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Carbapenem-Resistant Enterobacteriaceae Infections in Children

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Abstract

Carbapenem-resistant Enterobacteriaceae (CRE) are an emerging global public health threat. Infections due to CRE are associated with significant morbidity and mortality. Few therapeutic options are available for treatment of these infections, and optimal antibiotic treatment regimens are unclear. Along with the rapidly increasing prevalence of CRE in the United States and worldwide, several studies have described the epidemiology of CRE in the adult population. While CRE is now also reported sporadically in children, there is a significant lack of data on the epidemiology, risk factors, treatment, and outcomes in this population. This article provides a comprehensive review of what is known to date about CRE, including clinical and molecular epidemiology, microbiologic diagnosis, antibiotic treatment options, and outcomes. In particular, this review will focus on the available data on CRE in the pediatric population.

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Introduction

Infections due to antibiotic-resistant gram-negative organisms, including those caused by extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, are increasing worldwide and represent a significant public health threat [1]. Carbapenems have historically been the most effective antimicrobial therapy for infections due to these organisms. However, over the past two decades, carbapenem-resistant Enterobacteriaceae (CRE) have increasingly been identified as causes of healthcare-associated infections in adult patients. Infections due to CRE in adult populations have been associated with poor clinical outcomes, including mortality rates as high as 40–65% [2–5]. CRE have been reported infrequently in children, but increasing reports of infections both in the United States and worldwide, along with an increasingly medically complex pediatric population suggest that CRE may emerge as a significant nosocomial pathogen in pediatric centers over the coming years [6].

Molecular Epidemiology of CRE

The most common Enterobacteriaceae exhibiting carbapenem resistance is *Klebsiella pneumoniae* followed by *Enterobacter* species, with other members of the Enterobacteriaceae reported less frequently [7, 8]. Resistance to carbapenems develops by one of two general mechanisms: enzymatic or non-enzymatic mechanisms. The former involves production of carbapenemases, enzymes which hydrolyze the β -lactam ring of carbapenem antibiotics. The latter includes production of ESBLs and/or AmpC cephalosporinases in conjunction with decreases in membrane permeability. Carbapenemase-producing Enterobacteriaceae have largely been responsible for the rapid worldwide spread of CRE owing to easily transferred mobile genetic elements (e.g., plasmids, transposons) that encode carbapenemase genes. In contrast, decreases in membrane permeability are frequently associated with a loss in fitness to the organism and reduced transmissibility [6, 9]. It therefore becomes important for epidemiologic purposes to differentiate organisms that are carbapenemase producers (CP-CRE) from those that are carbapenem-resistant due to other mechanisms (non-CP-CRE). For example, while contact precautions are generally recommended for both CP-CRE and non-CP-CRE, CP-CRE may warrant more aggressive infection control interventions such as targeted active surveillance [10].

While the Ambler classification system differentiates carbapenemases based on molecular structure, key differences also exist with regard to specific resistance patterns, inhibitors, phenotypic characteristics, and geographic distributions (Table 1). Ambler class A carbapenemases include chromosomally as well as plasmid encoded carbapenemases, the most common of which is *K. pneumoniae* carbapenemase (KPC). The KPC gene *bla_{KPC}* is associated with a mobile transposon Tn4401 which has become established in some strains

particularly adept at clonal expansion, such as *K. pneumoniae* sequence type (ST) 258. ST258 is largely responsible for the epidemiologic success of KPC-producing organisms [9, 11]. KPC production accounts for up to 80% of carbapenem resistance in the United States and an increasing proportion of CRE worldwide [12–14]. While KPC producers have been identified on all continents, the United States, Israel, Greece, Poland, Italy, China, Columbia, Brazil, and Argentina represent highly endemic areas [15].

Ambler class B carbapenemases include the Verona integrin-encoded metallo-beta-lactamases (VIM), IMP types, and New Delhi metallo-beta-lactamases (NDM-1). VIM and IMP have historically been linked to the Mediterranean basin and Asia, although they have been isolated worldwide, including in the United States. NDM-1, which is endemic to the Indian subcontinent and accounts for as many as 50% of CRE isolates in this region, has now been identified throughout Europe, parts of Asia and Africa, and in the United States, often in individuals who have traveled from endemic regions [4, 9].

