Update on the main MDR pathogens: prevalence and treatment options

Silvano Esposito, Giuseppe De Simone
Department of Infectious Diseases, University of Salerno, Italy

SUMMARY

In recent years the proportion of multi-drug resistance (MDR) among the bacterial pathogens causing infections, particularly those acquired in healthcare settings has worryingly risen worldwide. It poses a serious public health threat as the multiple patterns of resistance limit the effective treatment options for such infections. Although many bacterial species have developed reduced susceptibility to a wide array of antimicrobial molecules, a particular group of pathogens acronymically referred to as “ESKAPE” (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) plays a clinically relevant role in the aetiology of life-threatening nosocomial infections. In this review, we represent the rise of MDR among the ESKAPE pathogens over the decades and report studies from each continent showing the current prevalence and burden of such infections worldwide.

Keywords: Multidrug-resistance, Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.

INTRODUCTION

Hospital-acquired infections (HAIs) can be defined as the infections contracted in healthcare facilities (including hospitals, nursing homes, clinics and other settings) occurring more than 48 hours after admission. HAIs represent a serious public health threat as they are one of the major causes of morbidity and death in hospitalized patients, leading to prolonged hospital stay and increased hospital charges [1, 2]. The burden of these infections has drastically risen worldwide over last decades. In 2002 the Centers for Disease Control and Prevention (CDC) estimated that the number of HAIs diagnosed in U.S. hospitals was approximately 1.7 million, while the estimated deaths associated with HAIs were 99,000 (most of them due to pneumonia and septicemia) [3]. In 2011, a large-scale survey conducted on 183 U.S. hospitals reported that 4% of all patients contracted one or more HAIs, therefore the estimated burden of HAI was about 722,000 cases [4]. In 2011-2012 a large study including a total of 273,753 patients from 1149 hospitals through Europe revealed that 5.7% of patients had at least one HAI; this data suggests that the total annual number of HAIs among patients referring to European hospitals was about 3.2 million [5]. Although few studies provide epidemiological data on HAI in the developing countries, it has been estimated that the prevalence of these infections is about 15 cases per 100 patients, thus much higher than that reported from Europe and USA [6]. The management of HAIs is complicated by the growing number of antimicrobial-resistant pathogens to which inpatients are exposed during their staying in healthcare facilities. Indeed, as largely reported in recent literature, different bacterial species become resistant to many classes of antimicrobial and chemotherapeutic agents, thus they have been defined as multidrug-resistant (MDR) [7-9]. Scarce adherence to infection control protocols, inappropriate and excessive use of antimicrobial molecules have contributed to the increase of the MDR phenomenon, that is due to various
adaptation mechanisms, including biofilm formation, drug inactivation and modification of drug targets [7]; moreover, the spread of antibiotic resistance can be enhanced by mechanisms of horizontal gene transfer among species [8]. In recent years, among the MDR bacterial species many authors have highlighted the clinical relevance of a group of antibiotic resistant pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.) acronymically named “ESKAPE”. These bacteria represent common causes of life-threatening HAIs, in particular for critically ill patients admitted in intensive care units (ICUs) [7].

Studies of surveillance are of paramount importance as they yield the actual proportion of the MDR problem, moreover, epidemiological studies by providing local data facilitate the efforts to define appropriate control measures in order to check the rise of resistances [10-12].

