RATIONAL USE OF ANTIMICROBIALS IN THE INTENSIVE CARE UNIT

ABSTRACT

Objective: to identify the main measures adopted for the rational use of antimicrobials in intensive care units. Method: this is a bibliographical study, type integrative review, with a temporal cut from 2012 to 2017, carried out in the Lilacs and Medline databases. The results were grouped according to the title, year of publication, database, authors, periodicals, design and levels of evidence. The results were presented in the form of figures. Results: the sample consisted of 16 articles describing the intensive care unit as the main site of bacterial mutation associated with the indiscriminate use of antimicrobials, prescriptions failures and contamination of the equipment by the health team. Strategies have been proposed to the pharmacist to reduce the number of strains of resistant microorganisms and to preserve the efficacy of the antibiotics available through their rational use. Conclusion: it is considered essential that the health team mobilizes so that the actions of control and prevention of bacterial resistance are effective. The role of the pharmacist acting in the control of bacterial resistances and in the rational use of the drugs in the intensive care unit is highlighted. Descriptors: Microbial Resistance to Medications; Intensive Care unit; Pharmaceutical care; Antimicrobials; Hospital Infection; Rational Use of Medications.

RESUMO

Objetivo: identificar as principais medidas adotadas para o uso racional de antimicrobianos em unidades de terapia intensiva. Método: trata-se de um estudo bibliográfico, tipo revisão integrativa, com um recorte temporal de 2012 a 2017, realizado nas bases de dados Lilacs e MEDLINE. Agruparam-se os resultados de acordo com o título, ano de publicação, base de dados, autores, periódicos, delineamento e níveis de evidência. Apresentaram-se os resultados em forma de figuras. Resultados: constituiu-se a amostra por 16 artigos que descrevem a unidade de terapia intensiva como o principal local de ocorrência da mutação bacteriana associada ao uso indiscriminado de antimicrobianos, às falhas nas prescrições e à contaminação dos equipamentos pelas mãos do equipe de saúde. Propuseram-se, ao farmacêutico, estratégias que reduziam o número de cepas de micro-organismos resistentes e preservavam a eficácia dos antibióticos disponíveis por meio do seu uso racional. Conclusão: considera-se essencial que a equipe de saúde se mobilize para que as ações de controle e prevenção da resistência bacteriana sejam eficazes. Destaca-se o papel do farmacêutico atuando de maneira firme na contenção das resistências bacterianas e no uso racional dos medicamentos na unidade de terapia intensiva. Descriptors: Resistência Microbiana a Medicamentos; Unidade de Terapia Intensiva; Assistência Farmacêutica; Antimicrobianos; Infecção Hospitalar; Uso Racional de Medicamentos.

RESUMEN

Objetivo: identificar las principales medidas adoptadas para el uso racional de antimicrobianos en unidades de terapia intensiva. Método: se trata de un estudio bibliográfico, tipo revisión integrativa, con un recorte temporal de 2012 a 2017, realizado en las bases de datos Lilacs y MEDLINE. Agruparon los resultados de acuerdo con el título, año de publicación, base de datos, autores, periódicos, delineamiento y niveles de evidencia. Se presentaron los resultados en forma de figuras. Resultados: se constituyó la muestra por 16 artículos que describen la unidad de terapia intensiva como el principal lugar de ocurrencia de la mutación bacteriana asociada al uso indiscriminado de antimicrobianos, a las fallas en las prescripciones y a la contaminación de los equipos por las manos del equipo de salud. Se propusieron, al farmacéutico, estrategias que reducían el número de cepas de microorganismos resistentes y preservaban la eficacia de los antibióticos disponibles a través de su uso racional. Conclusión: se considera esencial que el equipo de salud se mueva para que las acciones de control y prevención de la resistencia bacteriana sean efectivas. Se destaca el papel del farmacéutico actuando de manera firme en la contenición de las resistencias bacterianas y en el uso racional de los medicamentos en la unidad de terapia intensiva. Descriptors: Farmacorresistencia Microbiana; Unidades de Cuidados Intensivos; Servicios Farmacéuticos; Antinfecciosos; Infección Hospitalaria; Utilización de Medicamentos.
INTRODUCTION

It is emphasized that, in the hospital environment, especially in the closed health care sectors of high complexity, such as the Intensive Care Units (ICUs), hospitalized patients are affected by serious diseases and are more susceptible to nosocomial infections defined as manifestations occurring due to the submission of patients to a variety of invasive procedures and frequent exposure to microorganisms that cause this type of infection.

