Research, Society and Development, v. 12, n. 6, e7712642037, 2023
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v12i6.42037

The action of the pharmacist in front of bacterial resistance and rational use of antimicrobials in the hospital environment

A atuação do farmacêutico frente à resistência bacteriana e uso racional de antimicrobianos no ambiente hospitalar

La acción del farmacéutico ante la resistencia bacteriana y el uso racional de antimicrobianos en el entorno hospitalario

Received: 05/24/2023 | Revised: 06/02/2023 | Accepted: 06/04/2023 | Published: 06/09/2023

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Abstract
Antimicrobials are one of the best discoveries of the 20th century, which concomitant with their use came one of the biggest current problems in the world, bacterial resistance. Within this context, the present study aims to highlight the role of the pharmacist in the face of bacterial resistance and rational use of antimicrobials in the hospital environment. For the development of the study, a literature review was carried out for a reflective analysis based on studies published from 2010 to 2022 in the main databases found in Portuguese, English and Spanish. We selected 20 articles out of 6,650 found before applying the inclusion and exclusion criteria and performing the analysis. The clinical pharmacist plays a key role in combating bacterial resistance. In addition, the hospital environment is a place where there are more people in the same environment administering various antibiotics and different spectrums. The pharmaceutical professional has a direct and indirect impact on patients and medicines, being responsible for promoting the rational use of antibiotics, with standardization of medicines and possible interventions in the treatment, providing care, insurance, and health to the patient. Therefore, it is an important key in combating bacterial resistance, which is a public health issue, in addition to the possibility of promoting research and innovation in the field of microbiology and antimicrobial therapy.
Keywords: Antimicrobials; Bacterial resistance to antibiotics; Hospital assistance; Pharmaceutical.

Resumo

Os antimicrobianos são uma das melhores descobertas do século XX, que concomitante ao seu uso veio um dos maiores problemas atuais no mundo, a resistência bacteriana. Dentro deste contexto, o presente estudo tem como objetivo evidenciar o papel do farmacêutico frente à resistência bacteriana e uso racional de antimicrobianos no ambiente hospitalar. Para o desenvolvimento do estudo foi realizada uma revisão de literatura para uma análise reflexiva baseada em estudos publicados nos anos de 2010 a 2022 nas principais bases de dados encontrados em português, inglês e espanhol. Foram selecionados 20 artigos de 6.650 encontrados antes da aplicação dos critérios de inclusão e exclusão e realizada a análise. O farmacêutico clínico tem o papel fundamental no combate a resistência bacteriana. Além disso, o âmbito hospitalar é um local onde há maior número de pessoas em um mesmo ambiente realizando administração de vários antibióticos e diversos espectros. O profissional farmacêutico possui impacto direto e indireto aos pacientes e aos medicamentos, sendo responsável pela promoção do uso racional de antibióticos, com padronização de medicamentos e possíveis intervenções no tratamento, proporcionando cuidado, segurando e saúde ao paciente. Sendo assim, é uma chave importante no combate à resistência bacteriana que é uma questão de saúde pública além da possibilidade de promover pesquisa e inovação no campo da microbiologia e terapêutica antimicrobiana.

Palavras-chave: Antimicrobianos; Resistência bacteriana a antibióticos; Assistência hospitalar; Farmacêutico.

Resumen

Los antimicrobianos son uno de los mejores descubrimientos del siglo XX, que concomitantemente con su uso surgió uno de los mayores problemas actuales en el mundo, la resistencia bacteriana. En ese contexto, el presente estudio tiene como objetivo resaltar el papel del farmacéutico frente a la resistencia bacteriana y el uso racional de los antimicrobianos en el ámbito hospitalario. Para el desarrollo del estudio, se realizó una revisión bibliográfica para un análisis reflexivo a partir de estudios publicados entre 2010 y 2022 en las principales bases de datos encontradas en portugués, inglés y español. Seleccionamos 20 artículos de 6.650 encontrados antes de aplicar los criterios de inclusión y exclusión y realizar el análisis. El farmacéutico clínico juega un papel clave en la lucha contra la resistencia bacteriana. Además, el entorno hospitalario es un lugar donde hay más personas en un mismo entorno administrándose diversos antibióticos y de diferentes espectros. El profesional farmacéutico tiene un impacto directo e indirecto sobre los pacientes y los medicamentos, siendo el responsable de promover el uso racional de los antibióticos, con la estandarización de los medicamentos y las posibles intervenciones en el tratamiento, brindando atención, aseguramiento y salud al paciente. Por tanto, es una clave importante en la lucha contra la resistencia bacteriana, que es un problema de salud pública, además de la posibilidad de promover la investigación y la innovación en el campo de la microbiología y la terapia antimicrobiana.

