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Use of antimicrobials in the treatment of febrile neutropenia in pediatric patients in a teaching hospital

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Abstract

Objectives: to assess the use of antimicrobials for the treatment of febrile neutropenia in pediatric patients **Methods:** a cross-sectional, retrospective and observational study carried out in the pediatric units of a large teaching hospital with high and medium complexity. All patients aged between 28 days and 17 years old, 11 months and 29 days old, who had febrile neutropenia and started a venous antimicrobials, were included in the study. Data were collected using available systems and compared with the sectoral clinical protocol. **Results:** 40 patients were included in the study, most of them male and with a median age of 8 years old. There were 70 episodes of neutropenia, and 57% were in disagreement with the protocol. The most common errors were the use of antimicrobials for longer than necessary, followed by de-escalation not performed after the culture result was available and antimicrobial incorrectly replaced. Considering the antimicrobials, the most prevalent was cefepime, and considering the antifungals, it was micafungin. Prescribed doses were in accordance with protocol, except for eight polymyxin loading dose prescriptions and one teicoplanin loading dose. Blood cultures were positive in 25.7% of cases and the most common microorganisms were *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus* and *Staphylococcus hominis.* **Conclusion:** there were high rates of non-compliance in the use of antimicrobials for the treatment of febrile neutropenia with the sectoral clinical protocol, despite the fact that most prescriptions follow what is recommended when it comes to treatment initiation. It is essential to adapt the prescriptions to the institutional protocol so that the patient receives an effective and safe treatment, avoiding the occurrence of bacterial resistance due to the inappropriate use of medicines.

Keywords: anti-infective agents; febrile neutropenia; pediatrics; clinical protocol

Uso de antimicrobianos no tratamento da neutropenia febril em pacientes pediátricos em um hospital de ensino

Resumo

Objetivos: avaliar a utilização de antimicrobianos para o tratamento de neutropenia febril em pacientes pediátricos. **Métodos:** estudo transversal, retrospectivo e observacional, realizado nas unidades de pediatria de um hospital de ensino, de grande porte, com atenção de média e alta complexidade. Foram incluídos no estudo todos os pacientes com idade entre 28 dias e 17 anos, 11 meses e 29 dias, que apresentaram neutropenia febril e iniciaram algum antimicrobiano venoso no período de janeiro de 2022 a junho de 2022. Os dados foram coletados através dos sistemas disponíveis e foram comparados com o protocolo clínico setorial. **Resultados:** foram incluídos no estudo 40 pacientes, sendo a maioria do sexo masculino e com mediana de idade de 8 anos. Foram encontrados 70 episódios de neutropenia, sendo que 57% estavam em desacordo com o protocolo. As inadequações mais comuns foram o uso de antimicrobianos por tempo superior ao necessário, seguido de descalonamento não realizado após resultado de cultura disponível e antimicrobiano substituído de forma incorreta. Dos antimicrobianos usados, o mais prevalente foi o cefepime, e dos antifúngicos, foi a micafungina. As doses prescritas estavam de acordo com o protocolo, exceto em oito prescrições de dose de ataque de polimixina e uma de teicoplanina. As hemoculturas foram positivas em 25,7% dos casos e os microorganismos mais encontrados foram *Escherichia coli*, *Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus epidermidis*, *Staphylococcus haemolyticus* e *Staphylococcus hominis.* **Conclusão:** foram verificadas altas taxas de não conformidade no uso de antimicrobianos para tratamento da neutropenia febril com o protocolo clínico setorial, apesar de a maioria das prescrições seguir o recomendado quando se tratava do início de tratamento. É imprescindível a adequação das prescrições ao protocolo institucional para que o paciente receba um tratamento eficaz e seguro, evitando a ocorrência de resistência bacteriana pelo uso inadequado dos medicamentos.

Palavras-chave: anti-infecciosos; neutropenia febril; pediatria; protocolo clínico

Introduction

Neutropenia is defined as an absolute neutrophil count lower than 1,500 cells/µL or with a tendency to drop to this value over the next few hours. When neutrophils are below 100 cells/mm³, it is described as profound neutropenia[1–3]. The main causes of neutropenia are congenital syndromes (such as Kostmann's and Shwachman-Diamond's syndromes), some specific medications (such as phenothiazines, antithyroid drugs, chloramphenicol and antineoplastic chemotherapy), nutritional deficiency and viral diseases[4].

