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REVIEW

Epidemiology of antimicrobial resistance in bloodstream infections

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ABSTRACT

Antimicrobial resistance in bacterial pathogens is a worldwide challenge leading high morbidity and mortality in clinical settings. Multidrug resistant patterns in gram-positive and –negative bacteria have resulted in difficult-to-treat or even untreatable infections with conventional antimicrobials. Since the early identification of causative microorganisms and their antimicrobial susceptibility patterns in patients with bacteremia and other serious infections is lacking in many healthcare institutions, broad spectrum antibiotics are liberally and mostly unnecessarily used. Such practice has, in turn, caused dramatic increases in emerging resistance and when coupled with poor practice of infection control, resistant bacteria can easily be disseminated to the other patients and the environment. Thus, availability of updated epidemiological data on antimicrobial resistance in frequently encountered bacterial pathogens will be useful not only for deciding on empirical treatment strategies, but also devising an effective antimicrobial stewardship program in hospitals.

Introduction

Multidrug resistance (MDR) in various bacterial pathogens has reached to a pandemic level during the last 2 decades. The Centers for Disease Control and Prevention (CDC) estimates that in the US more than 2 million people are infected every year with antibiotic resistant microbes and at least 23.000 die due to these infections.[1] The calculated price tag is $20 billion in direct healthcare costs, with far more costs in lost productivity. A similar report from Britain predicts that the toll of global antimicrobial resistance will be 10 million deaths per year and up to $100 trillion lost to the global economy by 2050.[2] A recent study revealed that 30% reduction of efficacy of antibiotics for antibacterial prophylaxis in surgery and cancer chemotherapy may result in 120.000 additional surgical site- and post-chemotherapy-infections per year in the US and 6300 infection-related deaths.[3]

Any bacteria can develop antimicrobial resistance (AMR), but still maintain its susceptibility to many others, allowing successful treatment in clinical settings. Recently, a selected group of bacteria has been described by the acronym of ESKAPE and they predominantly cause most of the nosocomial infections in healthcare settings.[4] The term refers *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species*. However, selection of these bacteria and the acronym itself have been criticized by others since it excludes other enteric gram-negative pathogens including *Escherichia coli* which is one of the most frequent bacterial agents causing severe infections with significant MDR mechanisms. Thus, a more appropriate term ESCAPE has been proposed where "C" refers to *Clostridium difficile*, an important nosocomial pathogen that may easily acquire an MDR phenotype and "E" refers *Enterobacteriaceae* covering all gram-negative enteric bacteria including *E. coli, K. pneumoniae, Proteus spp.* and *Enterobacter spp.*[5]

Various risk factors have been described leading increased rates of AMR among which inappropriate and widespread use of antibiotics is the most significant one.[6] Poor governance and corruption have also been suggested to contribute to the levels of AMR in a given country.[7]

Epidemiology of global antimicrobial resistance

In its global report on surveillance in AMR, The World Health Organization (WHO) declared that AMR in wide range of infectious agents has become a serious public health problem and a post-antibiotic era is a real possibility for the 21st century.[8] Although, there was significant gaps in surveillance and lack of standards for methodology in many countries worldwide, WHO

reported very high rates of resistance both for health-care associated (HCA) and community-acquired (CA) infections. The data pointed out that fluoroquinolone resistance in *E. coli* has been reported in 92 member states out of 194 and 5 out of 6 WHO global regions. Similarly, the 3rd generation cephalosporin resistance (most probably due to an extended-spectrum cephalosporinase) was recorded in 86 member states and 5 regions. Comparable figures were noted for the 3rd generation cephalosporin or carbapenem resistance in *K. pneumoniae* and for methicillin resistance in *S. aureus*.[8]

Other major epidemiological surveillance networks including those in Europe (i.e., European Antimicrobial Resistance Surveillance Network -EARS-Net and Central Asian and Eastern European Surveillance of Antimicrobial Resistance-CAESAR) and in the US (The National Healthcare Safety Network-NHSN at the CDC) also documented that the antibiotic resistant bacteria have become much more prevalent during the last decade.[9-11] The details of their data will be summarized below for different types of bacteria which may cause bacteremia in different healthcare settings. An online tool is also available showing the current resistance rates and antibiotic use in various countries on an interactive map and data are updated as the new information becomes available (http://resistancemap.cddep.org).