Enterococcus faecium

The genus Enterococcus includes more than 20 species of Gram-positive, facultative anaerobes, bacteria. Amongst the Enterococcus species, the most clinically relevant pathogens are represented by Enterococcus faecium and Enterococcus faecalis [7]. These bacteria can survive for long periods in the hospital setting resisting to the action of some alcohol preparations and thus easily contaminate also the surfaces of medical equipment [13]. Indeed, in the U.S. Enterococci are the fourth most common causative organisms of nosocomial infections, the second cause of bacteraemia and the third cause of urinary tract infections [13-15]. Their ability to develop resistance to many antimicrobial molecules is due to the plasticity of their genomes: they rapidly accumulate genetic mutations and acquire plasmid genes conferring additional resistances. Although penicillin alone or in association with an aminoglycoside has been considered the gold standard against enterococcal infections for decades, most enterococci strains have developed tolerance to the activity of β-lactam antibiotics [13]. Ampicillin resistance has been reported in ~90% of hospital-isolated E. faecium strains and is due to the synthesis of penicillin binding proteins characterized by a low affinity for the penicillins (such as PBP5) [13]. An epidemiological study conducted in several microbiological laboratories throughout The Netherlands found that the rates of ampicillin-resistance among the Enterococcus faecium isolated from bloodstream specimens increased from 4% in 1999 to 20% in 2005 [16]. Because of the global emergence of this phenomenon, glycopeptides (e.g. vancomycin) have been used for years as reliable alternative to ampicillin for patients with allergy to β-lactams, or in case of infections caused by ampicillin-resistant enterococci [13]. But, once again, several mechanisms of resistance even to vancomycin (such as the acquisition of van gene clusters) were finally reported in Enterococci strains, at first in U.S. hospital settings in late 1980s, then, during the following years, the prevalence of vancomycin-resistant Enterococci (VRE) has worryingly increased worldwide [7, 17]. The number of hospitalizations due to VRE infections in United States increased from 4.60 to 9.48 hospitalizations per 100,000 population during the period 2003-2006 [18]. Currently, CDC estimates that 30% of Enterococcus HAIs are attributable to VRE, causing approximately 1,300 deaths each year in the United States [19]. A multicentre prospective study found that in South America the prevalence of vancomycin resistance among all the enterococci isolated was relatively low (6%) compared to that in the United States. In part, it may be due to the fact that in this study E. faecalis resulted to be the most frequent species isolated (with a high ratio of E. faecalis to E. faecium, 5:1) and it is known that the major reservoir of acquired vancomycin resistance is Enterococcus faecium whilst E. faecalis is characterized by lower antibiotic-resistance [20]. Also in Asia, the proportions of VRE phenomenon are still low: in Thailand, the incidence of VRE never exceeded 5.1% during the decade 1999-2009 [21]. As regards Europe, data from the ECDC Surveillance Atlas revealed that in 2015 VRE rates significantly vary across the continent with some countries reporting <1% of resistant isolates (France, Iceland and Scandinavian countries) whilst the majority of EU countries (including Germany, Italy and UK) have percentages included in the range 10-25%. Only few countries (Croatia, Cyprus, Ireland and Romania) have to front percentages higher than 25% [22]. Even more critical is the situation of aminoglycosides with high percentages of high-level gentamicin resistance (HLGR) among enterococcal strains worldwide: 45.5% in Brazil [23], 56.9% in Iran [15] and >40% in most of Eu-
rnicrobial resistances among the enterococci cir-
culating in nosocomial environments makes more challenging the treatment of enterococcal HAIs: 
daptomycin, linezolid or aminoglycosides are the 
main alternative antibiotics although various lev-
els of resistance to these drugs have already been 
described.

Staphylococcus aureus

S. aureus is a Gram-positive bacterium, normally 
present on human skin but it is also an opportu-
nistic pathogen able to cause a wide range of mild 
to life-threatening infections. For many years, 
penicillin has been used successfully to fight in-
fecations caused by Staphylococcus species but, 
since its first administration, resistances emerged 
rapidly within S. aureus in 1948 thanks to the syn-
thesis of the penicillinases enzymes [8]. The pro-
duction of penicillinases, conferring a significant 
advantage, became a common finding among S. 
aureus isolated both within healthcare facilities 
and within the community: over few years the 
rate of β-lactamase-production among Staphy-
lococci increased more than 80% [7, 24]. In the 
1950s, hospital-isolated S. aureus started showing 
resistance also to other antimicrobial classes (in-
cluding aminoglycosides, macrolides and tetracy-
clines); it led to the introduction of new molecules 
such as methicillin, cloxacillin and flucloxacillin 
[8]. However, as happened to penicillin, also re-
sistance to methicillin emerged easily among 
These findings represented the appearance of a 
new notable threat for public health: the methi-
cillin-resistant S. aureus (MRSA). The molecular 
mechanism conferring the ability of evading the 
activity of methicillin consists in the acquisition 
of these antibiotics over years exerted a selective 
pressure on S. aureus inducing some strains to 
become intermediate-susceptible to vancomycin, 
with a minimal inhibitory concentration (MIC) of 
4-8 μg/mL (vancomycin intermediate S. aureus 
[VISA]) and other strains to become vancomy-
cin-resistant S. aureus (VRSA), with a MIC≥16 μg/
/mL. The VISA isolates with reduced susceptibility 
to the other glycopeptide, teicoplanin, have been 
detected and defined glycopeptide-intermedi-
ate S. aureus [7, 15]. Fortunately, high level glyco-
peptide resistance is still rare in S. aureus and lim-
ited to strains that acquired the gene vanA from 
enterococci but, worrying, an increasing trend of 
vancomycin MIC in MRSA isolated has been 
reported by many authors [33]. This phenome-
non, known with the term “MIC creep”, indicates 
that the reduced vancomycin-susceptibility is 
now emerging in S. aureus but VRSA remain still 
rare with only few clinical cases reported in sev-
eral countries [15]. The rise of VISA is of particu-
lar concern because it implies the need for careful
epidemiological surveillance and the search of alternative treatments. Several antibiotics active \textit{in vitro} against VISA isolates are already available: daptomycin, the oxazolidinones linezolid and tedizolid that remains still highly active on \textit{S. aureus} (although mechanisms of resistance relating changes in the 23S rRNA have been shown \textit{in vitro}) and three lipoglycopeptides approved for Gram positive infections (dalbavancin, telavancin and oritavancin) [15, 34]. Finally, the treatment of CA-MRSA infections can rely on a high number of alternative molecules (including clindamycin, fluoroquinolones, gentamicin and tetracyclines) because, unlike most nosocomial-acquired MRSA strains, CA-MRSA strains have not developed relevant multidrug-resistance yet [8].

