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The Global Challenge of Carbapenem-Resistant Enterobacteriaceae in Transplant Recipients and Patients With Hematologic Malignancies

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(See the Editorial Commentary by Johnson and Boucher on pages 1284–6.)

Carbapenem-resistant Enterobacteriaceae (CRE) are emerging global pathogens. The spread of CRE to transplant recipients and patients with hematologic malignancies has ominous implications. These patients rely on timely, active antibacterial therapy to combat gram-negative infections; however, recommended empirical regimens are not active against CRE. Approximately 3%–10% of solid organ transplant (SOT) recipients in CRE-endemic areas develop CRE infection, and the infection site correlates with the transplanted organ. Mortality rates associated with CRE infections approach 40% in SOT recipients and 65% in patients with hematologic malignancies. Given that the current antimicrobial armamentarium to combat CRE is extremely limited, a multifaceted approach that includes antimicrobial stewardship and active surveillance is needed to prevent CRE infections in immunocompromised hosts. Improving outcomes of established infections will require the use of risk factor–based prediction tools and molecular assays to more rapidly administer CRE-active therapy and the development of new antimicrobial agents with activity against CRE.

Keywords. carbapenem resistance; Enterobacteriaceae; immunocompromised hosts.

Enterobacteriaceae cause approximately 30% of healthcare-associated infections in the United States [1]. With the emergence of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, carbapenems have been increasingly used against these organisms [2]. Unfortunately, carbapenem resistance among Enterobacteriaceae has now emerged, particularly in *Klebsiella pneumoniae*. The percentage of *Klebsiella* isolates from US hospitals that are carbapenem-resistant increased from <1% in 2000, to 8% in 2006–2007, to 12% in 2009–2010 [1, 3, 4]. Although initially largely confined to New York hospitals, carbapenem-resistant Enterobacteriaceae (CRE) have now been identified in 42 US states [5]. CRE also have become endemic in parts of South America, Europe, Africa, and Asia, posing a major international public health threat [6]. Infections caused by CRE are associated with mortality rates approaching 50% [7, 8].

Immunocompromised hosts depend on the immediate receipt of active antibacterial agents to combat gram-negative infections. However, recommended empirical regimens in these patients [9], such as antipseudomonal β-lactams, are not active against CRE and identification of CRE from clinical specimens typically takes 2–4 days [10]. Thus, the emergence of CRE in immunocompromised hosts has grave implications.

Given these concerns, we reviewed all published English-language manuscripts and abstracts of CRE infections in transplant recipients and patients with hematologic malignancies to summarize the current understanding of the epidemiology of CRE infections in these populations. We also review carbapenem resistance mechanisms and treatment options and propose strategies to minimize this threat.

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CARBAPENEM RESISTANCE MECHANISMS AMONG ENTEROBACTERIACEAE

Carbapenem resistance among Enterobacteriaceae is due to either a carbapenem-hydrolyzing enzyme (carbapenemase), the most common mechanism, or changes in outer membrane porins combined with overproduction of AmpC β-lactamases or ESBLs [6] (Table 1). Carbapenemases, like other β-lactamases, are organized by amino acid homology in the Ambler classification system [15]. Ambler Class A, C, and D β-lactamases have a serine at their active site, whereas class B enzymes require zinc and thus are called metallo-β-lactamases (MBLs).

Klebsiella pneumoniae carbapenemase (KPC) is a class A β-lactamase and is the most common carbapenem resistance mechanism among Enterobacteriaceae in the United States, South America, Mediterranean Europe, Israel, and China [6, 11–13]. KPC hydrolyzes all β-lactams and is stable against available β-lactamase inhibitors. KPC-producing isolates are also frequently resistant to agents of other classes, such as fluoroquinolones and aminoglycosides, leaving few therapeutic options [8, 11, 16]. The gene bla_{KPC} is located on plasmids that can be transferred within bacterial species and to different species and genera. Although KPC is most common in *K. pneumoniae,* it has also emerged in *Enterobacter* species and *Escherichia coli* [17, 18].

