Imminent Challenges: Carbapenem-Resistant Enterobacteriaceae in Transplant Recipients and Patients With Hematologic Malignancy

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(See the Immunocompromised Hosts Invited Article by Satlin et al on pages 1274–83.)

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In this issue of Clinical Infectious Diseases, Satlin and colleagues review the timely and important topic of carbapenem-resistant Enterobacteriaceae (CRE) in solid organ transplant (SOT) recipients and patients with hematologic malignancies. They review epidemiology of CRE infections, resistance mechanisms, potential treatments, and their limitations as well as avenues to reduce the impact of CRE in these patient populations [1].

New York was the initial epicenter of CRE in the United States, but this review demonstrates that the problem is now truly global with 3%–10% of SOT recipients infected in endemic areas. This is concerning as CRE species are sources of outbreaks and highly lethal, with mortality rates of 40% in SOT recipients and 65% in patients with hematologic malignancy. This report emphasizes the importance of infection prevention, antimicrobial stewardship, and development of new antibiotic therapy but leaves a few important questions.

CRE infection is common in transplant recipients and, in fact, SOT independently predicts risk for CRE infection. In some centers, nearly the entire burden of CRE infections resides in SOT recipients [2]. Perhaps just as concerning, CRE infections in transplant recipients have served as index cases of hospital-wide carbapenem-resistant Klebsiella pneumoniae outbreaks. It is worth noting that available data are based on retrospective small case series, some with missing duration of illness and mortality data; the impact of these infections may well extend beyond what we glean from these reports.

What can be done to reduce the threat of CRE infections in transplant recipients? Currently, surveillance for CRE is limited, even in hospitals. The authors logically suggest active surveillance in immunocompromised hosts with identification of colonized patients and point out that active surveillance programs and contact precautions have been successful in decreasing nosocomial transmission and preventing further CRE outbreaks. Currently, the Centers for Disease Control and Prevention recommends actively screening patients only in facilities with known CRE transmission or an epidemiologic link to unrecognized CRE [3]. Consideration of active surveillance for CRE colonization in all patients prior to transplant or chemotherapy in institutions with a high prevalence of CRE is also advocated; identification of CRE colonization in these patients may prevent further spread and provide the opportunity for intervention with chlorhexidine bathing to prevent infection. However, the exact contribution of surveillance cultures in decreasing CRE is not known, and to date there is no evidence that surveillance per se will actually reduce transmission. Such strategies may also decrease time to appropriate antibiotic therapy should serious infection occur in these patients. However, these interventions carry significant cost in both human resources and financial investment. For gastrointestinal colonization surveillance, staff cohorting, additional donor screening for CRE, and increased time and effort in the hospital microbiology laboratory may be required (eg, to perform cultures with selective media), as well as increased time and effort from the infection prevention team. Universal chlorhexidine bathing in high-risk areas to prevent or reduce colonization may be more feasible.

Antimicrobial stewardship has also been shown to be critical to preventing...
and managing these infections. The authors point out that usage of carbapenems, other β-lactams, and fluoroquinolones are independent risk factors for CRE infection. Marchaim and colleagues found that in comparing CRE and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, CRE and non-ESBL-containing Enterobacteriaceae, and CRE among all 3 comparison groups combined, antimicrobial exposure was an independent predictor of CRE isolation [4].

The most common antibiotics received by those with CRE were carbapenems and fluoroquinolones; many patients (85%) also had cephalosporin exposure. Demand exists for data on antimicrobial stewardship in the SOT population as there currently is nearly none [5]. Data on antimicrobial stewardship in hematologic malignancy are also lacking; strategies such as prospective audit of antibiotic prescribing in cancer patients with feedback have been proposed [6].

In 2014, clinicians have vanishingly few antibiotics in their armamentarium to treat CRE, and all available antibiotics have significant shortcomings. Polymyxins have uncertain pharmacokinetic and pharmacodynamic properties as well as challenges with antimicrobial susceptibility testing. Tigecycline has been associated with increased mortality and lower cure rates; its role is limited in the transplant population as it is inadequate for treating bloodstream infection and urinary tract infection. Fosfomycin, not available in intravenous form in the United States, has low rates of CRE susceptibility and an unclear optimal dose and dosing regimen. Aminoglycosides have variable activity against CRE, as well as major toxicities and poor efficacy when used as monotherapy in immunocompromised hosts. Based on in vitro and in vivo data, combination antimicrobial therapy is often recommended for these life-threatening infections. The authors present data from several retrospective studies detailing the use of combination therapies, notably of polymyxin-carbapenem and double carbapenem therapy to treat CRE infection. These combinations are thought to work based on the theory that ertapenem binds to Klebsiella pneumoniae carbapenemase (KPC) with greater affinity, reducing its availability for hydrolysis of the second carbapenem. This was successful in vitro in treating pan-resistant KPC-producing K. pneumoniae (KPC-Kp) [7]. The authors cite several case reports from around the world showing successful treatment of patients infected with KPC-Kp using combination carbapenem therapy. Combination therapy also appears to have mortality benefit over monotherapy, although the numbers of treated patients are small. We need additional data on optimal antibiotic regimens in treating these infections, particularly in immunocompromised hosts.

Other research gaps in CRE treatment include optimal dose regimen and duration of treatment. Bulik and colleagues studied the use of prolonged infusions (>4 hours) of doripenem against KPC-Kp isolates in both immunocompetent and neutropenic murine thigh models. Data from this in vivo model showed that high-dose doripenem maintained static effects in severely immunocompromised hosts and acceptable colony-forming unit reductions. Such dosing regimens may have utility in combination against infections caused by this pathogen [8]. There is no evidence that longer duration of treatment results in better outcomes, and few studies have examined these questions [9].

Unfortunately, the antibiotic pipeline remains practically dry; a recent report identified just 7 agents in clinical development for gram-negative infections, none of which are active against CRE that produce metallo-β-lactamases [10]. Of these, only 2, avibactam and plazomicin, have the potential to address the problem of CRE infection, but both have gaps in CRE activity. Although some gains have been made, especially in Europe, some fear remains that we may return to the preantibiotic era and will no longer be able to perform organ transplants and other life-saving therapies for our patients if new antibiotics are not developed soon [11]. The European Union has attacked this issue, with years of antibiotic resistance surveillance data, a well-articulated 12-point antimicrobial resistance plan supported by all key stakeholders, and a multimillion-euro investment to address this crisis [12].

We commend the authors for highlighting the critical problem of CRE in a most vulnerable patient population that we need to protect. In addition to improved surveillance and infection prevention strategies, clinicians urgently need better data to guide use of existing antibiotics, as well as a robust pipeline of new agents to treat these infections and protect our patients now as well as in the years to come. This review provides several tools for clinicians in managing cases of CRE and reveals important research gaps. Priority interventions include aggressive infection control practices such as active surveillance and decolonization in both recipient and donor, antimicrobial stewardship (especially for carbapenems and fluoroquinolones), and considering use of combination therapy. To boost development of antibiotics to treat infections caused by these organisms, the Infectious Diseases Society of America has proposed incentives including new regulatory pathways, public–private partnerships, and tax credits. Recently introduced legislation for a Limited Population Antibacterial Drug pathway would allow the US Food and Drug Administration to approve drugs for narrow use based on smaller clinical trials for treatment of patients with infections who have few or no treatment options. As more life-threatening superbugs emerge, we must rise to the challenge so we can continue to provide our transplant recipients the best chance of infection-free survival.

**Notes**

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