Bacterial Resistance in Hospital-Acquired Infections Acquired in the Intensive Care Unit: A Systematic Review

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ABSTRACT

Purpose: In this review we present the status of the prevalence of bacteria resistant to antibiotics and the main antibiotic resistance genes that are reported in infections acquired in intensive care units (ICU) around the world.

Methods: A systematic review based on the PRISMA guide was carried out, from the Science Direct, Redalyc, Scopus, Hinari, Scielo, Dialnet, PLOS, ProQuest, Taylor, Lilacs and PubMed/Medline databases. Inclusion criteria of this review were original research study published in a scientific journal in a 10-year time span from 1 January 2017 and 30 April 2022.

Results: A total of 1686 studies were identified, but only 114 studies were considered eligible for inclusion. *Klebsiella pneumoniae* and *Escherichia coli* resistant to carbapenems and producers of extended-spectrum β-lactamases (ESBL) are the most frequently isolated pathogens in ICUs in Asia, Africa and Latin America. The *bla*OXA and *bla*CTX were antibiotic resistance genes (ARG) most commonly reported in different geographic regions (in 30 and 28 studies, respectively). Moreover, multidrug-resistant (MDR) strains were reported in higher frequency in hospital-acquired infections. Reports of MDR strains vary between continents, with the majority of publications being in Asia and between countries, with Egypt and Iran being highlighted. There is a predominance of few bacterial clones with MDR phenotype, for example, clonal complex 5 Methicillin-Resistant *Staphylococcus aureus* (CC5-MRSA) circulates frequently in hospitals in the United States, clone ST23-*K. pneumoniae* is reported in India and Iran, and clone ST260 carbapenemase-producing *P. aeruginosa* in the United States and Estonia.

Conclusion: Our systematic review reveals that ESBL- and carbapenemase-producing *K. pneumoniae* and *E. coli* are the most problematic bacteria that are reported, mainly in tertiary hospitals in Asia, Africa, and Latin America. We have also found propagation of dominant clones with a high degree of MDR, becoming a problem due to its high capacity to cause morbidity, mortality and additional hospital costs.

KEYWORDS

drug resistance; antibiotic resistant bacteria; antibiotic resistance genes; intensive care units

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INTRODUCTION

Antibiotic resistance is defined as the ability of the bacterium to avoid the action of the antibiotic, which can be done by modifying target proteins due to point mutations or by acquisition of resistance genes through mobile genetic elements (1–5). This resistance can be accelerated by the incorrect and indiscriminate use of these drugs, which leads to multiple resistances in different strains of bacteria, with the consequent increase in hospital-acquired infections (6–8), that can have great influence to the health of the world population.

In the last decade, the increase in antimicrobial resistance in ICUs has been reported, mainly due to the spread of these multidrug-resistant (MDR) bacteria (8–12). MDR is defined as resistance to more than one agent in three or more antimicrobial categories, extensively-drug resistant bacteria (XDR), is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories), and pan-drug resistant bacteria (PDR) is defined as non-susceptibility to all agents in all antimicrobial categories (9). The situation is complicated by the presence of so-called "High-Risk Clones (HiRCs)", which corresponds to few lineages of bacteria that have the ability to adapt and remain for long periods of time in the hospital environment. Some of these clones would be involved in the appearance of resistance mechanisms that affect new antimicrobials. The development and speed of spread of HiRCs would have been potentiated by the high use of all antibiotics during the COVID-19 pandemic, as proposed by several researchers (13–15).

The risk factor of development of infection caused by antibiotic-resistant bacteria is hospital stay, especially in ICU. Patients in these facilities usually receive intensive antibiotic therapy and a lot of hands-on care, and their special condition makes them vulnerable to acquiring bacteria with various types of resistance (15, 16).

The objective of this review was to find the status of prevalence of bacteria resistant to antibiotics caused an infection in ICU around the world. The second aim was to find what antibiotic resistance genes (ARG) are reported in the same infections acquired in ICU, in order to contribute to the strengthening of antibiotic resistance control policies.

