

The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria

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From early this decade, Enterobacteriaceae that produce *Klebsiella pneumoniae* carbapenemases (KPC) were reported in the USA and subsequently worldwide. These KPC-producing bacteria are predominantly involved in nosocomial and systemic infections; although they are mostly Enterobacteriaceae, they can also be, rarely, *Pseudomonas aeruginosa* isolates. KPC β lactamases (KPC-1 to KPC-7) confer decreased susceptibility or resistance to virtually all β lactams. Carbapenems (imipenem, meropenem, and ertapenem) may thus become inefficient for treating enterobacterial infections with KPC-producing bacteria, which are, in addition, resistant to many other non- β -lactam molecules, leaving few available therapeutic options. Detection of KPC-producing bacteria may be difficult based on routine antibiotic susceptibility testing. It is therefore crucial to implement efficient infection control measures to limit the spread of these pathogens.

Carbapenems such as imipenem and meropenem are recommended as first-line therapy for severe infections caused by Enterobacteriaceae producing extended spectrum β lactamases (ESBLs).¹ The emergence of carbapenem-resistant enterobacteria is therefore worrisome, since consequently the antimicrobial treatment options are very restricted. Resistance to carbapenems may involve several combined mechanisms: modifications to outer membrane permeability and up-regulation of efflux systems—associated with hyperproduction of AmpC β lactamases (cephalosporinases) or ESBLs—or production of specific carbapenem-hydrolysing β lactamases (carbapenemases). Carbapenemases found in Enterobacteriaceae can be either metallo- β -lactamases, expanded-spectrum oxacillinases, or clavulanic-acid-inhibited β lactamases.^{2–4} The metallo- β -lactamases that belong to the Ambler class B (verona imipenemase [VIM], imipenemase [IMP]) have been identified in different countries as a source of several nosocomial outbreaks.^{2,4} The class D, OXA-48 β lactamase has been

identified mostly in *Klebsiella pneumoniae* from Turkey, and, very recently, also from Lebanon and Belgium.^{4–6} The clavulanic-acid-inhibited carbapenemases that are Ambler class A enzymes, are chromosome-encoded enzymes such as non-metallo-carbapenemase class A/*Serratia marcescens*-type and *Serratia fonticola* carbapenemase-1, plasmid-mediated enzymes such as imipenem-2, several Guyana extended spectrum-type variants, and the *K pneumoniae* carbapenemase (KPC) enzymes.^{4,7}

By far, the most frequent class A carbapenemases are the KPC enzymes, which are the focus of this Review. The KPC β lactamases are mostly plasmid-encoded enzymes from *K pneumoniae*. Their current spread worldwide makes them a potential threat to currently available antibiotic-based treatments. The purpose of this Review will be to detail their spectrum of hydrolysis, clinical features, epidemiology, molecular genetics, detection and discuss possible therapeutic options.

First detection, structure, and hydrolysis spectrum

The first KPC producing isolate was *K pneumoniae* from North Carolina, USA, identified in 1996.⁸ This *klebsiella* isolate was resistant to all β lactams, but carbapenem minimum inhibitory concentrations (MICs) were slightly decreased after addition of clavulanic acid, a β lactamase inhibitor. The discovery of this plasmid-encoded β lactamase, KPC-1, was followed by several publications of another single aminoacid variant, KPC-2, in hospitalised patients from the east coast of the USA.^{9–11} Recent resequencing of the *bla*_{KPC-1} gene revealed a perfect match with the *bla*_{KPC-2} gene.¹² Since discovery of KPC-1/2, five other variants (KPC-3 to KPC-7) have been reported in different countries, differing from KPC-1/2 by, at most, two aminoacid substitutions.^{13–18} The recently determined structure of KPC-2 revealed structural and functional similarities to the other class A carbapenemases, thus explaining its ability to hydrolyse carbapenems.¹⁹

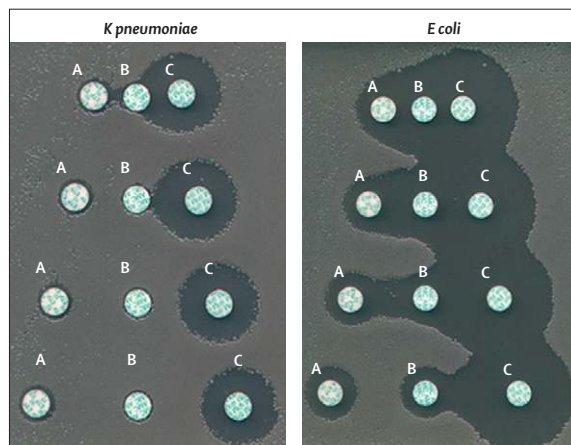


Figure 1: Double-disc synergy test

Microbiological detection of KPC-2-producing *K pneumoniae* and *Escherichia coli*. Clavulanic acid only weakly inhibits the resistance of *K pneumoniae* to ertapenem and imipenem. A=ertapenem. B=clavulanic acid. C=imipenem.