MBLs also hydrolyze carbapenems and other β-lactams and are stable against available β-lactamase inhibitors [6]. Unlike KPC, MBLs do not hydrolyze monobactams. Until recently, Verona integron–encoded (VIM) and IMP types were the most common MBLs among Enterobacteriaceae. However, in 2009, a novel plasmid-encoded enzyme, New Delhi MBL (NDM), was identified and quickly established as the dominant carbapenemase in India, Pakistan, and the United Kingdom [19]. Like KPC, NDM has spread to genera other than *Klebsiella* [20]. To date, few NDM-producing isolates have been reported in the United States, and all were from patients with recent travel to the Indian subcontinent [21].

OXA-type enzymes are class D β-lactamases named after their ability to hydrolyze oxacillin. Within this family, OXA-48-type enzymes have substantial carbapenemase activity and are prominent in Turkey, North Africa, and India [14].

CRE IN SOLID ORGAN TRANSPLANT RECIPIENTS

Enterobacteriaceae, and in particular *K. pneumoniae*, have become increasingly common causes of infections in recipients of solid organ transplant (SOT) [22]. Thus, one would expect the emergence of CRE to disproportionately affect this population. Indeed, a large proportion of CRE bacteremias occur in SOT recipients, and organ transplant is an independent risk factor for CRE infection [8]. Reports focusing on CRE in SOT recipients are outlined in Table 2.

Centers from CRE-endemic areas report a 3%–10% incidence of carbapenem-resistant *K. pneumoniae* (CRKP) infection in SOT recipients with similar rates after liver, kidney, lung, and heart transplant [23–26, 28, 31, 32]. The site of infection correlates with the transplanted organ, with pneumonia being most common after lung transplant, bacteremia and intra-abdominal infection after liver transplant, and urinary tract infection (UTI) after kidney transplant. SOT recipients infected with CRKP have a 30-day mortality rate of 37% (34 of 91 patients) [25–28, 30, 32, 33], and post-transplant CRKP bacteremia is associated with greater mortality than carbapenem-susceptible *K. pneumoniae* (CSKP) bacteremia [33]. Although KPC-producing *K. pneumoniae* (KPC-*Kp*) is the most common type of CRE in SOT recipients, infections caused

Table 1. Prominent Mechanisms of Carbapenem Resistance Among Enterobacteriaceae

Carbapenemases	Ambler Molecular Class	Requirement for Enzymatic Activity	Gene Location	Geographic Distribution[a] [6, 11–14]
KPC	A	Serine	Plasmid	US, Colombia, Brazil, Argentina, Greece, Italy, Malta, Israel, China
NDM	B	Zinc	Plasmid	India, Pakistan, Bangladesh, United Kingdom
VIM	B	Zinc	Plasmid	Greece
IMP	B	Zinc	Plasmid	Japan, Taiwan
OXA-48-types	D	Serine	Plasmid	Turkey, Morocco, Algeria, Tunisia, India
Other mechanisms				
ESBL or AmpC-type β-lactamase + OMP mutation	A/C	Serine	Plasmid or chromosomal	Worldwide[b]

Abbreviations: ESBL, extended-spectrum β-lactamase; IMP, "active on imipenem"; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OMP, outer membrane porin; VIM, Verona integron–encoded metallo-β-lactamase.

[a] Locations with the highest prevalence for each carbapenem resistance mechanism.

[b] Carbapenem resistance is more commonly due to carbapenemase production than these mechanisms in the geographic locations listed above.

Table 2. Studies of Carbapenem-Resistant *Klebsiella pneumoniae* Infections in Solid Organ Transplant Recipients