It is added that critical patients with these infections receive regular antimicrobial treatment (ATBs) of different classes, mainly in relation to the treatment of sepsis and its complications, in addition to its prophylactic use for the prevention of infections. It is understood that the use of treatment protocols with the use of antibiotics is common and that, in most cases, several of them are associated with the therapy, to increase their survival and to decrease considerably the mortality rates from hospital infections.

According to the National Agency of Sanitary Surveillance (ANVISA), infections in ICUs affect 2% of hospitalized patients, and about 35% to 45% present urinary infection related to the use of a bladder catheter. It was estimated that in the State of São Paulo, the median incidence of ventilator-associated pneumonia (VAP) was 9.87 cases per thousand days of ventilator use in the adult ICU in 2015.

It is known that the use of antimicrobials in an uncontrolled manner contributes to the emergence of infections with strains resistant to antimicrobials used and, in most cases, when exposed to therapy with this class of medications, patients admitted to the ICUs have immunological defenses compromised, which increases the risk of being colonized by more resistant bacteria.

It has been shown that in recent years, the emergence and development of different mechanisms of bacterial resistance in adult ICUs has been occurring, which results in the inefficacy of almost all antibiotics. As a consequence, a greater cost is incurred in inpatient therapeutics and an increase in hospitalization time and mortality.

It should be noted that one of the greatest challenges today is to develop measures to control infections and reduce the spread of resistant pathogens in hospital settings. It can be affirmed that the rational and effective use of ATBs is of paramount importance for the reduction of the rates of hospital infections and the reduction of mechanisms of microbial resistance.

It is noted that, according to Administrative Rule GM/MH 2616 of May 12, 1998, it is mandatory that the pharmacist be a consulting member of the Hospital Infection Control Commission (HICC). The importance of the role of the pharmacist as a member of the HICC is verified in some studies. It is established that, in this team, this professional acts in the selection of medications, in the preparation of therapeutic guides, in the monitoring of adverse drug events, such as adverse reactions, drug interactions, medication errors and therapeutic ineffectiveness, besides ensuring the quality of medicines. It is noted that this professional can still provide a diagnosis of how the drugs should be used, aiming at the rational use and control of infections more effective in health care.

It should be emphasized that the practice of the pharmaceutical professional in hospital settings plays a fundamental role, since it is also incumbent on him to carry out various practical and preventive activities, such as continuing education, the creation of policies for the use of antibiotics, provide alternative treatment options, audit the use of ATBs, research different approaches to minimize and prevent acquired infections in health care, among others.

OBJECTIVE

- To identify the main measures adopted for the rational use of antimicrobials in intensive care units.

METHOD

It is perceived that the Evidence-Based Practice (EBP) is the practice of adopting the best scientific evidence to support decision making. It is understood that the integrative literature review is one of the research methods used in EBP that allow the incorporation of the evidence into clinical practice. This research is a descriptive bibliographical study of the type integrative review of the literature, carried out in six stages: 1st) elaboration of the hypothesis followed by the guiding question; 2nd) establishment of the inclusion and exclusion criteria; 3rd) categorization of studies; 4th) critical analysis of selected studies; 5th) discussion of results and 6th) synthesis of results.

The following guiding question was established for this review: "What are the practices of the pharmacist employed in the..."
use of antimicrobials capable of minimizing bacterial resistance?”. Data was searched between September and December 2017, in the Virtual Health Library (VHL). The research was refined with the following inclusion criteria: primary articles published in the last five years in English, Portuguese or Spanish, describing the main mechanisms of microbial resistance, and the practices used by the pharmacist to minimize these mechanisms. Case reports and opinion articles were excluded. The following descriptors were indexed in the Health Sciences Descriptors (DeCS): “Microbial Resistance to Medications”, “Intensive Care Unit”, “Pharmaceutical Care” and “Antimicrobial Agents”, connected by the AND connector. The steps of the integrative review are briefly described in figure 1.

