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## Carbapenem-resistant Enterobacteriaceae: A menace to our most vulnerable patients

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### Abstract

The emergence of carbapenem-resistant Enterobacteriaceae (CRE) highlights the importance of effective antibiotics to maintain the safety of our health care system. Clinicians will encounter CRE as a cause of difficult-to-treat and often fatal infections in hospitalized patients. We review the mechanisms of carbapenem resistance, the dissemination and clinical impact of these resistant organisms, and challenges to their detection, treatment, and control.

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The past 10 years have brought a formidable challenge to the clinical arena, as carbapenems, until now the most reliable antibiotics against *Klebsiella* species, *Escherichia coli*, and other Enterobacteriaceae, are becoming increasingly ineffective.

Infections caused by carbapenem-resistant Enterobacteriaceae (CRE) pose a serious threat to hospitalized patients. Moreover, CRE often demonstrate resistance to many other classes of antibiotics, thus limiting our therapeutic options. Furthermore, few new antibiotics are in line to replace carbapenems. This public health crisis demands redefined and refocused efforts in the diagnosis, treatment, and control of infections in hospitalized patients.

Here, we present an overview of CRE and discuss avenues to escape a new era of untreatable infections.

### INCREASED USE OF CARBAPENEMS AND EMERGENCE OF RESISTANCE

Developed in the 1980s, carbapenems are derivatives of thyanamycin. Imipenem and meropenem, the first members of the class, had a broad spectrum of antimicrobial activity that included coverage of *Pseudomonas aeruginosa*, adequately positioning them for the treatment of nosocomial infections. Back then, nearly all Enterobacteriaceae were susceptible to carbapenems.<sup>1</sup>

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In the 1990s, Enterobacteriaceae started to develop resistance to cephalosporins—till then, the first-line antibiotics for these organisms—by acquiring extended-spectrum beta-lactamases, which inactivate those agents. Consequently, the use of cephalosporins had to be restricted, while carbapenems, which remained impervious to these enzymes, had to be used more.<sup>2</sup> In pivotal international studies in the treatment of infections caused by strains of *K pneumoniae* that produced these inactivating enzymes, outcomes were better with carbapenems than with cephalosporins and fluoroquinolones.<sup>3,4</sup>

Ertapenem, a carbapenem without anti-pseudomonal activity and highly bound to protein, was released in 2001. Its prolonged half-life permitted once-daily dosing, which positioned it as an option for treating infections in community dwellers.<sup>5</sup> Doripenem is the newest member of the class of carbapenems, and its spectrum of activity is similar to that of imipenem and meropenem and includes *P aeruginosa*.<sup>6</sup> The use of carbapenems, measured in a representative sample of 35 university hospitals in the United States, increased by 59% between 2002 and 2006.<sup>7</sup>

In the early 2000s, carbapenem resistance in *K pneumoniae* and other Enterobacteriaceae was rare in North America. But then, after initial outbreaks occurred in hospitals in the Northeast (especially New York City), CRE began to spread throughout the United States. By 2009–2010, the National Health-care Safety Network from the Centers for Disease Control and Prevention (CDC) revealed that 12.8% of *K pneumoniae* isolates associated with bloodstream infections were resistant to carbapenems.<sup>8</sup>

In March 2013, the CDC disclosed that 3.9% of short-stay acute-care hospitals and 17.8% of long-term acute-care hospitals reported at least one CRE health care-associated infection in 2012. CRE had extended to 42 states, and the proportion of Enterobacteriaceae that are CRE had increased fourfold over the past 10 years.<sup>9</sup>

Coinciding with the increased use of carbapenems, multiple factors and modifiers likely contributed to the dramatic increase in CRE. These include use of other antibiotics in humans and animals, their relative penetration and selective effect on the gut microbiota, case-mix and infection control practices in different health care settings, and travel patterns.

