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ORIGINAL ARTICLE

USE OF ANTIBIOTICS IN THE TREATMENT OF PATIENTS WITH BLOOD STREAM INFECTION

CONSUMO DE ANTIBIÓTICO NO TRATAMENTO DE PACIENTES COM INFECÇÃO DA CORRENTE SANGUÍNEA

EL USO DE ANTIBIÓTICOS EN EL TRATAMIENTO DE PACIENTES CON INFECCIÓN DEL TORRENTE SANGUÍNEO

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ABSTRACT

Objective: to determine the use of antimicrobials in the treatment of patients with bloodstream infection (BSI) by *Staphylococcus aureus* resistant and sensitive to oxacillin. **Method:** this is an epidemiological study of historical cohort. It was conducted at an intensive care unit of a large, private hospital in Belo Horizonte, MG, Brazil. The study sample was constituted by 62 patients with bloodstream infection by *Staphylococcus aureus*. Data were collected from medical files and records of the Commission for Hospital Infection Control. A descriptive and univariate analysis was carried out. The research project was approved by the Research Ethics Committee, ETIC No. 658/2011. **Results:** the most commonly used antibiotics for empiric treatment of the disease were: vancomycin (69.4 %), polymyxin (46.8 %), ertapenem (29.0 %), meropenem (24.2 %); whereas for the targeted treatment were: vancomycin (45.2%) and oxacillin (40.3%). **Conclusion:** broad-spectrum antimicrobials were largely used in the empirical treatment of BSI. Targeting of treatment after culture findings favored the reduction of the activity spectrum of antibiotics. **Descriptors:** Drug Resistance; Bacterial Infections; Antibacterial Agents; Therapeutic.

RESUMO

Objetivo: determinar o consumo de antimicrobianos no tratamento de pacientes com infecção da corrente sanguínea por *Staphylococcus aureus* resistentes e sensíveis à oxacilina. **Método:** estudo epidemiológico do tipo coorte histórica, realizado em uma unidade de terapia intensiva de um hospital privado de grande porte de Belo Horizonte/MG/Brasil, com 62 pacientes com infecção da corrente sanguínea por *Staphylococcus aureus*. Os dados foram coletados dos prontuários e registros da Comissão de Controle de Infecção Hospitalar. Realizou-se análise descritiva e univariada. O estudo teve a aprovação do projeto de pesquisa pelo Comitê de Ética em Pesquisa, ETIC n. 658/2011. **Resultados:** os antibióticos mais utilizados para o tratamento empírico foram: vancomicina (69,4%), polimixina (46,8%), ertapenem (29,0%), meropenem (24,2%); enquanto para o tratamento direcionado foram: vancomicina (45,2%) e oxacilina (40,3%). **Conclusão:** observou-se um uso de antimicrobianos de amplo espectro de ação no tratamento empírico. O direcionamento do tratamento favoreceu a redução do espectro de ação após o resultado das culturas. **Descritores:** Resistência a Medicamentos; Infecções Bacterianas; Agentes Antibacterianos; Terapêutica.

RESUMEN

Objetivo: determinar el uso de antimicrobianos en el tratamiento de pacientes con infección del torrente sanguíneo por *Staphylococcus aureus* resistente y sensible a oxacilina. **Método:** estudio epidemiológico de cohortes históricas realizado en una unidad de cuidados intensivos de un gran hospital privado ubicado en Belo Horizonte, MG, Brasil. La muestra del estudio estuvo compuesta por 62 pacientes con infección del torrente sanguíneo por *Staphylococcus aureus*. Los datos fueron obtenidos de las historias clínicas y registros de la Comisión de Control de Infección Hospitalaria. Se realizó un análisis descriptivo y univariante. El proyecto de investigación fue aprobado por el Comité de Ética en Investigación, ETIC n. 658/2011. **Resultados:** los antibióticos más utilizados para el tratamiento empírico de la enfermedad fueron: vancomicina (69,4%), polimixina (46,8%), ertapenem (29,0%), meropenem (24,2%); mientras que para el tratamiento dirigido se utilizaron: vancomicina (45,2%) y oxacilina (40,3 %). **Conclusión:** en el tratamiento empírico hubo un uso de antimicrobianos de amplio espectro de acción. El direccionamiento del tratamiento después de los resultados del cultivo favoreció la reducción del espectro de acción. **Descriptor:** Resistencia a Medicamentos; Infecciones Bacterianas; Agentes Antibacterianos; Terapéutica.

