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ORIGINAL ARTICLE

Impact of the national shortage of polymyxin B in critically ill patients during the COVID-19 pandemic

Impacto da escassez nacional de polimixina B em pacientes gravemente enfermos durante a pandemia de COVID-19

Impacto del desabasto nacional de polimixina B en pacientes críticos durante la pandemia de COVID-19

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ABSTRACT

Background and Objectives: during the COVID-19 pandemic, the number of critical patients requiring intensive care increased considerably, resulting in an increase in infections due to multi-resistant microorganisms. In Brazil, in 2021, due to the high demand for polymyxin B use, there was a national shortage of the medication. One strategy used to overcome this situation was aminoglycoside use. The work aimed to analyze the impact of replacing polymyxin B with amikacin and gentamicin in the final stage of patients. **Method:** an analytical study with an observational, cross-sectional design, with a quantitative approach, through a retrospective analysis through the analysis of medical records, with the primary stages being discharges or deaths. **Results:** mortality was similar between the group treated with aminoglycoside and the group treated with polymyxin B. Within the aminoglycoside group, mortality was higher in the group that had bacteria resistant to the drug than in the group that had infection with an organism sensitive to this drug. Mortality was not affected by comorbidities, age, or number of hospital infections. The main factor that led to the need for dialysis was the combination of two nephrotoxic medications. **Conclusion:** two hypotheses emerged: the first would be that replacing polymyxin B with aminoglycosides did not impact mortality; the other would be that, regardless of the antibiotic group used, patients had a high risk of death. Despite sample limitations, the study corroborates the adoption of strategies for the rational use of antimicrobials.

Descriptors: *Polymyxin B. Aminoglycosides. COVID-19.*

RESUMO

Justificativa e Objetivos: durante a pandemia de COVID-19, o número de pacientes críticos que necessitaram de cuidados intensivos aumentou consideravelmente, resultando em aumento de infecções por microrganismos

multirresistentes. No Brasil, em 2021, devido à grande demanda pelo uso da polimixina B, houve escassez nacional do medicamento. Uma estratégia utilizada para superar essa situação foi o uso de aminoglicosídeos. O trabalho teve como objetivo analisar o impacto da substituição da polimixina B por amicacina e gentamicina na fase final dos pacientes. **Método:** estudo analítico com desenho observacional, transversal, com abordagem quantitativa, por meio de análise retrospectiva por meio de análise de prontuários, sendo as etapas primárias as altas ou óbitos. **Resultados:** a mortalidade foi semelhante entre o grupo tratado com aminoglicosídeo e o grupo tratado com polimixina B. Dentro do grupo aminoglicosídeo, a mortalidade foi maior no grupo que apresentava bactérias resistentes ao medicamento do que no grupo que apresentava infecção por organismo sensível a este medicamento. medicamento. A mortalidade não foi afetada por comorbidades, idade ou número de infecções hospitalares. O principal fator que levou à necessidade de diálise foi a combinação de dois medicamentos nefrotóxicos. **Conclusão:** surgiram duas hipóteses: a primeira seria que a substituição da polimixina B por aminoglicosídeos não impactou a mortalidade; a outra seria que, independentemente do grupo de antibióticos utilizado, os pacientes apresentavam alto risco de morte. Apesar das limitações amostrais, o estudo corrobora a adoção de estratégias para o uso racional de antimicrobianos.

Descritores: Polimixina B. Aminoglicosídeos. COVID 19.

RESUMEN

Antecedentes y Objetivos: durante la pandemia de COVID-19, el número de pacientes críticos que requirieron cuidados intensivos aumentó considerablemente, resultando en un aumento de infecciones por microorganismos multirresistentes. En Brasil, en 2021, debido a la alta demanda del uso de polimixina B, hubo escasez nacional del medicamento. Una estrategia utilizada para superar esta situación fue el uso de aminoglucósidos. El trabajo tuvo como objetivo analizar el impacto de la sustitución de la polimixina B por amikacina y gentamicina en la etapa final de los pacientes. **Método:** estudio analítico con diseño observacional, transversal, con enfoque cuantitativo, mediante un análisis retrospectivo mediante el análisis de historias clínicas, siendo las etapas primarias las altas o defunciones. **Resultados:** la mortalidad fue similar entre el grupo tratado con aminoglucósido y el grupo tratado con polimixina B. Dentro del grupo de aminoglucósido, la mortalidad fue mayor en el grupo que tenía bacterias resistentes al fármaco que en el grupo que tenía infección con un organismo sensible a este. droga. La mortalidad no se vio afectada por las comorbilidades, la edad o el número de infecciones hospitalarias. El principal factor que llevó a la necesidad de diálisis fue la combinación de dos medicamentos nefrotóxicos. **Conclusión:** surgieron dos hipótesis: la primera sería que la sustitución de polimixina B por aminoglucósidos no impactó la mortalidad; la otra sería que, independientemente del grupo de antibióticos utilizado, los pacientes tenían un alto riesgo de muerte. A pesar de las limitaciones de la muestra, el estudio corrobora la adopción de estrategias para el uso racional de antimicrobianos.