Although neutropenia has several causes, the most common is the one induced by chemotherapy due to treatment aggressiveness and immune system impairment. Among patients undergoing chemotherapy, more than 80% will experience at least one fever spike during the neutropenia period. Of these, it is estimated that from 5% to 10% will evolve to death, even with broad-spectrum antibiotic therapy[5].

Fever may be the only sign of infection in neutropenic patients, as neutropenia limits the body's natural immune response to inflammation and obscures traditional signs and symptoms. Febrile neutropenia is considered a medical emergency, and hospitalization associated with immediate initiation of broad-spectrum intravenous antimicrobials (ATMs) is the most adopted approach[8,9].

The main ATMs recommended by the guidelines are those with a broad spectrum that also have activity against *Pseudomonas*, as this microorganism is frequently found in hospital environments and commonly infects immunocompromised patients. The most cited ones are cefepime, piperacillin + tazobactam, meropenem and ceftazidime[3,10,11].

In pediatric patients, fever during neutropenia periods is even more problematic, as this population group is more vulnerable to diseases and their consequences, and appropriate treatment is extremely important. ATM use in children should be done with caution due to the limited availability of data on pharmacokinetics, pharmacodynamics, efficacy and safety. The main challenge is to avoid unnecessary antimicrobial treatments but, at the same time, without restricting treatments to neutropenic patients, closely monitoring ATM use since, in this population group, the adverse effect of their inappropriate use is more severe[11,12].

Given the above, it is of utmost important to follow clinical guidelines or protocols designed to guide prescriptions and monitor ATM use in children to obtain better outcomes and reduce bacterial resistance. In this context, pharmacists play a fundamental role in detecting real or potential drug-related problems, solving those already detected and preventing new ones. An ATM use management policy can optimize their use and reduce microbial resistance[13,14].

The objective of this paper was to describe ATM use in the febrile neutropenia treatment in pediatric patients and to compare it with the hospital sectors' clinical protocol and the results of bacterial cultures, when available.

Methods

Study design and locus

This is an observational and cross-sectional study with retrospective data collection from pediatric units (emergency room, wards and pediatric intensive care center) from a large-size teaching hospital that provides high- and medium-complexity care located in Belo Horizonte/Minas Gerais.

Population

The study included all patients aged between 28 days and 17 years, 11 months and 29 days old, who presented febrile neutropenia and had initiated some venous ATM during the hospitalization time. Patients in this age group who were classified as with functional neutropenia by the medical team were also included.

Those who did not complete the treatment proposed were excluded, as well as those that were transferred to a sector considered ineligible for this paper or transferred from another institution.

Definitions

Neutropenia was defined as an absolute neutrophil count below 500 cells/mm³ or less than 1,000 cells/mm³ and expected to drop in the subsequent 48 hours and, as fever, axillary temperature greater than or equal to 38ºC or greater than or equal to 37.8ºC sustained for more than 1 hour[1,6,7]. This was the same definition presented in the sectors' clinical protocol.

The patient classified as with functional neutropenic had alterations in circulating neutrophils that, despite a normal cell count, presented a qualitative defect, which resulted in deficient phagocytosis as a result of the underlying hematological disease[1,2].

Data collection

The collection of sociodemographic, clinical, laboratory and pharmacotherapeutic data was carried out from January 1st, 2022 to June 30th, 2022. The patient's electronic prescription, electronic medical record and laboratory test results from the hospital under study were used as data sources.

All venous ATMs standardized in the hospital were used in the search, namely: amikacin, amoxicillin + clavulanate, ampicillin, amphotericin B (lipid, deoxycholate and liposomal complex), anidulafungin, azithromycin, cefepime, ceftriaxone, ciprofloxacin, clarithromycin, clindamycin, ertapenem, fluconazole, gentamicin, imipenem, levofloxacin, linezolid, meropenem, metronizadol, micafungin, oxacillin, piperacillin + tazobactam, polymyxin B, teicoplanin, tigecycline, vancomycin and voriconazole.