Epidemiology of antimicrobial resistance for selected, important human pathogens causing bacteremia

Gram-positive bacteria

Staphylococcus aureus (SA) and coagulase-negative staphylococci (CNS). *Staphylococcus aureus* is the most significant cause of gram-positive bacteremia in the developed world for which incidence varies 10 to 30 per 100.000 person years.[12] Methicillin resistance is the hallmark of antimicrobial resistance in both SA and CNS which can be regarded an indicator for multidrug resistance. During the last decade, the rates of nosocomial methicillin-resistant *S. aureus* (MRSA) bacteremia has been either stabilized or declined in many geographic regions of the world (Fig. 1).[13-16] Although this reduction was attributed to improved infection control practices in the West, the decline was also noted from the developing countries where infection control remains to be an unsolved problem, although the figures reported from these countries may be less reliable.[12] The most recent data available from ECDC in 2013 indicate that in Europe, Romania has the highest rates of MRSA (>50%) isolated from cerebrospinal fluid (CSF) or blood and additional 5 countries in the EU region (Cyprus, Greece, Hungary, Italy and Spain) have rates between 25% and 50%.[17] The lowest figures are from the Scandinavia and the Netherlands (<5%).

Methicilin sensitive *S. aureus* (MSSA) strains are generally sensitive to clindamycin, however resistance can be selected during treatment. Particulary in those strains initially resistant to erythromycin, if treated with clindamycin, resistance can rapidly be selected during therapy.[18]

Trimethoprim-sulfamethoxazole (TMP-SMX) is highly active against MSSA and community-acquired MRSA (CA-MRSA) isolates. Sensitivity varies among MRSA strains, ranging 26–100% in US and 0–92% worlwide.[19]

Reduced susceptibility to glycopeptides in *S. aureus* has emerged during the last 2 decades and may have significant implications for those receiving these antibiotics (i.e., vancomycin and teicoplainin). Vancomycin-intermediate *S. aureus* (VISA, vancomycin MIC 4–8 mg/L) and heteroresistant (hVISA) strains with vancomycin MICs within the susceptible range but with suppopulations that are able to grow in the presence of vancomycin were reported worldwide. VISA isolates exhibit decreased susceptibility to teicoplainin as well. The true incidence of hVISA are difficult to establish since the laboratory detection is too cumbersome. A 2009 report from the US indicated that the prevalence was 0.4% in MRSA isolates. This rate was increased as the MIC of vancomycin escalated (i.e. 10.5% in those with 2 mg/L vancomycin MIC vs 0.1% in those with 1 mg/L).[20] The strains with a high-vancomycin MIC, but still within susceptible range to vancomycin (i.e., . 1–2 mg/L) may cause treatment failure and constitute a public health problem. The rise of vancomycin MICs over time was described as 'MIC creep' and mainly reported in centers where large amounts of vancomycin are consumed.[21] However, recent data indicated that the '*MIC creep*' was not translated into increased mortality rates.[22,23]

Daptomycin is active against staphylococci with decreased glycopeptide activity. Development of resistance to this lipopetide antibiotic has been rarely reported.[24] However, in a study with *S. aureus* bacteremia with or without endocarditis, 6 of 120 patients treated with daptomycin had microbiological failure and daptomycin MICs increased from 0.25 mg/L baseline to >2 mg/L during therapy.[25]

The new lipogylcopeptide telavancin has potent bactericidal activity against all *S. aurues* isolates including those non-susceptible to daptomycin.[26] No clinically-relevant resistant isolates have been described for this agent, so far.

Staphylococcus aureus is the second most common pathogen only after *E. coli* causing community-acquired
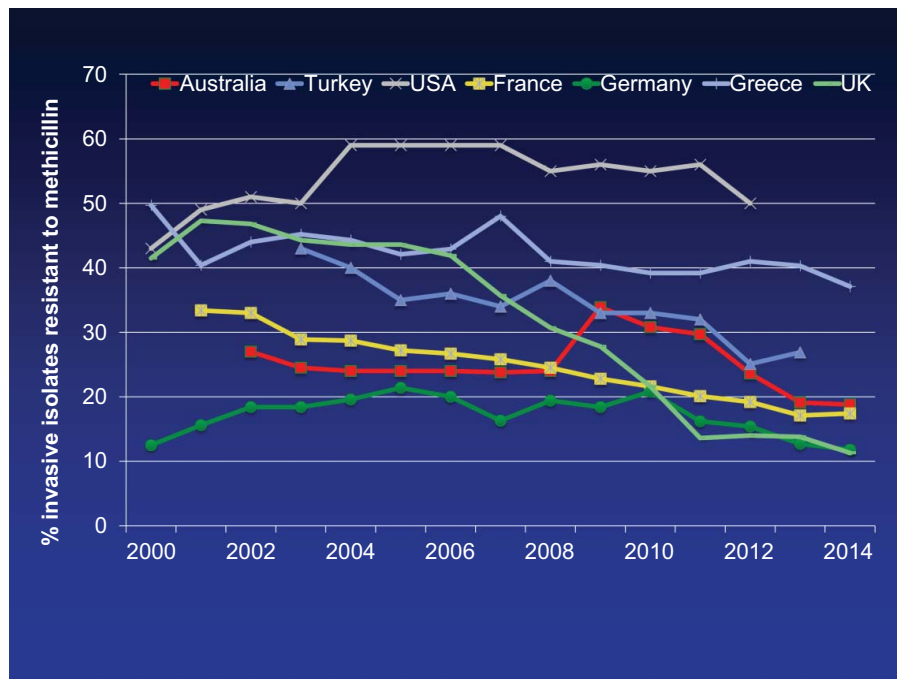
Figure 1. Data shown on the graph are obtained from the following sources: Australia: Australian Group on Antimicrobial Resistance (AGAR). Available at http://www.agargroup.org, France, Germany, Greece, UK: European Antimicrobial Resistance Surveillance Network (EARS Net). Available at http://www.ersnet.org, Turkey: The data for the period of 2003–2008 are derived from EARSS European Antimicrobial Resistance Surveillance System (EARSS) available at http://www.rivm.nl. For 2009–2010; personal communication with Dolunay Gulmez, M.D. For 2011–2013; from National Antimicrobial Resistance Surveillance System Yearly Reports 2011–2013. Turkish Public Health Insititution. Available at http://uamdss.thsk.gov.tr, **USA**: Resistance Map-The Center for Disease Dynamics Economics & Policy (CDDEP) 2015. Available at: http://resistancemap.cddep.org.

