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Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases

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Contributors

LSM-P provided the original idea and outline for the paper; wrote the infection control, treatment, and mortality sections; created the tables and figure; did the literature search; and coordinated, proofread, and edited all sections. LP cowrote the France and Latin America sections and edited the manuscript and figure. RAB cowrote the USA section and edited the manuscript and figure. MJS wrote the Israel section and contributed to the original idea for the manuscript. GLD wrote the Greece section and contributed to the original idea for the manuscript. MC wrote the Ireland section. GC wrote the Italy section. JG wrote the Spain section and the Portugal section. MG wrote the Poland section. MKH cowrote the USA section. KK wrote the India section. DML cowrote the UK section, wrote sections and the table on antibiotics in the pipeline and detection, and edited the manuscript and figure. JJM cowrote the information on Colombia. PN cowrote the France section. JBP cowrote the USA section. DLP wrote the Australia and New Zealand section. JP wrote the Canada section. MVV cowrote the information on Colombia. HW wrote the China section. NW cowrote the UK section. JPQ was the senior author; produced the outline for the paper; and edited the manuscript, tables, and figure.

Conflicts of interest

LSM-P has received speaking fees from Sage and Steris. LP and PN have received research funds from Merck. MG's work was partially financed by the grant Narodowy Program Ochrony Antybiotykow (NPOA) from the Polish Ministry of Health, and the grant SPUB MIKROBANK from the Polish Ministry of Science and Higher Education. DML has shareholdings in Dechra, Eco Animal Health, Merck, and Pfizer; has accepted grants, speaking invitations, and conference invitations from Pfizer, Novartis, AstraZeneca, and Astellas; and has advisory or consultancy relationships with Achaogen, AstraZeneca, Basilea, Bayer, Cubist, Curetis, Discuva, GlaxoSmithKline, Kalidex, McKinsey, Meiji, Pfizer, Roche, Tetraphase, Theravance, and Wockhardt. JP has received research funds from Merck and AstraZeneca. MVV has received research grants from Merck Sharp & Dohme, Pfizer SA, Janssen-Cilag SA, Novartis, Merck Colombia, AstraZeneca Colombia SA, bioMerieux Colombia SAS, and Colciencias. JPQ is an employee and potential shareholder in AstraZeneca. All other authors declare that they have no conflicts of interest.

See Online for appendix

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Abstract

Klebsiella pneumoniae carbapenemases (KPCs) were originally identified in the USA in 1996. Since then, these versatile β-lactamases have spread internationally among Gram-negative bacteria, especially *K pneumoniae*, although their precise epidemiology is diverse across countries and regions. The mortality described among patients infected with organisms positive for KPC is high, perhaps as a result of the limited antibiotic options remaining (often colistin, tigecycline, or aminoglycosides). Triple drug combinations using colistin, tigecycline, and imipenem have recently been associated with improved survival among patients with bacteraemia. In this Review, we summarise the epidemiology of KPCs across continents, and discuss issues around detection, present antibiotic options and those in development, treatment outcome and mortality, and infection control. In view of the limitations of present treatments and the paucity of new drugs in the pipeline, infection control must be our primary defence for now.

Introduction

First discovered in the USA in 1996,[1] *Klebsiella pneumoniae* carbapenemases (KPCs) are β-lactamases produced by Gram-negative bacteria. They efficiently hydrolyse penicillins, all cephalosporins, monobactams, carbapenems, and even β-lactamase inhibitors.[2] Since their first description,[1] KPC enzymes have spread across countries and continents (figure), although the exact epidemiology of their expansion varies by geographical location.

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. Many bacteria with these enzymes remain susceptible to colistin, tigecycline, and one or more aminoglycoside, but some are resistant even to these drugs. Moreover, only a few drugs are in development against KPC-positive bacteria.

In this Review, we summarise the epidemiology of KPC enzymes across continents. In addition to describing sentinel epidemiological events by region, we highlight crucial issues with regards to detection, present and future treatment, treatment outcome and mortality, and infection control.

The Americas

USA

The first strain recorded with a KPC enzyme, in 1996, was a *K pneumoniae* isolate collected in a North Carolina hospital and submitted to the Centers for Disease Control and Prevention (CDC) through Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE).[1] This finding was quickly followed by a report describing KPC-positive isolates from New York City hospitals from 1997 to 2001.[3] For the next few years, descriptions were largely confined to the northeastern USA,[4–7] but, isolates have since been detected in 39 states and in Puerto Rico.[8] Infections nevertheless remain uncommon: as recently as the first 6 months of 2012, fewer than 5% of short-stay acute-care hospitals reported infections with carbapenem-resistant Enterobacteriaceae to the National Healthcare Safety Network of the CDC.[8,9]

K pneumoniae ST258 is a specific lineage defined by use of multilocus sequence typing (MLST), which can help to trace strains at the genotype level and facilitate understanding of global epidemiology. This strain has played a major part in dissemination of KPC enzymes in the USA and worldwide. KPC-positive *K pneumoniae* ST258 have been identified in several health-care institutions in multiple states in the USA.[10] Many other KPC-positive *K pneumoniae* strains have also been characterised, with KPC enzymes occurring also in other Enterobacteriaceae species.[11–16] KPC-positive *Pseudomonas aeruginosa* have been reported in the continental USA[17] and Puerto Rico,[16] along with one case of KPC-positive *Pseudomonas putida* in Houston, TX.[18]

Most infections occur in patients in hospital, with several outbreaks reported in long-term care facilities (LTCFs).[19–23] Long-term acute-care hospitals, which care for patients with complex medical disorders who need acute-care medical services for prolonged periods, seem to play an important part in the spread of KPC-positive strains in some regions.[12,21] In a recent report from the National Healthcare Safety Network of the CDC,[9] 17·8% of long-term acute-care hospitals reported one or more infections due to carbapenem-resistant Enterobacteriaceae, con trasting with a lower rate (<5%) at short-stay acute-care hospitals. Foreign travel does not seem to be a risk factor for acquisition in the USA.

