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CHARACTERISTICS, EPIDEMIOLOGY AND MODERN METHODS OF INVESTIGATION OF KLEBSIELLA PNEUMONIAE

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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). 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 [1].

Key words: *Klebsiella pneumoniae*, antibiotic resistance, carbapenemases, KPC-positive bacteria, hvKp.

INTRODUCTION

First discovered in the USA in 1996, *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. Since their first description, KPC enzymes have spread across countries and continents (figure), although the exact epidemiology of their expansion varies by geographical location [2].

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 [3].

After more than 70 years of extensive use of antibiotics to treat infectious diseases, antibiotic resistance is now being recognized as a worldwide crisis in modern medicine (The Review on Antimicrobial Resistance, O'Neill 2016). The dramatic in-crease in prevalence of infections caused by multidrug-resistant (MDR) and extremely drug resistant (XDR) pathogens belonging to the *Enterobacteriaceae* group poses a great concern since these pathogens are common natural inhabitants of our microbiome. Moreover, infections caused by these strains are often associated with high mortality rates, prolonged hospitalization and costs [4].

Antibiotic resistance is a multifactorial complex process (Watkins and Bonomo 2016). However, from the bacterial perspective it reflects evolution in action, concomitant to the continuous exposure to antibiotics, where selective pressure gives rise to the evolvement of multiple genetic mechanisms (Davies and Davies 2010). This constant evolution over the years has led to the emergence of MDR and XDR *Enterobacteriaceae* strains (Magiorakos *et al.* 2012) that exhibit resistance to nearly all antibiotics available, without possible treatment options (Hersh *et al.* 2012). The risk of global dissemination of these XDR pathogens has become a recognized global threat [5].

HISTORY AND EVOLUTION

A genomic analysis of 328 *K. pneumoniae* isolates supports the division of *K.pneumoniae* into three distinct species, *K. pneumoniae*, *K. quasipneumoniae*, and *K. variicola* (23, 24). Human infection has been reported for all of these species, and *K. quasipneumoniae* and *K. variicola* are frequently misidentified as *K. pneumoniae* by clinical microbiology laboratories (25, 26). *K. pneumoniae* is responsible for the majority of human infections (24, 25, 27), and hvKp strains

belong to *K. pneumoniae* (28). Although hypermucoviscous strains of *K. quasipneumoniae* and *K. variicola* have been described (29, 30), these isolates do not have the genomic content that predicts a hypervirulent phenotype; however, it seems likely that this event will occur at some point or has already occurred and is unrecognized due to the difficulties for clinical microbiology laboratories to identify *K. quasipneumoniae* and *K. variicola*. Nonetheless, the focus of this review is on hvKp; therefore, *K. quasipneumoniae* and *K. variicola* will not be further discussed [6].

EPIDEMIOLOGY

Acquisition and Colonization May Lead to Infection

K. pneumoniae organisms can be members of normal animal and human microb-iotas and/or the microbiotas of various environmental habitats (10, 11). Acquisition of and colonization with *K. pneumoniae* appear to be requisite for, but do not necessarily lead to, infection (12–17). Otherwise healthy individuals from the community are at risk for developing hvKp infection, whereas it is uncommon for cKp infection to develop in this population. Healthy people can be colonized with cKp, but in the absence of some form of host compromise, infection rarely occurs. By contrast, healthy individuals colonized with hvKp are at much greater risk for developing infection. However, the frequency with which infection develops after colonization with hvKp a the factors that modulate this risk are not well understood. The relative importance of colonization versus that of the quantity of the colonizing hvKp strain, host factors, and degrees of hvKp virulence is an important issue that requires active investigation [7].

Although hvKp infections occur in all ethnic groups, even those acquired in Western countries commonly involve Asians (37, 39, 213–221) and (to a lesser degree) Pacific Islanders and Hispanics (9, 215, 216). One explanation could be that hvKp infection occurs more frequently in Asians from geographically defined pathogen exposure, acquisition, and increased colonization (113), a requisite step for subsequent infection. In some cases, there is a history of Asians infected in the West that travelled to or were exposed to individuals who had recently been in the Asian Pacific Rim (39). In fact, a case in a Caucasian from Denmark who traveled to Shanghai, China, suggests this very scenario (220). Alternatively, an underlying genetic abnormality that is more commonly, but not exclusively, present in Asians, Pacific Islanders, and Hispanics could also be contributory. This concept of genetic susceptibility is consistent with a case report involving a Japanese father and son who developed infection due to hvKp, but the mother was only colonized (114). Further, another report from Singapore suggests that genetic background may contribute to the development of hvKp infection. In 70 patients with liver abscess,

among whom 67 cases were probably caused by hvKp, only 1.4% of these infections were in Indians, despite Indians comprising 7.4% of the population and being more likely to be diabetic. However, differences in diet and colonization were potential factors that were not accounted for (81). Conversely, in a study from France, of 14 patients with hepatic abscess due to hvKp, 5 were Caucasian, 6 were African, and only 3 were Asian [8].

