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Quality analysis of prescriptions of polymyxin B in a high-complexity public hospital

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ABSTRACT

Objectives: The study proposed to evaluate the quality of polymyxin B prescription in a Brazilian high-complexity public teaching and reference hospital. *Methods:* This study of drug use describes the medical prescription habits, with the retrospective collection carried out with critically ill patients using polymyxin B. The dose by weight for each patient's first prescription was calculated from the Infectious Diseases Society of America (IDSA) guideline to assess the loading dose adequacy. The glomerular filtration rate (GFR) was estimated to evaluate the adequacy of the dose prescribed at the onset of treatment, based on the Kidney Disease – Improving Global Outcomes (KDIGO). *Results:* 346 prescriptions were analyzed, representing 259 patients. Only 61 (17.6%) included a loading dose of polymyxin B. On the other hand, no adjusted doses were identified in 147 (73.1%) prescriptions for patients whose GFR range requires renal adjustment. A total of 438 cultures were analyzed, and 97 carbapenem-resistant GNB were selected for the study (22.2%). A loading dose was identified in only 13 (13.4%) of these prescriptions, and 80 (82.5%) prescriptions had no dose adjustment by renal function. The prevalent microorganism was *Klebsiella pneumoniae* (70 [16.0%]). *Conclusion:* The study identified high rates of non-compliance with the protocol for using polymyxin B concerning the loading dose and a high percentage of cases in compliance with the protocol regarding the nonindication of renal adjustment. The development of institutional clinical protocols and the performance of the ASP team are critical to rationalizing the use and avoiding unsatisfactory clinical and microbiological results.

Keywords: anti-infective agents; drug resistance; clinical pharmacist; infection control services; polymyxin B.

ANÁLISE DO PERFIL DE UTILIZAÇÃO DE POLIMIXINA B EM UM HOSPITAL PÚBLICO DE ALTA COMPLEXIDADE DE BELO HORIZONTE/MG

RESUMO

Objetivos: Avaliar a qualidade da prescrição de polimixina B em um hospital público brasileiro de ensino e referência em alta complexidade. *Métodos*: Estudo de utilização de medicamentos que descreve hábitos de prescrição médica com coleta retrospectiva, realizado com pacientes críticos em uso de polimixina B. A dose por peso foi calculada para avaliar a adequação da dose de ataque baseando-se na diretriz da *Infectious Diseases Society of America* (IDSA). A taxa de filtração glomerular (TFG) foi estimada para avaliar a adequação da dose prescrita no início do tratamento, baseando-se na Kidney Disease – Improving Global Outcomes (KDIGO). *Resultados*: 346 prescrições de polimixina B foram analisadas, representando 259 pacientes. Apenas 61 (17,6%) contemplaram dose de ataque de polimixina B. Em contrapartida, em 147 (73,1%) não foram identificadas doses ajustadas. Foram analisadas 438 culturas, sendo identificadas bactérias gram-negativas *(*BGN) resistentes a carbapenêmicos selecionadas para o estudo em 97 (22,2%). Nessas prescrições foi identificada a presença de dose de ataque em apenas 13 (13,4%) e ausência de ajuste de dose de acordo com a função renal em 80 (82,5%). O microrganismo prevalente foi *Klebsiella pneumoniae* (70 [16,0%]). *Conclusão*: O estudo identificou altas taxas de não conformidade com protocolo de uso de polimixina B com relação à dose de ataque e um percentual elevado de casos em conformidade com o protocolo quanto a não indicação de ajuste renal. O desenvolvimento de novos protocolos clínicos institucionais e atuação da equipe de ASP (*Antimicrobial Stewardship Program*) são de extrema importância para racionalizar o uso e evitar resultados clínicos e microbiológicos insatisfatórios.

Palavras-chave: agentes anti-infecciosos; resistência a medicamentos; farmacêutico; serviços de controle de infecção; polimixina B.

