> ACESSE AQUI A REVISTA ONLINE

ORIGINAL ARTICLE

Use of carbapenemics and polymixin b in the general intensive care unit of a private hospital of Curitiba-PR

Uso de carbapenêmicos e polimixina B na unidade geral de cuidados intensivos de um hospital privado de Curiba-PR

Uso de carbapenems y polimixina B en la unidad de cuidados intensivos generales de un hospital privado en Curiba-PR

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SUMMARY

Background and objectives: It is estimated that in the next few years strains infections will be responsible for thousands of deaths and even higher-cost with health services. Antimicrobials are among the most commonly prescribed drugs in hospitals, and it is estimated that at least 50% of these are unnecessary or incorrect. These drugs are known to be increasing the dissemination of mechanisms that cause resistance to antimicrobials, a problem that is increasing worldwide and depleting pharmacotherapeutic options for the treatment of infections. This study had the purpose of quantifying the use of Carbapenemicos and Polymyxins, in the ICU of a private hospital of Curitiba-PR in 2017, as well as evaluates its employability, comparing with internal guidelines and protocols for the proper use of these drugs. **Methods:** Data were collected from the infection control unit of the hospital, pharmacy and support laboratory. Clinical data were analyzed as well as protocols for the use of the studied drugs. **Results:** During the study period, 1.3% of the patients used at least one of the antimicrobials. Meropenem was the most used, followed by Ertapenem, most often emplyed on April and December respectively.

RESUMO

Justificativa e objetivos: Estima-se que nos próximos anos as infecções por cepas serão responsáveis por milhares de mortes e custar ainda mais com os serviços de saúde. Os antimicrobianos estão entre os medicamentos mais comumente prescritos em hospitais, e estima-se que pelo menos 50% deles sejam desnecessários ou incorretos. Sabe-se que esses medicamentos estão aumentando a disseminação de mecanismos que causam resistência aos antimicrobianos, um problema que está aumentando mundialmente e esgotando as opções farmacoterapêuticas para o tratamento de infecções. Este estudo teve como objetivo quantificar o uso de Carbapenêmicos e Polimixinas, na UTI de um hospital privado de Curitiba-PR em 2017, além de avaliar sua empregabilidade, comparando-se com diretrizes e protocolos internos para o uso adequado desses medicamentos. **Métodos:** Os dados foram coletados na unidade de controle de infecção do hospital, farmácia e laboratório de apoio. Foram analisados dados clínicos e protocolos de uso dos medicamentos estudados. **Resultados:** Durante o período do estudo, 1,3% dos pacientes usaram pelo menos um dos antimicrobianos. Meropenem foi o mais utilizado, seguido por Ertapenem, mais frequentemente empregado em abril e dezembro, respectivamente.

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Página 01 de 05
não para fins de citação

RESUMEN

Antecedentes y objetivos: se estima que en los próximos años las infecciones por cepas serán responsables de miles de muertes e incluso de mayores costos con los servicios de salud. Los antimicrobianos se encuentran entre los medicamentos recetados más comúnmente en los hospitales, y se estima que al menos el 50% de estos son innecesarios o incorrectos. Se sabe que estos medicamentos están aumentando la diseminación de mecanismos que causan resistencia a los antimicrobianos, un problema que está aumentando en todo el mundo y está agotando las opciones farmacoterapéuticas para el tratamiento de infecciones. Este estudio tuvo el propósito de cuantificar el uso de Carbapenemicos y Polimixinas en la UCI de un hospital privado de Curitiba-PR en 2017, así como evaluar su emple-abilidad, comparándolo con las pautas y protocolos internos para el uso adecuado de estos medicamentos. **Métodos:** los datos se obtuvieron de la unidad de control de infecciones del hospital, farmacia y laboratorio de apoyo. Se analizaron los datos clínicos y los protocolos para el uso de los fármacos estudiados. **Resultados:** Durante el período de estudio, el 1.3% de los pacientes usaron al menos uno de los antimicrobianos. Meropenem fue el más utilizado, seguido de Ertapenem, que con mayor frecuencia se vació en abril y diciembre, respectivamente.