Initially, a search was made for patients who used ATMs during the period mentioned in the electronic prescription system. Subsequently, it was verified whether any of these patients were neutropenic (through laboratory tests) or functional neutropenic (by the medical team), and whether they had at least one fever spike or any indication of infection (as documented in the evolution of the electronic medical record).

Sectors' clinical protocol

The guideline of the institution under study was used, called PR 037 Protocol for the Management of Febrile Neutropenic Patients – Pediatrics, 3rd version, updated in November 2020. The protocol presented guidelines on the patient's clinical evaluation, tests that should be requested and treatment proposed. The focus of this paper was solely on the febrile neutropenia treatment.

After fever and neutropenia were detected in laboratory tests, the protocol proposed using cefepime as monotherapy or piperacillin-tazobactam as an alternative. For those patients known to be colonized with resistant gram-negative rods, meropenem use was

recommended as first choice. If the patient met the criteria in Table 1, vancomycin or teicoplanin should be associated (in cases of allergy to vancomycin or renal dysfunction).

Table 1 . Criteria to associate vancomycin to the initial therapeutic regime.

Hemodynamic instability
Suspected infection associated with central vascular catheter
Positive culture for unidentified gram-positive bacteria
Patients colonized by penicillin-resistant *pneumococci* or methicillin-resistant *Staphylococcus aureus* (MRSA)
Presence of skin lesions
In cases of severe pneumonia and hospital-acquired pneumonia

Source: PR 037 Protocol for the Management of Febrile Neutropenic Patients – Pediatrics, 3rd version, updated in November 2020

If there was clinical deterioration, in addition to using vancomycin, there would be additional treatment to cover gram-negatives, exchanging cefepime (or piperacillin + tazobactam) for meropenem (in cases where the patient was not colonized), combining polymyxin B or aminoglycosides (gentamicin or amikacin) in case of hemodynamic instability.

If fever persisted (maintained for 5 to 7 days after starting the antibiotic therapy) in patients at high risk for invasive fungal infection and persistent neutropenia, empirical antifungal therapy with micafungin or amphotericin B lipid complex would have to be initiated. In proven or probable *Aspergillus* infection, voriconazole or amphotericin B lipid complex would be used (for patients under 2 years of age).

In relation to treatment time, the protocol recommended suspending the empirical antibiotic therapy for patients with negative blood cultures within 48 hours, as long as they were afebrile for at least 24 hours and had evidence of bone marrow recovery (neutrophils > 500). For those cases in which there is no bone marrow recovery, two groups are assembled: low risk and high risk (Table 2). For low-risk patients, ATMs should be suspended after 72 hours if the blood culture is negative and there is no fever in the last 24 hours, with careful monitoring. For those at high risk, ATM suspension was still a controversial point, but it was recommended to discuss it for patients who had been afebrile for 5 – 7 days, as long as they had a good clinical evolution and no complications.

If there were clear signs of infection in the neutropenic patients, even in the absence of fever, the same measures described above should be taken, starting with empirical antibiotic therapy after collecting samples for blood culture, preferably within one hour of noticing the signs or fever spike. However, waiting for the test results to be collected should not delay treatment initiation. If immediate collection was not possible, the antibiotic therapy would be started even without collection.

Table 2. Patient risk classification parameters.

Low risk	High risk
Patients with solid tumors	Leukemia or non-Hodgkin's lymphoma and patients in the first 30 days after hemato-poietic cell transplantation
Patients with neutropenia lasting less than 7 days	Neutrophil count below 100 cells/mm³ or neutropenia lasting more than 7 days
Malignant neoplasm in remission	Extensive cellulitis, bacteremia, pneumo-nia or other severe infections
Patients hospitalized during fever risk	Acute organ dysfunction or systemic inflammatory response syndrome
Absence of comorbidities	Liver or kidney failure
Clinical stability	Hemodynamic instability

Source: PR 037 Protocol for the Management of Febrile Neutropenic Patients – Pediatrics, 3rd version, updated in November 2020

Immediately upon microorganism identification, it is imperative to tailor the treatment based on the culture and antibiogram findings, always prioritizing the ATM with lowest spectrum, reduced toxicity and that adequately penetrates the infection site once identified.