Ambler class D carbapenemases are oxacillinases and most notably include the OXA-48 carbapenemases. Class D carbapenemases are most frequently identified in *Acinetobacter* species. However, the OXA-48 carbapenemase has been increasingly reported in *K. pneumoniae* and *E. coli* isolates. OXA-48 was originally associated with the Middle East, North Africa, and remain endemic in Turkey, but like other groups of carbapenemases, have been isolated in several other geographic regions worldwide, including the United States [9, 16]. As international migration and medical tourism continue to increase, it is anticipated that geographic distinctions for the various carbapenemase-encoding genes will eventually disappear.

Epidemiology and Risk Factors

Defining the extent of the global CRE epidemic has been challenging for a number of reasons, including changing definitions of carbapenem resistance in both the United States and Europe, technical challenges of distinguishing carbapenemase production from other mechanisms of resistance, and incomplete reporting of CRE isolates worldwide [4, 10, 16–18]. In the United States, the Centers for Disease Control and Prevention (CDC) defines CRE as organisms resistant to imipenem, meropenem, doripenem, or ertapenem *or* documentation that isolates are carbapenemase-producing [19]. This revised 2015 definition is an attempt to increase the sensitivity of the prior definition which did not include ertapenem resistance, as a small subset of organisms that produce KPC are susceptible to all carbapenems except ertapenem. Additionally, the previous requirement for isolates to exhibit resistance to all third-generation cephalosporins was removed to simplify application of the definition and to account for some OXA-48 type carbapenemases that may not exhibit resistance to third-generation cephalosporins [19–21].

In the United States, KPC was first identified in a *K. pneumoniae* isolate in North Carolina in 2001 [22]. Since then, KPC-producing isolates have been identified in 48 states, The District of Columbia, and Puerto Rico, although rates remain highest in the mid-Atlantic region [10, 12]. The CDC's National Healthcare Safety Network (NHSN) reported carbapenem resistance in approximately 12% of *K. pneumoniae* and approximately 2% of *E.*

coli isolates in 2009–2010, with 3.9% of acute care hospitals and 17.8% of long term acute care hospitals (LTACHs) reporting at least one healthcare-associated CRE infection [2, 7]. Other recent studies report overall carbapenem resistance rates between 3.4% to 6% in *K. pneumoniae* and 0.8% in *E. coli*, a significant increase in the past decade primarily due to spread of KPC [8, 12, 23, 24].

Risk factors for CRE infections in adult patients have been incompletely characterized and conflicting results are reported in various studies likely due to differences in study design, inclusion of patients with both CRE infection and colonization, and diversity of study populations and health systems with reports from both the developed and developing world. LTACH residence has been well established as a risk factor for CRE, with 30% of residents demonstrating colonization with CRE in a point prevalence study of Chicago area LTACHs [2, 25]. Prior antibiotic exposure has also been shown to confer an increased risk of colonization and/or infection with CRE, although the agents implicated vary significantly among studies with anti-pseudomonal penicillins, beta-lactam/beta-lactamase inhibitors, extended-spectrum cephalosporins, carbapenems, glycopeptides and quinolones all reported [26–32]. Other identified risk factors include presence of medical devices, intensive care unit (ICU) stay, solid organ transplant, renal failure, and bedbound status [5, 27–32]. Reported mortality rates due to CRE infection among adult patients have varied across studies, but were as high as 65% in some populations despite antibiotic therapy [3, 5].

Pediatric Patients

Far less is known about CRE epidemiology and risk factors in children. Currently available data are largely limited to case reports, controlled and uncontrolled case series, and one systematic review summarizing available data through 2012 [6]. A recently published study reported that the frequency of carbapenem resistance increased from 0% in 1999–2000 to 0.47% in 2010–2011 among Enterobacteriaceae isolates in children in the United States [33]. Worldwide, the frequency of meropenem non-susceptibility among *K. pneumoniae* and *E. coli* isolates recovered from children is approximately 4% and <1%, respectively [34]. Most large national surveillance reports fail to include children's hospitals or do not report pediatric specific data [7, 8, 12, 23, 24].

