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Brief Review on Bacterial Resistance in K. *Pneumoniae*

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Abstract

In recent years, clinical and scientific interest in so-called beta-lactams has been largely due to the large number of reports of multidrug-resistant Gram-negative bacteria. being the indiscriminate use of antibiotics the main factor responsible for the increase of bacterial resistance, which in turn refers to the ability of certain bacteria to resist antimicrobial agents, result of the selective pressure generated by the inadequate use of antibiotics, where initially sensitive microbial populations, are gradually replaced by more resilient populations. The main mechanism of resistance of gram-negative bacteria is the production of β-lactamase enzymes, capable of hydrolyzing β-lactam antibiotics. Carbapenem antibiotics are widely used to combat multiresistant gram-negative bacteria that produce extended-spectrum β-lactamases (ESBLs). The enzyme Klebisiella Pneumoniae Carbapenemase (KPC), is a class A carbapenemase enzyme, encoded by the bla_{KPC} gene, which is located in transmissible plasmids and is very prevalent, especially in enterobacteria. Some bacteria have developed resistance to carbapenems by KPC production, first identified in a *Klebisiella pneumoniae* isolate in North Carolina (USA), encoded by the bla_{KPC} gene. Another class A enzyme carbapenemase was identified in Brazil, Brasiliensis Klebisiella Carbapenemase (BKC-1), encoded by the bla_{BKC-1} gene. Some measures that delay the increase of microbial resistance and reduce the proliferation of resistant microorganisms are the prudent use of antibiotics, hygienic habits on the part of health professionals and the control of the use of antibiotics in veterinary practice and animal production.

Keywords

β-Lactam Resistance, Carbapenemase, Klebisiella, KPC

1. Introduction

In recent years, clinical and scientific interest in antibiotics known as β-lactams has increased greatly due to the large number of reports of multiresistant Gram-negative bacteria, among them *Klebsiella pneumoniae*.

Bacterial resistance is a major public health problem, because as bacterial resistance against antibiotics increases many treatments considered good and cheap against hospital infections become increasingly ineffective [1]. The severity of the impact of bacterial resistance on human health and costs with the health sector, and its wider social impacts are still unknown [2]. The indiscriminate and inappropriate use of antibiotics is one of the main contributing factors for the evolution of this resistance because it generates a selective pressure in the microbial population and facilitates the acquisition of mechanisms of resistance in these bacteria [3].

β-lactam antibiotics, which include penicillins, cephalosporins, carbapenems and monobactams, are widely used to treat bacterial infections. The most common form of resistance to these antibiotics is the production of β-lactamase enzymes, which facilitate their degradation [4-5].

Carbapenems are a class of β-lactam antibiotics widely

used in the treatment of infections caused by multi-resistant gram-negative bacteria producing extended-spectrum β-lactamase – ESBL [6]. Thus, the increased frequency of carbapenem-resistant enterobacteria poses a serious threat to the management of nosocomial infections due to the lack of active antibiotics capable of combating them [7].

The enzyme *Klebisiella pneumoniae carbapenemase* (KPC), is a class A carbapenemase enzyme, encoded by the bla_{PKC} gene, which is located in transferable plasmids and is very prevalent, especially in gram-negative bacteria *Klebisiella pneumoniae* [8]. KPC was first identified in a *K. pneumoniae* isolate collected at a hospital in North Carolina (USA) in 1996 [9].

Another class A carbapenemase enzyme has been identified in Brazil, *Brasiliensis Klebisiella carbapenemase* (BKC-1), it is encoded by the bla_{BKC-1} gene [10]. Considering the importance of the theme "Bacterial Resistance", we did a brief review on the subject to gain knowledge related to it.

2. Bacterial Resistance

Resistance to antimicrobial agents represents a major public health problem worldwide, a phenomenon in which some bacteria have the ability to resist certain compounds [11]. Exposure to the product selects them; they retain the ability to replicate, thus replacing the original population with a more resilient one. Therapeutic options for the treatment of these infections are often limited due to the fact that this pathogen is resistant to various antimicrobials. In recent decades, Enterobacteriaceae species have become an important agent of health care-related infections, most often associated with opportunistic infections. [5, 7, 8]

According to Giedraitiene *et al*. [12], prolonged therapy with a given antibiotic may develop bacterial resistance in a microorganism that is initially sensitive to it, and thus bacteria can gradually adapt and develop resistance to antibiotics. These authors explain that sensitive bacterial cells die when exposed to certain antimicrobial agents, but those with some insensitivity will survive.