\textit{Klebsiella pneumoniae}

The genus \textit{Klebsiella}, member of the Enterobacteriaceae family, includes some of the main pathogens associated with infections acquired in healthcare settings. These infections, characterized by severe morbidity and mortality, include pneumonia, sepsis and urinary tract infections. Among the \textit{Klebsiella} species the most often detected as causative agent of community and hospital-associated infections is represented by the Gram negative bacillus \textit{K. pneumoniae} [7]. This species can rely on several virulence factors, such as its capsule and its fimbrial adhesins, but the most important is the ability of rapidly accumulating multidrug resistance determinants [35]. Indeed, in recent years, many authors reported a marked increasing trend of drug-resistance among \textit{K. pneumoniae} strains. The main routes to resistance to beta-lactams acquired by \textit{K. pneumoniae} consist in pore protein mutations (leading to reduction in outer membrane permeability) and in the synthesis of a large variety of \textit{ß}-lactamase enzymes [7, 36, 37]. Extended spectrum \textit{ß}-lactamases (ESBLs) were first detected in \textit{K. pneumoniae} strains isolated in Germany in 1983, since then ESBLs-producing \textit{K. pneumoniae} have been reported worldwide. An international prospective study conducted in seven countries across the world between 1996 and 1997, reported that 30.8% of nosocomial invasive \textit{K. pneumoniae} infections were attributable to ESBL-producing strains [38]. In 2001 a study merged data from the networks of resistance surveillance in European ICUs for the years 1990–1999, the results highlighted that the prevalence of ESBL-producing \textit{K. pneumoniae} was not uniform among European countries [39]. The highest prevalence (73%) was observed in \textit{K. pneumoniae} isolated in Turkish ICUs; also Portugal (34%), France (36%) and Russia (33%) presented high rates of resistance while Belgium, Germany, Spain and Sweden showed only a 1-4% prevalence of ESBL-producing \textit{Klebsiella} in ICU isolates [39, 40]. In 2013 the CDC estimated the number of infections due to ESBL-positive \textit{Klebsiella} about 17,000 cases with approximately 1,100 deaths attributable to these strains [19]. ESBL are active on penicillins, first-, second- and third- generation cephalosporins but aminoglycosides, fluoroquinolones and carbapenems have been successfully administrated for years to fight \textit{K. pneumoniae} infections, nevertheless the extensive use of these drugs inevitably posed a selective pressure. Therefore, recent data of antimicrobial resistance surveillance show that in most European countries the proportion of aminoglycosides- and fluoroquinolones-resistance among invasive \textit{K. pneumoniae} isolates is >25% [26]. Even the carbapenem group antibiotics, which were considered the drugs of choice for ESBL-producing \textit{K. pneumoniae} infections, often demonstrate only a reduced activity on \textit{Klebsiella} because microorganisms have developed an efficient carbapenem resistance mechanism based on the activity of several enzymes, known as carbapenemases. Carbapenem-resistant \textit{Klebsiella pneumoniae} (CRKP) is the most frequent and clinically relevant carbapenemase-producing species among the Enterobacteriaceae. A new enzyme, named New Delhi metallo-\textit{ß}-lactamase-1 (NDM-1) belonging to the metallo-\textit{ß}-lactamases, has recently been found in \textit{Klebsiella}. This “super enzyme” differs from other carbapenemases (such as Verona integron-encoded VIM-1/VIM-2) in its structure and affinity to \textit{ß}-lactams, moreover the gene encoding NDM-1 is often allocated in plasmids carrying also other antibiotic-resistance determinants [41]. The worldwide emergence of NDM-1 has furtherly increased the percentages of carbapenem-resistant \textit{K. pneumoniae} (CRKP) [42]. A large study from 42 centres in the USA reported that CRKP accounted for 6.1% of all \textit{K. pneumoniae} isolated [36, 43]. Similar results have been produced by the European Antimicrobial Resistance Surveillance Network (EARS-Net) demonstrating that, in Europe, the population-weighted mean percentage of carbapenem resistance among \textit{Kleb-
siella is 8%, although the majority of countries had percentages <5% while only three countries reported excessively high carbapenem resistance rates: Romania (24.7%), Italy (33.5%) and Greece (61.9%) [26]. The rapid spread of CRKP in these countries is noteworthy because only few alternative molecules retaining activity on CRKP are currently available (colistin, tigecycline, fosfomycin, gentamicin, amikacin and ceftazidime/avibactam) [26, 44, 45].