Modification of the initial empirical therapy (in the absence of microbiological growth) should not be solely based on fever persistence if the patient is clinically stable, as other fever causes should be considered. In addition to that, for children who were responding to the initial therapy, double coverage (vancomycin, polymyxin and/or aminoglycosides) should be discontinued within 24 to 72 hours, if they had been initiated and there was no microbiological growth to justify their use.

If there was no improvement or clinical worsening, extensive propaedeutics and assessment of expanding coverage for specific agents should be carried out. In case of growth of carbapenem-resistant gram-negative rods, it was suggested to change the ATM to polymyxin B, tigecycline or aminoglycosides. For vancomycin-resistant *Enterococcus*, linezolid or daptomycin should be prescribed.

Data analysis

The ATMs used in each case were compared to those recommended in the sectors' febrile neutropenia clinical protocol, checking whether the medical team followed the protocol guidelines or whether there was any different clinical practice.

A descriptive analysis of the results was performed using Microsoft Office Professional Plus 2019.

Ethical considerations

This paper is part of the research project entitled "Safety in the medication use process with a focus on Clinical Pharmacy in the hospital context", approved by the Research Ethics Committee of the Federal University of Minas Gerais (*Comitê de Ética em Pesquisa-Universidade Federal de Minas Gerais*, COEP-MG) under number 80169717.4.0000.5149.

Results

A total of 40 patients were included in the study, totaling 77 neutropenia episodes treated. During data verification, seven episodes were excluded considering the exclusion criteria, leaving 70 episodes for analysis.

The mean number of neutropenia episodes per patient was 1.75. The most common diagnosis was leukemia and the median age was 8 years old, with majority of male patients. The sociodemographic characteristics of the patients can be seen in Table 3.

Table 3. Sociodemographic characteristics of the patients from a teaching hospital located in Belo Horizonte/MG, included in the study from January 2022 to June 2022.

Characteristics		Patients (n)	Percentage (%)
Gender	Female	15	37.5
	Male	25	62.5
Age	28 days to < 2 years old	6	15
	2 to < 6 years old	11	27.5
	6 to < 12 years old	11	27.5
	12 to < 18 years old	12	30
Underlying disease	Leukemias and lymphomas	24	60
	Solid tumors	8	20
	No neoplasms	8	20

It was verified that, of the 70 neutropenia episodes analyzed, 30 (43%) followed the protocol correctly, whereas 40 (57%) showed behaviors deviating from the treatment proposed.

Among those treatments considered incorrect, the most common non-compliance was ATM use for longer than necessary, followed by de-escalation not carried out after the culture results were available, and incorrectly substituted ATM (Table 4).

Table 4. Non-conformities observed in the prescription of neutropenia treatment for patients from a teaching hospital located in Belo Horizonte/MG, included in the study from January 2022 to June 2022.

Error	Total	Percentage
Using an ATM for longer than necessary	11	27.5%
De-escalation not performed after culture available	8	20.0%
ATM exchanged incorrectly	7	17.5%
Meropenem prescribed as first choice in non-colonized patient	4	10%
Meropenem not prescribed for colonized patient	2	5%
Associated ATM without patient presenting criteria	2	5%
Absence of antifungical in a patient with criteria to associate it	1	2.5%
Need to add ATM	1	2.5%
Started antifungal medication not in accordance with recomendations	1	2.5%
Use of ATM not mentioned in protocol	1	2.5%
ATM- resistant microorganism used	1	2.5%
ATM suspended ahead of schedule	1	2.5%

In relation to the ATMs used, the most common was cefepime (45%), followed by meropenem (23%) and vancomycin (18%). Of the antifungals, the most used was micafungin (54%), followed by fluconazole (27%), voriconazole (14%) and amphotericin B lipid complex (5%).

Cefepime was the first-choice drug in 85.7% of the cases, meropenem in 8.6%, piperacillin + tazobactam in 4.3%, and amoxicillin + clavulanate in 1.4%. Vancomycin was already associated with the regime at treatment initiation in 10% of them. In relation to the antifungals, the most common first choice was micafungin (57.1%), followed by fluconazole (35.7%) and voriconazole (7.2%).