METHODS

Systematic search of various electronic databases such Science Direct (Elsevier), Redalyc, Scopus, Hinari, Scielo, Dialnet, PLOS, ProQuest, Taylor, Lilacs and PubMed/Medline was conducted to retrieve relevant published articles. Online library repositories of different institutions were also searched. The process of retrieving and including data closely followed PRISMA guidelines (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) as shown in Figure 1. Relevant MeSH terms and keywords were used

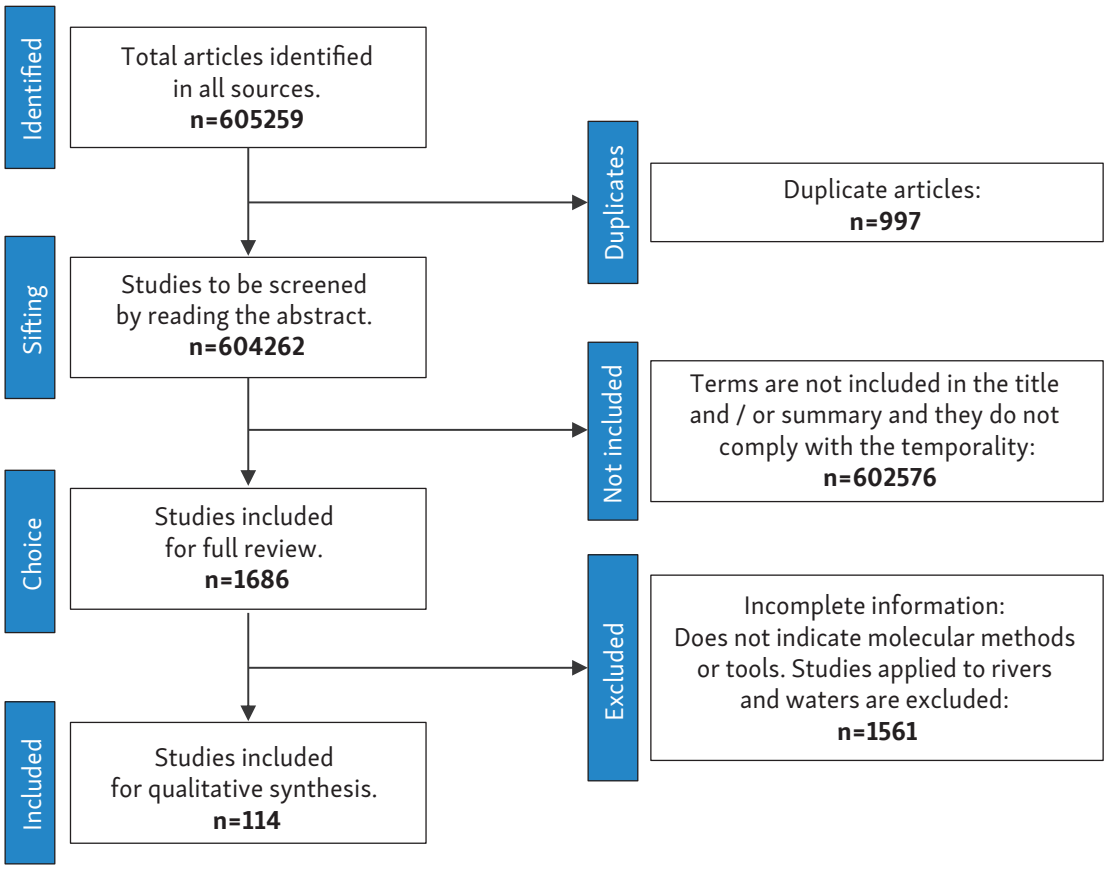

Fig. 1 Algorithm for the literature review.

to retrieve all relevant articles from the above-listed databases. The keywords and MeSH terms used were: "antibiotic resistance", "antimicrobial resistant strains", "Multidrug-resistant", "antibiotic resistant bacteria", "antibiotic resistance genes (ARG)", and "hospital-acquired infections". Studies published from 1 January 2017 and 30 April 2022 were included. We excluded review articles, systematic review, meta-analyses, editorials, policy statements, research exclusively in child populations, and those with data collection commencing prior to 2017. A full list of the data elements extracted from each study are reported in supplementary material.

RESULTS AND DISCUSSION

STUDY CHARACTERISTICS

Out of a total of 1686 unique records were screened, 114 studies met our inclusion criteria (Fig. 1). The maximum number of studies were found in Asia (n = 42), of which nine (7.9%) were conducted in China. From studies with specific diseases, the most common sample were urine (n = 92), blood (n = 86) and respiratory secretions (n = 76).