One of the main factors contributing to bacterial resistance is the inappropriate and excessive use of antibiotics, the negligence regarding hand hygiene and contamination of hospital equipment, as well as the inefficacy of control of the sale of medicines in pharmacies and the use of antibiotics in animals intended for human consumption [5, 13, 14].

Another fact that presents a potential risk of transmission of bacteria resistant to the human population is the use of manure of animals contaminated with these bacteria without previous treatment, this transfer between animals and humans of resistant microorganisms can occur through direct or indirect contact through consumption of malted meat [15-16].

Colonized patients with multidrug-resistant bacteria act as reservoirs for the horizontal transmission of resistance genes, and cross-transmission between patients facilitated by contact with health professionals and phytomedicines. This fact is an important cause of outbreaks both by single and multiple clones of *K. pneumoniae* [7-9].

Among the mechanisms of bacterial resistance are the modification of the antibiotic, or its destruction, through enzymatic action; the existence of antibiotic efflux pumps of bacterial cells or reduction of cellular permeability to the antibacterial; modifications in target molecules of antibiotics [17-19].

Several bacteria have ESBL production, which confers resistance to almost all β-lactams, mainly penicillins and cephalosporins, becoming a global shared therapeutic challenge that is aggravated by the low creation of new drugs [2, 10]. With the increase of ESBL producing lines, frequently presenting resistance to other antimicrobials, carbapenems became the main therapeutic option.

3. Resistance in Gram-Negative Bacteria

Gram-negative bacilli are enterobacteriaceae and non-fermenters that make up the human intestinal microbiota, which are responsible for the most common hospital and community infections [20-21].

The resistance of gram-negative bacteria to the most commonly used antibiotics, β-lactams (including penicillins, cephalosporins, carbapenems and monobactams), is predominantly due to enzymatic mechanisms, β-lactamases enzymes, which facilitate the degradation of these antibacterial agents [5]. Among the most common beta-lactamase enzymes are extended-spectrum beta-lactamases (ESBL), AmpC beta-lactamases and carbapenemases (MBL, KPC and class D oxacillinses) [12].

Likewise, for resistance to antibiotics in gram-negative bacteria, Hawkey and Jones [22] point out the production of β-lactamase enzymes as the main mechanism of resistance in these bacteria. They also say that the increase in the spread of resistance to cabarpenémicos is due to the increased use of these agents in the treatment of infections by multi-resistant enterobacteriaceae.

The production of β-lactamases presents as a form of resistance common to β-lactam antibiotics, these enzymes are capable of hydrolysing amides, amidines and other C-N bridges, breaking the β-lactam ring [23]. The production of these enzymes is much lower in gram-negative bacteria compared to gram-positive bacteria, but there is a higher concentration of the enzyme in gram-negatives due to their location in the periplasmic space of these microorganisms, improving their performance [24].

Thus, the production of beta-lactamase is one of the most important mechanisms of resistance of gram-negative bacteria [25]. These bacteria (producing ESBL and carbapenemase) are expanding in hospital and community settings, but microbial resistance is more common in hospitals where there is more selective-pressure [5, 21].

Genes encoding bacterial resistance are usually transported by mobile genetic elements that also harbor other resistance-generating determinants, facilitating their spread among various microorganisms, and limiting therapeutic options.

4. β-Lactamases of the Kpc Type

K. pneumoniae is a Gram-negative bacillus of the family Enterobacteriaceae, commonly found as saprophyte in the nasopharyngeal mucosa and in the gastrointestinal tract of humans and animals, is highly adaptable to adverse conditions and may develop resistance during antimicrobial therapy. It is usually related to hospital and community infections, mainly affecting immunosuppressed patients [26]. *K. pneumoniae* expands rapidly due to its ability to colonize, biofilm formation and acquisition of antibiotic resistance genes by lateral gene transfer [27].

With the increase of ESBL-producing strains, often presenting resistance to other antimicrobials, carbapenems have become the main therapeutic option. Carbapenems are widely used for the treatment of infections caused by multiresistant gram-negative bacteria that demonstrate the production of ESBL [6]. The emergence and spread of carbapenem-resistant enterobacteriaceae is a critical problem for the world health, since the antimicrobial treatment options are very restricted, which threatens the medical care of hospitalized patients [18, 28].

