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RESEARCH ARTICLE

IMPORTANCE OF THE BACTERIAL EXTENDED-SPECTRUM BETA LACTAMASES

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ABSTRACT

Antibiotic resistance is a global public health problem. Bacteria have developed different strategies that have allowed them to cope with the action of antibiotics, thus in a few years after the appearance of a new drug with antibacterial properties, strains of bacteria resistant to that new drug emerge. Extended spectrum beta lactamases are a group of bacterial enzymes that can inactivate different antibiotics. They have been found in different examples of Gram positive and negative pathogenic bacteria.

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INTRODUCTION

Within a few years, microbial resistance to antibiotics will become the leading cause of mortality worldwide, since it is estimated that up to 10 million in 2050 will be directly related to this problem. Within the wide range of microorganisms, viruses and bacteria are the ones that trigger epidemiological alerts due to their ability for damage and transmission (Chávez-Jacobo *et al.*, 2020). Despite advances in the knowledge and description of the various antibacterial resistance mechanisms, today there are several examples of superbacteria with increasingly complex survival characteristics. One of these resistance mechanisms corresponds to the production of extended spectrum beta-lactamases (Morejón, 2013). This enzymes have been described from long ago, initially for coding genes of proteins againts penicillins, however in a short time new enzymes were appearing and their effects were observed in other families of beta-lactam drugs for example cephalosporins. The extended-spectrum beta lactamases are produced by Gram positive and negative bacteria highlighting found in the genera *Streptococcus* sp., *Staphylococcus* sp. and in different species of the *Enterobacteriaceae* family. The resistance to extended-spectrum beta lactamases is conferred by intrinsic and acquired pathways. The latter are linked to indiscriminate use of antibiotics, self-medication and other bad practices (Olaitan and Rolain, 2014). Therefore, this work shows the most relevant aspects of the bacterial extended-spectrum beta lactamases and the medical importance.

THE BACTERIAL EXTENDED-SPECTRUM BETA LACTAMASES: There is an alarming increase of antibiotic resistance in bacteria that cause community infections or hospital acquired infections. Many of these multidrug pathogens are of particular interest such as, *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, penicillin-resistant

Streptococcus pneumoniae, vancomycin-resistant *Enterococcus*, and extensively drugs resistant *Mycobacterium tuberculosis* (Alekshun and Levy, 2007; Nagshetty *et al.*, 2021). The extended-spectrum beta lactamases are bacterial enzyme complex that promote resistance to multiple antibiotics, calling them "broad spectrum", unlike "the beta-lactamases" that only confer to bacteria a limited resistance (Biutifasari, 2018; Rawat and Nair, 2010). The breaking of the amide ring of penicillines, cefalosphorines and cephamycins is the main mechanism of action of extendend-spectrum beta lactamases (Pilmis *et al*., 2014). These peculiarities allow bacteria to increase survival against different antimicrobials, representing a therapeutic challenge priority in current health care and for the years to come. The extended-spectrum beta lactamases genes have chromosomal and plasmid location, being this the main mechanism of acquisition of multi-resistence and producing a high mutagenic rate (Päivärinta *et al*., 2020; Vaidya, 2011; Zhou *et al.,* 2021). On the other hand, at present the extended-spectrum beta lactamases can be classified into 4 important groups (A, B, C, D) according to their molecular characteristics such as the arrangement of amino acids. So A, C and D groups are in serine extended-spectrum beta lactamases class. For example, the A and C groups include the TEM (name of the Athenian patient Temoniera), SHV (sulfhydryl variable), CTX-M (cephotaximase) and AmpC (amoxicillin) varieties (Nagshetty *et al*., 2021). The group D include the OXA-type (oxacillinase). It has been established that A, C and D groups are homologous with a common origin. The group B corresponds to metallo extended-spectrum beta-lactamases, which are sensitive to chelating agents such as ethylenediamine tetraacetic acid (EDTA) and they are resistant to clavulanic acid and tazobactam (Hall and Barlow, 2005). Currently, extendend-spectrum beta-lactamases are classified in 16 groups according to the criteria of Bush-Jacoby-Medeiros, which include particular characteristics of each group, the molecular classes and subclasses and the substrate affinity (Bush and Jacoby, 2010). For example: the group 1 includes different lactamase enzymes such as AmpC, P99, ACT (ampC type 3), CYM-2, FOX-1, MIR-1, GC1, CMY-37, which act on cephalosporins and have been found in *Escherichia coli, Enterobacter cloacae, Serratia marcescens, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The group 2 includes different lactamase enzymes such as PC1, TEM-1, TEM-2, SHV-1, TEM-3. SHV-2, CTX-M-15, PER-1, VEB-1, TEM-30, SHV-10, TEM-50, which act on penicillins, cephalosporines, carbenicillins, cloxacicline, carbapenems, and have been found in *Staphylococcus* sp., other Gram-positive cocci, Kluyvera sp., *P. aeruginosa, Klebsiella pneumoniae* and and other bacteria in the family *Enterobacteriaceae* (Bush and Jacoby, 2010).

