Infections caused by carbapenem-resistant Enterobacteriaceae (CRE) are a significant cause of morbidity and mortality worldwide. CRE are defined by the Centers for Disease Control and Prevention (CDC) as those Enterobacteriaceae that are resistant in vitro to any carbapenem antimicrobial. This means a minimum inhibitory concentration (MIC) of $\geq 2$ mg/ml for ertapenem, or an MIC $\geq 4$ mg/ml for doripenem, meropenem, or imipenem. In addition, those Enterobacteriaceae that are documented to produce a carbapenemase are also considered CRE, regardless of carbapenem MIC. For Enterobacteriaceae species that have intrinsic imipenem resistance – such as Morganella morganii, Proteus spp. and Providencia spp – resistance to carbapenems other than imipenem is required. This phenotypic definition includes both carbapenemase-producing Enterobacteriaceae (CPE or CP-CRE) as well as non-carbapenemase-producing CRE. A retrospective study evaluating the impact of carbapenemase production on outcomes after monomicrobial CRE bloodstream infections (BSI) found that patients infected with CP-CRE were at increased risk of dying within 14 d as compared with patients with non-carbapenemase-producing CRE (adjusted odds ratio, 4.92; 95% confidence interval 1.01–24.81). The authors speculated that increased virulence of CP-CRE rather than patient factors were the cause of this observation.

Similar to carbapenem-susceptible Enterobacteriaceae, CRE have been reported to be the cause of many different types of infections. In most reports, urinary tract infections (UTI) are the most commonly observed infection type with CRE. While less common than UTI, CRE BSI and CRE pneumonia tend to be associated with the highest mortality rates. Also similar to other Enterobacteriaceae is the difficulty in distinguishing infection from colonization in patients with clinical CRE isolates that are obtained from non-sterile sites such as urine, sputum and wounds. In research settings, investigators often defer to surveillance definitions such as those outlined by the CDC to distinguish between infected and colonized patients. However, these definitions were designed with a different objective in mind, which is something to be considered when reading the CRE literature. In any case, it is clear that many patients, who would be considered “colonized” with CRE when applying the CDC definitions, are being treated with antibiotics for presumed infection by their clinicians. This is an especially common situation in asymptomatic bacteriuria. This often unnecessary treatment is associated with healthcare costs, drug adverse reactions, and subsequent resistance development.

Various carbapenemases may cause carbapenem resistance in Enterobacteriaceae. The most common enzymatic cause of carbapenem resistance is the family of Klebsiella pneumoniae carbapenemases (KPC). KPC are class A, serine-based $\beta$-lactamases. Of these, KPC-2 and KPC-3 are most frequently encountered. Another important class of carbapenemases is class B of metallo-$\beta$-lactamases. This class includes the New Delhi Metallo-$\beta$-lactamase (NDM) family. A third common cause of carbapenem resistance in Enterobacteriaceae is the class D OXA-48-like carbapenemases.

The global epidemiology of CRE is discussed by van Duin and Doi. Unfortunately, reliable estimates of the incidence and prevalence of CRE infections from many areas in the world are not available. Only a few states in the United States have mandatory reporting of CRE which facilitates a more complete knowledge of the epidemiology of CRE infections in those states. For the remainder of the US, estimates are limited to the occurrence of specific carbapenemases in those states as reported by the CDC. The epicenter of the CRE epidemic in the US appears to have been the New York area, although there is evidence that incidence in that
area is now decreasing. In addition, several European initiatives are tracking the epidemiology of CRE in Europe in greater detail.\textsuperscript{12} In Europe, countries bordering the Mediterranean Sea such as Italy and Greece have the highest incidence of CRE. These issues as well as the state of knowledge of the epidemiology of CRE in other parts of the world are described in detail by van Duin and Doi.\textsuperscript{1}

Regardless of geography, it is clear that certain patient populations are at increased risk for CRE infections. Three such populations of increased interest – solid organ transplant recipients, haematopoietic stem cell transplant recipients and patients with hematological malignancies – are highlighted by Pouch and Satlin.\textsuperscript{13} These groups of patients are characterized by an intense exposure to healthcare facilities and healthcare workers, high rates of antibiotic usage, and frequent need for medical devices such as intravenous lines and feeding tubes. Not surprisingly, these risk factors result in high rates of infections caused by multidrug-resistant organisms. The treatment of these infections is often further complicated by alterations in the immune status, pre-existing organ dysfunction, and drug-drug interactions.

Prevention is obviously of critical importance to curtail the spread of CRE. Wong and Spellberg review the role of antimicrobial stewardship in the prevention of CRE.\textsuperscript{14} Antimicrobial stewardship is a relatively new discipline that is gaining increasing recognition. Antimicrobial exposure is a key component in the development of any antibacterial resistance. In addition, high rates of antibiotic resistant pathogens are often observed in the setting of ongoing antibiotic pressure. It is no surprise that targeted interventions to optimize antibiotic use will not only lead to lower resistance rates, but also to improved outcomes, lower health care costs, and decreased adverse events associated with antibiotics.

