REVIEW

Epidemiology of carbapenem-resistant Gram-negative infections globally

Adrian J. Brink

Purpose of review

The spread of carbapenem-resistant Gram-negative bacteria (GNB) with changes in institutional epidemiology continues to evolve worldwide. The purpose of this review is to evaluate new data with regard to the epidemiology, mechanisms of resistance and the impact of carbapenem resistance on mortality.

Recent findings

The rapid expansion of acquired carbapenem resistance is increasingly propagated by mobile genetic elements such as epidemic plasmids that transfer carbapenemase genes within and between GNB. The risk of acquisition of carbapenem-resistant *Acinetobacter baumannii* increases four-fold with carbapenem exposure and new meta-analyses have confirmed excess mortality associated with carbapenem-resistant *Pseudomonas aeruginosa*. Carbapenemase-producing *Klebsiella pneumoniae*, the most commonly encountered carbapenemase-producing *Enterobacterales* (CPE) and a major cause of high-mortality hospital-related infections, represents the most rapidly growing global threat. Carbapenem use in patients colonized with such genotypes, leads to an increase in CPE abundance in the gastrointestinal tract, which in turn increases the risk of blood-stream infections four-fold.

Summary

High-resistance rates in carbapenem-resistant GNB in many countries will inevitably complicate treatment of serious infections in vulnerable patient groups and should accelerate global attempts to overcome the impediments we face with regard to effective antimicrobial stewardship and infection prevention and control programs.

Keywords

carbapenemase-producing *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, epidemiology

INTRODUCTION

The spread of carbapenem-resistant Gram-negative bacteria (GNB) with the consequent change in institutional epidemiology continues to evolve rapidly worldwide despite the considerable effort put into infection prevention and control (IPC) programmes and targeted antimicrobial stewardship (AMS) interventions [1,2].

Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), *Acinetobacter baumannii* (CRAB) and *Enterobacterales* (CRE) remain important causes of hospital-acquired infections (HAIs) and are prioritized by the WHO as critical pathogens requiring urgent drug research and the development [3]. In fact, *Klebsiella pneumoniae*, the most commonly encountered carbapenemase-producing *Enterobacterales* (CPE), and a major cause of high-mortality HAIs, represents the fastest growing threat to antibiotic resistance in terms of human morbidity and mortality in Europe [4■■].

Carbapenem resistance in GNB results from the expression of antibiotic-inactivating enzymes and/or nonenzymatic mechanisms [5]. These may occur from mutations in chromosomal genes, but most frequently from horizontal transfer of mobile genetic element-mediated carbapenemase genes via plasmids or transposons. In this regard, since the first descriptions of a metallo-β-lactamase (MBL) IMP-1 in *P. aeruginosa* in 1991, OXA-23 in *A. baumannii* in 1993, and KPC-1 in *K. pneumoniae* in 2001

Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Correspondence to Adrian J. Brink, Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, Western Cape, South Africa. Tel: +27 21 406 6083/+27 825737330; e-mail: adrian.brink@uct.ac.za

Curr Opin Infect Dis 2019, 32:609–616

DOI:10.1097/QCO.0000000000000608

KEY POINTS

- Carbapenem-resistant *P. aeruginosa* remain a major cause of high-mortality hospital-acquired infections.
- Carbapenemase encoding genes are rapidly expanding globally and are proliferating at an unprecedented rate among GNB.
- Carbapenemase-producing *K. pneumoniae* represents the fastest growing antibiotic resistance threat.
- Use of carbapenems in CPE gut colonized patients increases the risk of blood-stream infections 4× fold.
- A few international high-risk CPE clones are propagating nosocomial acquisition.

[6], carbapenemase-encoding genes have undergone exponential expansion and proliferation worldwide [7].

Up to 40% of ICU-acquired infections are caused by these three WHO priority pathogens [8] and recognition of the rapid expansion of carbapenem resistance as a consequence of the transfer of these promiscuous genetic elements within and between GNB, has changed the perspective of the magnitude of the problem and necessitated a re-evaluation of the immediate and future challenges we face (Fig. 1).

CARBAPENEM-RESISTANT *PSEUDOMONAS AERUGINOSA*

The capacity of *P. aeruginosa* to survive in an extraordinary variety of environmental niches, to acquire and concurrently express an astonishing array of resistance determinants and, despite these genetic transformations to maintain its virulence, endows it with all the properties necessary to have evolved into a formidable pathogen of paramount importance in HAIs. To date, the global epidemiology of CRPA has not been systematically evaluated and this is contributed to by a lack of global surveillance data and the myriad mechanisms by which *P. aeruginosa* develops resistance [9▪].

Resistance rates

The geographic and temporal antibiotic resistance patterns over 20 years (1997–2016) from the SENTRY surveillance program which included carbapenem resistance rates ($n=52\,022$ isolates) globally but excluding Africa and the Middle-East, have recently been published [10]. Utilising the Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing standards, carbapenem resistance rates were 17.4 and 10.9%, respectively. Multidrug resistant (MDR) phenotypes were most frequently isolated in Latin America (41.1%), followed by Europe (28.4%), North America (18.9%) and the Asia-Pacific region (18.8%).

