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Antimicrobial resistance in nephrology

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Abstract

The prevalence of antimicrobial resistance among many common bacterial pathogens is increasing. The emergence and global dissemination of these antibiotic-resistant bacteria (ARB) is fuelled by antibiotic selection pressure, inter-organism transmission of resistance determinants, suboptimal infection prevention practices and increasing ease and frequency of international travel, among other factors. Patients with chronic kidney disease, particularly those with end-stage renal disease who require dialysis and/or kidney transplantation, have some of the highest rates of colonization and infection with ARB worldwide. These ARB include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp. and several multidrug-resistant Gram-negative organisms. Antimicrobial resistance limits treatment options and increases the risk of infection-related morbidity and mortality. Several new antibiotic agents with activity against some of the most common ARB have been developed, but resistance to these agents is already emerging and highlights the dire need for new treatment options as well as consistent implementation and improvement of basic infection prevention practices. Clinicians involved in the care of patients with renal disease must be familiar with the local epidemiology of ARB, remain vigilant for the emergence of novel resistance patterns and adhere strictly to practices proven to prevent transmission of ARB and other pathogens.

Antibiotic resistance among common human bacterial pathogens is on the rise worldwide and is estimated to cause at least 700,000 deaths every year[1]. Compared with infections caused by antibiotic-susceptible bacteria of the same species, those caused by antibiotic-resistant bacteria (ARB) are associated with significantly higher mortality, prolonged hospitalization and greater health-care costs and economic burden. These poor outcomes are thought to be due to the severity of the underlying illness, delays in the initiation of effective

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antimicrobial therapy and/or toxic effects associated with some of the antibiotics used to treat infections caused by ARB. Crucially, optimal antimicrobial treatment regimens have not been defined for many ARB and treatment options are extremely limited for some. The emergence of clinical isolates of common pathogens (such as *Klebsiella pneumoniae* and *Acinetobacter* spp.) that are resistant to all currently available antimicrobial agents has caused some experts to predict a 'post-antibiotic' era[2]. In fact, some have predicted that infection due to ARB will be the most common cause of death worldwide by the year 2050, causing up to 10 million deaths annually[1].

Currently, substantial variability exists in clinical practice and the scientific literature with regard to the use of terms such as 'multidrug resistant' (MDR) to describe pathogens that are resistant to multiple antimicrobial agents. This inconsistency hinders the direct comparison of the epidemiology and clinical outcomes associated with ARB that are reported for different populations, and makes it challenging to accurately describe the global burden of specific antimicrobial resistance profiles. To address this important issue, an international panel of experts proposed standardized definitions for several common ARB on the basis of the number of specific antimicrobial categories to which the pathogen demonstrates non-susceptibility[3]. The defined terms include MDR, extensively drug resistant and pandrug resistant. However, these terms and definitions have not yet been widely adopted in the literature.

Infection is second only to cardiovascular disease as the leading cause of death among patients with end-stage renal disease (ESRD) and those who have undergone renal transplantation[4]. The growing problem of antimicrobial resistance is particularly relevant to patients with chronic kidney disease (CKD), as they are disproportionally affected by antimicrobial resistance when compared with the general population. Chronic dialysis, the presence of indwelling vascular and urinary catheters, renal transplantation, treatment with antibiotics and other health-care exposures have been identified as factors associated with an increased risk of colonization and infection with ARB[5]. However, data are somewhat limited regarding the prevalence of ARB colonization and infection among patients with CKD. Of note, the prevalence of many ARB varies substantially, both globally and regionally. Therefore, clinicians should be familiar with the local epidemiology of antimicrobial resistance and remain vigilant for the emergence of new resistance mechanisms and phenotypes within their region of practice.

Antimicrobial agents exert their antibacterial effect through various modes of action (FIG. 1a), but some of these microorganisms have, in turn, developed a variety of resistance mechanisms that can counter the effects of those drugs (FIG. 1b). These mechanisms, which vary by drug and organism, include the enzymatic destruction of the antibiotic, alteration of the antibiotic's target site, and seclusion or elimination of the antibiotic from the bacterial cell[6]. Acquired resistance refers to a resistance determinant that is not inherent to an organism but is attained, for example, through bacterial conjugation, mutation, transformation and transduction. Of note, bacteria often possess more than one mechanism of resistance. In this Review, we discuss the epidemiology, prevention strategies and treatment of infections caused by ARB, as well as future directions in the fight against antimicrobial resistance.

Gram-positive organisms

Staphylococcus aureus

β-Lactam antibiotics interrupt the formation of the bacterial cell wall by binding to penicillin-binding proteins (PBPs) involved in peptidoglycan synthesis, resulting in cell death. The development of resistance to β-lactam antibiotics by *Staphylococcus aureus* has been an ongoing clinical challenge since penicillin was first introduced into clinical use[7,8]. The resistance of *S. aureus* to penicillin was initially due to the production of penicillinases, which are β-lactamases that can degrade penicillin in the extracellular space by hydrolysing the β-lactam ring, a core structural component of β-lactam antibiotics (FIG. 1b). On the other hand, resistance to methicillin and other anti-staphylococcal penicillins, which were developed in response to the emergence and dissemination of penicillin-resistant strains, is due to the production of an altered PBP (PBP2a), encoded by *mecA*[6] (FIG. 1b). The production of PBP2a not only results in resistance to methicillin but also renders bacteria resistant to all other β-lactam antibiotics, which bind to PBP2a, with the exception of the more recently developed cephalosporin, ceftaroline, which has a much higher binding affinity for PBP2a[9]. Methicillin-resistant *S. aureus* (MRSA) was initially regarded as a health-care-associated pathogen, but community-associated strains of MRSA have since emerged and spread in many parts of the world since the 1990s, complicating its epidemiology[10]. Although data from some national surveillance programmes, including those in the United States and Europe, suggest that the rates of MRSA infection are declining in some areas, the global burden of MRSA remains substantial, with rates of resistance above 80% in some countries[2,11,12].

Compared with the general population, patients with renal disease are more likely to be affected by infection with both methicillin-susceptible and methicillin-resistant strains of *S. aureus*, which is associated with substantial morbidity and mortality. Reported rates of MRSA colonization in patients receiving haemodialysis range from 2.3% to 27.3%[13], and up to 35% of colonized patients subsequently develop MRSA infections within 1 year[14]. Data from the US Centers for Disease Control and Prevention (CDC) showed that invasive MRSA infections affect more than 4 out of every 100 dialysis patients, which is more than 100 times the incidence observed in the general population[15]. Among kidney transplant recipients, MRSA colonization ranges from 1.2% to 12.5%[16], and pre-transplant colonization with MRSA has been identified as an independent risk factor for graft failure[17].

The glycopeptide vancomycin, which inhibits bacterial cell wall synthesis by preventing peptidoglycan elongation and crosslinking, has long served as a first-line option for the treatment of serious MRSA infections. Thus, the emergence of strains with reduced susceptibility and even high-level resistance to vancomycin is concerning. The first case of infection with vancomycin-intermediate *S. aureus* (VISA) was reported in 1997 (REF.[18]), and since then, the number of new cases reported in the United States and around the world has continued to increase[19]. Heteroresistant or heterogeneous ViSA (hVISA) has also been implicated in cases of vancomycin treatment failure and persistent infection[20]. The reduced susceptibility to vancomycin in both VISA and hVISA strains results from thickening of the cell wall and mutations in or downregulation of a number of genes, including the accessory

gene regulator (*agr*) operon[21]; these changes are thought to be driven by prolonged exposure to vancomycin[22,23]. *S. aureus* with full resistance to vancomycin (VRSA) has also been described and was first reported in the United States in 2002, notably in a patient with multiple comorbidities that included haemodialysis-requiring ESRD[24]. Since 2002, 14 persons with VRSA colonization and/or infection have been identified in the United States; several of these patients were also affected by CKD[25]. Among the US isolates, the MRSA strain developed resistance to vancomycin by acquiring the *vanA* gene cluster from vancomycin-resistant *Enterococcus* (VRE) (see Enterococcus section below). Additional cases of VRSA have been sporadically reported around the world, including in Portugal, Iran, India and Pakistan[26,27]. In addition to dialysis, common risk factors for VRSA include prolonged exposure to health-care settings, previous treatment with vancomycin, chronic skin wounds and co-colonization with MRSA and VRE[28]. Thus far, VRSA is rare and the clinical impact of MRSA remains substantially higher.

Enterococcus *species*

Among the enterococcal species, *Enterococcus faecalis* and *Enterococcus faecium* are the most common human pathogens[29]. In the 1980s, acquired vancomycin resistance emerged in health-care-associated enterococcal strains, particularly *E. faecium*[29]. This resistance is due to the acquisition of gene clusters, which include genes such as *vanA* and *vanB,* that lead to the synthesis of an altered cell wall terminal peptide, d-alanyl-d-lactate, that replaces the normal d-alanyl-d-alanine peptide and prevents the binding of vancomycin[30] (FIG. 1b). The global prevalence of VRE varies widely[31] (FIG. 2). As with MRSA, VRE colonization and infection are relatively common among patients with CKD. Studies of patients on dialysis from around the world show that rates of VRE colonization range from 2.8% to 10.8%; previous antibiotic use and recent hospitalization are factors associated with colonization[32]. Among kidney transplant recipients, VRE colonization was detected in 13.6% of patients at a transplant centre in Brazil[33]. *Enterococcus* spp. were the second most common pathogen recovered from patients with bloodstream infections in US haemodialysis facilities in 2014 and 11.4% of those isolates were resistant to vancomycin[34]. In the early 2000s, the introduction of linezolid, an oxazolidinone antibiotic, and daptomycin, a lipopeptide antibiotic, offered greatly needed alternatives for the treatment of VRE and MRSA infections (FIG. 1a). However, reports of treatment failure with linezolid and daptomycin, as well as demonstration of in vitro resistance, are increasingly frequent, which is of particular concern for patients with CKD, in whom MRSA and VRE infections are common. VRE isolates resistant to both linezolid and daptomycin have also been described[35]. Linezolid inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, which includes the 5S and 23S rRNA subunits. Resistance to linezolid is thought to result from the cumulative effect of multiple mutations in 23S rRNA genes and has been associated with prolonged use of this antibiotic[36]. Although resistance is well described, one study reported that the rates of resistance detected in a large surveillance programme that involved 33 countries, excluding the United States, remained less than 1%[37]. Daptomycin penetrates the bacterial cell wall and interacts with the cell membrane phospholipid phosphatidylglycerol, which allows it to disrupt cell division and cause membrane depolarization. The Daptomycin Surveillance Programme Worldwide reported that daptomycin resistance across all geographic regions remained extremely low in both staphylococci (0.05% for *S. aureus*) and

enterococci (0.18% for *E. faecium*) clinical isolates collected between 2005 and 2012 (REF. [38]). However, daptomycin resistance in enterococci is increasing[39] owing to genetic mutations that cause stepwise adaptive changes in the physiology of the bacterial cell wall and cytoplasmic membrane[40]. Although resistance can emerge after prolonged daptomycin exposure, it has also been reported in patients not previously treated with daptomycin[41]. In fact, resistance can also be associated with vancomycin exposure and is thought to be caused by an adaptive thickening of the cell wall, which leads to reduced susceptibility to both daptomycin and vancomycin[40]. This risk factor may be particularly relevant to patients with ESRD as they have fairly high rates of exposure to vancomycin.