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* [9].

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 [10].

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 [11].

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 [12].

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 [13].

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 [14].

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 [15].

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 [16].

Klebsiella pneumoniae is an increasingly important bacterial pathogen that is capable of causing severe organ and life-threatening disease. A critical trait of K. pneumoniae that has enabled its ongoing evolution is the ability to acquire new genetic material. As a result, two pathotypes termed classical K. pneumoniae (cKp) and hyper-virulent K. pneumoniae (hvKp) are presently circulating, each of which

presents unique challenges for the clinician (1, 2). Both pathotypes are global pathogens, but theincidence of infections due to hvKp has been steadily increasing over the last 3 decades in countries that comprise the Asian Pacific Rim (3–7). By contrast, to date, cKp has been the dominant offending agent in Western countries, but infections due to hvKp are being increasingly recognized outside Asia [17].

Clinicians are all too familiar with cKp, which most commonly is an opportunistic pathogen causing infections primarily in the health care setting in hosts with comor-bidities, who are immunocompromised, or who have existing barrier breakdown (e.g., intravascular devices, endotracheal tube, or surgical wound). This pathotype has dem-onstrated the ability to acquire an increasing number of elements that confer antimi-crobial resistance, which has earned it a place among the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseu-domonas aeruginosa*, and *Enterobacter* species) pathogens (10). The most problematic are genes that encode extended-spectrum _-lactamases (ESBLs) (e.g., CTX-M, SHV, and TEM) that hydrolyze third-generation cephalosporins, aztreonam, and (in some in-stances) fourth-generation cephalosporins, and genes that encode carbapenemases (11). It is logical that extensively drug-resistant (XDR) cKp strains are able to thrive in the health care setting where significant antimicrobial use gives them a selective advan-tage. A major challenge with infections due to XDR cKp involves difficulties with treatment. XDR cKp has been responsible for lethal hospital outbreaks (12), and a woman infected with a pan-drug-resistant (PDR) cKp strain died from a lack of treat-ment options (13), a harbinger of the feared postantibiotic era [18].

The characteristics of hvKp and its differences from cKp are less well appreciated (Table 1). hvKp is best described as a virulent pathogen (14). The majority of reported infections due to hvKp have been acquired in the community. Features that are highly suggestive of hvKp infection are its ability to infect healthy individuals of any age and the propensity of infected patients to present with multiple sites of infection and/or develop subsequent metastatic spread, an unusual occurrence for other members of the family *Enterobacteriaceae*. The hallmark clinical syndrome is a hepatic abscess in the absence of biliary tract disease. However, hvKp can infect nearly every site of the body. A few examples of these infectious syndromes include nonhepatic abscesses, pneu-monia, necrotizing fasciitis, endophthalmitis, and meningitis. A trait that was initially believed to be sensitive and specific for hvKp strains was a hypermucoviscous pheno-type, which is defined by a positive string test (15). This has since been

shown not be the case; not all hvKp strains are hypermucoviscous, and some cKp strains possess this characteristic [19].

Plasmid-mediated AmpC genes

The remarkable versatility of *K. pneumoniae* to incorporate *β*-lactamase genes onto transferrable plasmids that enable their spread, gave rise to the emergence and spread of plasmid-mediated AmpC-like cephalosporins in this species (Jacoby 2009; Bush 2010). These genes emerged during the late 1980s and early 1990s, in parallel with the explosion of ESBL genes, and they are entirely plasmid-borne in *K. pneumoniae* (Jacoby 2009). The most abundant bla_{AmpC} gene families in this species belong to the CMY, DHA, FOX and MOX types, and their first years of occurrence in *K. pneumoniae* are shown in Fig. 2. Plasmid-encoded bla_{ACT}, bla_{MIR}, bla_{ACC} and bla_{LAT} seem to be highly rare AmpC genes in *K. pneumoniae*, and were not added to the time line. However, evolutionary tendency to incorporate resistant genes onto the chromosome occurred, and the first chromosomal AmpC $bla_{\text{CMY-2}}$ was identified in *K. pneumoniae* in 2009 (Fig. 2, Zamorano *et al.* 2015). *Klebsiella pneumoniae* strains showing enhanced resistance to *β*-lactams due to the existence of bla_{AmpC} combined with porin loss, or increased efflux, were also reported as with the case of $bla_{\text{ACT-1}}$. These genes can also be easily overexpressed on plasmids due to multiple copies, or increased promoter strength of plasmid genes, and even lead to carbapenem resistance [20,28].

