KPC-Producing Klebsiella pneumoniae Strains: A Threat to our Therapeutic Arsenal

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Abstract

In the last decade, extremely drug-resistant KPC-producing Klebsiella pneumoniae strains have emerged in the USA and sequentially in other parts of the world. In particular, K. pneumoniae producing carbapenemase (KPC) has been identified as a major public health threat because of the rapid plasmid mediated spread of resistance and limited available therapeutic options. These strains are resistant to almost all available antibiotics and are associated with high morbidity and mortality. Reported rates of mortality associated with KPC-Kp infections vary widely from 22% to 72%. The detection of KPC-2-producing K. pneumoniae strains belonging to CC11 in urban rivers is epidemiological evidence demonstrating that the environmental dissemination of high-risk multiresistant bacteria is ongoing in Brazil and other countries.

INTRODUCTION

In a recent report, WHO highlights the emergence of carbapenem resistance among Enterobacteriaceae as the harbinger for a potential post-antibiotic era, once bacteria have become resistant to carbapenems, very few treatment options remain [1].

Klebsiella pneumoniae carbapenemase (KPC) enzymes are, by far, the most common class A carbapenemases generally plasmid encoded within the Tn3-based transposon Tn4401, which has five known isoforms (a, b, c, d and e) as defined by insertions or deletions within a polymorphic region immediately upstream of blaKPC [2], and KPC-producing isolates are usually resistant to non-β-lactam antibiotics such as fluoroquinolones, aminoglycosides and co-trimoxazole [3].

Bacteria producing these enzymes are generally only susceptible to a few antibiotics, and there is high mortality among patients with bloodstream infections caused by these organisms [4]. For instance, the overall mortality in patients with KPC-associated infections has been estimated to be between 22% and 72% [1,5-7].

Substantial percentages of hospitalized patients are colonized by these microorganisms, which have caused several outbreaks of severe nosocomial infections, including bacteraemia and ventilator-associated pneumonia, since 2010 [8]. The aim of this review is to summaries the epidemiology of K. pneumoniae producing carbapenemase across continents circulating and discuss possible therapeutic options.

METHODS

Literature Search in Databases

It is a literary review of articles related to the subject published in the database of Scielo, Pubmed, EBSCOhost, Scopus and Web of Science being selected only articles in which the focus was Klebsiella pneumoniae carbapenemases producers. In addition, the African Journals Online database was searched using the keywords ‘β-lactamase in Africa’.

Class A Carbapenemases

KPC families of carbapenemases are plasmid encoded and have the greatest potential for spread due to its location on plasmids. The KPC carbapenemases differ from the other functional Group 2 enzymes by two important characteristics. First is the presence of the KPC enzymes on transferable plasmids. The second, their substrate hydrolysis spectrum includes the aminothiazole oxime cephalosporins, such as cefotaxime. Although, the KPC beta-lactamases are predominantly found in K. pneumoniae, there have been reports of these enzymes in Enterobacter species and in Salmonella spp [9,10]. However the blaKPC genes are flanked by the same transposon Tn4401 located on conjugative plasmids and are horizontally transferred [11]. This gives to this enzyme an extraordinary spreading capacity [Naas et al., 2014][12]. They have been detected more often in Klebsiella spp. [13], but have also been reported in other Enterobacteriaceae [14]. Thirteen variants of KPC are known so far; KPC-2 and KPC-3 are the most frequently worldwide variants [15,16].

KPC carbapenemases hydrolyse beta-lactams of all classes, with the most efficient hydrolysis observed for nitrocefin, cephalothin, cephaloridine, benzylpenicillin, ampicillin, and piperacillin. Imipenem, meropenem, cefotaxime, and aztreonam, are hydrolyzed 10-fold less efficiently than the penicillins and early cephalosporins. Weak but measurable hydrolysis is observed for cefoxitin and ceftazidime, giving the KPC family a broad hydrolysis spectrum that includes most beta-lactam antibiotics. The KPC family can spread easily due to its location on plasmids. It is the most often present in *K. pneumoniae*, an organism known for its ability to accumulate and transfer resistance determinants. The treatment of infections caused by these organisms is extremely difficult because of their multigene resistance and hence results in high mortality rates [9].