Reference	Geographic Location	Incidence of Posttransplant CRE Infection	Median Time From Transplant to Infection	Type of Infection[a]	Mortality Rate
Liver transplants					
[23]	NYC	3.6% (25/691)	20 d	Bacteremia: 60% Intra-abdominal: 76%	52% (in-hospital)
[24]	Italy	6.3% (16/252)	NR	Bacteremia: 50% SSI: 50%	NR
[25]	NYC	8.0% (14/175)	12 d	Bacteremia: 86% Intra-abdominal: 79%	50% (30-day)
[26]	Pittsburgh[b]	1.3% (8/610)	24 d	Bacteremia: 100% Pneumonia: 50%	25% (30-day)
[27]	Germany	NR (8 episodes)	23 d	Bacteremia: 63% Pneumonia: 50%	50% (30-day)
[28]	Brazil	12.9% (4/31)	16 d	Bacteremia: 100% Pneumonia: 25%	25% (30-day)
Kidney transplants					
[29]	NYC	NR (23 bacteriuria episodes)	65 d	UTI: 100% Bacteremia: 11%	40% (overall)
[24]	Italy	9.4% (12/128)	NR	UTI: 67% Bacteremia: 33%	NR
[30]	Italy[b]	NR (8 episodes)	NR	UTI: 100% Bacteremia: 100%	0% (30-day)
[31]	Argentina	13.3% (6/45)	36 d	UTI: 83% Bacteremia: 17%	33% (overall)
[28]	Brazil	26.3% (5/19)	17 d	UTI: 60% Bacteremia: 60%	60% (30-day)
Lung transplants					
[32]	Israel	6.6% (9/136)	25 d	Pneumonia: 56% Bacteremia: 22%	56% (30-day)
[24]	Italy	4.2% (2/48)	NR	Pneumonia: 50% Bacteremia: 50%	NR
[26]	Pittsburgh[b]	0.4% (2/546)	218 d	Bacteremia: 100%	0% (30-day)
Heart transplants					
[24]	Italy	7.5% (4/53)	NR	Bacteremia: 50% SSI: 50%	NR
[28]	Brazil	16.7% (2/12)	90 d	Bacteremia: 50% Pneumonia: 50%	50% (30-day)
All transplants					
[33]	Cleveland	NR (23 bacteremia episodes)	73 d	Bacteremia: 100%	43% (30-day)

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; NR, not reported; NYC, New York City; SSI, surgical site infection; UTI, urinary tract infection.

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

[b] The study evaluated episodes of CRE bacteremia only.

by NDM-producing *K. pneumoniae* and KPC-producing *Enterobacter cloacae* also have been reported [34, 35].

The emergence of CRKP has been best evaluated in liver transplant recipients, for whom the incidence of posttransplant CRKP infection in endemic areas is approximately 5% [23–25, 28]. CRKP infections occur early (median, 12–24 days) after liver transplant, 55% of infections are intra-abdominal, and two-thirds involve bacteremia. Lethal necrotizing soft tissue infections have also been reported [36]. In multivariate analysis, the mortality of patients with posttransplant CRKP infection is 5-fold higher than those without CRKP infection [25]. Liver transplant recipients also have been index cases of hospital-wide CRKP outbreaks [37].

CRKP primarily causes UTIs in kidney transplant recipients [24, 28, 29, 31]. In a study of 27 CRKP bacteriuria episodes in this population, only 3 (11%) had concurrent bacteremia [29]. Seventeen of 21 (81%) treated episodes achieved microbiologic clearance, but 8 (38%) had recurrence of CRKP bacteriuria. CRKP bacteriuria after transplant was associated with increased mortality compared with CSKP bacteriuria.

Two donor-derived CRKP infections have been reported. In the first case, the donor's respiratory tract was found to be colonized with CRKP after transplant of his organs [38]. Recipients of each of his lungs were given prophylactic intravenous colistin. However, one lung recipient developed CRKP pneumonia 4 weeks after transplant and died. The recipient's isolate was phenotypically identical to the donor's isolate. Recipients of the donor's liver and kidneys did not receive prophylaxis against CRKP and never developed CRKP infection. In the second case, the donor was known to have CRKP pneumonia and meningitis [39]. Four patients received organs from this donor and all received perioperative tigecycline. One of these patients, a kidney and liver recipient, developed peritonitis and an infected hematoma due to CRKP shortly after transplant. His isolates were genetically identical to the donor's isolates and he was successfully treated.

CRE IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES AND HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Patients with hematologic malignancies and hematopoietic stem cell transplant (HSCT) recipients may be particularly vulnerable to CRE infection because of chemotherapy-induced gastrointestinal mucositis, prolonged hospitalizations and neutropenia, and frequent use of broad-spectrum antibacterial agents. Previous reports of CRE infections have included patients with hematologic malignancies and HSCT recipients [8, 40], but few have focused exclusively on these populations.