Gram-negative organisms

Despite the lack of large epidemiological studies of colonization and infection with antimicrobial-resistant Gram-negative organisms in patients with CKD, the frequent exposure of these patients to health-care settings and antibiotics increases their risk of colonization with these ARB. In fact, available data suggest that these organisms are relatively common among dialysis patients. One prospective study conducted in an ambulatory haemodialysis facility in the United States showed that 28% of patients were colonized with a Gram-negative organism resistant to at least three of six antimicrobial agents tested. An additional 20% of patients acquired one of these MDR Gram-negative pathogens during a 6-month follow-up period[42].

Enterobacteriaceae

The Enterobacteriaceae family comprises several bacterial genera, including *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp., all of which have important roles in community-associated and health-care-associated infections. Antimicrobial resistance among the Enterobacteriaceae continues to evolve as new mechanisms of resistance emerge, which present substantial patient safety concerns and therapeutic challenges[43,44]. In addition to nosocomial infections and outbreaks caused by MDR Enterobacteriaceae, there is a growing number of reports of MDR Enterobacteriaceae in the community. Resistant organisms have been isolated from rivers, sewage, wild animals, food-producing animals and companion animals[45–47]. The following sections discuss some of the most common and concerning resistance determinants among the Enterobacteriaceae.

Extended-spectrum β-lactamases.—Extended-spectrum β-lactamases (ESBLs) are a heterogeneous family of primarily plasmid-mediated enzymes that inactivate β-lactam antibiotics by cleaving the β-lactam ring; common ESBLs include the TEM, SHV and CTX-M enzyme families. These enzymes confer resistance to penicillins and many cephalosporins including oxyimino-β-lactams (for example, cefotaxime, ceftazidime and ceftriaxone) but do not act against cephamycins or carbapenems, which include cefoxitin and meropenem, respectively. ESBLs are generally susceptible to β-lactamase inhibitors in vitro. However, a randomized trial reported in 2018 found that treatment with piperacillin–tazobactam, a β-lactam–β-lactamase inhibitor combination antibiotic, did not result in non-inferior 30-day mortality compared with the use of meropenem for the treatment of patients with ceftriaxone-resistant but piperacillin–tazobactam-susceptible *E. coli* or *K. pneumoniae*

bloodstream infection[48]. Although approximately 16% of the study participants had moderate or severe renal dysfunction, the study did not specifically provide outcome data for patients with ESRD. Community and hospital-acquired ESBL-producing organisms are globally widespread and are a growing problem, particularly in developing countries[49] (FIG. 3).

AmpC β-lactamases.—Similar to ESBLs, AmpC β-lactamases are enzymes that lead to oxyimino-β-lactam resistance[50]. However, in contrast to ESBLs, AmpC enzymes hydrolyse cephamycins and are not inhibited by most β-lactamase inhibitors. 'SPICE' organisms (that is, *Serratia*, *Providencia*, indole-positive *Proteus*, *Citrobacter* and *Enterobacter* spp.) are the primary producers of AmpC enzymes, although they are also found in other Enterobacteriaceae and several other Gram-negative organisms[50]. In most Enterobacteriaceae, AmpC enzymes are not constitutively expressed but their expression is induced by exposure to β-lactam antibiotics, which can thus create resistance in an apparently susceptible isolate following exposure to β-lactams. This particular feature of AmpC enzyme expression raises many challenges in the laboratory detection of AmpC-producing organisms. For example, whereas an isolate that is shown to be resistant to cefoxitin and oxyimino-β-lactams in vitro is likely to be an AmpC-producing organism, strains in which the AmpC enzyme can be produced but have not yet been induced often test as susceptible to third-generation cephalosporins. Thus, an organism that appears to be susceptible to a third-generation cephalosporin might quickly become resistant to that drug during the course of therapy and lead to treatment failure.

AmpC genes are most commonly encoded in bacterial chromosomes but, since their discovery in 1989, the prevalence of plasmid-mediated *AmpC* genes has risen around the world, increasing the epidemiological risk of transmission of this resistance determinant among and between different bacterial species[50]. In addition to previous exposure to β-lactam antibiotics[51], other potential risk factors for the acquisition of AmpC β-lactamase-producing organisms include the presence of external biliary or urinary drains, anatomic urinary abnormalities, urinary tract infection (UTI) in the past year and organ transplantation.

Carbapenemases.—In the past 30 years, several classes of carbapenem-hydrolysing β-lactamases, also known as carbapenemases, have emerged (FIG. 4). Most carbapenemases hydrolyse all β-lactam antibiotics and they are not generally inactivated by β-lactamase inhibitors. In addition, carbapenemase-producing organisms usually carry determinants of resistance to other antimicrobial drug classes, which renders these organisms resistant to most antibiotics. In the United States, *K. pneumoniae* carbapenemases (KPCs) are the most commonly encountered carbapenemases among Enterobacteriaceae isolates. Although first discovered in *K. pneumoniae*, the *blaKPC* gene, which encodes these Ambler class A serine carbapenemases, is found on plasmids that are transmissible from *Klebsiella* to other genera. Following the first reported case of KPC-producing Enterobacteriaceae in North Carolina in 1996 (REF.[52]), new cases have been reported from nearly every state in the United States and around the globe. Plasmid-mediated Ambler class B metallo-β-lactamases (MBLs), named for their dependence on zinc for the hydrolysis of β-lactams, were first reported in

Japan in 1991 (REF.[53]) but have since become a worldwide concern. Of the MBLs, the New Delhi MBL (NDM) has gained attention owing to the mobility of its encoding gene and its complex epidemiology[54] – whereas KPC remains largely associated with health-care exposure, NDM is also present in community-associated strains. Other MBLs identified among Enterobacteriaceae include active on imipenem MBL (IMP) and Verona integron-encoded MBL (VIM). The Ambler class D carbapenemases, such as oxacillinase-type carbapenem-hydrolysing β-lactamase 48 (OXA-48), are most commonly found in the Middle East and North Africa[55] (FIG. 4). Although substantial geographic variability exists in the prevalence of the various carbapenemases[55], frequent international travel, transfers between health-care facilities and 'medical tourism' have increased the rapidity by which these and other MDR organisms are globally disseminated[56].

Although carbapenemase-producing Enterobacteriaceae (CPE) are less prevalent than ESBL and AmpC-producing Enterobacteriaceae in most geographic regions, they have become a substantial worldwide public health concern as treatment options for infections with CPE are severely limited and these infections are associated with substantial morbidity and mortality. On the basis of data from 2013, the CDC estimated that carbapenem-resistant Enterobacteriaceae (CRE) are responsible for 7,900 infections and 520 deaths in the United States each year[57]. Moreover, in 2014, 10.9% of central-line associated bloodstream infections caused by *Klebsiella* spp., 1.9% of those caused by *E. coli* and 3.4% of those caused by *Enterobacter* spp., were resistant to carbapenems[58]. The European Centre for Disease Prevention and Control (ECDC) reported that in 2017, 7.2% of invasive *K. pneumoniae* isolates identified in 30 European countries were carbapenem resistant[11]. On the other hand, data from 703 intensive care units in developing countries showed that between 2010 and 2015 carbapenem resistance was detected in 43% of *K. pneumoniae* bloodstream isolates; the report included data from countries in Latin America, Europe, the eastern Mediterranean, Southeast Asia and the western Pacific that participate in the International Nosocomial Infection Control Consortium (INICC)[12]. It should be noted that not all carbapenem resistance among Gram-negative organisms, including Enterobacteriaceae, is due to the production of carbapenemases. For example, a carbapenemase was detected in only 32% of more than 4,000 CRE isolates submitted to the CDC for testing in 2017 (REF.[56]). Other mechanisms of carbapenem resistance include AmpC hyperproduction in combination with porin mutations and drug efflux pumps (FIG. 1b). As with other resistance mechanisms, the use of broad-spectrum antibiotics and prolonged antibiotic exposure are risk factors for CPE and other CRE; however, they are not essential[55]. Other factors associated with CRE colonization and infection include prolonged hospitalization, organ transplantation, use of immunosuppressive therapies and indwelling urinary or vascular catheters.

Other mechanisms of resistance.—Quinolone antibiotics inhibit bacterial DNA synthesis by interacting with DNA gyrase and topoisomerase IV, which modulate the topology of DNA during replication[59]. However, quinolone resistance among clinical isolates of Enterobacteriaceae is increasingly common. Indeed, fluoroquinolone non-susceptibility was detected in 34% of the nearly 300,000 urinary tract *E. coli* isolates identified by the US Veterans Affairs Health Care System between 2009 and 2013 (REF.[60]).

Resistance commonly occurs owing to chromosomal mutations in genes such as *gyrA* and *parC*, which encode the quinolone targets. In addition, downregulation of porin channels, chromosomal mutations in the genes that encode porin proteins and upregulation of chromosomally encoded drug efflux pumps can result in quinolone resistance[59] (FIG. 1b). Plasmid-encoded genes that mediate resistance include *qnr* genes, which encode proteins that protect DNA gyrase and topoisomerase IV from the action of quinolones, as well as genes that encode drug efflux pumps.

