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REVIEW

Carbapenem-resistant Enterobacteriaceae in special populations: Solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies

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ABSTRACT

Carbapenem-resistant Enterobacteriaceae (CRE) are a major global public health concern and pose a serious threat to immunocompromised hosts, particularly patients with hematologic malignancies and solid organ (SOT) and stem cell transplant recipients. In endemic areas, carbapenem-resistant *Klebsiella pneumoniae* infections occur in 1–18% of SOT recipients, and patients with hematologic malignancies represent 16–24% of all patients with CRE bacteremia. Mortality rates approaching 60% have been reported in these patient populations. Early diagnosis and rapid initiation of targeted therapy is critical in the management of immunocompromised hosts with CRE infections, as recommended empiric regimens are not active against CRE. Therapeutic options are limited by antibiotic-associated toxicities, interactions with immunosuppressive agents, and paucity of antibiotic options currently available. Prevention of CRE infection in these patients requires a multidisciplinary approach involving hospital epidemiology and antimicrobial stewardship. Large, multicenter studies are needed to develop risk-stratification tools to assist in guiding the management of these individuals.

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Carbapenem resistance among the Enterobacteriaceae, most notably in *Klebsiella pneumoniae*, has emerged as a global threat over the past decade. While initially confined to New York City hospitals, the proportion of Enterobacteriaceae that were carbapenem resistant in United States acute care hospitals increased from 1.2% in 2001 to 4.2% in 2011; the majority of this change was attributable to carbapenem-resistant *Klebsiella* spp, which increased from 1.6% to 10.4% during this time period.[1] CRE have been also become endemic in parts of Europe, Asia, South America, and Africa, reflecting a global public health emergency.[2] Further, mortality rates associated with CRE infection have ranged from 24% to as high as 70%.[3]

Patients with hematologic malignancies and transplant recipients are at increased risk for CRE infections due to prolonged hospital stays and frequent exposure to broad-spectrum antimicrobial therapy.[4-7] Recommended empiric antimicrobial regimens for these patients, which include antipseudomonal β-lactams, do not have activity against CRE, and identification of CRE from clinical isolates may take up to 3 d.[8] Further, targeted therapy for CRE infections may be complicated by the use of combination therapy with potentially toxic antimicrobials, including the polymyxins and aminoglycosides, as well as rifampin, which may interact with concomitantly administered immunosuppressive agents and prophylactic agents.[8-10]

This review summarizes our current understanding of the epidemiology and outcomes of CRE infections in solid organ and stem cell transplant recipients, as well as in patients with hematologic malignancies. We will also discuss CRE treatment and prevention strategies germane to the immunocompromised host.

Mechanisms of carbapenem resistance among Enterobacteriaceae

Mechanisms of carbapenem resistance vary, though the production of the *Klebsiella pneumoniae* carbapenemase (KPC) enzyme is the most commonly encountered resistance mechanism in the United States, South America, Mediterranean Europe, China, and Israel.[2,11-13] This Ambler Class A serine β-lactamase is stable against most β-lactamase inhibitors, and KPC-producing isolates also frequently demonstrate resistance to other antimicrobial

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agents, including aminoglycosides and fluoroquinolones.[4,12] The plasmid-based bla_{KPC} gene responsible for KPC production may be transferred between species, and KPC production has been identified in *Enterobacter* spp and *E. coli*.[14,15] The OXA-48-family of enzymes, Ambler Class D serine β-lactamases, hydrolyze oxacillin in addition to having carbapenemase activity and are common in India, Turkey, and North Africa.[16] Metallo-β-lactamases (MBLs), including the Verona integron-encoded and IMP MBLs, are also present among the Enterobacteriaceae. In contrast to KPC, MBLs require zinc at their active site and do not hydrolyze monobactams. Since 2009, the New Delhi MBL (NDM) has become the predominant carbapenemase in India, Pakistan, and the United Kingdom.[17]