Microbiologic Identification

A significant issue that is presently impeding optimal care of hvKp-infected patients is the inability of clinical microbiology laboratories to distinguish cKp from hvKp. To resolve this shortcoming, the availability of a commercial test that has been approved by appropriate regulatory bodies is needed. Identification of hvKp as the infecting agent would be important. Specifically, if infection due to hvKp was not previously considered, this would suggest to the treating physician the need to obtain additional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) in search of additional sites of infection, which may be unrecognized and could require source control (e.g., drainage) (295). Further, the identification of certain occult sites of infection, such as in cases of meningitis (which may be mistaken for sepsis-related changes in mental status), brain or prostatic abscesses, or endophthalmitis, would be important since site-specific antimicrobial regimens that achieve adequate drug concentrations are needed for an optimal outcome (31). Of particular note is endophthalmitis, a devastating complication of hvKp infection. Ocular infection may not be present or apparent at presentation. Due to the rapidity of tissue damage at this site, immediate treatment is required to maximize the odds of maintaining visual acuity. Therefore,

established or suspected hvKp infection dictates involvement of an ophthalmologist, who has the capability of performing an appropriate evaluation and immediately initiating treatment specific for endophthalmitis, such as vitrectomy and intravitreal antibiotics if needed [25,26,27]. The hypermucoviscous phenotype of hvKp can be problematic in the management of abscesses. Its increased viscosity can impede percutaneous drainage (PD) and increase the likelihood of the catheter becoming clogged (39, 310). If it is known at the time of catheter placement that hvKp is the infecting strain, then the clinician can consider the use of the largest bore practical. Once the drainage catheter is placed, it would be equally important to perform more frequent irrigations than usual to try to maintain drainage, which, in turn, will decrease the need for subsequent open surgical drainage (SD) if percutaneous drainage fails. Anecdotally, hvKp infection has been associated with relapse (69, 114, 245, 250). In the absence of controlled data, when hvKp is identified as the infecting agent, a more prolonged treatment course may be needed to maximize cure rates and minimize relapse [21,23,24].

CONCLUSIONS

Klebsiella pneumoniae plays a major role in the worldwide burden of antibiotic resistance. This burden is mainly hospital-associated, and involves HiR epidemic strains that possess a super resistome and cause infections with limited treatment options, leading to increased complications, higher mortality rates and costs .

Being a hospital-associated pathogen, *Klebsiella* is continuously exposed to multiple antibiotics resulting in constant selective pressure, which in turn leads to additional mutations that are positively selected. We showed that the resistome of *K. pneumoniae* encompasses a wide array of ARGs that continuously evolve and diversify (Fig. 2). Although various *K. pneumoniae* isolates may differ in their resistome repertoire, depending on geographic location, cultural population exchange, antibiotic stewardship and possible resistant reservoirs, this species shows a flexible ability to accumulate and switch resistances. Interestingly, ARGs that encompass the resistome can be located on the bacterial chromosome or on plasmids. Within a single genome, chromosomally encoded AR elements can move onto plasmids and vice versa. Plasmid-mediated resistome and transposons can also transfer and disseminate horizontally to other *K. pneumoniae* strains and occasionally to other bacterial species.

Plasmids are present in almost all *K. pneumoniae* strains, and the replicon content in this species very often diverges from other *Enterobacteriaceae* species replicons. Plasmid analysis high-lights the impressive diversity of replicon types associated with the same carbapenemase or ESBL gene. Among them, broad host

range, successful plasmids of the IncX3, IncA/C, IncN and IncL groups often associated with the *bla*$_{NDM}$, *bla*$_{OXA-48}$ and *bla*$_{CTX-M}$ genes. *Klebsiella pneumoniae* acquired these epidemic plasmids and then often acts as the harbinger of resistance determinants among other enterobacteria. In spite of these efforts, resistance rates have increased both in *Klebsiella* and in other human-affecting pathogens, giving rise to concerns about the importance of additional reservoirs.

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