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Evaluation of meropenem doses prescribed in an adult intensive care unit at a large hospital in Serra Gaúcha

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Abstract

Objective: To evaluate the conformity of dose and/or posology of meropenem prescribed in the setting of kidney impairment, otherwise to evaluate the microbiological profile of the germs isolated in those patients. In addition, to measure the extra costs of non-adjusted prescriptions. **Method:** This work is a Drug Utilization Review. Were included charts of adult patients, of both sex, that had meropenem prescribed between 01/01/2021 and 06/30/2021, while admitted in the ICU regimen, in a large hospital in Serra Gaúcha. For dose analysis, UpToDate was used as guideline, prescriptions from patients on renal replacement therapy, as well as prescriptions from patients who did not have a creatinine result in the 24 hours prior to the prescription of meropenem, were excluded. **Results:** A total of 2044 prescriptions were evaluated, of which 667 were excluded because they did not meet the inclusion criteria. Of the 1377 prescriptions included, 1003 were considered adequate (73%) and 374 inadequate (27%). Of the doses considered inadequate, 54 were by underdose (14%) and 320 by overdose (86 %). The extra cost measured was US$1.835,21, equivalent to 993 vials of 500 mg. Microbiologically, there was a higher incidence of Gram-negatives: 81% (383/473). Of these, 54% resistant to meropenem (208/383), 5% (20/383) presumed sensitive, 3% (11/383) intrinsically resistant, and 38% (144/383) sensitive in vitro. **Conclusion:** The findings support the promotion of the service provided by the clinical pharmacist and stewardship programs, both for the promotion of health in intensive care and for the preservation of the financial health of a philanthropic institution.

Keywords: meropenem, drug utilization review, drug dosage calculations

Avaliação das doses de meropenem prescritas em uma unidade de terapia intensiva adulta de um hospital de grande porte na Serra Gaúcha

Resumo

Objetivo: Avaliar a conformidade das doses e/ou intervalos prescritos frente a função renal do paciente e literatura, bem como avaliar o perfil de micro-organismos isolados nos materiais biológicos destes pacientes. Além disso, quantificar os custos extras oriundos de não ajustes. **Método:** Realizou-se uma DUR (*drug utilization review)* transversal e retrospectiva. Foram incluídos prontuários de pacientes adultos (maiores de 18 anos), de ambos os sexos, que tiveram meropenem prescrito entre 01/01/2021 e 30/06/2021, enquanto internados em regime de terapia intensiva em um hospital de grande porte na Serra Gaúcha. Para análise de doses, utilizou-se a base de dados *UpToDate*®, e foram excluídas prescrições de pacientes em terapia renal substitutiva, bem como prescrições de pacientes que não tiveram resultado de creatinina nas 24 horas anteriores a prescrição de meropenem. **Resultados:** Foram avaliadas 2044 prescrições, destas, 667 foram excluídas, por não contemplarem os critérios de inclusão. Das 1377 prescrições incluídas, 1003 foram consideradas adequadas (73%) e 374 inadequadas (27%). Das doses consideradas inadequadas, 54 foram por subdose (14%) e 320 (86%) por sobredose. O custo extra aferido foi de US$1.835,21, equivalente a 993 frascos de 500 mg. Microbiologicamente, aferiu-se maior incidência de Gram-negativos de 81% (383/473). Destes, 54% resistentes a meropenem (208/383), 5% (20/383) presumivelmente sensíveis, 3% (11/383) intrinsecamente resistentes e 38% (144/383) sensíveis *in vitro*. **Conclusão:** Os achados corroboram para o fomento do serviço prestado pelo farmacêutico clínico e para os programas de *stewardship*, tanto para a promoção da saúde em terapia intensiva, quanto para preservação da saúde financeira de uma instituição filantrópica.

