Uttar Pradesh Journal of Zoology

Volume 45, Issue 2, Page 5-15, 2024; Article no.UPJOZ.3170
ISSN: 0256-971X (P)

A Review on Antibiotic Resistance in Bacterial Pathogens

Kiran Kumar Mandapati [a], Uma Chinnaiyan [a++], Sowndarya Sivaprakasam [a] and Sivagurunathan Paramasivam [a++*]

[a] Department of Microbiology, Faculty of Science, Annamalai University, Annamalai Nagar, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.56557/UPJOZ/2024/v45i23859

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://prh.mbimph.com/review-history/3170

Review Article

Received: 09/11/2023
Accepted: 14/01/2024
Published: 18/01/2024

ABSTRACT

Human health has been greatly impacted by the use of antibiotics, which have become essential in modern medicine. The treatment of bacterial infections with antibiotics decreased childhood mortality and raised life expectancy. Global public health is seriously threatened by antibiotic resistance. The multi-drug resistance (MDR) pandemic has spread quickly throughout many nations, with some instances going untreated. This has led to greater mortality rates, longer hospital stays, increased medical expenditures, and more. The primary culprits behind nosocomial infections are thought to be a variety of multidrug-resistant (MDR) such as *A. baumannii, Pseudomonas aeruginosa, Enterobacteria* that produces extended-spectrum beta-lactamase (ESBL), and carbapenem-resistant CRE. The most prevalent bacterial pathogens have been identified as Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), according to recent reports. The primary factors in the development of antibiotic resistance are the subject of this review.

[++] Assistant Professor;
**Corresponding author: Email: sivaguru1981@gmail.com;*

Keywords: Multidrug resistance; antibiotic resistance; nosocomial infection; bacteria; genes.

1. INTRODUCTION

"Antibiotics have played a central role in modern medicine and their use has had a significant impact on human health. Their advancement has raised life expectancy, decreased childhood mortality, and given us a crucial tool for invasive surgery and the treatment of bacterial infections. One of the biggest threats to global public health is antibiotic resistance (AR). Antibiotic-resistant bacteria (ARB) infections are linked to higher rates of death, the need for hospitalisation, longer hospital stays, and greater medical expenses" [1].

"Water systems connect people at home, in hospitals, in agriculture, and on animal farms from their source to the stream. These systems take input from a variety of sources in a range of environmental circumstances" [2]. "They serve as networks for bacteria, plasmids, phages, antibiotic resistance genes (ARGs)" [3]. "The destiny of ARB and ARGs in the water systems is influenced by a number of factors, including temperature, the richness of organic matter, redox conditions, and the concentrations of metals, antibiotics, and biocides. These factors also affect the ecosystems and their habitats" [4]. "Mutations, horizontal gene transfer (HGT), and other genetic processes are the main factors facilitating the evolution of ARGs in aquatic environments. It is thought that conjugative transfer via mobile genetic elements—such as plasmids and transposons, or ICE—is widespread and has the ability to spread ARGs to bacteria in unrelated phyla" [5]. Another significant mechanism that non-antibiotic medications and disinfectants can support is natural transformation [6,7].

2. ANTIBIOTIC RESISTANT BACTERIA (ARB)

Genes or mutations that are beneficial to bacterial survival in the presence of antimicrobial drugs may be present in bacterial genomes. Bacteria that are susceptible to antibiotics can develop resistance through either de novo gene mutation or by obtaining resistance genes from other bacterial cells. Hence, selection pressure causes resistance to develop as a result of widespread misuse of antibiotics [8]. "Horizontal gene transfer (HGT) can result in the acquisition of antibiotic resistance in cells, even when those cells belong to different species or genera" [9]. "Nowadays, the release of a new antibiotic onto the market is nearly always accompanied by the rise of resistance bacterial strains. The creation of novel, potent antibiotics and antibacterial compounds depends on a thorough understanding of the mechanisms behind the emergence of drug resistance" [10].

"ARGs have been found in ancient DNA retrieved from both environmental and human ancestor samples, indicating that bacterial antibiotic resistance mechanisms predate human usage of antimicrobials" [11]. "The acquisition of ARGs may have been accelerated by resistance gene transfer and widespread use of antibiotics, as studies have also found higher numbers of ARGs in the genomes of contemporary strains of some bacteria (such as those belonging to the genera *Pseudomonas* and *Clostridium*) than in strains recovered from the microbiome of ancient human ancestors" [12].

3. MULTIDRUG RESISTANCE BACTERIA (MDR)

Pathogenic organisms that exhibit resistance to several chemotherapeutic drugs are said to have multidrug resistance. MDR is a perfectly normal process that occurs in bacteria, but it is becoming more common for a variety of reasons, including the use of unidentified antimicrobial agents, unsanitary, unclean settings, and subpar healthcare facilities. Because antibiotic-resistant microorganisms are a constant threat, there aren't many antimicrobial medicines available to treat other illnesses [13,14]. "The quick spread of multi-drug resistance (MDR) in many nations, some of which lack a treatment option, is one particular cause for concern. Extensive drug resistance (XDR) denotes non-susceptibility to at least one agent in all but one or two antimicrobial classes, and pan-drug resistance (PDR) denotes non-susceptibility to all agents in all available antimicrobial classes. MDR is defined as the acquired non-susceptibility to at least one agent among three or more antimicrobial classes" [15]. "Water, dirt, wastewater, sewage, plants (fruit, vegetables, herbs), raw meat, dairy products, the upper respiratory tract, the gastrointestinal tract, and human and animal skin are natural habitats and reservoirs for multi-drug resistance bacteria (MDRB). Another well-known source of MDRB is livestock, including pigs, cattle, and poultry. It is also feasible for MDRB to spread through food items and water. MDRB contamination of drinking water, milk, and meat products has been shown in numerous articles" [16].