## POWERFUL ENZYMES THAT TRAVEL FAR

Bacterial acquisition of carbapenemases, enzymes that inactivate carbapenems, is crucial to the emergence of CRE. The enzyme in the sentinel carbapenem-resistant *K pneumoniae* isolate found in 1996 in North Carolina was designated *K pneumoniae* carbapenemase (KPC-1). This mechanism also conferred resistance to all cephalosporins, aztreonam, and beta-lactamase inhibitors such as clavulanic acid and tazobactam.<sup>10</sup>

KPC-2 (later determined to be identical to KPC-1) was found in *K pneumoniae* from Baltimore, and KPC-3 caused an early outbreak in New York City.<sup>11,12</sup> To date, 12 additional variants of *bla*<sub>KPC</sub>, the gene encoding for the KPC enzyme, have been described.<sup>13</sup>

The genes encoding carbapenemases are usually found on plasmids or other common mobile genetic elements.<sup>14</sup> These genetic elements allow the organism to acquire genes conferring resistance to other classes of antimicrobials, such as aminoglycoside-modifying enzymes and fluoroquinolone-resistance determinants, and beta-lactamases.<sup>15,16</sup> The result is that CRE isolates are increasingly multidrug-resistant (ie, resistant to three or more classes of antimicrobials), extensively drug-resistant (ie, resistant to all but one or two classes), or pandrug-resistant (ie, resistant to *all* available classes of antibiotics).<sup>17</sup> Thus, up to 98% of

KPC-producing *K pneumoniae* are resistant to trimethoprim-sulfamethoxazole, 90% are resistant to fluoroquinolones, and 60% are resistant to gentamicin or amikacin.<sup>15</sup>

The mobility of these genetic elements has also allowed for dispersion into diverse Enterobacteriaceae such as *E coli*, *Klebsiella oxytoca*, *Enterobacter*, *Serratia*, and *Salmonella* species. Furthermore, KPC has been described in non-Enterobacteriaceae such as *Acinetobacter baumannii* and *P aeruginosa*.

Extending globally, KPC is now endemic in the Mediterranean basin, including Israel, Greece, and Italy; in South America, especially Colombia, Argentina, and Brazil; and in China.<sup>18</sup> Most interesting is the intercontinental transfer of these strains: it has been documented that the index patient with KPC-producing *K pneumoniae* in Medellin, Colombia, came from Israel to undergo liver transplantation.<sup>19</sup> Likewise, KPC-producing *K pneumoniae* in France and Israel could be linked epidemiologically and genetically to the predominant US strain.<sup>20,21</sup>

Even more explosive has been the surge of another carbapenemase, the Ambler Class B New Delhi metallo-beta-lactamase, or NDM-1. Initially reported in a urinary isolate of *K pneumoniae* from a Swedish patient who had been hospitalized in New Delhi in 2008, NDM-1 was soon found throughout India, in Pakistan, and in the United Kingdom.<sup>22</sup> Interestingly, several of the UK patients with NDM-1-harboring bacteria had received organ transplants in the Indian subcontinent. Reports from elsewhere in Europe, Australia, and Africa followed suit, usually with a connection to the Indian subcontinent epicenter. In contrast, several other cases in Europe were traced to the Balkans, where there appears to be another focus of NDM-1.<sup>23</sup>

Penetration of NDM-1 into North America has begun, with cases and outbreaks reported in several US and Canadian regions, and in a military medical facility in Afghanistan. In several of these instances, there has been a documented link with travel and hospitalizations overseas.<sup>24-27</sup> However, no such link with travel could be established in a recent outbreak in Ontario.<sup>27</sup>

In addition, resistance to carbapenems may result from other enzymes (TABLE 1), or from combinations of changes in outer membrane porins and the production of extended spectrum beta-lactamases or other cephalosporinases.<sup>28</sup>

## DEADLY IMPACT ON THE MOST VULNERABLE

Regardless of the resistance pattern, Enterobacteriaceae are an important cause of health care-associated infections, including urinary and bloodstream infections in patients with indwelling catheters, pneumonia (often in association with mechanical ventilation), and, less frequently, infections of skin and soft tissues and the central nervous system.<sup>29-31</sup>