Descriptores: Polimixina B. Aminoglucósidos. COVID-19.

INTRODUCTION

In recent decades, due to indiscriminate antimicrobial use and the selective pressure exerted by them, infections related to multi-resistant microorganisms have emerged. These microorganisms can range from bacteria, fungi, viruses and other parasites, which have the ability to render antimicrobials ineffective.[1]

Antimicrobial resistance (AMR), which occurs when a pathogen shows resistance to one or more AMR from three or more tested categories,[1-3] is a situation of worldwide concern and impact, so much so that the World Health Organization estimates that, by 2050, resistance to AMR will lead to the death of around one person every three seconds (more than ten million people per year). This prediction was made in 2019, before the emergence of the coronavirus pandemic, COVID-19.[4-7] COVID-19, one of the greatest pandemics in history, originated in China at the end of 2019,[7,8] and its causal agent is SARS-CoV-2, a strain of coronavirus that causes an upper respiratory tract infection, which can progress to pneumonia as a secondary infection and severe acute respiratory syndrome. With so many patients suffering from severe respiratory conditions, hospital admissions have increased, mainly in an intensive care environment, with a significant increase and indiscriminate antibiotic use throughout the country, resulting in antimicrobial resistance as a public health consequence.[5,6]

With increasing rates of antimicrobial resistance due to indiscriminate AMR use (such as azithromycin) to combat healthcare-associated infections, one of the antibiotics used against organisms resistant to carbapenems was polymyxin B. Due to the high demand for this drug, a national shortage of the drug occurred during 2021.[8]

Based on previous studies to restrict broad-spectrum antibiotic use, replacing polymyxin B with aminoglycosides, the strategy adopted by many institutions to overcome the national shortage crisis was to use aminoglycosides, mainly amikacin and gentamicin, as an alternative. However, these studies were carried out in ideal situations, where drug replacement was a choice and not a necessity, as observed during the pandemic.[9-14]

Taking into account this historical moment and the public health crisis that has taken place, the hypothesis of this work is that the replacement of polymyxin B with aminoglycosides did not lead to greater mortality among critically ill admitted to hospital patients, provided

that the multidrug-resistant bacteria were sensitive to amikacin and/or gentamicin. Regarding the outcome of renal failure, using both drugs is expected to harm the organ, as both classes are known to be nephrotoxic.[15] However, there is still no comparison in the literature between polymyxin B and aminoglycoside and the greater possibility of using one or the other leading to renal replacement therapy.

Therefore, the study's main objective was to analyze the impact that replacing polymyxin B with amikacin and gentamicin had on patient outcomes. To this end, the mortality of patients who received aminoglycoside versus polymyxin B and the recovery duration from the infectious condition for each of the antibiotics used were assessed. Data on progression to renal replacement therapy and length of stay in a critical environment were also collected.

METHOD

This is an analytical study with an observational, cross-sectional design, with a quantitative approach, through a retrospective analysis, which was carried out based on data obtained from medical records of critically ill patients admitted to a small tertiary hospital in the Metropolitan Region of Curitiba, in the drug shortage period, from August and September 2020 and August and September 2021.[16, 17]

Critical patients who required polymyxin B use during 2020 and those who used amikacin or gentamicin during 2021 were included. Patients who used AMR concomitantly and who were only over 18 years of age were also included. Incomplete medical records and those of patients who died within 24 hours of using antibiotics or being admitted to hospital were excluded.