bloodstream infections (CA-BSIs).[28] It has been estimated that in the Western countries, the incidence of CA-BSIs due to SA is approximately 15 per 100.000 and a mortality rate of 3 per 100.000.[29] Community-acquired MRSA infections have emerged as a global problem since the turn of the 21st century.[30-32] Five major clones are found to be associated with most of the CA-MRSA infections worldwide including multilocus sequence type 1 (ST-1)/USA400 and ST-8/USA300 dominantly found in North America, ST-59 observed in South East Asia, ST-80 observed in Europe and ST-30 distributed worldwide[28]. The clonal structure remains to be determined in CAESAR countries.[10] Although CA-MRSA strains initially caused mainly skin and soft tissue infections in healthy individuals and in homeless and imprisoned population, recently increased rates of bacteremia and other invasive infections with CA-MRSA strains have been reported. Moreover, these strains moving into the hospital settings increasingly caused HCA infections including ventilator associated pneumonia, surgical site infections and bacteremia.[33,34] They usually remain susceptible to many non-beta-lactam antibiotics including clindamycin and TMP-SMX.[27]

Coagulase-negative streptococci are the most common cause nosocomial BSIs and are responsible almost one third of all healthcare associated bacteremia. The incidence is highest in those with cancer and neutropenia and those with catheter- and/or prosthetic-device related infections.[35,36] Multiple antibiotic resistance is highly encountered among hospital isolates and usually related with methicillin resistance.[37]

Resistance rates up to 90% for methicillin, 78.6% for levofloxacin, 68% for ciprofloxacin, and 48.5% for clindamycin have been reported in US.[38] Multidrug resistancein CNS was found to be related with levofloxacin prescribing patterns.[38]

Resistance to vancomycin is very rare, however a 20.8% resistance to teicoplanin was reported from UK, particulary in *S. haemolyticus*.[37] Although the reported rates are usually <1 .5%, linezolid resistance is emerging and might be a future concern in CNS.[39,40] At present, the resistance is negligible for daptomycin, tigecycline and newer agents such as televancin, oritavancin and dalbavancin.[41] Ceftobiprole, a new anti-MRSA cephalosporin, is highly active to both MRSA and methicillin-resistant CNS, but not approved for the treatment of bacteremia caused by any of these pathogens.[42] Another anti-MRSA cephalosporin, ceftaroline, although not approved for the treatment of bacteremia, has been used off-label for *S. aureus* bacteremia frequently caused by

MRSA and successful results were reported.[43] The results of a currently completeed prospective, non-comparative study for the treatment of *S. aureus* bacteremia is yet to be released.[44]

Streptococcus spp. *including* **S. pneumonia** *and viridans streptococci.* *Streptococcus pneumonia* is the third most common cause of CA bacteremia. Its prevalence in the Western World ranges between 10 and 20 per 100.000 population.[28] Only 10% of cases are related with healthcare associated infections.[45] One of the important aspects of invasive pneumococcal infections related with bacteremia is that the universal use of conjugate pneumococcal vaccine in infants and more recently in the adult population: Decreased exposure from infants led the adult population have a lower incidence of invasive pneumococcal disease which is also described as herd protection.[46]

