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New Bacterial Species Resistant To Antibiotics, Current Situation

AUTHORS DETAIL

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INTRODUCTION

According to various international institutions, antimicrobial resistance (AMR) is such a severe problem that, within 30 years, it could cause the death of more people than those affected by chronic problems such as cancer. The World Health Organization indicates that (World Health Organization, 2015), that AMR is responsible for up to 700 000 deaths worldwide, which could increase up to 10 million deaths annually. In the United States of America, up to 2 million people contract infections associated with AMR bacteria annually leading to the death of almost 23,000 people (Dadgostar 2019). AMR affects not only mortality but also morbidity. It triggers a high economic burden and more extended periods of hospitalization and on a large scale, it causes economic losses in healthcare systems worldwide (Shrestha et al. 2018; Christaki et al. 2020). Statistics show that in 30 years, there may be a reduction of up to three percent of the Gross Domestic Product due to antimicrobial resistance, impacting the world with a loss of up to $100 billion. (Shrestha et al. 2018; Dadgostar 2019). However, these data might be underestimated, as they only consider a subset of drug-resistant bacteria due to the lack of available data on emerging resistant bacteria (Rodríguez-Medina et al. 2019).

When bacteria escape the drug's effect due to the development of cellular mechanisms of response to the aggression, it is reffered as antibiotic resistance (Jubeh et al. 2020). One of the operational definitions of antimicrobial resistance indicates that a strain has antimicrobial resistance if its minimum inhibitory concentration is higher than that exhibited by its similar wild-type strain (Martínez et al. 2015).

Each antimicrobial agent has a unique mode of action that depends on two fundamental aspects which include bacterial cell characteristics and antibiotic targets. Regarding bacterial cell characteristics, differences are distinguished between Gram stain-positive and Gram stain-negative bacteria. Although the structures of both are similar, there are some critical discrepancies. Gram-negative bacteria possess an outer membrane that confers resistance to a high number of antibiotics as it is one of the main targets of their mode of action (Assoni et al. 2020). Alterations in their hydrophobicity properties and changes in porins or lipopolysaccharides contribute to the potential for resistance (Jubeh et al. 2020).

Gram-positive bacteria lack an outer membrane but the presence of thick peptidoglycan layers dominates their anatomy. Lacking the outer membrane, they are more sensitive to the effect of antibiotics. That is why Gram stain-negative species show a higher frequency of resistance and are resistant to more antibiotics (Jubeh et al. 2020). Some agents act against both types of bacteria. These are known as broad-spectrum antimicrobials (Bearden and Danzinger 2001).

Antimicrobial agents can interfere with cell wall synthesis, protein synthesis, nucleic acid synthesis or inhibit a metabolic pathway. Bacteria, for their part, counteract these effects through mechanisms such as 1- intrinsic resistance, a natural property of each bacterial group; 2- acquired resistance, a trait that is a direct function of bacterial genetic variability and may be due to mutations and horizontal gene transfer; 3- Genetic changes in DNA, also called mutational resistance, involve modification of the drug's mode of action, e.g., decreased absorption, activation of exit mechanisms to extradite the harmful molecule or global changes in critical metabolic pathways; and 4- horizontal gene transfer (transformation or conjugative transduction) (Munita and Arias 2016).

Microorganisms possess intrinsic resistance to one or more antimicrobials naturally. The problem occurs when they generate acquired resistance in clinical settings, which causes a bacterial population that was initially susceptible to an antimicrobial to subsequently no longer be so, causing morbidity and mortality (Paterson 2006; Ruppé et al. 2015 2015; Jubeh et al. 2020).

Causes of Antibiotic Resistance

Intrinsic resistance has been well known since the discovery of penicillin. Before its use, the first resistant strains of *Staphylococcus* had already been described. Subsequently, methicillin was introduced, and soon after, a resistant strain

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was reported (Sengupta et al. 2013) and to counter its ineffectiveness, vancomycin was introduced and after two decades later, *Staphylococcus* resistant was reported (Barberato-Filho et al. 2020).

Enabling elements for acquired resistance include misuse and overuse of antibiotics (Zaman et al. 2017; Chokshi et al. 2019; Dadgostar 2019), agricultural use (Chang et al. 2015), rising income levels conducive to overconsumption (Chaw et al. 2018; Klein et al. 2018), travel routes exposing humans to resistant pathogens and their dissemination in various countries, as well as lack of knowledge creating a gap in awareness of antibiotic use globally (Frost et al. 2019).