Palabras clave: Antimicrobianos; Resistencia bacteriana a los antibióticos; Asistencia hospitalaria; Farmacéutico.

1. Introduction

The accidental discovery of the antibiotic through penicillin by the Scottish physician and bacteriologist Alexander Fleming is a milestone in the history of medicine and science in general. He realized that a culture of Staphylococcus aureus that he had left on his laboratory bench had been contaminated with a type of fungus, which ended up killing the surrounding bacteria (Fleming, 1929). During the First World War, the infection was one of the main causes of death in wounds of soldiers, already in the Second World War, after the discovery, the penicillin was used in great scale to treat wounds of soldiers and, since then, it has been a of the most used antibiotics in the world (Fleming, 1945).

Antimicrobials act by inhibiting the synthesis of cell wall, cytoplasmic membrane, nucleic acids, or bacterial proteins, leading to death or inhibition of bacterial growth (Abbas et al., 2023). In fact, antibiotic therapy is considered one of the best discoveries in health, as it provides control of several diseases and enables the reduction of morbidity and mortality that affect all of humanity in a ferocious way. However, parallel to the advancement of new drug discoveries, the indiscriminate use of antibiotics has also increased, which are inconsequentially prescribed or not by health professionals and because of this, bacterial resistance in the environment occurs, which is often part of the hospital environment (Miranda et al., 2022).

Bacterial resistance is a growing concern in global public health due to inappropriate use of antibiotics, 50% of antimicrobial prescriptions are incorrect, being the most prescribed drug in hospitals today (WHO, 2015). Studies indicate that bacterial resistance has caused major impacts, especially in the hospital environment, affecting hospitalized patients. To reduce some adverse effects, the dose of antibiotics must be adequate to inhibit the proliferation of microorganisms, acting in the host

organism in a selective way and with low toxicity (Mitrel et al., 2017). In addition, inappropriate use of antibiotics allows bacteria to develop resistance, making them able to survive lower doses of the drug that would previously be lethal (Brasil, 2018).

According to Santos et al. (2017), it is up to the pharmacist to guide the population on the implications of the inappropriate use of antibiotics, to promote the rational use of these drugs, in addition to correctly dispensing them. With that in mind, aiming to address the problem of the indiscriminate use of antibiotics in the hospital environment, this work is justified by taking into account the current scenario on the role of the pharmacist in the face of the rational use of these drugs in hospitals, with the interest in this research having arisen through an internship carried out in the hospital, mainly because it deals with how lives can be saved and improved through the pharmacist's performance.

Therefore, the implementation of antibiotic administration management led by clinical pharmacists enables beneficial impacts on the control of antimicrobial-resistant pathogens, resulting in the reduction of their consumption (Kannebley Júnior et al., 2020). Therefore, it is possible to note that the role of the pharmacist can directly or indirectly impact patients, the hospital institution and public health policies, bringing greater safety and efficiency in patient treatment, correct guidance, optimization of treatments, making possible interventions in the treatment, reducing hospitalizations that imply a reduction in hospital costs, and reducing possible adverse reactions to the antimicrobial (Donizete et al, 2020).

In this context, the objective of this study was to carry out a qualitative and exploratory approach, based on a bibliographical review, presenting an overview of the role of the pharmacist in the face of bacterial resistance due to the irrational use of antimicrobials in the hospital environment and its consequences for the population. More specifically, we sought to describe the importance of the pharmacist in the hospital environment and proposals for action in the inappropriate use of antimicrobials, analyzing the adverse effects caused by antibiotic therapy in an irrational way.

2. Methodology

For the development of the study, a literature review was carried out for a reflective analysis based on the systematic search of studies published in the years 2010 to 2023. Data were collected through a survey of the bibliography published in the main PUBMED databases; the Virtual Health Library (VHL); SCIELO (Online Scientific Electronic Library); Academic Google; from MEDLINE and LILACS (Latin American and Caribbean Health Sciences Literature). The following descriptors used in the search: antimicrobials; bacterial resistance to antibiotics; hospital care; pharmaceutical.