Biochemical data showed that KPC enzymes (KPC-2 and KPC-3 studied in detail)^{8,14} hydrolyse all β -lactam molecules including penicillins, cephalosporins, and monobactams (aztreonam). Cefamycins and ceftazidime are weakly hydrolysed. Imipenem, meropenem, ertapenem, cefotaxime, and aztreonam are hydrolysed less efficiently than penicillins and narrow-spectrum cephalosporins. The KPC enzymes may be mistaken for ESBLs, such as the well known TEM, SHV, VEB, and CTX-M derivatives since they also hydrolyse expanded-spectrum cephalosporins. However, unlike ESBLs, KPCs display substantial carbapenem hydrolysis activity, which is only weakly inhibited by clavulanic acid and tazobactam (figure 1).⁸ KPCs alone reduce susceptibility to carbapenems, they do not confer resistance. To achieve full resistance to carbapenems, impaired outer-membrane permeability is often required.^{13,17,20}

Clinical features and epidemiology

KPC-associated enterobacterial infections do not seem to be specific to sites, organs, or tissues. Most of the infections are either systemic infections, occurring in patients with multiple invasive devices or urinary tract infections without an indwelling catheter, particularly in immunocompromised patients.^{21,22}

Specific virulence factors associated with KPC-producing bacteria have not been reported. Risk factors associated with the acquisition of KPC-producing bacteria

included prolonged hospitalisation, intensive care unit (ICU) stay, invasive devices, immunosuppression, and multiple antibiotic agents before initial culture.^{13,21} One study has shown that only 12 of 58 patients with carbapenem-resistant *K pneumoniae* infections had previous therapy with a carbapenem, whereas all patients received another β lactam or fluoroquinolones.²¹

A recent study showed that mortality was higher for patients infected with imipenem-resistant KPC-producing *Enterobacter* spp (11 of 33 patients) than for those infected with imipenem-susceptible strains (three of 33 patients).²² Another study reported that 14-day mortality was nine of 19 patients with bacteraemia due to KPC-producing *K pneumoniae*.²¹

Importantly, creating an additional degree of complexity in their identification and detection, KPC-producing bacteria are not only present in acute-care facilities but also in tertiary-care facilities.²³ Identification in rural settings in Pennsylvania, USA, is also worrisome, since routine diagnostic tests for detecting multidrug-resistant (MDR) Gram-negative organisms are not readily available in these areas.²⁴

After the initial report of KPC-1/2, incidence of KPC-producing *K pneumoniae* isolates rose gradually in the New York City area, USA.^{21,25–32} Ribotyping of KPC-2-producing *K pneumoniae* isolates from ten hospitals in the New York area revealed that 78 of 95 isolates belonged to a single ribotype, suggesting cross