The most common enzyme carbapenemase is *Klebisiella pneumoniae carbapenemase* (KPC), which are capable of hydrolysing virtually all β-lactam molecules, thus reducing the susceptibility of the bacteria to carbapenems [18]. These enzymes are encoded by the bla_{KPC} gene, which has been identified in plasmids that vary in size and structure [18, 29]. Already 23 variants of the bla_{KPC} gene has been described worldwide [30]. *K. pneumoniae* producing KPC occurred in Brazil for the first time in 2006 [31].

These microorganisms showed resistance through the production of KPC (Klebsiella pneumoniae carbapenemase) enzymes that are capable of becoming almost all β-lactams [32]. The enzymes are encoded by bla_{KPC} genes, reported in continents such as Europe, the Americas and Asia (BUSH, FISHER, 2011) and more recently by $bla_{BKC\text{-}1}$, located only in Brazil, encoding an isoform of the KPC enzyme called BKC – *Klebsiella carbapenemase Brasiliensis,* a clone that spreads between the two wings of the city of São Paulo [10, 31].

The genes that encode carbapenemase are usually transported by mobile genetic elements that also harbor other resistance-generating determinants, facilitating their spread among various microorganisms and limiting the therapeutic options [32]. However, the $bla_{BKC\text{-}1}$ gene is located in a low-transfer region in an unconjugated plasmid, justifying the low frequency of isolates [10, 33].

The first description of KPC enzymes occurred in 2001 in North Carolina (USA) from a *K. pneumoniae* isolate collected in 1996. Subsequently, KPC reports became prevalent on the East Coast of the United States and expanded rapidly, being described in various parts of the world [34].

In Brazil, a new class A carbapenemase enzyme, *Brasiliensis Klebisiella carbapenemase* (BKC-1), encoded by the $bla_{\text{BKC-1}}$ gene, has been identified in clinical isolates of *K. pneumoniae* derived from a single clone that has spread between two Sao Paulo City [10].

The first KPC enzymes identified in Brazil occurred in isolates of *K. pneumoniae*, collected in 2005 in a hospital in São Paulo [35] and in 2006 in Recife [31]. Since then, several cases have been reported, with the outbreak of *K. pneumoniae* producing KPC in 2010, with 113 positive cases distributed in 11 states and the Federal District, reaching all Brazilian regions, and 11 positive isolates were identified in Ceará [36].

In this outbreak, a high level of resistance to different classes of antimicrobial agents was observed in KPC-producing isolates, mainly polymyxin and tigecycline, the latter being the last option for the treatment of severe infections caused by KPC-producing organisms [36].

Some measures to prevent and combat bacterial resistance include: the prudent use of antibiotics in ICUs and the active surveillance of antibiotic consumption; infection control measures such as disinfection of hospital equipment and surfaces, hand washing; restriction of the use of antibiotics in veterinary practice and animal production [14, 37, 38].

In addition, surveillance programs can significantly aid the reduction of multiresistant germs as they contribute to the adequate implementation of protocols to strengthen infection control strategies and the rational management of antibiotics in hospitals [14].

5. Conclusion

The indiscriminate use of antibiotics is the main factor responsible for the increase of bacterial resistance, which in turn refers to the ability of certain bacteria to resist antimicrobial agents. The selective pressure generated by the inappropriate use of antibiotics selects the most resistant microorganisms of a certain microbial population (initially sensitive), which multiply and gradually substitute the sensitive population for a more resistant one.

The main mechanism of resistance of gram-negative bacteria is the production of β-lactamases enzymes, capable of hydrolyzing β-lactam antibiotics. Carbapenem antibiotics are widely used to combat multi-resistant gram-negative bacteria that produce extended-spectrum β-lactamase (ESBL).

Some bacteria have developed resistance to carbapenems through the production of carbapenemase enzymes, with *Klebsiella pneumoniae carbapenemase* (KPC), first identified in a *K. pneumoniae* isolate in North Carolina (USA), encoded by the bla_{KPC} gene. Another class carbapenemase enzyme has been identified in Brazil, *Brasiliensis Klebisiella carbapenemase* (BKC-1), it is encoded by the $bla_{\text{BKC-1}}$ gene

Some measures that delay the increase of microbial resistance and reduce the proliferation of resistant microorganisms are the prudent use of antibiotics, hygienic habits on the part of health professionals and the control of the use of antibiotics in veterinary practice and animal production.

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