Questions and controversies surrounding screening methods and the selection of individuals for screening are discussed by Richter and Marchaim.\textsuperscript{15} In addition, Banerjee and Humphries review rapid diagnostic options for CRE detection.\textsuperscript{16} These reviews highlight the recent developments in diagnostic options for active CRE infection as well as for screening for CRE carriage. These novel approaches hold much promise. However, more clinical studies remain to be performed to measure the impact of various methods on actual patient outcomes in the setting of infection, and on spread of CRE in the setting of measuring CRE carriage rates. As for any test, the positive and negative predictive values of these various screening tests and rapid diagnostic methods will vary based on the incidence of CRE in a specific population. Furthermore, the underlying mechanisms of resistance will be crucially important. It is likely that a combination of tests – phenotypic and genotypic – will be preferable to detect all circulating types of CRE. More rapid detection of carbapenem resistance in infections caused by Enterobacteriaceae will hopefully decrease the interval between infection and start of optimal \textit{in vitro} active antibiotic treatment. It is clear that – in addition to enhanced clinical microbiologic methodologies – timely and systematic communication with treating clinicians is required for these novel diagnostic options to have an impact on patient care.\textsuperscript{17}

The topic of optimizing treatment of CRE infections is approached in several ways. Neuner and Gallagher review the evidence on appropriate dosing of critically ill patients who are infected with CRE.\textsuperscript{18} Pharmacodynamics and pharmacokinetics may be significantly impacted by critical illness as well as by measures such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) which are often needed to support such patients. Antibiotics may need to be dosed more or less frequently, dose adjustments may be required and more frequent monitoring of antibiotic levels may be desirable in such settings. Unfortunately, for several commonly used antibiotics, optimal dosing strategies for critically ill patients remain to be established. Trecarichi and Tumbarello discuss current treatment options while antibiotics that are in development are discussed by Thaden et al.\textsuperscript{19} Antibiotics such as polymyxins, aminoglycosides and tigecycline have been used in the treatment of CRE infections, either alone or in combination. Furthermore, the addition of a carbapenem – despite \textit{in vitro} resistance – to an anti-CRE regimen may be associated with improved clinical outcomes, especially in those CRE with relatively lower carbapenem MICs.\textsuperscript{20} Various newer agents are being developed that have \textit{in vitro} activity against CRE. Of these, the novel $\beta$-lactamase inhibitor avibactam is approved in the US to be given in combination with ceftazidime.\textsuperscript{21} Unfortunately, none of the currently available randomized controlled trial data for ceftazidime-avibactam has focused on CRE infections. Several uncontrolled case series have described initial experiences with ceftazidime-avibactam in CRE infections.\textsuperscript{22,23} Of great concern is the treatment-emergent resistance to ceftazidime-avibactam observed by Shields et al.\textsuperscript{23} The relative efficacy and toxicity of newer agents as compared with polymyxin-based treatment regimens remains to be determined. Similarly, whether combination therapy – currently considered gold standard for most severe CRE infections – will have value over monotherapy in this upcoming era of newer agents, is an important question for future studies.

However, several methodologic issues complicate the study of CRE infections. This topic is reviewed by Evans and Harris.\textsuperscript{24} As with other multidrug resistant
organisms, patients who are at risk for CRE colonization and/or infection tend to be more chronically and acutely ill as compared with their counterparts infected with more susceptible organisms. Therefore, assigning any increase in poor clinical outcomes such as mortality directly to the resistance pattern of the organism is fraught with potential bias. In fact, in the Consortium on Resistance against Carbenapenems in Klebsiella and other Enterobacteriaceae (CRACKLE), about a third of the total in-hospital mortality risk of patients with bacteremia or pneumonia caused by CRE was explained by a baseline mortality rate that was also observed in patients colonized by CRE. Furthermore, this degree of illness combined with the fact that infection with susceptible Enterobacteriaceae far outnumbers CRE infections in most settings is a threat to timely enrollment in prospective studies that require informed consent. As most randomized controlled trials for antibiotics have strict limits on the time that a patient may be treated with antibiotics before randomization, timely diagnosis of patients with subsequent enrollment into the study becomes key.

In summary, in this Special Focus issue, currently relevant issues surrounding carbapenem-resistant Enterobacteriaceae are reviewed in detail. The articles included in this issue highlight that many advances have been made in a relatively short time-frame in the areas of prevention, diagnosis and treatment of CRE infections. However, at the same time, it is evident that much work still remains to be done in these areas. Furthermore, research into multidrug-resistant organisms is always a moving target, as bacteria continue to evolve new ways to evade treatment and prevention efforts.

Disclosure of potential conflicts of interest

David van Duin has served on Advisory Boards for Allergan, Achaogen, Shionogi, Tetraphase, Sanofi-Pasteur, MedImmune, and Astellas. He has received research funding from Steris, Inc, and from Scynexis.

Funding

This work was supported by the National Institute Of Allergy and Infectious Diseases of the National Institutes of Health under Award number R21AI114508.

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