Available data, however, suggests that CRE epidemiology, risk factors, and outcomes in the pediatric population reflect many of the trends observed in studies in adult populations. Nosocomial outbreaks with CP-CRE have been reported in pediatric facilities, including a California neonatal intensive care unit (NICU), a Spanish pediatric intensive care unit (PICU), and a Nepali NICU associated with IMP, VIM, and NDM-1 carbapenemases, respectively [35–37]. Pediatric long-term care facilities (LTCF), similar to adult LTACHs, may also serve as reservoirs of CRE; in the one pediatric report investigating this association, KPC rectal colonization was detected in 12 of 26 (46%) pediatric LTCF residents [38]. Lastly, geographic trends in the distribution of carbapenemases are generally comparable in adult and pediatric populations [6, 35–37, 39–51].

Patient-level risk factors for CRE infection in children include underlying chronic medical conditions, invasive medical devices, frequent or prolonged hospitalizations, prior antibiotic exposure, age, and travel from endemic regions [6, 35, 36, 39–44, 46, 48–50, 52, 53].

Neonates seem to be a particularly at risk group with several reported outbreaks of NDM-1-producing Enterobacteriaceae in the neonatal population in the Indian subcontinent [35, 37, 47, 51]. Although mortality rates of children vary across reports, the highest rates are seen in the neonatal population [35–37, 39–49, 51].

In the United States, a recent case series in the pediatric population included 11 CRE isolates from 10 patients, of which 4 had clinical infection with CRE in Los Angeles, California. Carbapenemases were identified in 5 isolates, including two NDM-1 type carbapenemases and three KPCs. Three patients had CRE isolated from the blood, 3 from the urine, and 2 each from wounds and the respiratory tract. All but one patient had underlying medical conditions, including 3 with malignancies. In addition, 8 patients had central venous catheters, 1 had traveled to India, and 8 had been treated at an adult hospital in the year prior to CRE diagnosis. In the 6 months prior to CRE isolation, patients received a median of 28 days of antibiotics. Four patients in this series died [39].

Another series from the United States described 6 patients with CRE infection including 5 with bacteremia and 1 with a urinary tract infection (UTI) in Seattle, Washington. One patient had KPC-producing *K. pneumoniae*, two had IMP-4-producing *E. coli*, one had SME-producing *Serratia marcescens* and two had ESBL-producing *E. coli* with associated porin mutations. Five of the 6 patients had underlying hematologic malignancies and the sixth had a renal transplant. There was one death [40].

Lastly, a series of 13 patients with CRE isolated from clinical specimens identified in The District of Columbia reported underlying medical conditions and prior antibiotic exposure in 12 of 13 patients, of which gastrointestinal disease was most common. When compared to age-matched controls, previous antibiotic use, including carbapenems, third-generation cephalosporins, and fluoroquinolones, was significantly associated with CRE isolation. Among these 13 patients, 7 developed CRE infection, including bacteremia (2), UTIs (3), skin and soft tissue (1), and intra-abdominal infection (1). No patients died in this series. Of note, this study did not distinguish CP-CRE from non-CP-CRE [52].

Internationally, Greece, Italy, the United Kingdom (UK), China, Pakistan, and Turkey have all described similarly small case series of CRE in children, with findings corroborating those from US studies [41–45, 50–53]. A report from Italy identified 15 CP-CRE isolates, of which 6 were associated with clinical infection, including 4 bacteremias and 2 UTIs. There were 2 deaths. In this study, 11 of the patients had malignancies and all patients were treated with 20 days of gram-negative active antibiotics in the 90 days prior to CRE detection [41]. In the UK study, notable findings include detection of CRE colonization in approximately 5% of study patients. Of these, 21% developed an infection with the same organism, suggesting that active surveillance could be of potential utility in identifying patients at risk of subsequent CRE infection [45]. An even higher burden of CRE colonization was detected in a Turkish series with 29% of pediatric patients colonized with CRE. These patients were more likely to have received a carbapenem prior to CRE isolation and have been transferred from another healthcare facility. Notably, 3.4% of these colonized patients went on to develop CRE infections [53]. Another Turkish study reported that 84% of CP-CRE

colonization occurred in pediatric patients, which was attributed to the ease of dissemination within open units common in neonatal and pediatric ICUs [46].