Most infections due to KPC-positive bacteria occur at least 48 h after admission, with isolates identified in urine, respiratory, blood, and wound specimens.[24] Community-onset infection can occur, mostly in patients with extensive previous health-care exposure.[9] In a case-control study at a New York City hospital, patients infected with carbapenem-resistant *K3 pneumoniae* had 48% inhospital mortality and 38% infection-specific mortality.[25] These rates were significantly higher than those for patients infected with carbapenem-susceptible *K pneumoniae* (20% and 12%, respectively; p<0·001). More recently, a highly publicised

nosocomial outbreak of KPC-positive *K pneumoniae*, tracked by whole-genome sequencing, had 33% attributable mortality.[26]

Guidance for the detection and control of KPC-positive isolates was initially developed by public health departments in those states where the isolates first proliferated. National recommendations by the CDC followed in 2009,[27] and an expanded toolkit was released in 2012 (appendix).[28] This toolkit emphasises the need for coordinated regional control efforts when several health-care institutions are involved.[12]

Canada

The first published case of KPC-positive *K pneumoniae* was in 2008, when the Toronto Public Health Laboratory (Toronto, ON) received a clinical isolate obtained from urine and sputum of a 73-year-old man with renal-cell carcinoma.[29] Molecular investigation was not done. The patient did not have any recent travel outside Canada and died of respiratory failure, presumably due to the *K pneumoniae* infection.[29] The second report, 1 month later, described three elderly patients in Ottawa, ON, who harboured bla_{KPC-3}-positive *K pneumoniae*;[30] two of whom had recently visited the USA, the third occupied an adjacent hospital room and thus their infection represented a secondary spread.[30] The third report was from Calgary, AB, in 2012, where KPC-2-positive *K pneumoniae* was isolated from the urine of an 82-year-old patient—who had recently visited Greece—with community-associated urinary tract infection.[31] MLST showed that the isolate belonged to ST258, which is widespread in Greece. Seven KPC-3-positive isolates were described as part of the Canadian Nosocomial Infection Surveillance Program during 2009–10,[32] comprising four *K pneumoniae*, one *Escherichia coli*, one *Klebsiella oxytoca*, and one *Serratia marcescens*, all from the same hospital. MLST identified the *K pneumoniae* isolates as ST258 or its single-locus variant ST512; their plasmids—carrying bla_{KPC-3}—belonged to the repFIIA replicon type, implying intraspecies and interspecies transfer of bla_{KPC}.[32]

Latin America

KPC enzymes are endemic and disseminated throughout Colombia, mostly among Enterobacteriaceae.[33] They were first detected in 2005 in two patient isolates of *K pneumoniae*, both with bla_{KPC-2};[34] neither patient had travelled abroad. Subsequently, in 2006, Colombia was the first country in which a KPC enzyme was identified in *P aeruginosa*.[35] 2 years later, an outbreak of KPC-3-producing *K pneumoniae* was reported: 20 (63%) of 32 patients died, and 14 fatalities were attributed to the infections. The index case was a patient who travelled from Israel,[36] where *K pneumoniae* with KPC-3 enzymes have caused many outbreaks.

Detailed investigations have identified *K pneumoniae* ST258 and ST512[33] and *P3 aeruginosa* ST308, ST235, ST1006, and ST1060 as the main sequence types that host KPC enzymes in Colombia.[37] Rapid dissemination had become a substantial problem by 2009, when PCR screening revealed that KPC β-lactamases had spread from three to all of the seven metropolitan areas surveyed.[33]

The SENTRY antimicrobial surveillance programme shows that Argentina and Brazil had increases in KPC-positive organisms in 2008–10.[38] In Argentina, the first isolate was a KPC-2-positive *K pneumoniae* identified in 2006 from a patient without substantial previous travel.[39] Surveillance since 2008 shows sporadic isolation of KPC-2-positive isolates until mid-2009, followed by abrupt dissemination of an ST258 *K3 pneumoniae* clone.[40] In recent surveillance in seven cities,[41] 65 (13%) of 514 *P aeruginosa* isolates carried bla_{KPC}, most of which belonged to the ST654 lineage.