For the sake of consistency and technical rigor, the review of the articles in the sample was added for the purpose of classifying its scientific evidence. To that end, the classification of scientific evidence that was applied to the drawings of the sample studies.
RESULTS

In figure 2, for a better understanding of the content extracted from the articles, the synthesis of the main information of the studies analyzed from the following variables are presented: title of the article; author(s); data base; periodical and year of publication; goal; type of study, levels of scientific evidence results.

<table>
<thead>
<tr>
<th>Title/Year</th>
<th>Databases</th>
<th>Author(s)</th>
<th>Journals</th>
<th>Outline/ Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>“International Centres of Excellence in Hospital Pharmacy”: a SEFH new initiative; the role of the clinical pharmacist in the hospital antibiotic stewardship in Northern Ireland1/2016</td>
<td>MEDLINE</td>
<td>Alváro-Alonso, Aldeyab, Ashfield, Gilmore, Encinas.</td>
<td>Sociedad Española de Farmacia Hospitalaria Journal</td>
<td>Observational study/VII</td>
</tr>
<tr>
<td>Bacterial resistance and the role of pharmacist in the face of irrational antimicrobial use: integrative review 12/2015</td>
<td>LILACS</td>
<td>Franco, Mendes, Cabral, Menezes.</td>
<td>e-Ciência Journal</td>
<td>Historical cohort study/IV</td>
</tr>
<tr>
<td>Carbenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study12/2017</td>
<td>MEDLINE</td>
<td>McConville, Sullivan, Simmonds, Whittier, Uhlemann.</td>
<td>Journals PlosOne</td>
<td>Cohort study/IV</td>
</tr>
<tr>
<td>Strategies for prevention of bacterial resistance: contributions to patient safety 15/2014</td>
<td>LILACS</td>
<td>Paim, Lorenzini.</td>
<td>Cuidarte Journal</td>
<td>Descriptive study with a qualitative approach /VI</td>
</tr>
<tr>
<td>A Simulation Study to Assess Indicators of Antimicrobial Use as Predictors of Resistance: Does It Matter Which Indicator Is Used?16/2015</td>
<td>MEDLINE</td>
<td>Fortin, Quach, Fontela, Buckridge, Platt.</td>
<td>Journals PlosOne</td>
<td>Simulation study/IV</td>
</tr>
<tr>
<td>Adecuada prescripción antimicrobiana em serviços de medicina interna en un hospital público de Perú17/2016</td>
<td>LILACS</td>
<td>Arteaga-Livias, Panduro-Correa, Salviaterra, Dáimaso-Mata Schellack, Pretorius, Messina</td>
<td>Acta Médica Peruana Journal</td>
<td>Descriptive and cross-sectional study /VI</td>
</tr>
<tr>
<td>“Esprít de corps”: Towards collaborative integration of pharmacists and nurses into antimicrobial stewardship programmes in South Africa18/2016</td>
<td>MEDLINE</td>
<td>Luyt, Bréchot, Trouillet, Chastre</td>
<td>Journal of the Medical Association of South Africa</td>
<td>Observational study/VII</td>
</tr>
<tr>
<td>Antibiotic stewardship in the intensive care unit19/2014</td>
<td>MEDLINE</td>
<td></td>
<td>J. Critical Care</td>
<td>A quasi-experimental observational cohort study /III</td>
</tr>
</tbody>
</table>
It is detailed that, of the 17 articles in the sample, eight were published in Portuguese, seven in English and two in Spanish, and two were published in 2012, two in 2014, six in 2015, five in 2016 and two in 2017.

