[70,71] In this case, candidates for retransplantation may be at risk for infection with colonizing MDR pathogens. In fact, the management of this condition may consist in prolonged and/or recurrent antibiotic treatment while awaiting transplantation,[71] which is the ultimate cure for such infections. Thus, transplantation should not be delayed in hopes of curing such infections.

Patients with end-stage kidney disease receiving hemodialysis are at increased risk of developing hemodialysis catheter-related BSI or local access-related infections. Although these infections are typically associated with a low mortality rate, severe complications such as endocarditis and metastatic localizations are not unusual. Outpatients receiving hemodialysis are commonly considered a group of patients at risk of infection caused by MDR pathogens. In addition, colonization with MDR pathogens is frequent. In a study evaluating surveillance cultures of patients receiving outpatient hemodialysis, the rates of MDR gram-negative bacteria, VRE, and MRSA isolation were 16%, 13%, and 5%, respectively.[72] Among episodes of infections, gram-positive cocci are prevalent, with MRSA and VRE isolated in 0% to 14% and 2% to 21% of cases, respectively.[73,74] In addition, recent studies have reported an increased rate of ESBL-producing Enterobacteriaceae in 12% to 25% of cases.[73,74]

Chronic respiratory infections remain a significant cause of morbidity and mortality in patients with cystic fibrosis. *P aeruginosa* is commonly isolated in the respiratory tract of 41% to 60% of these patients.[75,76] Although studies have shown a trend toward a decrease in the number of cases of *Pseudomonas* spp isolation over the past decade, the rate of MDR/XDR and pandrug-resistant (PDR) *P aeruginosa* strains seems to have increased.[76] A similar trend is observed for other pathogens such us MRSA, CR-AB, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*.[75,76]

SCREENING FOR SPECIFIC PATHOGENS

Methicillin-Resistant Staphylococcus aureus

Different studies focused on the role and necessity of active pretransplant and posttransplant screening and treatment of MRSA nasal carriers. Pretransplant MRSA colonization is common in liver transplant candidates. In a study conducted in a single liver transplant unit, 22% of patients were found to be pretransplant carriers, developing an MRSA infection in 31% of cases during the posttransplant period.[77] Similarly, pretransplant nasal carriage was found to be a risk factor for posttransplant MRSA infection in several other studies.[10,14,24] Posttransplant colonization was also found in 9% to 22% of liver transplant recipients in studies performed in Brazil and Japan. Factors associated with posttransplant colonization were advanced age (>60 years), indwelling urinary catheter for greater than 5 days, postoperative bleeding at the surgical site, renal replacement therapy, prolonged ICU stay, and preoperative (but not postoperative) use of fluoroquinolones. In patients who experienced postoperative colonization, an increased number of MRSA infection was observed and, in a postoperative study, MRSA contraction was an independent predictor of infection.[78–80] A recent metanalysis of 17 published studies found that both pretransplant and posttransplant colonization had increased the risk of MRSA infection during the posttransplant period.[81]

Nasal mupirocin is commonly used in the preoperative period to reduce the risk of postoperative MRSA infection. However, in liver transplant recipients, a lack of mupirocin efficacy is reported. In a study conducted in a center characterized by a high prevalence of MRSA colonization among liver transplant candidates (44%), mupirocin

was initially effective in decolonizing 86% of carriers. However, 37% of decolonized patients experienced recolonization and most of methicillin-susceptible *S aureus* carriers eventually became MRSA carriers.[82] In a second study performed in the same center, the application of a more aggressive infection control bundle that included surveillance cultures, cohorting, and contact precaution for all MRSA-colonized or -infected patients plus mupirocin treatment for carriers, was effective in reducing the rate of new MRSA acquisition from 46% to 10% and of MRSA infection from 40% to 4% of patients.[83]

Vancomycin-Resistant Enterococci

Outbreaks of VRE are described in transplant units and in most cases were associated with extensive environmental contamination in addition to human-to-human spread.[84,85]