To examine the threat posed by CRE to these immunocompromised hosts, we reported 18 patients with hematologic malignancies who developed CRE bacteremia [41]. Despite using recommended regimens [9], empiric therapy was inadequate in almost all cases. Three patients died before antimicrobial susceptibilities were available and never received active therapy. There was a median of 55 hours from blood culture collection until receipt of an active agent in the other 15 patients. Nine of 13 (69%) neutropenic patients died, with a median of 4 days from presentation until death. Infections were caused by a heterogeneous group of isolates, including KPC-producing *K. pneumoniae*, *E. cloacae*, *E. coli*, and *Klebsiella oxytoca*, and isolates resistant to carbapenems because of altered outer membrane porins and ESBL production. Other reports have confirmed these observations of high in-hospital mortality rates for CRE bacteremia in this highly immunocompromised population (65%; 22 of 34 patients). Moreover, the majority of these deaths were attributable to CRE infection (Table 3) [40–45].

THERAPEUTICS

The only available antibacterial agents with activity against CRE are polymyxins (colistin and polymyxin B), tigecycline, fosfomycin, gentamicin, and amikacin (Table 4).

Table 3. Studies of Carbapenem-Resistant Enterobacteriaceae Bacteremia in Hematopoietic Stem Cell Transplant Recipients and Patients With Hematologic Malignancies

Reference	Geographic Location	Patients, No.	CRE Isolate(s) (No.)	Hematologic Malignancies (No.)	HSCT Recipients, No.	Neutropenic Patients, No.	In-Hospital Mortality Rate	CRE-Attributed Mortality Rate
[41]	NYC	18	*Klebsiella pneumoniae* (14) *Enterobacter cloacae* (3) Polymicrobial (1)[a]	Acute leukemia (11) Lymphoma (4) Multiple myeloma (2) Myelofibrosis (1)	6	13	56%[b]	56%
[42]	Israel	8	*K. pneumoniae*	Acute leukemia (3) Lymphoma (2) Aplastic anemia (2) Multiple myeloma (1)	5	7	50%	38%
[40]	Bethesda, Maryland	6	*K. pneumoniae*	Aplastic anemia (2) Lymphoma (2) Primary immunodeficiency (2)	4	NR	100%	67%
[43]	Israel	1	*K. pneumoniae*	Acute leukemia	0	1	1/1	1/1
[44]	Israel	1	*Escherichia coli*	Acute leukemia	1	0	NR	0/1
[45]	NYC	1	*Enterobacter gergoviae*	Acute leukemia	0	1	1/1	1/1

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; HSCT, hematopoietic stem cell transplant; NR, not reported; NYC, New York City.

[a] Infection with carbapenem-resistant *Klebsiella pneumoniae*, carbapenem-resistant *Klebsiella oxytoca*, and carbapenem-resistant *Escherichia coli*.

[b] The mortality rate in neutropenic patients was 69%.

Table 4. Approved and Investigational Antibacterial Agents With Activity Against Carbapenem-Resistant Enterobacteriaceae

