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Carbapenem-resistant Enterobacteriaceae: biology, epidemiology, and management

Elizabeth Temkin,[1] Amos Adler,[1,2] Anat Lerner,[1] and Yehuda Carmeli[1,2]

[1]Division of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Israel. [2]Sackler Faculty of Medicine, Tel Aviv University, Israel

Address for correspondence: Yehuda Carmeli, M.D., M.P.H., Division of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Weizmann St. 6, Tel Aviv 64239, Israel. yehudac@tlvmc.gov.il

Introduced in the 1980s, carbapenem antibiotics have served as the last line of defense against multidrug-resistant Gram-negative organisms. Over the last decade, carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a significant public health threat. This review summarizes the molecular genetics, natural history, and epidemiology of CRE and discusses approaches to prevention and treatment.

Keywords: carbapenem-resistant Enterobacteriaceae; antimicrobial resistance; carbapenemases; molecular genetics; infection control; treatment

Background and history

Carbapenems, the most broad-spectrum beta-lactam antibiotics active against Gram-negative organisms, are very slowly hydrolyzed by most beta-lactamases. Because of this, agents from this class have been used successfully and have served as the last line of defense against multidrug-resistant Gram-negative organisms since their introduction in the early 1980s. Carbapenemases—beta-lactamases that hydrolyze carbapenems efficiently, such as the serine carbapenemase SME and the metallo-beta-lactamase IMP—were detected in Enterobacteriaceae in the 1980s.[1–3] However, with the exception of limited spread of IMP-producing bacteria in Japan,[4,5] most reports remained anecdotal, with no significant spread for over 20 years.

The serine carbapenemases include the group A enzyme families SME, GES, IMI, NMC, KPC (of which only KPC has gained epidemiologic success and will be discussed here), and the class D OXA enzymes (of which OXA-48 has gained success among Enterobacteriaceae and will be discussed). Two metallo-carbapenemases, VIM and NDM, have become important threatening pathogens. Other metallo-carbapenemases, including IMP, SPM, GIM, and SIM, are spreading locally and will not be addressed here.

Widespread carbapenemase production in the Enterobacteriaceae was unknown until the early 2000s; almost all carbapenemase-resistant isolates reported were sporadic cases of hyperproduction of the beta-lactamase AmpC or of extended spectrum beta-lactamase, combined with porin loss. In 2001, the first report of carbapenem-resistant *Klebsiella pneumoniae* carrying a new carbapenemase, KPC, was published.[6] This strain was previously isolated in a North Carolina intensive care unit (ICU) in 1996, but went unnoticed at the time. However, the strain was stored at the Centers for Disease Control and Prevention (CDC) as part of an ICU pathogen collection, and then investigated several years after its first isolation. Through 2004 only a few isolates of KPC-producing strains from various localities extending from Baltimore to New York City were reported in the literature. Retrospectively, it is clear that large outbreaks, some reported to the CDC, occurred in multiple hospitals in the northeastern United States and Arizona. Indeed, in 2004 investigators from England's Health Protection Agency, together with colleagues from Tisch Hospital in New York City, reported on a KPC-producing *K. pneumoniae* outbreak in 2000–2001 that affected 24 patients and had a case fatality rate of 33%.[7] The medical community began to pay attention

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to the problem only after researchers from Brooklyn, N.Y. reported, in several publications, that 62 (24%) of 257 *K. pneumonia*e isolates in their center were KPC producers,[8] and, later, that 96 isolates collected from 10 Brooklyn hospitals during 2003–2004 were KPC producers.[9] The magnitude of the problem became clear when the National Healthcare Safety Network reported that among the nosocomial pathogens reported during 2006–2007 from 463 hospitals throughout the U.S., 10–11% of all *K. pneumoniae* isolates causing central line-associated bloodstream infections or urinary tract infections were resistant to carbapenems.[10] Thus, between 1996 and 2006, KPC-producing *K. pneumoniae* had spread endemically throughout the U.S. as an important nosocomial pathogen. In parallel, from 2005 onward, reports of the spread of KPC-producing strains appeared from multiple countries and various parts of the world, with notable nationwide outbreaks in Israel,[11,12] Greece,[13,14] and Italy.[15]

The VIM family of enzymes was first reported in Italy in 1997 in *Pseudomonas aeruginosa* isolates. The first VIM-producing Enterobacteriaceae were isolated in 2001 in Greece,[16] strains that gained endemicity in Greece and eventually led to 50% carbapenem resistance among *K. pneumoniae* isolates from Greek ICUs in 2006.[17] VIM-producing Enterobacteriaceae have also spread locally in Italy[18] and, to a limited extent, in Spain.[19]

The spread of KPC and VIM was followed and paralleled by the spread of NDM, primarily in the Indian subcontinent and from there elsewhere, and by the spread of OXA-48 around the eastern and southern parts of the Mediterranean basin. The spread of these four enzymes resulted in high endemicity of carbapenem-resistant Enterobacteriaceae (CRE) in multiple regions and threatening to spread elsewhere.

Molecular genetics of CRE

The epidemic of KPC

KPC is a serine class-A type enzyme that exhibits activity against all types of β-lactam agents.[20,21] The primary mode of KPC spread is via the clonal dissemination of *K. pneumoniae*. The dominant KPC-producing clones are the sequence type (ST) 258 clone [22] and its related single locus variant (SLV) ST-512,[23,24] and ST-11, a more distant SLV of ST-258.[22,25–27] The basis for the success of the ST-258 clone remains to be explained. A comparison between KPC-producing strains belonging to the ST-258 epidemic clone (from Israel and the U.S.) and 21 strains belonging to other, infrequently occurring clones (from Israel and the U.S.) identified a set of supposedly unique genes.[28] In a follow-up large multinational study (Israel, U.S., Colombia, Greece, and Italy) using other strains, the uniqueness of some of the genes was not confirmed. [29]

In contrast with the dominant monoclonal spread of KPC-producing *K. pneumoniae*, the initial reports of KPC-producing *E. coli* and *Enterobacter* species showed mainly polyclonal spread.[30,31] This raises the particular concern that the transfer of the KPC gene (bla_{KPC}) into global epidemic clones, such as the reported ST-131 *E. coli* strain,[32–34] will lead to wide dissemination of KPC in the population at large. Thus far, however, community-acquired infections have not been reported. The KPC gene has also been identified in many other bacterial species, including species that are rarely detected in humans,[35] and in non-Enterobacteriaceae such as *P. aeruginosa*.[36]