**DISCUSSION**

It is reported that in the studies that analyzed the resistance to antimicrobials in the health environments, great concern regarding this subject, it is underlined its increase in the world, which presents significant challenges for the HICCs. New pharmacological classes were developed and, as a result, there was an increase in the pressure on existing antibiotics, in addition to the increase in bacterial resistance, proving that resistance rates are higher in higher consumption drugs, leading, consequently, to greater challenges in the treatment of patients.11-10

It is pointed out that hospital infection rates are higher in large and teaching hospitals, varying according to the type of surveillance used and the degree of hospital complexity. It is estimated that the rates of ICU infections vary between 18 and 54%, being about five to ten times higher than in other hospitalization units.11 In a recent study, the increased risk of infection with carbapenem-resistant Enterobacteriaceae (CRE) and mortality in patients with this type of colonization at the time of ICU admission were increased. It is pointed out as necessary future investigations to evaluate how the colonization of CRE can guide more appropriate empirical choices of antibiotics, since this family produces beta-lactamases, one of the main bacterial resistance mechanisms that act against beta-lactam drugs.12

It should be noted that contamination of ICU equipment is common, making them reservoirs of microorganisms such as Acinetobacter sp., Staphylococcus aureus, Staphylococcus coagulase negative (SCN), Staphylococcus saprophyticus, Enterococcus sp., Klebsiella pneumoniae and Streptococcus viridans. Cultures were carried out in a UTI of a teaching hospital in Rio de Janeiro to track microorganisms, with specimens being found in the hands of health care staff members in sinks, faucets, bed rails, bed rails, mattresses, on top of the tables and on the portable hemodialysis equipment. It was thus confirmed that professionals, through their hands and equipment, can disseminate resistant bacteria, which favors colonization and cross infection, in addition to hindering the prognosis and leading to outbreaks of Health Related Infections (HRI). It is known that, frequently, these microorganisms act synergistically among themselves in the production of the infection due to the mechanisms of resistance to ATBs.13-14

It is described that antimicrobials are drugs with the property of suppressing or destroying the pathogens, as well as improving the...
prognosis of infectious diseases. It is observed that they can be used prophylactically and therapeutically, but their increasing and indiscriminate use is the main factor related to the emergence of resistant microbial strains. It is essential, for the rational use of antimicrobials, a system of prevention of nosocomial infections.10

It is shown that the system of selection of antimicrobials prescribed by the multidisciplinary team is the most effective way to rationalize its use, being a fundamental tool for the preventive system. It is assessed that adapting the use of ATBs is crucial in the ICU, since the increase of inappropriate prescriptions, excess and abusive use can develop multiresistant pathogens, the selection of resistant mutants or the development of resistant pathogens colonizing the flora.15

It is surmised that the initial drug treatment with ATBs is almost always empirical, although of a long spectrum, considering that the microorganism is still unknown. The spectrum of the antibiotic should therefore be extended to cover all possible pathogens, and the dose to be determined, as well as frequency, duration of treatment and route of administration appropriate for the type of infection and its gravity.6-7

It is indicated that, in order to select the initial therapy with the ATBs, the patients must be identified in the ICU and have some type of HRI to obtain the appropriate bacterial cultures before the administration of antibiotics, being essential confirmation infection and identification of the responsible pathogens.18 The emergence of multiresistant gram-negative bacilli (GNB) (eg, Pseudomonas aeruginosa and Enterobacteriaceae, which produce extended-spectrum B-lactamase, and Klebsiella pneumoniae, a producer of carbapenemase) and the increasing role of Gram- positive patients, such as methicillin-resistant Staphylococcus aureus or MRSA, justified the use of broad spectrum empiric antibiotics for the majority of patients suspected of clinically identified infections. The drug regimen is based on local antimicrobial susceptibility patterns, diagnostic tests and anticipated side effects, taking into account the pharmacological properties of antimicrobials, as found in pharmacokinetics and pharmacodynamics, when considering the antibiotics received in the two weeks prior to suspicion of infection, where possible, for the variation of these classes of medicinal products.15-9

In another study on the profile of the use of anti-infectives in an ICU, the evaluation of the consumption pattern of ATBs is presented. It was concluded that the 4th generation cephalosporins (cefpime), followed by carbapenem and glycopeptides, are the most consumed drugs in an ICU. There is also a significant increase in the use of drugs such as meropenem, as well as telocoplamine and vancomycin.19 It is emphasized that antimicrobial prescription should follow priorities such as disease severity, drug efficacy, previous use of antibiotics, presence of comorbidities, resistance pattern of in-hospital microorganisms, hospitalization time, epidemiological impact and costs. Increased prescriptions with associations between these drugs are added to the data obtained to achieve therapeutic success and minimize the possibilities of resistance. However, there was a significant potential for the development of drug interactions of greater severity, involving simultaneously prescribed antimicrobials.11-20