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INTRODUCTION

Healthcare-Associated Infections (HAIs) are infections that are acquired by patients as a result of healthcare interventions within a healthcare setting and at different levels of care: primary, secondary or tertiary.¹ They are considered a major worldwide public health problem, especially due to their high prevalence, morbidity, mortality, personal, professional and emotional damages, as well as increased healthcare costs.¹

In the United States it is estimated that more than two million cases of nosocomial infections occur annually, with records of about 90 thousand deaths and costs of over five million dollars.² In Brazil, there are no systematic data available on this topic. The Ministry of Health estimates that the overall infection rate is 14%, and 9% of patients diagnosed with infection evolve to death as a direct or indirect result of it.³

Among the microorganisms that cause HAIs, bacteria are responsible for approximately 95% of infections, and these may show resistance to one or more classes of antimicrobial agents.⁴

Intensive Care Units (ICU) are considered the epicenter of bacterial resistance, especially due to the fact that high-complexity care is provided to critically ill patients in these settings, with high use of invasive procedures, high severity of patients, greater demand for intensive care services, antibiotics, among others. Usually, in ICUs, one of the most frequent HAIs is bloodstream infection (BSI). They almost always have *Staphylococcus aureus* as a causative agent, both in developed and developing countries.⁵⁻⁶

Drug resistance has become an increasing challenge as therapeutic options for the treatment of certain infections caused by resistant microorganisms (RM) have become increasingly restricted and consequences of HAIs become more pronounced when associated with the occurrence of RM. Additionally, the finding that about 70% of the pathogens isolated in U.S. hospitals are resistant to at least one antibiotic (ATB) reaffirms the concern with this scenario, since in Brazil there is no systematic data on its distribution.¹

The indiscriminate use of antibiotics has been described as a predisposing factor for the occurrence of bacterial resistance since the 1950s. Yet even today there is an abusive use of antibiotics, with high rates of inappropriate prescriptions.⁷⁻⁸

Taking into account the reduction of the therapeutic arsenal for the treatment of HAIs and the various mechanisms of resistance evidenced in bacterial strains, it becomes relevant to determine the use of antimicrobials in the treatment of patients with bloodstream infection caused by *Staphylococcus aureus* resistant and sensitive to oxacillin (MRSA and MSSA, respectively).

OBJECTIVE

- To determine the use of antimicrobials in the treatment of patients with bloodstream infection by *Staphylococcus aureus* resistant and sensitive to oxacillin.

METHOD

This is an epidemiological study of historical cohort. It was conducted at an intensive care unit of a large, private hospital in Belo Horizonte, MG, Brazil.

The study population was constituted by all patients who were diagnosed with BSI by *Staphylococcus aureus* during the period from March 2007 to March 2011, according to the criteria established by the National Healthcare Safety Network (NHSN): Signs and symptoms + laboratorial tests. We also considered the confirmation of the causative microorganism of BSI and its resistance profile for patients who completed treatment during their hospitalization period. Patients who had bloodstream infections concomitantly caused by resistant and sensitive microorganisms were excluded. In order to preserve the assumption of independence of the observations, only the first properly treated bloodstream infection of each patient was included in the study. The group of patients infected with oxacillin-resistant *Staphylococcus aureus* was compared to the group of patients infected with oxacillin-sensitive *Staphylococcus aureus*.

Information on the occurrence of BSI and the number of antimicrobial doses dispensed in the treatment were collected from medical files and records of the Commission for Hospital Infection Control of the institution under study.

Data were analyzed in SPSS (19.0). We performed a descriptive analysis with presentation of the median values and interquartile range (25% percentile value - 75% percentile value) for continuous variables and absolute and percentage value for categorical variables. Subsequently, in order to identify differences between the variables related to the occurrence of infection by RM or SM, we conducted the chi-square or Fisher's exact test

in case of categorical variables; and the Mann-Whitney test in case of continuous variables.