For this reason, international bodies have launched guidelines that aim to help and safeguard the efficacy of antimicrobials (WHO, 2015, 2022; McEwen and Collignon 2018). The World Health Organization (WHO) classified AMR bacteria that posing an imminent threat to human health (De Oliveira et al. 2020) and published a list of priority pathogens that require urgent research and development of new treatments (WHO 2017).

Priority Bacteria with Antibiotic Resistance

The critical priority group includes multidrug-resistant bacteria that are of great attention because they affect hospitalized patients requiring devices such as catheters and ventilators. The high and medium priority categories contain bacteria with increasing drug resistance (WHO 2017) as mentioned in Table 1.

In addition to the priority resistance determined by the WHO, the bacteria included in the list present resistance profiles to other drugs, which shows their capacity to develop diverse resistance mechanisms. Within this list, we can locate a group of pathogens with a high capacity to escape the antimicrobial effect under the acronym "ESKAPEE": *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp. and *Escherichia coli* (Arato et al. 2021; Mancuso et al. 2021) as mentioned in Table 2.

New Bacterial Species Resistant to Antibiotics

The evolution of antimicrobial resistance and its spread and appearance in diverse ecosystems is due, among other factors, to the interconnection between animal, human and environmental habitats. The spread of resistant clones and antibiotic resistance determinants has been described among microorganisms that previously did not exhibit this characteristic. From this derives the concept of "emerging antibiotic-resistant pathogens," defined as those microorganisms that have recently developed antibiotic resistance, affecting a population by rapidly increasing their incidence or geographic range (Vouga and Greub 2016). Among these, we can find the following:

Klebsiella variicola

It is found within the *Klebsiella pneumoniae* complex and in 2004, it was described as a new species (Wyres et al. 2020). Its natural niches are plants; however, the most current reports show an increasing incidence of strains of clinical origin with AMR (Rivera-Galindo et al. 2021), implicating it in bacteremias, infections of the respiratory system, and urinary tract infections in humans. Therefore, it is considered as an emerging pathogen (Srinivasan and Rajamohan 2020).

One of the main variables to consider when studying antibiotic-resistant strains is the correct identification of the strain to be able to carry out an adequate epidemiological follow-up. In the case of *Klebsiella* (*K.*) *variicola*, the biochemical tests routinely used in the clinical microbiology laboratory or automated systems worldwide has resulted in its misclassification as *K. pneumoniae*. (Long et al. 2017; Fontana et al. 2019; Piepenbrock et al. 2020; Kiley et al. 2021; Rivera-Galindo et al. 2021). Derived from this, there is scarce data on its susceptibility patterns, epidemiological characteristics of distribution in the population, and its actual clinical implications (Rodríguez-Medina et al. 2019).

The few existing reports indicate that it is intrinsically resistant to ampicillin due to the chromosomal LEN β-lactamase (Rodríguez-Medina et al. 2019; Morales-León et al. 2021). It is a carbapenemase-producing species. It is resistant to ertapenem, meropenem and imipenem (Hopkins et al. 2017). Recently, its resistance to colistin, mediated by chromosomal mechanisms, was reported (Jayol et al. 2017; Lu et al. 2018). Likewise, there is evidence of horizontal gene transfer between members of the complex as they have been found to share plasmids, which favors the spread of AMR genes. Because of this, accurate identification is essential (de Campos et al. 2021).

Mycobacterium abscessus

It is a fast-growing, multidrug-resistant, nontuberculous mycobacterium species that has recently become a significant threat to people with chronic lung conditions (Bryant et al. 2021). Infection rates caused by this species are increasing globally, likely due to its dispersal via aerosols and spread through fomites (Bryant et al. 2016). Its intrinsic resistance mechanisms are due to a highly impermeable cell envelope, multidrug exit pumps, and the ability to encode several enzymes that can inactivate antibiotics (Nessar et al. 2012; Luthra et al. 2018; Gorzynski et al. 2021).

Due to extensive, repeated, or inappropriate use of antimicrobials, most strains of this species are resistant to macrolides due to the expression of an erythromycin ribosome methylase gene (erm) (Nessar et al. 2012; Luthra et al. 2018; Lopeman et al. 2019). They are also resistant to aminoglycosides, due to the presence of a mutation in the rrs gene responsible for coding for the 16S rRNA (Johansen et al. 2020). They are resistant to beta-lactams due to the presence of class A beta-lactamase.