Antimicrobial Agent	Mechanism of Action	Dosage	Dosage Adjustment for Renal Impairment	Limitations
Approved agents				
Polymyxins (IV) [46–54]				
Colistin	Binds to LPS and phospholipids in the outer membrane, leading to leakage of intracellular contents Administered as a prodrug: CMS	• US: Coly-Mycin M: 2.5–5 mg/kg/d of CBA (divided into 2–4 doses) • Europe: Colomycin: 6–9 million IU/d[a] (divided into 2–3 doses)[b]	Yes	• Nephrotoxicity and neurotoxicity • Suboptimal clinical efficacy when used as monotherapy • Optimal dosing regimen and antimicrobial susceptibility testing method unclear • Heteroresistance common • Low concentrations in the respiratory tract
Polymyxin B	Same as colistin, except administered as an active drug	1.5–2.5 mg/kg (15 000–25 000 units) per day	No	Same as colistin, except also achieves low concentrations in the urinary tract
Tigecycline (IV) [55, 56]	Binds to the 30S ribosomal subunit, blocking the binding of tRNA	100 mg loading dose, followed by 50 mg every 12 h	No	• Low bloodstream and urinary tract concentrations • Not bactericidal • Use associated with increased mortality in randomized trials
Fosfomycin (IV or oral) [57–59]	Inhibits peptidoglycan (and thus cell wall) biosynthesis	• US: oral formulation only: 3 g in 3–4 oz of water (once, or every 2–3 d for 3 doses) • Europe: IV formulation available: 2–4 g every 6–8 h	No	• IV formulation not available in the United States • Optimal dose vs CRE is unknown • Low barrier to the development of resistance • Limited efficacy data vs CRE
Aminoglycosides[c] (IV) [19, 60–64]				
Gentamicin	Binds to a 16S rRNA portion of the 30S ribosomal subunit, blocking mRNA translocation. Also binds to the outer membrane, leading to leakage of intracellular contents.	• Extended-interval: 5–7 mg/kg every 24 h • Conventional: 2–3 mg/kg loading dose, followed by 1.5–2 mg/kg every 8 h	Yes	• Nephrotoxicity and otovestibular toxicity • Suboptimal clinical efficacy when used as monotherapy for bacteremia • Low concentrations in the respiratory tract and diminished activity in acidic environments • Variable activity vs CRE (40% of KPC producers in the United States and nearly all NDM producers are resistant)
Amikacin	Same as gentamicin	• Extended-interval: 15 mg/kg every 24 h • Conventional: 7.5 mg/kg every 12 h	Yes	• Same as gentamicin, except: • Less nephrotoxicity and ototoxicity • Less activity vs CRE
Investigational agents in phase 3 clinical trials				
Avibactam (IV) [65–67]	A non–β-lactam, β-lactamase inhibitor with activity against class A carbapenemases	The combination of ceftazidime-avibactam at doses of 2000/500 mg every 8 h is being evaluated in phase 3 trials	Yes	Not active against metallo-β-lactamase producers (eg, NDM)
Plazomicin (IV) [68]	Same mechanism as other aminoglycosides, but its activity is not diminished by aminoglycoside-modifying enzymes	A dose of 15 mg/kg every 24 h is being evaluated in phase 3 trials	Yes	• Less nephrotoxic and ototoxic than other aminoglycosides • Not active against isolates that are aminoglycoside-resistant due to ribosomal methyltransferases (eg, most NDM producers)

Abbreviations: CBA, colistin base activity; CMS, colistimethate sodium; CRE, carbapenem-resistant Enterobacteriaceae; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; LPS, lipopolysaccharide; mRNA, messenger RNA; NDM, New Delhi metallo-β-lactamase; rRNA, ribosomal RNA; tRNA, transfer RNA.

[a] One million IU of CMS is equivalent to approximately 30 mg CBA.

[b] A loading dose of 9 million IU may be considered to quickly achieve sufficient plasma colistin concentrations [49].

[c] Tobramycin is rarely active against CRE.

Each of these agents has significant limitations. Polymyxins are associated with nephrotoxicity rates of 43%–60% and also cause neurotoxicity [46–48]. The optimal dosing of polymyxins is unclear, as pharmacokinetic and pharmacodynamic properties are only recently being elucidated [48–50]. Antimicrobial susceptibility testing for polymyxins is problematic. Polymyxins are large cations that diffuse poorly in agar and bind to glass and plastic surfaces, leading to concentrations in test systems that are lower than expected [51]. Additionally, many CRE isolates have resistant subpopulations (heteroresistance) [52]. Thus, common antimicrobial susceptibility testing methods, such as disk diffusion and Etest, are often inaccurate [53]. Compounding this problem, the ability to interpret results is limited by the absence of breakpoints for polymyxins and the Enterobacteriaceae. In addition to these concerns, polymyxins have suboptimal clinical efficacy. Observational studies suggest that infections treated with polymyxin monotherapy have worse clinical outcomes than those treated with β-lactams, even after adjustment for confounders [54, 69].

Tigecycline's limitations against CRE are even more problematic. It is not bactericidal [55], which may limit its effectiveness in immunocompromised patients, and is not active against *Pseudomonas aeruginosa*. Tigecycline achieves low bloodstream and urinary tract concentrations and thus is inadequate for bacteremias and UTIs [55]. It has US Food and Drug Administration (FDA) approval for complicated skin, soft tissue, and intraabdominal infections and community-acquired pneumonia. However, even when used for these indications, randomized trials show increased mortality and lower cure rates with tigecycline compared with other antibiotics [56]. Thus, tigecycline cannot be relied upon to treat serious CRE infections in immunocompromised hosts.

Fosfomycin is available as an intravenous formulation in Europe, but only as a powder that is mixed with water and ingested in the United States. Rates of CRE susceptibility to fosfomycin vary (45%–93%) and depend on the testing methodology used [57, 58]. The optimal dosage and duration of fosfomycin for treatment of CRE infections is unknown. Moreover, data supporting its efficacy for CRE infections are limited, and resistance may develop rapidly on therapy [59].