Alleles, promoters, and mobile genetic elements

Although more than 14 different bla_{KPC} allele sequences have been submitted to the National Center for Biotechnology Information (NCBI) database, the majority of clinical reports have been the bla_{KPC-2} or bla_{KPC-3} alleles.[12] The KPC gene is located inside the ∼10 kb Tn3-related transposon Tn*4401*, for which there are five isoforms that differ in the promoter areas upstream of bla_{KPC}.[37] Factors found to be related to the carbapenem minimum inhibitory concentration (MIC) in clinical isolates include the copy number and the presence of a permeability defect, such as the loss of OmpK36 in *K. pneumoniae*.[38] The bla_{KPC}-containing Tn*4401* transposon has a high efficiency of mobilization and no target size specificity, which together provide the capacity to mobilize to a wide variety of genetic environments.[39] Indeed, Tn*4401* has been identified in a wide variety of plasmids from different incompatibility (Inc) groups, such as FII, L/M, and N.[22,40]

The data regarding the association between different types of bla_{KPC}-harboring plasmids and different species and geographic locations are complex. In Israel, several studies have identified a common IncFII type plasmid (designated pKpQIL) in the epidemic ST-258 *K. pneumoniae* clone,[41] whereas

IncN type plasmids were common in other species and *K. pneumoniae* clones.[22,35] pKpQIL was identified in KPC-producing *K. pneumoniae* strains from New York and New Jersey, predating the Israeli outbreak;[42] this plasmid has also been reported from various countries including Poland, Italy, and the United States.[25,43] In some areas, a wide variety of plasmids have been found in all clones, including ST-258.[22,25,40] Thus, while clonal expansion is the primary mechanism of spread of bla_{KPC}, complex modes of horizontal gene transfer also play an important role in the spread of KPC.[44,45]

OXA-48 and related enzymes

The OXA-48 enzyme is a serine class D type β-lactamase that exhibits high activity against penicillins, minimally hydrolyses carbapenems, and shows weak activity against expanded-spectrum cephalosporins.[46] However, because OXA-48–producing strains often also carry extended-spectrum beta-lactamase (ESBL) enzymes, they are resistant to expanded-spectrum cephalosporins. Unlike other OXA-type carbapenemases that are common in, for example, *Acinetobacter baumannii* and other non-fermenting Gram-negative rods, OXA-48 and its related variants (OXA-162, -163, -181, -199, -204, -232, -244, and -245) are present in Enterobacteriaceae.[47–53] The OXA-48 enzymes have mixed modes of spread: plasmid, transposon, and clonal, the latter being characterized by polyclonal dissemination on a global scale, as well as local clonal outbreaks. Some of the dominant OXA-48 producing *K. pneumoniae* clones, such as ST-11[52,54,55] and ST-147,[54,56] are also frequently reported as ESBL-producing clones.[57] As with KPC, OXA-48 was identified in the pandemic ST-131 *E. coli* clone, although this is a single case report.[58]

The OXA-48 gene (bla_{OXA-48}), carried by Tn*1999*—a composite transposon made of two copies of the insertion sequence IS1999, has several variants that may differ in their mobilization efficiency.[59,60] Tn*1999* is almost universally located inside an IncL/M-type 63-kb plasmid, designated pOXA-48a,[61] which has been shown to exhibit extremely efficient self-conjugation potential, both intra- and inter-species,[62] and is linked to many of the plasmids outbreaks. OXA-48–producing Enterobacteriaceae (and hence the bla_{OXA-48} gene) originated in the Middle East and North Africa and spread to many other countries in Europe and elsewhere.[52,63,64] In contrast, $bla_{OXA-181}$ (and its closely related allele $bla_{OXA-232}$) likely originated from the environmental species *Shewanella xiamenensis*,[65] and are located on a different transposon, Tn*2013*, with the insertion sequence IS*Ecp1* at one end.[51,53] Tn*2013* is found on relatively small ColE-type non-conjugative plasmids.[51,53] OXA-181–producing Enterobacteriaceae show different epidemiology from OXA-48–producing Enterobacteriaceae, and they have been identified almost exclusively among patients originating from India.[66]

Metallo-beta lactamases: NDM and VIM

NDM-1

The epidemic of New Delhi metallo-beta-lactamase (NDM) is primarily the dissemination of bla_{NDM} spreading between plasmids, clones, and strains; bla_{NDM} is found on many different types of plasmids and can be chromosomal as well.[67,68] Not uncommonly, more than one NDM-producing species can be isolated in a single patient, suggesting transmission via mobile genetic elements.[69] The molecular epidemiology of NDM in the most commonly isolated species, *E. coli* and *K. pneumoniae*, is also complex. In some cases NDM has been related to clonal spread, whereas in other locations the clonal structure is diverse.[67,68,70] NDM-producing *E. coli* ST-101 has been commonly reported;[67,70] and bla_{NDM} has been identified in the epidemic clone ST-131.[67] As of July 2014, there were 12 known alleles of bla_{NDM} (deposited at http://www.lahey.org/Studies/); most were identified in Enterobacteriaceae, but some also in *Acinetobacter* species.[71–77] The alleles exhibit more than 99.4% similarity and have similar or even higher catalytic activity compared to bla_{NDM-1}.[71]

VIM

VIM (Verona integron-encoded metallo-beta-lactamase) is an important MBL that is spread in non-fermenter strains, as well as among Enterobacteriaceae.[78] As of July 2014, 41 different bla_{VIM} allelic variants have been identified (deposited at http://www.lahey.org/Studies/). The bla_{VIM-2} group of genes was detected mainly in non-fermenting Gram-negative bacteria, such as *Pseudomonas* spp. and *Acinetobacter* spp., while the bla_{VIM-1} group was detected mostly among Enterobacteriaceae.[78–80]

The bla_{VIM} genes are often located in class 1 integrons as gene cassettes that reside on plasmids

with different replicon types, for example, IncN, IncA/C, and IncI.[78,79,81–83] In *K. pneumonia*, many of the VIM-1/4 genes are carried on plasmids with Inc group N, whereas those genes carried by *E. coli* are often IncFI/II.[84] Isolates of *K. pneumoniae* carrying both $bla_{\text{VIM-1}}$ and $bla_{\text{KPC-2}}$ were reported initially from Greece and, later, from other countries including Italy, Germany, and Colombia.[85–89]