The doses prescribed were in accordance with the protocol, except for eight prescriptions for polymyxin, in which the loading doses were not administered as determined by the protocol, as well as one prescription for teicoplanin, which remained at the loading dose even when the maintenance dose indicated in the protocol should have already been prescribed.

Although tests were collected in all cases, only 20 positive blood cultures were identified, two of which were considered contaminated. The remaining 18 blood cultures characterized 25.7% of the total neutropenias.

A total of 22 microorganisms were isolated: 12 gram-negatives and 10 gram-positives. Among the gram-negatives, the most common were *Escherichia coli*, *Pseudomonas aeruginosa* and *Serratia marcescens*. Among the gram-positives, the most common were *Staphylococcus epidermidis*, *Staphylococcus haemolyticus* and *Staphylococcus hominis*, each of which was isolated twice. Their sensitivity profile can be seen in Table 5.

In addition to these bacteria, *Pseudomonas putida* sensitive only to polymyxin B and *Klebsiella pneumoniae* sensitive only to ceftazidime + avibactam were found, both gram-negative.

Table 5. Sensitivity and resistance profile of the main bacteria isolated from patients at a teaching hospital located in Belo Horizonte/MG, included in the study from January 2022 to June 2022.

Bacteria	Sensitivity	Resistance
Escherichia coli	Cefepime, ceftazidime, ceftriaxone, ertapenem, meropenem and piperacilin + tazobactam	Amoxicilin + clavulanate, ciprofloxacin, gentamicin and sulfamethoxazol + trimethoprim
Escherichia coli	Ceftazidime + avibactam	Resistent to remainder
Pseudomonas aeruginosa	Meropenem	Intermediate to aztreonan, cefepime, ceftazidime, ciprofloxacin, imipenem and piperacilin + tazobactam
Pseudomonas aeruginosa	Meropenem	Intermediate to aztreonan, cefepime, ceftazidime, ciprofloxacin, imipenem and piperacilin + tazobactam
Serratia marcescens	Ceftazidime, ceftriaxone, ciprofloxacin, ertapenem e meropenem	Amoxicilin + clavulanate e sulfamethoxazol + trimethoprim
Serratia marcescens	Cefepime, ceftazidime + avibactam, ceftriaxone, ciprofloxacin, ertapenem, gentamicin, meropenem and piperacilin + tazobactam	Amoxicilin + clavulanate
Staphylococcus epidermidis	Clindamycin, rifampin and vancomycin	Oxacilin and sulfamethoxazol + trimethoprim
Staphylococcus epidermidis	Rifampin and vancomycin	Clindamycin, gentamicin, levofloxacin and oxacilin
Staphylococcus haemolyticus	Vancomycin	Clindamycin, gentamicin, levofloxacin, oxacilin, rifampin and sulfamethoxazol + trimethoprim
Staphylococcus haemolyticus	Rifampin e vancomycin	Clindamycin, gentamicin levofloxacin, oxacilin, rifampin and sulfamethoxazol + trimethoprim
Staphylococcus hominis	Clindamycin, oxacilin, rifampin and sulfamethoxazol + trimethoprim	Intermediate to levofloxacin
Staphylococcus hominis	Rifampin, vancomycin and sulfamethoxazol + trimethoprima	Clindamycin and oxacilin

Discussion

Febrile neutropenia is associated with increased hospitalization times, costs and mortality. Although infections are only diagnosed in 20% to 30% of the patients, a number of studies show a 75% mortality rate before ATM initiation. This high morbidity and mortality risks require immediate administration of broad-spectrum ATMs as soon as fever is detected[15]. In this study, most of the initial prescriptions for the febrile neutropenia treatment were in line with the sectors' protocol, with 77.1% being prescriptions for monotherapy with cefepime. Only in 8.6% of the episodes was combined therapy with cefepime and vancomycin prescribed and, in these cases, skin (5.7%) or catheter (2.9%) infection was suspected. These results were similar to those found by Reinecke *et al.*, with cefepime monotherapy in 80% and combined therapy with cefepime and vancomycin or aminoglycosides in 8%[16]. In our study, there was no combination of cefepime with aminoglycosides in dual therapy.