Most of the articles report bacteria with resistance to antibiotics based on conventional methods (as disk diffusion method, Double disc synergy test, dilution methods, Epsilometer test), especially in countries of Africa (2, 11, 17–34), Asia (35–60) and Latin America (1, 6, 61–66). Phenotypic detection of antibiotic resistance by Disk Diffusion Method was reported in 60.5% of the total studies, followed by the Vitek 2 system (18.4%). Most studies (79.6%) used the CLSI as the breakpoint reference guidelines (18.4%) (Table 1). The most commonly used molecular methods for the study of bacterial resistance corresponded to the conventional PCR technique (refers to the basic type of PCR reaction) (40.4%). A low number of reports (11.4%) were found that use last generation molecular methods (such as, Next Generation Sequencing, which is the large-scale DNA sequencing technology that allows the analysis of entire genomes or specific genes).

DISTRIBUTION OF ISOLATES

Figure 2 shows distribution of bacterial species in clinical samples. *K. pneumoniae* (n = 57) and *E. coli* (n = 51) were the most reported bacteria, especially in urine samples,

Tab. 1 The number of studies about bacterial identification method, phenotypic and molecular detection method in the present systematic review.

Characteristics	No of studies	References
Bacterial Identification method		
Morphology / Biochemical testing	30 (26.3%)	1–4, 6, 11, 13, 15, 17–21, 34–42, 60–62, 66, 67
API	7 (6.1%)	21, 27–30, 75, 76
VITEK®	17 (14.9%)	4, 14, 15, 25, 35, 66, 75, 77–86
MALDI-TOF	18 (15.8%)	5, 12, 14, 15, 22, 66, 67, 69, 71, 73, 74, 76, 79, 87–90
COMBO DISC, QUBIT® 2.0 FLUOROMETER	1 (0.9%)	91
Not mentioned	1 (0.9%)	92
Phenotypic detection method		
Disk Diffusion Method (Kirby Bauer disk diffusion method / Mueller Hinton agar)	69 (60.5%)	2–4, 6–9, 11, 12, 14, 16–37, 39–59, 61–74
Double disc synergy test	2 (1.8%)	26, 29
Dilution / test-broth microdilution / MicroScan autoSCAN-4 automated System	18 (15.8%)	12, 13, 70–74, 77, 80, 89, 93–100
E Test	3 (2.6%)	21, 38, 70
VITEK® 2	21 (18.4%)	14, 15, 25, 34, 75, 78, 79, 87, 89, 101–111
Neo-Rapid CARB	1 (0.9%)	8
Automated system Phoenix™ AST/ID	7 (6.1%)	20, 112, 37, 13, 88, 108, 109
MALDI-TOF (mass spectrometry)	8 (7%)	14, 22, 31, 46, 70, 71, 86, 90
Molecular detection method		
PCR assay (conventional PCR, multiplex PCR)	46 (40.4%)	2, 9,17, 18, 20, 22, 25–32, 34, 36, 39–41, 47, 49–51, 54, 55, 57, 58, 62, 63, 67–72, 86, 95–97, 101, 109–114
RT-qPCR	5 (4.4%)	14, 48, 51, 71, 104
ERIC-PCR (or rep-PCR, box PCR)	5 (4.4%)	51, 25, 28, 64, 81
pulse field gel electrophoresis (PFGE)	7 (6.1%)	7, 8, 15, 38, 79, 89, 97
multilocus sequence typing (MLST)	7 (6.1%)	6, 10, 63, 96, 97, 106, 107
Sequencing by Sanger ABI 3730/ ABI PRISM®3500, whole genome sequencing (WGS)/ Illumina sequencing	13 (11.4%)	26, 37, 44, 47, 57, 58, 64, 72, 89, 104, 108, 109

