

The Spread of *Klebsiella pneumoniae* Carbapenemases: A Tale of Strains, Plasmids, and Transposons

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(See the brief report by Sidjabat et al, on pages 1736–8.)

Carbapenemases are a large and diverse family of microbial enzymes that hydrolyze not only carbapenems but also other β -lactams, with the occasional exception of monobactams, such as aztreonam. For clinicians, the nomenclature of carbapenemases, like that of other β -lactamases, is confusing. In keeping with other β -lactamases, carbapenemases can be classified on the basis of function or structure. The most commonly used classification—Ambler—is based on molecular structure. In this classification, carbapenemases may belong to classes A, B, or D [1]. Class A and D are serine carbapenemases, meaning that they have a serine at their active sites, like extended spectrum β -lactamases (ESBLs). In contrast, the class B enzymes are known as metallo- β -lactamases, because they require zinc as a cofactor [1]. Although the metalloenzymes were first described in the early 1990s, mostly in *Pseudomonas aeruginosa*, they remain uncommon in the United States [1]. A more recent arrival seems to pose a greater

threat. *Klebsiella pneumoniae* carbapenemases (KPCs) of molecular class A have become the most frequently found carbapenemase in the United States [2].

First isolated in 1996 from a patient in North Carolina, over the past 5 years, KPCs have spread across the East coast of the United States and are now considered endemic in certain areas of New York and New Jersey [3]. Furthermore, clonal expansion has been recently described, with ST 258 being the predominant strain in 70% of all US KPC-producing *K. pneumoniae* isolates received by the Centers for Disease Control and Prevention [4]. Since 2005, outbreaks have occurred all over the world, including Israel, Colombia, Greece, France, India, Norway, Sweden, China, Puerto Rico, Argentina, and Brazil [2].

Intercontinental travel has been directly linked with the spread of KPCs. The first KPC producer identified outside the United States was isolated from a patient at a French hospital who had received previous care in New York City [5]. Similarly, KPC-3-producing *K. pneumoniae* in Israel was found to be genetically linked to a US strain, which suggested intercontinental transfer of strains as the most likely etiology [6].

KPC variants are subclassified on the basis of single amino-acid mutations that expand from KPC-1 up to the recently described KPC-10 [7]. The most com-

monly reported variants in the United States are KPC-2 and KPC-3, which are clinically and microbiologically quite similar [4]. KPCs acquired their name because they were first detected in *K. pneumoniae*, and this is still the species most likely to harbor them. However, they are now widely disseminated in other enterics, such as *Escherichia coli*, *Enterobacter* species, *Serratia* species, *Morganella morganii*, *Citrobacter freundii*, *Salmonella enterica*, and *Klebsiella oxytoca* [2]. More disturbingly, KPCs have been identified in nonfermenters, such as *P. aeruginosa* and *Pseudomonas putida* [2], where they typically cause a much higher degree of resistance because of the additional contribution of diminished outer membrane permeability.

KPC genes are typically located on mobile genetic elements, especially a particular transposon known as Tn4401, which facilitates transfer between plasmids and across bacterial species [8, 9]. Tn4401 and related transposons have been detected in many species from different continents. Genes encoding other β -lactamases (eg, TEM and SHV class ESBLs) have been detected within Tn4401 [8]. In fact, most KPC producers carry multiple additional β -lactamases; in one case, 7 unique enzymes were detected [10]. Furthermore, Tn4401 has been found to be associated with genes conferring resistance to non- β -lactams, such as plasmid-mediated re-

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sistance to quinolones (*qnr*) and aminoglycosides [2]. As expected, the accumulation of this formidable array of resistance genes produces a multidrug-resistant phenotype.

In this edition of *Clinical Infectious Diseases*, Sidjabat et al [11] elegantly describe the sequential transfer of KPC-3 among 3 different gram-negative species; this occurred in a single patient with a prolonged and complicated hospital stay. Molecular data suggest that the gene transferred from *K. pneumoniae* to *E. coli* occurred because of a Tn4401 recombination event and then spread to *Serratia marscescens* on a plasmid. This illustrates the various routes by which KPC genes can spread between species. There are previous reports that describe >1 organism expressing identical KPCs in the same patient, presumably reflecting the same phenomenon. In Texas, KPC-2-producing *Enterobacter* species and *P. putida* were identified in a liver transplant recipient [12]. Similarly, KPC-2-producing *E. coli* and *Enterobacter* species were reported in a patient with a psoas abscess treated at a French hospital who had been recently discharged from an Israeli health care facility [13].

KPC enzymes may be difficult to detect, because they only cause weak hydrolysis of carbapenems. As a result, automated systems of clinical microbiology laboratories can erroneously report imipenem or meropenem as susceptible in up to 52% of isolates [2]. Phenotypically, ertapenem resistance is the most useful characteristic to screen for KPC production [1]; resistant enterics should then undergo either a modified Hodge test or a boronic acid screening test and, if results are positive, a confirmatory polymerase chain reaction [1, 2]. Molecular confirmation is necessary, because ertapenem resistance in enterics is commonly conferred by unrelated mechanisms, such as the combination of porin loss, production of other β -lactamases (such as AmpCs or CTX-M), and upregulation of efflux pumps.

KPC-producing organisms are clinically

important because of the limited treatment options available and a high crude mortality rate. Most strains are susceptible only to colistin or tigecycline. There are very limited data to support either of these. Tigecycline achieves low serum levels and probably should not be used in bloodstream infections [14], and colistin can cause nephrotoxicity in up to 20% of patients [15]. Despite the lack of controlled studies, some clinicians combine agents using either tigecycline, colistin, or rifampin, sometimes adding inhaled agents for lower respiratory tract infections. Further evolution of resistance of KPC-producers to include tigecycline or colistin has been described, although rarely. In a recent study, factors associated with KPC-producing *K. pneumoniae* were transplantation, receipt of mechanical ventilation, long duration of hospital stay, and exposure to cephalosporins and carbapenems. Patients had a 48% mortality rate, compared with 26% among patients infected with carbapenem-susceptible *K. pneumoniae* [16].

Given the dire state of the pipeline for new antibiotics to treat gram-negative pathogens, infection control will be our main weapon against these organisms for the short term. Heightened contact precautions and active surveillance have proven to be helpful in outbreak control [17]. Although community spread has not yet been recognized, patients from long-term acute care hospitals were recently identified as a reservoir in a city-wide outbreak [18].

KPC-producing gram-negative pathogens are evolving rapidly. Until new agents are developed, we agree with Srivivisan and Patel, who stated recently: “a pound of prevention really is worth a pound of cure” [19, p. 1107].

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