Palavras-chave meropenem, revisão de uso de medicamentos, cálculos da dose de medicamentos

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Introduction

After the introduction of antibiotics into the clinical practice, outcomes associated with infections have greatly improved and overall life expectancy has increased significantly[1]. However, irrational and indiscriminate use of these drugs promoted the induction of a phenomenon known as bacterial resistance, which can be defined as an evolutionary mechanism that allows bacteria to adapt to the environment in which they is inserted. The World Health Organization (WHO) considers multidrug-resistant microorganisms as one of the 10 greatest threats to public health worldwide and has listed 12 priority pathogens for the development of new antimicrobial drugs, classifying them as of critical, high and medium priority. All three pathogens considered as of critical priority are Gram-negative, namely: *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P aeruginosa), carbapenem-resistant enterobacteria (CRE) or extended spectrum β-lactamases (ESBL) producers and carbapenem-resistant *Acinetobacter baumannii* (CRAB)[2].

Carbapenems are a class of broad-spectrum β-lactam antimicrobials that provide coverage for a variety of pathogens, from aerobic Gram-positive cocci and aerobic Gram-negative bacilli (fermenters and non-fermenters) to anaerobic germs. Resistance to carbapenems was first demonstrated in 1991 and is currently one of the biggest problems related to antibiotic therapy in the world[2,3]. Meropenem is an ultra-broad spectrum carbapenem, with various indications. International guidelines instruct these indications and establish when there is benefit from using it, as well as the most suitable dose for the best possible outcome. The suitable meropenem doses can vary according to the infection site, the causing micro-organism and the patient's renal function. The most accepted guidelines suggest doses from 1,000 mg to 2,000 mg every 8 hours for patients with creatinine clearance above 50 mL/min, with dosage adjustments depending on severity of renal failure[4,5].

It has been already shown *a priori* that not adjusting the dose for renal function is a recurring problem in health services, both for antimicrobial drugs and for other medications[6]. Thus, this study aimed at evaluating the compliance profile of meropenem doses prescribed in an intensive care unit for adults of a large-size hospital in Serra Gaúcha, as well as to evaluate the profile of pathogens isolated from these patients.

Methods

A Drug Utilization Review (DUR) with a cross-sectional and retrospective design was conducted. The medical records included were those of adult patients (over 18 years old), of both genders, hospitalized in intensive care at a large philanthropic hospital from Serra Gaúcha. To be included in the study, the patients should have received at least one meropenem prescription during the period between January 1st, 2021 and June 30th, 2021, in addition to not being undergoing renal replacement therapy. For such patients, sociodemographic data (age, gender and race) were collected, as well as clinical data (infectious focus, microorganism isolated and glomerular filtration rate), and compliance of the prescribed doses and intervals was evaluated in view of the meropenem monograph in the UpToDate® database.

The renal function estimate can be obtained by means of different methods; however, the equation developed by the *Chronic Kidney Disease Epidemiology Collaboration*(CKD-EPI) for estimating the glomerular filtration rate (GFR) is currently considered the most accurate and was used in this measurement[7]. The following doses were considered as adequate prescriptions[8]:

1,000 mg or 2,000 mg every 8 hours for patients with estimated glomerular filtration rates >50 mL/min/1.73m².

1,000 mg or 2,000 mg every 12 hours for patients with estimated glomerular filtration rates from >25 to ≤50 mL/min/1.73m².

500 mg or 1,000 mg every 12 hours for patients with estimated glomerular filtration rates from >10 to ≤25 mL/min/1.73m².

500 mg or 1,000 mg every 24 hours for patients with estimated glomerular filtration rates ≤10 mL/min/1.73m².

The aforementioned doses were considered adequate for any infectious focus, except for the Central Nervous System, in which only the maximum dose allowed for the GFR range was considered adequate. Dose adequacy against the isolated microorganism was not evaluated.

In addition to assessing dose conformities, a preliminary analysis was performed in order to identify possible additional costs arising from unadjusted doses for renal function. These costs were measured by means of the following equation: Ac=CDp-CDa, where Ac means "Additional cost", CDp is "Cost/Day of the dose prescribed" and Cda represents "Cost/Day of the adjusted dose". Thus, at the end of data collection, all the Ac values were added up to measure the total additional cost. The value was initially measured in reais and later converted to US$, according to the Purchasing Power Parity in force in 2021[9].

