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Emergence of *Klebsiella pneumoniae* Carbapenemase (KPC)-Producing Bacteria

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Abstract

Klebsiella pneumoniae carbapenemase (KPC)-producing bacteria are a group of emerging highly drug-resistant Gram-negative bacilli causing infections associated with significant morbidity and mortality. Once confined to outbreaks in the northeastern United States (US), they have spread throughout the US and most of the world. KPCs are an important mechanism of resistance for an increasingly wide range of Gram-negative bacteria and are no longer limited to *K pneumoniae*. KPC-producing bacteria are often misidentified by routine microbiological susceptibility testing and incorrectly reported as sensitive to carbapenems; however, resistance to the carbapenem antibiotic ertapenem is common and a better indicator of the presence of KPCs. Carbapenem antibiotics are generally not effective against KPC-producing organisms. The best therapeutic approach to KPC-producing organisms has yet to be defined; however, common treatments based on in vitro susceptibility testing are the polymyxins, tigecycline, and less frequently aminoglycoside antibiotics. The purpose of this review is to identify the various challenges that KPC-producing bacteria present to clinicians. These include the need for special techniques for microbiological detection, the potential for nosocomial transmission, and therapeutic challenges related to limited, relatively unproven antimicrobial treatment options.

Keywords

Enterobacteriaceae; multi-drug resistant; carbapenem-resistant; Klebsiella

Introduction

Infections caused by bacteria-producing *Klebsiella pneumoniae* carbapenemases (KPCs) are becoming an increasingly significant problem worldwide since the first detection of these enzymes greater than a decade ago.[1] Although KPCs do not represent the first or the sole

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mechanism of carbapenem resistance, they are remarkable because they are often not detected by routine susceptibility screening and possess an exceptional potential for dissemination. In addition to the infection control challenges that have arisen, infections caused by these organisms present clinicians with serious treatment challenges, due to limited antibiotic options.

Efforts are underway to address these varied clinical challenges and have concentrated on enhanced infection control practices, better screening methods, determination of optimal usage of existing antibiotics, and development of novel antimicrobials.

Significance of Klebsiella pneumoniae carbapenemases

In 1983, the first report of plasmid-mediated beta-lactamases capable of hydrolyzing extended-spectrum cephalosporins was made. They were named extended-spectrum beta-lactamases (ESBLs) and they have since been described worldwide.[1] The fact that carbapenems are the treatment of choice for serious infections caused by ESBLs, along with an increasing incidence of fluoroquinolone resistance among *Enterobacteriaceae,* has led to an increased reliance on carbapenems in clinical practice.[2]

In 2001, the first KPC-producing *K pneumoniae* isolate was reported in North Carolina.[3] The enzyme (KPC-1), an Ambler class A beta-lactamase, was not the first carbapenemase to be detected in *K pneumoniae*, as isolates harboring Ambler class B metallo-beta-lactamases capable of hydrolyzing carbapenems had previously been reported in Japan as early as 1994.[1] However, metallo-beta-lactamases are uncommon in the US and the production of KPC enzymes has become the most prevalent mechanism of carbapenem resistance in the US today.[4] KPCs are encoded by the gene bla_{KPC}, whose potential for inter-species and geographic dissemination is largely explained by its location within a Tn3-type transposon, Tn4401. This transposon is a genetic element which is capable of inserting into diverse plasmids of Gram-negative bacteria. Plasmids carrying bla_{KPC} are often also associated with resistance determinants for other antibiotics. Although *K pneumoniae* remains the most prevalent bacterial species carrying KPCs, the enzyme has been identified in several other Gram-negative bacilli (Table).[5]

In 2009, the Centers for Disease Control and Prevention (CDC) released a report on KPC-producing bacteria in which the term Carbapenem-Resistant Enterobacteriaceae (CRE) was proposed as more accurate, given the understanding that multiple species of Gram-negative bacteria can harbor the KPC-resistant element.[6] We have used the terminology ‘KPC,’ given the preponderance of the literature using this term to date.