The most common infections from which *P. aeruginosa* was isolated were pneumonia in hospitalized patients (44.6%) followed by bloodstream infections (BSIs) (27.9%). In data extracted from a large US hospital database ($N=358$ hospitals) respiratory samples were also the most frequent source of carbapenem nonsusceptible isolates (35.2%) [11].

It is important to note that MDR rates in the SENTRY program were highest in 2005–2008 and have subsequently decreased [10]. Similarly, in data from Europe in 2017, despite large intercountry variation and high carbapenem-resistance rates in Southern and Eastern Europe (25–60%, with up to 10–50% classified as MDR), a small but significant decrease in carbapenem resistance was recorded [12].

Irrespective of this, the high-resistance rates in *P. aeruginosa* in many countries will inevitably complicate treatment of serious infections and should accelerate attempts to overcome the impediments we face with regard to effective AMS and IPC interventions.

Mechanisms of resistance

In *P. aeruginosa*, carbapenem resistance may emerge following sequential chromosomal mutations, which have the effect of altering permeability and simultaneously resulting in hyperexpression of MDR efflux (MEX) pumps [5,9▪] (Table 1). *P. aeruginosa* has the dubious distinction of potentially harbouring the most efflux pump genes ($n=39$) of all GNB, and the best studied carbapenem efflux determinants are MexAB-OprM and MexEF-OprN [13,14].

A critical feature of these is that different antibiotic classes may be substrates for a single MEX pump [14] and that concurrent with hyperexpression of these MEX pumps, OprD mutants which cause in-vivo carbapenem resistance may be selected [5,9▪,14]. Spontaneous mutation with expression of resistance occurs at frequency of one in 10^{6-7} wild type organisms. This process may be accelerated by overuse of antibiotics with antipseudomonal activity such as the carbapenems, particularly if therapy is prolonged [15]. It is therefore not surprising, that prior carbapenem exposure has consistently been shown on multivariate analysis to be a significant risk factor for CRPA infections in the ICU [16,17].

An equally important mechanism of resistance, and a cause of multiple outbreaks globally, is the