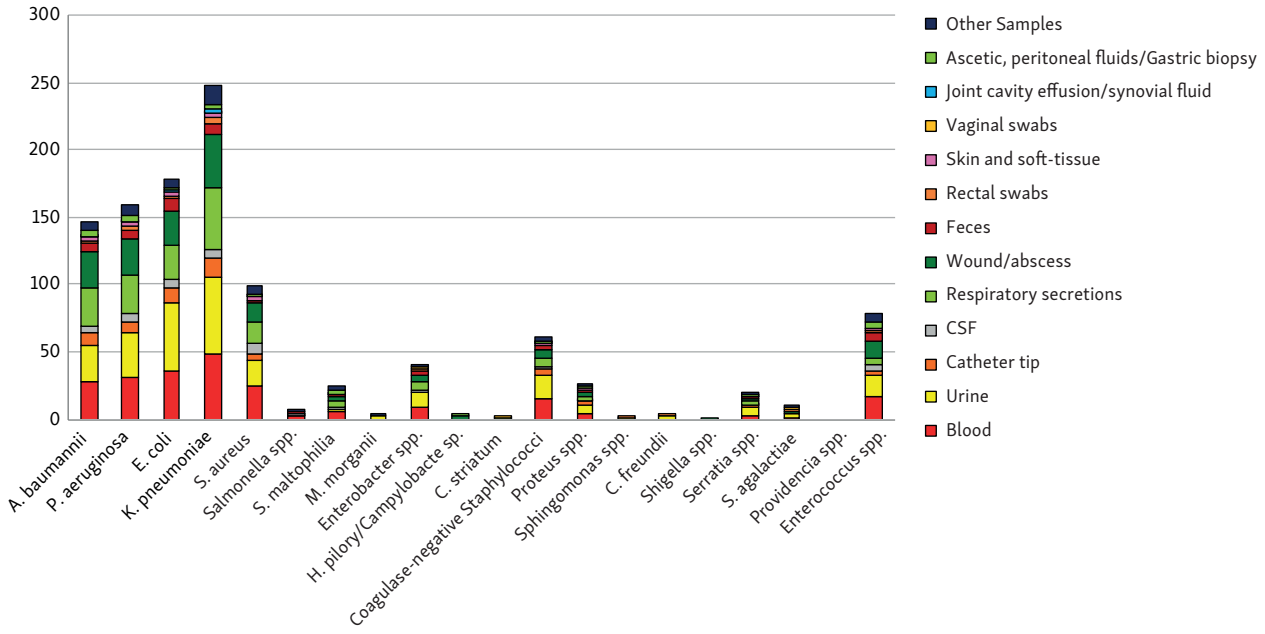

Fig. 2 Distribution of bacterial species between different clinical samples.

most of them presented often resistance to fluoroquinolones, ampicillin, co-trimoxazole and cephalosporins (3, 4, 11, 17, 21, 26, 33, 39, 54, 62, 64, 73, 85, 110). Moolchandani et al., recommends not using these antibiotics for empirical therapy of urinary tract infections acquired in ICUs in South India; instead, they suggest considering imipenem, pipericillin-tazobactam, amikacin, and nitrofurantoin for initial therapy with prompt de-escalation after culture and sensitivity results are received (3).

K. pneumoniae was also the most reported in blood samples, respiratory secretions, and swabs from wounds (n = 49, 46, 40, respectively). In blood samples, *E. coli, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* were reported in 36, 31, and 28 articles, respectively. An important feature among these Gram-negative bacteria was the production of extended-spectrum β-lactamases (ESBL) and carbapenemase.

Among Gram-positive bacteria, Methicillin-Resistant *Staphylococcus aureus* (MRSA) was the most reported in blood and urine samples in 25 and 19 studies, respectively, followed by Vancomycin-Resistant *Enterococcus* (VRE) in 17 and 15 studies, respectively. Urine samples from which the MRSA was isolated corresponded to a urine catheter positioned in the bladder or in the ureter (2, 7, 13, 19, 49, 59, 82, 84, 93, 108).

There are a large number of studies reporting MDR pathogens in different parts of the world, which would explain the factors that trigger the increase in epidemic outbreaks, morbidity and mortality, with significant direct and indirect costs (8, 10, 11, 12, 15, 17, 29, 34, 37, 50, 62, 65, 68, 87, 91). The most frequently reported MDR microorganisms in this last decade were found among isolates of *K. pneuomaniae, E. coli, P. aeruginosa, A. baumannii*, SARM and VRE. The number of reports of MDR microorganisms varied geographically, with the highest number of reports being made in Asia (25 studies) and the lowest number being in North America (3 studies). These differences occur not only between continents, but even between countries, with the highest number of reports recorded in Egypt (in 8 studies) and Iran (in 7 studies). Infection in elderly patients, long duration of hospitalisation, use of broad-spectrum antibiotics and long-term or continuous use of a single antibiotic have been recognize as risk factors for development of infection caused by MDR pathogens as suggested by Buetti et al. (16).