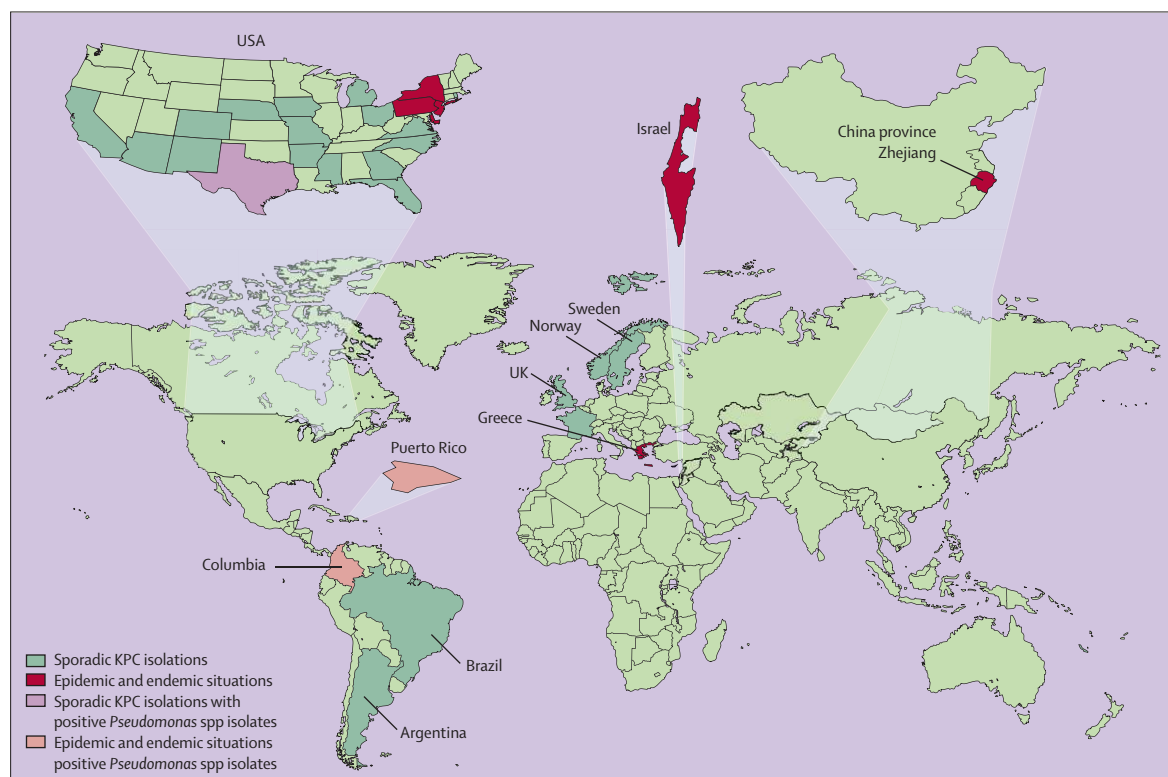


Figure 2: Geographic distribution of KPC worldwide

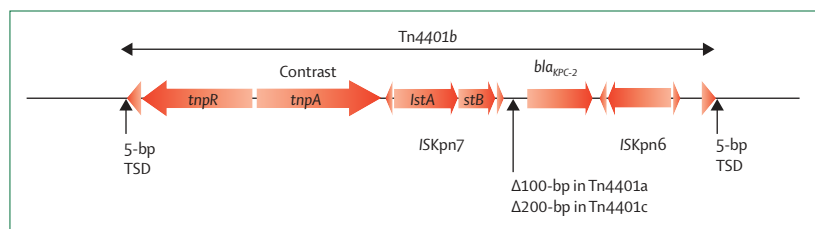


Figure 3: Schematic representation of Tn4401 structures identified on naturally occurring plasmids
Genes and their corresponding transcription orientations are indicated by horizontal arrows. Tn4401 is delimited by two inverted repeat sequences (large triangles at either end). The small triangles represent the inverted repeats of the two unrelated insertion sequences, ISKpn6 and ISKpn7. Tn4401 target site duplications (TSD) of 5 bp are indicated.⁶² Tn4401a was the first transposon characterised from two *K pneumoniae* strains isolated from patients directly admitted to Parisian hospitals from Greece and from New York City hospitals.^{55,56,62} Tn4401b, initially characterised from two *K pneumoniae* isolates and one *P aeruginosa* isolate from Colombia, tends to be the most frequent structure encountered in the USA, at least from the partial sequence information available in the Genbank databases.⁶² Tn4401a differs from Tn4401b by a 100 bp deletion just upstream of the β -lactamase gene. Tn4401c, identified in an *E coli* strain isolated in a Parisian hospital, differs from Tn4401b by a 200 bp deletion in the same region as for Tn4401a.^{57,62} The deleted region in Tn4401 is indicated.

transmission.²⁸ A surveillance study conducted in 2004 in Brooklyn hospitals, NY, showed that none of the *Escherichia coli* and *Enterobacter* spp isolates carried a bla_{KPC} gene, whereas 62 of the 257 *K pneumoniae* isolates were KPC positive.²⁶ Concurrent with the increasing reports of KPC-2, KPC-3 was reported from a *K pneumoniae* and *Enterobacter* spp outbreak in Brooklyn, New York. At present, 378 of 997 *K pneumoniae* isolates identified in New York City hospitals are KPC positive.³³ Although KPCs are mostly identified from *K pneumoniae*, KPC enzymes have now also been reported from *E coli*, *Salmonella cubana*, *Enterobacter cloacae*, *Proteus mirabilis*, and *Klebsiella oxytoca* in as many as 20 US states and in the territory of Puerto Rico (figure 2).^{9,10,16,24,29,33–38} KPC-2 and KPC-3 are widespread and correspond to the most frequent carbapenemases identified in Enterobacteriaceae in the USA.^{33,34} The prevalence of KPC-producing bacteria in the USA over a 6-year period (2000–2005) was estimated to be 0.15%.³⁹ Novel KPC-variants have been found in Puerto Rico in Enterobacteriaceae and *P aeruginosa*, and in Texas in *Pseudomonas putida*.^{16,40,41}