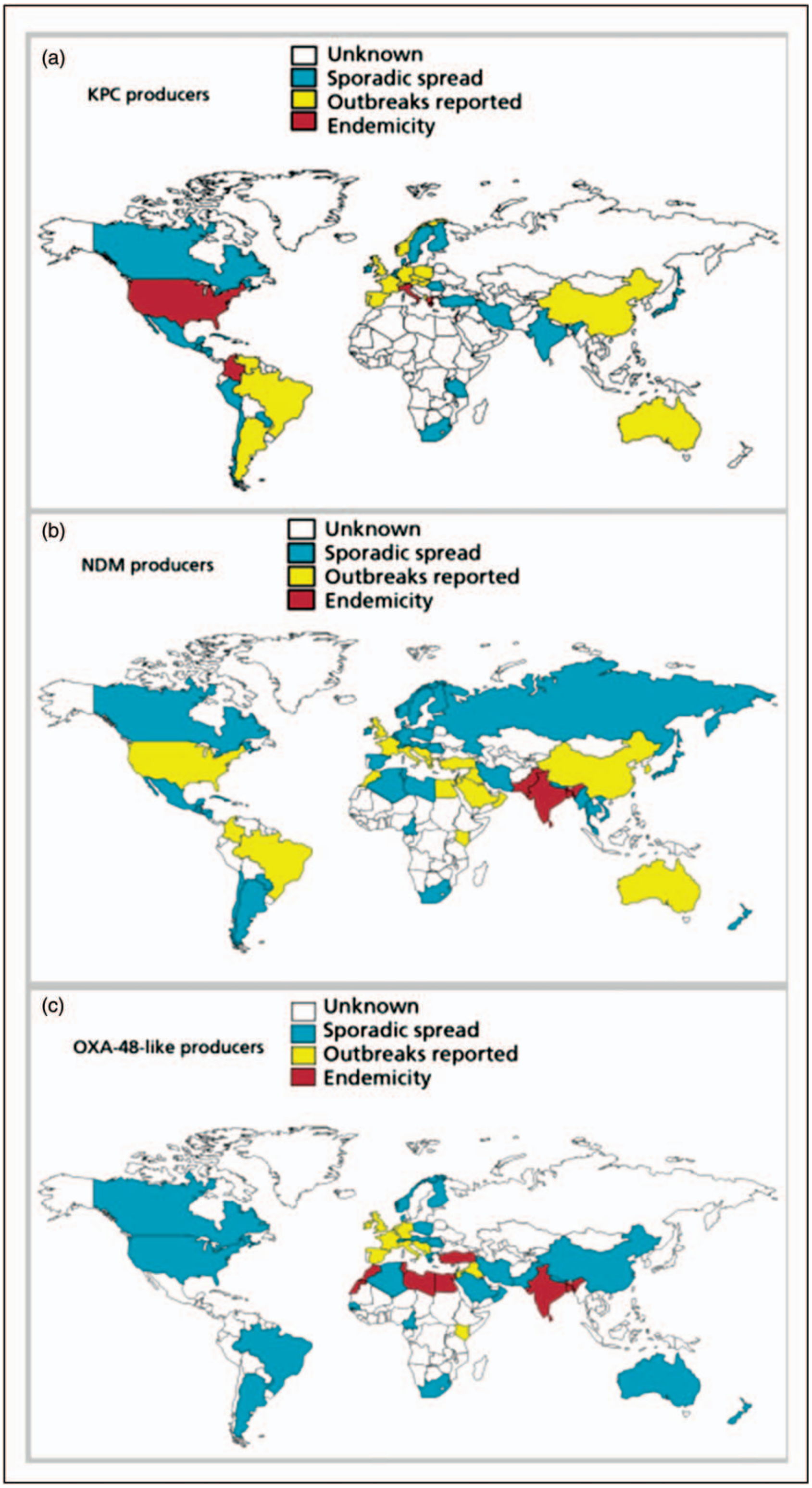

FIGURE 1. Global distribution of carbapenemase-producing Gram-negative bacilli. (a) *Klebsiella pneumoniae* carbapenemase producers in *Enterobacteriaceae* and *Pseudomonas aeruginosa*. (b) New Delhi metallo-β-lactamase producers *in Enterobacteriaceae* and *P. aeruginosa*. (c) Oxacillinase-48-like producers in *Enterobacteriaceae*. KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase-48. Reproduced with permission [49].

Table 1. Major mechanisms of carbapenem resistance in *Pseudomonas aeruginosa*

Mechanism	Genetic event	Determinant
β-lactamases:		
Class A. Serine carbapenemases	MGE	KPC[a]
Class B. Metallo-β-lactamase	MGE	VIM[b] ($n=24$ variants)
		IMP[b] ($n=33$ variants)
		SIM[a]
		GIM[a]
		KHM[a]
		SPM[a]
		AIM[a]
		SMB[a]
		TMB[a]
		FIM[a]
		SIM[a]
		DIM[a]
		NDM[a]
Class D. Oxacillinase-type	MGE	OXA-40[a]
		OXA-198[a]
Impermeability	CM	Loss of OprD
Efflux pumps	CM	MexAB-OprM
		MexEF-OprN
		MexCD-OprJ

CM, chromosomal mutation; KPC, *Klebsiella pneumoniae* carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.
[a]Geographically variable but less common or rare and sporadic.
[b]Most common.

ability of *P. aeruginosa* to acquire B-lactamases including MBLs and serine and OXA-type carbapenemases [5,14,18] (Table 1). Of these, VIM has been predominant and has played a pivotal role in the spread of CRPA globally.

P. aeruginosa demonstrates substantial genomic variability [9▪], although the more resistant strains including CRPA belong to a few widely distributed, disease causing, dominant clones. Ninety percentage of all antibiotic-resistant *P. aeruginosa* strains belong to one of three 'high-risk' clones viz. ST111, ST175 or ST235 [9▪].

Impact on outcome

The clinical and economic consequences of *P. aeruginosa* resistance were highlighted in a meta-analysis that demonstrated a more than two-fold increased risk of mortality with MDR, and a 24% increased risk with any resistant *P. aeruginosa* [19]. Subsequent meta-analyses specifically comparing carbapenem-resistant and carbapenem-susceptible *P. aeruginosa* BSIs, confirmed a significant excess in mortality with the former [11,20]. Similarly, in neutropaenic patients, the global prevalence of carbapenem resistance and the substantial increase in mortality in association with resistant relative to susceptible strains [odds ratio (OR) 4.89] was recently described [21].

CARBAPENEM-RESISTANT *ACINETOBACTER BAUMANNII*

A. baumannii primarily affects compromised long-term patients and is an important cause of HAIs with major outbreaks occurring globally. It is almost exclusively isolated from hospital environments where it persists for long periods and thus is notoriously difficult to eradicate once inveterated [22]. Infections are mostly acquired in ICU but are increasingly seen in the general wards and in long-term care facilities [23,24].

The organism is also known for its capacity to acquire resistance genes rapidly and for most to be extremely drug resistant (XDR). Prior colonization with CRAB and carbapenem use are significant risk factors for CRAB infections [23] with the risk for acquisition increasing four-fold following carbapenem exposure [24]. *A. baumannii* is accountable for more than 12% of hospital-acquired BSI in ICU [25], but wide geographic variations exist.