Table 1: Priority bacteria with antibiotic resistance, according to WHO (2017)

Priority level	Name	Priority resistance
Critic	*Acinetobacter baumannii,*	Carbapenem-resistant
	Pseudomonas aeruginosa,	Carbapenem-resistant
	Escherichia coli	Carbapenem-resistant, extended-spectrum beta-lactamase (ESBL)-producing carbapenemics
	Klebsiella pneumoniae	
	Enterobacter sp	
High	*Enterococcus faecium*	Vancomycin-resistant
	Staphylococcus aureus	Methicillin-resistant, with intermediate sensitivity and vancomycin resistance
	Helicobacter pylori	Resistant to clarithromycin
	Campylobacter spp	Resistant to fluoroquinolones
	Salmonellae	Resistant to fluoroquinolones
	Neisseria gonorrhoeae	Cephalosporin-resistant, fluoroquinolone-resistant
Medium	*Streptococcus pneumoniae*	Penicillin resistant
	Haemophilus influenzae	Ampicillin resistant
	Shigella spp	Resistant to fluoroquinolones

Table 2: Resistance characteristics of bacteria named ESKAPEE (De Oliveira et al. 2020)

Priority level	Name	Priority resistance	Resistance to other antimicrobials	Mechanism of resistance	Reference
High	*Enterococcus faecium*	Vancomycin	Ampicillin, penicillin, cephalosporins, vancomycin and aminoglycosides such as tobramycin, kanamycin, gentamicin, and fluoroquinolones.	Chromosomal gene pbp5 encodes a class B penicillin-binding protein, aminoglycoside-modifying enzymes, enzyme modification, and ribosomal target modification.	(Emaneini et al. 2008; Cattoir and Giard 2014; Novais et al. 2016; Gorrie et al. 2019).
High	*Staphylococcus aureus*	Methicillin, with intermediate sensitivity and resistance to vancomycin.	Fluoroquinolones	Plasmid-encoded penicillinase, penicillin-binding protein, a mutation in genes encoding target enzymes for DNA replication	(Chambers and Deleo 2009; Tanaka et al. 2000)
Critical	*Klebsiella pneumoniae*	Carbapenemics and extended-spectrum beta-lactamase producer.	Multiresistant	Plasmid accessory genomes and chromosomal gene loci	(Cifuentes-Castaneda et al. 2018; Nakamura-Silva et al. 2022)
Critical	*Acinetobacter baumannii*,	Carbapenemics	Tigecycline, aminoglycosides, colistin	Production of four β-lactamases (A, B, C, D) exit pumps, three classes of enzymes, including acetyltransferases, adenylyltransferases, and phosphotransferases, and loss of lipopolysaccharide.	(Lee et al. 2017; Trebosc et al. 2019; De Oliveira et al. 2020)
Critic	*Pseudomonas aeruginosa*	Carbapenemics	Multidrug resistant	Overexpression of exit pumps and decreased outer membrane permeability, genes encoding for porins and other protein β-lactamases class A, C, and D, aminoglycoside-modifying enzymes.	(Langendonk et al. 2021; Mancuso et al. 2021)
Critic	*Enterobacter sp*	Carbapenemics and extended-spectrum beta-lactamase producer	Fluoroquinolones and aminoglycosides	β-lactamases type A and type B.	(Davin-Regli et al. 2019)
Critic	*Escherichia coli*	Carbapenemics and extended-spectrum Beta-lactamase producer	Broad-spectrum cephalosporins, polymyxins, Fluoroquinolones	Carbapenemases aminoglycoside, 16S rRNA methylases, mcr genes.	(Raphael et al. 2021; Wu et al. 2021; Rodríguez-Avial et al. 2013; Jayol et al. 2017; Sadecki et al. 2021).

They also show resistance to tetracyclines due to enzymatic inactivation by flavine-adenine dinucleotide inactivator monooxygenase (Nessar et al. 2012; Ananta et al. 2018; Luthra et al. 2018; Victoria et al. 2021). As for

fluoroquinolones, their resistance to these compounds is due to a mutation in the quinolone resistance determinant region (Johansen et al. 2020).