4. RESISTANCE EVOLUTION IN THE ENVIRONMENT

Antibiotic resistance can result from foreign DNA absorption as well as alterations in the bacterium's pre-existing genome. In the patient or animal receiving the antibiotic, mutations easily develop and become fixed. Somewhere else, diseases are not subject to such a strong selection pressure. Furthermore, the process is not influenced by the genetic reservoir found in other species. Therefore, it is generally less expected that external factors will play a significant role in the mutation-based evolution of resistance that most infections experience. The variety of the human and domestic animal microbiota is far less than that of the gene pool found in water, soil, and other habitats with highly varying ecological niches when it comes to the uptake of novel resistance components [17,18]. The ambient microbiome is remarkably diverse, offering a multitude of genes that pathogens may acquire and utilise to counteract the effects of antibiotics. This is, in fact, its most remarkable characteristic [19]. At least some of the pathogens targeted by all licenced antibiotic classes to date—whether they are synthetic, semi-synthetic, or natural compounds—have developed resistance to them. According to this, unless we have a paradigm shift in the way we think about the design of antibiotics, external surroundings already include resistance elements for any antibiotics that will ever be discovered [20]. “Genes can be transferred into human infections, therefore their presence is concerning even although few studies have established the existence of ESBL, MRSA, and VRE producers in the environment, where they can operate as a reservoir of such resistance” [21]. “Numerous multidrug resistant (MDR) bacteria have been identified in hospital and municipal sewage systems, as well as in the soil surrounding animal farms and contaminated rivers. These findings raise the possibility that these bacteria could contribute to the spread of antibiotic resistance and develop into pathogens. Because of their increasing clinical significance and resistance to several medicines, they have begun to resemble both environmental and clinical microorganisms” [22,23].

5. COMMON ANTIBIOTIC-RESISTANT BACTERIAL SPECIES

Globally, infections linked to health care increase rates of morbidity and mortality. Antimicrobial resistance, which restricts the use of antibiotics and makes it more challenging to treat infections brought on by multiresistant microbes, is directly linked to the rise in mortality. Infections with gram-negative bacteria that are resistant to carbapenem, primarily Enterobacteria, emerged as a significant public health concern at the start of the twenty-first century [24]. Nosocomial infections are thought to be mostly caused by MDR gram-negative bacteria, such as *A. baumannii, Pseudomonas aeruginosa, Enterobacteria* that produce extended-spectrum beta-lactamase (ESBL), and Enterobacteria that are resistant to carbapenem [25]. “The World Health Organization (WHO) has identified the genera *Pseudomonas, Acinetobacter* and *Enterobacter* as those belonging to the Gram-negative family of bacteria for which new and effective medications are desperately needed. They are used as “the last line of antibiotic defence” against resistant organisms because, among other things, they produce an extended spectrum of β-lactamases (ESBLs) that confer resistance to antimicrobials like cephalosporins, penicillins, and monobactams. Additionally, they include an increasing number of strains that are resistant to carbapenem” [26,27]. Concerningly, during the past 10 years, there has been a noticeable global rise in nosocomial CRB (carbapenem-resistant bacterium) infections; infections caused by *Acinetobacter* and *Pseudomonas* have been linked to 40–80% mortality in intensive care units [28,29].

According to current reports, the most prevalent bacterial diseases are vancomycin-resistant Enterococcus (VRE) and methicillin-resistant *S. aureus* (MRSA). Hospitals have also been shown to harbour animal products, water, and animals. Although some strains of MDR P. aeruginosa, Carbapenem-resistant *Enterobacteriaceae*, and *A. baumannii* have also been recovered from foods, animals, and water, clinical samples have been the primary source of these germs.

A large number of these organisms are opportunistic infections that contaminate the ill or immunocompromised. A lot of these bacteria seem to be found in large quantities in nature, and a contaminated environment can promote their proliferation. Public health is also greatly concerned about the Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) bacteria. It is well recognised that both have the capacity to spread epidemics [30].

The World Health Organization released the first-ever list of antibiotic-resistant "priority pathogens," which is a catalogue of 12 bacterial

families that are the biggest threats to human health. According to how urgently new antibiotics are needed, the WHO list is split into three categories: critical, high, and medium priority [31].

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

5.1 What Mechanisms Bacteria Use to Adapt?

There is no one mechanism responsible for the fast spread of AMR throughout bacterial populations. Frequently, it is the outcome of intricate procedures. Therefore, before analysing the factors that cause resistance to these molecules, antibiotics must be divided into groups based on their distinct mechanisms of action. We have chosen to discuss the antibiotic classes that are most directly related to the development of antibiotic resistance in this review, despite the fact that there are many distinct classes of antibiotics. The modes of action and resistance of the major antibiotic families are presented in Table 1 the primary ways in which antimicrobial drugs function. Reduced drug uptake, altered drug targets, drug inactivation, and activation of drug efflux pumps are the primary causes of resistance [32,33].