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INTRODUCTION

Polymyxins (polymyxin A-E) were discovered and widely used over in the 1960 e 1970s. However, their use was restricted due to reports of serious adverse effects, such as nephrotoxicity. The recent emergence of infections caused by carbapenem-resistant Gram-negative bacteria (GNB), such as *Pseudomonas aeruginosa (P. aeuginosa)*, *Acinetobacter baumannii (A. baumannii)*, and *Klebsiella pneumoniae (K. pneumoniae)*, and the scarce discovery of new antimicrobials has led to the reintroduction of polymyxins B and E (colistin) in clinical practice as "rescue therapy". They have currently been used as a therapeutic reserve to treat nosocomial infections that no longer respond to conventional antimicrobials[1].

Understanding the pharmacokinetic and pharmacodynamic profile of polymyxins helps rationalize their use and reduce adverse effects and the development of microbial resistance[2]. Despite similarities in the chemical structure, spectrum of action, and antimicrobial activity, colistin (polymyxin E) and polymyxin B differ in their pharmacokinetic characteristics[3], which is mainly because polymyxin B is administered as a sulfate salt in its active form, and colistin is administered as a prodrug, in the form of colistin methanesulfonate (MSC), which makes the polymyxin B pharmacokinetic profile more predictable than colistin[4].

Most recent studies that compare the nephrotoxicity of both polymyxins concluded that the polymyxin B is significantly less nephrotoxic than colistin[8,9]. The hypotheses is that polymyxin B is eliminated mostly by nonrenal ways and it's total clearance has little relation with the creatinine clearance[10]. But, even though, the polymyxin B is prone to cause nephrotoxicity, since it goes through extent tubular reabsorption followed by glomerular filtration. The result of this process is that less than 5% of the drug is excreted in the urine, while tubular cells are exposed to a high amount of it[13].

The Antibiotic Stewardship Program (ASP) was proposed as a strategy to improve the quality of antimicrobial use. This is a scientific evidence-based program that mainly aims to rationalize the use of these drugs and to change prescribing and dispensing practices[6]. As they are indicated for the treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria, polymyxins are one of the evaluation targets of the ASP team. This program recommends that institutional protocols and clinical guidelines substantiate prescriptions to standardize the use of antimicrobials[7].

Thus, given the importance of polymyxin B use in clinical practice and the growing microbial resistance, investigations on the profile and quality of prescriptions of this drug becomes relevant for a better understanding of its use in patient care. Knowledge on the topic in a high-complexity public hospital can help guiding interventions to improve antimicrobials´ use.

The study intended to determine and evaluate the quality of polymyxin B prescription in a Brazilian high-complexity public teaching and reference hospital.

METHODS

Study design and location

This is a study of medical prescription habits [8], with a retrospective data collection, carried out in a public university hospital, a reference in the care of medium- and high-complexity diseases in Belo Horizonte, Minas Gerais, Brazil. The health institution has an Antimicrobial Use Management Committee that performs specific ASP interventions and activities, such as prospective auditing, pre-authorization form, and loading dose monitoring.

Study population

The study included all critically ill patients in the Coronary Unit, Intensive Care Unit of the hospital, and the Emergency using polymyxin B from November 2019 to November 2020. We chose polymyxin B because it was monitored by the ASP team and is a therapeutic reserve drug.

Data collection procedure and study variables

The following data were collected from the electronic prescription system and the laboratory tests system: i. patient data: age, sex, weight, and serum creatinine obtained on the first prescription day; ii: polymyxin B use: use length and prescribed dose; iii: infection that led to polymyxin B use: microorganism, and whether it was a carbapenem-resistant GNB.

The results of cultures performed closer to the prescription date of polymyxin B for each patient were searched to describe the microorganisms. The microorganisms selected for evaluation were non-fermenters, such as *A. baumannii* and *P. aeruginosa*, besides the enterobacteria *K. pneumoniae* and *Escherichia coli (E. coli)*, all carbapenem-resistant[9,10].

The dose by weight for each patient's first prescription was calculated from the data obtained to assess the adequacy of the loading dose. To this end, the guideline for the optimized use of polymyxin B published by the Infectious Diseases Society of America (IDSA) in 2019 was adopted as a parameter. It recommends a loading dose of 20,000-25,000 IU/kg and a maintenance dose of 12,500-15,000 IU/kg every 12 hours[11].