Epidemiology

Prior to the first hospital outbreaks in New York City, carbapenem resistance in *K pneumoniae* was rare in the US.[7] The initial outbreaks caused great concern as these bacteria had reduced susceptibility or resistance to all beta-lactams including penicillins, cephalosporins, monobactams, and carbapenems. Moreover, in vitro studies of 95 KPC isolates from Brooklyn hospitals during 2003-2004 revealed approximately half to be susceptible to aminoglycosides and very few to be susceptible to flouroquinolones.[8]

Following the initial sporadic outbreaks in New York City, bacteria-producing KPC enzymes became endemic in many hospitals in the New York and New Jersey area.[7] In the ensuing decade, KPC-producing bacteria have spread throughout the US and worldwide. Data regarding nosocomial infections reported to the CDC showed the overall prevalence of carbapenem resistance among *K pneumoniae* isolates rose from less than one percent in 2000 to eight percent in 2007.[6] At one academic medical center in New York City, the percentage of carbapenem-resistant *K pneumoniae* rose from 9% in 2002 to 18% in 2004,

then further to 38% in 2008.[9] To date, KPC-producing bacteria have been isolated in at least 33 states.[5] In 2005, the first report of a clinical isolate producing a KPC outside of the US occurred in France from a patient who had recently been hospitalized in New York City.[10] The first outbreak outside the US was in Israel,[11] and KPCs are now endemic in both Israel and Greece. *Enterobacteriaceae*-producing KPCs have also been reported in Brazil, China, Colombia, Norway, United Kingdom, India, Sweden,[5] and more recently, Italy and Finland.[12]

A closer look at the molecular epidemiology of KPC-producing bacteria has revealed that a few fit lineages have been responsible for dissemination of the bla_{KPC} gene. An examination of all KPC-producing *K pneumoniae* isolates sent to the CDC between the years 1996-2008 from 18 states as well as Israel and India revealed that a single dominant strain, multilocus sequence type 258 (ST258), accounted for nearly 70% of the isolates in the CDC database as well as an isolate from an Israeli outbreak.[5] Although seven variants of the enzyme have been reported (KPC 2-8), most ST258 strains produced KPC-3 and most non-ST258 strains produced KPC-2 (KPC-2 enzyme is genetically identical to KPC-1). The study also identified another fit strain, ST14, which was isolated in various facilities in the Midwestern states. Additionally, Endimiani et al performed clonal analysis of 42 KPC-producing *K pneumoniae* isolates from five different institutions in the eastern US and found 32 (76%) to be clonally related, suggesting interstate transmission of a single dominant clone.[13]

Microbiological Testing for KPC-producing Organisms

Misidentification of KPC-producing bacteria is common with standard susceptibility testing. It has been reported that automated systems will identify seven to eighty-seven percent of KPC-producing *K pneumoniae* as susceptible to imipenem or meropenem.[14] The great variability that has been observed in carbapenem minimal inhibitory concentrations (MICs) by routine testing is likely related to the phenotypic heterogeneity among isolates, giving the appearance of susceptibility *in vitro*. It is thought that additional factors such as reduced outer membrane permeability may be needed for the KPC-producing organism to achieve full resistance to carbapenems, which would make them easier to detect by clinical laboratories. Several groups have made the observation that an ertapenem MIC in the resistant range by standard susceptibility testing may be the most sensitive indicator for presence of a KPC. In two different studies, one involving 33 cases of KPC-producing *Enterobacter* spp and another involving 28 cases of KPC-producing *K pneumoniae*, determination of ertapenem MICs by automated testing identified all cases as ertapenem-resistant.[15,16] Ertapenem resistance has been found to be the most sensitive clinical test of KPC production regardless of the method used and is recommended by the CDC.[17]

Confirmatory testing for KPC-producing bacteria is recommended in geographical locations where *Enterobacteriaceae* are noted to have decreased susceptibility to carbapenems or resistance to most non-carbapenem beta-lactams by routine testing. The most easily performed confirmatory test for KPCs is the modified Hodge test, which has been found to be 100% sensitive for the detection of a carbapenemase, although not specific for KPC production.[17] This test is performed first by culturing a susceptible *Escherichia coli (E coli)* isolate on a Mueller-Hinton plate, after which a carbapenem disk is placed in the center. Isolates suspected of carbapenemase production then are streaked from the disk to the outer margin of the plate. Growth of *E coli* near the disk or along the isolate streak indicates that a carbapenemase is present (Fig.). In January 2009, the Clinical and Laboratory Standards Institute (CLSI) recommended all *Enterobacteriaceae* with elevated but susceptible carbapenem MICs be tested with a modified Hodge test.[6] Another emerging test is a chromogenic medium CHROMagar KPC, which has been shown to have a sensitivity of 100% and specificity of 98.4% relative to polymerase chain reaction (PCR).[18] Definite

confirmation of KPC production requires molecular methods such as PCR, but these are costly and rarely available outside of reference laboratories.14