Aminoglycoside resistance, which can be either intrinsic or acquired, is typically mediated by aminoglycoside-modifying enzymes[61]. Of note, cross-resistance between different aminoglycoside antibiotics is often incomplete and in vitro testing for each individual agent is typically recommended[62]. In the case of acquired aminoglycoside resistance, the modifying enzymes are encoded on plasmids that might also include genes for determinants of resistance to other antibiotics, such as KPCs or ESBLs[63], and the risk factors that predispose to acquisition of resistance to other antibiotics apply similarly to aminoglycosides. However, unlike other antibiotic classes, development of resistance while on therapy is rare for aminoglycosides and overall rates of resistance have remained stable and relatively low[61]. Despite their known risk of nephrotoxicity, which may be particularly problematic for patients with underlying renal disease, the use of polymyxins such as polymyxin B and polymyxin E (also known as colistin) has increased in recent years owing to their activity against many Enterobacteriaceae isolates, including CRE that are resistant to multiple antibiotic classes[64]. Unfortunately, resistance to the polymyxins is also emerging and is an independent risk factor for mortality[65]. Resistance is thought to be secondary to post-translational modifications of the polymyxin binding target, the lipid A component of outer membrane lipopolysaccharides[66]. Several studies have identified polymyxin exposure as the only independent risk factor for both colonization and subsequent infection with a polymyxin-resistant organism[67]. Polymyxin resistance is typically mediated by genes encoded in bacterial chromosomes, but the recent discovery of one of these genes (*mcr1*) in bacterial plasmids raised concerns over the potential rapid dissemination of polymyxin resistance[46]. This gene was first encountered in *E. coli* isolated from food-producing animals in China between 2011 and 2014, later found in hospitalized patients with Enterobacteriaceae infections and subsequently seen in animal and human isolates from multiple countries around the world[68].

Pseudomonas aeruginosa

Pseudomonas aeruginosa possesses intrinsic resistance to many antibiotics and can acquire resistance to additional antibiotic classes[69]. Mechanisms of resistance frequently found in *P. aeruginosa* isolates include AmpC β-lactamases, ESBLs, MBLs, downregulation of the porin protein outer membrane porin D (OprD) and multidrug efflux pumps (FIG. 1b). The emergence of resistance during therapy is well documented and is associated with higher morbidity, mortality and health-care costs[70]. A CDC report based on health-care-associated infection data collected in US hospitals in 2014 showed that *P. aeruginosa* was the sixth most commonly reported pathogen in cases of device-associated and surgery-associated infections. In these isolates, rates of resistance to fluoroquinolones, piperacillin–tazobactam and carbapenems were 11.5–32.6%, 7.4–18% and 7.7–25.8%, respectively[58]. ECDC data

from 2017 showed that 30.8% of *P. aeruginosa* isolates were resistant to at least one anti-pseudomonal antibiotic[11]. The rate of multidrug resistance, defined as non-susceptibility to at least one drug in three of five drug classes, ranged from 4.3% to 17.9%. Antimicrobial-resistant *P. aeruginosa* is a globally relevant problem, and countries with limited resources are heavily affected[12]. In fact, 46.3% and 44.4% of *Pseudomonas* bloodstream isolates from intensive care units in 50 resource-limited countries were resistant to cefepime (a cephalosporin) and carbapenems, respectively[12].

Acinetobacter species

Acinetobacter spp. are ubiquitous organisms found in water and soil that gained attention as an emerging nosocomial pathogen in the 1970s[71]. Since then, *Acinetobacter* spp., particularly *Acinetobacter baumannii*, have achieved global recognition for their ability to develop extensive drug resistance and to cause nosocomial outbreaks, particularly in intensive care units; AmpC β-lactamases are intrinsically present in all *A. baumannii*[72,73]. Acquired resistance mechanisms include MBLs, cell wall porin mutations and antibiotic efflux pumps (FIG. 1b); Ambler class D β-lactamases, also called OXA carbapenemases, have also been increasingly reported in *Acinetobacter* spp.[71]. Among *Acinetobacter* isolates from device-associated and surgery-associated infections reported to the US CDC in 2014, rates of carbapenem resistance ranged from 33% to 64% and rates of multidrug resistance ranged from 33% to 69%[58]. In Europe, the population-weighted mean percentage for combined resistance to fluoroquinolones, aminoglycosides and carbapenems was 28.4%, with substantial intercountry variation[11]. Among bloodstream isolates reported to INICC, 90.2% were resistant to carbapenems[12].

ARB infections in patients with CKD

This section discusses the epidemiology of ARB among infections commonly encountered in patients with CKD. When available, incidence and/or prevalence data specific to these patients are provided, otherwise data from a broader health-care setting are provided.

UTIs and pyelonephritis

The prevalence of antimicrobial resistance among organisms that cause UTIs varies by country, region and patient-level risk factors. Risk factors associated with ARB UTIs include health-care facility exposure (including nursing homes and long-term care facilities), previous antibiotic use, indwelling urinary catheters, prior history of ARB UTI and travel to or residence in a country or region with a high prevalence of ARB. Polycystic kidney disease (PKD) is associated with abnormal kidney anatomy and patients with PKD have an increased risk of recurrent UTIs, particularly pyelonephritis. Multiple exposures of these patients to antibiotics are likely to increase their risk of colonization and infection with ARB, but data for this population are limited.

In the general population, an analysis of 1,438 urinary tract *E. coli* isolates collected in hospitals in Canada and the United States between 2013 and 2014 showed that 12.6% of the Canadian isolates and 16.8% of the US isolates were ESBL positive[74]. Among the US isolates, those from health-care-associated infections were significantly more likely to be

ESBL positive than isolates from community-associated infections (21.8% versus 14.9%; $P < 0.05$); rates of fluoroquinolone resistance ranged from 28.6% to 35%. Antimicrobial resistance was even more prevalent among catheter-associated UTIs (CAUTIs) reported by US hospitals in 2014 (REF.[58]). For example, among *E. coli* isolates, the most commonly reported CAUTI pathogen, 16.1% were resistant to extended-spectrum cephalosporins and 34.8% were resistant to fluoroquinolones. Carbapenem resistance was reported in 4% of Enterobacteriaceae isolates and was even more common among *P. aeruginosa* (23.9%) and *Acinetobacter* spp. (64%) isolates. The percentage of MDR Gram-negative organisms was 8% for *E. coli*, 11.2% for *Enterobacter* spp., 14.6% for *Klebsiella* spp., 17.7% for *P. aeruginosa* and 69.1% for *Acinetobacter* spp. Among Gram-positive pathogens, 85% of *E. faecium* isolates were vancomycin resistant. In many developing countries, antimicrobial resistance among health-care-associated UTI pathogens is even greater. A 2016 report from the INICC described rates of resistance to third-generation cephalosporins of 64% and 77% for *E. coli* and *K. pneumoniae*, respectively, whereas resistance to carbapenems was detected in 6.6% of *E. coli* and 33.7% of *K. pneumoniae* isolates[12].

Dialysis-associated infections

Bacterial infections, including bloodstream infections associated with haemodialysis and peritonitis associated with peritoneal dialysis, are a leading cause of morbidity and mortality in patients with ESRD[75,76]. Complications such as endocarditis, disseminated infection (for example, haematogenous osteomyelitis) and limitation or loss of vascular and peritoneal access options contribute to these adverse outcomes. Moreover, pathogens that cause dialysis-associated infections often carry determinants of antimicrobial resistance.

Haemodialysis.—In 2014, outpatient haemodialysis facilities in the United States reported 29,516 bloodstream infections in patients receiving chronic haemodialysis; 76% of these infections were related to vascular access[34]. *S. aureus* was the most commonly reported pathogen, accounting for 30.6% of episodes; 39.5% of isolates were methicillin resistant. Among *Enterococcus* spp., which accounted for 5.5% of the reported bloodstream infections, 11.5% were vancomycin resistant. Antimicrobial resistance was also relatively common among Gram-negative pathogens, such as *E. coli*, *E. cloacae*, *K. pneumoniae* and *P. aeruginosa*, which collectively accounted for approximately 15% of bloodstream infection isolates. Among *E. coli* isolates, 17.8% were resistant to third-generation cephalosporins (for example, ESBL-producing organisms), 14.6% of *Klebsiella* spp. isolates were resistant to cephalosporins and 4.8% of *Enterobacter* spp. isolates were resistant to carbapenems. It should be noted that these reported infections include only those diagnosed in outpatient dialysis facilities or within 1 calendar day after a hospital admission. Thus, bloodstream infections that occur or are diagnosed more than 1 day after hospital admission are not included in the reported data. In addition, one study found substantial underreporting of events, particularly for events that are diagnosed during the first day of hospitalization[77]. Consequently, these data likely underestimate the incidence of bloodstream infections, and therefore the incidence of bloodstream infections with ARB, among patients on haemodialysis in the United States.

The distribution and antibiotic resistance patterns of pathogens linked to haemodialysis-associated bloodstream infections vary substantially among geographic regions. Reported rates of methicillin resistance among *S. aureus* bloodstream infection isolates range from 0% in a study from Denmark to 100% in a single-centre study conducted in Algeria[78–81]. Rates of antimicrobial resistance among enterococci and Gram-negative pathogens also vary widely and are very high in some regions. The above-mentioned Algerian study reported that 100% of *K. pneumoniae* isolates produced ESBLs[80], whereas a retrospective review of haemodialysis-associated bloodstream infections detected over 7 years at a single centre in Greece reported that 38% of Gram-negative organisms were resistant to fourth-generation cephalosporins and 24% were resistant to carbapenems[79].

Peritoneal dialysis.—Peritoneal-dialysis-related infections include exit-site infections, tunnel infections and peritonitis; peritoneal-dialysis-associated peritonitis is most commonly caused by Gram-positive organisms, such as coagulase-negative staphylococci and *S. aureus*, but a substantial minority of cases are due to Gram-negative organisms and other pathogens[82]. The available data are limited but suggest that, as in haemodialysis-associated infections, antimicrobial resistance is a growing problem among peritoneal-dialysis-associated infections and that the prevalence of antimicrobial resistance among these pathogens varies geographically. For instance, a review of cases of dialysis-associated peritonitis diagnosed between 2002 and 2011 at a single centre in northern India showed high rates of resistance among multiple pathogens[83]. In that study, 28.6% of *S. aureus* isolates were methicillin resistant; 15.4% of *Enterococcus* isolates were vancomycin resistant; 54% and 76% of Enterobacteriaceae isolates were resistant to third-generation cephalosporins and fluoroquinolones, respectively; and 11.5% and 23.5% of *P. aeruginosa* and *Acinetobacter* spp., respectively, were resistant to carbapenems owing to MBL production. Mortality was significantly higher among patients with peritonitis caused by VRE and by Gram-negative organisms that produce ESBL and MBL. However, other regions report lower levels of resistance. In Western Australia, resistance to fluoroquinolones, later-generation cephalosporins and carbapenems was detected in 6%, 18% and 0%, respectively, of Gram-negative pathogens that caused peritonitis between 2008 and 2013 (REF.[84]). In a single-centre study in Germany, rates of MRSA, VRE and third-generation cephalosporin-resistant Gram-negative pathogens were fairly low but increased over a 32-year study period (1974–2014)[85].