The glomerular filtration rate (GFR) reported by each patient was estimated to assess the adequacy of the prescribed dose at the start of treatment. The assessment of dose adjustment per renal function was based on information in the polymyxin B sulfate package insert [12], which indicates that the adjustment should be performed in patients with a GFR lower than 80% of the expected value.

The GFR defined as normal by the guideline published by Kidney Disease – Improving Global Outcomes (KDIGO) in January 2013 [13] is 90 mL/min/1.73m², estimated by the CKD-EPI method developed by the Chronic Kidney Disease Epidemiology Collaboration in 2009[14]. Therefore, the GFR of the patients included in the study was estimated by the following formula:

$$\mathbf{GFR = 141 \times \min(Cr/k, 1)^{\alpha} \times \max(Cr/k, 1)^{-1.209} \times 0{,}993^{age}\ (\times 1.018 \text{ if woman})}$$

Where GFR is glomerular filtration rate, Cr is serum creatinine, k is 0.7 for women and 0.9 for men, α is-0.329 for women and-0.411 for men, min indicates the minimum Cr/k or 1 and max indicates maximum Cr/k or 1.

The dose adjustment was then considered for patients with GFR less than 72 mL/min/1.73m² (80% of the expected value) and received a prescription of polymyxin B at a dose lower than that defined as maintenance (12,500 IU/ kg).

The adequacy of the prescriptions according to the IDSA guideline[11] was determined considering the need for a loading dose and non-indication for renal adjustment.

Data analysis

The study population was analyzed using frequency distributions for categorical variables and measures of central tendency and dispersion for continuous variables. The variables were evaluated against the normal distribution using the Kolmogorov-Smirnov test, considering the probability of significance of $p<0.05$ and a 95% confidence interval (CI).

The database was developed using Microsoft Excel®, and statistical analysis was performed using the Statistical Package for Social Sciences® software, version 25.0 (2017. Armonk, NY: IBM Corp.).

Ethical aspects

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE: 85804818.7.0000.5149).

RESULTS

The study included 346 polymyxin B prescriptions, totalizing 259 patients, as some patients received more than one treatment during the study period. The median age was 59 years (interquartile range [IQR] 47-67), with 145 (56.0%) male patients. The sociodemographic and clinical characteristics of the study are shown in Table 1.

Table 1 – Sociodemographic and clinical characteristics of patients using polymyxin B in a high-complexity hospital*

Characteristic	**Values**
Age [median, Interquartile range (IQR)]	59 years (47–67)
Sex [n, (%)]	
Female	114 (44.0)
Male	145 (56.0)
Dose [median, (IQR)]	14,286 UI/kg (11,538 – 16,667)
Clearance [median, (IQR)]	55.59 mL/min/1,73m² (26.92 – 93.23)
Treatment time [median, (IQR)]	4 days (2–7)
*Total of 346 prescriptions and 259 patients.	

Source: Elaborated by the authors.

Only 61 (17.6%) of the total prescriptions included a loading dose of polymyxin B. On the other hand, no dose adjusted per renal function was identified in 147 (73.1%) prescriptions for patients with a GFR lower than 72 mL/min/1.73m² (n=201 [57.8%)]), whose range requires adjustment. The overall median dose of the first prescription was 14,286 IU/kg (IQR 11,538-16,667), and creatinine clearance was 55.59 mL/min/1.73m² (IQR 26.92-93.23).

Among 438 cultures analyzed, 97 (22.2%) presented carbapenem-resistant GNB. In the prescriptions of patients infected by this type of microorganism, a loading dose was identified in only 13 (13.4%) prescriptions and a lack of dose adjustment according to renal function was identified in 80 (82.5%), as seen in Table 2. Thirty-six (54.6%) positive cultures for carbapenem-resistant GNB corresponded to blood cultures.