The first outbreak of KPC-producing *K pneumoniae* outside the USA was from Israel (figure 2).¹⁷ A single KPC-3-producing *K pneumoniae* clone and several KPC-2-producing *K pneumoniae* clones are responsible for ongoing outbreaks in Tel Aviv hospitals. The KPC-3-producing strain from Israel is genetically linked to those reported in the USA, suggesting strain exchange by travellers and patients between Israel and the USA.⁴² In Israel, novel KPC-producing *K pneumoniae* are still being identified and the reports of KPC-2 producing *Enterobacter* spp and *E coli* are increasing.^{22,43,44}

In South America, large dissemination of KPC was initially reported in *K pneumoniae* in 2006 and subsequently in several enterobacterial species from multiple Colombian hospitals (figure 2).^{45,46} KPC enzymes have also been identified in *P aeruginosa*, in Colombia,

showing an unexpected spread of these resistance determinants in non-enterobacterial species.⁴⁷ Other countries in South America (Brazil, Argentina) have reported identification of KPC-producing bacteria.^{48–50} In China, KPC enzymes are increasingly reported in *K pneumoniae* and also in *Citrobacter freundii*, *E coli*, and *Serratia marcescens* (figure 2).^{51–54}

In Europe, only a few cases have been reported. In France, the seven KPC-producing isolates were *K pneumoniae*, *E coli*, and *E cloacae* from patients transferred from hospitals located in the USA, Greece, or Israel.^{15,55–57} Similarly, the first KPC case reported from Stockholm, Sweden, was from a Greek patient, whereas there was no evidence of overseas travel for the other KPC cases from Sweden and Norway (Samuelsen O, University hospital of northern Norway, personal communication).⁵⁸ Recently, it has been suggested that Greece may be another country with epidemicity of KPC-producing bacteria.^{56,59} A retrospective analysis done in the UK and Ireland from 2001 to 2006 identified two KPC-4-producing *Enterobacter* spp isolates from a single patient in 2003–2004.⁶⁰ Two KPC-3-producing *K pneumoniae* isolates were reported from Scotland in 2007 and from London in 2008;⁶¹ a direct link with Israel was established for one of these patients.

Molecular genetics

Genetic analysis of bla_{KPC} genes indicates that their mobility may be associated with spread of strains, plasmids, and transposons.^{8,10,11,13–17,20,25,26,31,35–37,44,45,51–56,62} The fact that different bacterial species and different *K pneumoniae* clones may carry KPC β lactamases is evidence of their ease of transmission.³⁷ The bla_{KPC} genes have usually been identified in large plasmids varying in size and structure. In most cases, the plasmids were self-transferable to at least *E coli*.⁶² A report of in-vivo transfer of bla_{KPC} -carrying plasmids between two enterobacterial species has been documented.³⁷ These plasmids usually also carry aminoglycoside-resistance determinants, and have been associated with other β -lactamase genes such as the most widespread ESBL gene, $bla_{CTX-M-15}$.⁵¹ Up to seven different β lactamases were found associated with bla_{KPC} in one *K pneumoniae* isolate.⁶³ Reports indicate that the bla_{KPC-3} gene from several *K pneumoniae* isolates from Israel and the east coast of the USA may be associated with the plasmid-mediated quinolone-resistance determinants QnrA and QnrB.^{35,64} In a single case only,⁴⁷ the bla_{KPC} gene has been reported both at a chromosomal and a plasmid location in *P aeruginosa*.