Several studies have examined the clinical characteristics and outcomes of patients with CRE infections. Those typically affected are elderly and debilitated and have multiple comorbidities, including diabetes mellitus and immunosuppression. They are heavily exposed to health care with frequent antecedent hospitalizations and invasive procedures. Furthermore, they are often severely ill and require intensive care. Patients infected with carbapenem-resistant *K pneumoniae*, compared with those with carbapenem-susceptible strains, are more likely to have undergone organ or stem cell transplantation or mechanical ventilation, and to have had a longer hospital stay before infection.

They also experience a high mortality rate, which ranges from 30% in patients with nonbacteremic infections to 72% in series of patients with liver transplants or bloodstream infections.<sup>32–37</sup>

More recently, CRE has been reported in other vulnerable populations, such as children with critical illness or cancer and in burn patients.<sup>38–40</sup>

Elderly and critically ill patients with bacteremia originating from a high-risk source (eg, pneumonia) typically face the most adverse outcomes. With increasing drug resistance, inadequate initial antimicrobial therapy is more commonly seen and may account for some of these poor outcomes.<sup>37,41</sup>

## LONG-TERM CARE FACILITIES IN THE EYE OF THE STORM

A growing body of evidence suggests that long-term care facilities play a crucial role in the spread of CRE.

In an investigation into carbapenem-resistant *A baumannii* and *K pneumoniae* in a hospital system,<sup>36</sup> 75% of patients with carbapenem-resistant *K pneumoniae* were admitted from long-term care facilities, and only 1 of 13 patients was discharged home.

In a series of patients with carbapenem-resistant *K pneumoniae* bloodstream infections, 42% survived their index hospital stay. Of these patients, only 32% were discharged home, and readmissions were very common.<sup>32</sup>

Admission from a long-term care facility or transfer from another hospital is significantly associated with carbapenem resistance in patients with Enterobacteriaceae.<sup>42</sup> Similarly, in Israel, a large reservoir of CRE was found in postacute care facilities.<sup>43</sup>

It is clear that long-term care residents are at increased risk of colonization and infection with CRE. However, further studies are needed to evaluate whether this simply reflects an overlap in risk factors, or whether significant patient-to-patient transmission occurs in these settings.

## INFECTION CONTROL TAKES CENTER STAGE

It is important to note that risk factors for CRE match those of various nosocomial infections, including other resistant gram-negative bacilli, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Candida* species, and *Clostridium difficile*; in fact, CRE often coexist with other multidrug-resistant organisms.<sup>44,45</sup>

Common risk factors include residence in a long-term care facility, an intensive care unit stay, use of lines and catheters, and antibiotic exposure. This commonality of risk factors implies that systematic infection-prevention measures will have an impact on the prevalence and incidence rates of multidrug-resistant organism infections across the board, CRE included. It should be emphasized that strict compliance with hand hygiene is still the foundation of any infection-prevention strategy.

Infection prevention and the control of transmission of CRE in long-term care facilities pose unique challenges. Guidelines from the Society for Healthcare Epidemiology and the Association for Professionals in Infection Control recommend the use of contact precautions for patients with multidrug-resistant organisms, including CRE, who are ill and totally dependent on health care workers for activities of daily living or whose secretions or

drainage cannot be contained. These same guidelines advise against attempting to eradicate multidrug-resistant organism colonization status.<sup>46</sup>

In acute care facilities, Best Infection Control Practices from the CDC and the Health-care Infection Control Practices Advisory Committee encourage mechanisms for the rapid recognition and reporting of CRE cases to infection prevention personnel so that contact precautions can be implemented. Furthermore, facilities without CRE cases should carry out periodic laboratory reviews to identify cases, and patients exposed to CRE cases should be screened with surveillance cultures.<sup>47</sup>