In the US, >90% of all pneumococci causing infections other than meningitis are sensitive (<0.06 mg/L) and only 2% are resistant (>2 mg/L) to parenteral penicillin or oral amoxicillin. Only 1% of isolates are resistant to ceftriaxone.[47] In Europe, higher rates of resistance to penicillin (>0.06 mg/L) was reported in several countries in 2013: 54% in Turkey, between 25 to <50% in Spain, Croatia, Cyprus and Romania, 10 to 25% in Bulgaria, Latvia and Lithuania.[10,17] The remaining countries has lower rates (<10%) and France, UK, Norway, Belgium, Netherlands, Austria, Czech Republic, Slovenia and Estonia has the lowest rates (<1%).[17] It should be noted that European isolates are from blood or CSF origin and those of US are from non-meningitis isolates and not necessarily obtained from invasive infections. Much higher rates are reported from Asian countries.[48,49] Penicillin resistant pneumococci are more likely to show higher resistance to other classes of antimicrobials. Current figures of resistance in US include 35% to macrolides, 10% to clindamycin, 30% to trimethoprim sulfamehoxazole, 18% to doxycycline and 2% to respiratory quinolones.[47] Higher rates of macrolide resistance are reported from Europe.[17]

Viridans streptococci can cause infective endocarditis particularly in patients with compromised heart valves, although its prevalence has decreased particularly in the Western World.[50] They can also produce bacteremia and septic shock particularly in neutropenic patients.[51] Clinically significant bacteremia are attributed to viridans streptococci in 0.5% of all blood cultures received in clinical microbiology laboratory.[52] Although these bacteria are susceptible to most antimicrobials, *β*-lactam resistance has emerged and may cause a significant problem especially in patients with immunosuppression and bacteremia.[51,53] In the latter group, penicillin resistance rates

>50% is reported.[54] These bacteria do not produce a *β*-lactamase, the *β*-lactam resistance is due to altered penicillin binding proteins. Ceftriaxone and cefepime resistance has been reported up to 23 and 25%, respectively in strains isolated from hospitalized or cancer patients.[54,55] Viridans streptococci may cause bacteremia and septic shock in patients with neutropenia and with certain risk factors. Since the latter 2 cephalosporins are frequently used for initial empirical therapy, such resistance may have serious clinical implications[53]. Vancomycin is higly effective on such strains and should be preferred as the empirical agent of choice in this type of neutropenic patients.

Enterococci. Among all enterococci, *E. faecium* is the most challenging bacterium in terms of antibacterial resistance and therapy. In the US, enterococci are the second most common bacteria isolated from catheter related (CR)-BSIs.[11] Enterococci are intrinsically resistant to many antimicrobials, but also easily acquire mutations and exogenous genes to develop further resistance.[56] While aminopenicillin resistance is rare (<1%) to low (up to 25%) in *E. faecalis*, it is encountered around 90 % of nosocomial *E. faecium* isolates.[17,56] Beta-lactamase production is infrequently associated with resistance and can be overcome with the use of *β*-lactamase inhibitor compounds. The production of PBP5 with low affinity to penicillins is the major culprit for *β*-lactam resistance.[56]

High-level resistance to all aminoglycosides eliminates the synergistic activity of penicillins and vancomycin both of which can enhance activity of aminoglycosides in enterococci with low-to-moderate resistance. High-level aminoglycoside resistance has increased in both *E. faecalis* and *E. faecium* during the last 3 decades and current figures from Europe indicate between 5–>50% in *E. faecalis* and 25–>50% in *E. faecium*.[17]

Glycopeptide resistance in enterococci is a much bigger problem in the US than Europe and elsewhere. By 2007, >80% of *E. faecium* isolates in the US hospitals were reported to be resistant to vancomycin whereas in Europe only Ireland reported a resistance rate of >50%.[17,56,57] Similarly, MDR enterococci is much more prevalent in the US than elsewhere.[56]

Enterococci are the third most frequent agents of bacteremia in hematological cancer patients and stem cell transplant recipients and may affect up to 12% of all transplant patients.[51] In these patient groups, a shift from *E. faecalis* to to *E. faecium* has resulted in higher rates of vancomycin resistant enterococcus (VRE) infections.[51] However, similar to the general epidemiology, VRE infections are less of a problem in Western European transplant centers with <5 % of enterococci being

to resistant to vancomycin.[355] Resistance to linezolid and daptomycin is rarely reported.[58]

Clostridium difficile. *Clostridium difficile* very rarely causes bacteremia and usually constitutes one of the offending microorganisms of a polymicrobial etiology in bacteremic patients.[59] However, it is a major cause of antibiotic associated diarrhea and its prevalence has siginificantly increased during the last decade particulary in North America and Europe and recently in Israel.[60] This increase was associated with the emergence of hypervirulent *C. difficile* strains.[61] The most prominent hypervirulent strain is PCR-ribotype (RT) 027 which is responsible serious and frequently recurring infections and many of these strains carry an MDR phenotype. A European survey in 2005 indicated that 55% of 148 isolates with resistance to at least one antibiotic was multidrug resistant.[62] In the US, among 508 toxigenic *C. difficile* isolates collected between 2001 and 2013, 28.1% was RT027 strain.[63] Additionally, other hypervirulent strains not necessarily related with RT027 were identified. Among these RT078 cause *Clostridium difficile* disease both in community and hospital settings, and also in animals.[61]