CRE in solid organ transplant recipients

CRE infections, particularly those due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP), have become increasingly common in SOT recipients, owing to poor functional status, frequent need for antimicrobial therapy, intensive care unit admissions, mechanical ventilation, and prolonged hospitalizations.[4-7] SOT itself has also been independently associated with the development of CRE infection.[4,18] For example, a nationwide surveillance study of carbapenem-resistant Gram negative infections in Italian SOT recipients showed that CRE comprised 15.7% of Gram negative infections, with *Klebsiella* spp comprising 49% of carbapenem-resistant isolates.[19]

The incidence of post-SOT CRKP infection varies considerably by center and type of transplant (Table 1).[19-33] In general, CRKP infections occur early after transplant, with most studies reporting a median time of <50 days from transplant to infection. Reported mortality rates among SOT recipients with CRE infection generally range from 30–50%, and post-transplant CRKP infections have been associated with as much as a 10-fold risk of death.[19-33] However, a more recent cohort of 164 SOT recipients across 15 international sites confirmed that while CRE infection typically occurs in the early post-transplant period, the one-year survival rate of patients who developed CRE infection within the first year of transplant was 72%.[34] While CRKP infections remain the most common type of CRE infection in SOT recipients, infections due to carbapenem-resistant *Enterobacter* spp., as well as NDM- and OXA-48-producing *K. pneumoniae* have also been reported.[35-38]

The epidemiology of CRE infections in SOT has been best studied in liver and kidney transplant recipients. Centers from New York City and Italy have reported that 6–9% of liver transplant recipients develop CRE infection.[20,23,24,39] In this group, surgical site and intra-abdominal infections are common, and a high proportion of cases involve bacteremia.[23,24] Necrotizing soft

Table 1. Studies of carbapenem-resistant *Klebsiella pneumoniae* in solid organ transplant recipients.

Reference	Geographic Location	Incidence of Post-Transplant CRE Infection	Median Time from Transplant to CRE Infection	Type of Infection[a]	Mortality Rate
Heart Transplants					
[20]	Brazil	16.7% (2/12)	90 days	Bacteremia: 50% Pneumonia: 50%	50% (30-day)
Lung Transplants					
[21b]	Pittsburgh	0.4% (2/546)	218 days	Bacteremia: 100%	0% (30-day)
[22]	Israel	5.9% (8/136)	27 days	Pneumonia: 38% UTI: 25% Bacteremia: 25%	88% (overall)
Liver Transplants					
[20]	Brazil	12.9% (4/31)	16 days	Bacteremia: 100% Pneumonia: 25%	25% (30-day)
[21b]	Pittsburgh	1.3% (8/610)	24 days	Bacteremia: 100% Pneumonia: 50%	25% (30-day)
[23]	New York City	8% (14/175)	12 days	Bacteremia: 86% Peritonitis: 79%	71% (overall)50% (30-day)
[31b]	Greece	NR (17 cases)	13 days	Bacteremia: 100%	82% (ICU mortality)
[24]	New York City	6.6% (20/304)	11 days	SSI/intra-abdominal: 65% Bacteremia: 55%	45% (overall)
[95]	Italy	8.4% (20/237)	42 days	Bacteremia: 90% Pneumonia: 30%	45% (180-day)
Kidney Transplants					
[25]	Brazil	1.9% (21/1101)	49 days	SSI: 48% Bacteremia: 39%	42% (30-day)
[20]	Brazil	26.3% (5/19)	17 days	UTI: 60% Bacteremia: 60%	60% (30-day)
[26]	Argentina	13.3% (6/45)	36 days	UTI: 83% Bacteremia: 17%	33% (overall)
[27c]	New York City	1.1% (20/1852)	47 days	Bacteriuria: 100%	30% (overall)
[28]	New York City	2.5% (13/522)	185 days	UTI: 69% Bacteremia: 38%	46% (overall)
[30]	Italy	NR (8 episodes)	NR	UTI: 100% Bacteremia: 100%	0% (30-day)
Intestinal Transplants					
[21b]	Pittsburgh	5.4% (6/112)	209 days	Bacteremia: 100%	33% (30-day)

Notes. Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; UTI: urinary tract infection; NR, not reported; ICU, intensive care unit; SSI, surgical site infection