Infections after renal transplantation

Infection is an important cause of morbidity and mortality after renal transplantation. In the first month after transplantation, health-care-associated infections, including surgery-related infections and donor-derived infections, are the most common.[86] Two to six months post-transplantation, immunosuppression-related infections are most frequent and include both opportunistic infections and infections due to viral reactivation. After 6 months, immunosuppression is typically reduced and infections are primarily due to environmental or community exposures but patients remain at risk of opportunistic infections such as *Cryptococcus* and *Pneumocystis jiroveci*[86]. UTIs are the most common bacterial infections in kidney transplant recipients, and various single centres have reported an incidence of 20–50%[87–90]. Most patients present with uncomplicated cystitis, but serious infections such as

transplant pyelonephritis also occur[91]. Recurrent UTI, defined as more than three episodes of infection in 1 year, is also common in renal transplant recipients, as are other health-care-associated infections, including surgical-site infections, bloodstream infections and pneumonia.

Infections with ARB such as VRE, ESBL-producing Enterobacteriaceae and CRE and other Gram-negative pathogens are becoming increasingly common after renal transplantation. Patients acquire these ARB through a variety of mechanisms, including health-care-associated transmission via contaminated medical equipment, environmental surfaces and health-care workers' hands as well as direct transmission via the transplanted organ or within the community (for example, in the case of community-associated MRSA). Post-surgical anatomic abnormalities, including vesicoureteral reflux, ureterovesical junction stenosis or neurogenic bladder, might predispose transplant recipients to recurrent UTIs and increase the risk of acquiring or developing ARB due to repeated exposure to antibiotics and health-care settings[88]. Other risk factors include advanced age, surgical re-intervention, kidney–pancreas transplant, post-transplant requirement of renal replacement therapy, post-transplant nephrostomy, previous antibiotic exposure, urinary tract obstruction or instrumentation and the presence of a central venous catheter[89,92–94].

The prevalence of multidrug resistance among bacteria isolated from renal transplant recipients varies greatly and has been reported to range from 8% to 46%, depending on the type of infection, organism and region[87,92,95]. In one prospective study performed at a Spanish centre between 2003 and 2006, 58 (14%) of 416 renal transplant recipients developed a post-transplantation ARB infection[94]. The most commonly identified ARB were *E. coli*, *K. pneumoniae* and *P. aeruginosa*. In a retrospective study of renal transplant recipients in Brazil, the incidence of ESBL-producing Enterobacteriaceae among UTI isolates increased from 23.8% to 37.5% between 2003–2005 and 2006–2008 (REF.[96]). The reported incidence of CRE infection after renal transplantation ranged between 1.1% and 26%[97]. In another study of 280 kidney transplant recipients followed at a Brazilian centre between 2001 and 2003, the prevalence of VRE faecal colonization was 13.6%[33].

Treatment of infections caused by ARB

Empirical treatment of a suspected bacterial infection should be based on the anticipated pathogens, the suspected infection site, local antimicrobial resistance patterns and the individual patient's medical history, including prior colonization or infection with ARB (TABLE 1). In patients with renal dysfunction, issues such as vascular access requirements, the potential for nephrotoxicity and the need for dose adjustment of antibiotics that undergo renal clearance are important factors that need to be taken into account when selecting antimicrobial agents. In renal transplant recipients, knowledge of the donor's prior colonization and infection status should also be considered. Antimicrobial therapy should be adjusted on the basis of the results of antimicrobial susceptibility tests performed on the pathogen or pathogens isolated from the site of infection (TABLE 1). In addition to antimicrobial therapy, other basic principles of treatment, such as source control, which includes drainage of abscesses and removal of infected foreign bodies, have a critical role in optimizing the outcome of ARB infections[98]. Early consultation with an infectious diseases

physician should also be considered[99]. Antimicrobial treatment of ARB infections is a complex and rapidly evolving topic that is beyond the scope of this article. However, antibiotics that have recently been approved for use and that have activity against one or more ARB are reviewed below.

New antibiotics for ARB infections

β-Lactams.—Ceftaroline, often referred to as a fifth-generation cephalosporin, has a greater affinity for PBP2a than other β-lactam antibiotics and is effective against organisms such as MRSA, which produce this altered PBP. In vitro, ceftaroline has bactericidal activity against MRSA, VISA and VRSA[100], including some strains with reduced susceptibility to linezolid, daptomycin and/or vancomycin[101]. Ceftaroline has been used alone and in combination with other antibiotics to treat a variety of infections caused by susceptible organisms but is currently approved by the US Food and Drug Administration (FDA) only for the treatment of skin and soft tissue infections, including those caused by MRSA, and community-acquired pneumonia, excluding cases caused by MRSA.

Ceftolozane–tazobactam combines the novel cephalosporin, ceftolozane, with the β-lactamase inhibitor tazobactam to produce an antibiotic with activity against many ESBL-producing Enterobacteriaceae isolates and MDR *P. aeruginosa* isolates with chromosomal AmpC production, loss of outer membrane porins and/or upregulation of drug efflux pumps; however, this antibiotic is not active against serine carbapenemases or MBLs. International multicentre studies found that ceftolozane–tazobactam is active in vitro against more than 90% of MDR *Pseudomonas* and non-CRE ESBL-producing Enterobacteriaceae clinical isolates[102,103]. A randomized clinical trial demonstrated that ceftolozane–tazobactam plus metronidazole is non-inferior to meropenem in the treatment of intra-abdominal infections caused by ESBL-producing organisms[104]. Moreover, several retrospective clinical studies suggest a role for ceftolozane–tazobactam in the treatment of infections caused by susceptible strains of MDR *P. aeruginosa*, although the emergence of resistance during therapy has also been described[105,106].

Ceftazidime with avibactam is another β-lactam–β-lactamase inhibitor combination[107]. Avibactam has activity against Ambler class A and C β-lactamases, including ESBLs, AmpC and KPC, which means that it is effective against many resistant Gram-negative bacteria. Of note, ceftazidime–avibactam is not active against Ambler class B MBL-producing organisms or *Acinetobacter* spp. In a randomized clinical trial, treatment with ceftazidime–avibactam provided outcomes similar to the best-available therapy when used for the treatment of complicated UTIs and intra-abdominal infections caused by ceftazidime-resistant Enterobacteriaceae and *P. aeruginosa*[108]. Another trial found that ceftazidime–avibactam used in combination with metronidazole had a similar efficacy to meropenem for the treatment of complicated intra-abdominal infections caused by both ceftazidime-susceptible and ceftazidime-resistant pathogens[109]. Thus far, no randomized clinical trials have assessed the use of ceftazidime–avibactam for the treatment of CRE infections. However, a small prospective multicentre observational study reported better clinical outcomes for patients with infections caused by KPC-producing CRE who were treated with ceftazidime–avibactam than for those treated with colistin[110]. Although these results are

encouraging, further evaluation of this antibiotic for the treatment of KPC-producing CRE is needed to validate these findings.

Meropenem–vaborbactam combines meropenem with a non-β-lactam, boronic-acid-based β-lactamase inhibitor. In vitro and in vivo studies showed that this antibiotic combination is effective against Enterobacteriaceae that produce AmpC, ESBL and KPC[111]. Meropenem–vaborbactam has limited activity against other classes of carbapenemases, including MBLs such as NDM-1 and VIM, and OXA-type carbapenemases. Clinical studies that evaluate the clinical efficacy of meropenem–vaborbactam are limited. In one study, this combination antibiotic was found to be non-inferior to piperacillin–tazobactam for the treatment of complicated UTIs[112]. More relevant to this discussion of ARB, a small randomized, controlled and non-blinded clinical trial found that monotherapy with meropenem–vaborbactam was associated with increased clinical cure rates, decreased mortality and reduced nephrotoxicity when compared with best-available therapy for treatment of infections caused by CRE[113]. Meropenem–vaborbactam is currently approved by the FDA for the treatment of complicated UTIs caused by susceptible strains of *E. coli*, *K. pneumoniae* and *Enterobacter cloacae*.

Lipoglycopeptides.—The lipoglycopeptides dalbavancin, oritavancin and telavancin have in vitro activity against many staphylococci, including MRSA, as well as streptococci and enterococci, including many VRE isolates[114,115]. Unlike vancomycin, therapeutic drug monitoring is not required for these agents. Dalbavancin and oritavancin have long half-lives that allow for prolonged interval dosing or single-dose therapy, respectively. Whereas dalbavancin can be used in patients with renal failure and those being treated with intermittent haemodialysis[116], the need for dose adjustments of oritavancin in the setting of renal impairment has not been studied. In contrast to dalbavancin, telavancin has been associated with worsening renal function, which may limit its use in patients with renal disease[117]. These three lipoglycopeptide agents are currently approved by the FDA for the treatment of acute bacterial skin and soft tissue infections as data on their efficacy in the treatment of more serious infections are lacking.

Other novel antibiotics.—Plazomicin is a new aminoglycoside that remains active in the presence of many aminoglycoside-modifying enzymes, which gives it greater in vitro activity than other aminoglycosides against many MDR Enterobacteriaceae, including isolates that produce ESBL and carbapenemase, and other MDR Gram-negative organisms[118]. Plazomicin might also be associated with lower toxicity rates, including reduced nephrotoxicity, ototoxicity and vestibular toxicity, than other aminoglycosides[119]. A phase II study provided evidence for the microbiological and clinical efficacy of plazomicin in the treatment of complicated UTIs[120], for which the FDA approved the use of plazomicin in June 2018.

Eravacycline is a synthetic fluorocycline that is broadly active against many Gram-positive and Gram-negative bacteria, including several ARB[121]. Eravacycline is active against MRSA, VRE and many Gram-negative organisms that produce ESBLs and several carbapenemases, including KPC, NDM and OXA[121,122]. In a randomized clinical trial, eravacycline was found to be non-inferior to ertapenem for the treatment of complicated

intra-abdominal infections[123]; the FDA approved its use for the treatment of these types of infection.

Delafloxacin is a new fluoroquinolone with activity against MRSA; its Gram-negative spectrum of activity is similar to other fluoroquinolones. A randomized clinical study found that delafloxacin was non-inferior to vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections[124]; delafloxacin is approved by the FDA for the treatment of acute skin and subcutaneous tissue infections. Of note, delafloxacin is not recommended for use in patients with severe renal dysfunction and ESRD owing to insufficient data to inform appropriate dosing.

Prevention and control of ARB infection

Given the high rates of infection-related morbidity and mortality observed in patients with CKD, preventing pathogen transmission and the development of clinical infection is of critical importance.