**Acinetobacter baumannii**

Even though most species belonging to the *Acinetobacter* genus are ubiquitous bacteria with low pathogenicity, some *Acinetobacter* species are frequent causes of HAI as they easily spread into hospital environment and can be isolated from skin of patients and hospital staff [7, 46]. In recent years, they have been often detected as causative agents of a vast array of nosocomial infections (including urinary tract infections and ventilator-associated infections) particularly in highly vulnerable ICU patients, intubated or burn patients or those carrying intravenous lines and catheters; while community-acquired infections have been less commonly reported [47]. Among Acinetobacter species the most important nosocomial pathogen is by far *A. baumannii*, an aerobic Gram-negative bacillus, which has a relevantly high ability to survive for prolonged periods in nosocomial environment and on human surfaces, that may explain the frequent cross contamination among hospitalized patients [7]. The clinical relevance of *A. baumannii* as nosocomial pathogen increased in the 1980s, with the emergence of strains developing the ability to evade the action of many antimicrobial molecules, including carbapenems, which were used as the drug of choice for treating *A. baumannii* infections; therefore, they remain susceptible to relatively few drugs (colistin, meropenem, rifampicin and tigecycline) [48]. Not only carbapenem-resistance has been widely reported in Europe but it is also often found combined with resistance to other antimicrobial groups (in particular to fluoroquinolones and aminoglycosides). This pattern of combined resistance to multiple antibiotics has become of concern in countries of southern and south-eastern Europe, where in 2015 the rates of resistance were higher than 50% (72.6% in Italy; 82.2% in Greece and 87% in Croatia) [26]. *Acinetobacter* represents a public health threat also in USA where it is estimated that about 2% of all HAIIs diagnosed in 2013 were due to *Acinetobacter* with approximately 12,000 cases each year (63% of which were attributable to multi-drug resistant *A. baumannii*) [19]. In Turkey, imipenem susceptibility among *A. baumannii* strains has shown a drastic reduction from 50% to 19% during the period 2007-2010 [46]. In China, a nationwide surveillance program conducted from 2005 to 2014, revealed that the rates of imipenem and meropenem resistance among *Acinetobacter* spp. were 57 and 61%, respectively [49]. These species acquired resistance to a vast spectrum of antibiotics through several mechanisms: mutations in ribosomal proteins confer resistance to aminoglycosides; upregulation of efflux systems can explain reduced susceptibility to fluoroquinolones and tigecycline; while resistance to carbapenems is often due to the acquisition of plasmid-mediated genes encoding for metallo-beta-lactamase (MBL) and extended spectrum beta-lactamase (ESBL) enzymes [26, 50, 51]. The most commonly found ESBLs in *A. baumannii* are the PER-, GES- and VEB-type beta-lactamases that confer resistance to expanded-spectrum cephalosporins while other ESBLs such as TEM-, SHV- and CTX-M-type, known to be widespread among Enterobacteriaceae, have been rarely identified in *A. baumannii* [52]. This bacterium is also able to produce several metallo-beta-lactamases (MBLs), including the recently identified NDM-1. MBLs inactive carbapenems and other beta-lactams (except monobactams) and are not inhibited by the beta-lactamase inhibitors such as clavulanic acid or tazobactam [52]. However, the high resistance to carbapenems among *A. baumannii* isolates can be explained by the combination of several mechanisms: the synthesis of carbapenem-hydrolysing beta-lactamases, the mutational loss of outer membrane proteins and the overexpression of efflux systems [50, 52]. The spread of carbapenem-resistant *A. baumannii* in hospitals has drastically restricted the reliable options for effective antibiotic treatment of *A. baumannii* infections. Currently, colistin alone or in combination with other antimicrobials, including ampicillin-sulbactam, rifampin, tigecycline and carbapenems, is considered the mainstay for infections caused by multidrug resistant (MDR) *A. baumannii*, in particular for patients...
who are already under carbapenem therapy [47, 53, 54]. Nevertheless, the return to the use of colistin led bacteria to develop mechanisms of resistance also to colistin (such as mutations of lipopolysaccharide outer membrane) thus the first cases of colistin-resistant A. baumannii have already been reported worldwide [54].