The bla_{KPC} genes have been identified within a roughly 10 kb Tn3-type transposon, Tn4401 (figure 3).⁶² Tn4401 possesses transposase (*tnpA*) and resolvase (*tnpR*) genes and two unrelated insertion sequences ISKpn6 and ISKpn7. This transposon may be the origin of bla_{KPC} -like gene dissemination. This structure has been identified in *K pneumoniae* isolates in France from patients transferred from hospitals in Greece and in the USA.⁶² Similar, but

not identical, Tn4401-like structures have also been identified from French and Colombian isolates (Tn4401a, Tn4401c; figure 3).⁶²

Detection

Detection of KPC-producing bacteria based only on susceptibility testing is not easy, due to heterogeneous expression of β -lactam resistance (table). Several KPC-producing bacteria have been reported as susceptible to carbapenems.^{21,32} To fully express the carbapenem-resistance trait, a second mechanism, such as an outer-membrane permeability defect, may be required.^{8,13,20,51} Detection of the level of susceptibility of KPC-producing bacteria remains difficult whatever the technique used: antibiotic susceptibility testing by liquid medium or disk diffusion. Detection of carbapenem resistance with automatic systems may be problematic, since these systems report as few as 7% and as many as 87% of KPC-producing *K pneumoniae* as being susceptible to imipenem or meropenem. Part of the problem is inherent to bacterial strains that express variable levels of carbapenem resistance, but inocula that were below the recommended values (cell count) of the manufacturers have also been implicated.^{65,66}

Testing via agar diffusion methods can also be inconsistent. In general, susceptibility testing using imipenem or meropenem is not sensitive enough for the detection of KPC-producing Enterobacteriaceae. Ertapenem susceptibility rates of KPC-producing *K pneumoniae* range from 0–6%, compared with 26–29% for imipenem and 16–52% for meropenem.^{65,66} Similarly, in a recent study from Israel,²² KPC-producing *Enterobacter* spp were detected in all cases using ertapenem, whereas meropenem misclassified 24% of those isolates as being susceptible. Although ertapenem is not the best hydrolysed substrate, it seems to be the best molecule for the detection of KPC-producing *Enterobacter* spp on a routine basis.^{21,56,67} However, ertapenem resistance by itself is not a marker for KPC expression, since most ertapenem resistance arises from other factors, such as ESBL or AmpC production associated with outer membrane defects.^{68,69} Confirmatory tests are necessary, since in the case of KPC production, therapeutic options using carbapenems may be prohibited whereas in the case of combined mechanisms associating ESBL and outer-membrane permeability defects, use of imipenem or meropenem remains debatable. Conversely, detection of KPC-producing *P aeruginosa* cannot be based on susceptibility to carbapenems since these isolates are resistant to all β lactams (table).^{47,62} Susceptibility testing of KPC-producing bacteria using the Etest technique is difficult to interpret. Scattered inner colonies can make the inhibition zones difficult to read, especially for *K pneumoniae* (figure 4).

The hidden spread of KPC-producing bacteria may be related to the failure to detect these strains in clinical

	<i>K pneumoniae</i> ^{8,47} 43,45,51,55,62	<i>E coli</i> ^{23,27,44,51}	*Other enterobacterial isolates ^{9,10,26,36,37,51}	<i>P aeruginosa</i> ^{47,62}
Amoxicillin	>256	>256	≥256	>256
Amoxicillin+CLA	32 to >256	8 to 32	64 to 256	>256
Ticarcillin	>256	128 to >256	32 to 128	>256
Ticarcillin+CLA	>256	128 to >256	128 to >256	>256
Piperacillin	>256	128 to >256	128 to >256	>256
Piperacillin+TZB	32 to >256	16 to >256	128 to >256	>256
Cephalothin	>256	≥256	..	>256
Cefoxitin	4 to >32	2 to >32	8 to >32	>32
Cefotaxime	64 to >32	3 to >32	16 to ≥32	>32
Cefotaxime+CLA	16 to >32	0.25 to 2	>32	>32
Ceftazidime	4 to >256	4 to >256	8 to 256	≥256
Ceftazidime+CLA	32 to >256	0.5 to 8	4 to 256	48 to 256
Aztreonam	≥256	16 to 256	64 to 256	>256
Aztreonam+CLA	64 to >256	0.32 to 8	>32	>256
Cefepime	16 to >32	1 to >32	8 to >32	>32
Imipenem†	2 to >32	1 to 32	4 to >32	>32
Imipenem+CLA	0.5 to >32	0.25 to 2	2 to 4	2 to >32
Meropenem†	1 to >32	0.25 to >32	2 to 32	>32
Meropenem+CLA	1 to >32	0.094 to 0.38	4	3 to >32
Ertapenem†	8 to >32	1 to >32	4 to 16	>32
Ertapenem+CLA	2 to >32	0.25 to 4	..	2 to >32

CLA=clavulanic acid at a fixed concentration of 2 mg/L. TZB=tazobactam at a fixed concentration of 4 mg/L. ..=not determined. **C freundii*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *S marcescens*, *K oxytoca*, and *Salmonella cubana*.
†According to Clinical and Laboratory Standards Institute guidelines, cut-off values for imipenem and meropenem are ≤4 mg/L to ≥16 mg/L, and for ertapenem are ≤2 mg/L to ≥8 mg/L.