The epidemiology of CRE in the neonatal population warrants separate consideration as they are among the most vulnerable pediatric patients. In a Pakistani NICU, a reported 72% of *K. pneumoniae* isolates were carbapenem resistant [47]. Between 2007 and 2011, carbapenem resistance in an Indian NICU were reported as 33% for *E. coli* and 13% for *K. pneumoniae*, with 14% of Enterobacteriaceae producing NDM-1 [51]. Lastly, a large outbreak of NDM-1 producing Enterobacteriaceae was described in a Nepali NICU involving 26 neonates and was associated with a 64% mortality rate [37].

Diagnosis of CRE

In 2010, the Clinical and Laboratory Standards Institute (CLSI) lowered carbapenem susceptibility minimal inhibitory concentration (MIC) breakpoints for Enterobacteriaceae in part to eliminate the need for confirmatory testing for carbapenemase production. The reported MICs under these new guidelines reflect achievable pharmacokinetic-pharmacodynamic (PK-PD) targets with standard, intermittent carbapenem dosing, regardless of the mechanism of resistance [54]. The result was a decrease in the carbapenem MIC considered susceptible for imipenem and meropenem from 4 µg/mL to 1 µg/mL. The MIC breakpoint for ertapenem was lowered from 2 µg/mL to 0.25 µg/mL, and subsequently increased to 0.5 µg/mL [18]. These guidelines, along with the CDC's revised definition of CRE, remove the requirement for additional testing for carbapenemase production [55]. While this approach is appealing for its relative ease of interpretation and decreased need for laboratory resources, failure to differentiate CP-CRE from non-CP-CRE has important epidemiologic implications, including the potential for more aggressive infection control interventions than may be necessary for non-CP-CRE. An additional concern is that the lowered breakpoints may result in use of unnecessarily broad, toxic, or less effective antibiotic therapy, such as polymyxins or tigecycline [56, 57]. Therefore, depending on considerations such as regional endemicity and laboratory resources, confirmatory testing for the presence of a carbapenemase may be warranted [10, 17, 55, 58].

Phenotypic Testing

The modified Hodge test (MHT), also known as the “clover leaf” test, is a phenotypic test for carbapenemase production in which the suspected carbapenemase-producing organism is streaked onto Mueller-Hinton agar. Carbapenemase production is detected when the isolate produces a carbapenemase, allowing for growth of a carbapenem-susceptible strain along the streak of the inoculum toward the carbapenem disc. The MHT is highly sensitive for class A and D carbapenemases, inexpensive, and easy to perform, and is included in CLSI and CDC recommendations for confirmatory testing for carbapenemase production [10, 18]. However, it is limited by frequent false positive results from ESBL or AmpC production combined with porin mutations, subjective interpretation, 72–96 hour turnaround time from the time of culture attainment, and reduced sensitivity in detecting MBL-type carbapenemases, although this is improved with addition of zinc to the medium [59, 60].

Another group of phenotypic assays are the rapid chromogenic assays, most notably the Carba NP test in which a bacterial lysate is incubated with imipenem and a color change occurs in the presence of imipenem hydrolysis. Tazobactam or EDTA can also be added to samples to discriminate among Ambler class A, B, and D carbapenemases [61, 62]. Sensitivity of the Carba NP test varies among studies from 80% to 100%, with lower sensitivity attributed to inconclusive results or false negatives with OXA-48 type carbapenemases, as well as for NDM-1-producing *Proteus* and *Providencia* isolates. Specificity remains 100% across studies, which when coupled with the ease of performance and rapid turn around time (30 minutes to 2 hours), makes it an attractive alternative to the MHT [61–64]. Another advantage of chromogenic assays, as opposed to the MHT, are their ability to identify carbapenemases in nonfermenters such as *Acinetobacter* spp. and *Pseudomonas* spp. and not just Enterobacteriaceae. Other available rapid chromogenic assays include the Rapid CARB Screen Kit (Rosco Diagnostica), the Rapid CARB Blue Kit (Rosco Diagnostica), and the RAPIDEC CARBA NP assay (bioMérieux) [65].

Genotypic testing

Single and multiplex polymerase chain reaction (PCR) assays and microarray assays are available for common carbapenemases, including KPC, VIM, IMP, NDM, and OXA-48, with sensitivity and specificity of these tests approaching 100% [66–68]. Clear advantages of these molecular methods include identification of specific carbapenemase genes with superior sensitivity and specificity as well as rapid turn around time. Disadvantages include relative expense of these methods as well as need for specialized equipment and trained personnel. Furthermore, use of these assays at present requires in-house validation as none are approved by the United States Food and Drug Administration (FDA) or recommended by the CLSI. Molecular methods only have the ability to detect resistance genes included in their platform and cannot detect novel carbapenemase genes. Enhancements to existing matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry observed in the research setting may enable this technology to detect CP-CREs in diagnostic laboratories in upcoming years [69–70].