In relation to treatment adequacy, the most frequent divergence found was ATM use for longer than necessary. Inappropriate ATM use can lead to a number of problems, including bacterial resistance, increased incidence of adverse reactions and hospital costs[17]. The failure related to discontinuing the drug early in time occurred only once, confirming this tendency to prolong treatments unnecessarily. Some factors that might explain this trend would be neutropenia severity, fear of complications from the infection and the fact that these are pediatric patients, a group that is more susceptible to infections due to immaturity of their immune system. All of these factors contribute to inappropriate medication use[12,18]. It is important to reduce the ATM use time, as longer treatments can pose a greater risk to patient safety[19].

In 20% of the cases, de-escalation was not performed after the culture results were available, which led to misuse of broad-spectrum drugs. Culture-guided ATM de-escalation reduces the bacterial resistance rate, hospitalization time and cost, and mortality[20]. A similar error occurred when the ATM was incorrectly substituted, only considering fever persistence as replacement criterion, where in stable patients with good clinical evolution, fever should not be the only factor for substitution, as Neutropenic patients can have other fever causes. The initial regime was changed in 34.3% of the cases. In a similar study, Reinecke *et al.* found an initial regime modification rate of 18%. According to the preliminary results, the main reasons were classification of the pathogen and discovery of an abdominal focus[16]. This difference in the results found in relation to pharmacotherapy change can be explained by the high non-compliance rate in relation to ATM substitution (17.5%).

Meropenem was prescribed as first choice in patients not colonized by multidrug-resistant gram-negative bacteria in 10% of the cases. Excessive meropenem use leads to increased resistant bacteria prevalence, such as carbapenem-resistant *Enterobacteriaceae*. Some studies show that agents with coverage against *Pseudomonas aeruginosa* are effective for the treatment of infections in febrile neutropenia, and that piperacillin + tazobactam do not present higher therapeutic failure rates, providing efficacy, safety and lower risk of adverse effects when compared to meropenem[21,22].

Another divergence found was ATM association without due identification of the criteria and, in all cases, vancomycin was associated after treatment initiation with other medications. The infection and colonization rates with vancomycin-resistant *Enterococcus* have been increasing in the last decade, leading to an increase in hospitalization times and costs and in mortality. Karandikar *et al.* showed that a guideline with empirical risk stratification reduces exposure to vancomycin and decreases the incidence of infection and colonization by vancomycin-resistant *Enterococcus*[15]. The sectors' clinical protocol of the institution where this paper was carried out presented a similar stratification, with indication of criteria for the drug to be initiated properly.

Contrary to what was reported above, a case was observed in which there was a need to include vancomycin in the therapeutic regime, which was not prescribed, with the possibility of leading to harms in the treatment since, in the presence of gram-positive bacteria suspicion, the initial pharmacotherapy should be complemented. However, the initially prescribed ATM was not effective in combating the microorganism, leading to non-control of the infection and to development of bacterial resistance[8].

The primary treatment for a patient was amoxicillin + clavulanate, which was not mentioned in the institution's protocol nor recommended by the main guidelines for neutropenia, as it did not have coverage against *Pseudomonas*[3,5,10,11]. In this study, 37.5% of the bacteria were resistant to amoxicillin + clavulanate, and 33.3% of them were resistant to this drug alone.

Use of a specific ATM was observed in a child, even after the culture results were available, indicating that the microorganism causing the infection was resistant to the drug initially prescribed. Microbial resistance is related to treatment failures and recurrent infections, causing an increase in the morbidity and mortality rates when the ATM used is not effective in combating the bacteria[23].

In relation to the antifungals, one patient met the criteria for initiating them and did not receive the medication. In another case, an antifungal was started not in accordance with the recommendations. As stated in the protocol and in previous studies, the antifungal should be initiated in high-risk patients who present persistent febrile neutropenia, after 96 hours of fever without response to the broad-spectrum ATMs used. Echinocandins are recommended as first line, with reduced risk of mortality and adverse effects, with caspofungin as the most indicated for pediatric patients[24]. The protocol advised micafungin use, as caspofungin was not standardized in the institution.