VIM-producing *K. pneumoniae* isolates from the SMART surveillance program were typed and 63% were found to belong to ST-147.[90] Clonal spread of the VIM-carrying ST-147 strains with IncF and IncA/C plasmids was shown to occur within and between hospitals, and even between countries (Greece, Italy, and Scandinavia).[90] In a report from the Czech Republic, 5 of 6 VIM-producing *K. pneumoniae* isolates belonged to ST-11.[91]

Diagnosis of CRE

Accurate and timely diagnosis of CRE is of great importance for determining appropriate treatment and infection control measures. Tests to detect CRE can be divided into *phenotypic* and *genotypic* tests. Phenotypic tests can be further divided into those that are directed at detection of elevated MIC to certain carbapenems (such as MIC testing, growth on selective carbapenem containing media) and those that are directed at detection of hydrolysis of carbapenem either directly (cell-free extract hydrolysis assay) or indirectly (the modified Hodge test, the Carba NP test). MIC-based methods have limited sensitivity and specificity. On the one hand, carbapenemase-producing strains may have low MICs; on the other hand, strains with combinations of either ESBL or AmpC and loss of a porin may have high MICs to carbapenems. Hydrolysis tests are more specific, but they are labor intensive and more difficult to perform, and can be applied to isolates but not directly to specimens. Therefore, MIC-based methods using a low cutoff are often used as a first screen that is supplemented with the more specific hydrolysis tests. To treat CRE that are extremely drug resistant, clinicians need maximum information from diagnostic tests; the exact accurate MIC for various antibiotics is required, as well as which carbapenemase is involved. Determining the carbapenemase involved is also important in order to understand the local epidemiology and to design infection control measures. Genotypic tests, which involve amplification and detection of specific *bla* genes using polymerase chain reaction (PCR), are highly specific and sensitive for detecting specific genes.[92]

In settings where PCR testing is not available, one may rely on imputing the carbapenemase family on the basis of phenotypic testing with and without specific inhibitors, such as EDTA and boronic acid; however, these tests have limited value. Commercial genotypic tests, including rapid ones, are available. The main limitation of PCR tests (beyond their cost) is that a specific gene test may not be sensitive enough to detect all possible carbapenemases.

For detection of CRE carriage in asymptomatic patients, rectal swabs, or stool samples should be used. These specimens are challenging both for phenotypic and genotypic testing. Chromogenic media have been developed and various brands differ in their sensitivity and specificity. As with any diagnostic test, the accuracy of the result is determined by the test characteristics (sensitivity and specificity) and by the prevalence of the condition (pre-test probability). In our opinion, there is no single testing strategy that fits all, and the strategy should be decided on the basis of local epidemiology, targets, and laboratory expertise and equipment. In most settings, the combination of phenotypic and genotypic testing will result in the best performance and most rapid result.

Geography of CRE

The worldwide presence of CRE has been reviewed in several comprehensive articles.[93–95] The accuracy of data about CRE depends on countries' capacities for surveillance, laboratory identification, and reporting; it is likely that the available data underestimate the true global prevalence of CRE. Munoz-Price *et al.* have published a helpful world map that classifies countries according to the predominant carbapenemase (KPC or others) and whether CRE is endemic, scattered, or unreported.[93] Countries with endemic KPC are China, Israel, Greece, Italy, Poland, Colombia, Argentina, Brazil, and some states in the United States. Other carbapenemases are endemic in India (NDM) and Turkey (OXA-48).

As of February 2014, cases of KPC-producing Enterobacteriaceae have been reported in all U.S. states except Maine, Idaho, and Alaska. The NDM carbapenemase has been reported in 15 states; VIM in California, Kentucky, and Washington; and IMP in California and Washington.[96] The National

Healthcare Safety Network (NHSN) tracks antibiotic resistance among organisms causing device-associated infections acquired in acute care hospitals. (Because hospitals' participation is voluntary, the findings may not be generalizable to the country as a whole and do not address regional variation within the United States.) In 2009–2010, carbapenem resistance was present in 12.8% of *Klebsiella* isolates responsible for central line-associated bloodstream infections (CLABSIs).[97] CRE infections are relatively uncommon in the United States. In the first half of 2012, among nearly 4000 hospitals participating in the NHSN, 4% of short-stay acute care hospitals and 18% of long-term acute care hospitals (LTACHs) reported at least one patient with either a catheter-associated urinary tract infection or a CLABSI caused by CRE.[93,98]

In Europe, the European Antimicrobial Resistance Surveillance Network (EARS-Net) monitors resistance among pathogens isolated from blood or cerebrospinal fluid. In 2012, among the 23 countries that contributed at least 100 isolates (samples that may not be representative of the whole country), the proportion of *K. pneumoniae* isolates that were carbapenem resistant was <1% in 18 countries, 1–7% in 3 countries, 29% in Italy, and 61% in Greece.[99]

Natural history of CRE

When considering CRE, it is various enterobacterial species and clones that carry mechanisms of resistance, and spread is via the fecal–oral route. Thus, acquisition of CRE begins with ingestion; following ingestion, CRE colonize the digestive tract of some patients. Whether colonization occurs depends on factors such as the inoculum ingested, characteristics of the specific clone, and patient characteristics that resist colonization, such as gastric acidity and the composition of the gut flora.[100] Antibiotics disrupt the normal gut flora, eradicate susceptible bacteria, and allow the overgrowth of resistant bacteria. Indeed, several studies have identified recent antibiotic use as a risk factor for CRE colonization.[101–103]

The source of ingested CRE can vary. Currently, KPC-producing strains spread primarily in healthcare settings from hospitalized patients who are carriers. The mode of transmission is via contaminated hands of healthcare workers or contaminated fomites. Preventing transmission and spread of KPC, therefore, should be directed at improving healthcare practices (such as hand hygiene) and patient isolation. The NDM-producing strains spread primarily in the Indian subcontinent and most transmission occurs in the community, possibly by contaminated potable water owing to poor sanitation systems.[104] We speculate that for the OXA-48–producing strains, community spread in southern and eastern Mediterranean countries may be explained by poor food hygiene. Thus, in these settings prevention should be directed at improving sanitation and hygiene.