Pretransplant fecal colonization can reach 44% of cases in liver transplant candidates. In a single-center study, risk factors for pretransplant VRE colonization were central venous catheterization, third-generation cephalosporine use, antianarobes treatment, rifaximin, neomycin or proton pump inhibitor use, paracentesis or endoscopic retrograde cholangiopancreatography, and admission to the liver unit.[28] Posttransplant colonization is also common in liver and kidney transplant patients and occurs in 13% to 18% of cases.[26,86] In 1 study, posttransplant VRE colonization was independently associated with reoperation and antianarobes treatment.[26] Both pretransplant and posttransplant VRE colonization is associated with increased risk of subsequent VRE infection.[81]

Enterobacteriaceae

Similarly to other MDR pathogens, ESBL-producing Enterobacteriaceae fecal colonization is frequent in liver and kidney transplant candidates during the pretransplant phase (4%–31% of subjects) and was found to be independently associated with posttransplant infection.[42,87]

Similarly, the prevalence of CRE fecal carriers before liver transplantation is reported at between 5% and 18% of cases. Studies evaluating the impact of pretransplant colonization on posttransplant infection risk report conflicting results.[48,50] Thus, the management of pretransplant CRE rectal colonization remains controversial, regarding both the transplant indication and the rationale for specific pharmacologic prophylaxis. In an Italian study of 237 liver transplant recipients, carriers at the time of liver transplantation developed CRE infection in the posttransplant period in 18% of cases, whereas those acquiring CRE colonization during the posttransplant period developed a clinically significant infection in 47% of cases.[48] In a second study performed in Brazil and evaluating 386 consecutive liver transplant recipients, those identified as carriers before transplantation (16% of cases) developed an invasive infection in 40% of cases.[50] This important difference in terms of invasive infection risk may be related to different epidemiologic features (eg, different carbapenemase types were detected in these studies) and differing definition of carriers. In fact, in the study by Giannella and colleagues,[48] only rectal swabs were used to identify carriers, whereas in the study by Freire and colleagues,[50] any CRE-positive surveillance or clinical specimen culture defined a patient as a CRE carrier, resulting in selection bias. In both studies, CRE colonization was found to be a risk factor for CRE infection. However, both studies were characterized by a small number of events, and additional large-scale studies are needed to have generalizable results.

Carbapenem-Resistant Nonfermentative Gram-Negative Bacilli

The extent and the clinical role of *P aeruginosa* colonization are poorly evaluated in settings other than lung transplantation. As stated, the impact of drug-resistant *P aeruginosa* lung colonization is a major concern in patients with cystic fibrosis and/or severe bronchiectasis awaiting lung transplantation. In this setting, however, the presence of MDR or even PDR *P aeruginosa* strains before transplantation do not affect short- or long-term survival.[88] In later studies, a significant increase in the prevalence of *S maltophilia* and *A xylosoxidans* has been observed. None of these pathogens constitute an exclusion criterion for lung transplantation. However, major concerns were raised for patients colonized by MDR *Burkholderia cepacia* complex; particularly subspecies *cenocepacia*, because this organism was associated with an unacceptable rate of futile transplants.[89,90]

Similarly, pretransplant CR-AB colonization seems to increase the risk of posttransplant infection. In a study conducted among 196 liver transplant recipients, pretransplant identification of CR-AB in both clinical samples or surveillance cultures was found to increase the risk of posttransplant infection. The study, however, was conducted during a clonal outbreak of CR-AB that involved one-third of the included patients and, therefore, the results may be disproportionally influenced. Another interesting finding of this study was that the adaptation of surgical prophylaxis to CR-AB–positive surveillance cultures with use of polymyxins for colonized patients did not lead to a decrease in the subsequent rate of infection. In addition, an increase in the rate of polymyxin-resistant strains was observed in patients receiving prophylaxis with polymyxins.[55]

Currently, the most comprehensive guidelines focusing on the management of MDR in SOT candidates and recipients are those of the American Society of Transplantation, published in 2013, those of the European society of Clinical Microbiology and Infectious Diseases, published in 2014 and the recently published consensus produced by the Spanish Transplantation Infection Study Group. Recommendations on screening and prevention management are summarized in **Tables 3** and **4**.[5,91–94]