Due to the need to estimate the patients' GFR, the absence of a serum creatinine result in a period of less than 24 hours renders the analysis of dose compliance unfeasible and, for this reason, such prescriptions were excluded from the analysis.

The analyses were performed using Microsoft Excel®, where the categorical variables were expressed as frequencies or percentages and the continuous variables as mean values and standard deviations.

For being a research involving human beings, the study was registered at *Plataforma Brasil* for analysis by a Research Ethics Committee (*Comitê de Ética em Pesquisa*, CEP) and data collection was only initiated after the CEP's approval opinion (CAAE No. 59609922.5.0000.5341, opinion No. 5,529,571).

Results

A total of 2,044 meropenem prescriptions made during the study period were analyzed. Of these, 1,377 met the inclusion criteria (totaling 194 patients — demographic and clinical data shown in Table 1), while 667 prescriptions were excluded, 137 due to absence of creatinine results in the 24-hour period prior to the prescription and 530 because the patients were on renal replacement therapy. The most prevalent infection focus was respiratory (74.7%), followed by abdominal (9.8%) and not identified (6.2%) (Table 1).

Table 1. Demographic and clinical data of the 194 patients included.

Characteristic	Result
Male gender	115 (59%)
Mean age in years old (±SD*)	62.5 (±15)
Black race	4 (2%)
Mean GFR** in mL/min/1.73 m² (±SD*)	76.19 (±48)
Infection foci	
Respiratory	145 (74.7%)
Abdominal	19 (9.8%)
Not identified	12 (6.2%)
Urinary	7 (3.6%)
Others	6 (3.1%)
Bloodstream Infection	3 (1.5%)
Cutaneous	2 (1%)

* SD = Standard Deviation; ** GFR = Glomerular Filtration Rate estimated by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

Among the GFR ranges estimated by means of the CKD-EPI equation, higher prevalence of GFR >50 mL/min/1.73m² was identified (67.7% of the prescriptions) (Figure 1). From the microbiological point of view, 81% prevalence of Gram-negative pathogens was assessed (383/473). Of these, 54.3% were meropenem-resistant (208/383), 5.2% presumptively sensitive (20/383), 2.9% intrinsically resistant (11/383) and 37.6% (144/383) sensitive *in vitro*, according to the classification of the *Brazilian Committee on Antimicrobial Susceptibility Testing*[10].

All meropenem prescriptions analyzed had a permissive indication of an *off-label* dose of 2,000 mg every 8 hours for normal renal function. From the analysis of the prescribed meropenem doses, it was evidenced that approximately 27% of them had some inconsistency when confronted with the patients' estimated renal function. The overdose index was 23% of the total of prescriptions analyzed, whereas the prescriptions of doses below the recommended had 4% prevalence (Figure 2). When evaluating adequacy of the meropenem doses in relation to the estimated GFR range, a smaller divergence is observed in the range above 50 mL/min/1.73m² (6% inadequacy), while the worst result was obtained for prescriptions referring to patients with a GFR range between 10 and 25 mL/min/1.73m² (80% inadequacy).

Figure 1. Distribution of the GFR values estimated by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in all 1,377 prescriptions evaluated.