Hypervirulent *K. pneumoniae* (hvKp) is an emerging pathotype that is more virulent than classical *K. pneumoniae.* hvKp carry plasmids with genes that code for a large number of virulence factors (such as the capsule that protects bacteria from both phagocytosis and lethal serum factors, fimbriae, lipopolysaccharides and siderophores) and resistance to heavy metals (copper, silver, lead and tellurite) (27, 46, 106). Although hvKp strains are usually susceptible to most antimicrobials, an increased prevalence of MDR-hvKp nosocomial strains, including carbapenemase-producing strains has already been described, mainly in patients with healthcare-associated infections in Egypt (27, 114), India (44), Iran (46), and China (101). Further limiting the range of therapeutic alternatives, since the dissemination of a hypervirulent strain in hospitalized patients could have serious consequences, it is recommended to implement contact precautions against suspicion.

Another important aspect found in this review was the report of *Stenotrophomonas maltophilia* and *Corynebacterium striatum*, which have been reported in recent years among the group of MDR opportunistic pathogen as a cause of infection particularly among hospitalized patients.

S. maltophilia is an opportunistic pathogen that has high intrinsic and acquired antimicrobial resistance, among the therapeutic options to treat infections due to MDR-*S. maltophilia* is trimethoprim-sulfamethoxazole. However, some strains resistant to this antibiotic are

already reported with prevalences between 2.4% and 10.7% in hospitals in Egypt (29), China (43), Iran (47, 48), North America (74, 95), and Mexico (83).

C. striatum is considered a normal component of the human skin and mucosal microbiota, however, it is frequently cited as a pathogen of hospital-acquired infections in some hospitals in Tunisia (76) and China (86). A high prevalence of MDR-*C. striatum* isolates (>50%) was reported in these hospitals, supporting the idea that it is an emerging MDR-bacterium.

DISTRIBUTION OF ANTIBIOTIC RESISTANCE GENES (ARG)

A total of 50 types of ARG were found in this systematic review. Asian hospitals present bacterial isolates with the greatest diversity of detected ARGs, followed by Africa, Europa, Latin America and North America. The highest ARG diversity was reported in bacteria that were causing hospital-acquired infections from Asia and Africa

In Asia, 80 ARGs were reported, distributed in 31 types, including *bla* (conferring resistance to β-lactam antibiotics) (27.5%), *aac* (cause resistance to aminoglycosides) (8.8%), and *tet* (cause resistance to tetracyclines (5%). In Africa, 47 ARGs distributed in 22 types are reported, *bla* gene was reported in 30.4%, followed by the *aac* gene with 8.7%. However, in some bacteria the mechanism of resistance to antibiotics is mainly mediated by chromosomal mutations, as is the case of *C. striatum,* all quinolone-resistant isolates showed mutations in the *gyrA* gene as reported in hospitals in Tunisian (76) and China (86).

Studies in Europe reported 24 types of ARGs with a higher abundance of *bla* genes (17.1%), followed by genes: *acc*, *mph* (cause resistance to macrolide), *qepA* (encodes an efflux pump that reduces susceptibility to fluoroquinolone), *sul* (cause resistance to sulfonamides), *aad* (cause resistance to aminoglycosides), *aph* (cause resistance to streptomycin), and *ddl* (mutations in this gene confer D-cycloserine resistance) (5.7% each), while in Latin America, of the 15 types of ARGs found in this review, 20.8% correspond to the *bla* genes followed by *acc, aph, sul, tet,* and *mcr* (cause resistance to colistin) (8.3% each). Although only 2 types of ARGs were reported in North America, they present greater abundance compared to reports in other parts of the world, the *bla* gene represented 83% and *van*A/B (cause resistance to vancomycin) (16.7%).

The highest number of ARGs (n = 24) was detected in *S. aureus*, followed by *K. pneumoniae* (20 ARGs), *A. baumannii* (16 ARGs), and *E. coli* (14 ARGs) (Fig. 3).