Resistance rates

Globally, resistance rates are increasing, with 40–70% of the isolates responsible for ICU-acquired infections, carbapenem resistant [5]. In the United States, the CRAB rates in central line-associated BSI and catheter-associated urinary tract infections are 47 and 64%, respectively [9▪,26]. In Europe in 2017, the mean CRAB and MDR rates in BSI were 33.4 and 28.4%, respectively [12], and in some countries, particularly those in Southern and Eastern Europe, carbapenem resistance and MDR is in excess of 80%. The prevalence of CRAB is similarly high in other parts of the world including South America (40–80%) and Asia (40–60%) [9▪].

Mechanisms of resistance

Similar to CRPA, *A. baumannii* possesses innate resistance mechanisms against multiple antibiotics and readily acquires more resistance mechanisms [5,8,9▪,25]. The most prevalent mechanism of carbapenem resistance is through carbapenem inactivation by carbapenemases, namely, the MBL and OXA-types [5,6,8,9▪]. Several of these occur, some with close geographic associations (Table 2).

Equally pertinent, *A. baumannii* also encodes for a high number of MEX genes [13] but only expression of the adeABC efflux pump system which is present in more than 80% of clinical isolates [27],

Table 2. Major mechanisms of carbapenem resistance in *Acinetobacter baumannii*

Mechanism	Acquisition	Determinant
Β-lactamase:		
Class A. Serine carbapenemases	MGE	KPC[a]
Class B. Metallo-β-lactamases	MGE	VIM (-1, -2, -3, -4, and -11) SIM-1 IMP (-1, -2, -4, -5, -6, -8, -10, -11, and -19) NDM (-1, -2)
Class D. Oxacillinase-type	MGE	OXA-23 cluster: (OXA-23, -27 and -49) OXA-24/40 cluster (OXA-25, -26, -40 and -72) OXA-58 OXA-51 cluster ($n = 14$ variants) OXA-48[a] OXA-235
	CM	High-level OXA-51
Impermeability	CM	Functional loss of porins CarO, Omp 33–36 and OprD homolog
Efflux pumps	CM	AdeABC
Altered penicillin-binding proteins	CM	Variable binding

CM, chromosomal mutation; KPC, *Klebsiella pneumoniae* carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.
[a]Rare.

and the combination with decreased permeability or with carbapenemases, leads to carbapenem resistance. The coexpression and synergy between resistance mechanisms is a common cause of high-level carbapenem, MDR and XDR [5,8,9▪,25].

Compared with *P. aeruginosa*, the *A. baumannii* population structure is clonal in nature, with eight international lineages (IC I–VIII) having been described [28]. The spread of most antibiotic resistant organisms has been shown to be associated with distinct epidemic clones that belong to these clonal lineages [22,28,29]. The dominance of these specific lineages is determined by the capacity of the *A. baumannii* pangenome to incorporate resistance determinants that support their ongoing adaptation to the hospital environment and to antibiotic pressure.

Impact on outcome

In a study of nosocomial pneumonia in 27 European ICUs, bacteraemia (primarily due to methicillin-resistant *Staphylococcus aureus* and *A. baumannii*) occurred in 14.6% of cases and was associated with prolonged ICU stay and increased mortality [30]. However, the attributable mortality due to CRAB remains controversial due to residual confounding factors (such as the severity of the underlying illness, the administration of inappropriate empirical antibiotics and inadequate sample sizes) [31]. Nevertheless, in a systematic review, patients with CRAB had a significantly higher risk of mortality and despite heterogeneity, the association remained significant in the pooled adjusted OR of 10 studies (OR 2.22) [31].

Furthermore, in a case–controlled study incorporating molecular techniques, infection with a specific CRAB clone may determine the prognosis of patients with BSI [32]. In a secondary analysis of a randomized controlled trial of patients with carbapenem-resistant, GNB infections treated with colistin or a colistin–meropenem combination, the lower mortality rates that occurred among patients with colistin resistant isolates (OR 0.285) may be explained by a loss of 'fitness' and virulence relative to the colistin susceptible strains [33].

CARBAPENEM-RESISTANT *ENTEROBACTERALES*

K. pneumoniae the most commonly encountered CPE is responsible for a dramatic increase in disease burden worldwide [4▪▪]. One of the challenges among hospitalized patients is the asymptomatic gastrointestinal carriage of CPE which precedes, and significantly increases, the risk of developing infections caused by these pathogens [34–36].

This is especially so, as was recently demonstrated, if patients concurrently receive an antibiotic [37▪]. In a long-term acute-care hospital (LTACH), colonized patients that received a carbapenem had an increased risk for a high relative abundance of KPC-producing *K. pneumoniae* in the gastrointestinal tract, which in turn was associated with an increased risk of KPC bacteraemia (relative risk 4.2) [37▪]. Complicating the impending CPE crisis, colonization is protracted, and may persist in more than 40% of patients for at least 1 year [35].