Clinical Features of KPCs

Infections caused by KPC-producing *K pneumoniae* have been associated with increased cost and length of stay as well as frequent treatment failures and death.[6] Risk factors for infection include advanced age,[19] being severely ill,[20] previous treatment with antibiotics,[7] organ or stem-cell transplantation, mechanical ventilation, and long hospital stays.[21] Reports are mixed as to whether previous carbapenem use is associated with the development of infections caused by KPC-producing bacteria.[7,19,16,22] In at least one study, prior fluoroquinolone and extended-spectrum cephalosporin use were both independently associated with infection or colonization with KPCs.[20]

Poor outcomes from infections with KPC-producing bacteria have been reported since the first reports of KPC outbreaks in New York City hospitals. A small series of patients with bloodstream infections caused by KPC-producing bacteria from New York City hospitals in 2005 revealed mortality rates of 47% to 66%.[7,19] The experience outside the US has been similar, as shown by a matched retrospective historical cohort study of 32 Israeli patients with bacteremia caused by carbapenem-resistant *K pneumoniae* compared to patients with infections caused by susceptible *K pneumoniae* that showed a crude mortality of 72%, and an attributable mortality of 50%.[23] None of the patients in this study received appropriate empiric antibiotics. In a cohort of 99 cases with KPC-producing *K pneumoniae* and 99 controls with susceptible *K pneumoniae*, KPC-production was associated with greater than two-fold increased risk of death.[21]

The difficulty of detecting KPC production with routine testing appears to have contributed to the poor outcomes observed with infections caused by KPC-producing bacteria by causing a critical delay in treatment. In the aforementioned study of 33 KPC-producing *Enterobacter* spp compared to imipenem-sensitive controls, significantly higher mortality was noted in conjunction with less frequent appropriate empiric antibiotics.[15] Weisenberg et al looked at 28 cases of confirmed KPC-producing *K pneumoniae* and found 46% of clinical isolates to have been reported inappropriately as imipenem-susceptible, which in turn led to the majority of these cases being treated with imipenem or meropenem.[16] KPC-producing bacteria present a significant problem in clinical situations where administration of effective empiric antibiotics is essential to preventing mortality. This applies to serious infections such as bacteremia, but also extends to other infections in patients undergoing organ transplants and cancer treatment, where the immunocompromised status of patients requires effective empiric antibiotics. Mathers et al reported two cases of orthotopic liver transplant recipients that died as a result of infections caused by KPC-producing *K pneumoniae*. Both patients were initially treated with meropenem based on the results of routine susceptibility testing.[24]

Nosocomial Transmission and Challenges in Infection Control

Enterobacteriaceae are among the leading causes of nosocomial infections.[25] Early identification of KPC-producing bacteria with *in vitro* testing is of paramount importance to the success of infection control efforts.6 In the appropriate setting, active surveillance can improve infection control by detecting colonization and preventing horizontal spread.[26] A study of 36 patients in an intensive care unit (ICU) in New York City during a KPC outbreak revealed 39% of all patients had gastrointestinal colonization while only 14% were identified by previous clinical culture.[7] The CDC released guidelines for surveillance in March 2009 recommending the use of active surveillance in outbreaks, and that even non-

endemic acute care facilities review all clinical cultures within the last 6-12 months for previously unrecognized KPCs.6

Aggressive infection control efforts have been effective at decreasing rates of infections with KPC-producing bacteria in intensive care units and long-term acute care hospitals.[26,27] Bundled interventions including enhanced environmental cleaning, active surveillance culturing and contact precautions, as well as antimicrobial stewardship are important in controlling KPC-producing bacteria.[19,28]

Current therapeutic options

With the spread of KPC-producing bacteria, clinicians are becoming increasingly dependent on polymyxins and tigecycline for treatment of these infections.[4] Some experts suggest that high-dose continuous infusion of a carbapenem may be helpful, though clear evidence of efficacy is lacking.[29] There is currently a need for information regarding the optimal use of these antibiotics with or without other partially active antibiotics in the treatment of infections caused by KPC-producing bacteria.

Polymyxins are a class of cyclic polypeptide antibiotics consisting of groups A-E, of which Polymyxin B and E (colistin) are currently available.[30] *In vitro* susceptibility to polymyxins among clinical KPC-producing isolates ranges from 90-100%.[13,8] Polymyxins achieve concentration-dependent bactericidal killing and are often the only agents active against KPC-producing bacteria that achieve adequate levels in the serum to treat serious bloodstream infections. However, in the past polymyxins were used infrequently, largely due to their associated nephrotoxicity and neurotoxicity. There is a small amount of retrospective data describing use of polymyxins as monotherapy for the treatment of KPCs. Three bloodstream infections during a Manhattan outbreak caused by KPC-producing *K pneumoniae* isolates susceptible to polymyxins were treated with polymyxin B, and one survived.[19]