DONOR-DERIVED INFECTIONS

One crucial issue in the management of MDR pathogens in transplantation is to avoid the transmission of possibly difficult-to-treat pathogens from donors to recipients, especially in cases of deceased-donor transplantation. Deceased donors are often typically critically ill patients admitted in the ICU and have several risk factors for developing and acquiring MDR pathogen-related colonization or infection. Approximately 5% of donors are bacteremic during organ procurement and, thus, microbiological data may not be available at the time of transplantation.[95] Thus, with the recent spread of MDR pathogens that are typically resistant to the standard antibiotic prophylaxis or preemptive therapy, transmission of MDR pathogens from donors to recipients has been reported increasingly.

The most exhaustive experience on the risk of DDI caused by MDR pathogens describes an Italian series of 30 transplants using patients with colonization or infection caused by carbapenem-resistant *K pneumoniae* (CR-KP) or CR-AB as donors, including 14 cases of undiagnosed donor BSIs at the time of transplant. Proven transmission occurred only when donor infection was underestimated or miscommunicated to caregivers, which occurred in 4 of the 14 bacteremic cases. In addition, infection occurred only when the donor was infected or colonized by CR-KP, but not when the donor was infected or colonized by CR-AB (15 cases)[96]

Table 3
Summary of recommendations of different guidelines or expert consensus on the pretransplant and posttransplant management of Gram-positive MDR pathogens

Scientific Society	AST[93,94]	ESCMID[5]
Year issued	2013	2014
Universal nasal or skin screening of transplant candidate for MRSA	Not recommended routinely. Consider in facilities with unacceptable high rate of MRSA transmission. Colonized patients can be identified with nasal or skin surveillance cultures.	Nasal screening is recommended in areas with low/moderate prevalence of MRSA.
Universal screening of transplant candidate for VRE	Not recommended routinely but should be implemented during outbreaks.	Not recommended routinely but should be implemented during outbreaks.
Antibiotic prophylaxis in MRSA carriers	MRSA-active preoperative prophylaxis.	Topic not discussed.
Antibiotic prophylaxis in VRE carriers	Consider adjusting perioperative prophylaxis.	Topic not discussed.
Decolonization for MRSA carriers and timing	Consider pretransplant decolonization with intranasal application of 2% topical mupirocin twice daily for 5 d combined with chlorhexidine baths for 7 d.	Recommended selective decolonization with mupirocin and chlorhexidine bath in areas with low/moderate prevalence of MRSA and universal decolonization in areas with high MRSA prevalence during the ICU stay, after transplantation.
Decolonization for VRE carriers	Not recommended.	Not recommended.
Other preventive measures for MRSA and VRE	Implement antimicrobial stewardship programs. Contact precautions for all carriers and infected patients. Use dedicated equipment. Environmental cleaning, Monitor compliance with hand hygiene.	Recommended isolation or cohorting of carriers, contact precautions, and environmental cleaning.

Abbreviations: AST, American Society of Transplantation; ESCMID, European Society of Clinical Microbiology and Infectious Disease; ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococci.

Cases of possible/probable DDI caused by MDR pathogens and reported in the literature are summarized in **Table 5**. The 34 cases of MDR pathogen transmission identified (33 infection, 1 airway colonization in a lung transplant recipient) include 8 CR-KP infections, 7 MDR *P aeruginosa* infections, 5 ESBL-producing Enterobacteriaceae, 1 CR-AB infection, 1 CR-KP airway colonization, 8 MRSA, and 4 VRE infections. In 22 of 34 cases, the results of donor culture were either not available, negative at the time of transplantation, or the results were not adequately communicated to the caregiver. In 5 additional cases, the information was underestimated. In

Table 4
Summary of recommendations of different guidelines or expert consensus on the pretransplant and posttransplant management of Gram-negative MDR pathogens