Staphylococcus xylosus

It is a coagulase-negative *Staphylococcus* that is implicated in animal infections. However, due to the reports of its ability to produce infections in humans; it is considered an emerging pathogen (Qu et al. 2021).

Human infections include brain abscesses, pyelonephritis, endocarditis, and septicemia. In addition, it is increasingly reported as a nosocomial infection-producing species. At the clinical level, it is possible to detect its resistance to macrolides, and it has been determined that this is due to the presence of the erm gene (Yuan et al. 2021).

Multidrug-resistant strains can also be found, i.e., with resistance to several families of antibiotics. We can consider in this sense that it presents resistance to lincosamide, tetracyclines, and aminoglycoside. There is little information on this species and its novel multidrug resistance, so accurate identification and monitoring should be corroborated with current epidemiological data (Wipf et al. 2017).

Elizabethkingia anophelis

This species is associated with human diseases, especially neonatal nosocomial outbreaks and increasing incidence of bacteremia and mortality (Huang et al. 2017). Recently, it has been a leading cause of life-threatening infections in Hong Kong, the United States, and Taiwan (Spurbeck and Arvidson 2010; Lau et al. 2016; Perrin et al. 2017; Choi et al. 2019; Wang et al. 2019). It is considered as an emerging opportunistic pathogen and is often misdiagnosed because automated identification systems routinely used at the public health service level lack sufficient data for its detection (Lin et al. 2018).

It is intrinsically resistant to many antimicrobial agents commonly used to treat Gram-negative infections, such as carbapenem, cephalosporins, and colistin. It was recently reported to exhibit resistance to at least 20 antibiotics due to genes encoding different beta-lactamases and efflux pumps (Wang et al. 2019). Isolates are usually resistant to cephalosporins, carbapenemics, aminoglycosides, fluoroquinolones, and vancomycin (Teng et al. 2021). Mutations in quinolone resistance determinant regions and amino acid alterations have been detected to be associated with levofloxacin resistance (Jian et al. 2018; Lin et al. 2018).

Escherichia fergusonii

It was classified in 1985 as a new species (Farmer et al. 1985). It is an opportunistic pathogen initially associated with septicemia and diarrhea in animals but is now associated with abdominal wounds, urinary tract infections, and bacteremia in humans (Tang et al. 2022). Recent reports consider it a species of great importance because it frequently affects neonates in intensive care units (Rivera-Galindo et al. 2021). Phenotypic methods generally identify it as *E. coli*; becauseat the epidemiological level, there is an underreporting of pathogenic microorganisms and that effective methods for their detection and treatment are not developed (Tang et al. 2020; Rivera-Galindo et al. 2021).

Escherichia (*E.*) *fergusonii* emerges as a microorganism of concern due to its potential for multidrug resistance. It is a producer of broad-spectrum beta-lactamases resistant to carbapenems (Tomilola et al. 2019). In 2016, a plasmid-borne resistance gene was identified as the primary factor contributing to its colistin resistance (Zhi et al. 2016; Wang et al. 2018; Tang et al. 2020; Liu et al. 2022).

Importantly, there is very little information on the pathogenic potential of this species in humans. However, information on its resistance mechanisms to strains isolated from animals is high; so, we can consider it an emerging zoonotic pathogen (Tang et al. 2020; Guan et al. 2022; Liu et al. 2022; Shah et al. 2022; Tang et al. 2022). As addressed above, the interconnectedness between human, animal and environmental habitats is conducive to the emergence, evolution, and spread of resistance, so the evolution of this species and those described above should be closely monitored.

Conclusion

Since many studies and clinical practice continue to rely on traditional methods based on bacterial culture and automated systems to identify nosocomial antibiotic-resistant microorganisms, it is imperative to show the incidence of new resistant bacterial species emerging as potential health problems. With this information, reference databases can be updated, and the need to migrate towards molecular techniques for accurately identifying emerging microorganisms which can be evidenced whenever possible. The increasing presence of antibiotic-resistant pathogenic species shows the need to minimize the use of inappropriate antimicrobial therapies as they represent risk factors for morbidity, mortality, and economic impact related to health care. If bacteria are accurately identified, epidemiological and clinical studies can make significant advances so that, in the short term, clinicians can prescribe targeted antibiotics that promote the reduction of antimicrobial resistance.

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