Basic infection control practices

Consistent implementation of basic infection prevention strategies is a crucial element in the effort to prevent transmission of and infection by ARB. These basic practices, which include hand hygiene, standard precautions and cleaning and disinfection of the health-care environment and medical equipment, are often referred to as ‘horizontal’ strategies because they reduce the risk of pathogen transmission and infection, including ARB. Public health agencies and professional societies have developed evidence-based guidelines that summarize best practices related to the insertion, use and maintenance of invasive devices (such as urinary catheters, central venous catheters and other forms of haemodialysis vascular access); the prevention of surgical-site infections and of infection among patients receiving chronic haemodialysis[125]; and other aspects of care for patients with renal disease. However, despite the availability of guidelines and the evidence showing that consistent implementation of the recommended practices is associated with reduced rates of infection, substantial evidence indicates that these practices are not consistently implemented.

Infection prevention in haemodialysis facilities.—Although relatively infrequent, outbreaks of infection, including infections caused by ARB, continue to occur among patients receiving care in haemodialysis facilities. Sources of such outbreaks have included contaminated tap water, reverse osmosis water storage tanks, antiseptic solutions and environmental surfaces, or have involved inadequate reprocessing and disinfection of dialysis equipment, and patient-to-patient transmission through health-care personnel[126–128]. Most of these outbreaks occur owing to lapses in the implementation of recommended infection prevention practices, and considerable evidence substantiates the need for improvement of basic policies and practices for the prevention of infection in haemodialysis facilities. One survey carried out in 37 hospital-based haemodialysis units in Quebec, Canada between December 2011 and March 2012 identified several opportunities to improve local protocols related to the insertion, use and maintenance of catheters by adding recommended evidence-based infection control practices[129]. For example, only 79% of protocols from the surveyed facilities called for the use of a full-body drape during catheter

insertion, only 44% called for application of an antimicrobial ointment at the catheter insertion site and only 67% required the use of a recommended chlorhexidine-alcohol antiseptic solution for skin preparation. In addition, most facilities (69%) did not conduct audits to assess compliance with written protocols for catheter insertion or maintenance.

An observational study in 34 US haemodialysis facilities conducted between 2011 and 2012 by independent evaluators also found multiple areas for improvement in infection prevention practices[130]. These included procedures for environment and equipment disinfection, hand hygiene, dialysis catheter maintenance, dialysis initiation and termination, and medication preparation and administration. For example, overall compliance with recommended hand hygiene practices was only 72%, appropriate disinfection of surfaces and non-disposable items occurred in only 18–41% of observed opportunities and disinfecting of the external and internal hubs of central venous catheters was observed in only 45% and 34% of indicated situations, respectively. The findings of these two studies are important and actionable, as every lapse in infection prevention practice increases the risk of pathogen transmission and clinical infection. Conversely, improved adherence to evidence-based prevention strategies has been associated with reductions in infections such as bloodstream infections associated with haemodialysis access[131,132]. In addition to assessing compliance, identifying the reasons for non-compliance, which might include factors related to individuals, organizations and the external environment, as well as addressing any facility-specific reasons for non-compliance might help to optimize adherence to evidence-based guidelines and minimize the risk of infection[133].

Another strategy to prevent bloodstream infections among haemodialysis patients is to select the vascular access option with the lowest associated risk of infection. The use of intravascular catheters, when compared with arteriovenous fistulas (AVFs), is associated with a higher risk of infection[34] and a higher rate of antibiotic exposures, including non-indicated antibiotic exposures[134]. Early AVF creation is thus recommended for patients who require chronic haemodialysis, but challenges to this strategy include patient preference and lack of access to a vascular surgeon or surgical facility[129]. Identifying and addressing patient-specific and facility-specific barriers might be helpful in reducing the prevalence of catheter-based haemodialysis[135].

The previously described ‘horizontal’ interventions prevent the transmission of and infection with a wide variety of potential pathogens, whereas ‘vertical’ strategies target one or more specific pathogens. Vertical strategies include the use of contact precautions for patients colonized or infected with ARB, the use of active surveillance testing to detect patients who are asymptomatically colonized with one or more ARB (for example, MRSA) and decolonization of MRSA carriage with the use of topical antiseptics with or without antibiotics[136]. The routine use of vertical strategies outside of outbreak situations remains controversial in many regions.

Antimicrobial stewardship

One of the major risk factors for propagation of antimicrobial resistance and the development of ARB infection is exposure to antibiotics, mainly due to antibiotic selection pressure. Although antibiotic therapy can be life-saving and the benefits of antibiotics often

outweigh the potential risk of development of antimicrobial resistance, inappropriate and unnecessary use of antimicrobial agents increases this risk without any benefit to the patient. Of note, antimicrobial use and, more importantly, misuse are common among patients with CKD. According to data submitted to the CDC's National Healthcare Safety Network (NHSN) in 2014, 149,722 patients receiving treatment in 6,005 outpatient haemodialysis facilities were started on antibiotics[34]. This equates to 3.27 antibiotic starts per 100 patient-months, ranging from 2.07 for patients with AVFs to 7.91 for patients with catheters. Studies conducted in haemodialysis facilities in the United States and Australia reported that 32–55% of patients received one or more doses of antibiotics in a time period that ranged from 6 to 12 months and that 22–35% of antimicrobial doses were inappropriate[134,137,138]. In these studies, commonly identified examples of inappropriate prescribing included administration of antibiotics in the absence of evidence of infection, use of antimicrobials with an inappropriate spectrum of activity, incorrect dosing and dosing frequency, and incorrect duration of therapy.

These data demonstrate that substantial opportunities exist to improve antimicrobial prescribing among patients with renal disease in order to optimize treatment outcomes and minimize adverse consequences, including propagation of antimicrobial resistance. Implementation of antimicrobial stewardship programmes in hospitals and ambulatory care settings is associated with improvements in the appropriateness of antimicrobial use, patient outcomes and antimicrobial susceptibility among targeted pathogens[139]. Thus, antimicrobial stewardship programmes (ASPs) are considered an important part of efforts to combat antimicrobial resistance. A 2016 model predicted that implementation of ASPs in outpatient dialysis facilities in the United States would result in 2,182 fewer ARB and *Clostridioides difficile* (formerly known as *Clostridium difficile*) infections, 629 fewer deaths and cost savings of $106 million per year[140]. Guidelines for the implementation of antimicrobial stewardship programmes in health-care facilities have been published[141] and specific strategies for developing and implementing such programmes in outpatient dialysis facilities have been reviewed[142].

Decolonization therapy

In many cases, ARB infection is preceded by acquisition of the organism followed by asymptomatic colonization; therefore, eliminating established colonization could reduce the risk of subsequent infection. Decolonization therapy refers to the application of antibiotic or antiseptic agents to suppress or eliminate carriage of an organism; this approach is most often used to eliminate *S. aureus*, including MRSA. Typical decolonization regimens include intranasal mupirocin with or without topical antiseptics such as chlorhexidine, but other agents have also been used. Several studies demonstrated that decolonization therapy reduced *S. aureus* infections among colonized patients on peritoneal dialysis[143] or haemodialysis[144]. It should be noted, however, that the optimal regimen and duration of treatment are not defined, and that current strategies for decolonization rely on antiseptics and/or antimicrobial agents, with a potential risk of resistance and collateral damage due to alterations of the patient's microbiome. In fact, some centres have reported the emergence of mupirocin resistance in association with the widespread use of mupirocin-based

decolonization therapy[145]. Elimination or suppression of antibiotic-resistant Gram-negative bacteria carried in the gastrointestinal tract has proven to be more challenging[146–148].

Novel strategies and future directions

Although the importance of adherence to basic infection prevention practices to reduce the risk of person-to-person transmission and decrease the risk of infection among carriers of an organism cannot be overstated, even high levels of compliance with these strategies are unlikely to be sufficient to address the growing problem of antimicrobial resistance. Similarly, although the development of several antibiotics with activity against some ARB, such as MRSA and CRE, is a much welcomed advance, the pipeline of new traditional antibiotics is unlikely to keep pace with the continued evolution of antimicrobial resistance. In addition, the use of traditional antibiotics will continue to exert collateral damage on the healthy human microbiota, further contributing to antibiotic selection pressure and the risk of emergence and propagation of antimicrobial resistance. Thus, novel approaches to prevent and treat bacterial infections that are more effective, that are less prone to the development of resistance and/or that avoid or reduce collateral damage are needed. Fortunately, several such strategies are under active investigation. A few examples are provided here (and reviewed elsewhere[149]).

Phage lysins are enzymes produced by bacteriophages that hydrolyse the bacterial cell wall peptidoglycan, resulting in a bactericidal effect with a high barrier to resistance[150]. The activity of each lysin is specific to certain bacterial species, thereby reducing the risk of significant microbiome disruption. Lysins are under active investigation for use in the eradication of important bacterial pathogens in both asymptomatic carriers and patients with infection. For example, animal models have demonstrated that lysins can reduce the burden of pathogens such as *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *S. aureus*, including MRSA, and even eliminate bacterial colonization when administered topically[151–153]. Systemic administration of lysins contributed to the successful treatment of invasive infections caused by pathogens such as *S. aureus* and *A. baumannii*[154,155]. The use of lysins for the treatment of bacterial infections in humans is currently under investigation.

Other natural products are similarly being investigated for their potential role in the treatment and/or prevention of human infection. For example, the common human commensal organism *Staphylococcus lugdunensis* produces lugdunin, a thiazolidine-containing cyclic peptide antibiotic that has activity against *S. aureus* and other Gram-positive bacteria[156]. In vitro and in vivo experiments suggested that, compared with current decolonization agents, this compound might prevent *S. aureus* colonization and subsequent infection with less risk of bacterial resistance. Additional novel sources of natural anti-infective products, such as deep sea actinobacteria[157], are also being actively sought and studied.