**EPIDEMIOLOGY**

The first isolate of KPC-producing bacteria was discovered through the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) surveillance program in a clinical specimen of *K. pneumoniae* from North Carolina in 1996 [17]. Soon after, KPC-producing organisms spread rapidly along the east coast and then became widely disseminated westward and throughout the country [17,4] (Figure 1). have now been reported almost in all States of the US except, Idaho and Maine [54]. The first KPC-producing organism detected outside of the United States occurred in Paris, France [18]. Interestingly, the patient was hospitalized in a New York City hospital 2 months prior, suggesting that the resistant organism was imported from the USA [17]. The European Centre for Disease Control and Prevention in 2015 reported highest prevalence of carbapenem-resistant *K. pneumoniae* in three countries (Greece, Italy and Romania) reported carbapenem resistance percentages considerably higher than any other country (62.3%, 32.9% and 31.5%, respectively). These countries also reported the highest percentages of polymyxin-resistant *K pneumoniae*, indicating an especially worrisome situation [17].

The first KPC-positive isolate recorded in Warsaw (Poland) from the urine of an inpatient without relevant travel history [19]. By the end of 2008, the national reference laboratory had identified 32 additional cases in five hospitals of this city [20].

In South America, the first report of KPC was detected in Colombia in 2006, since then, has become widespread in different parts of this country [21]. KPC-producing *K. pneumoniae* was first described as occurring in Brazil in 2006, isolates in an intensive care unit [21] and since then its incidence has greatly increased [22,23], observed the presence of the *bla*KPC-2 gene in *K. pneumoniae* strains isolated in five states from 2006 through to 2009. In 2010, however, a great dispersion of this gene was observed in this country, with the spread of carbapenem-resistant *K. pneumoniae* observed in several hospitals in different Brazilian cities and states [24]. Nevertheless, detection of KPC-2-producing *K. pneumoniae* strains in urban rivers [25] and in hospital wastewater [26], is epidemiological evidence demonstrating that the environmental dissemination of high-risk multiresistant bacteria is ongoing in Brazil. Similarly, Argentina have reported sporadic cases and clusters of infections with KPC-mediated resistance in different types of Gram-negative pathogens, including *K. pneumoniae* [27,28].

The first report of KPC in Middle East (Israel) was in a returned traveler who received health care in New York in 2005. However, since the first reported case, have firmly established endemic status in Israel [29]. The most common clinical site was the urinary tract, although several body sites have been involved in clinical infections [30].

As a region, Asia has widely disseminated KPC resistance

*Figure 1* Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin. Other carbapenemase types include VIM, OXA-48, or NDM (Munoz-Price et al, 2013)[4].

elements [31]. The first KPC-positive organisms recorded in India were clinical isolates of *E. coli*, *K. pneumoniae*, and Proteus mirabilis recovered from patients enrolled in clinical trials (2002–2006) [32]. From 2007 to 2010, nine further patients with bacteria that carried *bla*KPC were identified in an active microbiological surveillance study [33]. The first KPC-positive *K. pneumoniae* isolate recorded in China was identified in 2004 from a 75-year-old ICU patient in Zhejiang, and this province appears to be the epicenter for KPC-producing organisms in China [34,35]. Screening in nine Chinese cities, all 95 *K. pneumoniae* found that were not susceptible to carbapenem [36].

In Australia, the first report of KPC was detected in an isolate of *K. pneumoniae* from a returned traveler who was hospitalized during a holiday to Greece in the prior year [37]. Similarly, the first isolate of KPC in New Zealand was *K. pneumoniae* resistance obtained from a patient repatriated from a Chinese hospital [17].

In Portugal, there have been no reports of clinical cases involving KPC-positive isolates, but a KPC-2-positive *E. coli* strain was recently recovered from river water [38]. In 2009, an old Spanish man was the first of eight cases colonized with KPC positive *K. pneumoniae* to occur in a health-care facility in Madrid, Spain. These patients were in five different wards in the hospital, and none had recently travelled to KPC-endemic countries [39].

In June 2013, a 6-month-old child with hydrocephalus was admitted to neurosurgery ward of Sétif University Hospital, Algeria. After analysis of a cerebrospinal fluid sample was determined first case of infection by *K. pneumoniae* carrying the *bla*KPC gene isolated from a child in the North African [40]. In the year 2011 in Egypt, with a total of 45 samples of *K. pneumoniae*, 31.1% were positive KPC [41]. In the same year in South Africa were isolated 4 *K. pneumoniae* producing KPC [42], and in Tanzania between 2007-2012 were isolated and identified 8 KPC positive [43].

In Mozambique was isolated from *Lactuca sativa* (Lettuce) and *Allium fistulosum* L. (Welsh onion) carbapenem-resistant Enterobacteriaceae, believing that the contamination was due to the water used for irrigation. Molecular experiments had to be performed to better characterize these bacteria [44].