[a]The 2 most common sites of infection are listed

[b]The study evaluated episodes of CRE bacteremia only

[c]The study evaluated episodes of CRE bacteriuria only

tissue infections have also been described.[40] CRKP infections, particularly bacteremia, have been associated with a 5 to 7-fold increased risk of death in this patient population.[24,31] In one study, the mortality rates for liver transplant patients with CRKP infections was 78%, compared to 32% for carbapenem-susceptible *K. pneumoniae* infections (78% vs. 32%, respectively).[41,42]

Kidney transplant recipients have lower rates of CRE infection than liver transplant recipients. Centers from New York City, Brazil, and Italy, all areas with high rates of CRE, report that 1–3% of kidney transplant recipients develop CRE infections. Most of these infections are CRKP urinary tract infections (UTIs), with secondary bacteremia present in up to 32% of patients.[20,26-28,30,33] CRKP UTIs are associated with high rates of microbiological failure compared to carbapenem-susceptible *K. pneumoniae* UTIs, and the presence of post-transplant CRKP bacteriuria has been independently associated with a 3-fold risk of death in kidney transplant recipients.[27,33]

To date, 7 cases of CRKP donor-derived infection have been reported. In the first case, the donor was being treated for CRKP pneumonia, infected subdural hematoma, and meningitis. Four patients received organs from this donor and received tigecycline perioperatively. The combined kidney-liver transplant recipient ultimately developed a CRKP-infected hematoma and peritonitis. The recipient's CRKP isolate was phenotypically identical to that of the donor, and he was successfully treated.[43] In the second case, the donor sputum and bronchoalveolar lavage cultures were noted to grow CRKP 2 d following procurement. Recipients of the donor's liver and kidneys did not receive any CRKP-targeted prophylaxis, but the lung transplant recipients received 5 d of parenteral colistin. The liver and kidney recipients never developed CRKP infection, though one lung recipient developed CRKP pneumonia 4 weeks after transplant and died of the infection.[44] The third and fourth cases were linked to a donor colonized by a carbapenem-resistant *Acinetobacter* isolate in the respiratory tract. The recipients of the donor's kidney and liver developed OXA-48 carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections. The kidney transplant recipient also developed a surgical site infection with the same organism, requiring explanation. The surgical site culture from the kidney recipient, the kidney preservation fluid, and bloodstream isolates from both patients all grew *K. pneumoniae* of the same resistance profile, and pulsed-field gel electrophoresis profiles demonstrated genomic relatedness among the isolates. It was presumed that the infections were derived from cross-transmission of the OXA-48-producing carbapenemase from the donor, and both patients were treated with a carbapenem in combination with one additional active agent. The kidney transplant recipient was lost to follow up, but the liver transplant recipient was successfully treated.[38] In a more recent study, Mularoni and colleagues reported the outcomes of 14 SOT recipients who received organs from donors with carbapenem-resistant Gram-negative (CRGN; *Acinetobacter baumannii* or *Klebsiella pneumoniae*) bacteremia or CRGN infection of the donated organ. No CRGN infections occurred in the 8 recipients who received immediate treatment post-transplant with at least one week of therapy with activity against the CRGN organism (appropriate therapy). However, 3 of the 6 patients who were not immediately treated with appropriate therapy developed a post-transplant CRGN infection.[45]

Additional studies are required to better delineate the role of pre-transplant screening for CRE among SOT candidates and donors, as well as the impact of pre-transplant colonization on outcomes, including patient and graft survival. If a donor or recipient is known to be colonized or infected with CRE prior to transplantation, it is recommended that a risk-benefit evaluation be make, taking into account the source of positive donor cultures and the organ being transplanted.[46,47] A recent multicenter study evaluating 57 SOT recipients with CRE colonization or infection prior to transplant demonstrated that one-year post-transplant survival approached 80%, suggesting that prior CRE colonization or infection should not be considered an absolute contraindication to transplantation.[48] Strategies to prevent post-transplant CRE infection may improve survival, and post-transplant screening of SOT recipients may identify individuals at higher risk for post-transplant infection.