Scientific Society	AST[92]	ESCMID[5]	GESITRA- EIMC/REIPI[91]
Year issued	2013	2014	2018
Universal screening of transplant candidate for ESBL-producing Enterobacteriaceae	Not recommended	Not recommended in endemic areas, recommended during outbreaks	Not recommended
Universal screening of transplant candidate/ recipients for CRE	Not recommended	Not recommended in endemic areas, recommended during outbreaks	Recommended at transplantation After transplantation, in accordance with institutional policy
Universal screening of transplant candidate for MDR nonfermenters	Not recommended	Not recommended in endemic areas, recommended during outbreaks Recommended screening of respiratory samples in lung transplant candidates	Not recommended routinely
Delist carriers of GN-MDR	Decision on case-by-case basis	Decision on case-by-case basis for lung transplant candidates colonized by nonfermenting MDR/XDR rods	Not recommended in any case

Accept donor with MDR Enterobacteriaceae-positive cultures	Topic not discussed	Topic not discussed	Accept ESBL-E carriers Accept donor with nonbacteremic, non–graft-related CRE infection. In this case, donor should receive a 7-d CRE treatment at minimum Reject kidney from donor with CRE-UTI or lung from donor with CRE pneumonia
Accept donor with MDR nonfermenting positive cultures	Topic not discussed	Topic not discussed	Accept organs with positive MDR-*Pseudomonas aeruginosa* only in exceptional cases Accept donor with CR-AB Reject CR-AB colonized lungs and kidneys from donor with CR-AB
Antibiotic prophylaxis in ESBL carriers	Standard prophylaxis not exceeding 48 h of duration, with exception for lung transplant recipients	Topic not discussed	Specific prophylaxis is recommended Avoid carbapenem when possible Consider nebulized antibiotic in colonized lung transplant recipients, or recipients of colonized graft
Antibiotic prophylaxis in other GN-MDR	Standard prophylaxis	Topic not discussed	Adopt surgical prophylaxis in accordance with local patterns Lung transplant recipients should receive prophylaxis driven by pretransplant cultures Colonized lung candidate or recipients should receive nebulized colistin perioperatively

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Table 4
(*continued*)

Scientific Society	AST[92]	ESCMID[5]	GESITRA- EIMC/REIPI[91]
Decolonization for ESBL carriers	Not recommended	Not recommended	Not recommended
Decolonization for GN-MDR carriers	Not recommended	Not recommended	Not recommended
Other preventive measures for ESBL carriers	Same as other GN-MDR	Isolation of carriers of ESBL-producing *Escherichia coli* is not recommended Contact precautions and isolation of patients with other ESBL-producing Enterobacteriaceae are recommended	Screening for ESBL-E may be useful; handwashing or disinfection with alcohol-based gels are recommended in all cases Contact precautions are strongly recommended for ESBL- producing *K pneumoniae* and weakly recommended for ESBL-producing *E coli*
Other preventive measures for GN-MDR carriers	Reduce/avoid the unneeded antibiotic exposure in the pretransplant and posttransplant period Reduce the exposure to indwelling devices and reduce the duration of endotracheal intubation Promote hand hygiene Use of contact precautions: separate carriers in private room or cohort patients with same GN-MDR	Placement of patients in single-bed isolation Use of contact precautions and environmental cleaning	Perform surveillance cultures in the posttransplant period Promote and monitor compliance of hand hygiene Contact precautions is recommended for infected and colonized patients HCW should wear goggles and face mask when performing procedures on CR-AB colonized/infected patients Staff cohorting and active screening during outbreaks

Abbreviations: AST, American Society of Transplantation; CR-AB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant enterobacteriaceae; EIMC, Spanish Society of Infectious Diseases and Clinical Microbiology; ESBL-E, extended spectrum β-lactamase enterobacteriaceae; ESCMID, European Society of Clinical Microbiology and Infectious Disease; GESITRA, Group for Study of Infection in Transplantation; GN-MDR, gram-negative multidrug resistant; HCW, health care workers; REIPI, Spanish Network for Research in Infectious Diseases; UTI, urinary tract infection; XDR, extensively drug-resistant.