The project was approved by the Ethics Committee of the Institution and the precepts of Resolution 196/96 have been followed in what concerns research with human beings (ETIC No. 658/2011).

RESULTS

Between March 2007 and March 2011, 78 patients were identified with a diagnosis of bloodstream infection associated with *Staphylococcus aureus* as causative agent. Among them, eight were excluded for presenting infections related to concomitantly

resistant and sensitive microorganisms and another eight were excluded from the sample because they evolved to death before finishing the treatment. The remaining 62 patients were divided into two groups: 31 were included in the group of patients with resistant microorganisms and 31 in patients were included in the group of patients with sensitive microorganisms.

Table 1 shows the clinical and epidemiological characteristics of patients, according to the resistance profile of the causative agent of bloodstream infection (*Staphylococcus aureus* susceptible or resistant to oxacillin).

Table 1. Clinical and epidemiological characteristics of patients according to the resistance profile of the causative agent of BSI (MRSA or MSSA). Belo Horizonte, 2011.

Variables	MRSA % (N= 31)	MSSA % (N =31)	p-value
Gender			
Female	48.4	38.7	0.442
Male	51.6	61.3	
Age (years)	76 (53-86)	72 (56-81)	0.540
Diagnosis at Admission			
Diseases of the circulatory system	35.5	35.5	1.000
Diseases of the respiratory system	29.0	25.8	0.776
Diseases of the digestive system	12.9	16.1	0.718
Infectious diseases	9.7	3.2	0.612
External causes	3.2	16.1	0.195
Other	25.8	9.7	0.096
Clinical severity			
APACHE II score	15 (12-24)	15 (11-28)	0.617
Patient type			
Clinical	71	71	1.000
Surgical	29	29	
Invasive procedures			
Mechanical ventilation	87.1	93.5	0.671
Central venous catheter	90.3	87.1	1.000
Indwelling catheter drainage	90.3	87.1	1.000
intra-arterial pressure catheter	90.3	83.9	0.707
Colonization by resistant microorganism	80.6	45.2	0.004
Enterococcus sp			
Staphylococcus aureus	3.2	3.2	1.000
Klebsiella pneumoniae	54.8	16.1	0.001
Acinetobacter baumannii	25.8	22.6	0.767
Pseudomonas aeruginosa	58.1	32.3	0.041
Enterobacter sp.	32.3	16.1	0.138
	38.7	6.5	0.002
Length of stay			
Hospital (days)	88 (33-116)	51 (21-94)	0.118
ICU (days)	33 (18-70)	35 (13-57)	0.307
Outcome			
Death	67.7	51.6	0.196
Hospital discharge	32.3	48.4	0.196

Among the risk factors for the occurrence of BSI by MRSA, we highlight the colonization by resistant microorganisms (p<0.05).

It is important to say that the studied institution has standardized procedures for the antimicrobial treatment of BSI . Due to the long period of stay of patients in the intensive care unit and the high rates of bacterial resistance reported in this unit, an empiric treatment is usually begun with broad-spectrum antimicrobials (vancomycin, polymyxin B and meropenem or ertapenem), and later adjusted when culture results are available (targeted treatment). Such adjustment is called "de-escalation", whose

main advantage is the possibility of decreasing the activity spectrum of the antimicrobial agent used. This helps reduce costs and reduces the risk of selection of multiresistant bacteria. Moreover, the re-adjustment of the antimicrobial treatment allows a review of the medical prescription and favors the adequacy of treatment according to indication, dose and duration .

We found that most patients used empiric antibiotic (77.4%): 67.7% in the group of patients infected with resistant microorganisms, and 87% in the group of patients infected with sensitive microorganism (p = 0.068). Patients who did not receive

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empirical treatment were probably diagnosed with infection only after culture results were available.