Table 2 – Prescriptions analyzed according to the compliance with the IDSA guideline [16] of a high-complexity hospital

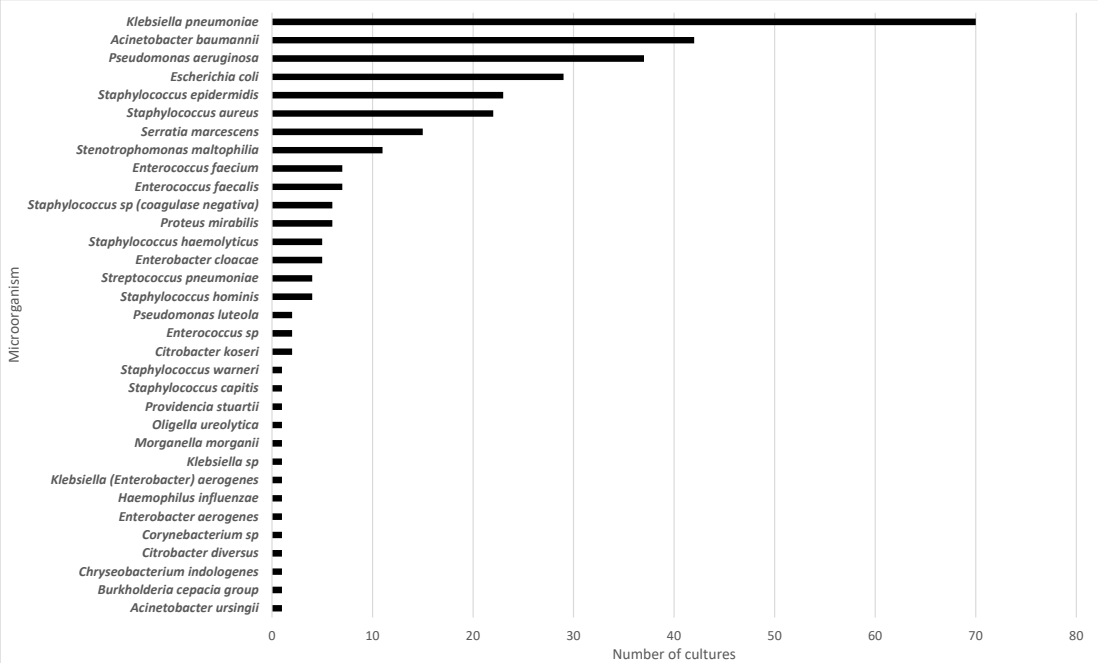
	Adequacy to IDSA n (%)	**Non-adequacy to IDSA n (%)**
Prescriptions (n=346)		
Loading dose	61 (17.6)	285 (82.4)
Dose adjustment	291 (84.1)	55 (15.9)
Positive culture for carbapenem-resistant GNB (n=97)		
Loading dose	13 (13.4%)	84 (86.6%)
Dose adjustment	80 (82.5%)	17(17.5%)

IDSA: *Infectious Diseases Society of America*

Source: Elaborated by the authors.