CRE in patients with hematologic malignancies and haematopoietic stem cell transplant recipients

Patients with hematologic malignancies and haematopoietic stem cell transplant (HSCT) recipients are at high risk of developing invasive infections due to enteric bacteria because of chemotherapy-induced neutropenia and gastrointestinal mucositis. In fact, Enterobacteriaceae are the most common causes of Gram-negative bacteremia in these patients.[49-51] Guidelines of the Infectious Diseases Society of America recommend that febrile neutropenic patients receive empirical antimicrobial therapy within 2 hours of presentation because outcomes are poor if effective therapy is delayed.[52] However, recommended empirical therapies, such as piperacillin-tazobactam, cefepime, and carbapenems are not active against CRE. Thus, the emergence of CRE in neutropenic

patients with hematologic malignancies and HSCT recipients has grave implications.

In areas where CRE are endemic nosocomial pathogens, such as the Northeast United States, Italy, and Israel, patients with hematologic malignancies represent 16–24% of all patients with CRE bacteremia.[53-55] These areas also report that alarmingly high proportions of Gram-negative bacteremias are due to CRE in this population. Multicenter studies from New York City and Italy have reported that CRE represent 5–6% of all Gram-negative bacteremias in patients with hematologic malignancies,[56,57] and single centers from Israel and Italy have reported that CRE represent 16–18% of Gram-negative bacteremias.[58,59] Pediatric oncology centers have also identified CRE as increasingly common bloodstream pathogens in children with hematologic malignancies.[60] Most of the CRE in these reports are KPC producers, but OXA-48- and NDM-producing CRE are also emerging in patients with hematologic malignancies in locations where these carbapenem resistance mechanisms predominate.[61,62] In one oncology center in India, colistin-resistant CRKP have emerged, leaving essentially no therapeutic options for patients infected by these pathogens.[63]

CRE are also emerging pathogens in HSCT recipients, particularly after allogeneic transplantation. Italian transplant centers reported that the post-transplant incidence of CRKP infection in allogeneic HSCT recipients increased from 0.4% in 2010 to 2.9% in 2013.[64] For comparison, the cumulative incidence of aspergillosis and candidiasis in HSCT recipients in the Transplant-Associated Infection Surveillance Network was 1.6% and 1.1%, respectively.[65]

There is typically a 2–3 day delay from the onset of CRE bacteremia until receipt of CRE-active therapy in patients with hematologic malignancies.[55] This delay reflects the time it takes to identify CRE as the cause of bacteremia using traditional diagnostic microbiologic methods. Thus, it is not surprising that these highly immunocompromised patients, most of whom are neutropenic, have very poor outcomes after CRE bacteremia (Table 2). Overall 30-day mortality rates after CRE bacteremia in patients with hematologic malignancies range from 52 to 63%. Furthermore, the vast majority of these deaths are related to CRE bacteremia, as CRE-related mortality rates of 51% and 54% have been reported in the 2 largest studies to assess this outcome.[55,64]

CRE treatment considerations in transplant and hematologic oncology patients

No randomized clinical trials have been completed to define the optimal treatment for CRE infections. Existing clinical evidence regarding treatment is based upon observational clinical data, *in vitro* data, and *in vivo* animal models.[66] As in the case of many infectious disease syndromes, source control is an important predictor of improved outcomes.[7,46] Antimicrobial therapy has largely relied on the use of older agents, including polymyxins, aminoglycosides, and fosfomycin, as well as tigecycline, all of which carry a high risk of toxicity and/or suboptimal efficacy.[4,46,66]

The polymyxins are considered among the most active agents against CRE.[67] The nephrotoxicity associated with the polymyxins, which approaches 43–60%, is of particular concern in the context of renal transplantation and with the use of concomitant nephrotoxins, including the calcineurin inhibitors. Polymyxin-associated neurotoxicity may also limit treatment.[68-70] The optimal dosing of the polymyxins is still being determined, as accurate pharmacokinetic and pharmacodynamic data have only recently been elucidated. As a

Table 2. Mortality rates after Carbapenem-resistant Enterobacteriaceae (CRE) Infections in patients with hematologic malignancies and haematopoietic stem cell transplant (HSCT) recipients.