**TREATMENT OPTIONS**

Carbapenems have been widely used in many countries due to the increasing rate of ESBL-producing Enterobacteriaceae, resulting in the emergence of resistance to these agents, especially in *K. pneumoniae*. Very few therapeutic options are left for patients infected with multidrug-resistant *K. pneumoniae* with additional resistance to carbapenems, and mortality is therefore high [45]. Furthermore, KPC producers frequently carry additional genetic determinants, which confer resistance to other antibiotics, such as fluoroquinolones, aminoglycosides, and cotrimoxazole [46,48,17].

Most study demonstrated that the vast majority of isolates were susceptible to amikacin, tigecycline, gentamicin or colistin [49,50,17,46]. This leaves colistin as the sole therapeutic alternative. Usage of colistina should be limited due to their neurotoxicity and nephrotoxicity [45]. [8], demonstrate also during the study period, rates of non-susceptibility to each of these drugs increased alarmingly among study isolates: from 6% (gentamicin), 11% (colistin) and 9% (tigecycline) in 2010 to 21%, 27% and 25%, respectively, in 2013. Emergence of resistance to polymyxins, especially in countries with already high percentages of multidrug and carbapenem resistance is another step towards pandrug resistance [17].

Fosfomycin has been used successfully to treat KPC-producing organisms that still showed in vitro susceptibility [17]. A study showed that fosfomycin retained in vitro activity against 93% of KPC-producing isolates collected in the USA in 2009 [50]. Notably, five out of six extremely drug-resistant KPC producers nonsusceptible to tigecycline and colistin were susceptible to fosfomycin. This drug causes very little toxicity and penetrates tissues readily; the concern with fosfomycin, however, is the propensity for resistance to rapidly develop when it is used in monotherapy [51,17]. Thus, many investigators have proposed using fosfomycin in combination with other agents, such as aminoglycosides, since synergism has been demonstrated [51].

Combination therapies may be an attractive option based on some in-vitro data, but clinical data supporting such recommendations are lacking [52]. One study has reported in-vitro synergy between colistin and rifampin against KPC-2-producing *K. pneumoniae* isolates [53]. Oral treatments such as fosfomycin and nitrofurantoin should be evaluated. In addition, β lactam and β-lactamase inhibitor combinations (carbapenem or cephalosporins, and clavulanic acid, sulbactam, or tazobactam) should at least be evaluated in animal models of urinary tract infections [45]. Recent findings suggest that combination treatment with colistin, tigecycline, and meropenem might improve survival among bacteraemic patients, but none is ideal for empirical use because colistin are nephrotoxic [5].

**PREVENTION AND INFECTION CONTROL**

The updated guidance for control of carbapenem-resistant Enterobacteriaceae (CRE) of Centers for Disease Control and Prevention recommends a set of core measures for all acute and long-term care facilities: first, sanitizing hands; second, minimize use of invasive medical devices and isolating CRE–infected patients; third, promotion of antibiotic stewardship and screening for patients with risks for CRE (CDC, 2012). Nevertheless, findings from several studies emphasize the importance of early identification of asymptomatic carriers and their subsequent grouping, and this factor was a key part of the successful national intervention in Israel [54,55].

[56], propose use a combination of the above interventions to curtail an outbreak of multidrug-resistant bacteria that included KPCs in their intensive care unit performing rectal swab screening for all new admissions to the intensive care unit and repeated the surveillance cultures weekly. KPC-infected or colonized patients were cohorted and were assigned dedicated nurses to care for them. Daily environmental cleaning was performed with a quaternary ammonium compound on all work surfaces in clinical areas.

Furthermore, a recent study in New York (USA) compared infection control practices among nine neighbouring hospitals and found that those that used active surveillance cultures had most success in decreasing the acquisition rate of KPC-positive
organisms [57].

CONCLUSION

Since their discovery 16 years ago, KPC-positive Gram-negative organisms have spread worldwide; however, their local epidemiology and clinical characteristics vary. Some countries have experienced endemically whereas others largely continue to have only imported cases [4].

Polymyxins, such as colistinand polymyxin B, are another class of drugs that have been used successfully to treat KPC-producers. These drugs are active against most genera of Gram-negative aerobic bacilli [17]. Polymyxin B and colistina have been increasingly used, but they are associated with high rates of nephrotoxicity and have been considered drugs of last resort [17]. There are recent data to show that the polymyxins may not be as nephrotoxic as previously thought; however, optimal dosing regimens for colistin are under evaluation [58].

REFERENCES