**Pseudomonas aeruginosa**

*P. aeruginosa* is a Gram-negative, facultative anaerobe opportunistic pathogen, that is present in the normal gut microbiota. Although the rates of *P. aeruginosa* carriers in the general population are not extremely high, this pathogen is widely detected in healthcare settings, being a leading cause of life-threatening HAI worldwide, in particular for immunocompromised patients admitted in ICUs [7]. *P. aeruginosa* has an intrinsic tolerance to many disinfectants and antimicrobial agents but also the ability to acquire adaptive resistance after drug administration, because of the production of efflux pumps and antibiotic-inactivating enzymes (including ESBLs, carbapenemases and metallo-β-lactamases) and the reduced outer membrane porin permeability [7, 55]. Carbapenems are still considered the antimicrobial class of choice to fight *P. aeruginosa* infections, thus the emergence of MDR strains with reduced susceptibility to carbapenems represent a serious concern as it severely compromises the efficacy of this treatment [55]. According to the antimicrobial resistance surveillance data of 2015, high rates of carbapenem resistance are common among invasive *P. aeruginosa* isolated across Europe, with national percentages ranging between <5% (in the U.K. and in The Netherlands) and 66.3% (in Romania). Overall, the mean European percentage for carbapenem resistance was 17.8 % in 2015 [26]. Even more alarming is the fact that in most of the European countries >10% of the *P. aeruginosa* isolates present a combined resistance to three or more antimicrobial groups tested under EARS-Net surveillance (aminoglycosides, carbapenems, ceftazidime, fluoroquinolones, piperacillin and tazobactam) [26]. In the U.S. approximately 13% of all the *Pseudomonas* HAIs are due to these multi-drug-resistant strains, that means 6,700 infections each year [19]. Several ESBLs (PER-1; VEB-1 and GES enzymes) are often detected in *Pseudomonas* strains conferring resistance to expanded-spectrum cephalosporins. AmpC is an intrinsic β-lactamase, expressed at low levels in standard conditions but sub-inhibitory concentrations of certain β-lactams can induce AmpC-synthesis leading to the overexpression of this cephalosporinase. This phenomenon results in the selection of *P. aeruginosa* strains resistant to ceftazidime, piperacillin and ticarcillin [52]. Even though *Pseudomonas* produces carbapenemases (mainly MBLs) its routes to resistance to carbapenems seems to be more related to porin deficiency, which causes a reduced uptake of antimicrobial molecules [52]. All these mechanisms explain the success of these bacteria in causing HAI, indeed such infections have been well described worldwide. In Kosovo, the rate of resistance against imipenem and meropenem among the *P. aeruginosa* collected in 2015 was 37.7% and 36%, respectively [55]. A retrospective study conducted in Italy during the period 2007-2010 reported that 20% of all the *P. aeruginosa* isolated were multi-drug resistant [56]. A recent meta-analysis on patients with pneumonia in China revealed that the resistance rates to cefoperazone, imipenem and meropenem among *P. aeruginosa* causing hospital-acquired pneumonia were 50%, 22.9% and 35.7%, respectively [57]. In the U.S. a large study based on data from a nationally representative sample of microbiology laboratories, reported that the prevalence of multidrug-resistance among *P. aeruginosa* causing pneumonia was 22%, that is a value nearly 15-fold higher than carbapenem-resistant Enterobacteriaceae causing the same type of infection [58]. Also in Taiwan, the overall prevalence of carbapenem-resistant *P. aeruginosa* is high, approximately 10.2% [59]. On the basis of such studies, reporting only scarce effectiveness of most antibiotics against *Pseudomonas*, except for some new molecules such as ceftolozane/tazobactam, the return to colistin represents a reliable option of treatment. Therefore, despite the risk of colistin adverse effects (nephrotoxicity and neurotoxicity), its use has been reconsidered in particular for the synergistic activity with other antibiotics (in order to avoid the emergence of resistance during monotherapy) [60].