Although the development of more effective treatment options for individuals infected with ARB is critical, better strategies for prevention of pathogen acquisition and infection could reduce the need for new treatments and abate the morbidity and mortality associated with infection. Such prevention strategies could include vaccination and interventions that

enhance resistance to colonization or infection with pathogenic bacteria. Vaccination has long been used for the prevention of communicable diseases. The pneumococcal vaccine exemplifies the ability of vaccines to reduce antimicrobial resistance among clinical isolates of common bacterial pathogens by providing protection against antimicrobial-resistant strains[158,159]. Compared with classic communicable diseases, the use of vaccines to prevent infection caused by endogenous pathogens is a relatively new concept, but it could serve an important role in efforts to control ARB[160]. For example, development of an effective *S. aureus* vaccine could dramatically reduce morbidity and mortality among patients on haemodialysis. Over the past two decades, several *S. aureus* vaccines have been developed and studied in vitro and in vivo. However, although some of these candidate vaccines demonstrated immunogenicity, they failed to protect against infection. This failure is exemplified by a vaccine containing *S. aureus* type 5 and 8 capsular polysaccharides that was immunogenic but did not prevent *S. aureus* bacteraemia when administered to patients with ESRD[161]. Another vaccine containing the *S. aureus* iron surface determinant B protein was immunogenic in adults with ESRD[162]. However, in patients undergoing cardiothoracic surgery, the same vaccine not only failed to reduce the rate of serious *S. aureus* infections but was also associated with increased mortality among vaccinated patients who later developed *S. aureus* infection[163]. Subsequent investigations suggested that inclusion of multiple antigens that target different virulence mechanisms might be needed for a vaccine to provide protection from clinical infection[164]. One study demonstrated that a vaccine containing four *S. aureus* antigens — polysaccharide conjugates of serotypes 5 and 8, recombinant surface protein clumping factor A and recombinant manganese transporter protein C — was immunogenic[164]; it is currently being tested in a phase II clinical trial. The NDV-3 vaccine contains the amino-terminal portion of the *Candida albicans* agglutinin-like sequence 3 protein (Als3p), which acts as an adhesin and invasin and has both sequence and structural homology with *S. aureus* surface proteins[165,166]. The ability of the NDV-3 vaccine to prevent *S. aureus* colonization is currently being tested in clinical trials.

Exposure to antibiotics that alter the normal microbiota can reduce colonization resistance and thus, microbiota transplantation, particularly faecal microbiota transplantation (FMT), has been explored as a potential approach to reduce the antibiotic-driven dysbiosis that increases the risk of colonization and infection with ARB. FMT might exert a beneficial effect by increasing bacterial diversity and/or altering local and/or systemic immune responses[167]. Although prevention of recurrent *C. difficile* infection (rCDI) is the most commonly studied indication for FMT, evidence suggests that FMT could offer protection against colonization with ARB. For example, FMT for rCDI has been associated with the loss of antimicrobial resistance genes in faecal samples[168–170]. Several case reports[171] and small, uncontrolled case series have assessed the ability of FMT to eradicate gastrointestinal carriage of ARB. In one study, FMT was associated with increased faecal bacterial diversity and loss of ESBL-producing Enterobacteriaceae in 3 of 15 (20%) carriers 1 month after the first FMT, and in an additional 3 of 7 (40%) patients who underwent a second FMT after failing to respond to the first FMT[172]. In another study, 20 patients with blood disorders and ARB gastrointestinal colonization that included VRE, ESBL-producing Enterobacteriaceae, CRE and carbapenem-resistant *P. aeruginosa* were treated with 25 FMT procedures. Decolonization was documented after 15 procedures (60%) at the 1-month follow-up

assessment and in 13 of 14 procedures (93%) for which a 6-month follow-up was performed. Of note, recurrence or relapse was detected in 20% of patients[173]. These data suggest that FMT is potentially promising for ARB decolonization and might reverse the gut dysbiosis that predisposes patients to colonization with ARB. Several clinical trials of this strategy are currently in progress, including studies in patients who have received kidney and other solid-organ transplants.

A potential alternative or complementary strategy to microbiota-driven colonization resistance is the enhancement of pathogen tolerance. One study reports that secreted antigen A (SagA), a bacterial peptidoglycan hydrolase produced by *E. faecium*, protects *Caenorhabditis elegans* from *Salmonella typhimurium* pathogenesis in a colonization-independent manner, possibly by enhancing the integrity of the intestinal epithelial barrier[174]. The potential role of such a strategy in preventing human infection remains to be explored.

Conclusions

The emergence of antibiotic resistance among many of the most common bacterial causes of human infection and the global dissemination of these ARB represent a major public health risk; patients with CKD are disproportionately affected. The lack of prevalence and outcomes data related to ARB colonization and infection, particularly for antibiotic-resistant Gram-negative pathogens, among patients with CKD represents an important gap in research and a public health need. The growing burden of multidrug resistance limits therapeutic options and increases the risk of infection-related morbidity and mortality. Thus, clinicians providing care to patients with renal disease must be familiar with local antimicrobial resistance patterns in order to select appropriate empirical antimicrobial therapy and to recognize the appearance of novel resistance profiles within the community. Although several new antibiotics with activity against one or more of these MDR pathogens have now been approved for clinical use, an ongoing and critical need exists for improved adherence to basic infection control practices, antimicrobial stewardship and the development of more effective prevention and treatment strategies.

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Key points

- Infections caused by antibiotic-resistant bacteria (ARB) are associated with higher mortality, longer hospitalization and a greater economic burden than those caused by antibiotic-susceptible bacteria of the same species.
- The growing global burden of antimicrobial resistance is particularly relevant to patients with chronic kidney disease who are disproportionally affected by antimicrobial resistance when compared with the general population.
- Consistent implementation of basic infection prevention strategies is a crucial element in the effort to prevent transmission of and infection by ARB.
- Critical infection prevention practices include hand hygiene, cleaning and disinfection of the environment and medical equipment, and use of evidence-based practices for insertion, use and maintenance of invasive devices.
- Novel mechanisms of antimicrobial resistance continue to emerge and spread, leading to infections that are difficult to treat and highlighting the need for development of new antimicrobial agents.
- Antimicrobial treatment of ARB infections is a complex and evolving topic. Consultation with an infectious disease specialist should be considered in order to optimize antimicrobial agent selection and patient outcomes.

Infections

Disease states produced by a microorganism that may be symptomatic or asymptomatic.

Multidrug resistant

(MDR). Non-susceptibility to at least one agent in three or more antimicrobial categories to which an organism does not possess intrinsic resistance.

Extensively drug resistant

Non-susceptibility to at least one agent in all but two or fewer antimicrobial categories to which an organism does not possess intrinsic resistance.

Pandrug resistant

Non-susceptibility to all agents in all antimicrobial categories to which an organism does not possess intrinsic resistance.

Colonization

The asymptomatic presence of a microorganism on or within the body.

Conjugation

Direct transfer of genetic material between bacterial cells.

Transformation

Acquisition of new genetic material (DNA) via uptake from the environment.

Transduction

Transfer of bacterial DNA from one bacterium to another via a viral vector.

Invasive MRSA infections

MRSA infections within a normally sterile body site, such as the blood.

Vancomycin-intermediate *S. aureus*

(VISA). An isolate of *Staphylococcus aureus* that exhibits an elevated minimum inhibitory concentration (MIC) for vancomycin but that does not reach the MIC considered to represent full resistance to vancomycin.

Heteroresistant or heterogeneous VISA

(hVISA). Subpopulations of *Staphylococcus aureus* with reduced susceptibility present among a larger population of fully susceptible organisms.

Drug efflux pumps

Proteins in the bacterial cell membrane that transport a drug, such as an antibiotic, out of the cell.

Haematogenous osteomyelitis

Infection of bone that results from inoculation of the bone by microorganisms present in the bloodstream.

Vesicoureteral reflux

Abnormal retrograde flow of urine from the urinary bladder into the ureter and, possibly, the kidney.

Ureterovesical junction stenosis

Narrowing at the site where the ureter enters the urinary bladder that may obstruct the flow of urine from the kidney into the bladder.

Neurogenic bladder

Dysfunction of the urinary bladder due to neurological damage.

Therapeutic drug monitoring

Measurement of medication concentrations in blood at specified time intervals in order to optimize treatment effectiveness and/or minimize toxicity.

Arteriovenous fistulas

(AVFs). Surgically created connections between an artery and a vein used for vascular access for haemodialysis.

Contact precautions

interventions used to reduce the risk of transmission of organisms transmitted by contact with the affected patient and their environment.

Antibiotic selection pressure

Reduction or elimination of bacteria that are susceptible to an administered antibiotic, allowing antimicrobial-resistant bacterial populations to gain a survival advantage and thus become predominant members of the microbiota.

Antimicrobial stewardship

A set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics and decreasing unnecessary costs.

Endogenous pathogens

Organisms that are part of the normal microbiota but that in some circumstances can cause symptomatic infection.

Colonization resistance

The ability of the body's microbiota, such as commensal gut bacteria, to prevent colonization and infection with pathogenic organisms.