Ref.	Geographic Location	Patients (N)	CRE isolate(s)	Types of Infection	HSCT recipients (N)	Neutropenic patients (N)	Overall mortality rate	CRE-related mortality rate
57	Italy 13 centers	161	*K. pneumoniae*	Bacteremia	NR	NR	52% 30-day	NR
64	Italy 52 centers	112	*K. pneumoniae*	Bacteremia (99) Pneumonia only (12) Skin (1)	112	84	52%30-day	54%
54	Italy 5 centers	89	*K. pneumoniae* KPC	NR	NR	70	40% 14-day	NR
56	New York City, USA2 centers	43	Enterobacteriaceae	Bacteremia	15	43	53% 30-day	51%
104	Sao Paolo, Brazil	19	*K. pneumoniae* KPC	Bacteremia (15)UTI (2) Other (2)	1	8	63% 30-day	NR
61	Istanbul, Turkey	16	Enterobacteriaceae OXA-48-type	Bacteremia	NR	15	67% 28-day	NR
105	Cleveland, OH, USA	9	*K. pneumoniae*	Bacteremia	NR	6	33% 14-day	NR
98	Israel	8	*K. pneumoniae*	Bacteremia	5	7	50%	38%
106	Bethesda, MD, USA	6	*K. pneumoniae*	Bacteremia	4	NR	100%	67%

Note. Abbreviations: Ref, reference; N, number; NYC, New York City; KPC, *Klebsiella pneumoniae* carbapenemase; OH, Ohio; MD, Maryland; NR, not reported.

result, US. Food and Drug Administration (FDA) recommendations may lead to suboptimal polymyxin exposures, and more aggressive dosing strategies are undergoing clinical evaluation.[71] When administered parenterally, the polymyxins poorly penetrate lung tissue, though aerosolized colistin may be used as adjunctive therapy for CRE pneumonia.[72,73]

Most CRE isolates maintain susceptibility to tigecycline *in vitro*, although there are limited data supporting its use as monotherapy. The role of tigecycline in treating urinary tract and bloodstream infections is controversial due to the inability to achieve adequate urine and serum concentrations.[4] Two cohort studies demonstrated high mortality rates in patients with CRE bloodstream infections who were treated with tigecycline monotherapy, and one showed similar rates of microbiologic clearance of CRKP bacteriuria between patients treated with tigecycline and untreated patients.[74-76]

Gentamicin is the most active aminoglycoside against CRE, with reported susceptibility rates of 13% to over 90%, depending upon the geographic region.[8,66] CRE susceptibility rates are typically lower to amikacin, and almost all CRE are resistant to tobramycin. In general, NDM-producing isolates are resistant to the aminoglycosides.[17] As with polymyxins, the nephrotoxicity associated with aminoglycosides is a major concern for kidney transplant recipients and potentially all SOT recipients, given the common use of other nephrotoxic agents, such as calcineurin inhibitors. Furthermore, aminoglycoside monotherapy for Gram-negative bacteremia has been associated with poor outcomes compared to β-lactam monotherapy in patients with hematologic malignancies.[77] Similar to the polymyxins, the aminoglycosides have poor penetration into lung tissue when administered parenterally; aerosolized formulations of these agents may be provided as adjunctive therapy for CRE pneumonia. On the other hand, aminoglycoside monotherapy may be efficacious in the treatment of CRE UTIs; however, rates of associated nephrotoxicity and clinical success have varied.[27,33,76,78]

While available as a parenteral agent in Europe, fosfomycin is only available in an oral powder formulation in the United States, and this formulation has only been evaluated for the treatment of UTIs. CRE are often susceptible to fosfomycin,[79] and thus fosfomycin is an attractive option as an oral therapy for CRE UTIs, particularly in kidney transplant recipients where it would be preferable to avoid aminoglycosides. However, clinical data to support its use for CRE UTI are limited. In a study of 13 patients with CRE UTI who were treated with fosfomycin, only 6 achieved a microbiologic cure and 3 developed fosfomycin resistance on therapy.[80] In this study, as well as a study demonstrating that fosfomycin was effective against extended-spectrum-β-lactamase-producing *E. coli* UTIs, fosfomycin was administered as a 3 g dose every 48 hours for 3 total doses.[81] However, the optimal dosing and duration of therapy for CRE UTIs is unknown.[8]