Outbreaks of CRE may require extraordinary infection control measures. An approach combining point-prevalence surveillance of colonization, detection of environmental and common-equipment contamination, with the implementation of a bundle consisting of chlorhexidine baths, cohorting of colonized patients and health care personnel, increased environmental cleaning, and staff education may be effective in controlling outbreaks of CRE.<sup>48</sup>

Nevertheless, control of CRE may prove exceptionally difficult. A recent high-profile outbreak of carbapenem-resistant *K pneumoniae* at the National Institutes of Health Clinical Center in Maryland caused infections in 18 patients, 11 of whom died.<sup>49</sup> Of note, carbapenem-resistant *K pneumoniae* was detected in this outbreak in both respiratory equipment and sink drains. The outbreak was ultimately contained by detection through surveillance cultures and by strict cohorting of colonized patients, which minimized common medical equipment and personnel between affected patients and other patients in the hospital. Additionally, rooms were sanitized with hydrogen peroxide vapor, and sinks and drains where carbapenem-resistant *K pneumoniae* was detected were removed.

## CHALLENGES IN THE MICROBIOLOGY LABORATORY

Adequate treatment and control of CRE infections is predicated upon their accurate and prompt diagnosis from patient samples in the clinical microbiology laboratory.<sup>50</sup>

Traditional and current culture-based methods take several days to provide that information, delaying effective antibiotic therapy and permitting the transmission of undetected CRE. Furthermore, interpretative criteria of minimal inhibitory concentrations (MICs) of carbapenems recently required readjustment, as many KPC-producing strains of *K pneumoniae* had MICs below the previous breakpoint of resistance. In the past, this contributed to instances of “silent” dissemination of KPC-producing *K pneumoniae*.<sup>51</sup>

In contrast, using the new lower breakpoints of resistance for carbapenems without using a phenotypic test such as the modified Hodge test or the carbapenem-EDTA combination tests will result in a lack of differentiation between various mechanisms of carbapenem resistance.<sup>28,52,53</sup> This may be clinically relevant, as the clinical response to carbapenem therapy may vary depending on the mechanism of resistance.

## GENERAL PRINCIPLES APPLY

In treating patients infected with CRE, clinicians need to strictly observe general principles of infectious disease management to ensure the best possible outcomes. These include:

**Timely and accurate diagnosis**, as discussed above.

**Source control**, which should include drainage of any infected collections, and removal of lines, devices, and urinary catheters.

### **Distinguishing between infection and colonization**

CRE are often encountered as urinary isolates, and the distinction between asymptomatic bacteriuria and urinary tract infection may be extremely difficult, especially in residents of long-term care facilities with chronic indwelling catheters, who are the group at highest risk of CRE colonization and infection. Urinalysis may be helpful in the absence of pyuria, as this rules out an infection; however, it must be emphasized that the presence of pyuria is not a helpful feature, as pyuria is common in both asymptomatic bacteriuria and urinary tract infection.<sup>54</sup> Symptoms should be carefully evaluated in every patient with bacteriuria, and urinary tract infection should be a diagnosis of exclusion in patients with functional symptoms such as confusion or falls.

### **Selection of the most appropriate antibiotic regimen**

While the emphasis is often on the antibiotic regimen, the above elements should not be neglected.

## **A DWINDLING THERAPEUTIC ARSENAL**

Clinicians treating CRE infections are left with only a few antibiotic options. These options are generally limited by a lack of clinical data on efficacy, as well as by concerns about toxicity. These “drugs of last resort” include polymyxins (such as colistin), aminoglycosides, tigecycline, and fosfomycin. The role of carbapenem therapy, potentially in combination regimens, in a high-dose prolonged infusion, or even “double carbapenem therapy” remains to be determined.<sup>37,55,56</sup>

### **Colistin**

Colistin is one of the first-line agents for treating CRE infections. First introduced in the 1950s, its use was mostly abandoned in favor of aminoglycosides. A proportion of the data on safety and efficacy of colistin, therefore, is based on older, less rigorous studies.