In Brazil, the first description of KPC involved identification of four KPC-2-positive *K3 pneumoniae* isolates in an intensive care unit (ICU) in 2006.[42] No overseas links could be traced. A later study revealed that most KPC-positive isolates were KPC-2-harbouring *K pneumoniae* of ST437 clone.[43] On the basis of the SENTRY surveillance[38] and other findings across the country, KPC-2-positive *K pneumoniae* are endemic in Brazil, with these organisms also described in hospital wastewater.[44] As with elsewhere in Latin America, KPC-2 has also become common in *Pseudomonas* spp.[45,46]

Europe

UK and Ireland

The first known KPC enzyme in the UK was a KPC-4 variant in an *Enterobacter* sp from a blood specimen in Scotland in 2003.[47] The first recorded *K pneumoniae* producing a KPC enzyme was also from Scotland, in 2007.[48] KPC-positive isolates confirmed by the national reference laboratory remained rare and geographically scattered in 2008 (five isolates from four hospitals) and 2009 (13 isolates from 12 hospitals), and were dominated by ST258 *K pneumoniae* (ten of 12 by MLST), with the source patients often having travelled to Cyprus, Greece, or Israel.[49] This epidemiological pattern then changed abruptly, with 231 KPC-positive isolates referred in 2010 (216 *Klebsiella* spp, ten *E coli*, and five *Enterobacter* spp), 368 in 2011 (286 *Klebsiella* spp, 41 *E coli*, 30 *Enterobacter* spp, and 11 other Enterobacteriaceae), and 293 from January to July, 2012 (251 *Klebsiella* spp, 24 *E coli*, 15 *Enterobacter* spp, and three other Enterobacteriaceae). 833 (93%) of the 892 post-2009 isolates were obtained from the Greater Manchester area.[50] This ongoing outbreak was mostly a result of horizontal spread of IncFIIK plasmids related to the Israeli plasmid pKpQIL among *K pneumoniae* and other Enterobacteriaceae, not to the clonal spread of producer strains. Many of the isolates remain susceptible to fluoroquinolones and several aminoglycosides, by contrast with ST258, which has a characteristic antibiogram (susceptible generally only to colistin, gentamicin, and tigecycline). Efforts to control this plasmid outbreak have been unsuccessful. By contrast, ST258, which continues to be imported, has not caused any substantial outbreaks. More generally, if the Greater Manchester situation is discounted, the UK has a mixed carbapenemase epidemi ological pattern, with VIM and NDM enzymes similarly prevalent to KPC types, and with OXA-48-like enzymes also regularly encountered.[49]

In Ireland, the first KPC-positive isolate was identified in February, 2009, in a patient with lower respiratory tract infection. By 2010, KPC-positive *K pneumoniae* had been isolated from six additional patients in different hospital units at the same facility.[51] In 2011, the same hospital experienced an outbreak involving ten patients, mostly in ICUs and surgical

wards; one patient was readmitted to a different hospital, with horizontal transmission to an additional patient.[52] All typed isolates were ST258, although there was substantial diversity in pulsed-field gel electrophoresis profiles. Of 11 patients, six (55%) were colonised and five (45%) had clinical infections; among the latter, three died.[52]

National surveillance in June, 2011, assessed the prevalence of carbapenem-resistant Enterobacteriaceae in patients in ICUs; 760 rectal swab samples were examined from 35 hospitals and no patients colonised with KPC-positive *K pneumoniae* were found.[53]

Spain and Portugal

In 2009, a 66-year-old Spanish man was the first of eight cases colonised with KPC-3-positive *K3 pneumoniae* to occur in a health-care facility in Madrid, Spain.[54] Seven isolates were ST384 and one was ST388. These patients were in five different wards in the hospital, and none had recently travelled to KPC-endemic countries. Despite implementation of infection control measures, the investigators' attempts to halt further horizontal transmission were unsuccessful.

Late in 2009, a second outbreak was detected in Madrid, Spain, with three clonally related KPC-2-positive *Citrobacter freundii*.[55] As in the earlier cluster, none of the patients had recently travelled abroad or been transferred from foreign hospitals. Since then, sporadic KPC-positive isolates have been identified in the same hospital and in other hospitals in Valencia, Spain. 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.[56]

France

The first clinical isolate with a KPC β-lactamase in France—a KPC-2-positive *K pneumoniae*—was found in 2005.[57] It was recovered from urine and blood cultures of a patient who had been admitted to hospital 3 months earlier in New York City (NY, USA). In the same year, a KPC-3-producing *Enterobacter cloacae* isolate was obtained from the abdominal abscesses of a patient who had a gastrectomy in New York City.[58] A subsequent report, published in 2008, described a KPC-2-positive *K pneumoniae* from wound samples of a patient transferred from a Greek hospital;[59] this was the first description of KPC-producing isolates linked to Greece. Also in 2008, two KPC-2-positive isolates were recognised among stored strains: these were collected in 2002 from the peritoneal fluid of a patient transferred from an Israeli hospital.[60] In 2011, an *E coli* strain with reduced susceptibility to carbapenems was isolated, at admission, from rectal samples of a patient transferred from a hospital in India.[61] At least one native case has also been reported:[62] in 2009, an *E coli* isolate with reduced susceptibility to carbapenems was identified in the urine of a 64-year-old woman admitted to hospital for pressure ulcers. This patient did not have any relevant travel history but had recently received imipenem for a urinary-tract infection caused by an extended-spectrum-β-lactamase-positive *Enterobacter aerogenes*. The *E coli* isolate belonged to ST131 and coproduced KPC-2 and CTX-M-15 enzymes.[63]

Subsequently, a couple of nosocomial clusters have been reported, with one of them associated with a contaminated endoscope.[64,65] In 2012, a national reference centre was established to examine all carbapenem-resistant Enterobacteriaceae. Throughout 7 months, 20 KPC-producing isolates were identified (unpublished). All but one were *K pneumoniae*, with KPC-2 and KPC-3 enzymes identified in 15 and five isolates, respectively. These 20 isolates accounted for 12·5% of the 160 carbapenemase-positive Enterobacteriaceae identified. Five of the 20 cases were linked to recent stays in Israel, Italy, Kuwait, and China, none were community acquired, and most were only colonisation.