Polymyxins and both rifampin and the carbapenems are generally synergistic against CRE *in vitro*.[82,83] However, the use of polymyxin-rifampin combination therapy should be used with caution in transplant recipients, as rifampin decreases the levels of mTOR and calcineurin inhibitors, as well as triazole antifungals. Combination therapy with agents such as polymyxins, tigecycline, aminoglycosides, and high-dose, prolonged-infusion carbapenems may have higher clinical success rates than monotherapy,[74,84] and combination therapy has been independently associated with survival.[75] Combination therapy using cefepime and levofloxacin has also been successfully utilized for the treatment of a KPC-2 *Enterobacter cloacae* empyema in a lung transplant recipient.[85]

In 2015, the US FDA approved ceftazidime-avibactam for the treatment of complicated intra-abdominal and urinary tract infections. A recent study evaluating the activity of ceftazidime-avibactam against 961 CRE isolates demonstrated that >97% of isolates were susceptible to the agent; its activity was only compromised by NDM-producing isolates.[86] However, clinical trials that led to approval of this agent included very few CRE infections or transplant/hematologic oncology patients. Clinical data to assess the effectiveness of this new agent for CRE infections and its effectiveness in immunocompromised hosts are urgently needed.

Prevention of CRE infection in transplant and hematologic oncology patients

Given the limited therapeutic options and associated morbidity and mortality, prevention of CRE infections in transplant recipients and patients with hematologic malignancies is critical. Furthermore, CRE infections in liver transplant recipients have been reported as the index cases of CRE in hospital outbreaks.[32,87] In 2012, the Centers for Disease Control and Prevention (CDC) published a toolkit providing guidance on the prevention of CRE in healthcare facilities. Updated recommendations in November 2015 included optimizing compliance with hand hygiene and contact precautions, healthcare personnel education, minimizing the use of indwelling devices such as central venous catheters, endotracheal tubes, and urinary catheters, antimicrobial stewardship, environmental cleaning, patient and staff cohorting, screening contacts of CRE patients, active surveillance, and chlorhexidine bathing. Such measures have been

successful in controlling outbreaks of CRE in liver transplantation units.[87,88] The update also stressed the importance of inter-facility communication,[89] which was shown to be a critical component of successful management of organ transplant recipients from a donor infected with CRKP.[43] Following the 2 recent CRE outbreaks related to contaminated duodenoscopes in the United States and during which one kidney-pancreas transplant recipient died,[90,91] the CDC has also provided guidance on surveillance for bacterial contamination of duodenoscopes after reprocessing.[92] In one outbreak, ethylene oxide sterilization of duodenoscopes halted CRE transmission.[93]

Antimicrobial stewardship also has an important role in preventing the emergence of CRE in immunocompromised hosts. While carbapenem use has been linked to the development of CRE infections, the receipt of other antimicrobials, including fluoroquinolones and β-lactams, has also been independently associated with CRE infection.[4,94]

Improving outcomes in transplant and hematologic oncology patients with CRE

Identification of CRE from clinical specimens can take up to 3 d. Thus, unless CRE-active therapy is administered empirically, patients with CRE infections will have long delays until administration of appropriate therapy.[8] These delays likely contribute to the poor outcomes associated with CRE infections in transplant and hematologic oncology patients, particularly in patients who are neutropenic. Strategies are needed to identify patients who are at high-risk of CRE infection, for whom empiric CRE-active therapy should be considered.