For the selection of studies, articles available online for free in full were adopted as inclusion criteria, which answered the guiding question, published in Portuguese, English and Spanish with at least one of the antimicrobial descriptors and bacterial resistance to antibiotics associated with hospital care and pharmacist in the title, and in the proposed time frame. Exclusion criteria: editorials, works that did not answer the question, published after the described interval, with less than two descriptors in the title, and the repeated ones, keeping only one. For the analysis of the articles that would remain in the study, the titles were initially read and, if there were inclusion criteria, the abstracts were read. If there was disagreement between the authors regarding the inclusion and exclusion criteria, a specific discussion about the work in question was held until a final consensus was reached. The articles that best met the scope of the work were selected and, after this selection, the selected articles were read in full.

3. Results and Discussion

According to the research, 6,650 old ones that contained at least one of the descriptors were obtained. Considering the inclusion and exclusion criteria to compose the results, 20 articles were selected between the years 2010 and 2022, using

inclusion and exclusion criteria. All abstracts described were read and selected because they met the objective of the study, the role of the pharmacist in the face of bacterial resistance and rational use of antimicrobials in the hospital environment (Table 1).

Table 1 - Selected articles that achieved the objective of the study on the role of the pharmacist in the face of bacterial resistance and rational use of antimicrobials in the hospital environment.

Author (Year)	***Aim***	***Main findings***
Davies, J; Davies, D (2010)	Report the origin and evolution of antibiotics.	The origin and evolution of bacterial resistance, as well as the creation of the term "antibiotic".
Mota L, M et al. (2010)	Introduce the second class of antibiotics and their risk.	The main drugs of the second class of antibiotics and below can cause harm.
Bush & Bradford (2011)	Highlight how beta-lactamase enzymes act negatively on beta-lactams.	Show how bacteria resist beta-lactam antibiotics.
Spellberg B., et al. (2011)	Report the importance of antibiotics for medicine.	How Antibiotics Brought a Breakthrough to Modern Medicine.
Hooper D.C. (2000)	Highlight how bacteria survive antibiotics.	Fluoroquinolone is an antibiotic capable of increasing bacterial resistance.
Li X.Z., et al. (2015)	Explain about the mechanism of action of the bacteria known as the efflux pump.	Functioning of bacterial resistance by means of an efflux pump.
Munita & Arias (2016)	Describe the mechanisms that bacteria create to resist, as well as their interaction with the environment.	Ways for the bacteria to resist the effect of the antibiotic.
Santos, F, L, S; *et al.* (2017)	Present the important aspects of the pharmacist as a health promoter.	The importance of the pharmacist in front of a better pharmacotherapy of the patient.
Mitrel, et al. (2017)	Describe how the action of antimicrobials occurs in the human body and where it is more conducive to develop bacterial resistance.	The most conducive place to acquire bacterial resistance.
Iverse, et al. (2018)	Investigate progressive resistance training.	Observation of antibiotic therapy risks in hospital patients.
Teixeira; Figueiredo & França (2019)	Describe the irrational use of antibiotics with bacterial resistance.	Factors that cause antibiotic resistance through their use.
Vega & Bravo (2020)	Evaluate the Rational Use of Antibiotics Program.	Way to reduce the indiscriminate use of antimicrobials in hospitals.
Sosa-Hernández, et al. (2020)	Describe the results of the rational use of antimicrobials program.	The evolution of the rational use of antibiotics program and the monitoring of therapy, with the aim of reducing costs.
Kannebley Júnior, et al. (2020)	Show how the pharmacist is important in the control of antibacterials.	The clinical pharmacist and his importance for the control of bacterial resistance.
Donizete, et al. (2020)	Report the significance of the pharmacist in relation to the safety and efficacy of the drugs indicated for the treatment carried out by patients.	Correct guidance, intervention in incorrect treatments can reduce morbidity and mortality risks.
Mello & Oliveira (2021)	Evaluate actions to combat bacterial resistance in hospitals.	Way to combat and prevent bacterial resistance to antibiotics in large hospitals.
Souza, Dias & Alvin (2022)	Report the main part of antimicrobial molecules and how bacteria resist classes.	Development of resistance in bacteria.
Miranda, et al. (2022)	Evaluate the importance of the antibiotic and the damage it can cause to the individual's life.	How antibiotics developed bacterial resistance.
Pereira, et al. (2022)	To describe the role of the pharmacist within hospitals and to form a way to reduce hospital infections.	The pharmacist's proposals for action in the hospital environment.
Larsson & Flach (2022)	Examine the factors that lead to antibiotic resistance.	Bacterial resistance and antibiotic exposure in the environment.

Source: Own authorship.