A study on how to improve the use of antimicrobials as a strategy for an educational program for health professionals is based on the application of a checklist containing established criteria for the rational use of ATBs, and it was concluded that there was a reduction of consumption of ceftriaxone, cefazidime, quinolones, vancomycin and carbapenems, in addition to a 55% reduction in costs. It has been proven that creating a rational use program coupled with the cooperation of prescribing physicians, in fact, leads to a reduction in the consumption of ATBs.14

It is mentioned that in most of the studies selected, there was the reference of the pharmacist and of the pharmaceutical assistance in the units as a fundamental element for the rational use of ATBs, in addition to prioritizing the increase of the safety in the prescriptions of medicines. Among the essential activities of the pharmacist as a qualified professional, the evaluation of hospital prescriptions, the proposal for the rational use of antimicrobials and the surveillance of resistance to ATBs, the study of the antimicrobial use of the population to understand the magnitude of the problems of resistance in hospitals, obtaining data for the development of interventions tailored to a Therapeutic Guide prepared by a multidisciplinary team for the standardization of the ATBs used in the hospital, the performance of pathogen identification tests and the sensitivity of the ATB to the correct of the pharmaceutical, the determination of Defined Daily Dose.
The practice of pharmaceutical care by offering information on drug use, stimulating sequential therapy (continuity of therapy), reporting on consumption and systematic trainings for the prevention of the propagation of the pathogen and its correct disposal of the environment. Antimicrobial administration error is an essential factor for the increase of resistance. It is pointed out that the time error of the administration has reached high incidence, as well as the excessive doses and the doses of short or prolonged duration. It is understood as another factor that can generate the time error, the inadequate functioning of the drug distribution system of the hospital pharmacy, which leads to delays in the delivery of medicines and, consequently, in their administration. Among the effective preventive measures are: double checking of dilutions and calculations of drug dosage; conservation and administration; attention to communication errors arising from medical prescription; beware of verbal prescriptions; the patient's safe identification; the education and guidance of the health team about the pharmacotherapy of the patient; the participation of the clinical pharmacist in the unit as a key element of the health team to carry out the follow-up of pharmacotherapy and ensure optimum therapeutic results with minimal potential risk. Figure 3, which describes strategies to increase patient safety in antimicrobial prescription, is presented below.

### Figure 3. Strategies to increase safety in antimicrobial prescription. Niterói (RJ), Brazil, 2018.

It is revealed that the incorrect use of antimicrobials prescribed and administered by the health team often goes unnoticed, being important the implementation of a correct policy for the use of ATB's and the control of bacterial resistance.

It is pointed out that ATB's costs, both for therapeutic indications and for prophylactic indications, account for 20% to 50% of the total cost of medications, and it is estimated that the inappropriate use of them occurs in around 50% of the cases. In a study on the costs of antimicrobials in the treatment of patients with infection, empiric treatment was more expensive than the targeted treatment, emphasizing the importance of adjusting the ATBs according to the results of the cultures to be performed as soon as possible, in order to reduce the emergence of bacterial resistance and, consequently, reduce costs in the antimicrobial treatment of patients. In another study on antimicrobial resistance in patients admitted to the ICU of a hospital in Rio de Janeiro, high levels of resistance to cefepime (94%), ceftazidime (96%), ertapenem (61%), imipenem (54%) meropenem (43%) and ciprofloxacin (69%). These drugs were used in patients with K. pneumoniae bacteria, producers of extended spectrum betalactamases (ESBL), showing the need to change the treatment of these patients who presented the resistance, thus generating a higher cost with the treatment previously started and that needed to be modified. It is therefore indicated that the pharmacist's role in cost reduction is fundamental, since he is responsible for recommending that antibiotics be differentiated according to their use in prophylactic, empirical and specific (therapeutic) prescribers and to prevent them from occurring discontinued and resistant to bacteria.

