Antibiotic consumption in Portugal - An overview

Consumo de antibióticos em Portugal – Uma visão

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ABSTRACT
Infections caused by opportunistic bacteria resistant to multiple antibiotics continue to be a major challenge in the hospital environment. Growing bacterial resistance results in compromising the success of immunosuppressive therapies and surgical interventions (transplantation), which associated with a high risk of bacterial infections during the procedure and post-operatively often culminate in the death of the patient.

Keywords: Antibiotic, Bacterial, Hospital.

RESUMO
As infecções provocadas por bactérias oportunistas resistentes a múltiplos antibióticos continuam a ser um grande desafio em ambiente hospitalar. A crescente resistência bacteriana resulta no comprometimento do sucesso de terapias imunossupressoras e intervenções cirúrgicas (transplantação), que associadas a um alto risco de infeções bacterianas durante o procedimento e o pós-operatório culminam muitas vezes na morte do paciente.

Palavras-chave: Antibióticos, Bactéria, Hospital.

1 INTRODUCTION

Infections caused by opportunistic bacteria resistant to multiple antibiotics continue to be a major challenge in the hospital environment[1] .

Growing bacterial resistance results in compromising the success of immunosuppressive therapies and surgical interventions (transplantation), which associated with a high risk of bacterial infections during the procedure and post-operatively often culminate in the death of the patient[2] .

Infections caused by resistant bacteria lead to increased mortality, prolonged hospitalizations and higher hospital costs[3] . Knowledge of the country's behavior in relation to antibiotic consumption and the growing development of resistance will allow us to predict its spread, making it possible to implement preventive measures in good time that will reduce hospital-acquired infections and mortality associated with infections caused by multi-resistant bacteria, as well as defining the course of community-acquired infections[4] .

2 OBJECTIVE

To analyze the evolution of antibiotic consumption in Portugal over a defined period.

3 METHODOLOGY

This is a literature review using articles published between 2010 and 2012 in the following electronic databases: Portal Capes, *Scientific Electronic Library Online* - Scielo, PubMed and Google Scholar, using the descriptors: antibiotics, consumption, Portugal, resistance and their respective synonyms, in Portuguese and English. Only published articles dealing with the topic and available online were included. Articles outside the proposed period, which did not deal with the topic, not available online and repeated articles found in different databases were excluded.

4 DEVELOPMENT

Healthcare-associated infections (HAIs) are defined as infections that are acquired during hospitalization and are identified at least 48 to 72 hours after the patient's admission to healthcare institutions[5] .

Among the most frequent types of hospital infections in hospitalized patients are urinary tract infections, surgical infections, meningitis, pneumonia and bacteremia. The most frequently isolated bacteria in hospitalized patients, depending on the type of procedure the patient has undergone, are *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Acinetobacter spp. and also Staphylococcus aureus, coagulase-negative Staphylococcus and Enterococcus spp*[5]

Multidrug-resistant organisms, including *Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus* (MRSA), and other extended-spectrum gram-negative bacteria producing beta-lactamases, even though they are considered commensal flora in asymptomatic carriers (as is the case with MRSA), are often implicated in chronic and acute infections that contribute significantly to the mortality and morbidity of patients[6] .

Bacterial urinary tract infections are among the most common community-acquired infections in humans. More than 80% of urinary tract infections are caused by *Escherichia coli* and other Gram-negative bacteria, including *Pseudomonas spp., Klebsiella spp., Acinetobacter spp.* many of these bacteria have been increasingly associated with antibiotic resistance[7] .

Carbapenem-resistant Enterobacteriaceae (CRE) currently represent a major challenge, as they cause numerous diseases that are very difficult to treat, and have the potential to spread within health services[8] .

The emergence of new Multiple Antibiotic Resistant Organisms, the increase in cases of community-acquired infections and the spread of these in clinical settings have highlighted the need to monitor these organisms[9] .

4.1 ESCHERICHIA COLI

E. coli is among the most prevalent causes of hospital-acquired and community-acquired infections[9] . It is a Gram-negative bacterium and is part of the commensal bacterial flora of the human intestine and has been identified as a predominant reservoir of antibiotic-resistant genes .[10, 11]

The production of ß-lactamases is the main mechanism of antibiotic resistance. Antibiotic combinations of ß-lactams and ß-lactamase inhibitors have been used, as well as extended-spectrum antibiotics (2nd and 3rd generation cephalosporins), but resistance to these antibiotics has been emerging, one of the reasons being the production of extended-spectrum ß-lactamases (ESBL). The problem is that these ESBL-producing organisms have acquired resistance to another important group of antibiotics, such as aminoglycosides and fluoroquinolones, greatly limiting the effectiveness of antibiotic therapy[10, 11, 12] .