Neurotoxicity and nephrotoxicity are the two main concerns with colistin, and while the incidence of these adverse events does appear to be lower with modern preparations, it is still substantial.<sup>57</sup> Dosing issues have not been completely clarified either, especially in relation to renal clearance and in patients on renal replacement therapy.<sup>58,59</sup> Unfortunately, there have been reports of outbreaks of CRE displaying resistance to colistin.<sup>60</sup>

### **Tigecycline**

Tigecycline is a newer antibiotic of the glycylcycline class. Like colistin, it has no oral preparation for systemic infections.

The main side effect of tigecycline is nausea.<sup>61</sup> Other reported issues include pancreatitis and extreme alkaline phosphatase elevations.

The efficacy of tigecycline has come into question in view of meta-analyses of clinical trials, some of which have shown higher mortality rates in patients treated with tigecycline than with comparator agents.<sup>62–65</sup> Based on these data, the US Food and Drug Administration issued a warning in 2010 regarding the increased mortality risk. Although these meta-analyses did not include patients with CRE for whom available comparators would have been ineffective, it is an important safety signal.

The efficacy of tigecycline is further limited by increasing in vitro resistance in CRE. Serum and urinary levels of tigecycline are low, and most experts discourage the use of tigecycline as monotherapy for blood stream or urinary tract infections.



## Aminoglycosides

CRE display variable in vitro susceptibility to different aminoglycosides. If the organism is susceptible, aminoglycosides may be very useful in the treatment of CRE infections, especially urinary tract infections. In a study of carbapenem-resistant *K pneumoniae* urinary tract infections, patients who were treated with polymyxins or tigecycline were significantly less likely to have clearance of their urine as compared with patients treated with aminoglycosides.<sup>66</sup>

Ototoxicity and nephrotoxicity are demonstrated adverse effects of aminoglycosides. Close monitoring of serum levels, interval audiology examinations at baseline and during therapy, and the use of extended-interval dosing may help to decrease the incidence of these toxicities.

## Fosfomycin

Fosfomycin is only available as an oral formulation in the United States, although intravenous administration has been used in other countries. It is exclusively used to treat urinary tract infections.

CRE often retain susceptibility to fosfomycin, and clearance of urine in cystitis may be attempted with this agent to avoid the need for intravenous treatment.<sup>29,67</sup>

## Combination therapy, other topics to be explored

Recent observational reports from Greece, Italy, and the United States describe higher survival rates in patients with CRE infections treated with a combination regimen rather than monotherapy with colistin or tigecycline. This is despite reliable activity of colistin and tigecycline, and often in regimens containing carbapenems. Clinical experiments are needed to clarify the value of combination regimens that include carbapenems for the treatment of CRE infections.

Similarly, the role of carbapenems given as a high-dose prolonged infusion or as double carbapenem therapy needs to be explored further.<sup>37,55,56,68</sup>

Also to be determined is the optimal duration of treatment. To date, there is no evidence that increasing the duration of treatment beyond that recommended for infections with more susceptible bacteria results in improved outcomes. Therefore, commonly used durations include 1 week for complicated urinary tract infections, 2 weeks for bacteremia (from the first day with negative blood cultures and source control), and 8 to 14 days for pneumonia.

## A SERIOUS THREAT

The emergence of CRE is a serious threat to the safety of patients in our health care system. CRE are highly successful nosocomial pathogens selected by the use of antibiotics, which burden patients debilitated by advanced age, comorbidities, and medical interventions. Infections with CRE result in poor outcomes, and available treatments of last resort such as tigecycline and colistin are of unclear efficacy and safety.

Control of CRE transmission is hindered by the transit of patients through long-term care facilities, and detection of CRE is difficult because of the myriad mechanisms involved and the imperfect methods currently available. Clinicians are concerned and frustrated, especially given the paucity of antibiotics in development to address the therapeutic dilemma posed by CRE. The challenge of CRE and other multidrug-resistant organisms requires the concerted response of professionals in various disciplines, including

pharmacists, microbiologists, infection control practitioners, and infectious disease clinicians (TABLE 2).