Table: MIC ranges (mg/L) of β lactams for KPC-producing bacteria

samples, and also the failure to identify patients whose gastrointestinal tracts are asymptotically colonised. According to one report, the gastrointestinal tracts of 14 of 36 patients in an ICU were colonised with KPC-producing *K pneumoniae*, but only two of 14 patients had positive clinical cultures.²¹ In addition, KPC-producing bacteria may have an environmental source.²¹ In high-risk situations (epidemic and endemic), targeted surveillance to identify patients with gastrointestinal colonisation is mandatory. Detection of carriers of KPC-producing bacteria has been proposed by screening faecal flora with a plating technique and screening using imipenem-containing disks.^{66,70} A novel chromogenic medium Chromagar KPC was compared with MacConkey agar with carbapenem containing-disks for rapid detection of carbapenem-resistant *K pneumoniae*. The sensitivity and specificity relative to PCR were, respectively, 100% and 98.4% for Chromagar KPC and 92.7% and 95.9%, respectively, for MacConkey agar.⁷¹ The Chromagar KPC medium has the potential to improve KPC screening. An alternative first screening tool for KPC-producing bacteria that could also be evaluated, is the ready to use chromID ESBL medium, designed for isolation of ESBLs, since these isolates are usually also resistant to expanded-spectrum cephalosporins (table).⁷² Such screening media may be

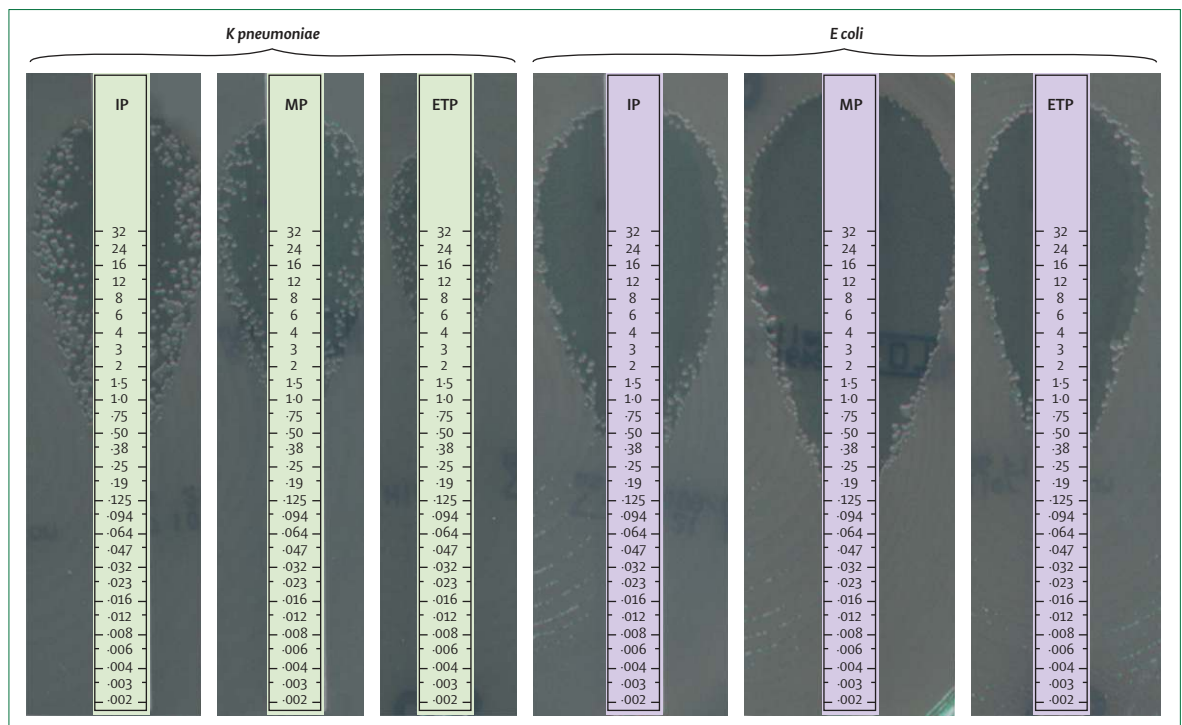


Figure 4: Susceptibility testing using Etest methodology

Microbiological detection of KPC-2-producing *K pneumoniae* and *E coli*. The presence of scattered colonies makes it difficult to read the defined endpoint. The numbers on the strips represent the MIC ($\mu\text{g/mL}$) for the antibiotic in question. IP=imipenem. MP=meropenem. ETP=ertapenem.