Polymyxins are commonly used in combination with other antimicrobials, although there are no prospective data to evaluate the efficacy of this approach. Combination therapy may improve outcomes and be helpful in preventing bacterial resistance. Lee et al looked at 16 patients with persistent infections caused by KPC-producing *K pneumoniae* and found that three of twelve treated with polymyxin monotherapy developed polymyxin resistance during treatment. None of four cases treated with polymyxin combined with tigecycline developed resistance to either antibiotic.[4] In terms of outcomes, there are limited data examining combination therapy in humans, but what is present suggests non-inferiority of monotherapy compared with combination therapy.[31] During an outbreak of KPC-2 infections in Greece, 88% of the patients were treated with combination therapy and 22% of the cases resulted in clinical failure.[22]

Tigecycline is a novel glycylcycline that is often used in treatment of infections caused by KPC-producing bacteria and other multidrug-resistant (MDR) Gram-negative bacteria. Using the Federal Drug Administration (FDA) susceptibility breakpoint of a MIC <2 mg/L, tigecycline has excellent *in vitro* activity against KPC-producing bacteria. All 95 KPC isolates from Brooklyn hospitals in 2005[8] and 73 KPC isolates from 2000-2005 in seven different states[32] were susceptible to tigecycline by *in vitro* testing. However, in the United Kingdom an increase in tigecycline resistance has been noted in *Klebsiella* spp from 2001-2006.[33]

Despite use in clinical practice for off-label indications, few studies have evaluated outcomes of serious MDR-*Enterobacteriaceae* infections treated with tigecycline, and even fewer have been dedicated to infections caused by KPC-producing bacteria. In a review of

10 studies including only 33 patients with infections caused by MDR-*Enterobacteriaceae*, Kelesidis et al reported favorable outcomes with tigecycline treatment in 70% of cases.[34] However, 49% of these were cases of intra-abdominal infections, for which tigecycline has been approved. In contrast, several studies reported delayed clearance of the organism, recurrence of pathogens, and the need for prolonged administration of the antibiotic to achieve favorable outcomes.[34] Tigecycline is not recommended for treatment of infections of the blood or urine, where it has low concentrations. Development of resistance during therapy has been described in several reports and remains a concern.[35,36] Between January and July of 2009 in one New York City hospital, 14 *K pneumoniae* isolates were identified as intermediate or resistant to tigecycline and six were intermediate or resistant to polymyxin; two of these *K pneumoniae* isolates were resistant to tigecycline, polymyxin and other antibiotics.[9]

Aminoglycoside resistance is increasing among KPC-producing bacteria. In susceptible strains, *in vitro* data have shown rapid bactericidal activity of gentamicin against gentamicin-susceptible strains.[8] Members of the successful ST258 clone usually remain sensitive to gentamicin.[37] However, other lineages may carry gentamicin-modifying enzymes and other aminoglycosides, namely amikacin and tobramycin, which have been shown to be less effective against KPC-producing *K pneumoniae* than other forms of MDR-*K pneumoniae*.[38] When aminoglycoside susceptibility is identified, aminoglycosides are an important therapeutic option for the treatment of KPC-producing bacteria. However, pan-resistant bacteria have been reported that are resistant to tigecycline, polymixin, and aminoglycosides.[9,39]

Other older antimicrobials including fosfomycin or nitrofurantoin have been discussed for use in noninvasive infections such as urinary tract infections, but data relating to clinical efficacy is absent.[14,40]

Therapeutic options in development

Available beta-lactamase inhibitors such as clavulanic acid may restore activity of beta-lactams *in vitro* against KPC-producing bacteria, but such additions do not lower the MIC values of beta-lactam antibiotics to within the susceptible range and should not be used.[41] A novel beta-lactamase inhibitor, NXL104 has activity against the KPC enzyme and is currently in development.[41,42] Several novel synthetic polymyxin derivatives, including NAB739 and NAB740, have been developed that may be less nephrotoxic yet retain equal antibacterial activity.[43] Two other novel members of existing antibacterial classes are in development including a novel tetracycline PTK-0796,[37] and a novel aminoglycoside, ACHN-490.[38]

Although there are new agents within existing classes of antimicrobials, currently there are no new classes of antimicrobials in the later phases of development with activity against MDR-Gram-negative bacteria.