Italy

In Italy, the first KPC-positive *K pneumoniae* was isolated in 2008 from an inpatient with a complicated intra-abdominal infection in Florence.[66] The isolate had KPC-3 enzyme, with the corresponding gene located in transposon Tn*4401*, which has been described in Israeli ST258 isolates. A second report described two KPC-2-positive *K pneumoniae* obtained in 2009 from patients admitted to a teaching hospital in Rome.[67] Neither patient had recently travelled to KPC-endemic countries. Active surveillance was done in two hospitals in Padua from 2009 to 2011, and almost 200 cases were identified.[68] The initial epidemiological pattern entailed dissemination of KPC-3-positive *K pneumoniae* ST258 and KPC-2-positive *K pneumoniae* ST14. Subsequently, the former lineage prevailed and spread from ICUs to medical, surgical, and long-term wards.[68] Simultaneously, seven clonally related KPC-3-positive *K pneumoniae* ST258 isolates were identified from wound cultures of different patients in a surgical ICU in Verona[69] and, more worryingly, horizontal transmission of colistin-resistant KPC-3-positive *K pneumonia*e was described in different wards of an acute general hospital in Palermo in 2011.[70]

KPC-positive *K pneumoniae* have spread rapidly and extensively in Italy, with a sharp increase reported by the EARS-Net surveillance system[71] for bacteraemia isolates, from 1–2% carbapenem resistance in 2006–09 to 30% in 2011, and by the Micronet surveillance network,[72] from 2% in 2009 to 19% in 2012. Infection control interventions at the national level are scarce, with only a few reports of local containment.

Poland

The first KPC-positive isolate recorded in Poland was recovered in Warsaw from the urine of an inpatient without relevant travel history.[73] By the end of 2008, the national reference laboratory had identified 32 additional cases in five Warsaw hospitals,[74] with almost 500 more cases confirmed from 2009 to 2012 (unpublished). *K pneumoniae* ST258 accounted for most of these isolates, with the urinary tract or stool as the most common sources.[74] KPC enzymes are thought to be the most prevalent carbapenemase type among Enterobacteriaceae in Poland.

Greece

The first KPC-positive *K pneumoniae* isolates linked to Greece were identified in 2007 in France and Sweden.[59,75] One patient had previously been admitted to hospital in mainland Greece and the other in Heraklion, Crete. Shortly afterwards, a tertiary hospital in Heraklion reported an outbreak of KPC-2-positive *K pneumoniae*.[76] Within 2 years of these reports,

KPC-positive *K pneumoniae* had disseminated into most acute-care facilities in Greece,[77–80] including all tertiary-care hospitals. Presently, KPC-positive *K pneumoniae* are dominant multidrug-resistant pathogens that affect not only patients in ICUs, but also patients in medical and surgical wards; 40% of infections occur outside ICUs.[81] An outbreak of KPC-2-positive *E coli* in a LTCF has been described recently;[82] however, on the basis of passive surveillance, there is no evidence of dissemination into the community (unpublished). In Greece, all-cause 28 day mortality among patients infected with bacteria that produce KPC enzymes is 34%.[81] Although there are claims that KPC-positive *K pneumoniae* were introduced into Greece from Israel,[83] no index case has been identified. International transmission of KPC-positive *K pneumoniae* from Greece via colonised patients has been confirmed on several occasions.[84]

In a recent surveillance study across 40 Greek hospitals, all 378 KPC-positive isolates had KPC-2 and 5% also had VIM-1 or VIM-4 carbapenemases.[85] In another survey of two tertiary-care hospitals, 38% of 338 consecutive blood isolates of *K pneumoniae* produced KPC enzymes, 12% produced VIM, 10% had both KPC and VIM, and 40% did not have any carbapenemase (unpublished). At the beginning of the epidemic, most KPC-positive isolates were genetically related and belonged to the ST258 strain.[86] This is still the dominant strain, but several other lineages are represented among the near 40% of *K pneumoniae* that now carry the KPC enzyme.[85,87]

Israel

Although KPC-positive Enterobacteriaceae were reported in Israel before the arrival of *K3pneumoniae* ST258,[88] the epidemiological effect of the ST258 strain was unprecedented. This strain, probably imported from the USA,[10,11] began to spread in Israeli hospitals in late 2005. Hospital-level interventions implemented in 2006 were unable to contain its spread and, by early 2007, the monthly incidence of new cases in acute-care hospitals peaked at 41·9 per 100 000 patient-days.[89] Risk factors included previous antibiotic use, ICU stay, and poor functional status.[90,91] The most common clinical site was the urinary tract, although several body sites have been involved in clinical infections.[90] Attributable mortality in patients with bacteraemia was 50%.[92] In 2007, the Ministry of Health launched a nationwide intervention (appendix), which rapidly halted the previous rise in incidence. By mid-2008, the outbreak had been contained nationally, with a 79% relative reduction of the incidence compared with its peak the previous year.[89]

Although infections with carbapenem-resistant Enterobacteriaceae are rare in the community, these organisms have succeeded in establishing a large reservoir of carriage in LTCFs,[93] and the frequent transfer of patients between these and acute-care hospitals has ramifications for continued containment in the latter. As a result, two additional measures were implemented: active interventions in LTCFs to match those in acute-care facilities[94] and mandatory active surveillance for rectal carriage of carbapenem-resistant Entero-bacteriaceae among high-risk inpatients.