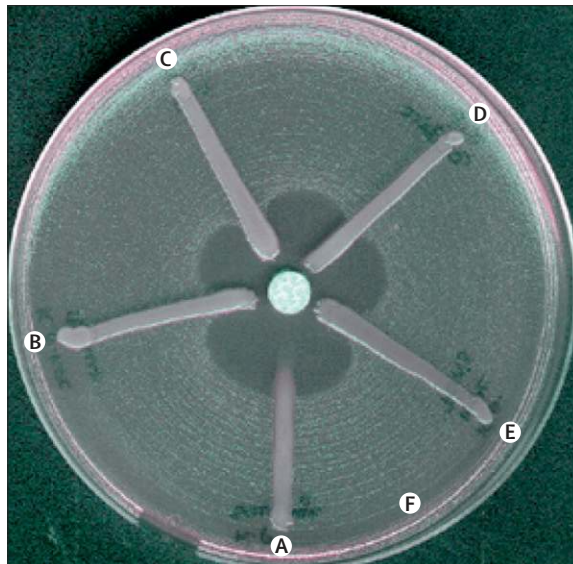


Figure 5: Modified Hodge test for screening for carbapenemase-producing bacteria

A susceptible isolate of *E coli* DH10B is cultured on a Mueller-Hinton plate to create a lawn of confluent growth. An imipenem disk is placed in the centre of the plate and each test isolate suspected of producing a carbapenemase is streaked from the imipenem disk. Growth of *E coli* near the imipenem disk or along the streak is evidence of carbapenemase activity.⁶⁶ A=wild-type *K pneumoniae* isolate. B=KPC-producing *K pneumoniae* GR from Greece.⁵⁶ C=KPC-producing *K pneumoniae* YC from the USA.⁵⁵ D=carbapenem-resistant *K pneumoniae* due to porin-loss, CTX-M-15 ESBL production, and cephalosporinase hyperproduction. E=carbapenemase GES-5-producing *E cloacae*. F=*E coli* DH10B as lawn bacteria.

used for detecting KPC-producing bacteria outside of endemic situations.

Several confirmatory tests have been proposed. The results of double-disc synergy testing between clavulanic acid or tazobactam and any carbapenem are difficult to detect due to the low inhibition of KPC by clavulanic acid (figure 1). A modified Hodge test may assist in confirming the presence of carbapenemase, but will not exclusively detect the KPC-type (figure 5). A microbiological assay employing cell-free extracts has been proposed for the rapid detection of Gram-negative carbapenemase-producers based on hydrolytic activities towards carbapenems.⁷³ Alternatively, a disk diffusion assay using ertapenem as substrate and 3-aminophenyl boronic acid as an inhibitor was capable of reliably differentiating isolates producing KPC-type β lactamase from those producing other types of β lactamases.^{59,74}

Identification of KPC-producing bacteria with molecular tools should become the gold standard. Several PCR-based techniques using endpoint or real time approaches have been developed directly with clinical samples or with colonies.^{75,76} These techniques, even though more specific, require technical knowledge, equipment, and are costly. Thus their implementation on a routine basis should depend on the frequency of KPC-producing bacteria.⁵⁶ Alternatively, molecular confirmation tests could be restricted to reference laboratories.

Treatment options

Options for treating infected patients with KPC-producing Enterobacteriaceae are limited. Although some isolates have been reported to be susceptible to cephamycins and cefepime, with MICs being close to, but below, the breakpoints, it is likely that neither expanded-spectrum cephalosporins nor carbapenems (including newer carbapenems such as doripenem)⁷⁷ could be indicated for treating systemic infections due to KPC-producing bacteria. Furthermore, it has been shown that, during imipenem and meropenem therapy, high level carbapenem-resistant KPC-producing bacteria may be selected.⁷⁸ Adding an inhibitor such as clavulanic acid, might slightly restore the activity of β lactams in vitro. However, the MICs of β lactams do not fall below the susceptibility breakpoints when combined with an inhibitor, and most KPC-producing bacteria produce other β lactamases resistant to inhibitors, such as oxacillinases or cephalosporinases. This rules out the use of β lactam combined with clavulanic acid or tazobactam in the treatment of systemic infections. Recently, the combination of oxyimino-cephalosporins with NXL104, a novel non- β -lactam β -lactamase inhibitor, was found to counteract the hydrolytic activity of KPC enzymes.⁷⁹