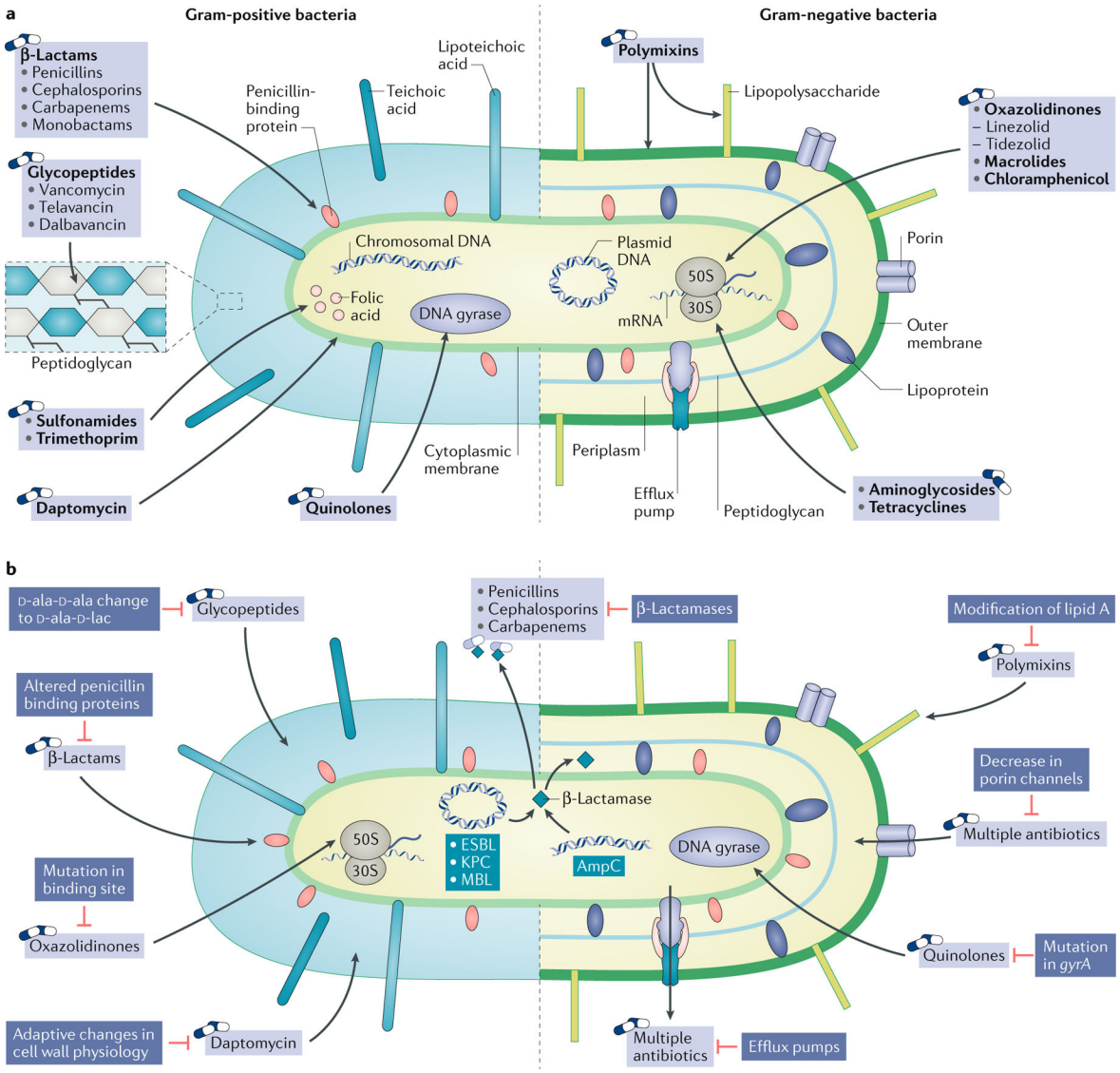

Fig. 1 |. Mechanisms of action of antibacterial agents and of antibacterial resistance.

Structures of Gram-positive (left) and Gram-negative bacteria (right). a | Sites and mechanisms of actions of antibacterial drugs. Bacterial cell wall synthesis is inhibited by β-lactam antibiotics and glycopeptides. Daptomycin and polymyxin disrupt the bacterial cell membrane. Bacterial protein synthesis is inhibited by oxazolidinones, macrolides and chloramphenicol, which bind to the 50S ribosomal subunit, and by tetracyclines and aminoglycosides, which bind to the 30S ribosomal subunit. Bacterial DNA synthesis is inhibited by fluoroquinolones via inhibition of DNA gyrase and topoisomerase IV. Bacterial folic acid synthesis, which is required for nucleic acid synthesis, is inhibited by sulfonamides and trimethoprim. b | Mechanisms of resistance to antibacterial drugs. Common mechanisms of resistance include destruction of the antibiotic via enzymes encoded by chromosomal genes or by plasmids, modification of the target of the antimicrobial agent, decreased penetration of the antimicrobial agent into the bacterial cell through alterations in the structure or reductions in the number of functional porin channels,

and enhanced elimination of the antimicrobial agent from the bacterial cell via drug efflux pumps.

ESBL, extended-spectrum β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase.

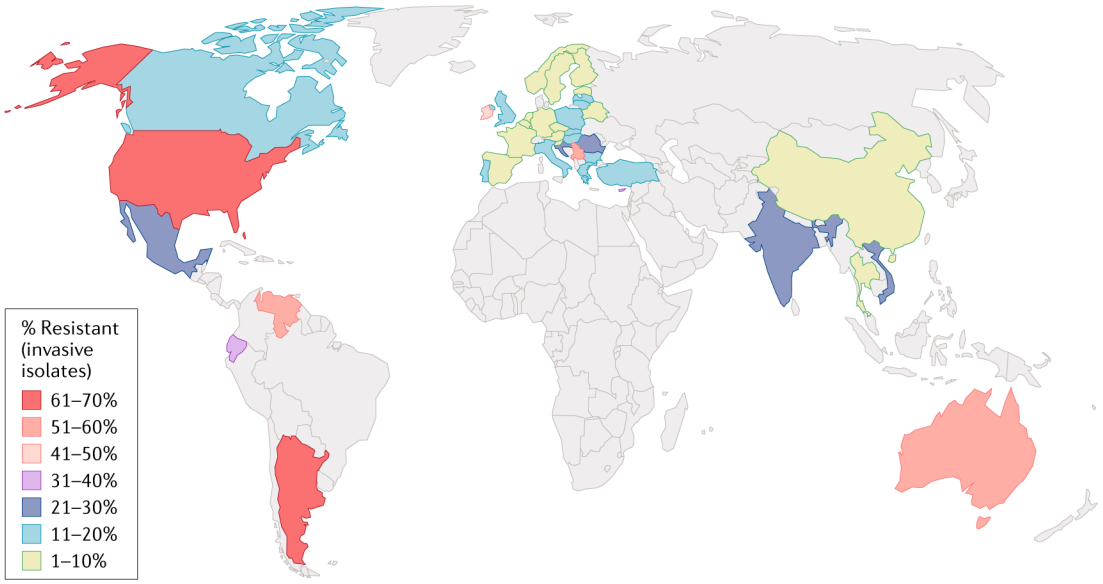

Fig. 2 |. Global prevalence of resistance of *Enterococcus faecium* to vancomycin.

World map displaying the frequency of invasive (that is, isolated from blood and/or cerebrospinal fluid) *E. faecium* non-susceptible to vancomycin.

Non-susceptible isolates include those that are resistant or are of intermediate susceptibility. Data from REF.[31].

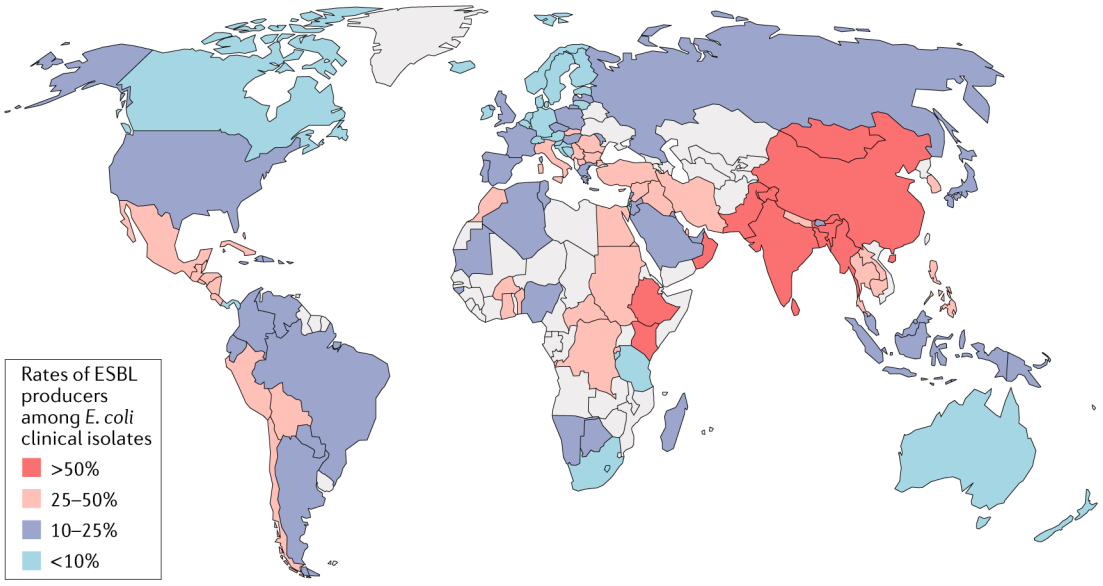

Fig. 3 |. Estimated global prevalence of eSBl-producing *Escherichia coli*.
World map displaying the frequency of extended-spectrum β-lactamase (ESBL) production among clinical *E. coli* isolates. Grey shading indicates insufficient data. Data from REF.[49].

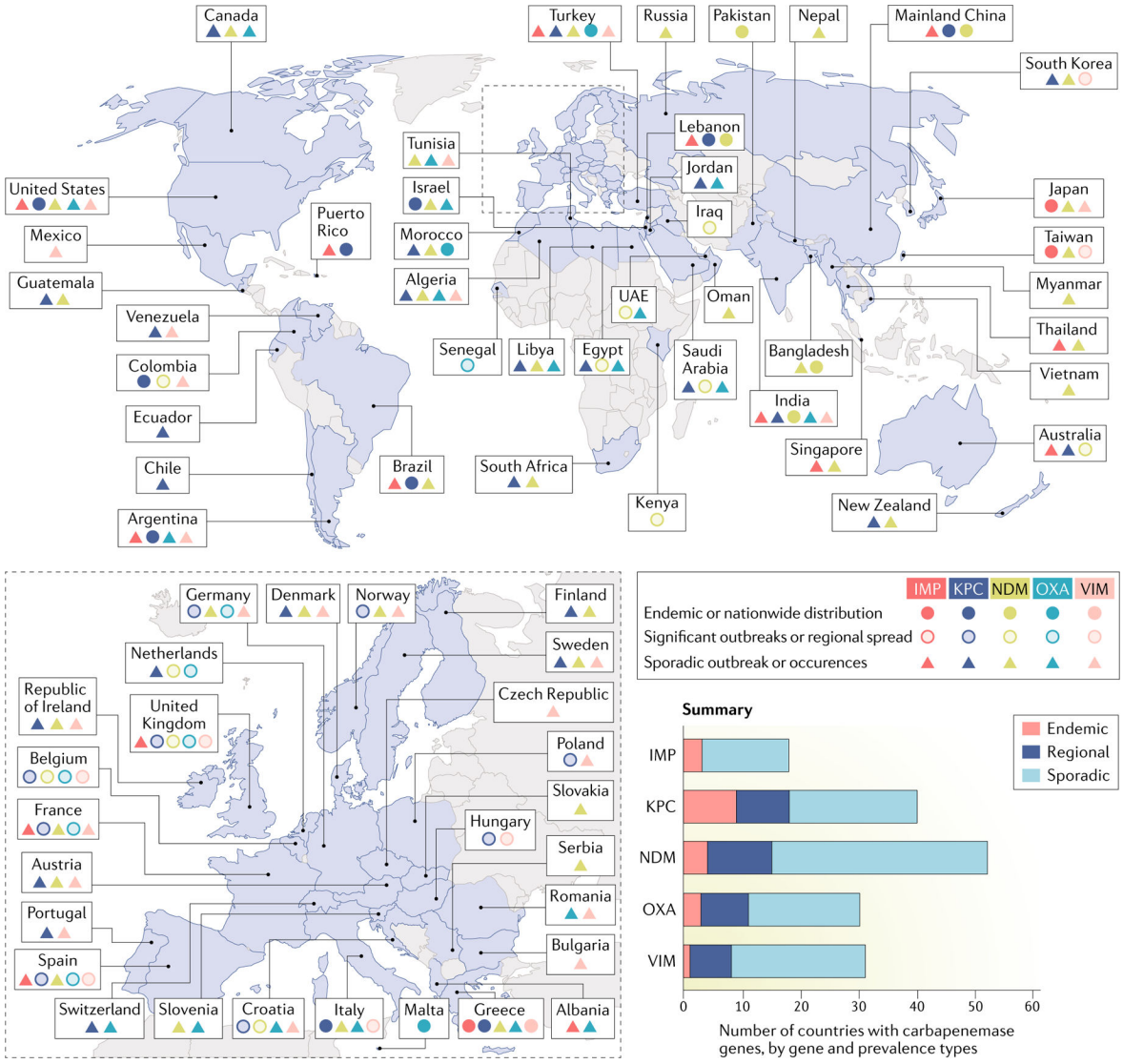

Fig. 4 |. Geographic distribution of carbapenemases in enterobacteriaceae.