Gram-negative bacteria

Escherichia coli

Production of one or more extended spectrum β-lactamases (ESBLs) is the main resistance mechanism to broad-spectrum penicillins and cephalosporins in enteric gram-negative pathogens. Among the numerous ESBLs, CTX-M type of enzymes have become clinically the most important β-lactamases and are highly prevalent in *E. coli*.[64,65]

Escherichia coli is one of the most frequent pathogens causing bacteremia both in CA and in HCA bacteremia including those in patients with cancer and neutropenia.[35,51,66] *Escherichia coli* sequence type (ST)131 with CTX-M-15 ESBL production has a high epidemic potential and spread worldwide.[64,65,67] EARS-Net data indicated that in the EU mean resistance rate to the 3rd generation cephalosporins was 11.9%, ranging 4.4% in Sweden, 38.1% in Bulgaria.[9] The ESBL-positive strains were reported between 71.5% and 100% in different European countries. The CAESAR data noted that resistance rates varied between 7.0% in Switzerland and 44% in Turkey among all invasive strains.[10] Higher rates of ESBL production were reported from India (>80%), and China (>60%), however these isolates were mainly from intraabdominal infections, but in some cases there were secondary bacteremia.[68,69] Current prevalence of ESBL production in bacteremic isolates in US varies between

8.1% to 13.7%.[70,71] Isolates from ICU patients and patients with hematological malignancies showed higher resistance rates.[66,71] In those countries where antimicrobial use is not strictly controlled, high prevalence of ESBL production has been reported in community-settings as well. Examples including countries in Asia including India[69], Cambodia[72] China[73], South Korea[74], Thailand[75], and in Europe including Turkey[76] and Romania[77] provide information about prevalence of ESBLs for both CA and HCA isolates of *E. coli* in various countries. Many ESBL-producing *E. coli* are also resistant to non-β-lactam antibiotics including aminoglycosides and quinolones with different resistance mechanisms.[66,78] ESBL-encoding plasmids may also encode resistance to aminoglycosides, tetracyclines, sulphonamides and trimethoprim.[67] These plasmids frequently encode an inhibitor-resistant β-lactamase, namely OXA-1 which confers resistance to β-lactamase inhibitors including amoxicillin-clavulanate and piperacillin-tazobactam.[67,79]

Quinolone resistance has been reported 41.8% in US in CR-BSIs and between 11 to 52 percent in invasive isolates from EU countries;[11,17] whereas CAESAR data indicated 8% and 41% resistance among isolates from blood and CSF in Switzerland and Turkey, respectively.[10]

Aminoglycoside resistance among *E. coli* and other enteric pathogens is determined by aminoglycoside-modifying enzymes which can be encoded on the same plasmid with ESBLs. This type of resistance in *E. coli* varied between 5–25% in Europe excluding Bulgaria where higher rates of resistance (32%) was recorded in isolated from HCA infections.[10,17]

Carbapenem resistance in *E. coli* in Europe is rarely reported, the highest rates are found in Bulgaria (2.6%) and Turkey (4.0%).[10,17] *Esherichia coli* was the second most frequent carbapenem-resistant *Enterobacteriaceae* (CRE) after *K. pneumoniae* in a recent US survey where the incidence of CRE was determined as 2.93 per 100.000 population.[80] A large surveillance study from China reported the prevalence of carbapenem-resistant *E. coli* is 1.0% and of *K. pneumoniae* 5.5%.[81] One of the most significant carbapenemases described in *Enterobacteriaceae* is New Delhi metallo-β-lactamase-1 (NDM-1). This enzyme is prevalent in the Indian subcontinent, but also frequently reported in Balkans and in the Middle East.[82] The bacteria harboring this enzyme have spread worldwide and are usually only susceptible to colistin, tigecycline and fosfomycin, although susceptibility is not universal.[83] So far, the resistant strains are endemic only in India, Pakistan and Sri Lanka where environmental strains carrying this enzyme were also found. The estimated prevalance of carriage among public in India is between 5 to 15%.[82] Outbreaks have been described in

UK, France, Italy, Greece, China, Australia and elsewhere in Africa and South America.[82] Since *E. coli* infections are very frequent in the outpatient settings, it is feared that a progressive increase in the prevalence of NDM-1 producing *E. coli* may occur and this pattern finally may replace the CTX-M producing strains in the community setting.[82]