The activity of aminoglycosides against CRE is variable, as isolates from Israel and Italy have higher gentamicin susceptibility rates (>90%) [16, 60] than do isolates from the United States and Greece (13%–61%) [8, 61, 62]. CRE are more likely to be susceptible to gentamicin than amikacin and are almost always resistant to tobramycin [61, 62]. NDM-producing CRE are typically resistant to aminoglycosides [19]. Even when active in vitro, aminoglycosides are suboptimal therapies because of high rates of nephrotoxicity and otovestibular toxicity [63], poor penetration into lung tissue [64], and comparatively poor efficacy when used as monotherapy for gram-negative bacteremia in immunocompromised patients [69, 70].

Not only do polymyxins, tigecycline, fosfomycin, and aminoglycosides have major limitations, but resistance to each of these agents has been increasingly reported among CRE [62, 71]. Given these considerations, combination therapy for CRE infections should be considered. In vitro synergy has been documented between polymyxins and both carbapenems and rifampin against CRE [61, 72], despite resistance to carbapenems and rifampin alone. In an observational study of 125 patients with KPC-*Kp* bacteremia, 30-day mortality was lower in patients who received combination regimens, compared with single-agent regimens (34% vs 54%) [60]. Other studies have confirmed these findings, most often demonstrating a benefit to polymyxin-carbapenem combination therapy [7, 73]. The polymyxin-rifampin combination is difficult to administer in transplant recipients because rifampin severely decreases levels of calcineurin and mTOR inhibitors and triazole antifungals.

The optimal treatment of CRE infections that are resistant to all of these agents is unknown. One approach for pan-resistant KPC-*Kp* infections is to combine ertapenem with imipenem, meropenem, or doripenem. The rationale for this combination is that KPC has greater affinity for ertapenem than for other carbapenems. This binding of the enzyme by ertapenem reduces its availability for hydrolysis of the other carbapenem. This approach has been effective in vitro and in a murine model [74], and has been used to successfully treat 4 patients with pan-resistant KPC-*Kp* infections [75, 76].

The pharmacokinetic limitations of CRE-active agents must be considered when treating pneumonia. Aminoglycosides and polymyxins achieve low concentrations in pulmonary epithelial lining fluid when administered intravenously [64, 77]. Aerosolized formulations of colistin and aminoglycosides deliver high drug concentrations at the site of infection, and thus should be considered as adjunctive therapies for CRE pneumonia [78–80]. Observational studies of patients with carbapenem-resistant gram-negative ventilator-associated pneumonia have demonstrated improved clinical cure rates [78, 80] and decreased duration of mechanical ventilation [80] in patients who received aerosolized and intravenous colistin, compared with matched controls who received only intravenous colistin. The role of aerosolized aminoglycosides for CRE pneumonia has not been evaluated.

FUTURE DIRECTIONS TO MINIMIZE THE IMPACT OF CRE ON IMMUNOCOMPROMISED HOSTS

Infection Prevention

Given the limited therapeutic options, prevention of CRE infection in these vulnerable populations is of paramount importance. The Centers for Disease Control and Prevention has established a CRE Toolkit for guidance on CRE prevention in

healthcare facilities [81]. Recommendations include optimizing compliance with hand hygiene and contact precautions, educating healthcare personnel, minimizing the use of indwelling devices (eg, central venous catheters), antimicrobial stewardship, and screening for CRE colonization.

Limiting unnecessary uses of antimicrobial agents through multidisciplinary stewardship programs is critical to minimize the emergence of CRE in immunocompromised patients. Antimicrobial exposures are consistently identified as risk factors for CRE infection in the general inpatient population and undoubtedly are also risk factors in immunocompromised hosts [8, 16]. Not only do carbapenems predispose to CRE, but other β-lactams and fluoroquinolones are also independent risk factors for CRE infection [8, 16].

