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Empirical antibiotic therapy in febrile neutropenic patients in a reference institution from Colombia: retrospective cohort study

Terapia antibiótica empírica en pacientes neutropénicos febriles en una institución de referencia de Colombia: estudio de cohorte retrospectivo

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ABSTRACT

OBJECTIVE: The objective of this paper is to describe and compare the empirical antibiotic therapy used in pediatric patients with onco-hematological pathology that presented febrile neutropenia (FN) during a period of 5 years at a referential institution in Bucaramanga, Colombia.
METHODOLOGY: Descriptive study of retrospective cohort type performed between the years 2013 and 2017, in patients with FN between 1 month of age and 18 years old, hospitalized at Materno Infantil San Luis Clinic (CMISL, for its Spanish acronym) (Bucaramanga, Colombia) with onco-hematological pathology. The data were collected with REDCap® tool and the bivariate analysis was performed in Stata 14.0.
RESULTS: The study included 130 patients for 315 FN total episodes, from which 64.13% of the cases were initially treated with monotherapy, being Piperacillin Tazobactam (PTZ) (n=91, 45.05%) and Cefepime (FEP) (n=84, 41.58%) the most used. The episodes treated with PTZ and FEP were compared.

RESUMEN

OBJETIVO: El objetivo de este trabajo es describir y comparar la antibioticoterapia empírica utilizada en pacientes pediátricos con patología onco-hematológica que presentaron neutropenia febril (NF) durante un periodo de 5 años en una institución de referencia en Bucaramanga, Colombia.
METODOLOGÍA: Estudio descriptivo de tipo cohorte retrospectiva realizado entre los años 2013 y 2017, en pacientes con NF entre 1 mes y 18 años, hospitalizados en la Clínica Materno Infantil San Luis (CMISL) (Bucaramanga, Colombia) con patología onco-hematológica. Los datos se recopilaron con la herramienta REDCap® y el análisis bivariado se realizó en Stata 14.0.
RESULTADOS: El estudio incluyó a 130 pacientes para 315 episodios totales de NF, de los cuales el 64.13% de los casos fueron tratados inicialmente con monoterapia, siendo Piperacilina Tazobactam (PTZ) (n = 91, 45.05%) y Cefepima (FEP), (n = 84 41.58%) los más utilizados. Al comparar los episodios que usa-

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Patients exposed to PTZ presented more signs of gastrointestinal focus (n=48 [31.17%] vs n=22 [18.49%], p. 0.02), higher bacterial isolates (n=55 [35.71%] vs n=33 [27.73%], p. 0.03), had predominance of Gram-negative bacilli (GNB) isolation (n=49 [31.82%] vs n=22 [18.49%], p. 0.01) and required higher use of granulocyte-colony stimulants (n=48 [31.17%] vs n=22 [18.49%], p. 0.02).
CONCLUSIONS: No significant differences in the outcomes were identified between the empirical therapy with PTZ and FEP; no evidence was found to conclude that one of these treatments is superior to the other in terms of safety or effectiveness.

KEY WORDS

Febrile neutropenia. Antibiotics. Cancer. Pediatrics.

ron la PTZ y FEP, aquellos expuestos a la PTZ presentaron mayor sospecha de foco gastrointestinal (n=48 [31.17%] vs n=22 [18.49%], p. 0.02), más aislamientos bacterianos (n=55 [35.71%] vs n=33 [27.73%], p. 0.03), predominio de aislamiento de bacilos gram negativos (BGN) (n=49 [31.82%] vs n=22 [18.49%], p. 0.01) y mayor necesidad de uso de estimulantes de colonias de granulocitos (n=48 [31.17%] vs n=22 [18.49%], p.0.02).
CONCLUSIONES: No se identificaron diferencias significativas en los resultados entre la terapia empírica con PTZ y FEP; no se encontró evidencia para concluir que uno de estos tratamientos sea superior al otro en términos de seguridad o efectividad.