Duration of carriage likely differs among species and clones, as some enterobacteria are more adapted to the human gut environment than others. Estimating the duration of CRE colonization is sometimes difficult because persistent carriers may have intermittent detectable levels of CRE in their stool. This creates several problems. For example, does a negative test indicate no carriage or is it a false negative owing to the concentration of CRE in the sample below the level of detection? (The level of CRE detection from rectal swabs on agar plates was found to range from 6.5×10^1 to 8.3×10^6 CFU/mL, depending on bacterial strain and laboratory methods.[105]) Another problem is that serial tests cannot distinguish between persistent carriage and clearance followed by re-acquisition. Feldman *et al.* screened KPC-producing *K. pneumoniae* carriers serially after hospital discharge;[106] only if two consecutive tests (both culture and PCR) were negative was the patient considered to have cleared carriage. At 1 to 30 days after the initial positive test, 74% of carriers were still positive; 54% remained positive after 30–60 days; 46% after 60–90 days; 28% after 6 months to 1 year; and 14% after 1 year. Heterogeneous studies using different time frames to define persistence have identified risk factors for persistent carriage; these include hospitalization or long-term care stay,[106–108] antibiotic use,[101,107] and poor functional status and multiple co-morbidities.[106]

In a proportion of carriers, CRE will migrate from the digestive tract to another site, such as the bloodstream, urinary tract, or a wound, resulting in CRE infection. The proportion of carriers in which this occurs is determined by a variety of factors, including their immune status, the presence of invasive devices or being subjected to invasive procedures, and antibiotic exposure. Two studies

among hospitalized patients estimated that between 7.6% and 9.1% of carriers will develop CRE infection.[109,110] However, in certain populations, such as bone marrow transplant recipients, this proportion may be much higher, reaching 75%.

Clinical manifestations of CRE

CRE, like other enterobacteria, may cause a variety of infections. Most commonly, infections caused by CRE include urinary tract, intra-abdominal, bacteremia, pneumonia (ventilator associated or not), and skin and soft tissue (including surgical site). Clinical symptoms of infections caused by CRE are identical to those caused by susceptible strains. A methodological concern in studies that compare the mortality and morbidity of patients infected with resistant bacteria to other patients is that the former group tends to have additional risk factors, such as more severe underlying illness and longer hospitalization, which make them more likely to have worse outcomes. Most well-designed studies that controlled for these potential confounders[111–115] found 3–6 times higher mortality among CRE-infected patients than those either infected with carbapenem-susceptible Enterobacteriaceae or without CRE infection, although another study found no difference.[116]

The higher mortality associated with CRE infections is likely not because the pathogen itself is more virulent but because adequate treatment is delayed or unavailable, and because available treatment options are less efficacious compared with agents used to treat susceptible organisms.[117] In a study by Ben-David *et al.*, in which the risk of death was nearly four times higher for patients with carbapenem-resistant *K. pneumoniae* (CRKP) bacteremia than for patients with carbapenem-susceptible *K. pneumoniae* bacteremia, only 12% of patients in the former group received appropriate empiric therapy compared with 79% in the latter group.[115] Even timely, appropriate treatment (i.e., antibiotics with *in vitro* activity against CRE) does not necessarily improve outcomes. In two studies comparing patients with CRKP infection who died during their hospital stay to those who survived, receiving an antibiotic with *in vitro* activity against CRKP did not improve survival.[113,118] The high in-hospital mortality (over 50% in both studies) among CRKP-infected patients who receive an active antibiotic may reflect confounding factors such as delayed treatment and greater severity of underlying illness, compared with patients with carbapenem-susceptible infections.

Epidemiology of CRE in healthcare settings

In developed countries CRE transmission occurs almost exclusively within healthcare settings. The main route of spread is from patient to patient via contaminated hands of healthcare workers, although transmission has also been traced to contaminated endoscopes[119] as well as sinks and drain pipes.[120] Three steps are required for a healthcare worker to spread CRE from patient to patient; the worker must touch a patient colonized or infected with CRE (or their contaminated surroundings), become temporarily contaminated with CRE, and then touch a non-colonized patient while still contaminated (e.g., without changing gloves or washing hands). *Colonization pressure* is defined as the proportion of patients who are already colonized or infected with a particular pathogen. When colonization pressure is zero, there is no chance that the first step will occur. When colonization pressure is high, it is highly likely that the first step will occur. Thus, the risk of acquiring CRE (or any MDRO (multidrug-resistant organism)) depends not only on characteristics of the individual patient but also on the status of other patients,[121] as well as on local conditions, for example, availability of isolation rooms, staff-to-patient ratio, and compliance with hand hygiene. A study conducted in two New York hospitals found that the odds of CRE acquisition increased by 15% per each 1% increase in colonization pressure.[102] Other risk factors for hospital-acquired CRE carriage or infection include prolonged hospital stay, ICU stay, antibiotic use, poor functional status, adult diaper use (either as a marker for being severely debilitated or representing the risk for fecal material contamination), and the presence of multiple invasive devices or mechanical ventilation.[31,102,103,111]

Long-term care settings—including LTACHs and post-acute care hospitals (PACH) that treat seriously ill patients, and nursing homes that provide custodial care—play a key role in the spread of CRE. In a study in the Chicago area, 30% of residents of LTACHs were CRE carriers, compared to 3.3% of patients in ICUs in general hospitals.[122] In a study in post-acute care facilities in Israel, 12%

of all patients and 26% of patients in skilled nursing wards were colonized with CRE.[101] Patients in these high-acuity long-term settings typically have many risk factors for CRE colonization, including advanced age, multiple co-morbidities, use of multiple invasive devices, high exposure to antibiotics, and prolonged hospitalization.[122] Few studies have been designed to discern whether CRE carriers in LTACHs acquired CRE while at the facility or arrived from general hospitals already colonized. In one LTACH involved in a multi-facility CRE outbreak in Indiana and Illinois, three patients were positive on admission and seven acquired CRE after admission.[123]

In affected regions, CRE are also prevalent in lower-acuity long-term settings such as nursing homes. A point prevalence survey in a West Virginia nursing home found that 9% of residents were colonized with CRKP.[124] The high prevalence in nursing homes stems both from resident characteristics that increase the risk of CRE acquisition (advanced age, co-morbidities) and facility characteristics that promote transmission (shared rooms and communal areas, undesirability of restricting activity in settings that serve as residents' homes, and lack of expertise in infection control).[124,125] Nursing homes, LTACHs, and PACH serve as CRE reservoirs: even when infection control measures in general hospitals have succeeded in stopping transmission, the influx of colonized patients from long-term care means that there is continual colonization pressure.[126] Several reports have described CRE outbreaks that spanned a web of general hospitals and long-term care settings.[123,127,128]

Epidemiology of community-acquired CRE

Transmission of CRE outside of healthcare settings has been documented rarely in developed countries[129–131] but is more common in developing countries. Suspicion of non-nosocomial CRE transmission was first raised after the initial discovery of NDM-1–producing *K. pneumoniae* in a patient in Sweden who had been hospitalized in New Delhi;[132] as NDM-1 was detected in more Westerners returning from the Indian subcontinent, it was noted that not all of them had been hospitalized while abroad.[133,134] In 2010, a study conducted in hospital laboratories in north and south India reported that the majority of the 148 CRE isolates analyzed were community-acquired infections.[68] Since then, other reports of community-acquired CRE in developing countries[135] and in Westerners returning from developing countries[136] have been published.