Control of transmission by infection prevention strategies and by antimicrobial stewardship is going to be crucial in the years to come, not only for limiting the spread of CRE, but also for preventing the next multidrug-resistant “superbug” from emerging. However, the current reality is that health care providers will be faced with increased numbers of patients infected with CRE.

Prospective studies into transmission, molecular characteristics, and, most of all, treatment regimens are urgently needed. In addition, the development of new antimicrobials and nontraditional antimicrobial methods should have international priority.

## Glossary of drugs mentioned in this article

|                        |                               |
|------------------------|-------------------------------|
| <b>Amikin</b>          | Amikacin                      |
| <b>Coly-Mycin</b>      | Colistin                      |
| <b>Doribax</b>         | Doripenem                     |
| <b>Invanz</b>          | Ertapenem                     |
| <b>Monurol</b>         | Fosfomycin                    |
| <b>Primaxin</b>        | Imipenem                      |
| <b>Merrem</b>          | Meropenem                     |
| <b>Tygacil</b>         | Tigecycline                   |
| <b>Bactrim, Septra</b> | Trimethoprim-sulfamethoxazole |

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**KEY POINTS**

The utility of carbapenems is being undermined by the emergence of resistance in Enterobacteriaceae and other bacteria.

The clinical impact of CRE falls on elderly patients exposed to these organisms in hospitals and long-term care facilities. In this vulnerable group, invasive infections with CRE exact a high death rate.

Long-term care facilities play an important role in the transmission dynamics of CRE.

Tigecycline and colistin are treatments of last resort against infections caused by CRE. Their use in combination with other agents, especially carbapenems, may improve outcomes and needs to be explored further.

Early detection of CRE in the microbiology laboratory is key to guiding infection control and treatment decisions and supporting surveillance efforts.

TABLE 1

Enzymes conferring carbapenem resistance in Enterobacteriaceae

| Enzyme  | Common genetic platform   | Species distribution in Enterobacteriaceae  | Geographic distribution  |
|---|---|---|--|
| <b>KPC</b> ( <i>Klebsiella pneumoniae</i> carbapenemase)    | <i>K pneumoniae</i> sequence type 258, various plasmids types, transposon Tn4401x | <i>K pneumoniae</i> , <i>Escherichia coli</i> , <i>Enterobacter</i> species, diverse Enterobacteriaceae | Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America |
| <b>NDM</b> (New Delhi metallo-beta-lactamase)               | Various plasmid types   | <i>K pneumoniae</i> and <i>E coli</i> predominantly, diverse Enterobacteriaceae                         | Indian subcontinent and the Balkan region, and around the world                            |
| <b>OXA-48</b> (oxacillinase)                                | Incl/M-type plasmid   | <i>K pneumoniae</i> predominantly, diverse Enterobacteriaceae   | Southern and Western Europe, Turkey and North Africa; rare in the United States            |
| <b>VIM</b> (Verona integron-encoded metallo-beta-lactamase) | Gene cassettes in class 1 integrons   | <i>K pneumoniae</i> predominantly   | Common in Italy, Greece, and the Far East, sporadic globally                               |
| <b>IMP</b>  | Gene cassettes in class 1 integrons   | <i>K pneumoniae</i> predominantly   | Common in the Far East and South America, sporadic globally                                |
| <b>SME</b>  | Chromosome  | <i>Serratia marcescens</i>  | Sporadic in North America and South America  |

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**TABLE 2**

## Present and future multidisciplinary approaches to combat carbapenem-resistant Enterobacteriaceae

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| Antibiotic stewardship programs enhanced with computer-based registries incorporating clinical and microbiological data  |
| Rapid and accurate detection of genetic determinants of carbapenem resistance in the microbiology laboratory to support targeted therapy and infection control efforts |
| Integrated surveillance of carbapenem-resistance mechanisms at the local, regional, and global level   |
| Targeted surveillance cultures (travel history, long-term care residents)  |