The most commonly prescribed antibiotics at this stage were: vancomycin (69.4%), polymyxin (46.8%), ertapenem (29.0%), meropenem (24.2%), cefepime (3.2%), and cefotaxime, zosyn, oxacillin and ampicillin (1.6% each). There was no significant difference between the analyzed groups for

any class of empirically prescribed antimicrobials ($p > 0.05$).

Figure 1 depicts the distribution of the classes of antibiotics most frequently prescribed before culture results were available, according to the sensitivity profile of the causative agent of BSI (MSSA or MRSA). There was no significant difference between the analyzed groups for any class of empirically prescribed antimicrobials ($p > 0.05$).

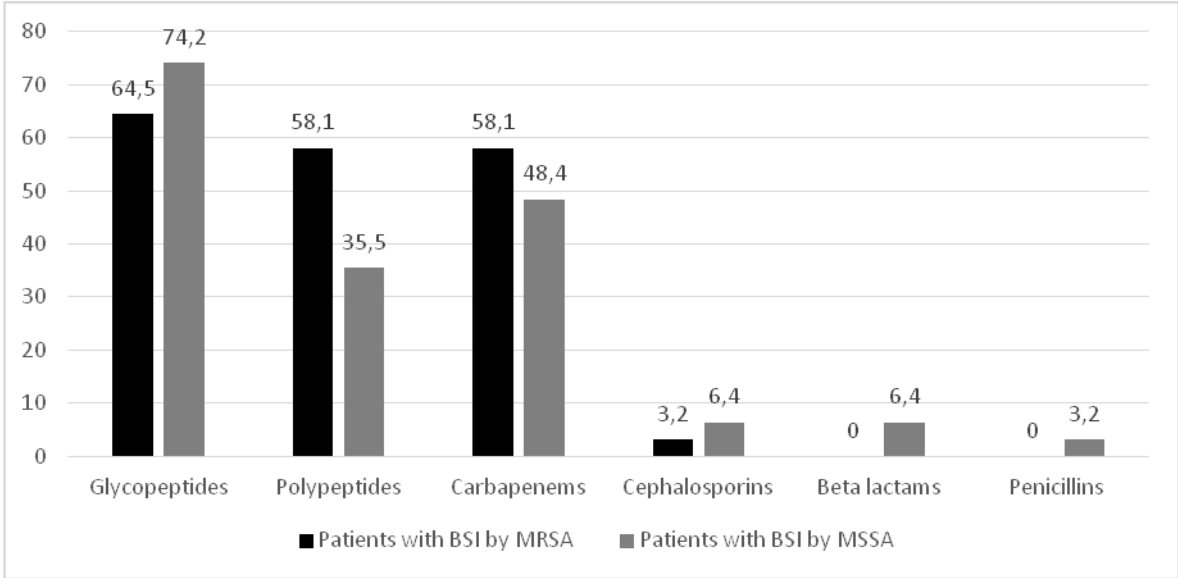


Figure 1. Distribution of the classes of antibiotics prescribed for empiric treatment according to the sensitivity profile of the causative agent of BSI (MSSA or MRSA). Belo Horizonte, 2011.

After culture results were available, 90.3 % of patients received targeted therapy: 93.5% of patients infected with MRSA and 87.1 % of those infected with MSSA ($p = 0.671$). Failure to adjust antimicrobial treatment probably occurred due to the delay in receiving the results of the culture from the laboratory, since the empiric treatment was already finishing in some cases or the patient did no longer presented symptoms of infection.

The most frequently prescribed antibiotics during the targeted treatment for both groups were: vancomycin (45.2%) and oxacillin (40.3%), followed by ampicillin (3.2%), and linezolid, teicoplanin, cefotaxime and ciprofloxacin (1.6% each). The group of patients infected with oxacillin-resistant *Staphylococcus aureus* used significantly more vancomycin, when compared with the group of patients infected with oxacillin-sensitive

Staphylococcus aureus ($p = 0.000$). By contrast, this group (MSSA) used more oxacillin after culture results were available than the first group (MRSA), which was already expected ($p = 0.000$).

Table 2 shows the percentage distribution of patients who received antimicrobials after culture results were available, according to the chemical classification of the ATB and the sensitivity profile of the causative agent of BSI (MRSA or MSSA).