**Enterobacter spp.**

*Enterobacter* species are emerging as common Gram-negative pathogens, being often detected as causative agents of HAIs, in particular septicaemia, respiratory and urinary tracts infections.
Currently, *Enterobacter* spp. are the eighth most common cause of HAI in the U.S., although they have also been implicated in community-acquired infections [61-63]. *Enterobacter* species have shown the ability to develop antimicrobial resistance thanks to the hyperproduction of a chromosomally encoded AmpC β-lactamase, which can hydrolyze broad-spectrum cephalosporins and penicillins [64, 65]. As explained above, the hyperproduction of AmpC can be induced by the exposure to beta-lactams and carbapenems, therefore previously sensible *Enterobacter* isolates often become resistant to cephalosporins during therapy and this change is associated with increased mortality [62, 64]. The prevalence of multidrug-resistance in the U.S. has proven to differ among species: 4.9% in *E. aerogenes* whilst 9.5% in *E. cloacae* [66]. A surveillance study conducted in Saudi Arabia during 2000-2006 reported that, on a total of 1,394 Enterobacter isolates, the resistance rate increased from 9 to 17.9% for ceftriaxone; from 8.3% to 17.4% for ciprofloxacin [67]. Many species belonging to Enterobacteriaceae family produce a wide array of ESBLs and carbapenemases that reduce their pattern of antimicrobial susceptibility but such enzymes were supposed to be only rarely detected in *Enterobacter* spp. However, in recent years the clonal dissemination of carbapenem-resistant *Enterobacter aerogenes* (CREA) and their ability to synthetize both metallo-(IMP-8, NDM-1, VIM-1) and non-metallo-(KPC-2) β-lactamases have widely been reported [68]. An outbreak of ESBL-producing *Enterobacter cloacae* has been reported in a neonatal intensive care unit in Spain, with 14 newborns infected or colonized by CTX-M-producing *E. cloacae* strains [69]. Moreover, a recent study reported that during a 1-year period several strains of *E. cloacae* producing ESBLs and carbapenemases have been isolated in a Spanish hospital from patients with critical underlying conditions [65]. In Brazil, 20% of *Enterobacter* spp isolated in patients with bacteremia were ESBLs-producers [70]. In Japan only 6% of the Enterobacter strains isolated produce ESBLs and all these bacteria were resistant to ampicillin and piperacillin and most of them were also resistant to piperacillin-tazobactam and cefoxitin [71]. In 2011, in a neurosurgical ward of a Chinese teaching hospital, all the carbapenem-resistant *Enterobacter aerogenes* (CREA) isolated were non-susceptible to cefotaxime, ceftazidime, cefoxitin, ertapenem, imipenem or meropenem and were proved to carry the gene encoding *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) [72]. In another study in China the 72.7% of the carbapenem-resistant *E. cloacae* isolated were able to produce also the New Delhi metallo-β-lactamase 1 (NDM-1) [73]. Only few antimicrobial compounds still remain effective against the multidrug resistant *Enterobacter* spp, as these bacteria can rapidly develop resistance during treatment. Therefore, the treatment options are often limited to colistin and tigecycline [35].

**CONCLUSIONS**

The emergence of multidrug-resistance bacteria represents a serious public health threat because their multiple patterns of resistance make the choice of an effective treatment even more challenging. Fortunately, although the number of antimicrobial compounds retaining activity on these pathogens has gradually decreased over the years, the recent development of new molecules with anti-Gram-positive (dalbavancin and telavancin) and anti-Gram-negative bacteria (ceftolozane/tazobactam and ceftazidime/avibactam) activity contributes to increase the treatment options for these infections. Among the MDR bacterial species the group of ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* spp.) plays a clinically relevant role, in particular in the aetiology of life-threatening HAIs. In this review we report many studies showing that the burden of these infections has drastically risen worldwide over last decades. ESKAPE pathogens have developed a wide array of strategies to evade the killing activity of the most commonly administrated antibiotics, including the horizontal gene transfer among species, which furtherly enhances the spread of antibiotic-resistances. The only weapons we have to front the rise of these multi-resistant bacteria in the near future are the continuous finding of new active antimicrobial molecules, the careful epidemiological surveillance and the implementation of appropriate infection control programs.

**Conflict of interest**
The authors declare no conflict of interest.
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Prevalence and treatment of MDR pathogens