Data were collected and tabulated in spreadsheets using Excel®. For descriptive analysis, categorical variables were presented according to their frequencies, prevalence and percentages, while quantitative variables were described according to means, deviation and standard error. Participants were divided into groups according to drug use. In most analyses, the sample was composed of two groups: 1) aminoglycosides (AM); and 2) polymyxin (PL). In other analyses, a subdivision of the drug was carried out, with four groups: 1) sensitive aminoglycoside (SAM); 2) aminoglycoside resistance (AMR); 3) PL; and 4) PL + AM (PLAM).[18, 19]

For inferential analyses, data tabulated in Excel® were transferred to the Statistical Package for the Social Sciences (SPSS, IBM Statistics, v.23, 2015). The Mann-Whitney U test was used to compare, between AM and PL groups, age, total length of stay, length of stay in a critical environment, duration of use and number of antibiotic cycles. With the aim of investigating the primary outcome, which is equivalent to the patient being discharged from hospital or death, and the secondary outcome, which is equivalent to progressing to dialysis, the chi-square test was used to compare the frequency of occurrence of these variables between groups.[18, 19]

The Spearman correlation test was used to correlate Polymerase Chain Reaction (PCR), creatinine and urea values on D3, total length of stay and length of stay in a critical environment, duration of use and number of antibiotic cycles with hospital discharge/death outcomes. The correlation between palliative care and age was also analyzed.[18, 19]

Generalized Estimating Equation (GEE) models with appropriate link function (identity or log) and (linear, gamma or tweedie) distribution assumed were used to compare the quantitative variables (PCR, creatinine and urea) between groups (AM and PL) and length (D0, D3, D7, D10 and D14). Thus, group and duration were the effects analyzed as well as their interaction. The distribution model was selected (best overall fit) based on the lowest value of Quasi-likelihood under Independence Model Criterion (QIC, 2007). AR1 structure matrix was used, and, when necessary, Bonferroni post-hoc for subsequent comparisons. The significance of all analyzes was set at 5% ($p < 0.05$).[18, 19]

As it involves reviewing medical records, the project was previously submitted to the Research Ethics Committee of São José dos Pinhais, under Consubstantiated Opinion 5,549,515 (CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration): 58850522.9.0000.9587), in compliance with the Standards for Conducting Research on Human Beings of the Brazilian National Health Council, in accordance with Resolution 466/12.

RESULTS

Thus, 22 patients comprised the sample of this study. Depending on drug use, the AM group had 10 patients (69.9 ± 7.82 years, 8 men, 2 women), and the PL group had 12 (70.4 ± 8.26 years, 8 men, 4 women). There was no significant difference in age between groups (U = 56.000; p = 0.791).

The main point researched, which was to compare the outcome of discharge or death between groups, is presented in Tables 1 and 2. For this result, two analyzes are presented, dividing patients into 2 (Table 1 – PL and AM) or 4 groups (Table 2 - SAM, AMR, PL and PLAM), in order to try to remove the influence of the low sample number. The chi-square test found no difference in the frequency of death and discharge in either of the two analyzes.

However, it is noteworthy that, when observing the groups of patients who received only AM, mortality was higher in those who were sensitive to the drug (75%) than in those who were not resistant to it (33%).

Table 3 presents different outcomes. It was observed that there was no difference between length of stay, number of antibiotic cycles, number of care-related infections or number of antibiotics between AM and PL groups.

According to table 3, it can be seen that there was a statistical difference in relation to length of stay in a critical environment, which was longer for patients in the PL group as well as a longer period of antibiotic use. In

Table 1. Comparison of frequency of hospital admission outcome between AM and PL groups.

	Discharge	Death	Death for other causes	X^2	p
AM (n = 10)	2 (20%)	8 (80%)	-	0.078	0.781
PL (n = 12)	3 (25%)	9 (75%)	-		

Source: the authors.

Table 2. Comparison of frequency of hospital admission outcome among AMR, PL and PLAM groups.

	Discharge	Death	Death for other causes	X^2	p
SAM (n = 4)	0 (0%)	4 (100%)	-	3.731	0.292
AMR (n = 6)	2 (33%)	4 (67%)	-		
PL (n = 4)	2 (50%)	2 (50%)	-		
PLAM (n = 8)	1 (12%)	7 (88%)	-		

Source: the authors.

Table 3. Comparison of length of stay and use of antibiotics between groups.

	AM (n = 10)	PL (n = 12)	U	p
Length of stay (days)	24.4 ± 7.97	39.8 ± 20.51	31.50	0.060
Length of stay in a critical environment (days)	17.8 ± 11.23	38.7 ± 18.88	23.50	0.016*
Antibiotic use duration (days)	6.9 ± 3.31	12.66 ± 7.37	28.50	0.037*
Antibiotic cycles (n)	4.7 ± 1.49	5.92 ± 2.06	41.00	0.200
Care-related infections (n)	3.1 ± 1.66	2.75 ± 1.05	55.50	0.757
Comorbidities (n)	2.3 ± 1.64	1.9 ± 1.24	50.00	0.491

*Note: data presented as mean ± standard deviation; n = number; *indicates statistical difference when comparing groups.*
Source: the authors.

order to justify these results, the duration between the start of treatment and the outcome of death was also compared between groups in the hypothesis that there was a positive correlation in relation to the duration of antibiotic use with greater survival. However, the Mann-Whitney test did not observe a significant difference in this variable (U = 21.00; p = 0.147), possibly due to the variability of values and the reduced number of patients, since the mean number of days is descriptively longer in the PL group (AM = 8.5 ± 5.75 vs. PL = 15.2 ± 11.2 days).