Asia

India

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 (2002–06).[95] From 2007 to 2010, nine further patients with bacteria that carried bla_{KPC} were identified in an active microbiological surveillance study (eight *K pneumoniae* [seven KPC-2 and one KPC-3] and one *E coli* [KPC-2]). One of the *K pneumoniae* isolates coproduced KPC-2 with NDM-1, CTX-M-15, SHV-12, TEM-1, OXA-1 β-lactamases, and RmtB, which confers broad aminoglycoside resistance.[96]

A French report showing colonisation of a patient transferred from India with a KPC-positive *E coli* in 2011[61] suggests India might have an unrecognised problem. Nevertheless, KPC-positive isolates seem rare, and the most prevalent carbapenemases in the country are NDM types followed by OXA-48-like enzymes.[97,98]

China

The first KPC-positive *K pneumoniae* isolate recorded in China was identified in 2004 from a 75-year-old ICU patient in Zhejiang Province.[99] Shortly afterwards, a wide variety of KPC-positive Enterobacteriaceae were reported in eastern China.

KPC-2 is the most common carbapenemase in China, with *K pneumoniae* the predominant host species. In a recent screening in nine Chinese cities, all 95 *K pneumoniae* found that were not susceptible to carbapenem were positive for bla_{KPC-2}.[100] The bla_{KPC-3} gene—often found abroad in *K pneumoniae* and *E cloacae*—has been reported in only one *E coli* and one *C freundii* strain in Shanghai.[101]

The dominant clone of KPC-positive *K pneumoniae* is ST11, which is closely related to ST258.[100] Most isolates are from lower respiratory tract and urinary tract infections. Most patients are admitted to hospital, often to ICUs, and have many comorbidities; most have had invasive procedures and received repeated doses of broad-spectrum antibiotics, particularly carbapenems. All but one of the patients identified so far are native Chinese (unpublished). Alarmingly, hospital sewage in China has been found to harbour KPC-positive *C freundii* and *E cloacae*, raising concern about the potential contamination of water reservoirs.[102] Community infections with KPC-2-positive isolates have been described.[103] At present, no infection control interventions are in place at national levels.

Australia and New Zealand

Less than 1% of hospital-acquired Enterobacteriaceae in Australia and New Zealand carry KPC enzymes (unpublished). Indeed, fewer than ten cases of KPC producers have been found in these countries so far and most of these had a history of hospital admission in countries where KPC-positive strains are endemic (eg, Greece) or had shared a hospital room with a patient who had been transferred across continents (unpublished). The reasons for the low prevalence in these countries include a history of close attention to infection control for multidrug-resistant *K pneumoniae*, antibiotic stewardship in ICUs, and a

predominance of intercontinental hospital transfers from Asian facilities rather than from the USA, southern Europe, or Israel, where KPC enzymes are most common.

In Australia, recognition of the risk for intercontinental spread of resistant bacteria increased with the transfer of large numbers of patients after terrorist bombings in Bali in 2002 and the Indian Ocean tsunami of 2004. Since then, many hospitals have routinely done surveillance for carbapenem-resistant Enterobacteriaceae on such transfers (appendix).

Challenges with KPC-positive isolates

Detection

Detection of isolates with KPC enzymes or other carbapenemases is challenging because resistance is often low level, and low-level carbapenem resistance can also arise through combinations of impermeability and activity of AmpC or extended-spectrum β-lactamase. Carbapenemase production should be suspected when Enterobacteriaceae have resistance or reduced susceptibility to carbapenems; suspicion should increase when they also do not show strong the cephalosporin–clavulanate and cephalosporin–cloxacillin synergies typical of strains with extended-spectrum β-lactamases or high-level AmpC.[104] Carbapenemase activity can be confirmed by the Hodge test (also known as the clover-leaf test) and by acidimetric tests with carbapenems as the substrate,[104] or by MALDI-TOF (matrix assisted laser desorption/ionisation-time of flight).[105] However, these tests are imperfect and high-level AmpC can give false-positive results, particularly in Hodge (clover leaf) plates, which have poor sensitivity and specificity.[106] The inclusion of inhibitors (boronic acid for KPC and either EDTA [edetic acid] or dipicolinic acid for metalloenzymes) can help discrimination between carbapenemase types, and cloxacillin can be used to inhibit the interfering activity of AmpC.[107] Definitive identification of carbapenemases in clinical isolates is best achieved by PCR of the corresponding genes, or with arrays.