5.2 Antibiotic-Resistant Pathogens

5.2.1 Acinetobacter baumannii

"Gram-negative aerobic bacillus *Acinetobacter baumannii* is a member of the group of pathogens known by the acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species*), which stands for the ability of these bacteria to evade the effects of antibiotic bactericidal activity" [34]. *A. baumannii* is an opportunistic pathogen that can become resistant to antibiotics through a variety of ways. It is a global cause of hospital-acquired infections.

Table 1. Antibiotic resistance mechanisms and modes of action

Antimicrobial Groups	Mechanism of Action	Resistance Mechanism
β-Lactams Penicillins Cephalosporins Carbapenems	Inhibits cell wall production	Beta-lactamase production Penicillinase Cephalosporinase Carbapenemase
β-Lactamase inhibitors	Block the activity of beta-lactamase enzymes	Extended-spectrum beta-lactamase (ESBL)
Aminoglycosides, Chloramphenicol Macrolides, Tetracyclines	Inhibit ribosome assembly by binding to the bacterial 30S or 50S (inhibit protein synthesis)	Multifactorial (enzymatic modification, target site modification and efflux pumps)
Fluoroquinolone	Inhibit DNA replication	Multifactorial (target-site gene mutations, efflux pumps and modifying enzyme)
Sulfonamides and trimethoprim	Inhibit folic acid metabolism	Horizontal spread of resistance genes, mediated by transposons and plasmids, expressing drug-insensitive variants of the target enzymes.

The rapid evolution of this strain toward multi-resistance could be attributed to the creation of all four classes of β-lactamases (A, B, C, and D) by the integration of exogenous DNA into its genome [35]. Furthermore, genes encoding for ESBL (GES-11 and CTX-M) and narrow-spectrum β-lactamases (TEM-1, SCO-1, and CARB-4) have been found in Acinetobacter spp. [36]. With the exception of monobactams, class B β-lactamases are metallo-β-lactamases (MBLs) with a wide substrate range of inhibition [37]. A class of widely distributed enzymes known as class C β-lactamases is typically resistant to cephamycins (cefoxitin and cefotetan), penicillins, and cephalosporins [38]. Additionally, *A. baumannii* has Class D, or OXAs β-lactamases, which are capable of hydrolyzing carbapenems and extended range cephalosporins [39]. Additionally, AmpC cephalosporinase is inherent to *A. baumannii* [40].

"Efflux pumps have a role in *A. baumannii* bacterial resistance to many antibiotics from different chemical classes, including trimethoprim, aminoglycosides, tetracyclines, erythromycin, chloramphenicol, fluoroquinolones, and various beta-lactams" [41,42].

"Three kinds of enzymes—phosphotransferases, adenylyl transferases, and acetyltransferases—are essential to *A. baumannii* resistance to aminoglycosides. Transposons and plasmids are two ways that the genes encoding for aminoglycoside-modifying enzymes can be transmitted" [43].

For the treatment of MDR *A. baumannii* bacteraemia, the combination of ampicillin, sulbactam, and carbapenem is the most effective [44]. Even while considerable rates of resistance have been reported, minocycline treatment is also beneficial [45]. Combining minocycline and colistin is the recommended treatment for *A. baumannii* infections that are resistant to minocycline, whereas colistin/rifampin is the most efficient treatment for *A. baumannii* infections that are resistant to colistin [46]. Moreover, carbapenem-resistant *A. baumannii* is quickly killed by trimethoprim-sulfamethoxazole in combination with colistin [47].

5.2.2 Methicillin-Resistant *Staphylococcus aureus*

"S. aureus is the leading cause of nosocomial infections by gram-positive bacteria [48]. It is notoriously resistant to penicillin and many other antimicrobials" [49]. "Strains of *S. aureus* have developed resistance to many commonly used antimicrobial due to indiscriminate use. Staphylococcal resistance to penicillin is mediated by β-lactamase production. First report of a penicillin-resistant strain of *S. aureus* was published in 1945, revealing its association with β-lactamase enzyme produced by the bacteria. The methicillin resistant *staphylococcus aureus* (MRSA) is a specific strain of the *S. aureus* bacterium that has developed antimicrobial resistance to all penicillin 's, including methicillin and other narrow-spectrum β-lactamase-resistant penicillin antimicrobials" [50].

The first evidence of methicillin resistance was found in *Staphylococcus aureus* in 1961 as a result of widespread penicillin use. Penicillinase-producing *S. aureus* also became more prevalent after penicillin was introduced. While hospital-acquired methicillin-resistant *S. aureus* (HA-MRSA) is becoming less common, methicillin-resistant *S. aureus* (MRSA) is still a major burden in U.S. health care settings. In contrast to this discovery, there has been a notable rise in the frequency of community-acquired MRSA (CA-MRSA) infections within the same area [51]. Due to the lack of the mecA gene, BORSA is not actually methicillin resistant or sensitive, and frequent misidentification puts patient treatment and outcomes at serious risk because severe infections may not respond to high oxacillin doses [52]. Overall, MRSA infections result in higher health care costs due to morbidity and length of hospital stay [53]. Methicillin resistance is independently linked to higher mortality, and the death rate after *S. aureus* blood stream infection surpasses 20 % [54,55].

