COMO DETER A PROPAGAÇÃO DE SUPER BACTERIAS?

HOW TO STOP THE SPREADING OF SUPER BACTERIA?

Mishell Poleth Ortiz Jacome[1], Fernando Alexis Gonzales Zubiate[2]

Resumo: Segundo a Organização Mundial da Saúde (OMS), o número de bactérias resistentes a antibióticos aumentou exponencialmente, causando atualmente cerca de 700.000 mortes a cada ano. O uso exagerado de antibióticos usados no tratamento de infecções humanas e veterinárias contribuiu para o surgimento e disseminação de cepas resistentes a múltiplos fármacos, tornando os antibióticos obsoletos e contribuindo para o prognóstico desfavorável de várias infecções. Atualmente, o problema mais crítico para a saúde pública é o crescente número de bactérias resistentes aos antibióticos beta-lactâmicos, como penicilinas, cefalosporinas, cepamicina e carbapenêmicos, amplamente utilizados em medicina humana e veterinária. De fato, as enterobactérias produtoras de beta-lactamases de espectro estendido (BLEE) foram classificadas como patógenos prioritários pela OMS. Nesta revisão, vamos explicar os mecanismos de resistência antimicrobiana e discutir soluções potenciais para evitar uma maior disseminação.

Palavras-Chave: Resistencia antimicrobiana. Antibióticos. Beta-lactamase. BLEE.

Abstract: *According to the World Health Organization (WHO), the number of antibiotic-resistant bacteria has increased exponentially, currently causing about 700,000 deaths each year. The exaggerated use of antibiotics used in the treatment of human and veterinary infections has contributed to the appearance and spread of multidrug resistant strains, making antibiotics obsolete and contributing to the unfavorable prognosis of several infections. Present day, the most critical problem for public health is the growing number of bacteria resistant to Beta-lactam antibiotics such as penicillins, cephalosporins, cepamycin and carbapenems, widely used in human and veterinary medicine. In fact, enterobacteria producing extended-spectrum Beta-lactamase (ESBL) have been classified as critical priority pathogens by WHO. In this review, we will explain the mechanisms of antimicrobial resistance and discuss potential solutions to prevent further spread.*

Keywords: *Antimicrobial resistance. Antibiotics. Beta-lactamase. ESBL.*

I. INTRODUCTION

Antimicrobial resistance (AMR) is defined as the ability of any microorganism to survive to the effect of antibiotics through distinctive responses, in other words, it is considered as the decrease or lack of sensitivity of a bacterial strain to one or more antibiotics. According to the World Health Organization (WHO) 700000 deaths globally are attributed to AMR only in 2017 and would climb to 10 million deaths in the following 35 years. Indeed AMR is considered one of the top ten threats to global health in 2019.

Increase of antibiotic resistance is mainly caused by misuse and abuse of antibiotics in an inappropriate manner: attributed to self-medication, free access to antibiotics without a prescription, lack of dose compliance, inadequate prescription, prescription and use of antibiotics in agriculture and agriculture that alter the human microbiota. (Rosdahl et al., 2002; Smith et al., 2002; Phillips et al., 2004; Silva-Cevallos et al., 2012). Another factor that contributes to the resistance of bacteria is the constant dumping of antibiotics into the environment through wastewater, especially in places such as sewage treatment plants, wherein a small space, we can find human, animal and environmental bacteria (reviewed in Alós, 2015).

[1]Estudante de School of Biological Sciences and Engineering, Yachay Tech University. e-mail: mishell.ortiz@yachaytech.edu.ec

[2]Doutor em Ciências, Professor e Pesquisador de School of Biological Sciences and Engineering, Yachay Tech University. e-mail: fgonzales@ychaytech.edu.ec

In addition, the food chain can be considered a route of antibiotic resistance transmission between animals and the human population. As part of the evidence, it is that poultry meat or pork meat could be a possible source of quinolone-resistant Escherichia coli in the rural villages of Barcelona (Zaman et al., 2017).

According to ReAct Latin America (Action on Antibiotic Resistance), which aims to monitor antibiotic resistance, in 2008 were registered 8200 cases of multi-drug resistant tuberculosis (MDR-TB) were diagnosed, finding the highest rates in the Dominican Republic (6.6%), Peru (5.3%), Ecuador (4.9%) and Guatemala (3.0%).