Summary

After initial outbreaks in the northeastern United States, KPC-producing bacteria have emerged in multiple species of Gram-negative bacteria across the world. They have created significant clinical challenges for clinicians as they are not consistently identified by routine screening methods and are highly drug-resistant, resulting in delays in effective treatment and a high rate of clinical failures. Effective antibiotics are limited to polymyxins, tigecycline and occasionally aminoglycosides. Hospitals must prepare so that they can identify these organisms early and institute enhanced infection control efforts when necessary. Clinical microbiology laboratories need to recognize the signature of ertapenem

resistance as a marker for KPC-producing bacteria, and should alert physicians to assume cross resistance to all carbapenems when it is present. Furthermore, clinicians need to appreciate that KPC-production can occur in many Gram-negative bacilli and become familiar with the limited effective antibiotics against KPC-producing bacteria as the frequency of KPC-producing bacteria is expected to continue to increase.

Brief Description

Klebsiella pneumoniae carbapenemase (KPC)-producing bacteria are emerging, highly drug-resistant pathogens whose incidence is rapidly increasing in a variety of clinical settings. This review describes the evolution from sporadic localized outbreaks to international emergence and addresses the difficulties these organisms present to clinicians, particularly in relation to common misidentification by routine susceptibility testing and limited treatment options leading to significant morbidity and mortality.

Key points

- *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria are becoming increasingly prevalent worldwide.
- KPC-producing bacteria are frequently misclassified as carbapenem-susceptible by routine susceptibility testing, and should be suspected with ertapenem resistance.
- KPCs are not restricted to *Klebsiella spp*, but instead are found in a variety of Gram-negative bacteria.
- Antimicrobial options are generally limited to polymyxins, tigecycline, and less often aminoglycosides.

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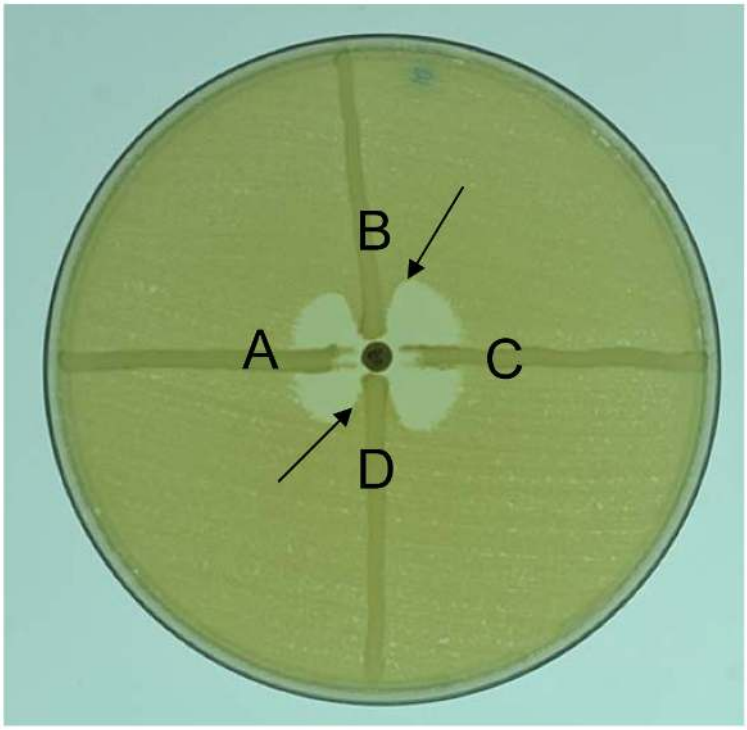

Fig.

Modified Hodge Test. A laboratory strain of pan-susceptible *Escherichia coli (E coli)* is streaked across the entire plate and a carbapenem disc placed in the center of the plate. Isolates A-D are clinical isolates suspicious for KPCs by initial screening. They are streaked linearly from the periphery to a central carbapenem disk. Isolates A and C are negative for KPC. Isolates B and D are positive for KPC as indicated by arcing growth of the carbapenem-sensitive *E coli* along the clinical KPC isolates toward the carbapenem disk.

Table

Bacterial species that have been found to produce *Klebsiella pneumoniae* carbapenemase (KPC) resistance enzymes. *Klebsiella pneumoniae* remains the most common organism to harbor KPCs, however relative frequency in other organisms has not been reported

Enterobacteriaceae	Non-Enterobacteriaceae
Citrobacter freundii	*Pseudomonas aeruginosa*
Escherichia coli	*Pseudomonas putida*
Enterobacter aerogenes	*Acinetobacter spp*
Enterobacter cloacae	
Enterobacter gergoviae	
Klebsiella pneumoniae	
Klebsiella oxytoca	
Proteus mirabilis	
Salmonella enterica	
Serratia marcescens	