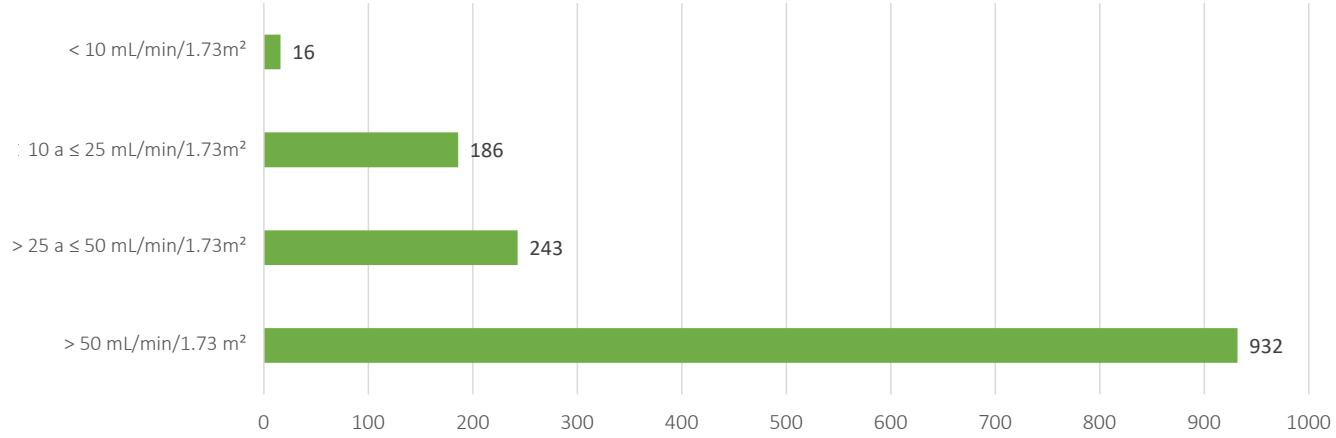

Figure 2. Adequacy percentage of general doses and of doses stratified by GFR range.