During outbreaks or in endemic situations, screening of stool specimens is appropriate to detect colonisation by carbapenemase producers. Various media are marketed for this purpose—the CDC advocates enrichment in 5 mL tryptic soy broth with a meropenem or ertapenem 10 μg disc, followed by a modified Hodge test. Wilkinson and colleagues[108] found these types of methods could all detect high loads of carbapenemase producers (about 103 colony forming units of inoculum) but detection sensitivity deteriorated—particularly for IMP and OXA-48 carbapenemases, less so for KPC types—with lower inocula. In general, the ChromID Carba (bioMérieux, La Balme-les-Grottes, France) medium had the highest sensitivity with low numbers of bacteria, although an unmarketed medium, SuperCarba, seems to offer further improvement, at least in terms of sensitivity.[109]

Treatment options and mortality

Members of the *K pneumoniae* ST258 lineages are often susceptible only to colistin, tigecycline, and gentamicin. Various combinations of these antibiotics have been used as treatment,[110] but none is ideal for empirical use. Gentamicin and colistin are both nephrotoxic, and tigecycline has a mixed record of success in clinical trials. Moreover, colistin-resistant outbreak strains of *K pneumoniae* with KPC enzymes are already circulating (eg, in Italy). Other aminoglycosides and even fluoroquinolones are active

against some non-ST258 isolates, and resistance to temocillin, an α-methoxy penicillin, is often only low-level (minimum inhibitory concentrations 16–32 mg/L),[111] suggesting that it deserves assessment at doses above those licensed.

Most reports on the treatment of infections caused by KPC-positive organisms are case reports or small case series of various types of infections.[112] However, three retrospective studies have examined mortality in relation to antibiotic treatment for bloodstream infections (table 1). Tumbarello and colleagues[113] assessed 125 bloodstream infections due to KPC-positive isolates and reported a crude 30-day mortality of 42%.[111] The investigators assessed single, double, and triple antibiotic combination treatments, and only the triple combination of colistin, tigecycline, and meropenem was associated with increased survival (odds ratio 0·27, 95% CI 0·07–1·01; p=0·009). Similarly, Zarkotou and colleagues[80] described 53 bloodstream infections caused by KPC-positive *K pneumoniae*, with a crude 30-day mortality of 53% and an infection-attributable mortality of 34%. All patients treated with appropriate combination treatment survived whereas patients treated with monotherapy —including colistin monotherapy—experienced a high infection-attributable mortality (47%). In the third study, Qureshi and colleagues[114] reported crude 28 day mortality of 13% and 58%, respectively, among patients treated with combination and monotherapy. Based on the findings from these studies, combination treatment seems to be the best approach for bacteraemic patients. However, data are still limited for other types of infections, such as ventilator-associated pneumonia, and any role for inhaled colistin, in particular, is unclear.[115]

Drugs in the pipeline

The paucity of treatment options emphasises the need for new treatments and table 2 summarises those in clinical development. Many are β-lactamase inhibitor combinations. Ceftazidime–avibactam is the furthest advanced and was active in a mouse model of sepsis with a KPC-positive *K pneumoniae* strain.[123]

Infection control

Infection control interventions generally are implemented as bundles, since no one action can be singled out as effective (table 3).[124] Nevertheless, findings from several studies emphasise 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 described earlier.[127,129,130] Furthermore, a recent study in New York (NY, 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.[134] Future studies are needed to identify the role of individual interventions in controlling the spread of KPC enzymes. Additionally, plasmid outbreaks (rather than clonal outbreaks) might respond more favourably to antibiotic stewardship interventions rather than the infection control interventions described earlier.

Conclusions

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 endemicity (eg, Israel, Greece, and Colombia) whereas others largely continue to have only imported cases (eg, Australia, New Zealand, and Canada). Most heavily affected countries have described clonal expansion of KPC-producing *K pneumoniae*, typically members of the ST258 lineage, which is the predominant clone worldwide. However, exceptions, such as the UK, have experienced a plasmid expansion instead of clonal expansion. Intercontinental travel seems to be closely linked with the detection of index KPC-producing isolates (eg, travel from the USA to Europe). Some countries are more affected by other carbapenemases than KPC: examples include Spain (VIM), India (NDM), France (OXA-48) and—although not reviewed here—most of the Middle East (except Israel), along with north Africa (OXA-48).[135] Most cases involving bacteria with KPC enzymes have been detected in acute-care hospitals rather than in community settings, but LTCFs act as reservoirs of colonised patients in some countries (eg, Israel and the USA).

Antibiotic treatment is limited to a few choices, typically including colistin, tigecycline, and one or more aminoglycoside. Recent findings suggest that combination treatment with colistin, tigecycline, and meropenem might improve survival among bacteraemic patients.[113] A major concern is the emergence of colistin-resistant KPC-positive *K pneumoniae* isolates, including ST258 variants,[79,136] which is worrying since colistin is the core component of treatment combinations. The selection of colistin-resistant KPC-producing strains probably results from heavy and increasing use of colistin, including empirical use in areas where KPC-positive *K pneumoniae* have spread. Even if not formally identified, the association between the intense selective pressure and the appearance of resistance is likely. Clinicians must be aware of the possibility for selection of pandemic drug-resistant strains.