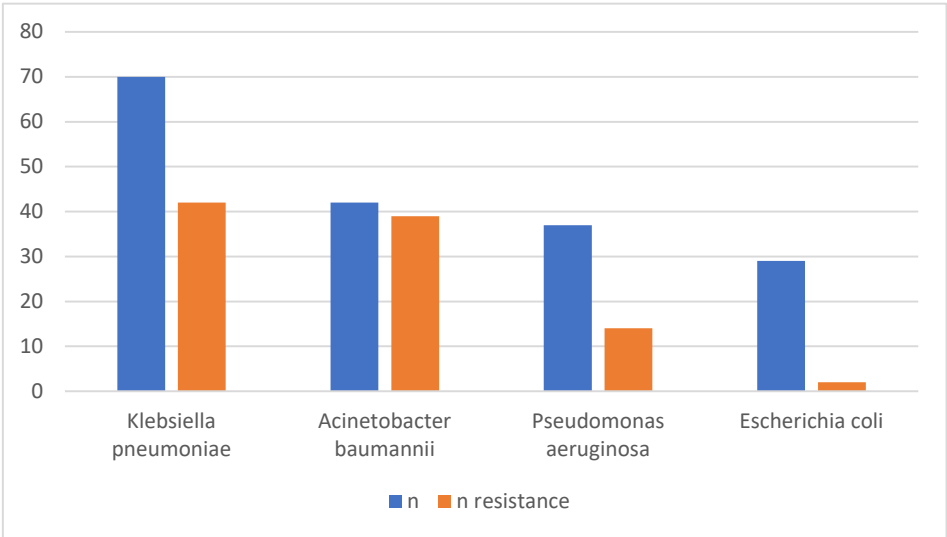
The most prevalent microorganisms in all cultures analyzed were *K. pneumoniae* (70 [16.0%]), *A. baumannii* (42 [9.6%]), *P. aeruginosa* (37 [8.5%]), and *E. coli* (29 [6.6%]) (Figure 1). Of these microorganisms, *K. pneumoniae* was resistant to carbapenems in 42 (60.0%) analyzed cultures, *A. baumannii* in 39 (92.9%), *P. aeruginosa* in 14 (37.8%), and *E. coli* in 2 (6.9%) (Figure 2). Seventy-seven (29.7%) patients had positive cultures for carbapenem-resistant GNB, and 31 (40.3%) of them had blood culture results.

Figure 1 – Description of microorganisms, by identification frequency in number of cultures



Source: Elaborated by the authors.

Figure 2 – Frequency of resistance to carbapenems in the most prevalent microorganisms in number of cultures (n)



Source: Elaborated by the authors.

DISCUSSION

This study evaluated whether polymyxin B prescriptions met the following quality criteria: loading dose and no dose adjustment for renal function, verifying compliance to the IDSA clinical protocol. The use of polymyxin B

targeted carbapenem-resistant GNB, with negligible use of a loading dose and dose adjustment by renal function. The clinically relevant microbial resistance to carbapenems among Gram-negative pathogens such as *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, and *E. coli* required re-evaluating polymyxin dose regimens to make them effective against multidrug-resistant Gram-negatives while minimizing the probability of adverse events[4]. Fortunately, resistance to polymyxins among these bacterial species varies among institutions, but it is still very low, undoubtedly due to their limited use over the last decades[15].

Considering that a small percentage of polymyxin B is excreted in the urine as an unchanged drug, we could state that renal function does not influence polymyxin B clearance. Thus, the daily dose should not be based on the patient's renal function, as low doses can lead to plasma underexposure with potential adverse consequences on clinical and microbiological results, besides the emergence of microbial resistance to polymyxin B[16].

As discussed earlier, the IDSA guide published a guideline that advocates the need of a loading dose of 20,000-25,000 IU/kg for one hour [11.] In this study, a few patients on polymyxin B were prescribed doses compatible with the loading dose (61 [17.6%]), and this percentage decreased when the analysis was performed only in the group of patients with positive cultures for carbapenem-resistant GNB (22 [15.4%]).

A population pharmacokinetic study shows that doses of 15,000 IU/kg of polymyxin B administered every 12 hours were unable to reach minimum inhibitory concentrations (MIC) greater than 0.5 mg/L. Therefore, a loading dose is necessary for more severe infections, such as those caused by carbapenem-resistant GNB, as the MIC is usually not known before the start of treatment[17]. Moreover, the use of a loading dose, necessary for the rapid achievement of MIC, apparently does not impact nephrotoxicity[18].

The IDSA guideline also recommends that maintenance doses of polymyxin B should not be adjusted in patients with renal dysfunction [11]. In this study, most patients did not receive adjusted doses of polymyxin B, which agrees with current evidence. This data indicates that the behavior of prescribers of the studied hospital is as recommended by the IDSA guideline, [11] corroborating that polymyxin B has no significant renal excretion and that its clearance does not depend on the GF[5].

