



# The United Sludge-Free Alliance Recommended Reading

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## **Expert Column**

### **Klebsiella pneumoniae Carbapenemase: Extended-Spectrum beta-Lactamase Continues to Go Global**

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Introduction to Klebsiella pneumoniae Carbapenemases Carbapenems, such as imipenem and meropenem, are often used to treat infections caused by extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria. A new class of bacterial enzymes capable of inactivating carbapenems, known as Klebsiella pneumoniae carbapenemases (KPCs), has rapidly spread in the United States and continues to be extensively reported elsewhere in the world. KPCs are class A carbapenemases[1] that reside on transferable plasmids and can hydrolyze all penicillins, cephalosporins, and carbapenems.

The options for treating infections caused by KPCs are limited, and often require the use of polymyxins, which fell into disuse in the 1980s due to high rates of nephrotoxicity. The epidemiology of KPC-producing organisms remains largely unknown, and is being intensively studied by researchers. The following aims to review our current understanding of KPCs and to summarize important results presented at a special session on KPCs at the 2008 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and Infectious Diseases Society of America (IDSA) joint annual meeting in Washington, DC.

#### First Isolate of KPC-producing Bacteria

In 1996, the first isolate of KPC-producing bacteria was discovered in a clinical specimen of *K pneumoniae* from a hospital in North Carolina involved in the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) surveillance program.[2] KPCs were infrequently isolated until 2001, when KPC-producing Enterobacteriaceae were reported in several extended outbreaks in metropolitan hospitals of New York and New Jersey.[3-5] KPC-producing organisms have continued to spread over time and have now been reported in 27 states in the United States,[6] and in many countries around the world, including China,[7] Colombia,[8] Brazil,[9] France,[10] and Israel.[11]

The epidemiology of KPC-producing organisms continues to evolve. Although most KPCs are detected in isolates of *Klebsiella* and *Escherichia coli*, KPCs have been extensively reported in other genera of the Enterobacteriaceae family, such as *Proteus*,[12] *Serratia*,[13] *Salmonella*,[14] and *Citrobacter*. [15] Worse still, KPC resistance has been reported in inherently resistant organisms such as *Pseudomonas*. [16] Akpaka and colleagues,[17] from Trinidad, studied an isolate of multidrug-resistant *Pseudomonas aeruginosa* that harbored a novel KPC-6 gene, and presented their findings at the recent ICAAC/IDSA meeting. Of interest, the isolate was obtained from a patient who had no history of recent travel, suggesting that the specific isolate of KPC-producing *Pseudomonas* emerged locally, and probably continued to circulate in that region of the world.

#### Global Spread of KPC-producing Organisms

The global spread of KPC-producing organisms appears to have been rapid, perhaps because KPC infection and colonization were previously unrecognized, or because several factors can complicate their detection. First, KPC carbapenemases may only confer reduced susceptibility, and not complete resistance to carbapenems.[5,18] Second, some phenotypic tests may mistakenly label KBC producers as ESBL producers.[18] Third, automated susceptibility testing systems may have low sensitivity and specificity for detection of KPC carbapenemases when using imipenem or meropenem as testing agents.[19] Finally, KPC carbapenemases may not be detected if low inocula of the organism are used in automated testing.[5,20,21] Difficulties in detection may result in an underestimation of the true incidence of KPC-producing organisms and the duration of KPC epidemics.

Recent molecular studies examined the diversity and homology of KPC genes. The KPC gene identified from the first isolate in North Carolina was named KPC-1.[2] Subsequent variants of the KPC gene were named in sequential numeric order from KPC-2 to KPC-4. A recent correction in the BlaKPC-1 sequence revealed that KPC-1 and KPC-2 were in fact identical enzymes.[22] KPC-2 and KPC-3 genes are the most commonly detected KPC genes in clinical specimens; these 2 genes differ in structure by just a single amino acid.[6] Recent evidence derived from minimal spanning tree analysis showed that the KPC-2 gene was most likely the founding or ancestral sequence from which subsequent variants arose via amino acid substitution. Of note, KPC-5 and KPC-6, which have been described by researchers at the same academic institution in Puerto Rico, also differ from the ancestral KPC-2 by just 1 amino acid substitution. KPC-5 was detected in an isolate of *Pseudomonas* obtained during a surveillance study, and its genetic sequence differed from the KPC-2 gene by an arginine substitution (Pro 103 to Arg).[23]

The discovery of KPC-6 was presented at the recent ICAAC/IDSA annual meeting. KPC-6 was isolated and identified from the blood culture of an HIV-infected patient,[24] and it differed from the KPC-2 gene by a different glycine amino acid substitution (Val 239 to Gly).[23] Cumulative evidence suggests that gene elements conferring KPC resistance are genetically stable and are increasingly common because such genetic changes are adaptive for the organism against ongoing antibiotic pressure. Thus, the global spread of KPC-producing organisms is likely to continue.