The main challenges at a national and institutional level are early and accurate recognition of patients carrying strains with KPC enzymes. These patients can be identified by the implementation of adequate surveillance measures, such as screening of patients with recent travel history using selective media (many of which are better optimised for KPC than for other carbapenemases),[108] or identification of carbapenemases by biochemical or molecular techniques. Once bacteria with KPC enzymes are identified, appropriate infection-control bundle interventions should be put in place to prevent spread. Only efficient and proactive surveillance aligned with regional interventions will enable control and prevention of the spread of these threatening microorganisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Search strategy and selection criteria

We searched PubMed between January, 1990, and June, 2013, for the terms “Klebsiella pneumoniae carbapenemase” or commonly used acronyms (eg, KPC, CRE, CPE) in combination with the names of individual countries, “treatment”, “detection”, or “prevention” or “infection control”. Furthermore, to give an accurate representation of each nation, relevant references were provided by the authors of this Review who are experts from most of the countries highlighted.

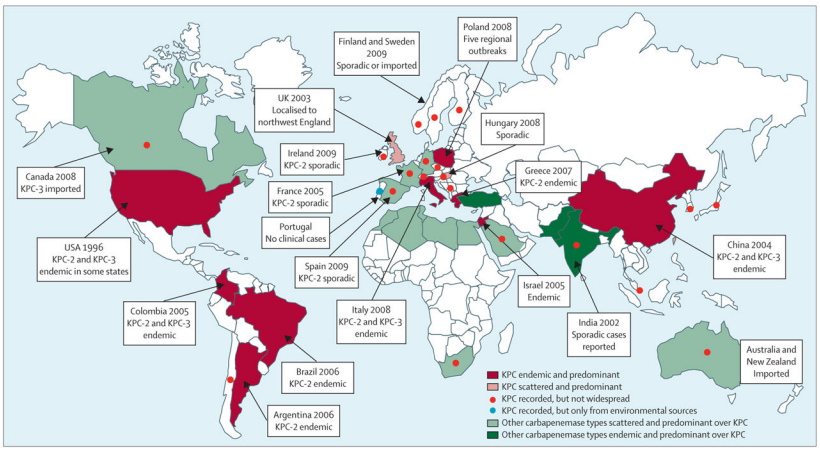

Figure. Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin

Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

Table 1

Treatment combinations and mortality among patients with bloodstream infections caused by Enterobacteriaceae producing *Klebsiella pneumoniae* carbapenemases

	Years of collection and origin	Number of cases	Source of infection	Overall mortality	Mortality			Mortality with most frequent combinations	Mortality with most frequent monotherapy	Risk factors associated with mortality in multivariable analysis
					Combination treatment	Monotherapy	p value			
Tumbarello et al (2012)[113]	2010–2011, Italy	125	Unknown (75; 60%), lower respiratory tract (28; 22%), urinary tract (17; 14%), line related (13; 10%), and other (5; 4%)	Crude 30 day mortality: 52 (42%)	27/79 (34%)	25/46 (54%)	0·002	Colistin with tigecycline (7/23; 30%), tigecycline with gentamicin (6/12; 50%), and tigecycline with colistin and meropenem (2/16; 13%)	Colistin (11/22; 50%), tigecycline (10/19; 53%), and gentamicin (4/5; 80%)	Septic shock at presentation, inadequate empirical therapy, APACHE score, and triple combination therapy
Zarkotou et al (2011)[80]	2008–2010, Piraeus, Greece	53	Primary bacteraemia (23; 43%), line related (12; 23%), respiratory tract (7; 13%), urinary tract (6; 11%), soft tissues (4; 8%), and CNS (1; 2%)	30 day attributable mortality: 18/53 (34%),* and crude mortality: 28/53 (53%)*	0/20 (0%)†	7/15 (47%)†	0·001	Colistin with tigecycline (0/9; 0%) and tigecycline with gentamicin (0/2; 0%)	Colistin (4/7; 57%), tigecycline (2/5; 40%), gentamicin (0/2; 0%), and carbapenem (1/1; 100%)	Absence of appropriate antimicrobial treatment combination, APACHE score, and age
Qureshi et al (2012)[114]	2005–2009, New York City and Pittsburgh, USA	41	Line related (13; 32%), pneumonia (10; 24%), urinary tract (7; 17%), and primary bacteraemia (6; 15%)	Crude 28 day mortality: 16 (39%)‡	2/15 (13%)‡	11/19 (58%)‡	0·01	Carbapenem with colistin (1/5; 20%) and carbapenem with tigecycline (0/3; 0%)	Colistin (4/7; 57%); tigecycline (4/5; 80%) and carbapenem (2/4; 50%)	Absence of appropriate combination as definitive therapy

APACHE=acute physiology and chronic health evaluation.

*Only included 35 patients who completed at least 48 h of appropriate antibiotic treatment.

†Attributable mortality was assessed during the index hospitalisation.

‡28 day mortality among 34 patients who received definitive therapy.