IMPORTANCE OF EXTENDED-SPECTRUM BETA LACTAMASES FOR HUMAN HEALTH: Bacterial resistance is a global public health problem. Due to the austerity of new and more powerful antibiotic molecules available on the market, the presence of multidrug resistance in bacteria is becoming more and more frequent among the population (Nikaido, 2009). *E. coli* is the microorganism most frequently implicated in nosocomial and community bacteriemia. The extended spectrum beta-lactamases-producing strains of *E. coli* are increasing more and more, having multi-resistant strains that circulate day by day among the population (Kayastha *et al,.* 2020; Sangama and Pereyra, 2018).

Infections with strains of *E. coli* that possess extended spectrum beta-lactamases have undergone important epidemiological changes in recent times (Terlizzi *et al.*, 2017). Thus, infection and colonization by these strains have increased in community patients, especially in health institutions where CTX-M variants predominate compared to other types of extended-spectrum beta-lactamases (Varela *et al.,* 2017). The presence of these enzymes in bacteria associated with nosocomial and community infections has increased the mortality in patients, thus bacteriemia caused by *E. coli* containing extended-spectrum beta-lactamases have complicated seriously when patients receive inadequate treatment (Chang *et al.,* 2020). Therefore, it is important to identify the presence of extended-spectrum beta-lactamases-producing strains in order to provide better treatment to patients as soon as possible. Regarding the measures to control the spread of extended-spectrum beta-lactamases, as an immediate measure, it has been proposed to implement the correct and responsible use of antibiotics (Hall and Barlow, 2005).

Staphylococcus aureus is a Gram-positive bacterium that causes a large number of nosocomial infections associated with surgical and postsurgical complications. It has the ability to cause accumulation of purulent material, which can migrate to neighboring structures and deepen systemically through the circulatory stream, and consequently, can produce systemic infections (Echevarría and Iglesias, 2003). Penicillin initially promised to be an effective treatment against bacterial infections, however in less than twenty years, resistance cases by extended-spectrum beta-lactamases have been reported in *S. aureus* strains (Lyon and Skurray, 1987; Abarca and Herrera, 2001). To counteract the observed resistance to penicillins, methicillins began to be used, however, the case of resistance was presented again, giving rise to a new variety known as MRSA (Methicillin-Resistant *Staphylococcus aureus*), which has increased its incidence and it has been reported as a serious problem in hospitals due the therapeutic ineffectiveness has been extended to cephalosporins and carbapenems (Grema *et al.,* 2015). Methicillin-resistant strains of staphylococci are also resistant to the action of beta-lactams, and resistance to glycopeptides has recently been reported (Castro-Orozco *et al*., 2018; Del Río *et al*., 2016). *S. epidermidis* is also an infectious agent that can cause hospital infections. This bacterium can adhere and colonize surfaces, vascular and parenteral access routes, as well as medical devices (such as surgical implants) causing infectious processes. It is considered less virulent than S. *aureus*, however it has been reported that it has the same resistance profile to antibiotics (Echevarría and Iglesias, 2003). On the other hand, it has been reported that bacteria of the ESKAPE group such as *Acinetobacter baumannii*, are responsible for nosocomial infections, especially in patients with prolonged hospital stays and associated with circulatory conditions (Smiline *et al.*, 2018). This bacterium produces extended-spectrum beta-lactamases of group D as OXA-5 (oxacillinases). Metallo beta-lactamases such as IMD, VIM, SIM, SPM and NDM (resistant to aminoglycosides) have also been found in *A. baumannii*. These extended-spectrum beta-lactamases cannot be inactivated with beta-lactam inhibitors, so these strains of *A. baumannii* have been reported to be resistant to almost all types of antibiotics (Vanegas-Múnera, 2014; Zarabadi-Pour *et al.*, 2021). *E. coli* is another infectious agent that in decades has been related to various infectious processes due to the fact that it presents many pathotypes that adapt to any organ in the host (Miranda-Estrada *et al.*, 2017;

Sarowska *et al.*, 2019). It also causes hospital and community infections and cases of the presence of extended-spectrum beta-lactamases have been reported among these strains, especially in uropathogenic *E. coli* (Salame-Khouri *et al*., 2018).

CONCLUSION

The rapid emergence of resistance to antibiotics (such as extended-spectrum beta-lactamases) among hospital and community pathogens, represents a serious threat to the management of infectious diseases in the world. Therefore, strategies to control and to prevent the development of antibiotic-resistant bacteria require the participation of all, as well as surveillance in hospitals and environmental monitoring as important aspects for a policy to control infectious diseases.

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