Table 5
Cases of donor-derived infection involving MDR pathogens

Strain	Donor Infection/ Colonization	Recipients' Organ(s)	Posttransplant Infection	Information Available Before Infection Development	Prophylaxis/ Preemptive Treatment of Recipient	Outcome	Confirmation of Transmission with Genotyping
CR-KP[140]	Lung colonization	Liver	BSI	No	Standard prophylaxis	Survived at 1 y posttransplant	No
CR-KP[141]	Meningitis and pneumonia	Liver and kidney	Intraabdominal	Yes	Targeted with tigecycline	Alive 5 mo after transplantation	No
CR-KP[142]	Lung and rectal colonization	Kidney-pancreas	IAI	No	Colistin, meropenem and tigecycline	Died 6 mo after transplant	Yes (PFGE)
CR-KP[96]	BSI	Right lobe split liver	SSI	Yes	Meropenem	Alive at 18-mo follow-up	Yes (PFGE)
		Lungs	Airway colonization	Yes	Meropenem	Alive	Yes (PFGE)
CR-KP[96]	Blood, urine, and BAL	Liver	SSI – intraabdominal collection	Yes	3 d of meropenem and gentamicin	Alive 6 mo after transplant	Yes (PFGE)
CR-KP[96]	CR-KP urine	Kidney	Perigraft collection	No	Standard prophylaxis	Died 2 mo after transplant	Yes (PFGE)
CR-KP[143]	Unknown	Kidney	BSI	No	Standard prophylaxis	Lost to follow-up	Yes (PFGE and MLSG)[a]
		Liver	IAI	No	Standard prophylaxis	Alive 6 mo after transplant	

(*continued on next page*)

Table 5
(*continued*)

Strain	Donor Infection/ Colonization	Recipients' Organ(s)	Posttransplant Infection	Information Available Before Infection Development	Prophylaxis/ Preemptive Treatment of Recipient	Outcome	Confirmation of Transmission with Genotyping
ESBL-producing *Escherichia coli*[144]	UTI	Kidney	UTI complicated with pseudoaneurysm	No	Standard prophylaxis	Survived but underwent nephrectomy	No
		Kidney	Pyelonephritis	No	Standard prophylaxis	Survived but underwent nephrectomy	No
ESBL-producing *Klebsiella pneumoniae*[145]	Unknown	Liver	IAI	No	Standard prophylaxis	Died within 3 mo after transplant	No[a]
ESBL-producing *K pneumoniae*[145]	Unknown	Liver	IAI	No	Standard prophylaxis	Alive 3 mo after transplant	No[a]
ESBL-producing *Enterobacter aerogenes*[145]	Unknown	Liver	BSI	No	Standard prophylaxis	Alive after 3 mo form transplant	No[a]
CR-AB[146]	Lung	Lung	Tracheobronchitis	No	Standard prophylaxis	Died 65 d after transplant	Yes (PFGE and RAPD)
MDR *Pseudomonas aeruginosa*[147]	Pneumonia	Kidney	SSI and brain mycotic aneurysm	No	Standard prophylaxis	Died	No
		Kidney	BSI	No	Standard prophylaxis	Died	No
MDR *P aeruginosa*[148]	Urine and peritoneal fluid	Kidney	SSI-Perigraft collection	No	Standard prophylaxis	Alive 1 y after transplant	Yes (PFGE)