Community transmission of CRE in developing countries is presumably oral–fecal (i.e., waterborne and foodborne).[100] The presence of CRE in water was confirmed by Walsh *et al.*, who sampled public tap water and seepage water in New Delhi.[104] They detected NDM-1–producing species, including Enterobacteriaceae, in both water sources. Similar studies have detected NDM-1–producing *K. pneumoniae* in river water in Vietnam[137] and OXA-48–producing *Serratia marcescens* in puddles in Morocco.[138] Other research failed to detect resistance genes in bacteria isolated from raw vegetables in India.[139]

Interventions to control and prevent CRE

Few interventions to control and prevent CRE have been rigorously evaluated in randomized, controlled trials. Rather, most of the evidence for or against a measure comes from either quasi-experimental studies that compare CRE incidence or prevalence before and after the interventions were implemented or descriptive studies that report resolution of an outbreak. These studies have been nicely summarized in two reviews[20,140] and nearly all report striking success. For example, a national intervention in Israel reduced the incidence of CRKP detected in clinical cultures from 55.5 to 11.7 per 100,000 patient-days.[11] In an LTACH in Chicago, the prevalence of CRKP carriage fell from 21% to 0%;[141] in an ICU in a New York hospital, the incidence of CRKP detected in clinical cultures decreased from 9.7 to 3.7 per 1000 patient-days.[142] As is standard in the field of infection control, nearly all of the intervention studies involve a bundle approach in which multiple measures are implemented simultaneously. Therefore, it is difficult to determine the effect or relative importance of any individual measure[140] except by using mathematical models.[143] Table 1 compares guidelines for CRE control issued by the Israeli Ministry of Health,[126] the U.S. Centers for Disease Control and Prevention,[144] and the European Society of Clinical Microbiology and Infectious Diseases' (ESCMID) Study Group for Antimicrobial Resistance Surveillance.[145]

Table 1. Comparison of guidelines for prevention and control of CRE transmission

Intervention	Israel	United States[a]	ESCMID Study group for antimicrobial resistance surveillance
Hand hygiene	Required	Core measure	Not addressed
Active surveillance:			
On admission	Required for patients (1) transferred directly from another healthcare facility, (2) hospitalized in an ACH or LTCF in recent months, or (3) hospitalized since 2008 in countries with known non-KPC–producing CRE (e.g., India)	Supplemental measure. Possible candidates for screening: patients admitted from LTCF or from high CRE prevalence areas or from institutions known to have CRE; patients admitted to high-risk units such as ICU	For countries with no or sporadic CRE: goal is complete eradication of CRE (search and destroy). Screen patients transferred from countries or institutions with epidemic or endemic CRE; preemptive isolation while waiting for results. For countries with endemic or ongoing outbreaks of CRE: goal is maximum containment of CRE. Screen patients with previous contact with medical facilities with known ongoing CRE outbreaks.
During hospitalization	Required for patients epidemiologically linked to a patient newly diagnosed with CRE carriage or infection; optional routine periodic screening in high-risk units	Core measure for patients epidemiologically linked to a patient newly diagnosed with CRE carriage or infection; routine periodic screening in high-risk units is optional supplemental measure	Advised for patients epidemiologically linked to a patient newly diagnosed with CRE carriage or infection
Patient cohorting	Required in ACH. Within the cohort, patients with KPC are in separate rooms from patients with other carbapenemases (OXA-48, NDM-1, and VIM) to prevent cross-transmission; not required in LTCF rehabilitation wards (i.e., wards without medically complex or ventilated patients) if prevalence < 3%.	Core measure for ACH and LTCF	Advised
Dedicated staffing	Required in ACH; not required in LTCF	Core measure for ACH and LTCH	Advised
Dedicated equipment	Required in ACH and LTCF: medical equipment (e.g., blood pressure cuffs) is not shared among patients with CRE and patients without CRE	Not addressed	Not addressed
Contact precautions	Required in ACH and LTCF	Core measure for ACH; in LTCF use only for patients at high risk of transmitting CRE (i.e., ventilator dependent, require full assistance with activities of daily living, incontinent of stool, have wounds with drainage that are difficult to control)	Advised
Mandatory reporting	Hospitals send daily census of incident and prevalent CRE cases (carriage or infection) to National Center for Infection Control	Recommended that laboratories report positive test for CRE to health department, particularly in regions with no known CRE prevalence	For countries with no or sporadic CRE: have action plan in place that includes reporting all cases to public health authorities For countries with endemic or ongoing outbreaks of CRE: hospitals should send daily census of CRE carriers to public health authorities (national CRE task force)
Chlorhexidine baths	Not addressed	Supplemental measure when core measures are not successful in decreasing CRE incidence	Not addressed

Continued

Table 1. *Continued*

Intervention	Israel	United States[a]	ESCMID Study group for antimicrobial resistance surveillance
Minimize use of invasive devices	Not addressed in context of CRE	Core measure	Not addressed
Selective digestive decontamination	Not addressed	Not addressed	Not advised because of lack of evidence
Antimicrobial stewardship	Not addressed in context of CRE	Core measure	Not addressed

[a]Core measures are required. Supplemental measures are to be used if core measures have failed to control CRE.
ACH, acute care hospital; LTCF, long-term care facility.