Screening for CRE

The CDC provides a laboratory protocol for detection of CRE from rectal or perirectal swabs for surveillance purposes [71]. This process, which involves inoculation of the specimen onto MacConkey agar and use of carbapenem discs, has been validated for *E. coli* and *Klebsiella* species. Alternatively, chromogenic media are available commercially and have reasonable sensitivity for detection of CRE, are relatively inexpensive, and are easily interpretable [72, 73]. PCR-based methods are more sensitive than chromogenic media, but are associated with the same disadvantages described above [74].

Treatment of Infections due to CRE

Data on optimal treatment regimens for CRE are hampered by a lack of randomized trials evaluating the effectiveness of various therapeutic approaches. Current recommendations are guided by case reports, case series, and cohort studies with significant heterogeneity in populations and treatment regimens evaluated [75]. Overall, available data support

combination therapy with at least 2 agents given significant reductions in mortality with this approach compared to monotherapy, with cited mortality rates as low as 13% [13, 76–78]. There are insufficient data at this point, however, to recommend a particular combination regimen, and antibiotic selection should be guided by clinical source of infection, local susceptibility patterns, and expert consultation.

Carbapenems

Currently available data suggest that carbapenem-containing combination therapy appears to have a mortality benefit over monotherapy or non-carbapenem containing combination therapy [13, 76–78]. Along these lines, the largest review to date evaluating treatment of CRE infections reported a mortality rate of 19% with carbapenem-containing combinations compared to 31% for carbapenem-sparing combinations [13]. Modeling studies suggest that prolonged or continuous infusion of meropenem can achieve target concentrations for isolates with MICs as high as 8 µg/mL – 16 µg/mL, although extrapolating this into clinical practice is difficult given a recent study reporting increased mortality with MICs between 2–8 µg/mL compared with MIC < 1 µg/mL [79, 80]. Few data exist in the pediatric population on the potential benefit of extended or continuous infusions of carbapenems. However, carbapenems remain a mainstay of pediatric therapy based on the available adult literature and experience with these agents in pediatric populations [81, 82].

Polymyxins

Polymyxins, including colistin and polymyxin B, have re-emerged as first-line therapy for serious infections due to carbapenem-resistant organisms. However, their use is limited by increasing resistance rates, which have been reported to be as high as 25% for CRE and 8% for all Enterobacteriaceae [75, 83, 84]. In addition, polymyxins have been associated with significant renal toxicity, with rates of acute kidney injury occurring in as many as 40 to 60% of adult patients [57, 85]. Available evidence suggests that mortality is higher in patients with CRE infections that are treated with colistin monotherapy compared with those receiving colistin-containing combination therapy [77, 86]. No pediatric studies have directly evaluated the use of colistin for CRE specifically, but studies including patients with all multidrug-resistant gram-negative infections cite favorable outcomes in 70–80% of all patients, with incidence rates of acute kidney injury up to 20% [87–89].

Tigecycline

Tigecycline remains active *in vitro* against the majority of Enterobacteriaceae in the United States, with resistance rates reported at 1.7% overall and less than 0.1% among pediatric patients. Among CRE, tigecycline resistance is reported in approximately 12% of isolates [34, 84, 90]. As with carbapenems and colistin, outcomes are poor with tigecycline monotherapy but improved when tigecycline is combined with another agent [76, 78, 91]. However, there are emerging data suggesting increased mortality in patients treated with tigecycline for any indication, the etiology of which is not well understood but thought to be most likely related to poorly sustained serum concentrations; as a result, the FDA has issued a black box warning for this agent [56, 92]. In pediatric settings, experience with tigecycline is limited to case reports, and along with the potential for increased mortality, association

with enamel hypoplasia, tooth discoloration, and availability of other agents should limit its use to situations when other treatment options have been exhausted [40, 41, 48, 49, 81, 93].