MDR *P aeruginosa*[149]	Peritoneal fluid	Heart	Empyema	Yes	Standard prophylaxis	Alive	No
		Liver	Cholangitis	Yes	Meropenem	Died 38 d after transplant	No
		Kidney	SSI	Yes	Meropenem	Died	No
		Kidney	SSI	Yes	Unknown	Lost to follow-up	No
MRSA[150]	Mitral valve endocarditis	Liver	BSI	Yes	Vancomycin	Alive 1 y after transplant	Yes (WGS)
MRSA[151]	Nasal carrier	Living-donor-liver	Pneumonia	No	Standard prophylaxis	Deceased	Yes (PFGE)
MRSA[152]	BSI	Heart	Myocarditis	No	Standard prophylaxis	Died	Yes
MRSA[153]	Endocarditis	Liver	Recurrent BSI	Yes	Daptomycin	Alive	Yes (PFGE)
MRSA[154]	Endotracheal tube colonization	Liver	BSI with disseminated localizations	No	Standard prophylaxis	Alive	Yes
		Kidney	BSI	No	Vancomycin	Alive	Yes
MRSA[155]	Endocarditis	Liver	BSI	Yes	Daptomycin	Alive	Yes (WGS)
		Lung	Pneumonia	Yes	Vancomycin	Alive	Yes (WGS)
VRE[156]	Unknown	Liver	IAI	No	Standard prophylaxis	Deceased after 7 mo	Yes (WGS)[b]
		Kidney	Perigraft collection	No	Standard prophylaxis	Alive	Yes (WGS)[b]
		Kidney	UTI	No	Standard prophylaxis	Alive	Yes (WGS)[b]
VRE[157]	BSI	Liver	IAI	No	Standard prophylaxis	Alive	Yes (WGS)

Abbreviations: BAL, bronchoalveolar lavage; BSI, bloodstream infection; CR-AB, carbapenem-resistant *Acinetobacter baumannii*; CR-KP, Carbapenem-resistant *Klebsiella pneumoniae*; MDR multidrug-resistant; ESBL, extended spectrum β-lactamase; IAI, intraabdominal infection; MLSG, multilocus sequence genotyping; MRSA, methicillin-resistant *Staphylococcus aureus*; PFGE, pulsed-field gel electrophoresis; RAPD, random amplification of polymorphic DNA; SSI, surgical site infection; UTI, urinary tract infection; VRE, vancomycin-resistant Enterobacteriaceae; WGS, whole-genome sequencing.

[a] The strain was not recovered in the donor. However, the recipients undergoing transplantation in different hospitals acquired an identical strain and the hypothesis of donor-derived infection is likely. Contamination during the harvesting procedure may have occurred.

[b] In this report, the same teicoplanin-resistant VRE was recovered from 3 different recipients receiving an organ from the same donor. Whole-genome sequencing confirmed the identity of the strains.

all of these cases (27 of 34), patients did not receive adequate preemptive treatment. Preemptive therapy or prophylaxis failed to prevent DDI in 5 of the 8 reported cases of MRSA transmission and in 2 cases of MDR *P aeruginosa* transmission. Mortality was reported in 11 cases, 9 of which did not receive preemptive antibiotics. Two kidney transplant recipients experienced graft loss; neither received preemptive treatment.

TREATMENT

Treatment of MDR pathogens in SOT recipients is extremely challenging for several reasons. First, the diagnosis may be difficult or delayed. In fact, multiple simultaneous conditions such as infection and graft rejection or multiple infectious processes may overlap. For instance, viral replication (eg, cytomegalovirus) or opportunistic infections may be diagnosed together with bacterial infections. Second, the wide differences of the epidemiology between centers and the varying risk factors found in different studies may hamper the ability to identify those patients who may need broader spectrum empirical treatment. Third, most patients have indwelling devices (eg, urinary catheters or ureteral stents in kidney transplantation) that may be responsible for recurrence of infection even after adequate treatment. In addition, infection source control may be more challenging than in non-SOT patients owing to surgical complexity. Fourth, drug comparative studies in SOT recipients are limited and most data come from mixed populations that comprise both transplant and nontransplant patients. Finally, drug–drug interactions may occur between immunosuppressive drugs and antimicrobials, altering the drugs' pharmacokinetics and pharmacodynamics and potentially worsening the clinical course of patients. Thus, several aspects should be kept in mind when choosing empirical antimicrobial treatment. Regarding the risk for MDR organisms, the most important factors are by far prior antibiotic exposure, and prior infection or colonization with an MDR organism.