In this study, less than half of the patients using polymyxin B (77 [29.7%])) had positive cultures for carbapenem-resistant GNB. From these, 31 (40.3%) presented bacteremia. It is often associated with a considerable increase in morbimortality rates, being one of the most significant complications of infectious process, often related to hospital infections[19]. Polymyxin B has resurfaced in the clinical context to treat infections caused by these bacteria, which are already resistant to most of the currently available antimicrobials. The indiscriminate use of this agent can favor the emergence of resistance in these microorganisms.

Studies have shown that carbapenem-resistant enterobacteria such as *E. coli* and *K. pneumoniae* have caused severe infections and were associated with high mortality rates (40-50%). Infections caused by this bacteria present mortality

rates twice as high as infections with sensitive enterobacteria. In contrast, *P. aeruginosa* and *A. baumannii* are opportunistic pathogens that benefit from factors such as prolonged intensive care unit (ICU) stay, use of invasive devices, and previous antimicrobial therapy with fluoroquinolones, broad-spectrum cephalosporins or carbapenems, and both bacteria are associated with higher mortality rates[20].

According to official Brazilian data, the main microorganisms that caused laboratory-confirmed bloodstream infection in adult ICUs were *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*. Of these, 51.8% of *K. pneumoniae*, 79.5% of *A. baumannii*, and 39.7% of *P. aeruginosa* are carbapenem-resistant. These bacteria also showed high percentage of resistance to polymyxins, ranging 2.3-12.3%[21]. Elevated microbial resistance has already been associated with the increased use of antimicrobials[22], which may favor infections by multi-resistant microorganisms mentioned above, escalating the severity of the patient's condition and limiting treatment options. Thus, it becomes so essential to rationalize the use of agents such as polymyxin B.

One hundred twenty-five (28.5%) of the total cultures were negative, which characterizes empirical treatment, performed after the clinical diagnosis of infection, and before accessing the culture result, based on the microbiological profile of the institution to assess possible pathogens, the clinical condition of the patient, and the infection site[23]. While this type of treatment can elevate the incidence of microbial resistance due to possibly unnecessary exposure to antimicrobials, it is a crucial practice in clinical deterioration, especially in the context of the study, in which the analyzed population is located in ICUs and critically ill. Furthermore, it is challenging to conduct a targeted treatment due to the rapid evolution of the infectious condition and delay in the results of cultures and detection of the microorganism.

Thus, developing guidelines and clinical protocols becomes extremely important to the institutional adequacy of polymyxin B use, and the clinical pharmacist, the microbiology laboratory, and the entire ASP team play a fundamental role[7]. Polymyxin B use standardization involves performing a loading dose and maintaining daily doses without adjustments according to renal function, which can be achieved through ASP-related interventions, including pre-authorization and prospective auditing.

This study had some limitations, such as analyzing only the prescription of polymyxin B, without verifying whether the drug was effectively administered to the patient. Moreover, because this work is retrospective, we did not access electronic medical records to confirm the prescriber's intention to adjust the dose by renal function, basing the adjustment only on renal function and prescribed dose calculations. The study design does not allow assessing causality but assists in elaborating hypotheses for testing in future studies.

Studying the quality of polymyxin B prescription in a Brazilian hospital can contribute to a better understanding of our healthcare reality. The sample size composed of critically ill patients stands out as one of the strengths of this study. Furthermore, this is a study on good prescribing practices, evaluating the adequacy of use according to available pharmacokinetic and pharmacodynamic

studies of the drug and the IDSA guideline, which highlights essential points to be included in institutional protocols and evaluated for promoting the proper use of polymyxin B in national and international institutions.

CONCLUSION

High rates of non-compliance with the protocol for the use of polymyxin B concerning the prescription of loading doses were identified in this study on assessing the quality of prescriptions. However, we observed a high percentage of cases in compliance with the protocol regarding the nonindication of renal adjustment. Given these results, we need to standardize polymyxin B use in hospitals, especially according to the loading dose. Developing new institutional clinical protocols based on the latest evidence and the performance of the ASP team is extremely important to rationalize the use and avoid unsatisfactory clinical and microbiological results.

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DECLARATION OF CONFLICTING INTERESTS

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