It is judged necessary to establish the Defined Daily Dose (DDD), which is a unit of measurement of drug consumption created to overcome the difficulties derived from the use of more than one type of unit in drug use studies. It is also conceptualized as "the average daily dose of caring maintenance, usually by an adult individual, as the main therapeutic indication of that medication." It is understood that DDD for antimicrobials is the unit recommended by the WHO Drug Utilization Research Group and is calculated

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**Correct Patient Identification**

Ensure that manual prescriptions are legible; Use the Brazilian Common Denomination (BCD) to describe antimicrobials; Do not use abbreviations for antimicrobial names (eg SMZ-TMP); Differentiate medicines with sound or similar spelling, highlighting, in the upper case, the difference between them in manual and computerized prescriptions (ex.: cefOTAXima x cefOXitima); Adopt the metric system to describe doses, abolishing expressions such as "spoon", "cup" or "ampoule"; Avoid fractional numbers (ex.: 2.5 mg); Avoid using zero before the comma (ex.: 0,5 mg); Avoid using a dot to designate fractional numbers (ex.: 2.5 or 0.5 mg); Abolish abbreviations and symbols that tend to cause misinterpretation (eg U or UI should be written in full - units, abolishes "μg", which can be interpreted as "mg"); Do not use vague expressions such as "to use as usual" or "continuous use"; Record changes in prescription on all routes in a readable and non-erratic way.

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**English/Portuguese**

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by the following formula: \( \text{DDD} / 100 \text{ beds} / \text{day} = A / B / P \times 1000 \) where (A) represents the total quantity of drug consumed over the period of time considered (in g or IU); (B) is the standard daily dose of antimicrobial calculated in adult grams of 70 KG without renal failure and (P) are the patients/day in the same time period considered.21

Other factors that merit the attention of the pharmacist include the appearance of adverse drug reactions (ADRs) and drug interactions (DIs), which can cause more severe or lethal damage, causing permanent effects to the patient. It is argued that when it is essential to use concomitant ATBs that may interact, it is recommended to analyze the possible effects of the DI in question and the careful monitoring of the individual submitted to such therapy.20

It is stated that, in the majority of the studies that pointed to the performance of the pharmaceutical professional in the HICC team, it is incumbent on him to offer pharmaceutical care services and, together with the Nursing and the physicians who are part of the health team in the ICU, better treatment strategy, follow the clinical evolution of the patient and guide users in antimicrobial treatment on the correct use of these drugs. It has been shown that when the multidisciplinary team acts competently and in an ideal position through health efforts, the patient's results can be improved, and that this team also acts to reduce antimicrobial resistance, minimizing the risk development of resistant microorganisms in the ICU and preserving the efficacy of antimicrobials.10-25

**CONCLUSION**

It was found that bacterial and antimicrobial resistances have increased absurdly and frighteningly in hospitals all over the world and that the ICU is the main place where these resistances have developed.

It was verified that the performance of the pharmaceutical professional is essential to the work of the team of health professionals in hospital environments. The importance of its actions in the control of hospital infection rates and in the safer practices directed at the rational use of ATBs.

It was also pointed out that, in the multiprofessional health team, it is the duty of the pharmacist to act effectively on the containment of microbial resistances. Among the measures necessary for this professional to act effectively in this scenario, to promote the rational use of medicines, to evaluate, together with other professionals, the pathogens present in ICU equipment and in the hands of the active health team, to guide the therapeutics, to participate effectively in the HICC, to guide prescribers regarding the associations of ATBs for each patient and to verify the occurrence of adverse reactions and drug interactions.

In addition, the correct use of antimicrobials and the understanding of bacterial resistances that are still barely visible and discussed in the articles published in periodicals with national and international impact were also highlighted in the role of the pharmacist. Also revealed are publications that have scarcely addressed the performance of the pharmaceutical professional in the development of continuing education activities among health professionals, especially in the area of specific knowledge on antimicrobials.

It is considered that permanent education contributes to the prevention and control of hospital infections and the rational use of ATBs, since, in addition to socializing the knowledge produced for the health team, it strengthens the pharmaceutical assistance, giving greater visibility to the pharmacist. It is necessary, for this, the incentive of the professionals to access and investigate the studies related to this subject.

It is concluded that there are still gaps in this area of knowledge, but the growing dissemination of scientific production on the subject may help pharmaceutical professionals in the implementation of actions, which will certainly contribute to the consolidation of their position and autonomy with the teams within health institutions.

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