ANTIBIOTICS: MODE OF ACTION

Antibiotics are used to fight infections in living beings and inhibit the proliferation and growth of microbes by inhibiting cell wall formation, protein and nucleic acid synthesis (Ali et al., 2018). Antibiotics are considered indispensable in diverse sectors such as health care, agriculture, or production of livestock and poultry. On the one hand, they are utilized in hospitals for transplants of solid organs and from hematopoietic progenitors, survival of premature and immunosuppressed patients, and surgery of prosthetic material and vascular catheters where infections are common (Alós, 2015). On the other hand, antibiotics in livestock are observed as growth stimulants however use of antibiotics to increase the production can be dangerous, a Salmonella multi-drug resistant affected 25 people in Denmark in 1998, it was confirmed that this organism was resistant to seven different antibiotics (Quizhpe et al., 2011).

The era of antibiotics began as an optimistic belief, where drugs would play an important role in human health and therefore it was believed that it would eliminate communicable diseases. Alexander Fleming was one of the precursors of antibiotics, he discovered Penicillin (Zaman et al., 2017) and warned about bacterial resistance as a phenomenon, also, he pointed out that "There will come a time when penicillin can be bought by anyone in the business. There is a danger that an ignorant man can easily apply an insufficient dose of antibiotic and, by exposing microbes to a non-lethal amount of the drug, makes them resistant" (Quiñones, 2017).

ACQUIRED ANTIMICROBIAL RESISTANCE GENES

How bacteria acquire antibiotic resistance? This event occurs with alterations in the bacterial genetic information, through either mutations in the chromosome or transfer of genetic material from one bacterium to another (horizontal gene transfer). Horizontal gene transfer is the primary mechanism for the spread of antibiotic resistance in bacteria (Koonin et al., 2001). There are three known mechanisms of horizontal gene transfer: conjugation, transduction, and transformation (Southwick, 2008). Bacterial conjugation is the transfer of a genetic material between bacterial cells by direct cell-to-cell contact or by a bridge-like connection between two cells (Holmes and Jobling, 1996) and the genetic material to be transferred is a plasmid; a small circular DNA molecule physically separated from chromosomal DNA containing genes. Transduction employs the use of bacteriophage, a type of virus that infects bacteria, as vector to introduce DNA from a bacterium previously infected to new one. Transduction does not require physical contact between the cell donating the DNA and the cell receiving the DNA. Finally, the transformation is the process when donor bacteria release linear segments of chromosomal DNA that can later be absorbed by another recipient bacteria and incorporated into its genome, this process occurs more in species like Streptococcus, Haemophilus y Neisseria (Southwick, 2008).

ß-LACTAMICS AND EXTENDED-SPECTRUM BETA-LACTAMASES (ESBL)

Antimicrobial resistance evolves mostly in Beta-lactam antibiotics, which constitute different classes such as penicillins, cephalosporins, carbapenems, monobactams and beta-lactam inhibitors that are considered as the most commonly used antibiotics in the treatment of bacterial infections and that represent 50% of all medical prescriptions worldwide. It is necessary that beta-lactamase inhibitors will be molecules that have a high affinity towards these enzymes, thus avoiding the inactivation of beta-lactam, the three most important examples in medicine are clavulanic acid, sulbactam and tazobactam (Quiñones, 2017; Ortega, 2017).

Beta-lactam antibiotics mimic the natural substrate D-Ala-D-Ala of PBP enzymes (penicillin-binding proteins), which are responsible for participating in the formation of cell wall peptidoglycan, inducing bacterial autolysis (Worthington and Melander, 2013; Ortega, 2017). This type of antibiotic is constituted by the presence of a beta-lactam ring, which must be attached to other radicals to activate, the grouping of different linear chains together that result in the formation of two rings that give rise to different properties to the compounds (Ortega, 2017).

There are two mechanisms for resistance to Beta-lactam antibiotics: the first consists in the production of Beta-lactamases, mostly used for Gram-negative bacteria, which act in the phase of cell division by breaking the amide bridge of the beta-lactam ring. The immediate consequence of Beta-lactam ring degradation is the unsuccessful bind of the antibiotic to PBPs. The second mechanism is altered PBP production with a lower affinity for most Beta-lactam antibiotics (Worthington and Melander, 2013; Ortega, 2017).