5.2.3 Pseudomonas aeruginosa

"Aerobic gram-negative *P. aeruginosa* is a prevalent environmental pathogen that can cause a wide range of acute and chronic nosocomial infections, including severe respiratory infections in patients with compromised host defences" [56]. "*P. aeruginosa* is the third most frequent gram-negative bacterium in this environment that causes nosocomial bloodstream infections" [57]. "Due to several resistance mechanisms that are both intrinsic and acquired from other species, *P. aeruginosa* has demonstrated intrinsic resistance to a variety of antibiotics" [58]. "The overexpression of efflux pumps, a decrease in

the permeability of the outer membrane, and the acquisition or mutation of resistance genes that encode for proteins that regulate the passive diffusion of antibiotics across the outer membrane are the key mechanisms of resistance" [59]. "Broad-spectrum antimicrobials with *P. aeruginosa* coverage, ceftazidime and cefepime, which belong to the third and fourth generations of cephalosporins, respectively, have been identified" [60]. "Numerous β-lactams, including imipenem and benzylpenicillin, can stimulate endogenous β-lactamase, such as AmpC β-lactamase. Furthermore, a gene mutation that results in the overexpression of AmpC β-lactamases can give *P. aeruginosa* resistance" [61]. "Transferable aminoglycoside modifying enzymes (AMEs), which reduce the binding affinity to their target in the bacterial cell, cause pseudomonas resistance to aminoglycosides" [62,63]. "Colistin is used in conjunction with an anti-pseudomonas medication such as imipenem, piperacillin, aztreonam, ceftazidime, or ciprofloxacin to treat MDR *P. aeruginosa"* [64].

5.2.4 *Klebsiella pneumoniae*

K. pneumoniae is a non-fastidious, frequently encapsulated, gram-negative bacillus that belongs to the Enterobacterales family [65]. Particularly in patients with impaired immune systems, *K. pneumoniae* can cause a variety of nosocomial and community-acquired infections, such as bloodstream infections, pneumonia, liver abscesses, urinary tract infections, and surgical site infections [66, 67]. Person-to-person contact is necessary to get a *Klebsiella* infection because the germs cannot be transmitted through the air [68]. Because *Klebsiella* has acquired genes encoding enzymes like ESBLs and carbapenemases widely, the bacteria has developed a high level of resistance to antibiotics [69]. The most clinically significant strains of carbapenem-resistant *Enterobacteriaceae* (CRE) are *K. pneumoniae* strains that are resistant to the antibiotic [70]. Since carbapenems are frequently the last line of defence against gram-negative persistent infections, the rising number of *K. pneumoniae* (KPC) strains that produce the enzyme that codes for the blaKPC-3 gene poses a serious risk to public health [71,72].

5.2.5 *E. coli*

AMR *Escherichia coli* is known to be a major source of bloodstream infections and urinary tract infections (UTI) in both community and healthcare settings worldwide, despite not being officially recognised as a member of the ESKAPE group of pathogens [73]. One of the most typical signs of an *E. coli* UTI is sepsis. *E. coli* is the most common Gram-negative bacterial species identified from blood and urine cultures in Australian emergency rooms and inpatient settings [74]. A number of pandemic clones of MDR uropathogenic *E. coli*, including as ST131 and ST95, have spread around the world in the last ten years [75]. *E. coli* usually obtains resistance genes from other Enterobacterales members through horizontal gene transfer. All throughout Europe, there is a high prevalence of resistance to aminopenicillins, fluoroquinolones, aminoglycosides, and third-generation cephalosporins [76]. The general state of CRE, including *E. coli*, in Europe was demonstrated to deteriorate between 2010 and 2018, notwithstanding the rarity of carbapenem resistance in invasive strains of the bacteria [77]. Moreover, strains of *E. coli* obtained from Chinese pig farms were found to be resistant to colistin, the last-resort polymyxin, in 2016 [78]. One of the biggest clinical burdens on human and animal health at the moment is AMR *E. coli*.

There were comparatively many *E. coli* isolates resistant to tetracyclines, sulphonamides/trimethoprim, quinolones, and β-lactams. The proportion of *E. coli* isolates that responded to phenicol and aminoglycosides was low. Furthermore, the presence of resistance genes 592 in *E. coli* isolates suggested a higher likelihood that 593 of them carried bla-genes, tetA, qnrS, and sul2. Ampicillin (AMP), amoxicillin plus clavulanic acid (AMC), and sulfamethoxazole/trimethoprim were found to have the highest resistance rates (SXT). The antibiotics used as last resort, meropenem (MEM) and ertapenem (ETP), have the lowest rates of resistance [79]. Treated effluent samples included *E. coli* resistant to cefoxitin, ciprofloxacin, and cefotaxime (containing manufacturers of extended-spectrum beta-lactamases [ESBL] [80].