World map displaying the global distribution of carbapenemases among Enterobacteriaceae. The colour of the marker indicates a specific carbapenemase. The shape of the marker (solid circle, open circle or triangle) refers to the prevalence of the carbapenemases (endemic, significant outbreaks or regional spread and sporadic outbreak and occurrences, respectively). Owing to lack of available data, information cannot be provided for the countries shaded in grey. IMP, active on imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase-type carbapenem-hydrolysing β-lactamase (OXA largely refers to OXA-48, except in India, where it refers to OXA-181); VIM, Verona integron-encoded metallo-β-lactamase. Data from REF.[55].

Table 1 |

Antimicrobial agents with potential in vitro activity against common and emerging mechanisms of resistance

Organism	Common and emerging mechanism(s) of resistance	Resistance phenotype	Antimicrobial agents with potential in vitro activity against resistant organisms[a,b]
Staphylococcus aureus	PBP2a (*mecA*)	Methicillin resistance	• Vancomycin[c,d] • Ceftaroline[c] • Daptomycin • Linezolid • Lipoglycopeptides (dalbancin[c], oritavancin and telavancin[c,d]) • Trimethoprim–sulfamethoxazole[c] • Tetracyclines (for example, doxycycline)
	Alterations in cell wall peptidoglycan (*vanA*)	Reduced susceptibility or full resistance to vancomycin	• Ceftaroline[c] • Daptomycin • Linezolid • Trimethoprim–sulfamethoxazole[c] • Quinupristin–dalfopristin • Tigecycline • Tedizolid
Enterococcus species	Alterations in cell wall peptidoglycan (*vanA* and *van* B)	Vancomycin resistance	• Daptomycin • Linezolid • Tigecycline • Quinupristin–dalfopristin • Tedizolid • Lipoglycopeptides (dalbancin[c], oritavancin and telavancin[c,d])
Enterobacteriaceae (for example, *Escherichia coli, Klebsiella pneumoniae* and *Enterobacter* spp.)	ESBL	Resistance to penicillins, oxyiminocephalosporins and monobactams with retained susceptibility to cephamycins, β-	• Carbapenems[c] • Ceftolozane–tazobactam[c]

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Organism	Common and emerging mechanism(s) of resistance	Resistance phenotype	Antimicrobial agents with potential in vitro activity against resistant organisms[a,b]
		lactam–β-lactamase inhibitor combinations and carbapenems	• Ceftazidime–avibactam[c] • β-Lactam and/or β-lactamase inhibitors[c] • Fluoroquinolones[c]
Gram- negative 'SPICE' organisms (for example, S*erratia*, *Pseudomonas*, *Providencia*, indole-positive *Proteus*, *Citrobacter* and *Enterobacter* spp.) and *Acinetobacter*	AmpC β-lactamases	Resistance to oxyiminocephalosporins (for example, cefotaxime, ceftazidime and ceftriaxone), cephamycins (for example, cefoxitin) and many β-lactam-β-lactamase inhibitor combinations	• Carbapenems[c] • Ceftazidime–avibactam[c] • Ceftolozane–tazobactam[c] • Meropenem–vaborbactam[c] • Fluoroquinolones[c] • Aminoglycosides[c,d] • Nitrofurantoin[e] • Trimethoprim–sulfamethoxazole[c]
Enterobacteriaceae (for example, *Proteus*, *E. coli*, and *Klebsiella* spp.)	Carbapenemases[f] • Ambler class A: serine β-lactamasesand penicillinases (for example, KPC) • Ambler class B: metallo-β-lactamases (for example, NDM, VIM and IMP) • Ambler class D: oxacillinases (for example, OXA-48)	Carbapenem resistance and resistance to other β-lactam antibiotics	• Polymyxins[c,d] • Aminoglycosides[c,d] • Tigecycline and minocycline • Meropenem-vaborbactam[c] (active against serine β-lactamases such as KPC) • Ceftazidime–avibactam[c] (active against class A and class D β-lactamases, not active against metallo-β-lactamases such as NDM) • Combination regimens such as polymyxin[c,d] plus carbapenem[c]
	AmpC β-lactamases plus cell wall porin mutations	Resistance to most β-lactam antibiotics, often including carbapenems	• Variable • Polymyxins (polymyxin B and colistin)[c,d] • Ceftazidime–avibactam[c] • Tigecycline and minocycline

Organism	Common and emerging mechanism(s) of resistance	Resistance phenotype	Antimicrobial agents with potential in vitro activity against resistant organisms[a,b]
			• Meropenem–vaborbactam[c]
	• Mutations affecting DNA gyrase and topoisomerase IV (for example, *gyrA*, *gyrB* and *parC*)	Fluoroquinolone resistance	Variable
	• Plasmid-mediated (*qnr*)		
	Drug efflux pumps	Resistance to various antibiotics	Variable
	• Acquired resistance via modifications to lipopolysaccharide (lipid A)	Polymyxin resistance	Variable
	• Chromosomal and plasmid-mediated[f] (*mcr1*)		
Pseudomonas aeruginosa	ESBL	Resistance to penicillins, oxyiminocephalosporins and monobactams, with retained susceptibility to cephamycins,β-lactam and/or (β-lactamase inhibitor combinations and carbapenems	• Carbapenems[c,g] • Ceftolozane–tazobactam[c] • Ceftazidime–avibactam[c] • β-Lactam and/or β-lactamase inhibitors[c] • Fluoroquinolones[c] • Aminoglycosides[c,d]
	AmpC β-lactamases	Resistance to oxyiminocephalosporins (for example, cefotaxime, ceftazidime and ceftriaxone), cephamycins (for example, cefoxitin) and many β-lactam and/or β-lactamase inhibitor combinations	• Carbapenems[c,g] • Ceftazidime–avibactam[c] • Ceftolozane–tazobactam[c] • Fluoroquinolones[c] • Aminoglycosides[c,d]
	Carbapenemases (for example, OXA-48)[f]	Carbapenem resistance and resistance to other β-lactam antibiotics	• Polymyxin[c,d] • Aminoglycosides[c,d]

Organism	Common and emerging mechanism(s) of resistance	Resistance phenotype	Antimicrobial agents with potential in vitro activity against resistant organisms[a,b]
	Gene mutations affecting outer membrane protein (porin) mutations (for example, OprD)	OprD confers only carbapenem resistance; other porin mutations may affect the other β-lactams	• Ceftolozane–tazobactam[c] • Aminoglycosides[c,d] • Polymyxin[c,d] • Possibly anti-pseudomonal β-lactams[c]
	Gene mutations affecting DNA gyrase and topoisomerase (*gyrA* and *parC*)	Quinolone resistance	Variable
	Drug efflux pumps	Variable: can actively expel β-lactams, quinolonesand aminoglycosides	Variable
Acinetobacter spp.	ESBL	Resistance to penicillins, oxyiminocephalosporins and monobactams, with retained susceptibility to cephamycins, β-lactam and/or (β-lactamase inhibitor combinations and carbapenems	• Sulbactam[c,h] • Carbapenems[c] • Aminoglycosides[c,d]
	AmpC β-lactamases	Resistance to oxyiminocephalosporins (for example, cefotaxime, ceftazidime and ceftriaxone), cephamycins (for example, cefoxitin) and many β-lactam and/or β-lactamase inhibitor combinations	• Sulbactam[h] • Polymyxins[c,d] • Combination regimens (for example, polymyxin[c,d] plus carbapenem[c]) • Aminoglycosides[c,d]
	• Carbapenemases • Ambler class B: metallo-β-lactamases (for example, VIM and IMP) • Ambler class D: oxacillinases (for example, OXA)	Carbapenem resistance and resistance to some β-lactam antibiotics	• Sulbactam[c,h] • Polymyxins[c,d] • Aminoglycosides[c,d] • Combination regimens (for example, polymyxin[c,d] plus carbapenem[c])
	Outer membrane protein (porin) mutations	Carbapenem resistance and resistance to some β-lactam antibiotics	Variable
	Aminoglycoside-modifying enzymes (acetylating, adenylating and phosphorylating)	Aminoglycosides	Variable
	gyrA and *parC*	Quinolone resistance	Variable

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Organism	Common and emerging mechanism(s) of resistance	Resistance phenotype	Antimicrobial agents with potential in vitro activity against resistant organisms[a,b]
	Drug efflux pumps	Varies: can actively expel β-lactams, quinolonesand aminoglycosides	Variable

ESBL, extended-spectrum β-lactamase; IMP, active on imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OprD, outer membrane porin D; OXA, oxacillinase-type carbapenem-hydrolysing β-lactamase (OXA largely refers to OXA-48, except in India, where it refers to OXA-181); PBP2a, penicillin-binding protein 2a; VIM, Verona integron-encoded metallo-β-lactamase.

[a] Selection of empirical therapy for an individual patient should be based on the patient's history, epidemiological risk factors and local susceptibility patterns. Definitive antimicrobial therapy should be guided by the results of antimicrobial susceptibility testing.

[b] These antibiotics frequently demonstrate in vitro activity against the specific organism and resistance mechanism. However, susceptibility should be confirmed as bacteria may harbour multiple mechanisms of resistance that can render them resistant to the listed antibiotic.

[c] May require dose adjustment in patients with reduced creatinine clearance and/or dialysis dependence.

[d] Potential for nephrotoxicity.

[e] Contraindicated for patients with renal impairment.

[f] Emerging mechanism of resistance.

[g] Ertapenem does not possess activity against *P. aeruginosa*.

[h] Available in the United States only as ampicillin–sulbactam.

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