Besides, there are two types of ß-lactam antibiotic structures: serine Beta-lactamases and metallo-Beta-lactamases (MBL). In the first structure there are an extended-spectrum Beta-lactamases (ESBL), and its groups are SHV, TEM and CTX-M, which have been detected in Enterobacteria E.coli and Klebsiella pneumonia, Gram-negative bacilli, which have as a function to hydrolyze and cause resistance or decreased sensitivity to penicillins, oxy-cephalosporins and monobactams, but not to cephamycins, or carbapenems (Worthington and Melander, 2013; Quiñones, 2017). These enterobacteria are related to urinary infections and according to INEC (National Institute of Statistics and Census) urinary tract infections, are the most common infections in patients and affects 150 million people per year, Ecuador is in the eighth position of causes of mortality and morbidity. As additional information, INSPI (National Institute for Public Health Research) has been reported in 2015 that E. coli strains showed an incidence of resistance to cefotaxime (CTX) and a ceftazidime (CAZ) greater than 28% and in K pneumoniae greater than 60% for the same antibiotics (Ortega, 2017).

Detection and control of ESBL: According to the recommendations of the National Institute of Health and Pan American Health Organization, the detection of ESBL regarding pathogens isolated in urine is carried out by means of disk diffusion tests (Kirby Bauer antibiograms (KB)) on Muller-Hinton agar. This detection consists in the correlation of the diameter of inhibition presented with the sensitivity of the microorganism to a certain antibiotic, in addition the molecular detection of ESBL is by PCR and Whole Genome Sequencing (Ortega, 2017).

VACCINES AS A SOLUTION

The technology of vaccines can prevent the infections caused by AMR pathogens because decrease the use of antibiotics by reducing the symptoms, also, the use of vaccines prevents the proliferation of bacteria. There are important vaccines that combat AMR pathogens like Streptococcus pneumonia, Haemophilus influenza, Mycobacterium tuberculosis, Salmonella typhi, P. aeruginosa, S. aureus, pathogenic Escherichia coli, and Clostridium difficile (Baker et al., 2018). Many examples employ innovative vaccine technologies like reverse vaccinology, novel adjuvants, and rationally designed bacterial outer membrane vesicles (OMV). The reverse technology consists of the sequence the genome of pathogens allowed the setup of computer and experimental screening programs to discover genome-encoded antigens. The vaccine adjuvants, where the first adjuvant was aluminum, but with the progress of scientists develop more effective vaccine adjuvants that improve the speed, potency and persistence of immune response such as adjuvant AS01, recently licensed for a vaccine against malaria and a novel herpes zoster vaccine. Finally, the rationally designed OMV consist of membrane vesicles that have natural content of bacterial surface-exposed proteins in the correct conformation. Therefore have the potential to be more protective when used as vaccine components, one good result of this type of vaccine was in New Zealand, where the use of this vaccine based on OMV has been administered to effectively prevent Meningococcus B infections during an outbreak (Baker et al., 2018).

II. CONCLUSIONS

Currently, the most critical problem for public health is the growing number of bacteria resistant to Beta-lactam antibiotics such as penicillins, cephalosporins, cephamycins and carbapenems, widely used in human and veterinary medicine. In fact, enterobacteria producing extended spectrum Beta-lactamases (ESBL) have been classified as pathogens of critical priority by WHO.

As part of the solution to control antimicrobial resistance, there is the use of alternative therapies for the treatment of infectious diseases, which include strategies such as virulence, biological therapies (use of monoclonal antibodies, insulin, erythropoietin, etc.) and vaccines (vaccines against MRSA, MDR M. tuberculosis). The use of medicinal plants that have disease-promoting properties could also be considered (Aslam et al., 2018).

According to WHO, there are some strategies to prevent antimicrobial resistance in education, hospitals, livestock animal. In education is important educate to patients and community about the use of antimicrobials through educative programs ,teach about simple measures to reduce the transmission of infection in the house (washing the hands), communicate about the searching of information of attention in hospitals, educate to all groups of people that prescribe antimicrobials on disease prevention. In hospitals, the strategies are the antimicrobial use monitoring, including quantity and modality of use, ensure the performance and quality assurance of diagnostic tests, microbiological determination and sensitivity of bacterial pathogens and timely report on the results, formulate and periodically update guidelines for antimicrobial treatment. In livestock, make mandatory the prescription of all antimicrobials that are used in the fight against animal diseases destined for human consumption, create national surveillance systems for the administration of antimicrobials to animals intended for human consumption, carry out resistance monitoring to detect new health problems and take corrective measures to protect human health (Quizhpe et al., 2011).

Finally, we need to implement strategies that promote appropriate use of antibiotics in microbial infections in order to preserve the efficacy of these vital drugs and avoid the rise of bacteria with new resistances.

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