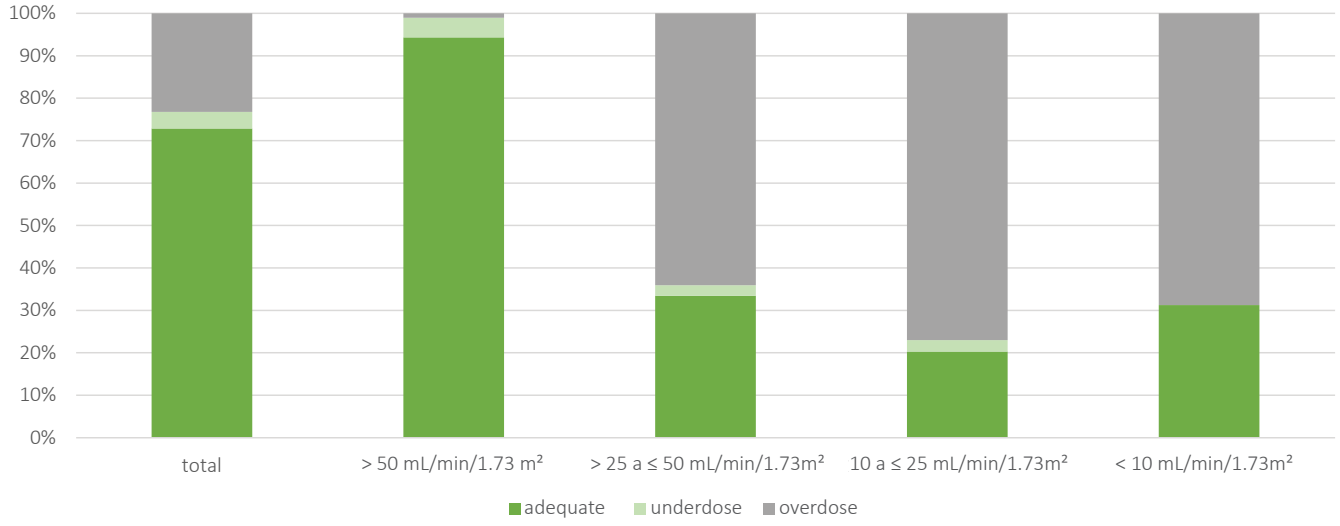

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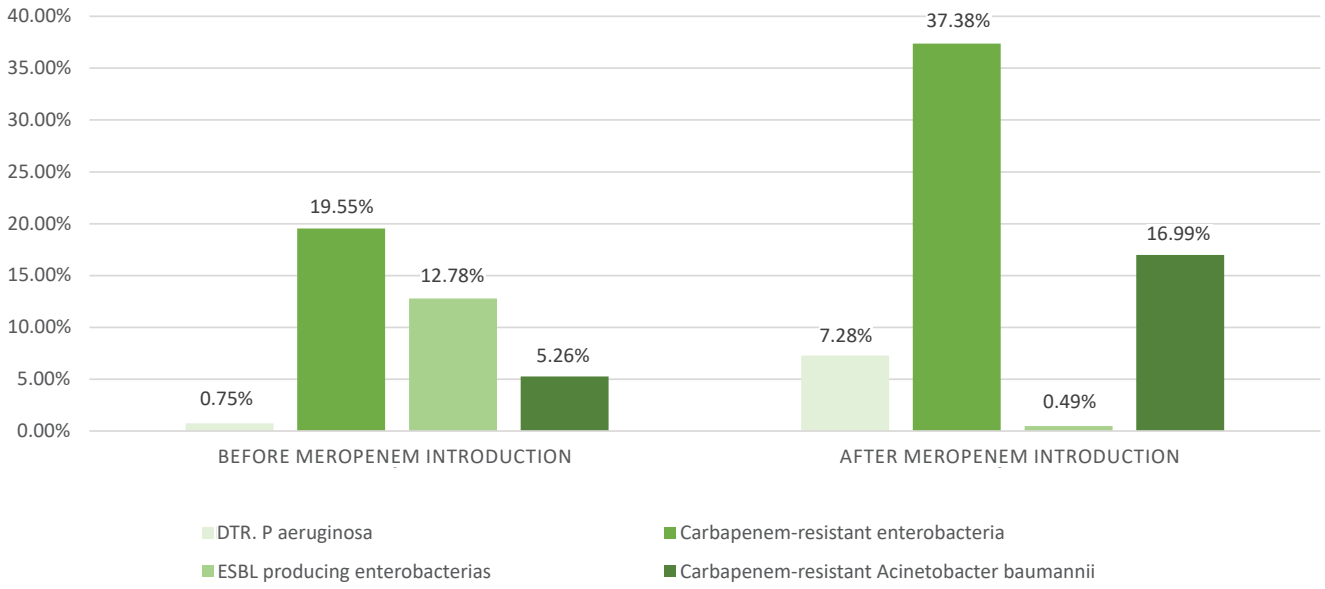
Figure 3. Prevalence of Gram-negative cocci considered critical by the WHO, before and after introducing meropenem.



Data were collected from the positive cultures for the Gram-negative microorganisms considered critical by the WHO. Based on the collection date for the biological material, the results were separated into three groups — collected before meropenem use, collected during meropenem use and collected after meropenem use — in order to evaluate the selection potential of multidrug-resistant Gram-negatives inherent to meropenem. To such end, the cultures collected during meropenem use were excluded from this analysis. The prevalence of microorganisms considered critical by the WHO (DTR-P aeruginosa, carbapenem-resistant enterobacteria or producers of extended-spectrum β-lactamases, and carbapenem-resistant *Acinetobacter baumannii*) is shown in Figure 3. The prevalence of critical microorganisms, isolated before introducing meropenem, was approximately 38.3% of the Gram-negative ones. On the other hand, their prevalence after introducing meropenem was approximately 62.1% of the Gram-negative microorganisms.

The additional cost arising from dosage non-adjustment was estimated at US$ 1,835.21, which equals 993 meropenem vials (500 mg presentation). The inputs required to administer the drug were not considered for this analysis.

Discussion

A number of studies suggest that 23% to 60% of the antimicrobial prescriptions in intensive care units have some inconsistency, and this data converges with the findings of the current study, in which 27% of the analyzed meropenem prescriptions presented dosages considered inadequate for the patients' renal function[11,12]. Other studies focusing on beta-lactam antimicrobials have already reported similar findings, in which dose adjustments to the patients' renal function were not performed, as well as reporting higher incidence of adverse effects correlated to the high serum concentration of the antimicrobial. In addition to that, there are studies suggesting that, during the COVID-19 pandemic, inappropriate use of antimicrobials may have worsened the global rates of bacterial resistance[12–15].