Table 2

Drugs in clinical development that are active against Enterobacteriaceae with *Klebsiella pneumoniae* carbapenemases

	Class	Status	Advantages	Caveats
Ceftazidime–avibactam (AstraZeneca/Forest, Wilmington, DE, USA)	Cephalosporin-BLI	Phase 3	Furthest advanced BLI combination; uses well-established cephalosporin at high doses (up to 2 g plus 0·5 g avibactam every 8 h)	Occasional resistance if other enzymes are also present.[116] Strains with metallocarbapenemases, rather than KPC enzymes, are resistant
Ceftaroline–avibactam (AstraZeneca/Forest, Wilmington, DE, USA)	Cephalosporin-BLI	Entering phase 3	Also covers meticillin-resistant *Staphylococcus aureus* but (unlike ceftazidime-avibactam) not *Pseudomonas aeruginosa*	Higher doses might be needed than used for ceftaroline alone. Strains with metallocarbapenemases, rather than KPC enzymes, are resistant
Plazomicin ACHN-490 (Achaogen, San Francisco, CA, USA)	Aminoglycoside	Completed phase 2	Active versus most isolates with KPC enzymes;[117] evades aminoglycoside-modifying enzymes	Compromised by rRNA methylases, which sometimes accompany KPC enzymes in China,[118] although these are not present in typical ST258-KPC strains elsewhere
EravacyclineTP-434 (Tetraphase, Watertown, MA, USA)	Tetracycline	Completed phase 2	Active *vs* Enterobacteriaceae with KPC or other carbapenemases[119]	Efficacy of tetracyclines in severe infections is debated
Imipenem-MK7655 (Merck, Summit, NJ, USA)	Carbapenem-BLI	Phase 2	Uses a well established carbapenem[120]	Strains with metallo-carbapenemases, rather than KPC enzymes, are resistant
Aztreonam-avibactam (AstraZeneca/Forest, Wilmington, DE, USA)	Monobactam-BLI	Phase 1	Also covers Enterobacteriaceae with metallocarbapenemases[116]	Spectrum mostly confined to Enterobacteriaceae
Biapenem-RPX7009 (Rempex, San Diego, CA, USA)	Carbapenem-BLI	Phase 1	Novel boronate inhibitor; biapenem is less compromised than other carbapenems *vs* Enterobacteriaceae with metallocarbapenemases	Resistance can arise in isolates with high biapenem minimum inhibitory concentrations, probably owing to hyperproduction of KPC enzymes
BAL30072 (Basilea, Basel, Switzerland)	Monosulfactam	Phase 1	Stable to metallocarbapenemases and OXA-48 carbapenemases as well as KPC enzymes[121]	Vulnerable to the SHV extended-spectrum β-lactamases, which often accompany KPC enzymes (eg, in ST258 *K pneumoniae*)[122]

BLI=β-lactamase inhibitor. KPC=*Klebsiella pneumoniae* carbapenemase.

Table 3

Infection control interventions for the containment of Enterobacteriaceae positive for *Klebsiella pneumoniae* carbapenemase

	USA[125] (2009)	Crete[76] (2009)	USA[21] (2009)	USA[126] (2010)	Israel[127] (2010)	USA[23] (2010)	USA[128] (2010)	Israel [129] (2011)	Israel [130] (2011)	Italy[131] (2011)	Italy[70] (2012)	Greece[132] (2012)	Spain[133] (2012)
Increased hand hygiene precautions	Yes	Yes	Yes	Yes*	··	··	Yes	··	Yes	Yes*	Yes	Yes*	Yes
Increased compliance with gowns and gloves	Yes	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	Yes*	Yes	Yes*	Yes
Rectal surveillance initiated	Yes	··	Yes	Yes†	Yes	Yes	Yes	Yes	Yes	Yes*	··	Yes‡	Yes
Grouping of KPC-positive patients	Yes	··	Yes	Yes†	Yes	Yes	Yes	Yes	Yes	Yes†	Yes	Yes†	Yes
Grouping of staff caring for KPC-positive patients	Yes	··	Yes	Yes†	Yes	Yes	Yes	Yes	Yes	Yes†	··	Yes‡	··
Education on hospital epidemiology of KPC among health-care workers	Yes	Yes	··	··	··	Yes	Yes	Yes	Yes	Yes*	Yes	··	Yes
Increased environmental cleaning	Yes	Yes	··	··	··	Yes	Yes	Yes	Yes	Yes*	Yes	Yes†	Yes
Cultures of environmental surfaces in patients' rooms	··	Yes	··	··	··	Yes	Yes	··	··	··	Yes	Yes*	Yes
Daily chlorhexidine baths	··	··	··	··	··	Yes	Yes	··	··	··	··	··	Yes
Regular infection control reports of new cases to affected units	··	··	··	··	Yes	Yes	Yes	Yes	Yes	··	··	Yes†	··
Flagging of cases in hospital database	··	··	··	··	Yes	··	··	Yes	Yes	··	··	··	··
Closing the ICU	Yes	··	··	Yes*	··	··	··	··	··	··	··	··	··
Surveillance cultures obtained from staff	··	··	··	··	··	··	··	··	··	··	··	··	Yes
Dedicated equipment for KPC-positive patients	··	··	Yes	··	··	··	··	··	Yes	··	Yes	··	··
Decreased antibiotic use or antibiotic restriction	··	··	··	Yes*	··	··	··	··	Yes	··	··	··	··
Outbreak improved or controlled	Yes	Yes	Yes	Yes, during second phase	Yes	Yes	Yes	Yes	··	Yes, during second phase	No	Yes, during second and third phases	Yes

ICU=intensive care unit. KPC=*Klebsiella pneumoniae* carbapenemase. ··=not reported. Symbols represent bundles that were implemented in a staggered fashion:

*first phase;

†second phase;

‡third phase.