Antibiotics

The era of antimicrobials began when there was the hypothetical discovery of penicillin by Alexandre Fleming in 1928, based on a culture filtrate technique of a fungus known as *Penicillium nonatum* (Fleming, 1929). So, from that moment on, antibiotics played a key role in transforming modern medicine and saving many lives from serious infections (Spellberg et al, 2011). The definition of the generic term "antibiotic" was proposed by Selman Waksman, the discoverer of streptomycin, to denote the class of organic molecules that kill or inhibit microorganisms that interact with bacterial targets. Thus, antibiotics are considered one of the best discoveries of modern times, not only for their activity in the treatment of infectious pathologies, but because of a variety of other biological activities, surpassing the importance of antibiotic activity, such as antiviral, antitumor or anticancer (Davies & Davies, 2010).

Studies indicate that there are other important concepts that should be carefully evaluated for the selection of antimicrobials for the treatment of bacterial infections. In the selection of antibiotics, they can be classified according to some criteria, firstly as antibiotics of synthetic or semi-synthetic origin and secondly based on their mechanism of action which is classified into two bacteriostatic groups that kill at low rates but do not allow them to reproduce, and bactericides that kill at higher rates (Hasan et al., 2021).

Antibiotics of semi-synthetic origin include antibiotics classified as B-lactams, which have a broad class of antibiotics, with a molecular structure of a beta-lactam ring that irreversibly inhibits the transpeptidase enzyme, between the peptidoglycan layers of the bacterial cell wall, among which we can mention cephalosporins, penicillins, carbapenems and monobactams (Teixeira et al., 2020). Antibiotics of synthetic origin are sulfonamides, fluoquinolones and oxazolidinones. They are second-class antibiotics and are mostly used in outpatient clinics on long scales, however these second-class drugs do not only affect microorganisms, but also the patient's microbiota, which may allow the appearance of even greater adverse effects (Mota et al., 2010).

Bacterial resistance

According to the World Health Organization (WHO), antibiotic resistance is one of the three most relevant public health threats of the 21st century. Resistance to antimicrobials is ancient, resulting from the interaction of organisms with their environment. In this sense, most antimicrobials are naturally created molecules, so bacteria develop their own mechanisms to resist their actions, creating resistance to one or more classes of antimicrobial, usually achieved by several biochemical pathways. (Souza et al., 2022).

Some bacteria can survive the effect of the antibiotic, such as fluoroquinolones, which can coexist with a bacterium increasing its level of resistance, through different biochemical pathways (Hoper et al., 2013). Among them, one of the ways bacteria deals with the presence of the antibiotic is through enzymatic production that inactivates the drug, producing specific chemical substances capable of modifying its receptors, making the antibiotic unable to act on its target (Munita & Arias, 2016).

Another mechanism of resistance is through the efflux pump, since some bacteria have active transport systems that pump antibiotics out of the cell, reducing their intracellular concentration and preventing them from exerting their bactericidal effect (Li et al., 2015). Some bacteria produce enzymes, such as beta-lactamases, which destroy or inactivate the chemical structure of beta-lactam antibiotics, rendering them ineffective (Bush & Bradford, 2016). In addition, it can happen through changes in permeability, which happens by reducing the penetration of the drug into the bacteria, due to the modification of the liposaccharide content of the membrane surface, lowering the level of antibiotic inside the bacterial cell, causing resistance to the antimicrobial (Teixeira et al., 2020).

Antimicrobial resistance can occur through absorption of foreign DNA or by mutations in the pre-existing genome in a bacterium. In addition, all classes of antibiotics, when classified as natural, already show resistance in some pathogens to which they are targeted, due to the external environments to which they are exposed. On the other hand, antibiotics can also appear in the environment through the excretion of urine and feces of humans or domestic animals, also through the disposal and inappropriate use of medicines, contamination in aquaculture, plant production and the flow paths in the production of antibiotics. Just as the environment is a problem for the evolution of antibiotic resistance and transmission routes, it can provide ways to manage them, as environmental microorganisms have served to create antibiotic-requesting molecules, in increasing the drug development (Larsson & Flach, 2021).

Pharmacist's role in the hospital environment and its relationship with the rational use of antibiotics

In the Resolution No. 585 of 2013 (Brasil, 2013), in the clinical attributions of the pharmacist, the professional must aim to promote the rational use of medicines, contributing to the protection and care of the patient, family and community, achieving improvements in quality of the patient. Therefore, a set of actions is necessary to be carried out so that there is intervention in the indiscriminate use of medicines, with this, we see that the pharmacist is more than essential in the health team, his skills promote better results in the pharmacotherapy of individuals (Santos et al., 2020).