#### Epidemiology of KPC-producing Organisms

To date, our understanding of the epidemiology of KPC resistance is limited to outbreaks and infections reported from tertiary care academic medical centers. The epidemiology of KPC infections in the community setting remains poorly understood. Several abstracts at the recent ICAAC/IDSA meeting provided further insight into the spread of KPCs in the community.

Our group presented preliminary results from an investigation of a KPC outbreak in a 310-bed community hospital in Virginia.[25] The start of the outbreak dated back to January 2007 when an astute laboratory manager noted a substantial increase in the number of ESBL isolates with elevated minimum inhibitory concentration (MIC) to imipenem. In conjunction with the Duke Infection Control Outreach Network (DICON), a local outbreak investigation was conducted. We defined a case of probable KPC-producing organism as any Gram-negative organism with an ESBL phenotype and an MIC to imipenem of 1.5g/mL or greater on broth microdilution. Probable KPC producers were later confirmed by modified Hodge test to have carbapenemase activity.[26]

The epidemiologic curve (Figure) shows that the first case of KPC was detected in February 2007, although the outbreak did not become established until May of that year. An interim analysis was conducted in May 2008, even though the outbreak was ongoing. The epidemiologic curve revealed an outbreak consistent with extended person-to-person transmission and not compatible with common vehicle exposure. A total of 58 patients were identified as having probable KPC-producing organisms, and interestingly, all of the organisms were *K pneumoniae*. These patients with probable KPCs were older, with a median age of 70 years, and 36% were admitted from nursing homes or long-term care facilities (LTCFs).

Figure.  
Epidemiologic curve constructed from 16 months of case finding.

Most (54%) KPCs acquired during the study period were classified, using standard infection control surveillance definitions, as community-onset.[27] In fact, the median time to isolation of a KPC-producing organism was 1.5 days from time of admission. This suggests that KPC-producing organisms were acquired in the community and that person-to-person transmission of KPC-producing organisms in the community is possible.

Patients who were infected or colonized with KPCs had numerous medical comorbidities and poor outcomes. For instance, most patients had comorbidities associated with advanced age, such as diabetes mellitus (48%), cardiac disease (40%), and chronic airway disease (30%). Furthermore, 35% of the patients spent part of their hospital admission in the intensive care unit (ICU). Finally, KPCs were associated with an in-hospital crude mortality rate of 22% during the study period.

Twenty-nine probable KPC isolates that tested positive on modified Hodge test were sent to collaborators in Israel for further molecular typing by pulsed-field gel electrophoresis (PFGE). The first and most important finding was that none of the probable KPC isolates were identical. Furthermore, 2 of these 29 isolates (7%) did not harbor KPC genes. As in other surveillance studies, KPC-2-producing and KPC-3-producing organisms were the only 2 genotypes involved in this outbreak. We found that 34% of the isolates had KPC-2 genes, whereas 59% had KPC-3 genes.[6] There were 5 distinct PFGE types (I-V) within the 27 isolates of KPCs with 83% homology in the PFGE types I-IV, and 76% homology between PFGE type V and the first 4 PFGE types. Overall, the isolates of KPC obtained in this study had high clonal relatedness. Their molecular epidemiology suggested an extended outbreak in which related isolates evolved from a common ancestor.[28] Furthermore, patients admitted from the same nursing home facilities had the same KPC gene types, lending support to the previous finding that transmission of clonally related KPC-producing organisms was occurring within the hospital environment as well as within the community setting.

Endimiani and colleagues[29] presented a similar epidemiologic study of KPC-producing organisms in patients of an LTCF in South Florida. Case finding was performed by studying isolates of probable KPC with reduced susceptibility to carbapenems (MICs  $\geq 4$  mg/L) obtained from a regional laboratory in Ft. Lauderdale, Florida. Ten isolates of KPCs were identified from 7 patients; all isolates were *K pneumoniae*. Isolates obtained from patients residing in LTCFs were closely related and belonged to the KPC-3 genotype. Three isolates detected in hospitalized patients were not related to the LTCF isolates. This study provided further evidence that KPC-producing organisms could easily disseminate outside the hospital environment.