Assessing for CRE gastrointestinal colonization may be a tool to identify transplant recipients and patients with hematologic malignancies who are at high-risk of CRE infection. Current data suggest that liver transplant and HSCT recipients who are colonized with CRKP are at high risk of post-transplant CRKP infection. In a large single-center CRKP outbreak, 89% of liver transplant recipients who became colonized ultimately developed CRKP infections.[41] Giannella and colleagues described rectal CRKP carriage in 41 of 237 liver transplant recipients at their center; 11 patients were colonized at the time of liver transplant, and 30 become colonized post-operatively. The rates of CRKP infection among non-colonized patients after liver transplant was 2%, compared to 18.2% and 46.7% among those colonized at the time of transplant and after transplant, respectively. The authors proposed a scoring system that consisted of the need for renal replacement therapy, >48 hours of mechanical ventilation, histological recurrence of hepatitis C virus, and CRKP rectal carriage at any time, to discriminate patients at low versus higher risk for CRKP infection following liver transplant.[95]

In a nationwide study of Italian HSCT centers, over 5,000 patients were screened for colonization with CRKP prior to transplantation.[64] Of these, 1% of autologous and 2.4% of allogeneic HSCT recipients were colonized with CRKP prior to their transplant. Eight (26%) of the 31 colonized autologous HSCT recipients and 20 (39%) of the 52 colonized allogeneic HSCT recipients developed a subsequent post-transplant CRKP infection, and the vast majority of these infections were bacteremia. The high rates of colonization to infection in liver transplant and HSCT recipients, combined with poor outcomes associated with delays in CRE-active therapy in these populations, warrant consideration of screening for gastrointestinal CRE colonization to guide empirical antimicrobial therapy in these patients in areas where CRE are highly endemic. In the case of liver transplant recipients, data from Giannella et al. suggest that gastrointestinal surveillance should continue after the transplant.[95] Further studies are needed to validate the above findings and assess the role of screening for CRE in other types of SOT recipients and patients with hematologic malignancies who do not undergo HSCT.

An additional rationale for screening for CRE colonization is that colonized patients could be candidates for gastrointestinal CRE decolonization. In the pre-transplant setting, small studies evaluating the role of selective digestive decontamination (SDD) with oral gentamicin with or without oral colistin have demonstrated a significant decline in CRKP carriage rates.[96,97] However, this strategy was not effective in preventing CRKP infections in HSCT recipients[98] and has also been associated with the development of colistin and gentamicin resistance.[97,99] The development of resistance to some of the only treatment options for CRE infections is a major concern and thus the use of SDD prior to SOT or HSCT cannot be routinely recommended.[46] Another strategy to consider in patients who are colonized with CRE and undergoing SOT is to administer peri-operative CRE-active prophylaxis. One single-center report in a CRE-endemic area reported that there were no CRKP infections after initiation of perioperative gentamicin prophylaxis in renal transplant recipients.[100] Additional studies are required to better assess the role of targeted CRE perioperative prophylaxis in the context of SOT.

Important advances in the clinical microbiology laboratory may also decrease the time to initiation of appropriate antimicrobial therapy for CRE infections in immunocompromised hosts. Two real-time, multiplex polymerase chain reaction systems have recently been approved in the US and can identify carbapenemase

genes within 2 hours of blood culture positivity.[101-103] Implementation of these tools can decrease the time from blood culture collection until detection of CRE from 3 d to less than 24 hours. Furthermore, these systems also allow clinicians to de-escalate therapy when appropriate and avoid the attendant toxicities of CRE-active agents.

Conclusions

CRE continue to be an evolving threat to immunocompromised hosts, particularly SOT and HSCT recipients, as well as those with hematologic malignancies. Prospective multicenter studies are needed to better inform our understanding of the epidemiology of these infections, the role for CRE screening and preventative management strategies, and the management of CRE-colonized SOT donors and their recipients, particularly in the current era of donor shortages. There is also an urgent need for research and development of new antimicrobials active against CRE in an attempt to improve outcomes and minimize toxicities and drug interactions in this vulnerable population.

Abbreviations

CDC	Centers for Disease Control and Prevention
CRE	carbapenem-resistant Enterobacteriaceae
CRGN	carbapenem-resistant Gram-negative
CRKP	carbapenem-resistant *Klebsiella pneumoniae*
FDA	Food and Drug Administration
HSCT	haematopoietic stem cell transplant
KPC	*Klebsiella pneumoniae* carbapenemase
MBL	metallo-β-lactamase
NDM	New Delhi metallo-β-lactamase
SDD	selective digestive decontamination
SOT	solid organ transplant
UTI	urinary tract infection

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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