Mortality was high in both groups. A complementary analysis to assess whether older age would be a predisposing factor for a worse outcome was performed. The Mann-Whitney test did not identify a difference in age (U = 28.00; p = 0.254) nor in the number of infections (U = 35.50; p = 0.567) among patients who were discharged or died.

When comparing the frequency of need for dialysis (Table 4), the chi-square test identified a significant difference between groups, such that patients in the PL group needed dialysis more than those in the AM group. When analyzing patients divided into 4 groups (Table 5 - SAM, AMR, PL and PLAM), SAM, AMR and PL groups were very similar in terms of the need for dialysis, however, when there was a combination of two drugs (PLAM), the frequency of dialysis was much higher, showing that using two nephrotoxic medications had a more significant impact on the dialysis outcome.

Another analysis was carried out with patients divided between the discharge and death groups, regardless of the medication used, to assess how much comorbidities influenced the outcomes. The comorbidities asses-

Table 4. Comparison of dialysis use between AM and PL groups.

	With dialysis	Without dialysis	X^2	p
AM (n = 10)	2 (20%)	8 (80%)	4.791	0.029*
PL (n = 12)	8 (67%)	4 (33%)		

Source: the authors.

Table 5. Comparison of dialysis use among SAM, AMR, PL and PLAM groups

	With dialysis	Without dialysis	X^2	p
SAM (n = 4)	0 (0%)	4 (100%)	10.068	0.018*
AMR (n = 6)	2 (33%)	4 (67%)		
PL (n = 4)	1 (25%)	3 (75%)		
PLAM (n = 8)	7 (88%)	1 (12%)		

Source: the authors.

sed were hypertension (HT), type 2 diabetes mellitus, coronary artery disease, heart failure and chronic obstructive pulmonary disease (COPD). The chi-square test found no difference in the frequency of occurrence of any comorbidity both when comparing drug groups and outcome groups (X^2 < 2.426; p > 0.119). As a complementary analysis, patients were classified into those who had 3 comorbidities or more and 2 comorbidities or less. The chi-square test was used to investigate whether those with more than 3 comorbidities had a higher frequency of death in the sample. The results showed that 100% of patients with more than 3 comorbidities (n = 7) died, compared to 67% of patients with 2 comorbidities or less (n = 10). Despite the descriptive difference, the test did not find a significant difference (X^2 = 3.020; p = 0.082).

The drug and outcome groups were also compared in relation to the reason for hospital admission. It was analyzed whether patients who were admitted to hospital due to COVID-19 died more often than due to other causes (all others grouped into a single category), but there was no statistical difference. Descriptively, 30% (n = 3) of patients in the AM group were admitted to hospital due to COVID-19, and in the PL group, 58% (n = 7).

In the AM group, 70% (n = 7) used the antibiotic for ventilator-associated pneumonia (VAP), and 30% (n = 3) for urinary tract infection (UTI). In the PL group, 84% (n = 10) used it for VAP, 1% (n = 1) for UTI, and only 1% for other causes (1 patient with osteomyelitis). No differences were found in comparisons between groups in any of these variables either.

Finally, one of the secondary objectives of this study was to assess the recovery duration from the infectious condition for each of the antibiotics used through PCR analysis, in addition to the progression of renal dysfunction with urea and creatinine data on D0, D3, D7, D10 and D14. However, this analysis was hampered due to the low sample number, and it was not possible to obtain reliable data due to the high death rate within the first 5 days of hospital admission.

DISCUSSION

The work's main objective was to assess the primary outcome – death or discharge – of patients. The tests showed no difference in the frequency of death and discharge in either of the two analyses. In other words, polymyxin B use did not protect patients from the final negative outcome – death, even when only AM was used in organisms resistant to these. This result is consistent with the two studies that used AM to replace polymyxin B without an increase in mortality.[9-13] Once again, it is highlighted that the replacement of polymyxin B with gentamicin or amikacin was not a strategic option for antimicrobial control, but rather a necessity due to the current restriction and shortage of polymyxin B. However, in terms of public health, considering costs and antimicrobial resistance, this result is consistent with the possibility of strategies to restrict broad-spectrum antibiotic use.