5.2.6 Anti-regulators

The Gram-negative bacteria *Vibrio cholerae* is the cause of the cholera epidemic in humans. A toxin-coregulated pilus and cholera toxin (CT) are the two primary virulence factors in the pathophysiology of *V. cholerae* (TCP). An osmotic imbalance caused by the two subunits of CT, an ADP-ribosylating toxin, causes intestinal cells to produce more cAMP, which in turn causes diarrhoea [81]. When intestinal colonisation by *V. cholerae* occurs, TCP, a type

IV bundle-forming pilus, is involved [82]. ToxT, the master regulator, controls the expression of TCP and CT [83]. In a mouse infection model, Hung et al. found that virstatin (4-[N-(1,8-naphthalimide)]-n-butyric acid) inhibits ToxT dimerization and lowers V. cholera colonisation [84]. ToxTazin, another small molecule inhibitor, decreases the pathogenicity of V. cholera by preventing the synthesis of an activator (TcpP) required for the expression of the toxT gene [85].

6. CONCLUSION

In Conclusion, antibiotic resistance poses a formidable threat to global public health, requiring urgent and concerted efforts from the scientific, medical, and policy-making communities. Antibiotic resistance could usher in a post-antibiotic era, where common infections and minor injuries become life-threatening. Addressing antibiotic resistance demands a multifaceted approach. First and foremost, there is an urgent need for global cooperation to curb the inappropriate use of antibiotics in human medicine, agriculture, and animal husbandry. Public awareness campaigns can play a crucial role in educating the public and healthcare professionals about responsible antibiotic use. Additionally, fostering the development of new antibiotics and alternative treatment strategies is essential to stay ahead of evolving bacterial resistance.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: Mortality, length of hospital stay, and health care costs. Clinical Infectious Diseases, (Supplement_2). 2006;42:S82-S89.
2. Quintela-Baluja M, Abouelnaga M, Romalde J, Su JQ, Yu Y, Gomez-Lopez M, Graham DW. Spatial ecology of a wastewater network defines the antibiotic resistance genes in downstream receiving waters. Water Research. 2019;162:347-357.
3. Marti E, Variatza E, Balcázar JL. Bacteriophages as a reservoir of extended-spectrum β-lactamase and fluoroquinolone resistance genes in the environment. Clinical Microbiology and Infection. 2014; 20(7):O456-O459.
4. Gullberg E, Albrecht LM, Karlsson C, Sandegren L, Andersson DI. Selection of a multidrug resistance plasmid by sublethal levels of antibiotics and heavy metals. MBio. 2014;5(5):10-1128.
5. Zhang XX, Zhang T, Fang HH. Antibiotic resistance genes in water environment. Applied Microbiology and Biotechnology. 2009;82:397-414.
6. Jin M, Liu L, Wang DN, Yang D, Liu WL, Yin J, Li JW. Chlorine disinfection promotes the exchange of antibiotic resistance genes across bacterial genera by natural transformation. The ISME journal. 2020;14(7):1847-1856.
7. Wang J, Chu L, Wojnárovits L, Takács E. Occurrence and fate of antibiotics, antibiotic resistant genes (ARGS) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: An overview. Science of the Total Environment. 2020;744:140997.
8. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. The American journal of Medicine. 2006;119(6):S3-S10.
9. Fernandez-Lopez R, De Toro M, Moncalian G, Garcillan-Barcia MP, De la Cruz F. Comparative genomics of the conjugation region of F-like plasmids: Five Shades of F. Frontiers in Molecular Biosciences. 2016;3:71.
10. Ashbolt NJ, Amézquita A, Backhaus T, Borriello P, Brandt KK, Collignon P, Topp E. Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. Environmental Health Perspectives. 2013; 121(9):993-1001.
11. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews. 2010;74(3): 417-433.
12. Martínez JL. Antibiotics and antibiotic resistance genes in natural environments. Science. 2008;321(5887):365-367.
13. Nikaido H. Multidrug resistance in bacteria. Annual Review of Biochemistry. 2009;78: 119-146.
14. Vivas R, Barbosa AAT, Dolabela SS, Jain S. Multidrug-resistant bacteria and alternative methods to control them: An overview. Microbial Drug Resistance. 2019;25(6):890-908.
15. Sweeney MT, Lubbers BV, Schwarz S, Watts JL. Applying definitions for multidrug resistance, extensive drug resistance and pandrug resistance to clinically significant