### Infection Control and Treatment

The spread of KPC-producing organisms in the community and in the hospital environment represents a serious infection control and therapeutic challenge. Detection of KPC-harboring organisms was erratic before the recent adoption of ertapenem-based screening. McGettigan and colleagues[30] presented an abstract demonstrating that ertapenem susceptibility testing is highly sensitive (80%) but only moderately specific. Additionally, the same study demonstrated that imipenem and meropenem screening for KPC producers would miss approximately 50% of the KPC-producing organisms. In light of increasing supportive evidence, laboratories should switch over to ertapenem-based screening to improve detection for KPC-producing Gram-negative bacilli.

Containment of KPC-producing organisms has been a focus of intense study.

Several abstracts presented at the recent ICAAC/IDSA meeting highlighted the trials and tribulations involved in controlling outbreaks of KPC. Some effective strategies to control the spread of KPCs include (1) performing active surveillance for KPCs by perirectal swabs or stool cultures,[31] (2) cohorting KPC-colonized and KPC-infected patients,[31,32] (3) assigning dedicated nursing staff to cohort units,[31,32] and (4) intensifying hand hygiene and environmental cleaning.[31]

An example of success in controlling KPCs came from Kocher and colleagues[31] at SUNY Downstate Medical Center, Brooklyn, New York, who used a combination of these interventions in their ICU to curtail an outbreak of multidrug-resistant bacteria that included KPCs. The

investigators obtained rectal swab cultures on all new admissions to the ICU and repeated the surveillance cultures weekly. KPC-infected or colonized patients were cohorted and assigned a dedicated group of nurses to care for them. Daily environmental cleaning was performed with a quaternary ammonium compound on all work surfaces in clinical areas. As a result of these interventions, the number of KPC infections/colonizations significantly decreased over the ensuing 12 months.

Despite the apparent effectiveness of some or all of the aforementioned interventions, questions remain about how patients should be screened for KPCs, whether or not contacts should be screened, and which laboratory method to use to screen patients for KPCs. The first question is easier to answer than the others. Kotlovsky and colleagues[33] compared the effectiveness, labor burden, and turnaround time of 3 laboratory methods to screen for KPC-producing organisms. Plating of rectal swab samples directly onto McConkey agar with imipenem and ertapenem discs provided accurate results within 24 hours of test initiation, and 96.5% concordance with the polymerase chain reaction (PCR) assay for KPC detection. Thus, the study authors recommended that unless KPC results are urgently required, direct plating onto agar with imipenem and ertapenem discs is the most accurate and cost-effective laboratory method to screen for KPCs.

The mortality associated with infection caused by KPC-producing organisms is estimated to be between 22% and 59%.[25,34] and many clinicians have resorted to the use of tigecycline and the polymyxins for treatment.[35] Limited experience and lack of familiarity with tigecycline have largely limited the use of this agent. Fortunately, most KPC-producing organisms remain exquisitely susceptible to tigecycline. Castanheira and colleagues[36] tested 178 isolates of KPC-producing organisms against tigecycline and found only 1 (0.6%) isolate that was not susceptible to tigecycline by standard CLSI broth microdilution methods.

Polymyxin B and colistin have been associated with high rates of nephrotoxicity and thus must be considered drugs of last resort. Emerging data have shown that the polymyxins may not be as nephrotoxic as previously believed. Despite this finding, polymyxins should only be used cautiously. Furthermore, there are increasing reports of polymyxin resistance in KPC-producing organisms.[36]

## Conclusion

Carbapenems have long been a reliable last line of defense in the treatment of infections caused by antimicrobial-resistant Enterobacteriaceae. The emergence of KPC resistance is a major threat to global health. Recent results show that KPC genes are diverse, stable genetic elements that can be difficult to detect. Furthermore, KPC-producing organisms can spread inside hospitals as well as in the community setting. Treatment of KPCs often requires the use of tigecycline and the polymyxins. This epidemic of Gram-negative resistance must be stopped. Increased awareness and intensified infection control practices are the keys to curtail the spread of this terrifying antimicrobial resistance.

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