INTRODUCTION

Bacterial infections at the hospital environment have been the target of discussions, as there is a worldwide concern regarding the antimicrobial resistance, a problem that has been depleting pharmacotherapeutic options. It is estimated that in the coming decades infections with multiresistant bacterias will be responsible for thousands of deaths and even higher expenses in health services.[1,2]

Intensive care units (ICUs) among the hospital wards have the highest risk for bacterial infections. Several factors are related to this growing number of infections, such as the complexity of care, need for invasive procedures, severe clinical cases, patients with impaired immunity and extensive use of antimicrobials.[3,4]

The use of antimicrobial is linked to resistance and may also increase toxicity and adverse effects. It is estimated that around 50% of antimicrobials were used unnecessarily and reducing overuse is a priority in the world health system.[2,5,6]

The World Health Organization (WHO), National Surveillance Agency (ANVISA) and Centers for Disease Control (CDC) recommend that all hospitals implement programs for the rational use of antimicrobial agents, which consist of a set of multidisciplinary activities which seeks to improve the quality of prescriptions, reduce costs and offer better therapy without emerging the problem of antimicrobial resistance.[7]

Carbapenems and polymyxins represent the latest options today for multi-resistant strains, and mechanisms for resistance to these drugs are often reported.[2,6]

Carbapenems are broad-spectrum drugs that were inserted into therapy after the dissemination of mechanisms with resistance to other beta-lactams and for this reason should not be the first drug of choice for treating any infection. The representatives of this class are imipinem, meropenem, ertapenem and doripenem.[4]

The polymyxin are also broad-spectrum antimicrobials, but restrictive to Gran negatives. It was discovered in the 1940's and its use was suspended after some years due to its toxic effect, and substituted or safer options. In the 90's these drugs were reintroduced in therapeutics due to its extreme resistance to antimicrobials used ate the time. There are five types in this set but only Polymyxin B and Polymyxin E (colistin) are used in pharmacotherapy.[8]

According to the World Health Organization (WHO) to the quantification of the medication, the defined daily dose (DDD) is used as an international unity to statistically measure the operation of a medication, defined by ANVISA as the average dose used by an adult on its pharmacotherapy. This initiative was created to avoid further issues in studies that manipulate these drugs and to ease comparisons between researches with different aspects.[9]

To know the prescription profile in the health services is extremely necessary, since this data can help with a proper assemble of this medication, contribute to adequate the protocols for a rational use and economically favorable, and also to aware how important is the correct management of broad-spectrum antibiotics.

This study seeks to determine the use of these drugs in the ICU of a medium-sized hospital in the city of Curitiba-PR, as well as quantify and determine their employability, comparing with indicators and internal protocols for broad-spectrum drug use.
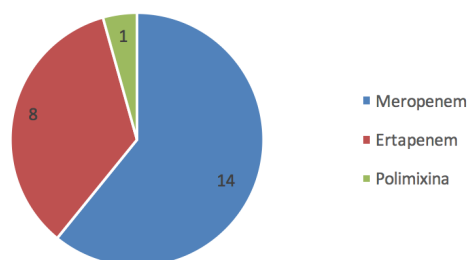
METHODS

This is a retrospective observational study that sought to quantify the use of carbapenems and polymyxin B in the general ICU of a private hospital located in Curitiba-PR from January to December of 2017. The hospital studied is considered to be medium size, with 123 beds, in which 36 correspond to beds of the general ICU. The institution only provides care to patients with health insurance. Data regarding the number of hospitalizations, use of drugs and culture results were collected from the hospital infection control unit (HICU), hospital pharmacy and support laboratory. The medical records were evaluated in order to collect data regarding the history and clinical evolution of the patients. For comparison with other studies we used DDD data/100 beds-day.

Data were represented with graphs by the Microsoft Excel® 2016 program.

The study was approved by the Research Ethics Committee (CEP) and for being research with secondary data, the use of Informed Consent (IC).

RESULTS

According to data collected at the hospital infection control unit, during the study period, 1712 patients were admitted to the general ICU and among those, 23 (1.3%) used at least one of the antimicrobials under study. Meropenem was the most administrated followed by ertapenem, and polymyxin B, which was prescribed for only one patient (Figure 1). The other carbapenems and polymyxin E (colistin) were not represented because they are not part of the drugs adopted by the hospital.


Figure 1. List of number of patients using meropenem, ertapenem and/or polymyxin B in 2017.

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Página 02 de 05
não para fins de citação

During the year studied, 50 patients had some type of infection according to HICU reports that assess the entire history and clinical course. Of these, 45 were cultured and 13 were negative. (FIGURE 2). The pathogens isolated from these cultures are represented in FIGURE 3, where the highest incidences are on *Escherichia coli* and *Klebsiella pneumoniae* and glucose non-fermenter *Pseudomonas aeruginosa* (19% each).
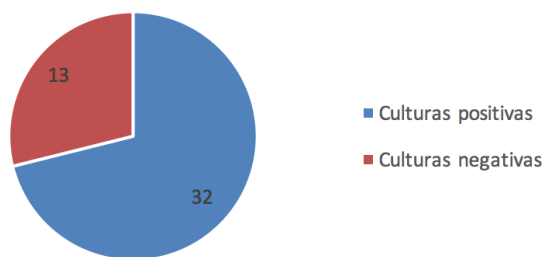

Figure 2. Number of positive and negative cultures in the general ICU in 2017.
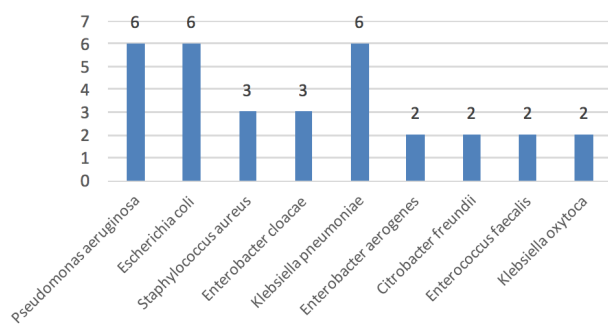
Figure 3. Bacteria isolated from cultures performed in the general ICU in 2017.