Plasmid-mediated colistin resistance (via *mcr*-1 colistin resistance gene) has recently described in *E. coli* isolates worldwide from mainly livestock and less frequently in human samples.[84-89] The implications of this finding may be horrendous since the offending plasmid can easily be transferred between *E. coli* strains including those with epidemic potential (e.g. ST131) and to *K. pneumoniae* and *P. aeruginosa*.[90] As a matter of fact, recent reports already noted the presence of this gene from plasmids in *Salmonellae*[91,92] and *K. pneumoniae*.[93,94] Recovery of an *E. coli* strain from chicken meal in China co-producing plasmid-mediated MCR-1, NDM-9, CTX-M-65 and FosA3 (accounted for fosfomycin resistance) proteins is highly concerning that such strains can colonize the human intestine and transfer resistance plasmids to other gram-negatives. [95]

Klebsiella pneumoniae

The third generation cephalosporin resistance in *K. pneumoniae* in Europe ranged between 2.7% in Finland to 70.1% in Greece and 88% in Serbia; the highest resistance rates were reported from Central, Eastern and South of Europe.[10,17] The ESBL positivity in these isolates were between 65% and 100%.[4] The data from the NHSN indicated that 28.8% of *K. pneumoniae* causing CR-BSIs in participating centers in the US were resistant to the 3rd generation cephalosporins.[11] In Asia, China and Thailand were reported to have the highest prevalence of ESBL producers (33.7% and 40.7%, respectively).[96]

Carbapenem resistance has become the most important epidemiologic and therapeutic challenge in *K. pneumoniae*.[82] There are mainly 3 classes of carbapenemases involved including KPC (Class A), OXA-48 (Class D) and NDM (Class B) for which different epidemiological reservoirs exist. For KPC, the highest-prevalence countries are Greece and Italy in Europe and US and Israel.[82,97] OXA-48 are most prevalent in Turkey, North Africa and India.[82] The main reservoirs for NDM are Indian subcontinent, Middle East and Balkan countries.[83]

KPC-producing isolates are also endemically reported in various Latin American countries[82], China[98,99] and Taiwan[100]. A specific KPC-2 or KPC-3-producing clone (sequence type 258) has been widely disseminated worldwide contributing the spread of resistance.[82]

OXA-48-producing isolates were first described in and then spread from Turkey where frequent nosocomial outbreaks were reported.[101-105] These isolates have now been disseminated to many European countries.[82] OXA-48 producing *K. pneumoniae* strains have been reported in many Middle Eastern and African countries, but rarely from North and South Americas.[82]

Similar to *E. coli* isolates described above, NDM-producing *K. pneumoniae* and other enteric gram-negatives are extensively isolated from out- and in-patient settings and also from the environment in Indian subcontinent.[106]

EARS-Net database in 2013 indicated that Greece (59.4%), Italy (34.3%) and Romania (20.5%) have the highest rates of carbapenem resistance in *K. pneumoniae*.[17] The remaining countries in the EU have a prevalence <2%. However, trend analyses showed a significantly increasing pattern in carbapenem resistance.[17] In the CAESAR program, resistance rates were reported from Serbia (36%), Turkey (11%), and Switzerland (1%).[10] In the US, a recent epidemiological survey from 7 different geographic areas identified 599 CRE isolates in 481 patients of which 58.6% were *K. pneumonia*. The only carbapenemase identified in all isolates was KPC.[57] The frequency of CRE infections in children are increasing, but still low as compared with ESBL-producing strains.[107]

Carbapenem resistant isolates usually show a MDR pattern and are susceptible only to colistin, fosfomycin and tigecycline. However, there is also emergence of resistance against these antibiotics. A multicenter survey from Italy indicated that 43% of KPC- producing *K. pneumoniae* are already resistant to colistin.[108] A very recent multicenter study from the same country reported that during a 4.5 y period, the colistin resistance increased >3-fold in participating centers and related with a mortality rate of 51%.[109]

Pseudomonas aeruginosa

In Europe, *P. aeruginosa* strains with high resistance rates to aminoglycosides, ceftazidime, quinolones, piperacillin-tazobactam and carbapenems are usually reported from Southern and Eastern part of the continent.[9] However, ECDC reported that a trend analysis for 2009 to 2012 indicated a stable resistance pattern for these antimicrobials.

In the US, 10% aminoglycoside resistance in *P. aeruginosa* isolates from catheter-related blood stream infections was reported 10% during 2009–2010.[11] In Europe, 9 out of 29 EU member countries reported >20% aminoglycoside resistance from invasive isolates in 2014.[17] Serbia and Romania have the highest (>50%) resistance rate to aminoglycosides in invasive isolates.