A recent systematic review to identify risk factors for CRE acquisition, showed that use of medical devices generated the highest pooled estimate (OR 5.09) followed by carbapenem use (OR 4.71) [38]. While this may direct and inform a bundled approach to prevention [38], another unexplored risk for CPE is disturbance of the gastrointestinal microbiome [2,37▪,39,40]. In this regard, innovative strategies that are required to ameliorate and restore colonization resistance, needed to be explored urgently [2,37▪]. One option is targeted bacteriophage therapy which has recently been shown to eradicate long-term CPE colonization safely [2,35].

Prevalence rates

The global epidemiology of CRE and CPE has not been systematically evaluated. The most comprehensive continental survey to date is the European Survey of Carbapenemase-Producing *Enterobacteriaceae* initiative [41▪]. The infection prevalence of CPE was shown to be 1.3 per 10 000 hospital admissions. Subsequent genomic analysis of carbapenemase producing *K. pneumoniae* established that the epidemic of carbapenem nonsusceptible *K. pneumoniae* in Europe is driven by the expansion of a small number of high-risk clones [42▪▪]. Of paramount importance, most were nosocomially acquired, intrahospital and interhospital spread was far more frequent within, rather than between, countries and that antibiotic use served as a major effect modifier.

In the United States, a reported incidence of 0.3–2.93 infections per 100 000 person-years with the highest rates occurring in LTACH, has been reported [43]. CRE pose a serious threat to immunocompromised hosts where, in endemic areas, carbapenem-resistant *K. pneumoniae* infections occur in 1–18% of solid organ transplant recipients, and similarly patients with hematologic malignancies represent 16–24% of all patients with CRE bacteraemia [44].

The prevalence of CRE infections in the community is largely unknown [45], but a recent review found that percentages range from 0.04 to 29.5% [46]. From a One Health perspective the occurrence of CRE also poses a risk for public health. Notably, a prevalence of less than 1% among livestock and companion animals in Europe, but 2–26% in Africa, and 1–15% in Asia [47], has been documented.

A system-wide molecular ecological study from Algeria confirmed that clonal expansion of *K. pneumoniae* occurred in different niches (e.g. human gastrointestinal tract, animal farms, food products and in wastewater treatment plants) due mainly to the spread of an epidemic plasmid [48▪]. The survey highlighted that *K. pneumoniae* and commensal *Escherichia coli* are potential reservoirs of carbapenemase genes, contributing to their dissemination and transfer to diverse bacteria among different sources.

Mechanisms of resistance

The most important mechanism of carbapenem resistance in the *Enterobacterales* order is the acquisition of plasmid mediated carbapenemases, specifically three of the four Ambler classes (Table 3). These are rapidly expanding globally (Fig. 1), are proliferating at an unprecedented rate, are distributed in many species of *Enterobacterales* but are dominated by *K. pneumoniae* [42▪▪].

While the different carbapenemases were previously typically associated with specific regions or countries [49] the geographical distributions are increasingly converging [50]. This evolving epidemiology may progressively complicate management and choice of new beta-lactam/beta-lactamase inhibitors, as an optimal antibiotic regimen might be difficult to attain in the presence of coproduction

Table 3. Major mechanisms of carbapenem resistance in *Enterobacterales*

Mechanism	Acquisition	Determinant
β-lactamases:		
Class A. Serine carbapenemases	MGE	KPC[a] ($n = 22$ variants) IMI (-1,-2) SME[b] GES[b,c] NMC-A[b] FRI-1[b] IMI-1[b] SFC[b] SHV-38[b]
Class B. Metallo-beta-lactamases	MGE	VIM[a] ($n = 46$ variants) NDM[a] ($n = 16$ variants) IMP ($n = 52$ variants) GIM-1[b] SIM[b] SPM[b]
Class C. Cephalosporinase	MGE	CMY-10[b]
Class D. Oxacillinase-type	MGE	OXA-48-like[a] ($n = 13$ variants)
Impermeability (porin lesions)	CM	ompK35 ompK36 ompC ompF ompK37

CM, chromosomal mutation; KPC, *Klebsiella pneumoniae* carbapenemase; MGE, mobile genetic element; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona-integrated metalloprotease.
[a]Most common.
[b]Geographically variable but less common or rare and sporadic.
[c]Low-level carbapenem hydrolysis.

of multiple resistance determinants [51,52]. The major epidemic high-risk international clones vary but mostly belong to ST11, ST15, ST101, ST147 and ST258, as well as their derivatives with ST258 the most global distribution [6,9■,39,42■■].

Carbapenem resistance may also emerge *in vivo* in extended-spectrum-β-lactamase or AmpC hyperproducing *Enterobacterales* spp. concurrent with mutation-derived outer-membrane porin lesions or loss [5].

Impact on outcome

The magnitude of the CPE burden is exemplified in recent data from the United States where it is estimated that CRE infections result in 26% mortality and cost hospitals $275 million annually [11]. In addition, a meta-analysis that compared serious CPE infections with those due to carbapenem-susceptible organisms, showed that there was a significant risk of excess mortality (OR 3.39) [53■].