Vega and Bravo (2020), in a study for the rational use of antibiotics, reports the need to identify bacterial microorganisms in patients, to withdraw empirical treatments and initiate antibiotic therapies, reducing inadequate exposure to antimicrobials and increasing resistance bacteria, as well as its adverse effects. In addition, it is necessary to withdraw from the list of treatment drugs or suspend antibiotics in some cases, with important analyzes of the risk factors of patients who may have some type of resistance to antimicrobial treatment.

The implementation of programs for the rational use of antibiotics in the hospital environment has shown clear economic benefits worldwide. Therefore, in order to better strengthen this program of rational use of antimicrobials, it is necessary to integrate pharmacists into the institutions, as they have a direct impact on this type of medication, performing treatment optimization resources through improvements in prescription, control infections, health education and monitoring of antibiotic use (Sosa-Hernández, et al, 2020).

The clinical pharmacist in the hospital environment is a key element in the multidisciplinary team, since he has a fundamental role in the control of bacterial resistance, through treatment interventions, standardization of antibiotics and assessments of prescriptions, with the ability to interact with the patient making decisions. Therefore, it combats the reality caused by the irrational use of these drugs, through pharmaceutical plans that indicate the medical evaluation, as well as the sensitivity to antimicrobials, their dosage, dilution and possible interactions (Pereira et al., 2020).

The World Health Organization (2019) considered the impact of bacterial resistance on public health to be of great global precedence, considering five actions to control this problem. In the first, it established clear protocols and guidelines for the prescription of antibiotics, considering bacterial resistance patterns, the patient's profile and updated therapeutic recommendations. In the second, it considered education and awareness through capacity building and training of health professionals on the appropriate use of antibiotics, including information on bacterial resistance, and the importance of adherence to guidelines and good prescribing practices.

In the third, the implementation of epidemiological monitoring and surveillance systems to monitor antibiotic consumption, bacterial resistance, and clinical results, allowing the identification of problems and the adoption of corrective measures. In the fourth, limiting the use of certain antibiotics considered to be of high importance or associated with a greater risk of resistance, as well as selective restriction of specific antibiotics based on local needs and characteristics. And finally,

the establishment of antibiotic programs, in which a multidisciplinary team, including physicians, pharmacists and other health professionals, can act in monitoring and optimizing the use of antibiotics, through regular reviews of prescriptions, education and feedback to prescribers (WHO, 2019).

Some hospital institutions report the existence of guidance protocols in carrying out medical prescriptions for antibiotics through audits, as these antimicrobial standardizations are related to policies that promote the rational use of these drugs, highlighting the extreme importance in reducing bacterial resistance and optimization of antimicrobial treatment (Mello & Oliveira, 2021). The policy of rational use of antibiotics, promoted in the hospital environment, reduces the risks of bacterial resistance. The presence of the pharmacist in the hospital pharmacy or in the clinic strengthens the program of rational use of antimicrobials, helping to control infections, ensuring the health and well-being of the patient, correct dispensing, selection, storage, distribution, and good management with a focus on in the reduction of costs and permanent hospitalizations in the hospital environment.

Therapeutic risks of antibiotics in hospitalized patients need to be based on observational studies. Therefore, long patient stays can lead to physical and psychological problems, whereas shorter stays demonstrate better disease outcomes and cost reduction (Iversen et al., 2018). Therefore, it is of great importance that hospital institutions invest in the implementation of processes and policies that promote improvements in adherence to good practices, aiming at the quality and safety of patients and their health professionals.

4. Conclusion

Bacterial resistance is one of the greatest concerns in public health, according to the WHO. In turn, all classes of antimicrobials already have some type of resistance, even those that are yet to be developed, due to their exposure to microorganisms in the environment. In this sense, the pharmacist has an important role in combating and preventing antibiotic resistance, being the professional who directly impacts drugs.

The pharmacist is the key element in the hospital environment and in the multidisciplinary team, which through pharmaceutical care contributes to patient safety, in the evaluation of prescriptions, optimization of treatment, pharmaceutical interventions, possible interactions with the medication, and rational use of the medication. Furthermore, combating bacterial resistance is a public health issue and requires a multifaceted approach. This includes the prudent use of antibiotics, the development of new antibiotics, the implementation of infection prevention and control measures, the education of health professionals and the general public on the appropriate use of antibiotics, and the promotion of research and innovation in the field of microbiology and antimicrobial therapy.

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