Treatment of Gram-Positive Multidrug-Resistant Pathogens

Vancomycin is considered the treatment of choice for MRSA infection in most cases. Although the superiority of other drugs versus vancomycin was poorly demonstrated in clinical trials, observational studies suggest that alternative regimens could be associated with improved outcomes under specific situations.[97,98] More specifically, with the spread of strains with reduced susceptibility to vancomycin, treatment failure with this drug was reported.[99] In a metaanalysis including 22 studies, higher mortality was reported in infections caused by MRSA strains with vancomycin a minimum inhibitory concentration of 2 mg/mL or greater, especially in case of BSI.[100] In 1 case-control study, the use of daptomycin was associated with an improved outcome compared with vancomycin.[97] According to the Infectious Diseases Society of America guidelines, MRSA pneumonia should be treated with either vancomycin or linezolid.[101] In a randomized trial enrolling patients with nosocomial pneumonia caused by MRSA, patients treated with linezolid achieved a better clinical and microbiological cure and a lower rate of nephrotoxicity when compared with those treated with vancomycin.[102]

Although vancomycin-resistant *Enterococcus faecalis* may be susceptible to ampicillin, most of vancomycin resistant enterococcus infections have been attributed to *Enterococcus faecium.*

Options for treating vancomycin-resistant enterococcus infections are linezolid, daptomycin, or tigecycline. Well-designed comparative studies are not available to assess the best treatment for VRE. However, a metanalysis of 10 retrospective studies

comparing outcome of patients treated with linezolid or daptomycin for VRE bacteremia found an increased risk of mortality in patients receiving daptomycin.[103]

Treatment of Gram-Negative Multidrug-Resistant Pathogens

Although ESBL-producing gram-negative bacteria emerged as a major global public health concern more than 2 decades ago, issues concerning the best treatment choices continue to be unresolved.[104] The major challenge regards the right place in therapy of carbapenems and β-lactam β-lactamase inhibitors (BLBLI) combinations: the efficacy of carbapenems is well-recognized, however, carbapenem overuse can induce several resistance pathways, including the selection of carbapenemases. Therefore, efforts toward the use of carbapenem-sparing regimens whenever an alternative exists should be encouraged.

The role of BLBLI combinations for ESBL-Enterobacteriaceae infections is controversial. Observational studies suggest that BLBLI may be an alternative to carbapenems in infections originated from the urinary tract or with adequate source control; for other sites, treatment failures may occur mainly when the minimum inhibitory concentrations are above a minimum level.[105,106] A recent study showed that when susceptible in vitro, treatment other than with a BLBLI for ESBL-E infections such as aminoglycosides or fluoroquinolones is not associated with worse outcome compared with carbapenems[107]

Although tigecycline does not feature in vitro activity against *P aeruginosa* or certain Enterobacteriaceae (*Proteus spp*., *Serratia spp*., *Morganella morganii*, *Providencia stuartii*), it is still an option for complicated intraabdominal infections because of its favorable pharmacokinetics in the abdominal organs and in vitro activity against anaerobic organisms, enterococci, several ESBLs, and some strains of carbapenemase-producing Enterobacteriaceae.[108,109] However, because of poor plasma concentration, tigecycline performs poorly in bacteremic patients, with a much higher risk of failure to clear bacteremia.[110] Similarly, tigecycline shows poor urine concentration with standard dosage. Therefore, tigecycline should not be considered as a first-line therapy in patients with health care–associated pneumonia, bacteremia, and UTI when other effective drugs are available. In addition, reported experience in an SOT setting is limited.[111]

The recent challenges in the management of gram-negative MDR organism infections, especially in critically ill patients, have revived the clinical use of polymyxins, fosfomycin, and minocycline.[112,113] There remain open questions about the need for combination therapy and the role of carbapenems, administered at high doses and by extended infusions, in the treatment of infections with CRE. In large observational trials, combination treatment including high-dose carbapenems and colistin or aminoglycosides were associated with better outcomes, especially in critically ill patients.[114,115]

Ceftolozane/tazobactam and ceftazidime/avibactam have recently been approved in some national agencies for the treatment of complicated UTIs, intraabdominal infections, and nosocomial pneumonia.[116,117]