The *bla* genes were reported in 53 studies and distributed in 11 bacterial species, representing 46.5% of the AGRs found in this systematic review. *K. pneumoniae* was the most reported with *bla* genes (28 studies), followed by *E. coli* (21 studies), and *P. aeruginosa* (12 studies). The *bla* genes were also detected in other emerging MDR organisms, such as *C. striatum*, all penicillin resistant isolates were positive for the *bla* gene in Tunisian hospitals (76).

The *bla*OXA subtype (cause production of oxacillinases and resistance to *β-lactam* antibiotics, including carbapenems) is the most reported in this group (30 studies), followed by *bla*CTX (cause production of cefotaxime-hydrolyzing *β-lactamase* and resistance to *β-lactam* antibiotics,

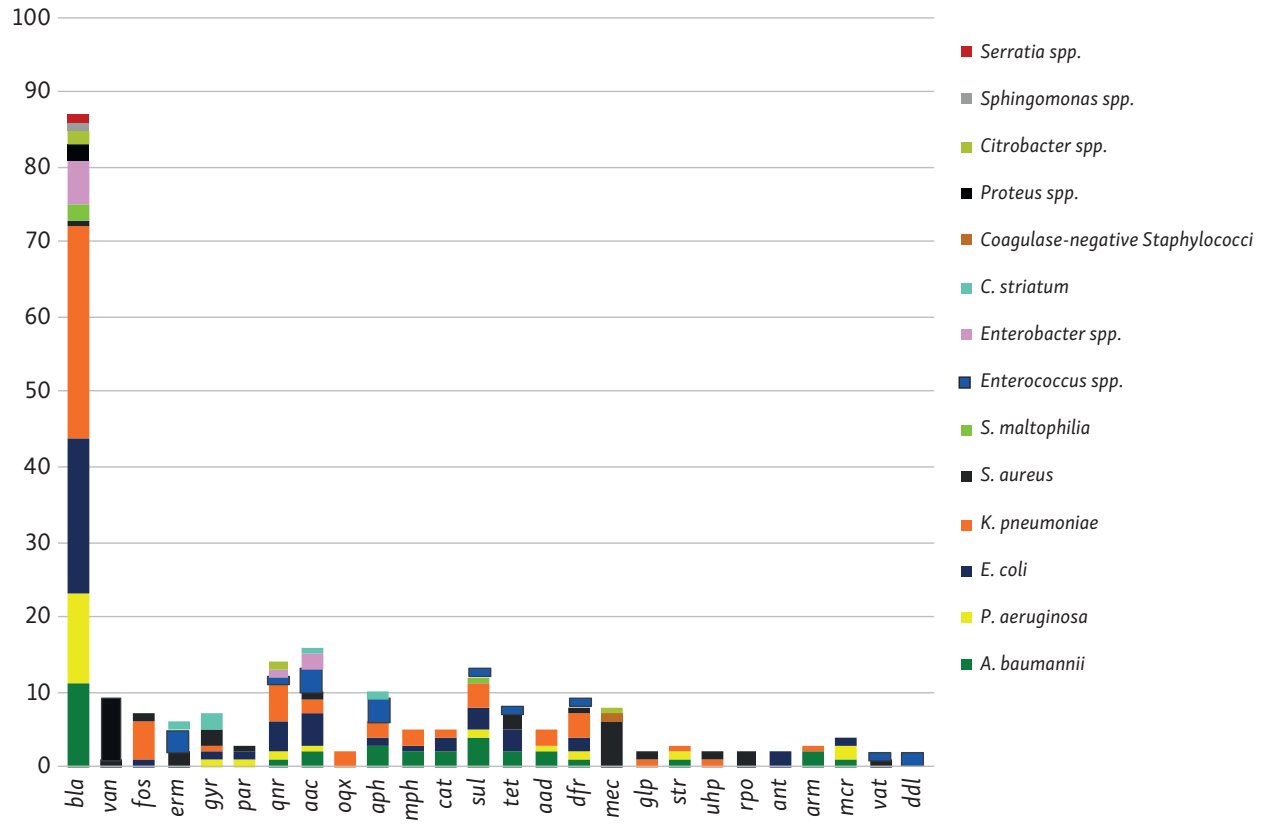

Fig. 3 Abundance and diversity of antibiotic resistance genes (ARG) in individual bacteria.

especially cefotaxime and ceftriaxone) (28 studies) and *bla*TEM (cause production of narrow-spectrum β-lactamases and resistance to to penicillins and early cephalosporins) (25 studies). The ARGs *aac* was reported in 15 studies (13.2%) and *sul* in ten studies (8.8%). However, resistance to aminoglycosides presented the greatest diversity of ARGs (*aac, smeD/F, aad, ant, arm rmt, aph, msr*).