According to Table 2 (as expected), the group of patients infected with oxacillin-resistant *Staphylococcus aureus* used significantly more vancomycin, when compared with the group of patients infected with oxacillin-sensitive *Staphylococcus aureus*. In contrast, the latter (MSSA) used more oxacillin after culture results were available than the first group (MRSA).

Table 2. Distribution of patients who received antimicrobials after culture results were available, according to the chemical classification and the sensitivity profile of the causative agent of BSI (MRSA or MSSA). Belo Horizonte, 2011.

Classes of antibiotics	MRSA % (N=31)	MSSA % (N=31)	p-value
Glycopeptides			
Vancomycin	83.9	6.5	0.000
Teicoplanin	3.2	0.0	1.000
Oxazolidinone			
Linezolid	3.2	0.0	1.000
Penicillin			
Oxacillin	0	80.6	0.000
Ampicillin	3.2	3.2	1.000
Others			
Cefotaxime	0	3.2	1.000
Ciprofloxacin	3.2	0	1.000

DISCUSSION

With regard to the antimicrobial treatment, we emphasize that the use of ATBs with broad activity spectrum in empirical therapy is associated with lower rates of mortality among critically ill patients.⁹⁻¹⁰ For this reason, the guidelines for treatment of BSI recommend that patients who have risk factors for infections by resistant microorganisms should receive empirical therapy with at least two broad-spectrum antimicrobials.^{9,11-13}

Thus, the choice of empirical treatment should be based on the time of onset of infection, previous use of antibiotics, prolonged use of invasive procedures, advanced patient age (over 65 years), previous hospitalizations, presence of colonizations and, particularly, knowledge of the prevalence of the most frequent microbial agents in the institution.¹²⁻¹⁴

Although the quality of prescriptions has not been assessed in this study, studies show a low rate of appropriate empirical therapy prescription, ranging from 26 to 51.8 %.¹⁴ Thus, we stress the importance of performing the ATB adjustment according to the culture results as soon as possible, in order to reduce the emergence of bacterial resistance and consequently reduce costs in the antimicrobial treatment of patients.¹⁴

At the ICU of the studied hospital no difference was found in the use of broad-spectrum antibiotics in the empirical treatment of patients with SM or RM due to the similarities in their risk profiles. However, we highlight that other strategies were employed to ensure the rational use of antimicrobials. Among them, we can cite: the antimicrobial de-escalation, i.e., the adjustment to the most suitable antibiotic as soon as culture results are available; the audit of antimicrobials; and the restriction of some drugs, which are just authorized for use after the medical auditors from the Commission for

Hospital Infection Control give their permission. These measures are reported in the literature as essential to contain bacterial resistance, in what concerns the proper management of antimicrobials.^{10,15}

The choice of ATB to be used after microbiological confirmation should be performed by evaluating five basic principles: efficacy, safety, ease of administration, cost of the selected ATB and especially the narrowest possible activity spectrum. Thus, we emphasize the fundamental importance of the antimicrobial de-escalation for the containment of antimicrobial resistance.¹⁶

Regarding the most used ATB, both in the empiric and in the targeted treatment of patients with bloodstream infection (ertapenem, meropenem, oxacillin, polymyxin B, and vancomycin), the literature reports that vancomycin and oxacillin are the antimicrobial agents that are commonly used when the infections agents are gram-positive bacteria such as *Staphylococcus aureus*.^{4, 17-18}

Oxacillin or methicillin is a narrow-spectrum antimicrobial that belongs to the group of semi-synthetic beta-lactamase and staphylococcus penicillinase resistant penicillins. It is indicated for the treatment of infections in various sites that are mainly caused by gram-positive aerobic organisms such as *Staphylococcus aureus*.⁴ However, the resistance of such a microorganism to this drug is known, and its use is restricted to empiric therapy. It should only be used after culture results are available, when pathogens sensitive to this agent are known.¹¹