A study on effect of carbapenem resistance on outcome of *Enterobacterales* BSIs in low and middle-income countries (PANORAMA) was recently published [54■■,55]. In this analysis, CRE BSI was associated with a 75% increased probability of in-hospital mortality, an almost 40% decreased probability of being discharged alive, and an increased length of hospital stay of 3.7 days.

CONCLUSION

Carbapenem-resistant GNB is increasing globally at an unimaginable rate and to an alarming extent. Collective efforts at the highest level have to be directed at the systematic evaluation of the global epidemiology across a One Health platform.

To inform a public health response, it has to include prevalence and incidence rates in addition to identifying reservoirs, transmission dynamics and antibiotic selection determinants. It will require unparalleled funding for global surveillance and molecular laboratory standardization including system-wide whole-genome sequencing.

To reduce the substantial excess mortality associated with carbapenem-resistant pathogens such as CPE, more than new antibiotics are required. Novel IPC management and decolonization strategies are essential if we are to avert 'our worst nightmare'.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
■■ of outstanding interest

1. Bassetti M, Giacobbe DR, Vena A, Brink A. Challenges and research priorities to progress the impact of antimicrobial stewardship. Drugs Context 2019; 8:212600.
2. Bassetti M, Poulakou G, Ruppe E, *et al.* Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med 2017; 43:1464–1475.
3. World Health Organization. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis. WHO; 2017; Available at: http://www.who.int/medicines/areas/rational_use/prioritization-of-pathogens/en/. [Accessed August 2019]
4. ■■ Cassini A, Högberg LD, Plachouras D, *et al.* Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019; 19:56–66.

Estimation of the burden of infections caused by antibiotic-resistant bacteria of public health concern in Europe, measured in number of cases, attributable deaths and disability-adjusted life-years. The first study to estimate the burden of all types of infections with antibiotic-resistant bacteria expressed in disability-adjusted life years and established carbapenemase-producing *Klebsiella pneumoniae* as the fastest growing resistance threat in Europe.

5. Ruppé E, Woerther PL, Barbier F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. Ann Intensive Care 2015; 5:21.
6. Diene SM, Rolain JM. Carbapenemase genes and genetic platforms in Gram-negative bacilli: *Enterobacteriaceae*, *Pseudomonas* and *Acinetobacter* species. Clin Microbiol Infect 2014; 20:831–838.
7. Bassetti M, Peghin M, Vena A, Giacobbe DR. Treatment of infections due to MDR Gram-negative bacteria. Front Med 2019; 6:74.
8. Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. Curr Opin Microbiol 2017; 39:106–112.
9. ■ Eichenberger EM, Thaden JT. Epidemiology and mechanisms of resistance of extensively drug resistant Gram-negative bacteria. Antibiotics 2019; 8:37.

A comprehensive concise updated review of mechanisms and epidemiology of antibiotic resistance in carbapenem-resistant *Enterobacterales* (CRE), extremely drug resistant (XDR) *Pseudomonas aeruginosa* and XDR *Acinetobacter baumannii.*

10. Shortridge D, Gales AC, Streit JM, *et al.* Geographic and temporal patterns of antimicrobial resistance in *Pseudomonas aeruginosa* over 20 years from the SENTRY antimicrobial surveillance program. Open Forum Infect Dis 2019; 6(S1):S63–S68.
11. McCann E, Srinivasan A, DeRyke A, *et al.* Carbapenem-nonsusceptible Gram-negative pathogens in ICU and non-ICU settings in US hospitals in 2017: a multicenter study. Open Forum Infect Dis 2018; 5:1–7.
12. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe. Annual report of the European Antimicrobial Resistance Surveillance Network (EARSNet) 2017. 2017. https://ecdc.europa.eu/sites/portal/files/documents/EARS-Net-report-2017-update-jan-2019.pdf. [Last accessed 23 August 2019].
13. Brooks LE, Ul-Hasan S, Chan BK, Sistrom MJ. Quantifying the evolutionary conservation of genes encoding multidrug efflux pumps in the ESKAPE pathogens to identify antimicrobial drug targets. mSystems 2018; 3:e00024-18.
14. Bassetti M, Vena A, Croxatto A, *et al.* How to manage *Pseudomonas aeruginosa* infections. Drugs Context 2018; 7:212527.
15. Paramythiotou E, Lucet JC, Timsit JF, *et al.* Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: role of antibiotics with antipseudomonal activity. Clin Infect Dis 2004; 38:670–677.
16. Tsao LH, Hsin CY, Liu HY, *et al.* Risk factors for healthcare-associated infection caused by carbapenem-resistant *Pseudomonas aeruginosa*. J Microbiol Immunol Infect 2018; 51:359–366.
17. Coppry M, Jeanne-Leroyer C, Noize P, *et al.* Antibiotics associated with acquisition of carbapenem-resistant *Pseudomonas aeruginosa* in ICUs: a multicentre nested case–case-control study. J Antimicrob Chemother 2019; 74:503–510.
18. Karampatakis T, Antachopoulos C, Tsakris A, Roilides E. Molecular epidemiology of carbapenem-resistant *Pseudomonas aeruginosa* in an endemic area: comparison with global data. Eur J Clin Microbiol Infect Dis 2018; 37:1211–1220.