Plasmids and others active mobile elements such as transposons and integrons are horizontal gene transfer vehicles, that give bacteria great capacity to adapt to changes in the environment. These mobile elements play a crucial role in the dissemination of ARGs in populations of pathogenic bacteria, favoring multiresistance. The most frequent antibiotic resistance genes, such as genes coding the production of ESBL, are located in plasmids. Recent studies point to plasmid-mediated transfer in hospitals in Africa (17, 19, 25–28, 33, 52, 101), Asia (35, 40, 42, 45, 57, 94, 98, 105), Latin America (63–65), Europe (67, 72, 91), and North America (89, 100, 103).

Other types of ARGs located on plasmids have been reported, such as the *mcr-1* gene they have been detected in isolates of *A. baumannii* and *P. aeruginosa* resistant to colistin (41, 58, 97). The *aac* and *ant* genes responsible for aminoglycosides resistance were detected in isolates of *K. pneumoniae* (19), VRE (20, 36), *S. maltophilia* (48) and *E. coli* (50), and *fos* genes, which confer resistance to fosfomycin, have been reported on plasmids and active mobile genetic elements of *E. coli* (54), *K. pneumoniae* (79, 54, 56, 72, 104) and MRSA (59, 96).

Next type of active mobile elements such as transposons and integrons have also been shown to be very efficient in the propagation of AGRs in bacteria that cause infections in the ICU. In MDR *A. baumannii*, the transportable elements, Tn2006, Tn2007, Tn2008, and Tn2009, play a key role in the transfer of the *bla*OXA-23 gene. Isolates with Tn2006 has been detected in predominantly in Iran (113), while Tn2008, and Tn2009 in China (90, 106). Also, high frequency of MDR pathogens harboring class 1 and 2 integrons have been detected in *K. pneumoniae* (9, 14), *A. baumannii* (10, 65, 57, 77, 90, 113), *P. aeruginosa* (18, 94, 101), and *E. coli* (38, 64, 110).

GENETIC DIVERSITY OF ANTIBIOTIC RESISTANT ISOLATES

Bacteria that cause hospital-acquired infections are chracterised by a genetic structure composed of a high genotypic diversity, but a predominance of several clones can be found. Whole genome analysis (WGS)-based analysis on MDR and ESBL-positive *E. coli* evidenced high genetic diversity in hospitals in Benin (22) and Bangladesh (35). However, a study conducted in Mozambique using ERIC-PCR analysis revealed that despite evidence of high genetic diversity among *E. coli* isolates, there was a predominance of few clones adapted to the hospital environment, what would they probably be HiRCs (17). Similar findings were reported in hospitals in Ethiopia (25) and Colombia (64). Analysis by pulsed field gel electrophoresis (PFGE, technique used to produce a DNA fingerprint for a bacterial isolate) also supports these findings: among the great diversity of pulse types (ST), ST405 and ST1284 circulate mainly in hospitals in Lebanon (38), while ST131 in Bangladesh (35) and USA (89, 100).

The genetic structure of *A. baumannii* shows a similar behavior. MLST analysis performed on clinical isolates of carbapenem-resistant *A. baumannii* identified carriers of *bla*OXA-23, belonging to ST2 circulating in hospital settings in South Africa (77), and ST195, ST540, and ST208 in China (90).

The phylogenetic analysis using WGS in *A. baumannii* showed that all isolates analyzed in a hospital in Iran belonged to the same clade, within lineage 2 of global clone1 (113).

The population structure of *K. pneumoniae* is more heterogeneous than that observed in isolates of *E. coli* and *A. baumannii,* which emphasizes the opportunistic nature of these species. The results obtained among KPC producing *K. pneumoniae* also reflect the well-known dominance of ST258 clone in USA (100). Multilocus sequence typing in carbapenem-resistant *K. pneumoniae* strains showed that ST15 was prevalent in Portugal (4), ST395 in France (69), ST11 in China (106, 107), and ST14, ST5188, ST1861 in Iran (98).