Surveillance cultures of the gastrointestinal tract identify a relatively large number of asymptomatic patients who are colonized with CRE [82]. Rates of subsequent CRE infection in patients found to be colonized by screening cultures are 9% among the general inpatient population [83], 27% among intensive care unit patients [82], and perhaps even higher among neutropenic patients. In a study of 15 patients with hematologic malignancies who were colonized with CRKP, 8 developed CRKP bacteremia after chemotherapy or HSCT, despite receiving oral gentamicin [42]. Collecting surveillance cultures to identify colonized immunocompromised hosts also may limit nosocomial CRE transmission. Active surveillance, when accompanied by implementation of contact precautions for colonized patients, daily decontamination of environmental surfaces, and cohorting of patient care staff, has led to major reductions in CRE infection rates in outbreak and endemic settings [84–86]. Given these considerations, institutions with a high prevalence of CRE should consider screening patients for gastrointestinal colonization prior to transplant or administration of chemotherapy and periodically thereafter during their admission.

To prevent donor-derived CRE infections, transplant centers should consider performing surveillance rectal, urine, and respiratory tract cultures of donors from a CRE-endemic area. This approach identified a high rate of asymptomatic CRE colonization among potential donors at an Italian center [87]. The safety of transplanting organs from CRE-colonized donors is unclear. Of the 9 reported organ recipients from colonized donors, 2 developed CRKP infection and 1 died [38, 39]. The death of a lung recipient from a donor with respiratory tract CRE colonization warrants caution in the use of organs that are colonized with CRE [38]. If organs from CRE-colonized donors are used, CRE-active therapy should be administered to donors prior to harvest and to recipients before and after transplant.

Improving Outcomes of Infected Patients

Unless CRE-active therapy is administered empirically, relying on culture-based techniques to identify CRE leads to a 48- to 72-hour delay from blood culture collection until administration of appropriate therapy [41]. Given the high mortality rates with CRE infections and the association between delay in active therapy and mortality from gram-negative bacteremia [70, 88], strategies are needed to administer CRE-active therapy in a more timely manner. The administration of an empirical polymyxin to all transplant or neutropenic patients who develop fever or sepsis is not justifiable because of high toxicity rates and the potential for the emergence of resistance to these last-line agents. Instead, a rational strategy to pursue in CRE-endemic areas is to use colonization status and epidemiologic risk factors to administer polymyxins empirically, in combination with a broad-spectrum β-lactam, only to patients at high risk for CRE infection. However, more data are needed on risk factors that are unique to immunocompromised hosts, such as immunosuppressive therapies, neutropenia, and transplant-associated surgical procedures, before this strategy can be successfully implemented.

Another important approach to decrease the time until administration of active therapy is the use of novel molecular diagnostic tests to rapidly identify CRE. Polymerase chain reaction (PCR)–based assays are available that detect the most common carbapenemase-encoding genes, such as bla_{KPC}, and can be performed directly on blood from culture bottles that signal for growth of gram-negative rods [10]. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry assays are also promising tools that detect bacterial species and carbapenemases within a few hours [89]. If these assays were implemented, the time from culture collection until identification of CRE could be decreased from 2–3 days to <24 hours. Not only would earlier identification of CRE lead to more rapid administration of appropriate therapy, but in cases where toxic CRE-active therapies are administered empirically, it would lead to more rapid de-escalation from these agents. Further research is needed to improve these assays and optimize their use in clinical care.

The paucity and limitations of available CRE-active antimicrobial agents underscore the urgent need for new agents with activity against CRE. The investigational CRE-active compounds that are closest to FDA approval are avibactam (NXL-104) and plazomicin (ACHN-490) (Table 4). Avibactam is a novel β-lactamase inhibitor that inhibits class A and C β-lactamases, including KPC [65]. The combination of ceftazidime and avibactam has excellent in vitro activity against KPC-producing Enterobacteriaceae and is in phase 3 clinical trials. Notably, avibactam does not have activity against MBLs. Phase 2 trials of ceftazidime-avibactam show comparable safety and efficacy to carbapenems for intraabdominal infections and UTIs due to carbapenem-susceptible organisms [66, 67]. Plazomicin is a next-generation aminoglycoside that is in phase 3 trials and has activity against CRE that are resistant to traditional

aminoglycosides due to aminoglycoside-modifying enzymes, including KPC-producing isolates [68]. However, plazomicin is not active against most NDM producers, which are typically resistant to aminoglycosides due to ribosomal methylation. The limitations of these new agents, as well as the lack of other promising investigational compounds, highlight the urgency of increasing the investment in antibiotic development [90].

Notes

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