Ceftolozane/tazobactam is a new antibiotic that has been approved for treatment of complicated intraabdominal infections (in combination with metronidazole), including infection by ESBLs and *P aeruginosa*, and may be valuable for treating infections caused by gram-negative MDR organisms to preserve carbapenems.[118,119] It may be useful as empirical therapy to preserve the use of carbapenems for use in critical patients with risk factors for ESBL isolation or as targeted therapy in patients with isolation of a susceptible ESBL-producing Enterobacteriaceae or MDR *P aeruginosa*. It should be pointed out that, in some countries, the production of

metallo-β-lactamase enzymes that are not inactivated by ceftolozane/tazobactam may be one of the mechanisms of carbapenem resistance in *P aeruginosa.*

Ceftazidime-avibactam (CAZ-AVI) is a novel drug that combines a third-generation cephalosporin with an inhibitor of β-lactamase.[120,121] Despite the settings of registration trials, a greater interest for CAZ-AVI is due to the activity of avibactam in inactivating a large number of β-lactamase enzymes, including carbapenemase KPC and most OXA-48, representing the first β-lactam antibiotic combination showing this characteristic.[122]

Recent case series have reported on the use of CAZ-AVI in patients with CRE infection.[123–125] Although reporting efficacy in a variety of clinical situations, first-line therapy, and compassionate use, the overall success rates ranged from 45% to 74%, with relapse rates of up to 23%. Three observational studies have reported higher rates of clinical success and lower mortality with CAZ-AVI compared with other regimens for CRE infection.[46,126,127] In the clinical studies on CRE infection, CAZ-AVI was used in combination in 27% to 63% of cases.[46,123,124,126,127] There was great variety in the combination antibiotics, with aminoglycosides, carbapenems, and tigecycline used most frequently. However, direct comparisons between monotherapy and combination therapy, and between different kinds of combinations, were not performed.[46,123,124,126,127] In a study by Shields and colleagues,[123] where SOT recipients constituted 21% of the population, CAZ-AVI was predominantly used as monotherapy, and approximately 30% of patients received combination regimens, primarily with aminoglycosides as the second agent. There was an alarmingly high rate (24%) of CRE relapse after completion of therapy. Most relapsing patients had received monotherapy (7 of 10), and 3 of them (8% of the entire cohort) developed reinfection by a strain that had developed resistance (minimum inhibitory concentration of $\geq$16 μg/mL) to CAZ-AVI after only 10 to 19 days of therapy. Whether combination therapy can be used to prevent the emergence of resistance to CAZ-AVI in CRE is not known.

Vaborbactam is another novel β-lactamase inhibitor that shows an important activity against KPC producers. Unfortunately, it has no activity against OXA-48 or metallo-β-lactamase enzymes.[128] Vaborbactam was evaluated in combination with meropenem in a phase III randomized study and was compared with piperacillin-tazobactam for treatment of complicated UTIs. Meropenem-vaborbactam was statistically superior to piperacillin-tazobactam in clinical cure and eradication of baseline pathogen.[129] Meropenem-vaborbactam was also evaluated in a small phase III trial including 70 patients with CRE infection randomized (2:1) to receive meropenem-vaborbactam (2 g and 2 g every 8 hours) or best available treatment. The latter consisted of monotherapy (26%), dual therapy (46.7%), triple therapy (6.7%), and therapy with 4 or more drugs (13.3%). Overall, meropenem-vaborbactam showed higher clinical cure (57.1% vs 26.7%; absolute difference, 30.5%; 95% confidence interval, 1.5%–59.4%) and a lower rate of nephrotoxicity. Despite these promising results, the study was characterized by important heterogeneity of treatment administered in the comparator arm, limiting direct comparison between regimens.[130]

SUMMARY

The magnitude of the challenge of MDR pathogens is huge; this problem affects several aspects of the management of transplant candidates and recipients. Areas of uncertainty are predominant in this field concerning selection of candidates, infection prevention, infection control policies, and treatment. In addition, continually updated recommendations are needed to face the ever-present and evolving epidemiology of bacterial infection in this setting.

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