livestock and companion animal bacterial pathogens. Journal of Antimicrobial Chemotherapy. 2018;73(6):1460-1463.
16. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Shen J. emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in china: A microbiological and molecular biological study. The Lancet Infectious Diseases. 2016;16(2):161-168.
17. Rinke C, Schwientek P, Sczyrba A, Ivanova NN, Anderson IJ, Cheng JF, Woyke T. Insights into the phylogeny and coding potential of microbial dark matter. Nature. 2013;499(7459):431-437.
18. Schulz F, Eloe-Fadrosh EA, Bowers RM, Jarett J, Nielsen T, Ivanova NN, Woyke T. Towards a balanced view of the bacterial tree of life. Microbiome. 2017;5:1-6.
19. Forsberg KJ, Reyes A, Wang B, Selleck EM, Sommer MO, Dantas G. The shared antibiotic resistome of soil bacteria and human pathogens. Science. 2012; 337(6098):1107-1111.
20. Dantas G, Sommer MO, Oluwasegun RD, Church GM. Bacteria subsisting on antibiotics. Science. 2008;320(5872):100-103.
21. Czekalski N, Sigdel R, Birtel J, Matthews B, Bürgmann H. Does human activity impact the natural antibiotic resistance background? Abundance of antibiotic resistance genes in 21 Swiss lakes. Environment International. 2015;81:45-55.
22. Zong Z, Zhang X. bla NDM-1-carrying Acinetobacter johnsonii detected in hospital sewage. Journal of Antimicrobial Chemotherapy. 2013;68(5):1007-1010.
23. Serwecińska L, Kiedrzyńska E, Kiedrzyński M. A catchment-scale assessment of the sanitary condition of treated wastewater and river water based on fecal indicators and carbapenem-resistant acinetobacter spp. Science of the Total Environment. 2021;750:142266.
24. Tacconelli ECMA, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, Cookson B. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clinical Microbiology and Infection. 2014;20:1-55.
25. Teerawattanapong N, Kengkla K, Dilokthornsakul P, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Prevention and control of multidrug-resistant gram-negative bacteria in adult intensive care units: a systematic review and network meta-analysis. Clinical Infectious Diseases. 2017;64(suppl_2): S51-S60.
26. Bush K, Jacoby GA. Updated functional classification of β-lactamases. Antimicrobial Agents and Chemotherapy. 2010;54(3):969-976.
27. Miyagi K, Hirai I. A survey of extended-spectrum β-lactamase-producing *enterobacteriaceae* in environmental water in okinawa prefecture of Japan and relationship with indicator organisms. Environmental Science and Pollution Research. 2019;26:7697-7710.
28. Joshi SG, Litake GM. Acinetobacter baumannii: An emerging pathogenic threat to public health. World Journal of Clinical Infectious Diseases. 2013;3(3):25-36.
29. Safaei HG, Moghim S, Isfahani BN, Fazeli H, Poursina F, Yadegari S, Nodoushan SAH. Distribution of the strains of multidrug-resistant, extensively drug-resistant, and pandrug-resistant pseudomonas aeruginosa isolates from burn patients. Advanced Biomedical Research. 2017;6.
30. Arora S, Gautam V, Rana S, Ray P. Novel chromogenic medium for detection of extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, methicillin resistant *Staphylococcus aureus* and vancomycin resistant Enterococcus. Journal of Medical Investigations and Practice. 2014;9(2):98.
31. Available:https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
32. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS microbiology. 2018;4(3): 482.
33. Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial antibiotic resistance: The most critical pathogens. Pathogens. 2021; 10(10):1310.
34. De Oliveira DM, Forde BM, Kidd TJ, Harris PN, Schembri MA, Beatson SA, Walker MJ. Antimicrobial resistance in ESKAPE pathogens. Clinical microbiology reviews. 2020;33(3):10-1128.
35. Harding CM, Hennon SW, Feldman MF. Uncovering the mechanisms of Acinetobacter baumannii virulence. Nature Reviews Microbiology. 2018;16(2):91-102.