Interventions to prevent transmission of CRE

Active surveillance

Asymptomatic gastrointestinal carriers of CRE can be reservoirs for transmission. The purpose of active surveillance (screening) is to identify carriers so that the infection control measures discussed below can be implemented to prevent carriers from transmitting CRE to susceptible patients. The alternative to active surveillance—identifying carriers only when a culture performed as part of clinical care is positive for CRE—misses a large proportion of carriers; in an Israeli study, for example, 52% of patients with CRE were identified by screening and 48% by clinical culture.[146] Active surveillance is generally performed by rectal swab, although stool specimens, perirectal swabs, or cultures of wounds or urine (from catheterized patients) have also been used.[144] Surveillance specimens may be processed using molecular (PCR) or culture-based methods. Compared to culture-based methods, the advantages of molecular methods are rapid turn-around time (particularly important when results trigger the isolation of potential transmitters) and higher sensitivity. Disadvantages are that they test for typically only a single mechanism of resistance and thus may miss others, and they do not identify species or antimicrobial susceptibilities and so cannot be used to guide empiric therapy if clinical infection develops.[147,148]

An active CRE surveillance program must specify whom and when to screen. Different recommendations regarding screening are listed in Table 1. Patients at risk for CRE carriage may be screened *on admission* to a facility (hospital). Although Israeli and U.S. guidelines consider a patient's region or country of origin in assessing risk, the European Centre for Disease Prevention and Control rejects classifying countries as low- or high-risk and screening only patients from the latter group, as the true CRE prevalence of any country is unknown.[149] Ideally, patients screened on admission should be placed on preemptive contact precautions in a single room until the test results are reported.[150]

Screening *during the course of hospitalization* is recommended for patients who are epidemiologically linked to a patient with newly detected CRE carriage or infection. If the index case is detected in a high-risk unit, such as an intensive care or transplant unit, all other patients in the unit should undergo screening. In lower-risk units, the infection control staff should determine which patients are epidemiologically linked to the index case depending on proximity, duration of contact, and shared caregivers.[126] Institutions may also choose to perform ongoing screening in units with a high incidence or prevalence of CRE. In a study conducted in one New York hospital, all ICU patients were screened for CRE on admission and then weekly. Of the 79 patients (out of over 11,000 screened) in whom CRE carriage was detected, 46% tested positive on admission and 54% were identified on weekly screening.[151] It is important to stress that active surveillance is not in and of itself an effective infection control measure. For example, one hospital that implemented CRE screening but not subsequent measures to limit the transmission potential of carriers detected by screening was unsuccessful in reducing CRE incidence.[140]

Cohorting and dedicated staffing

Cohorting refers to housing patients with CRE carriage/infection together in an area physically separated from non-carriers in order to minimize opportunities for transmission from carriers to non-carriers. In dedicated staffing (also known as *staff cohorting*), on any given shift, nurses who care for patients in the CRE cohort do not also care for CRE

non-carriers, thus preventing nurses from serving as vectors of transmission.[11] In one hospital that instituted CRE control measures in a stepwise fashion, simply isolating CRE carriers in single rooms was unsuccessful in slowing the outbreak; cohorting and dedicated staffing were the actions that led to the steepest decline in CRE incidence.[152] The burdens imposed by dedicated staffing are not negligible. Hospital-wide staffing is strained as nurses assigned to the CRE cohort are unavailable to fill in elsewhere; morale may wane among nurses in the cohort who are isolated from colleagues and prevention fatigue may lead to lapses in infection control technique.[153]

Contact precautions

Contact precautions—recommended for control of all MDROs, not just CRE—aim to limit the spread of organisms transmitted by direct or indirect contact with patients or their environment.[154] The three components of contact precautions are hand hygiene before donning a gown and gloves, donning a gown and gloves before entering the patient's room, and removing gown and gloves and performing hand hygiene before leaving the patient's room.[144] The impact of contact precautions is limited by healthcare workers' compliance. During a CRE outbreak in a Puerto Rican hospital, staff performed adequate hand hygiene in 48% of encounters with patients on contact precautions and wore gowns and gloves in 62% of such encounters.[155] One U.S. hospital confronting a CRE outbreak achieved nearly total compliance by assigning to each cohort area a healthcare worker whose sole duty was to enforce hand hygiene and contact precautions.[153]

Environmental cleaning

CRE carriers shed the organism into their surrounding environment. Lerner *et al.* cultured the bed sheets, bedside tables, and infusion pumps of 34 CRE carriers and detected CRE on at least one of these surfaces in the vicinity of 88% of the carriers.[156] Although the exact role of environmental contamination in CRE transmission remains unknown, increasing the frequency and extent of cleaning has been a component of most infection control bundles to reduce CRE. In outbreak situations, it may be necessary to shut down affected units in order to perform thorough cleaning.[142,157] Observation of environmental cleaning practices may expose previously unidentified gaps that can be corrected. During a CRE outbreak in a U.S. LTACH, observers discovered that cleaning personnel never cleaned surfaces close to patients, such as bed rails and intravenous pumps. It was explained that as part of a policy to prevent patient injury, nurses had been assigned to clean these surfaces; interviews with nurses, however, revealed that they did not do so. The problem was solved by transferring all responsibility for cleaning to the cleaning staff.[141]

Chlorhexidine baths

Chlorhexidine gluconate is a broad-spectrum antiseptic. The rationale for chlorhexidine baths is to reduce the microbial burden on patients' skin to prevent secondary contamination of the environment.[158] In a multicenter, cluster-randomized, crossover trial comparing daily patient baths with 2% chlorhexidine wipes or non-antimicrobial washcloths, chlorhexidine reduced the acquisition of methicillin-resistant *S. aureus* or vancomycin-resistant *Enterococcus* by 23%.[158] No similar trial has been conducted for CRE, but two studies[141,159] included 2% chlorhexidine baths for all patients in the bundle of interventions to control a CRE outbreak. The CDC recommends chlorhexidine baths as a supplemental strategy when core measures have failed to reduce CRE incidence.[144] Notably, isolates belonging to the dominant clone of KPC-producing *K. pneumonia*e, ST-258, were found to have reduced susceptibility to chlorhexidine, which may in part explain that clone's success in hospital settings.[160]

Interventions to prevent CRE carriage from progressing to infection

Selective digestive decontamination

Selective digestive decontamination (SDD) involves administering oral non-absorbable antibiotics with the immediate aim of eradicating gastrointestinal carriage of MDROs. The ultimate aims of SDD are to prevent MDRO carriage from progressing to infections, such as bacteremia and pneumonia, and to prevent MDRO transmission to other patients. Three studies with a control group have examined SDD using gentamicin and/or colistin to eradicate CRKP carriage. Two studies[161,162] found a significant reduction in short-term CRKP carriage among patients treated with SDD compared to controls, while the third study[163] found no difference. Lubbert's study,[163] the only one that measured secondary antibiotic resistance, also found that resistance to colistin and gentamicin increased in the

SDD group. In Saidel-Odes' study,[161] the difference in CRKP carriage between the SDD group and the control group was no longer statistically significant after 6 weeks. Conclusive data on SDD's effectiveness for preventing infections and transmission, and its ecological safety regarding antibiotic resistance, are lacking.[164,165] Therefore, SDD for CRE carriage should be reserved for special cases such as a carrier awaiting high-risk chemotherapy or transplant. When used, resistance to the agents used for SDD should be anticipated and monitored to prevent the spread of even more resistant CRE strains.