In relation to the doses, the only disagreement found was in relation to the loading dose. For polymyxin B, a loading dose is necessary so that the plasma concentrations are reached faster and for it to exert its therapeutic effect in a timely manner, mainly for those patients in more critical conditions. The survival rates were correlated with appropriate loading dose rates and appropriate treatment duration. Underdosing can lead to treatment failures, poor results and potential bacterial resistance development[25–27]. Teicoplanin also requires a loading dose of 12 mg/kg every 12 hours for 3 doses, followed by a maintenance dose of 6 mg/kg every 24 hours, according to the protocol guidelines, shown in Table 5. One patient who used the medication remained on the loading dose for 4 days: a total of 8 doses. Although considered incorrect by the protocol, some studies show that prolonging the loading dose can be beneficial for combating infections, mainly in more severe cases[28,29].

Positive blood culture results were found in 25.7% of the neutropenia episodes, 54.5% of which were gram-negative microorganisms. Alali *et al.* found positive blood cultures in 21.4% and 54% of the gram-positive pathogens[30]. Some studies show that, in recent decades, there has been an increase in

gram-positive bacteria and that this trend may change the initial profile of ATMs chosen in the future[2,16]. There are no previous data on pathogens at the institution mentioned in this paper so that a comparison can be made with studies already published in the literature, but valuesvery close to gram-positives and gram-negatives are verified.

Most of the pathogens detected are sensitive to the ATMs described in the protocol, mainly to cefepime and vancomycin, which are the most used at treatment initiation. It is observed that few microorganisms are resistant to the main ATMs, such as *Escherichia coli* and *Klebsiella pneumoniae* sensitive only to ceftazidime + avibactam, *Pseudomonas putida* sensitive only to polymyxin B and *Pseudomonas aeruginosas* sensitive only to meropenem. It is important for physicians to follow the protocol recommendations, as they are adapted to the reality of the institution, promoting proper ATM use and avoiding resistant bacteria selection. A study conducted by Scheler *et al.* verified that more than 90% of the cancer hospitals in Europe have an internal protocol for handling and managing neutropenia[19].

Current guidelines recommend that neutropenic patients be monitored constantly and that, in the presence of a fever spike, the ATM should be administered within the first hour, in order to improve care and minimize adverse outcomes. Admittedly, this group of patients is at risk for infection-related complications due to their immunocompromised state[9]. As a result of the complexity of these patients and the urgency in initiating ATM, pharmacists play a fundamental role in reviewing the prescriptions, providing guidelines to the patients, companions and other health professionals, and participating in clinical case discussions. Pharmacotherapy monitoring showed a reduction in the use of inappropriate and unnecessary ATMs, dosing errors and hospital expenses[31,32].

The pharmacists' main objective when using an ATM is to improve treatment results and alleviate and reduce the consequences of this use. These professionals assist in all stages, from auditing prescriptions, optimizing dose and duration and oral sequencing therapy, the activities included in the *Antimicrobial Stewardship Program*, including auditing medical prescriptions, optimizing dose and duration and therapy oral sequencing[33].

The current study had some limitations, such as the analysis of the institutional clinical protocol, only updated every two years, which can sometimes result in outdated information, as in the case of the teicoplanin loading dose. In addition to that, as this is a retrospective study, incomplete data from medical records, as well as absence of information on changes in pharmacotherapy, can exert impacts on the pharmaceutical evaluation of ATM use for the febrile neutropenia treatment in pediatric patients.

Conclusion

Although most of the prescriptions follow the recommendations when it comes to treatment initiation, there were high non-compliance rates in terms of ATM use for the febrile neutropenia treatment with the sectors' clinical protocol of the hospital under study. It is indispensable to adapt the prescriptions to the institutional protocol, so that the patients receive effective and safe treatments, avoiding the occurrence of bacterial resistance due to inappropriate ATM use. In addition to that, it is important to perform cultures to adapt the treatments, if necessary.

Updating the institutional protocol is also a relevant aspect. The presence of a pharmacist in processes related to ATMs is fundamental to carry out the pharmacotherapy monitoring of patients using these medications and to indicate any new data in the literature, contributing to adequate and safe use.

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Collaborators

CSL, LPS and SRA participated in project design and in data analysis and interpretation; CSL, LPS, SRA, RRM and CC participated in writing the article and critically reviewing the intellectual content. All authors approved the final version of the article.

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Declaration of conflict of interests

The authors declare that there are no conflicts of interests in relation to this article.

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