However, the results showed that, contradictorily, the group of patients who had an infection with AM-resistant bacteria (and were treated with this drug due to the scarcity of polymyxin B) had lower mortality (33%) than the group who had an infection with AM-sensitive bacteria.

This contradiction allows us to raise two hypotheses for the results obtained. The first would be that replacing polymyxin B with AM did not impact death. The second would be that patients treated during the pandemic had a high risk of death, and this would occur regardless of the class of antimicrobial used.

Although polymyxin B is a broad-spectrum antibiotic for gram-negatives, especially for *Acinetobacter spp*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae carbapenemase* (KPC),[15,20] its use was not superior to AM use, as it did not lead to fewer infections and did not reduce the need to use other antibiotic cycles or total hospital stay. In other words, once again, in terms of public health, antimicrobial resistance and global development, using AM instead of polymyxin B would be justified.

The results shown in table 3 showed that patients who used polymyxin B remained admitted to hospital in a critical environment longer than the group that used AM. The attempt to justify these results was a complementary analysis to assess whether these patients remained alive longer because they had used the antibiotic. However, no statistical difference was observed between these variables, i.e., the hypothesis raised did not justify the difference in days of hospital admission in a critical environment. However, it is worth noting that, possibly, different and more enlightening results would be obtained with a larger sample, since the average number of days is descriptively longer in the PL group (AM = 8.5 ± 5.75 vs. PL = 15.2 ± 11.2 days). It is worth noting that, even though they remained in a critical environment for longer and used antibiotics for longer, this did not influence the primary outcome (death or discharge).

The secondary outcome assessed was in relation to progression to dialysis. The first result obtained showed that patients in the PL group needed dialysis more than those in the AM group. Although both classes of drugs are known to be nephrotoxic,[15,20] it was expected that the group that used AM would have a worse renal outcome. The complementary analysis carried out to clarify the result obtained demonstrated that, in reality, when two drugs were used in the same patient (i.e., the sum of two nephrotoxic drugs), there was a greater progression to dialysis.

Regarding comorbidities, there was no statistical difference between groups, i.e., having HT, type 2 diabetes mellitus, coronary artery disease, heart failure or COPD alone. did not cause more patients to die, even when assessing whether having 3 or more comorbidities (e.g., the impact of the sum of diseases) also did not demonstrate a worse outcome. However, the results showed that 100% of patients with more than 3 comorbidities died, demonstrating the need for a larger sample group (with a possible result different from that obtained). It is assumed that this result would be different due to the fact that the impact of comorbidities on the death outcome has already been analyzed in previous studies, in which

it was seen that patients with comorbidities (mainly cardiovascular) had worse outcomes compared to patients without comorbidities.[21-23]

Regarding age or number of infections, there was no difference between groups. The reason that led to antibiotic use and hospital admission also did not impact the outcome.

Although, descriptively, more patients admitted to hospital due to COVID-19 died than due to other causes, there was no statistical difference in the tests performed. In other words, hospital admission for COVID-19 was not what impacted the death of patients.

The evolutionary comparison of PCR from treatment was hampered, as most patients died within the first 5 days after starting antibiotic therapy.

The study has restrictions, mainly due to the small sample size, which did not allow for a more meaningful analysis of the impact of some variables (such as age and comorbidities). The high number of patients who died within the first 5 days after identifying the infectious process was also a limiting factor (impairing the evolutionary comparison of laboratory tests, such as PCR, urea and creatinine). Despite the limitations, the study contributes to clinical practice by reinforcing the importance of carrying out more studies comparing broad-spectrum AMR use, helping the medical community when making decisions related to the prescription and rational use of these drugs. The study also helps professionals assess the results of drug substitution measures in scenarios of national shortages of these drugs.

CONCLUSION

The temporary shortage of polymyxin B led to its therapeutic replacement, with AM use. The results of this action showed that there are two viable hypotheses: that this replacement did not change the primary outcome (death); or regardless of the drug used, the outcome would be the same. No differences were observed between comorbidities and age between groups. Although both drugs are nephrotoxic, it was seen that the greatest need for dialysis occurred when there was concomitant use of the two classes of AMR. The study demonstrates the importance, in terms of public health, of using broad-spectrum AMR in a rational manner, aiming at the possibility of replacement by smaller-spectrum AMR. However, the work has limitations due to the low number of patients, and these data require further studies.

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AUTHORS' CONTRIBUTIONS:

Fernanda Piazza Fernandes contributed to data collection, analysis and interpretation manuscript writing. **Maria Claudia Hahn Ferrucio** contributed to research design and data interpretation and manuscript review.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.