36. Vrancianu CO, Gheorghe I, Czobor IB, Chifiriuc MC. Antibiotic resistance profiles, molecular mechanisms and innovative treatment strategies of Acinetobacter baumannii. Microorganisms. 2020;8(6): 935.
37. F Mojica M, A Bonomo R, Fast W. B1-metallo-β-lactamases: where do we stand? Current drug Targets. 2016;17(9):1029-1050.
38. Shaikh S, Fatima J, Shakil S, Rizvi SMD, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi journal of biological sciences. 2015;22(1): 90-101.
39. Hammoudi Halat D, Ayoub Moubareck C. The current burden of carbapenemases: Review of significant properties and dissemination among gram-negative bacteria. Antibiotics. 2020;9(4):186.
40. Beceiro A, Dominguez L, Ribera A, Vila J, Molina F, Villanueva R, Bou G. Molecular characterization of the gene encoding a new AmpC β-lactamase in a clinical strain of Acinetobacter genomic species 3. Antimicrobial agents and chemotherapy. 2004;48(4):1374-1378.
41. Abdi SN, Ghotaslou R, Ganbarov K, Mobed A, Tanomand A, Yousefi M, Kafil HS. Acinetobacter baumannii efflux pumps and antibiotic resistance. Infection and Drug Resistance. 2020;423-434.
42. Basatian-Tashkan B, Niakan M, Khaledi M, Afkhami H, Sameni F, Bakhti S, Mirnejad R. Antibiotic resistance assessment of Acinetobacter baumannii isolates from Tehran hospitals due to the presence of efflux pumps encoding genes (adeA and adeS genes) by molecular method. BMC Research Notes. 2020;13:1-6.
43. Chen L, Tan P, Zeng J, Yu X, Cai Y, Liao K, Huang B. Impact of an intervention to control imipenem-resistant Acinetobacter baumannii and its resistance mechanisms: An 8-year survey. Frontiers in Microbiology. 2021;11:610109.
44. Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G. The “old” and the “new” antibiotics for MDR gram-negative pathogens: For whom, when, and how. Frontiers in public health. 2019;7:151.
45. Vázquez-López R, Solano-Gálvez SG, Juárez Vignon-Whaley JJ, Abello Vaamonde JA, Padró Alonzo LA, Rivera Reséndiz A, Barrientos Fortes T. Acinetobacter baumannii resistance: A real Challenge for Clinicians. Antibiotics. 2020; 9(4):205.
46. Górski A. Jo nczyk-Matysiak, E. The Role of Antibiotic Resistant A. baumannii in the Pathogenesis of Urinary Tract Infection and the Potential of Its Treatment with the Use of Bacteriophage Therapy. Antibiotics. 2021;10:281.
47. Nepka M, Perivolioti E, Kraniotaki E, Politi L, Tsakris A, Pournaras S. *In vitro* bactericidal activity of trimethoprim-sulfamethoxazole alone and in combination with colistin against carbapenem-resistant Acinetobacter baumannii clinical isolates. Antimicrobial Agents and Chemotherapy. 2016;60(11): 6903-6906.
48. Simpson S. Methicillin resistant *Staphylococcus aureus* and its implications for nursing practice: A literature review. Nursing Practice (Edinburgh, Scotland). 1992;5(2):2-7.
49. Mulligan ME, Murray-Leisure KA, Ribner BS, Standiford HC, John JF, Korvick JA, Victor LY. Methicillin-resistant *Staphylococcus aureus*: A consensus review of the microbiology, pathogenesis, and epidemiology with implications for prevention and management. The American journal of medicine. 1993;94(3): 313-328.
50. Cuevas O, Cercenado E, Vindel A, Guinea J, Sánchez-Conde M, Sánchez-Somolinos M, Bouza E. Evolution of the antimicrobial resistance of *Staphylococcus* spp. in Spain: five nationwide prevalence studies, 1986 to 2002. Antimicrobial agents and chemotherapy. 2004;48(11):4240-4245.
51. Kourtis AP, Hatfield K, Baggs J, Mu Y, See I, Epson E, Cardo D. Vital signs: epidemiology and recent trends in methicillin-resistant and in methicillin-susceptible *Staphylococcus aureus* bloodstream infections—United States. Morbidity and Mortality Weekly Report. 2019;68(9):214.
52. Skinner S, Murray M, Walus T, Karlowsky JA. Failure of cloxacillin in treatment of a patient with borderline oxacillin-resistant *Staphylococcus aureus* endocarditis. Journal of Clinical Microbiology. 2009; 47(3):859-861.
53. Pada SK, Ding Y, Ling ML, Hsu LY, Earnest A, Lee TE, Fisher D. Economic and clinical impact of nosocomial meticillin-resistant *Staphylococcus aureus* infections in Singapore: A matched case–control

study. Journal of Hospital Infection. 2011; 78(1):36-40.

54. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: A meta-analysis. Clinical infectious diseases. 2003;36(1):53-59.
55. Kaasch AJ, Barlow G, Edgeworth JD, Fowler Jr VG, Hellmich M, Hopkins S, Sabg U. *Staphylococcus aureus* bloodstream infection: A pooled analysis of five prospective, observational studies. Journal of Infection. 2014;68(3):242-251.
56. Jurado-Martín I, Sainz-Mejías M, McClean S. Pseudomonas aeruginosa: An audacious pathogen with an adaptable arsenal of virulence factors. International Journal of Molecular Sciences. 2021; 22(6):3128.
57. Recio R, Mancheño M, Viedma E, Villa J, Orellana MÁ, Lora-Tamayo J, Chaves F. Predictors of mortality in bloodstream infections caused by Pseudomonas aeruginosa and impact of antimicrobial resistance and bacterial virulence. Antimicrobial Agents and Chemotherapy. 2020;64(2):10-1128.
58. Hwang W, Yoon SS. Virulence characteristics and an action mode of antibiotic resistance in multidrug-resistant Pseudomonas aeruginosa. Scientific reports. 2019;9(1):487.
59. Henrichfreise B, Wiegand I, Pfister W, Wiedemann B. Resistance mechanisms of multiresistant Pseudomonas aeruginosa strains from Germany and correlation with hypermutation. Antimicrobial Agents and Chemotherapy. 2007;51(11):4062-4070.
60. Sader HS, Huband MD, Castanheira M, Flamm RK. Pseudomonas aeruginosa antimicrobial susceptibility results from four years (2012 to 2015) of the international network for optimal resistance monitoring program in the United States. Antimicrobial agents and chemotherapy. 2017;61(3):10-1128.
61. Dehbashi S, Tahmasebi H, Alikhani MY, Keramat F, Arabestani MR. Distribution of Class B and Class A β-lactamases in clinical strains of Pseudomonas aeruginosa: Comparison of phenotypic methods and high-resolution melting analysis (HRMA) assay. Infection and Drug Resistance. 2020;2037-2052.
62. Ahmed S, Sony SA, Chowdhury M., Ullah MM, Paul S, Hossain T. Retention of antibiotic activity against resistant bacteria harbouring aminoglycoside-N-acetyltransferase enzyme by adjuvants: a combination of in-silico and in-vitro study. Scientific Reports. 2020;10(1):19381.
63. Ontong JC, Ozioma NF, Voravuthikunchai SP, Chusri S. Synergistic antibacterial effects of colistin in combination with amin-oglycoside, carbapenems, cephalosporins, fluoroquinolones, tetracyclines, fosfomycin, and piperacillin on multidrug resistant Klebsiella pneumoniae isolates. Plos one. 2021;16(1):e0244673.
64. Pungcharoenkijkul S, Traipattanakul J, Thunyaharn S, Santimaleeworagun W. Antimicrobials as single and combination therapy for colistin-resistant Pseudomonas aeruginosa at a university hospital in Thailand. Antibiotics. 2020;9(8):475.
65. Santajit S, Indrawattana N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. BioMed Research International; 2016.
66. Caneiras C, Lito L, Melo-Cristino J, Duarte A. Community-and hospital-acquired Klebsiella pneumoniae urinary tract infections in Portugal: Virulence and antibiotic resistance. Microorganisms. 2019;7(5):138.
67. Eghbalpoor F, Habibi M, Azizi O, Asadi Karam MR, Bouzari S. Antibiotic resistance, virulence and genetic diversity of Klebsiella pneumoniae in community-and hospital-acquired urinary tract infections in Iran. Acta Microbiologica et Immunologica Hungarica. 2019;66(3):349-366.
68. Young TM, Bray AS, Nagpal RK, Caudell DL, Yadav H, Zafar MA. Animal model to study Klebsiella pneumoniae gastrointestinal colonization and host-to-host transmission. Infection and immunity. 2020;88(11):10-1128.
69. Effah CY, Sun T, Liu S, Wu Y, Klebsiella pneumoniae: an increasing threat to public health. Annals of Clinical Microbiology and Antimicrobials. 2020;19(1):1-9.
70. Lasko MJ, Nicolau DP. Carbapenem-resistant Enterobacterales: Considerations for treatment in the era of new antimicrobials and evolving enzymology. Current Infectious Disease Reports. 2020;22:1-12.
71. Gualtero S, Valderrama S, Valencia M, Rueda D, Muñoz-Velandia O, Ariza B,