Limiting the use of invasive devices

Invasive devices such as central venous catheters and indwelling urinary catheters increase the risk that CRE carriers will develop clinical infections with CRE.[109,110] Invasive devices may facilitate the progression from carriage to infection by providing a portal of entry. Likewise, caring for these devices without adequate hand hygiene and aseptic technique creates opportunities for introducing CRE from contaminated areas to clean areas on the patient.[110] The CDC classifies limiting the use of invasive devices as a core measure for controlling CRE.[144] Clearly there is room for reducing the use of these devices. Studies conducted in ICUs found, for example, that 32% of urinary catheter-days were unnecessary[166] and that 28% of patients with central venous catheters had no indication for their use.[167]

Interventions to prevent the development of carbapenem resistance

Antimicrobial stewardship

Many studies have demonstrated that recent exposure to antibiotics is a risk factor for CRE carriage or infection.[101,102,168,169] Therefore, efforts to optimize antibiotic use and limit unnecessary use (antibiotic stewardship) are considered a core measure to control CRE.[144] Several hospitals have restricted carbapenem use as part of a bundle of interventions that successfully controlled CRE outbreaks.[155,170,171] However, in a single (non-bundled) intervention in an Iranian ICU, a 60% decrease in carbapenem use with no concomitant change in total antibiotic use failed to increase the proportion of Enterobacteriaceae isolates susceptible to imipenem.[172] Because carbapenem resistance among Enterobacteriaceae can develop following exposure to nearly any class of antibiotics, reducing overall antibiotic use is more important than restricting carbapenems.[94,140]

Treatment of CRE infections

Currently there is no licensed antibiotic with proven effectiveness against CRE. No randomized controlled trials have compared the available options to determine which is best for treating CRE infections at different sites. What is known about different agents' effectiveness in humans is based on syntheses of case series.[20,173–175] Weaknesses of these case series—even when combined—that limit the conclusions that can be drawn from them include the frequent adjustments of drugs and dosages during treatment, confounding by indication (i.e., severely ill patients receive different regimens than less sick patients, making comparisons difficult), and the small number of patients studied.

Clinical decisions about treatment are based on laboratory tests that classify a specimen as susceptible, intermediate, or resistant to a given antibiotic. However, as mentioned earlier, treatment with an antibiotic in the susceptible category does not predict clinical success; several studies found no difference in mortality between patients who did or did not receive treatment with a drug with *in vitro* activity against CRE.[113,116,118,176]

Colistin

Colistin (polymixin E) has been in use since the late 1950s. Because it can cause nephrotoxicity and neurotoxicity, its use waned in the 1970s and was replaced by less toxic aminoglycosides. Beginning in the early 2000s, there was a revival of interest in colistin for the treatment of multidrug-resistant organisms; however, several problems complicate its use for the treatment of CRE infections. First, determining *in vitro* susceptibility is not straightforward, as isolates may be falsely labeled "susceptible," and there is disagreement as to what should be considered the susceptibility breakpoint.[177] Second, the optimal dosage of colistin is unknown. Because the drug was developed in the era before rigorous drug development trials, data on pharmacokinetics and pharmacodynamics, which form the basis of prescribing recommendations are lacking.[177] Third, nephrotoxicity remains a common, albeit reversible, adverse event. In recent studies, estimates of the proportion of patients who develop nephrotoxicity during colistin therapy range from 33%

to 54%; higher doses were associated with greater toxicity.[178–182] The clinical effectiveness of colistin is poor; in a review of 72 patients treated with colistin only, treatment failed in 47% of them. When colistin was combined with tigecycline or an aminoglycoside, treatment failed in 17 of 53 patients (32%). The combination of colistin and a carbapenem was most successful, with only 1 out of 17 patients failing treatment.[20]

Tigecycline

Tigecycline was approved by the U.S. Food and Drug Administration in 2005. Because tigecycline poorly penetrates certain anatomical sites, including serum, urine, and epithelial lining fluid,[100] it is not approved for the treatment of hospital-acquired pneumonia, bacteremia, or urinary tract infections. In 11 studies in which a total of 26 patients with CRE infections were treated with tigecycline, treatment failed in 29% of those who received tigecycline alone and in 37% of those who received tigecycline plus another antibiotic.[174] In 2013, the FDA issued a black box warning noting the increased risk of death with tigecycline (2.5%) compared with other antibiotics (1.8%); the deaths resulted from worsening infections, complications of infections (i.e., treatment failure), or underlying medical conditions. The FDA advised limiting tigecycline use to situations in which alternative treatments are not suitable.[183] It is prudent to limit its use to treatment of skin and skin structure infections and complicated intra-abdominal infections, two anatomic sites where tigecycline penetrates adequately.

Aminoglycosides

Among this class of antibiotics, amikacin, gentamicin, and tobramycin are commonly used. A fourth drug with increased resilience to carbapenemases, plazomicin, is still in development.[184] First introduced in 1944, aminoglycosides fell out of favor in the 1980s, as new drugs, such as β-lactams combined with β-lactamase inhibitors and broad-spectrum cephalosporins, became available. Side effects, primarily nephrotoxicity, contributed to aminoglycosides' decline, but lack of treatment options for multidrug-resistant Gram-negative organisms has led to renewed use of this drug class.[185,186] *In vitro* susceptibility of CRE isolates to aminoglycosides varies with the resistance mechanism and the specific isolate. In a study of 82 CRE isolates, 1/12 KPC producers, 5/19 OXA-48 producers, and 17/17 NDM producers were resistant to gentamicin.[187] In studies of patients with KPC-producing *K. pneumoniae* infections, aminoglycoside treatment failed in 1/10 cases of monotherapy and in 8/32 cases of combination therapy.[20] Among patients with CRE bacteriuria, aminoglycoside monotherapy achieved a microbiological cure in 88% of patients, significantly more than colistin (64%), tigecycline (43%), or no treatment (36%).[188]