By monthly assessing the use of antimicrobials in a study using the DDD methodology/100 patient days, it was observed that on March and April, the highest consumption of meropenem occurred. The consumption of this antimicrobial agent experienced falls during the five months following its peak. The ertapenem showed less variation in consumption during the year presenting two peaks (October and December), one of which coincided with the month of lower meropenem consumption (Figure 4). Polymyxin B presented consumption only in the month of May, and for this reason, is not represented in the figure.
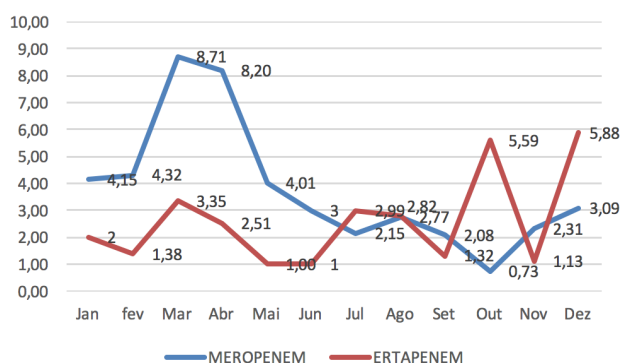
Figure 4. DDD / 100 bed-days ertapenem and meropenem in the general ICU in the year.

DISCUSSION

Antimicrobials changed perspectives on treating disease caused by bacterias. But since we've started to use these drugs, mechanisms of resistance are observed and disseminated.[6] Its inappropriate use has been described as the main contributor to this problem. Studies show that adequacy of protocols, implementation of guidelines and prescribing guides more judicious of these drugs can control this problem.[11,12]

In this study the use of two classes of broad-spectrum antimicrobials was quantified, currently considered the best treatment on infections by multidrug-resistant bacteria. The hospital chosen uses antimicrobial management programs to a better control of these drugs.

In the present study, 50 patients with infection according to the data collected by the HICU. Whereas only 23 patients required treatment with the antimicrobials under study, it can be concluded that the other infections were caused by less resistant bacteria and therefore treated with less potent antimicrobials. To correlate the number of patients with evident signs of infection (50) with the total number of patients admitted to the general ICU in 2017 (1712), 2.9% are patients with infection. This result is much lower than the one found by Custovic[3] in the ICU he studied (11.27%).

Studies show that the cephalosporin class is the most used in hospitals.[13] Rodrigues[14,15] evaluated the profile of antimicrobials used at a private hospital and a cancer hospital, respectively, and observed this prevalence (43.4 - 38.8%) being followed by quinolones (13 - 21.9%).

On the other hand, the study by Souza et al. at a public hospital in northern Brazil pointed to meropenem as the antimicrobial drug most commonly used in the general ICU (19.8%). Polymyxin E (Colistin) appeared in third place (8.2%) and polymyxin B in fourth (7.4%). These results were attributed to the use of meropenem as empirical therapy in serious infections and continued treatment even after result of culture with other therapeutic options. As for polymyxins, their high use was attributed to the emergence of bacteria resistant to other therapies and is generally used in combination with amikacin to increase the effectiveness of treatment.

Data collected from 411 hospitals in the state of Paraná by the Hospital Infection Notification (SONIH) from January to June 2018, appoint meropenem as the second most used antimicrobial in ICUs (15.40 DDD / 100 patient-days), second only to ceftriaxone. The polymyxin B is in 8th place (3.61 DDD / 100 patient-days) and imipenem 17th day (0.61 DDD / 100 patient days).[13]

An increased use of carbapenems has been reported by Zhang D, et al. (17), in a study conducted in China for 4 consecutive years. According to the published data, it was observed that throughout the study the carbapenems were consumed increasingly and significantly (2.8 for 4.9 DDD / 100 beds day). By contrast, the overall reduction in consumption of antimicrobials was abrupt (77 to 39.5 DDD / 100 beds day). The author relates the data found for the global increase in bacteria resistant to several drugs and also relates the abuse of carbapenemics to the increase in carbapenemase producing bacteria. In the present study it was not possible evaluate such trends due to the short period analyzed.