The GWAS analysis that was performed on KPC-producing *K. pneumoniae* isolates from epidemic outbreaks in hospitals in Switzerland during 2013 and 2015 revealed low variability among isolates, contrary to the results given by plasmid analysis. Each epidemic outbreak was dominated by clone ST512, which was probably adapted to the antibiotic therapy used at the time (72).

GWAS analysis was also performed on HvKp strains obtained from hospital-acquired infections in Indian, and showed that these strains evolved in few clones (ST23, ST240, and ST2319 (44). The study by Sanikhani et al, in two Iranian teaching hospitals also detected clone ST23 in all hvKp isolates (46).

The number of carbapenemase-producing *P. aeruginosa* strains has also been increasing in medical settings in ICUs (18, 24, 28, 32, 43, 101). ST1816 has emerged and evolved in the medical environment of Japan (99), and ST260 is the most frequent in hospitals in USA and Estonia (5, 91, respectively), mostly with a MDR phenotype.

In relation to Gram-positive pathogens, it is reported that MRSA strains are leading causes of hospital-acquired infections in the United States, and clonal complex 5 (CC5) is the predominant lineage responsible for these infections (74). ST772-t657 is the most reported MRSA clone in tertiary hospitals in Pakistan (59), and ST239-t030 is detected in all cases of hospital-acquired infections in Yunnan Province of China, it belongs to 'Turkish clade' from Eastern Europe (96). Genetic relatedness of MDR-*E. faecium* isolates in university hospitals in Serbia was established by Multiple-locus variable-number tandem-repeat (VNTR) analysis (MLVA), which revealed polyclonal setting with 25 unique MT profiles, which are either single-locus or double-locus variants of clones MT-340 and MT-159, known to cause infections in hospitalizied patients in Serbia. These are isolates that have most likely been selected by antibiotic pressure and develop in hospital-adapted clones that occur sporadically (109). Using PFGE analysis, Kohler *et al*. demonstrated a high clonality in strains of *Enterococcus spp.* causing bacteremia in several Canadian ICUs (112).

Among the mechanisms to control problematic pathogens in ICUs, some authors propose implementing close surveillance and detection of resistant pathogens, changes in resistance pattern, s as well as applying strict cleaning protocols, antibiotic administration policies and adequate control guidelines to the specific conditions for each hospital (5, 7, 8, 13, 15, 24, 66, 81).

Our study provides information on the epidemiological behavior of pathogens that cause infections in adult ICUs. Disadvantage of our study is that the studies used for the analysis were heterogeneous and some studies did not report ARGs or did not perform genetic diversity analyses. There were very few reports that used state-of-the-art molecular techniques to carry out the analysis of the genetic structure of bacteria isolated from nosocomial infections.

CONCLUSIONS

In this systematic review it is evident that *K. pneumoniae* and *E. coli* were the most reported in urinary tract infections, bacteremia and pneumonia in hospitals in Asia, Africa and Latin America, being the production of ESBL and carbapenemases mediated by *bla*OXA *and bla*CTX genes, the mechanism of resistance most common in these bacteria. However, it is evident that there are important differences between regions, such as the reports of *P. aeruginosa* in Europe and North America as the second most prevalent pathogen after *K. pneumoniae* or *E. coli,* respectively. The main concerns about MDR-pathogens are usually associated with gram-negative bacilli, ESBL, and carbapenemase-producing strains of *E. coli* and *K. pneumoniae*, as well as carbapenemase-producing *P. aeruginosa* and *A. baumannii*. Among gram-positive nosocomial pathogens, MRSA and VRE are often reported. In some ICUs around the world there is a marked presence of MDR, XDR and PDR organisms, shows great diversity, probably due to the selective action exerted by the use of intensive empirical antibiotic therapy. However, there is a predominance of few clones that have adapted efficiently to the hospital environment: mainly CC5 MRSA strains are leading causes of hospital-acquired infections in the United States (74). Clone ST23 KPC-producing *K. pneumoniae* is isolated from infections in India (46) and Iran (47) and ST260 carbapenemase-producing *P. aeruginosa* is the most frequent in hospitals in United States (85) and Estonia (91) and have a great ability to survive for a long time. These are the high-risk clones that must be closely monitored due to their spread ant to the greater capacity to cause additional morbidity, mortality, and hospital costs.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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