Carbapenems

Paradoxically, carbapenems have a role in the treatment of CRE infections. In 2011, the EUCAST lowered its Enterobacteriaceae resistance breakpoint for imipenem/meropenem from >8 mg/L to >4 mg/L. It appears that isolates in the zone between the old and new breakpoint may respond to carbapenem therapy. In a review of 44 CRE-infected patients from 10 studies who received carbapenem monotherapy, treatment succeeded in 69% of patients whose isolates had an MIC ≤ 4 mg/L, 60% of patients with an MIC of 8 mg/L, and 29% with an MIC > 8.[189] At least two researchers have concluded that carbapenems are a reasonable option for treating CRE when the MIC is ≤4 or even ≤8 mg/L, when a second antibiotic is added, and when the carbapenem is given by a high-dose prolonged infusion regimen to achieve high serum concentrations.[20,189] One animal study has suggested that double-carbapenem therapy may be an effective strategy for treating CRE infections; in this therapy the drug more easily hydrolyzed by carbapenemases (e.g., ertapenem) saturates the enzymes (the carbapenemases), leaving higher concentrations of less hydrolysable drug (e.g., doripenem) available to treat the infection.[190]

Monotherapy versus combination therapy

Possible advantages of combination therapy include (1) synergistic effects observed *in vitro* that lead to better clinical outcomes and (2) secondary resistance may emerge to a drug given alone.[191,192] Evidence regarding the first point is inconclusive. In a review of 20 observational studies, Falagas *et al.* reported that the majority found no significant differences in mortality or treatment failure between patients who received monotherapy and those who received combination therapy; however, in three studies that included only critically ill patients with CRE bacteremia, mortality was significantly lower in patients given combination therapy.[175] In the largest

Table 2. Antibiotics in development with activity against CRE

Drug	Class	Description	Activity against carbapenemase producers	Phase of development	Do trials include a specific aim of evaluating efficacy against CRE infections?[a]	Infections targeted in clinical trials	Reference
Beta-lactamase inhibitors that inhibit carbapenemases							
Ceftazidime–avibactam	Cephalosporin + beta-lactamase inhibitor	Avibactam: non-beta-lactam agent with excellent inhibition of class A and class C beta-lactamases, including KPC.	Active against KPC and OXA-48 but not MBLs.	III	Yes	Complicated intra-abdominal infection; complicated urinary tract infection; nosocomial pneumonia; targeted study of resistant organisms.	197
Ceftaroline–avibactam	Cephalosporin + beta-lactamase inhibitor		Active against KPC and OXA-48 but not MBLs.	II	No	Complicated urinary tract infection.	197
Aztreonam–avibactam	Monobactam + beta-lactamase inhibitor		Active against KPC, OXA-48 and MBLs.	I	No		197
Imipenem–MK7655	Carbapenem + beta-lactamase inhibitor	MK-7655: non-beta-lactam agent with excellent inhibition of class A and class C beta-lactamases, including KPC.	Active against KPC; weakly active against OXA-48; not active against MBLs.	II	Yes	Complicated urinary tract infection; complicated intra-abdominal infection.	198
Carbavance (RPX2014/RPX7009)	Carbapenem + beta-lactamase inhibitor	RPX-7009: boronic acid-containing inhibitor of class A beta-lactamases, including KPC.	Active against KPC, not active against OXA-48 or MBLs.	III	Yes	Complicated urinary tract infection; nosocomial pneumonia; bacteremia; targeted study of resistant organisms.	199
Aminoglycosides							
Plazomicin	Aminoglycoside	Semi-synthetic aminoglycoside, retains activity against isolates with transferable aminoglycoside-modifying enzymes, but not against those with ribosomal methyl-transferases.	Active against most carbapenemase-producing Enterobacteriaceae, with the exception of many NDM-1 producers.	III	Yes	Complicated urinary tract infection; CRE bacteremia; CRE nosocomial pneumonia.	187
Tetracycline derivatives							
Eravacycline	Tetracycline	Fluorocycline active against the main acquired tetracycline-specific resistance mechanisms (efflux pumps and ribosomal protection).	Active against KPC; few isolates with other carbapenemases have been tested.	III	No	Complicated urinary tract infection; complicated intra-abdominal infection.	200

[a]Descriptions of clinical trials available at http://clinicaltrials.gov.

of these three studies, which included 125 patients, 30-day mortality was 54% for monotherapy and 34% for combination therapy; 30-day mortality was lowest (25%) when combination therapy included a carbapenem.[193]

To date, only one study comparing monotherapy to combination therapy for CRE has examined resistance as an outcome.[194] That study compared 12 patients whose CRKP infections were treated with polymixin B (a drug closely related to colistin) alone to four patients treated with polymixin B plus tigecycline. Samples taken after treatment showed rising MICs to polymixin B in three of the patients given monotherapy and in none of the patients given both drugs.

Currently, there is no convincing evidence that combination therapy is superior or inferior to single therapy, and treatment decisions should be made on clinical grounds according to the individual patient and strain characteristics. Two large trials, one funded by the U.S. National Institutes of Health and one funded by the European Commission, are now being conducted to examine this question.[195,196]

Drugs in development

Table 2 outlines the antibiotics in development that are active against CRE. For an in-depth review, see Refs. 20 and 184.

Conclusions

Carbapenem resistance in Enterobacteriaceae, primarily due to the spread of the four carbapenemases KPC, NDM, OXA-48, and VIM, is an emerging clinical and public health problem that threatens the effectiveness of the last currently available antibiotic group highly active against multidrug-resistant Enterobacteriaceae. The spread of these extremely drug-resistant organisms may limit the ability of healthcare institutions to provide complex medical treatment in a safe manner. The epidemiology of CRE varies between countries; however, it is evident that without stringent infection control measures these organisms may rapidly become endemic. Treatment options for CRE are limited and of uncertain benefit. CRE, due to their rapid spread, poor treatment options, and associated severe outcomes, challenge our healthcare systems and highlight weaknesses in sanitation and hygiene. Fortunately, the problem of CRE has attracted the attention of the pharmaceutical industry and regulatory agencies, and new agents are currently in advanced development. Until these new drugs are available, understanding the local epidemiology and designing and implementing control measures that are tailored to the local modes of spread are of highest priority.

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Conflicts of interest

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