With this, the importance of stewardship programs is reiterated since, in this scenario, prescription errors promote exposure of microorganisms to hostile but ineffective environments and, therefore, selection/induction of resistant strains. It can be seen that the GFR range greater than 50 mL/min/1.73m² generated a lower percentage of inadequate doses, probably due to the fact that dose adjustment was not necessary. The GFR range that showed the highest rate of dose inconsistencies was 10-25 mL/min/1.73m². This result can be explained by the need for dose adjustment in view of renal function, which requires knowledge and commitment from the clinician to monitor the patient's GFR and adjust accordingly.

The predominant infectious focus was the respiratory tract. This can be attributed to the study period: one of the most critical moments of the COVID-19 Pandemic. Invasion of the respiratory tract to supply oxygen through an endotracheal tube is an important entry point for infections, increasing the rate of infections related to this site[16,17].

In addition to the findings related to doses and dosages, it was possible to analyze the profile of microorganisms isolated from these patients, as well as to correlate the resistance profile with meropenem use. The incidence of multi-drug resistant microorganisms was higher after the introduction of meropenem, and this data can be attributed to the bacterial selection promoted by this carbapenem; however, other variables (such as hospitalization time and previous use of antimicrobials) may also have exerted an influence on these data, although it was not possible to carry out such an analysis.

Despite the high incidence of meropenem-resistant microorganisms, it is not possible to assert that use of this medication was incorrect in these contexts. Meropenem is a very dynamic drug and is indicated for the treatment of infections caused by bacteria that are resistant (*in vitro*) to it when associated with other drugs; however, drug combinations (aminoglycosides and polymyxins, especially with meropenem) were not the subject of this study and, therefore, such data was not collected[18]. However, the high incidence of these pathogens draws the attention and serves as an alert to the problem of inadequate use of broad-spectrum antimicrobials such as meropenem.

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Economically, there was an additional cost of US$ 1,835.21, equivalent to 993 500-mg meropenem vials, in the period analyzed. Such data represents a low financial volume if compared to the overall billing of a large-sized hospital; however, it is relevant because it refers to a single medication, prescribed for a specific profile of patients and in a period of only 6 months.

As this is a retrospective study based on secondary sources, it is worth mentioning some limitations. In the first place, the data were collected from medical records; thus, flaws in the charts can affect interpretation of the information. In addition to that, only prescriptions released while the patients were in the Intensive Care Unit were evaluated. Therefore, clinical outcomes (discharge, hospitalization time, death) were not evaluated, nor the possibility of antimicrobial therapy de-escalation. Finally, information collection was manual, therefore being subjected to human error. In addition to that, the economic analysis was carried out in a simplistic and preliminary way, not taking into account indispensable factors for pharmacoeconomics studies. However, these limitations do not invalidate the relevance of the work performed and the results found.

Conclusion

Through this research it was possible to quantify the percentage of meropenem prescriptions made for patients hospitalized in the ICU, with indication of dosage adjustment in which this was not performed, as well as the additional costs arising from non-adjustments. In addition, the microorganisms isolated from these patients were compiled before and after introducing meropenem into the therapy.

The findings corroborate promotion of the service provided by the clinical pharmacists and the stewardship programs, both for health promotion in intensive care and for preserving the financial health of a philanthropic institution. However, this is not a pharmacoeconomics study and, therefore, it does not take into account other indispensable factors for this type of analysis.

The microbiological findings are in line with the global trends of increasing prevalence for this resistance profile but, even so, they should serve as a warning, especially regarding the selective potential of the drug under study.

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Collaborators

BF: Conception of the project; data analysis and interpretation; writing of the article.

BRA: Conception of the project; relevant critical review of the intellectual content; writing of the article.

Conflict of interest statement

The authors declare no conflicts of interest regarding this article.

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