Niño A. Factors associated with mortality in Infections caused by Carbapenem-resistant *Enterobacteriaceae*. The Journal of Infection in Developing Countries. 2020; 14(06):654-659.

72. Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR. Infections caused by carbapenem-resistant *Enterobacteriaceae*: an update on therapeutic options. Frontiers in Microbiology. 2019;10:80.
73. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, Monnet DL. G. Burden of AMR Collaborative, Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect. Dis. 2019;19(1): 56-66.
74. Australian Commission on Safety and Quality in Health Care. AURA 2019. Third Australian report on antimicrobial use and resistancein human health; 2019. Available:https://www.safetyandquality.gov .au/sites/default/files/2019-06/AURA-2019-Report.pdf. Accessed 10 November 2019.
75. Schembri MA, Ben Zakour NL, Phan MD, Forde BM, Stanton-Cook M, Beatson SA. Molecular characterization of the multidrug resistant Escherichia coli ST131 clone. Pathogens. 2015;4(3):422-430.
76. European Antimicrobial Resistance Surveillance Network. 2019. Surveil-lance of antimicrobial resistance in Europe. Annual report of the Euro-pean Antimicrobial Resistance Surveillance Network (EARS-Net); 2018.
77. Brolund A, Lagerqvist N, Byfors S, Struelens MJ, Monnet DL, Albiger B, Kohlenberg A. European antimicrobial resistance genes surveillance network eurgen-net capacity survey group. Worsening epidemiological situation of carbapenemase-producing *Enterobacteriaceae* in Europe, assessment by national experts from 37 countries, July 2018. Euro Surveill. 2019;24(9): 1900123.
78. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Shen J. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study. The Lancet Infectious Diseases. 2016;16(2): 161-168.
79. Crettels L, Burlion N, Breyer R, Mainil J, Servais P, Korfer J, Thiry D. Antimicrobial resistance of Escherichia coli isolated from freshwaters and hospital effluents in Belgium. Letters in applied Microbiology. 2022;74(3):411-418.
80. Galvin S, Boyle F, Hickey P, Vellinga A, Morris D, Cormican M. Enumeration and characterization of antimicrobial-resistant Escherichia coli bacteria in effluent from municipal, hospital, and secondary treatment facility sources. Applied and Environmental Microbiology. 2010;76(14): 4772-4779.
81. Komiażyk M, Palczewska M, Pikula S, Groves P. Bacterial type AB_5 enterotoxins--structure, function and mechanism of action. Postepy biochemii. 2015;61(4): 430-435.
82. Childers BM, Klose KE. Regulation of virulence in Vibrio cholerae: the ToxR regulon; 2007.
83. Weber GG, Klose KE. The complexity of ToxT-dependent transcription in Vibrio cholerae. The Indian Journal of Medical Research. 2011;133(2):201.
84. Hung DT, Shakhnovich EA, Pierson E, Mekalanos JJ. Small-molecule inhibitor of Vibrio cholerae virulence and intestinal colonization. Science. 2005;310(5748): 670-674.
85. Anthouard R, DiRita VJ. Small- molecule inhibitors of toxT expression in Vibrio cholerae. MBio. 2013;4(4):10-1128.

Peer-review history:
The peer review history for this paper can be accessed here:
https://prh.mbimph.com/review-history/3170