Thus, the use of vancomycin for empiric treatment in the institution studied is explained by the high prevalence of oxacillin-resistant *Staphylococcus aureus*. Vancomycin is a glycopeptide that acts by inhibiting cell wall synthesis and shows antibacterial activity mainly on gram-positive bacteria. This supports its widespread use for the treatment of such microorganisms.^{4,19} However, it causes

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significant nephrotoxicity, especially in patients treated with doses exceeding 4g/day for over ten days. Thus, plasma levels of vancomycin should be monitored and it should be administered using a regimen of continuous infusion, rather than multiple doses.¹¹⁻¹²

Nevertheless, there are reports about the emergence of strains of *Staphylococcus aureus* with intermediate resistance to vancomycin.^{18,20} Thus, the use of such ATB for the treatment of *Staphylococcus aureus* infections needs to be weighed carefully and the physician should be aware of the need for new treatment options. This justifies the conduction of recent studies, which are testing other drugs as an alternative to vancomycin. Among these drugs, we highlight linezolid, a newly developed (2001) antimicrobial agent that belongs to the class of oxazolidinones. It has bacteriostatic action against gram-positive organisms such as *Staphylococcus aureus* and *Enterococcus* spp.²¹⁻²²

Studies comparing the effectiveness of linezolid with that of vancomycin have shown that, although the former is more expensive, the additional cost can be considered neutral due to the benefits achieved with the use of such antibiotics, such as: availability in oral form; very few reports of resistant strains in the literature up to now; and reduced adverse effects (the most common being thrombocytopenia, which is reversed by the discontinuation in the use of this agent). These features result in greater safety for the patient.²¹⁻²³

Another therapeutic option for the treatment of bloodstream infections by oxacillin-resistant *Staphylococcus aureus* is teicoplanin, a glycopeptide belonging to the group lipoglycopeptide antibiotics. It has bactericidal activity against gram-positive bacteria and is mainly used in cases of resistance to penicillins or cephalosporins or in case of allergy to beta-lactam agents.² Moreover, the use of daptomycin, a lipopeptide that is active against gram-negative bacteria, should be considered for patients with low response to conventional treatment, persistent infection, worsening of renal function or infections associated with VISA.²⁴

Regarding polymyxin B, we stress that this drug is a polypeptide that has broad activity against gram-negative organisms, especially *Pseudomonas aeruginosa*. Despite showing high rates of nephrotoxicity and neurotoxicity, the use of polymyxin in the treatment of ARF (mainly caused by *Pseudomonas aeruginosa*)

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has been growing due to the increase in imipenem-resistant strains of this organism.^{4,25}

Ertapenem (as well as meropenem) is an antibacterial agent of the carbapenem class which has bactericidal activity against gram-positive and -negative bacteria, as well as bacteria resistant to 3rd and 4th generation cephalosporins. It has a more limited spectrum of activity than other classical carbapenems, since it does not exhibit good activity against *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus* and *Enterococcus* spp. Its use has been reconsidered due to the resistance of *Pseudomonas aeruginosa* strains and other prominent gram-negative bacteria.^{4, 21}

The use of polymyxin B, meropenem and ertapenem as antimicrobial for empiric treatment in the institution studied is justified by the high prevalence of multidrug-resistant gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

In this study, bacterial resistance was related to a greater use of glycopeptides, particularly vancomycin, since this is still the first drug of choice for the treatment of oxacillin-resistant *Staphylococcus aureus* in institutions where there is no record of strains with intermediate resistant to this antimicrobial.¹⁸

CONCLUSION

In the present study, we observed how the colonization by resistant microorganisms acted as an important risk factor for the occurrence of infections by resistant microorganisms. The most commonly used antibiotics for empiric treatment of patients were broad-spectrum ATB, such as vancomycin, polymyxin, ertapenem and meropenem. This was justified due to the microbiological profile of the institution and the severity of patients. In the targeted treatment for patients with MRSA, vancomycin was the drug of first choice, whereas for patients with MSSA oxacillin was the most used drug.

The use of broad-spectrum antimicrobials is recommended due to the need of initiating an appropriate treatment as soon as possible. However, with the reduction of the therapeutic arsenal, strategies for a rational use of antibiotics should be considered (such as targeting of treatment).

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