Carbapenem resistance was described in >50% of isolates in 3 countries, between 25 to <50% in 7 countries and 10 to <25% in 11 out of 29 reporting countries.[17] However, a trend analysis indicated that the rate of resistance have been stable in invasive isolates between 2009 and 2012, no significant increase was detected.[9] In CAESAR database, resistance to amikacin, quinolones, piperacillin-tazobactam, ceftazidime and carbapenems in Switzerland was reported as 1%, 10%, 7%, 6% and 9%, respectively; whereas the same rates were 11%, 22%, 27%, 26% and 33% in Turkey.[10] Resistance is high in South America and Southeast Asia and intermediate in the US.[11,110] Several β-lactamases have been described for causing resistance and these include AmpC, ESBL (particularly PER-1) and metallo-β-lactamases.[67] PER-1 producing *P. aeruginosa* which shows high-level resistance to ceftazidime, but susceptible to clavulanate and tazobactam was widely detected in Turkey and less frequently in several European and Asian countries.[111] Carbapenem resistance in *P. aeruginosa* is mostly due to porin deficiencies and rarely caused by carbapenemase production. A detailed resistance mechanisms of antibiotics and their epidemiology in *Pseudomonas aeruginosa* have recently been reviewed.[112] Emergence of colistin resistance in *P. aeruginosa* has also been reported worldwide.[113]

Acinetobacter baumannii

In EARS-Net database, in 18 countries in the EU from where susceptibility rates for *A. baumannii* were reported >50% of all isolates were resistant to carbapenems, quinolones and aminoglycosides.[9] Carbapenem resistance was reported in >50% of isolates in Portugal, Greece, Italy, Cyprus, Romania and Bulgaria. Lower rates were detected in other countries (e.g., France, UK, and Germany). These isolates are usually co-resistant to aminoglycosides and quinolones. In CAESAR surveillance, Serbia reported 91% quinolone and 93% carbapenem resistance, whereas Switzerland's figures for both antibiotics were 11%. In the US, with CR-BSI, the resistance to carbapenems was detected in 62.6% and an MDR phenotype in 67.6% of isolates.[11]

The most frequent Class A ESBLs found in *A. baumanni* are PER-, GES- and VEB-type enzymes. These β-lactamases confer resistance to extended-spectrum cephalosporins, but inhibited by tazobactam and clavulanic acid.[112] PER-1 producing *A. baumannii* are prevalent in Turkey, but also disseminated in several Eastern European countries including Russia, Hungary, Romania, East and Southeast Asia including China and Korea and finally detected in the US.[112] TEM, SHV and CTX-M-type ESBLs are rarely found in *A. baumannii*.

Class B β-lactamases (metalloenzymes) are also reported in *A. baumannii* and include IMP-, VIM- and NDM-type enzymes. These β-lactamases provide activity against not only to carbapenemes, but also to broad-spectrum cephalosporins and penicillins. The majority of NDM-producing *Acinetobacter spp* are reported from China and the Middle-East.[106] Species identification may be important within the *A. baumannii* group since carbapenem resistance is more frequently reported in *A. baumannii* and mortality is much higher in patients with bacteremia casused by these strains as compared with other species such as *A. pittii* and *A. nosocomialis* which are the other clinically important members of the *A. baumannii* group.[114] Various carbapenemases including (NDM-type and Class D enzymes) are also described in *A. pittii*, recently.[115,116]

Class D, OXA-type carbapenemases are responsible for most carbapenem resistance in *A. baumannii*.[67] OXA-51 is a naturally occurring β-lactamase in *A. baumannii* and normally has weak carbapenemase activity.[112] However, several additionally acquired class D enzymes are described and include OXA-23, −40, −58, −143, and −235. These enzymes cause weak resistance to carbapenems, but are not active against extended-spectrum cephalosporins. Thus, high-level resistance usually require other mechanisms involved such efflux and porin loss.[112] OXA-23 enzymes are the most prevalent β-lactamases in *A. baumannii* and detected worldwide.[117]

The ArmA enzyme is the most frequently found methylase which is responsible for high-level resistance to all aminoglycosides in *A. baumannii*. The gene responsible for this enzyme is often identified among OXA-23 producing *A. baumannii* strains. Other methylases are also described.[112]

Overexpression of efflux pumps can provide resistance to quinolones. These pumps also use aminoglycosides, tetracyclines, chloramphenicol and trimethoprim as substrates, thus the quinolone resistance can be selected by non-quinolone antibiotics as well. Usually several of these mechanisms are present in MDR *Acinetobacter* isolates.

Tigecycline, although not approved for the treatment of *Acinetobacter* infections, has been frequently prescribed for various nosocomial infections caused by MDR *A. baumanni*. Efflux pumps were described to cause resistance in clinical *A. baumanni* isolates. A brief exposure to the drug during therapy may trigger resistance and hamper the efficacy of tigecycline.[118]

Colistin is one of the most important therapeutic alternatives for treating *A. baumanni* infections. Resistance to this agent in *Acinetobacter* is rarely reported.[112] Laboratory errors are frequent and most laboratories do

Table 1 Frequent resistance mechanisms for selected antibacterial antibiotics in clinically important gram-negative bacteria (47,48,50,55,58,59,61,63,70,76,84,91) Main resistance determinants.