Fosfomycin

Fosfomycin remains active against most CRE isolates tested, and the intravenous form has been used successfully to treat CRE infections in adult patients outside the United States, generally in combination with a second agent due to the risk of developing resistance while on therapy [94, 95]. Intravenous dosing is available for pediatric patients, although the intravenous form of the drug is not currently available in the United States [96]. The oral form of the drug, however, is available in the United States and achieves high concentrations in the urine, making it a favorable option for treatment of cystitis caused by CRE [48, 95].

Emerging agents

Ceftazidime-avibactam was approved in by the FDA in February 2015 following a priority review of phase II trial data showing efficacy and safety comparable to imipenem-cilastatin and meropenem for treatment of complicated urinary tract and intra-abdominal infections in adult patients [97, 98]. Avibactam is active against both KPC and some OXA-type carbapenemases but not metallo-beta-lactamases [99, 100]. A phase I trial in pediatric patients was completed in late 2014 (NCT01893346) and two phase II studies enrolling infants as young as 3 months of age are currently ongoing to evaluate the role of ceftazidime-avibactam in children with complicated urinary-tract and intra-abdominal infections (NCT02475733 and NCT02497781) [101–103]. Other agents in development include ceftaroline-avibactam, imipenem - MK7655, biapenem - RPX7009, plazomicin (a novel aminoglycoside), and eravacycline, all with variable activity against the different carbapenemase classes based on existing *in vitro* data [75, 81, 104].

Prevention and Control of CRE

In the United States, the CDC recommends several “core measures” for CRE prevention and control, including hand hygiene, antimicrobial stewardship, minimizing use of invasive devices, and contact precautions and patient cohorting for patients with CRE colonization or infection [10, 16]. Surveillance procedures for CRE colonization in institutions with few or no CRE cases may include a point prevalence screen of those at highest risk, including LTACH residents, patients transferred from other facilities with known CRE transmission, patients who recently received medical care in regions of the world endemic for CRE, or patients admitted to high risk units such as ICUs [10]. If a patient harboring CRE is identified, institutions should screen epidemiologically linked contacts and units. In institutions with ongoing CRE transmission, active surveillance should be performed on admission in high-risk patients as well as periodically throughout their stay. Although outbreaks of carbapenemase-producing organisms have been difficult to control, there are data that if systematically implemented, rigorous infection control procedures can halt the spread of these organisms in both hospital and LTACH settings [105–107].

Conclusion

While CRE represents an emerging threat in pediatric patients, little data exist at the present time on epidemiology, risk factors, treatment, or outcomes in this increasingly vulnerable population. Furthermore, the lack of currently available treatment options is exacerbated by limited data on their use in pediatric patients, emerging resistance to these therapies, and a lack of clinical trials evaluating novel agents or PK-PD of many available CRE-active antibiotics in the pediatric population. Future research efforts should focus on filling these gaps in knowledge.

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- ☐ ☐ Of major importance
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Table 1

Characteristics of carbapenemases found in Enterobacteriaceae by Ambler class

Ambler Class	Examples	Molecular Structure	Inhibitors	Laboratory Diagnosis Notes	Epidemiologically Important Enterobacteriaceae ¹	Geographic Distribution ¹
A	KPC, IMI-1, SFC-1, SME-1 to -3	Serine at active site	Boronic acid, clavulanic acid, and tazobactam		<i>K. pneumoniae</i> most common; <i>E. coli</i> , other Enterobacteriaceae	United States, South America, Israel, Greece
B	VIM, IMP	Zinc at active site	EDTA; not inhibited by beta-lactamase inhibitors	Modified Hodge test less sensitive, improved sensitivity with addition of zinc sulfate Carba NP less sensitive for NDM-1 producing <i>Proteus</i> and <i>Providencia</i>	<i>K. pneumoniae</i> most common	Greece, Asia
	NDM-1		EDTA; not inhibited by beta-lactamase inhibitors		<i>K. pneumoniae</i> , <i>E. coli</i>	India, Pakistan
D	OXA-48, OXA-181	Serine at active site	Slight to no inhibition by EDTA and clavulanic acid	Carba NP less sensitive for detection of OXA type carbapenemases	<i>K. pneumoniae</i> , <i>E. coli</i>	Mediterranean countries, Turkey

¹ Both Enterobacteriaceae recognized as producing specific carbapenemases and their geographic distribution continue to evolve [9, 56, 58, 61, 62]