KPC-producing isolates are usually resistant to many non- β -lactam molecules. Most isolates are resistant to fluoroquinolones, aminoglycosides, and co-trimoxazole.^{21,22,56} Several isolates remain susceptible to amikacin or gentamicin,^{21,22} and most isolates remain susceptible to colistin and tigecycline. Tigecycline is a glycylcycline with expanded activity against many Enterobacteriaceae, including those producing ESBLs or KPC. One study³⁹ has reported 100% in-vitro activity of tigecycline against KPC-producing Enterobacteriaceae. However, treatment failures have been documented, and, in one case, while pneumonia was efficiently treated, the empyema recurred in association with a treatment-emergent tigecycline MIC increase from 0.75 to 2 mg/L.⁸⁰ Low serum concentrations of tigecycline warrant caution when using this agent to treat bacteraemic infections. Furthermore, it should not be recommended for treating urinary tract infections due to its low urine concentration. This leaves polymyxins (colistin) as the sole therapeutic alternative. Usage of polymyxins should be limited due to their neurotoxicity and nephrotoxicity. Moreover, breakpoints for *Acinetobacter* spp (MIC is 2 mg/L and greater) and *P. aeruginosa* (MIC is more than 16 mg/L) are applied to polymyxins since they are not available for Enterobacteriaceae.⁸¹ Most published experiences on the usage of these molecules are for enterobacterial infections that produce other types of carbapenemases, VIM or IMP.^{82,83} Very limited in-vivo data are available in the case of KPC infections.^{21,28,39,83} However, colistin resistance in KPC-producing *K. pneumoniae* has been observed.^{21,28,55} Combination therapies may be an

Search strategy and selection criteria

Data for this Review were obtained from publications identified by systematically searching PubMed, focusing on those published from 2000 to 2008. Search items included "KPC", "carbapenemases", and "carbapenem-hydrolyzing β -lactamases". Articles retrieved were in English. In addition, unpublished data presented at the 47th Interscience Congress on Antimicrobial Agents and Chemotherapy in Chicago (USA, 2007) were referenced.

attractive option based on some in-vitro data, but clinical data supporting such recommendations are lacking.⁸³ One study has reported in-vitro synergy between polymyxin B and rifampicin against KPC-2-producing-*K. pneumoniae* isolates.²⁸

Further studies are needed into the treatment of urinary tract infections due to KPC-producing bacteria. 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.

Conclusions

KPC-producing bacteria have increasingly been isolated worldwide, mostly in the form of *K. pneumoniae*. The spread of KPC-producing *K. pneumoniae* is worrying, from a public health point of view, since this species is prone to be the source of many hospital-acquired infections in severely ill patients, and is well-known for its ability to accumulate and transfer resistance determinants as illustrated with ESBLs. In addition, the recent identification of KPC in *E. coli* infected patients hospitalised in long-term facilities may indicate another source of transfer to acute care facilities.

Current reports indicate that KPC-producing bacteria are widespread in China, Israel, Greece, South America, and the USA. Fortunately, in western and northern Europe, KPC-producing bacteria are still rare. The detection of these bacteria remains difficult, and cannot rely only on results of antibiotic susceptibility testing since carbapenem-susceptible KPC-producing bacteria have been reported. Detection should be based on careful analysis of any decreased susceptibility to carbapenems in Enterobacteriaceae.

Multidrug-resistant and even pandrug-resistant (ie, resistant to all available classes) KPC-producing bacteria may be the source of therapeutic dead-ends, since novel anti-Gram-negative molecules are not expected in the near future. Careful and conservative use of antibiotics combined with good control practices is therefore mandatory. Based on US and Israeli experiences, strict infection control measures have to be implemented to prevent further spread of KPC-producing bacteria.⁴³

Further work should evaluate the role of transposon Tn4401, the plasmids, and the strains in the spread of the *bla*_{KPC} genes. Finally, the natural reservoir of the *bla*_{KPC} gene needs to be identified. Control of this reservoir, and of the antibiotic therapy that may enhance its spread, might help to stop the current dissemination of these emerging resistance determinants.

Conflict of interests

We declare that we have no conflicts of interest.

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