Bacteria	Cephalosporins	Carbapenems	Aminoglycosides	Quinolones	Polymyxins
Enterobacteriacea (*E. coli, Klebsiellae*)	ESBLs, mainly CTX-M type are major concern. E. coli ST131 with CTX-M-15 has epidemic potential worldwide. Isolates retain sensitivity to carbapenems if not co-produced with carbapenemsases. Many are also resistant to non-beta-lactams for which resistance genes are encoded on the same plasmid.	KPC, OXA-48 and NDM are most important carbapenemases. Isolates only susceptible to colistin, tigecycline and fosfomycin, although not all strains are susceptible. Less frequently, porin loss coupled with ESBL and AmpC beta-lactamase production can lead resistance to carbapenems.	Mainly due to aminoglycoside modifying enzymes or ribosomal (r)RNA methylases that may block aminoglycosides to bind modified bacterial ribosomes. These enzymes are frequently encoded on the same plasmid with ESBLs.	Mutations affecting chromosomal topoisomerase genes *gyrA* and *parC* are main reistance mechanisms.	Chromosomally mediated modificiation of Lipid A component of lipopolysccharide (LPS) leading reduced affinity for polymyxins. Recently described plasmid-mediated colistin resistance through *mcr-1* gene in China, East and South-East Asia and Europe is a big concern.
Other enterobacteriaceae (e.g. *Enterobacter* spp. *Citrobacter spp.* and *Serratia spp.*)	In addition to ESBL, hyperproduced chromosomally mediated beta-lactamases (e.g. AmpC).	Same as above	Same as above	Same as above	Same as above, but less frequent. *mcr-1* has shown only in Salmonella, so far.
Non-fermenters *P. aeruginosa*	ESBLs (e.g. PER-1 and VEB-1), hyperproduction of AmpC beta-lactamases, upregulated efflux are major resistance mechanisms.	Porin mutations blocking carbapenem entry through outer membrane is the most frequent cause. Various carbapenemases including IMP, VIM, SMP, GIM and NDM are less frequently reported.	In addition to above mechanisms, decreased outer membrane permeability and upregulated influx are invloved.	In addition to topoisomerase mutations, upregulated efflux is a major resistance determinant.	Same as above. Plasmid-mediated resistance is yet to be identified.
A. baumannii	ESBL production is the main resistance mechanism. PER, VEB and GES-type ESBLs are prevalent worldwide. CTX-M type enzymes are rare.	Several carbapenemases are involved and main causes of resistance (see text).	Arm-A meythlase confers high-level resistance. rRNA methylases are also described. Efflux-mediated multidrugresistance is also important.	Upregulated efflux is main mechanism of resistance usually leading co-resistance to aminoglycosides, trimetoprim, tetracyclines and chloramphenicol.	In addition to above, complete loss of LPS production has been described.

Abbreviations: ESBL: Extended-spectrum β-lactamase.
ST131: sequence type 131.

not use a microdilution method which should be the standart test for evaluating colistin resistance. Most of the resistant isolates are described from South Korea, Spain, the US and Iran.[112]

A concise summary of main resistance mechanisms in clinically important gram-negative bacteria is given in Table 1.

Reversing the tide of emerging antimicrobial resistance

The main drive behing emerging and spreading resistance is antibiotic consumption both in humans and animals, in the latter for promoting growth and prophylaxis.[84,119] Environmental contamination with antibiotics may lead emergence of antibiotic resistance and in turn creates a reservoire for antibiotic resistance genes.[120] On the other hand, it has been consistently shown that those areas where the usage is high, the resistance is widespread both in community and hospital settings.[7,121,122,123] Since the problem of emerging resistance is multifaceted, its prevention and control will require multiple, coordinated interventions by various parties.[119] At the hospital level; education and promotion of prudent use of antimicrobials, development and effective use of rapid and point of care diagnostic tests, devising effective surveillance systems for monitoring resistance and implementation of effective infection control programmes are essential parts of an antibiotic stewardship program. These programmes are desparetely needed and may be lacking even in hospitals in the developed part of the world.[124,125]

Conclusions

Antimicrobial resistance, particularly MDR phenotype in clinically important community and nosocomial

pathogens are prevalent and its incidence is increasing. As the rate of resistance escalates in a given environment, antimicrobials with broader-spectrum of activity are more frequently used in empirical fashion fearing that a delay in initiating effective antimicrobial therapy may result in higher mortality especially in patients with severe underlying diseases and immunosuppression. Such practice may cause a vicious circle leading further increase in resistant isolates. A thorough knowledge about local epidemiology of resistance may contribute to limiting resistance and may have a significant role in designing effective antimicrobial stewardship policies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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