According to data published in the *European Antibiotic Resistance Surveillance* (EARS-2012), in 2011 the percentage of resistant *E. coli* continued to rise throughout Europe. This bacterium has shown an extremely high rate of resistance to 3rd generation cephalosporins and fluoroquinolones. The fact that it also shows a significant increase in ESBL propagation and an increase in combined resistance could lead to an increase in the use of carbapenems and consequently to the development of carbapenemase-producing Enterobacteriaceae[13] . In Portugal, from 2008 to 2011, this bacterium has shown a considerable increase in combined resistance to fluoroquinolones, and in relation to cephalosporins in 2011 there was an increase of more than 15%. Portugal is the 6th country with the highest rate of resistance to aminoglycosides[13, 14] .

4.2 PSEUDOMONAS AERUGINOSA

P. aeruginosa has been globally considered the most challenging agent due to its high rate of resistance to antimicrobials[15] .

IMP-type enzymes were the first acquired Metho β-Lactamases (MBL) to be detected in Gram-negative bacteria and remain among the most prevalent MBLs. In addition to resistance to beta-lactams, high rates of resistance have been observed against carbapenems, quinolones and 3rd generation cephalosporins[16] .

It also has a large arsenal of virulence-related factors, such as secretion systems for effector proteins (type II, III and VI), such as proteases and extracellular phospholipases. It also carries flagella and pili (type IV), which are involved in mobility and adhesion to host cells. It also regulates the genetic expression of virulence factors, including most of the genes involved in the acquisition of iron (pyoverdin), the production of toxins (hydrocyanic acid), the biosynthesis of exopolysaccharides and the formation of biofilms[15] .

As an opportunistic bacterium, it causes infections such as pneumonia, septicaemia, urinary tract infection, endocarditis, skin, ear and eye infections and appears as one of the main causes of morbidity and

mortality among hospitalized burn patients[17] . In addition, it is the most prevalent agent in patients with cystic fibrosis, as it causes potentially fatal lung diseases[15] .

P. aeruginosa carries intrinsic resistance to a large number of antibiotic classes and additional acquired resistance severely limits the treatment of infections caused by this bacterium. In Portugal, resistance to fluoroquinolones stood out in 2011, with a resistance rate to this class of drugs of over 25%. Combined resistance was common throughout the European Union, with 15.3% showing resistance to at least three classes of antibiotics and 4.6% showing resistance to all five classes of antimicrobials that are currently under surveillance[13] .

Despite the data provided by the ESAC showing little variation in the evolution of resistance to this bacterium, it is important to keep it under control in health services due to its ubiquitous nature and its great potential for virulence[13] .

4.3 KLEBSIELLA PNEUMONIAE

K. pneumoniae is one of the most commonly isolated agents in hospital infections, associated with pneumonia, meningitis and exhibiting multidrug resistance (MDR)[18] .

In 2003, the National Hospital Infections Surveillance System reported a 47% increase in resistance of *K. pneumoniae to* 3rd generation cephalosporins isolated from patients in Intensive Care Units (ICUs)[19] .

The production of carbapenemases (KPC enzymes) is the most important resistance mechanism of *K. pneumoniae*[19] . Resistance to carbapenems can involve several combined mechanisms, such as hyperproduction of AmpC β-lactamases (cephalosporinases) and/or production of ESBLs and/or carbapenem-specific hydrolytic enzymes (carbapenemases), as well as alterations in bacterial outer membrane proteins and hyper-expression of efflux systems[19] .

There is currently a worldwide spread of ESBL isolates in hospitals. In response to this, the use of carbapenems has increased, resulting in an increase in bacterial resistance to them[18, 19] .

Carbapenemase-producing microorganisms confer resistance to multiple and different antimicrobial classes, including all β-lactams, fluoroquinolones and aminoglycosides. As such, infections caused by *K. pneumoniae* are associated with a high rate of therapeutic failure and mortality, with representative rates of over 50%[20] .

Like *E. coli*, the situation in Portugal is quite alarming, with more than 25% resistance to 3rd generation cephalosporins, fluoroquinolones and aminoglycosides. In 2011, the percentage of resistance increased considerably to 3rd generation cephalosporins. Fluoroquinolones reached a rate of approximately 40% in 2011. It should be noted that this bacterium exceeded 20% combined resistance in 2011. There are currently few drugs that are effective in treating infections caused by this microorganism[13] .

5 FINAL CONSIDERATIONS

In general, there has been a widespread increase in the ability of bacteria to resist antibiotics, and effective control measures are needed so that public health is not jeopardized by the rise of increasingly resistant strains.

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