A recent study conducted in Turkey[18] sought to determine consequences of carbapenem use on the development of resistance topolymxins. The authors report a high rate of infected patients or colonized by colistin-resistant bacteria in the hospital evaluated. Consider although previous use of carbapenems and polymyxins, whether empirically or not, is a problem regarding the susceptibility of Acinetobacterbauman-

J. Infect. Control, 2019 Abr-Jun;8(2):48-52 [ISSN 2316-5324]

Página 03 de 05
não para fins de citação

nii and Klebsiella pneumoniae. A warn for the risk of possible outbreaks due to these microorganisms because the control of infections in the units studied have not been effective since evidence of cross-transmission has been reported.

Although polymyxin B was not widely used in the hospital studied, carbapenems have shown significant use and should always be carefully observed, as they are related to the development of resistance to polymyxins.

The hospital studied has antimicrobial control in wide spectrum action and expensive costs. They undergo evaluation and the release takes place only through HICU in conjunction with the hospital pharmacy. In this scenario, it is clear that actions recommended by WHO and other agencies, when employed and followed produce positive results, as shown by a study conducted in Korea, where it was possible to observe considerable reductions in the consumption trends of broad-spectrum antimicrobial agents after intervention.[12]

The prevalence of Klebsiella pneumoniae and Escherichia enterobacteria coli (Figure 4) is compatible with data collected by SONIH[13] showing that the hospital studied represents the reality observed in the state of Paraná. Unlike the present work where Pseudomonas aeruginosa appears tied to the bacteria mentioned above, the third most isolated pathogen in the Paraná was Staphylococcus aureus. Since the data collected by SONIH regarding culture results does not separate hospital wards, this difference should be related to the fact that Pseudomonas aeruginosa infections are mainly associated with immunocompromised patients which are mainly concentrated in the ICUs.

An interesting fact observed when comparing general data from Paraná[13] is that bacteria of the *Acinetobacter baumannii* complex are in fifth place and these are not represented in the present work being a point positive for the hospital under analysis. These bacteria represent serious problems in hospitals as they produce a wide variety of ßlactamases and have a broad spectrum of intrinsic mechanisms of resistance.[6]

The months of March and April were the most significant in the consumption of carbapenems, especially meropenem. Among the cultures, the presence of enterobacteria and non-fermenters, resistant of first choice drugs, as well as resistant Staphylococcus aureus methicillin (MRSA) in bloodstream isolates. Another factor that may correspond to these numbers is that these antimicrobials are used in the prophylaxis in special cases, such as surgery for limb amputations. The number of hospitalizations remained in the average of the other months and there were no reports of any outbreak that can justify these numbers. It is remarkable that in the second half of the year the numbers remained more stable and this may be related to infection control strategies and the use of more efficient drugs.

In assessing the culture outcome of the only patient who was treated with polymyxin B, isolation of carbapenemase producing strain was observed. The aggravation is that the patient had previously used other antimicrobials and had a long hospital stay, thus justifying the use of this drug. As the use in other patients has not been reported, it is observed that the strategies for controlling the spread of this multiresistant microorganism have been efficient.

Imipenem and meropenem are most widely used in the carbapenemic class and are used primarily in the treatment of moderate to severe nosocomial infections and polymicrobial infections. Clinical studies show its effectiveness in treating many infections from moderate to severe ones including intra-abdominal infections, pneumonia nosocomials, septicemia and neutropenic fever. While imipenem is slightly more active against gram positive and meropenem is slightly more active against Gram negative, direct comparisons between the two drugs report similar clinical and bacteriological cure rates. Besides that, meropenem is best indicated for the treatment of meningitis, as imipenem has a high potential to cause seizures.[19]

When comparing DDD / 100 bed-day values with other studies, many discrepancies were observed.[13-16] This methodology was created to allow comparisons between the drugs used. However, it should be taken into account that each study site has its own characteristics and these differences should be considered so that comparisons have practical meaning. Comparisons made with data from the same hospital in different periods, may serve as an indication of a tendency in using these medicines.[16]

This study has limitations regarding the characteristics of each patient, such as age, gender, etc. As for the type of infection and time, this should be taken into consideration for further deepened studies. Each hospital has its own characteristics and this can determine a more accurate conduct.

CONCLUSION

The data collected show that the use of carbapenems and polymyxin B was controlled in the ICU of the hospital studied in 2017, mainly due to a surveilance of antimicrobial use. These barriers to control the use of antimicrobials, when applied, help significantly to reduce the consumption. These actions must be continuous and expanded, to change or at least control the global scenario of untreatable infections and decline in new drug discovery.

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J. Infect. Control, 2019 Abr-Jun;8(2):48-52 [ISSN 2316-5324]

Página 04 de 05
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J. Infect. Control, 2019 Abr-Jun;8(2):48-52 [ISSN 2316-5324]

Página 05 de 05
não para fins de citação