19. Nathwani D, Raman G, Sulham K, *et al.* Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis. Antimicrob Resist Infect Control 2014; 3:32.
20. Zhang Y, Chen XL, Huang AW, *et al.* Mortality attributable to carbapenem-resistant *Pseudomonas aeruginosa* bacteremia: a meta-analysis of cohort studies. Emerg Microbes Infect 2016; 5:e27.
21. Righi E, Peri AM, Harris PN, *et al.* Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis. J Antimicrob Chemother 2017; 72:668–677.
22. European Centre for Disease Prevention and Control. Rapid risk assessment: carbapenem-resistant Acinetobacter baumannii in healthcare settings – 8 December 2016. Stockholm: ECDC; 2016; http://ecdc.europa.eu/publications-data/rapidrisk-assessment-carbapenem-resistant-acinetobacter-baumanniihealthcare. [Last accessed 24 August 2019]
23. Bassetti M, Carnelutti A, Peghin M. Patient specific risk stratification for antimicrobial resistance and possible treatment strategies in Gram-negative bacterial infections. Expert Rev Anti Infect Ther 2017; 15:55–65.
24. Munoz-Price LS, Rosa R, Castro JG, *et al.* Evaluating the impact of antibiotic exposures as time-dependent variables on the acquisition of carbapenem-resistant *Acinetobacter baumannii*. Crit Care Med 2016; 44:e949–e956.
25. Garnacho-Monteroa J, Timsit JF. Managing *Acinetobacter baumannii* infections. Curr Opin Infect Dis 2019; 32:69–76.
26. Weiner LM, Webb AK, Limbago B, *et al.* Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention. Infect Control Hosp Epidemiol 2016; 37:1288–1301.
27. Yoon EJ, Courvalin P, Grillot-Courvalin C. RND-type efflux pumps in multidrug-resistant clinical isolates of *Acinetobacter baumannii*: major role for AdeABC overexpression and AdeRS mutations. Antimicrob Agents Chemother 2013; 57:2989–2995.
28. Zarrilli R, Pournaras S, Giannouli M, Tsakris A. Global evolution of multidrug-resistant *Acinetobacter baumannii* clonal lineages. Int J Antimicrob Agents 2013; 41:11–19.
29. Matsui M, Suzuki M, Suzuki M, *et al.* Distribution and molecular characterization of *Acinetobacter baumannii* International Clone II lineage in Japan. Antimicrob Agents Chemother 2018; 62:e02190-17.
30. Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. Eur J Clin Microbiol Infect Dis 2017; 36:1999–2006.
31. Lemos EV, de la Hoz FP, Einarson TR, *et al.* Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. Clin Microbiol Infect 2014; 20:416–423.
32. Nutman A, Glick R, Temkin E, *et al.* A case–control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. Clin Microbiol Infect 2014; 20:O1028–O1034.
33. Dickstein Y, Lellouche J, Amar MBD, *et al.* Treatment outcomes of colistin- and carbapenem-resistant *Acinetobacter baumannii* infections: an exploratory subgroup analysis of a randomized clinical trial. Clin Infect Dis 2019; 69:769–776.
34. Tischendorf J, Almeida de Avila R, Safdar NS. Risk of infection following colonization with carbapenem-resistant *Enterobacteriaceae*: a systematic review. Am J Infect Control 2016; 44:539–543.
35. Corbellino M, Kieffer N, Kutateladze M, *et al.* Eradication of a multidrug resistant, carbapenemase-producing *Klebsiella pneumoniae* isolate following oral and intra-rectal therapy with a custom-made, lytic bacteriophage preparation. Clin Infect Dis 2019; pii: ciz782. doi: 10.1093/cid/ciz782. [Epub ahead of print]
36. Tamma PD, Kazmi A, Bergman Y, *et al.* The likelihood of developing a carbapenem-resistant *Enterobacteriaceae* infection during a hospital stay. Antimicrob Agents Chemother 2019; 63; e00757-19.
37. ▪ Shimasaki T, Seekatz A, Bassis C, *et al.* Increased relative abundance of *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* within the gut microbiota is associated with risk of bloodstream infection in long-term acute care hospital patients. Clin Infect Dis 2019; 68:2053–2059.
Study involving long-term acute-care hospital patients, 16S ribosomal RNA gene sequencing and the *K. pneumoniae* carbapenemase (KPC) resistome in the gut. Carbapenem receipt was associated with increased hazard for high relative abundance of KPC, which in turn increased relative risk of 4.2 for KPC bloodstream infections (BSIs).
38. van Loon K, Voor in 't holt AF, Vos MC. A systematic review and meta-analyses of the clinical epidemiology of carbapenem resistant *Enterobacteriaceae*. Antimicrob Agents Chemother 2017; 62:e01730-17.
39. Van Duin D, Doi Y. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence 2017; 8:460–469.
40. Caballero S, Carter R, Ke X, *et al.* Distinct but spatially overlapping intestinal niches for vancomycin-resistant *Enterococcus faecium* and carbapenem-resistant *Klebsiella pneumoniae*. PLoS Pathog 2015; 11:e1005132.
41. ▪ Grundmann H, Glasner C, Albiger B, *et al.* Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis 2017; 17:153–163.
The most comprehensive, prospective continental CRE survey to date representing a model for other country-wide or continental surveillance programs.
42. ▪▪ David S, Reuter S, Harris SR, *et al.* Epidemic of carbapenem-resistant *Klebsiella pneumoniae* in Europe is driven by nosocomial spread. Nat Microbiol 2019; doi: 10.1038/s41564-019-0492-8. [Epub ahead of print]
Subsequent genomic analysis of carbapenemase producing *K. pneumoniae* recruited from the European Survey of Carbapenemase-Producing Enterobacteriaceae survey established that the epidemic of carbapenem nonsusceptible *K. pneumoniae* in Europe is driven by the expansion of a small number of high-risk clones (ST11, 15, 101, 258/512). Most acquisition occurred nosocomially and interhospital spread was common rather than intercountry spread.
43. Livorsi DJ, Chorazy ML, Schweizer ML, *et al.* A systematic review of the epidemiology of carbapenem-resistant *Enterobacteriaceae* in the United States. Antimicrob Resist Infect Control 2018; 7:55.
44. Poucha SM, Satlin MJ. Carbapenem-resistant *Enterobacteriaceae* in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. Virulence 2017; 8:391–402.
45. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. J Infect Dis 2017; 215:S28–S33.
46. Kelly AM, Mathema B, Larson EL. Carbapenem-resistant *Enterobacteriaceae* in the community: a scoping review. Int J Antimicrob Agents 2017; 50:127–134.
47. Köck R, Daniels-Haardt I, Becker K, *et al.* Carbapenem-resistant *Enterobacteriaceae* in wildlife, food-producing, and companion animals: a systematic review. Clin Microbiol Infect 2018; 24:1241–1250.
48. ▪ Mairi A, Pantel A, Ousalem F, *et al.* OXA-48-producing *Enterobacterales* in different ecological niches in Algeria: clonal expansion, plasmid characteristics and virulence traits. J Antimicrob Chemother 2019; 74:1848–1855.
A country-wide molecular survey of oxacillinase-48-producing *Enterobacterales* in different ecological niches (human carriage, animal farms, wild animals, pets, food products, aquatic environment and wastewater treatment plants) and elucidates clonal expansion, plasmid characteristics and virulence traits. Existence of reservoirs contributing to the dissemination and transfer of this gene to diverse bacteria among different sources.
49. Bonomo RA, Burd EM, Conly J, *et al.* Carbapenemase-producing organisms: a global scourge. Clin Infect Dis 2018; 66:1290–1297.
50. Park SC, Wailan AM, Barry KE, *et al.* Managing all the genotypic knowledge: approach to a septic patient colonized by different *Enterobacteriales* with unique carbapenemases. Antimicrob Agents Chemother 2019; 63:e00029-19.
51. Stewart A, Harris P, Henderson A, Paterson D. Treatment of infections by OXA-48-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 2018; 62:e01195-18.
52. Chen CM, Guo MK, Ke SC, *et al.* Emergence and nosocomial spread of ST11 carbapenem-resistant *Klebsiella pneumoniae* co-producing OXA-48 and KPC-2 in a regional hospital in Taiwan. J Med Microbiol 2018; 67:957–964.
53. ▪ Martin A, Fahrbach K, Zhao Q, Lodise T. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to *Enterobacteriaceae*: results of a systematic literature review and meta-analysis. Open Forum Infect Dis 2018; 5:ofy150.
A new systematic literature review evaluating outcomes in hospitalized patients with CRE infections from a blood, urinary, pulmonary or intra-abdominal source. Meta-analysis for mortality performed on 22 studies and confirming risk for excess mortality increases more than three-fold.
54. ▪▪ Stewardson AJ, Marimuthu K, Sengupta S, *et al.* Effect of carbapenem resistance on outcomes of bloodstream infection caused by *Enterobacteriaceae* in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. Lancet Infect Dis 2019; 19:601–610.
For the first-time comprehensive clinical and microbiological outcome of BSIs caused by CRE in patients from low and middle-income countries (16 hospitals in 10 countries). Carbapenem resistance was associated with a profound impact on outcomes including mortality.
55. Perez F, Bonomo RA. Carbapenem-resistant *Enterobacteriaceae*: global action required. Lancet Infect Dis 2019; 19:561–562.