PALABRAS CLAVE

Neutropenia febril. Antibióticos. Cáncer. Pediatría.

Introduction

Febrile Neutropenia (FN) is a frequent infectious emergency in patients with cancer, due to the implicit risk of potentially fatal invasive infections. In this antibiotic era, it is a huge challenge to deal reasonably with those pathogenic microorganisms. An increase in bacteria resistant to several groups of antibiotics has been observed, mainly Gram-negative pathogens such as *Enterobacteriaceae* that produce extended spectrum beta-lactamases (ESBLS) and carbapenemases (EPC), multi-drug resistant (MDR) *Pseudomonas aeruginosa*, Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus* (VRE).[1,2] Inadequate antibiotic coverage has been shown to favor increased mortality and prolonged hospitalizations.

Therefore, it is important to consider that the used antibiotics are selected under institutional epidemiology based on the most frequent microorganisms and their susceptibility/resistance pattern, focused on the use of a broad spectrum regimen. The broad spectrum regimen covers GNB (including *Enterobacteriaceae, P. aeruginosa*), for which the use of antipseudomonal agents like extended-range penicillin/β-lactamase inhibitor combination (e.g., PTZ), fourth- or higher-generation cephalosporins (e.g., FEP), or a broad-spectrum carbapenem (e.g., Meropenem [MEM], Imipenem Cilastatin [IC]) is recommended for initial empirical management.[3-6]

Empirical monotherapy in children with oncological diseases and FN is supported by several meta-analyses in cases of stable patients with benefits such as a lower risk of adverse effects such as nephrotoxicity, without significant differences in mortality and therapeutic failure compared to combined therapy.[3,7-10]

Additionally, the stratification of the risk of presenting bacteremia leads to a rational use of resources for its clinical approach. Those patients with high or not established risk should be hospitalized to start immediate intravenous antibiotic therapy, looking for the main pathogens for a later directed management.[3,6]

However, according to Surviving Sepsis Campaign 2020, certain clinical scenarios may require multi-drug antimicrobial therapy, such as in patients at high risk for resistant gram-negative infections with sepsis. In these cases, a beta-lactam/beta-lactamase inhibitor agent could be used combined with an aminoglycoside (i.e., Gentamicin), not for synergy, but for expanded coverage to treat both susceptible and resistant

pathogens until final specific identification is achieved and t is possible to avoid resistance during treatment.[4]

The addition of a second glycopeptide antibiotic such as Vancomycin (VAN) should be reserved for patients with risk factors such as the presence of hemodynamic instability or infectious sources due to Gram-positive cocci (GPC), including coagulase negative *Staphylococcus* (central catheter infection, cellulitis, soft tissue infection or pneumonia), or for those in centers where MRSA is a common pathogen associated with vascular catheters.[3,6,11,12]

Carbapenems should be avoided as empirical agents for uncomplicated patients and without risk for bacterial resistance; they should be reserved for seriously ill patients: sepsis, nosocomial infection, suspected tiflitis, relapse episode with parenteral administration of cephalosporin in the previous 7 days, or suspicion of infection by *B. cereus* according to microbiological documentation.[1,13] Anti-anaerobic agents (such as Metronidazole, MEM and PTZ) should be added in cases with intra-abdominal infections, odontogenic and perianal abscesses, necrotizing gingivitis and severe mucositis, particularly if diarrhea secondary to *Clostridium difficile* infection is suspected.[1,14]

Though studies indicate that mortality is lower with fourth-generation cephalosporins,[6] antibiotic selection should be according to the institutional resistance profile. **Table 1** shows the most used antibiotics as initial monotherapy in the pediatric population.

Article	Type of study	Population	Episodes	Dosage	Results
Kebudi *et al.* Turkey 2005 (15)	RCT	31 pacients. Age: 13 (2-14) yo.	40	PTZ 99 mg/kg/day FEP 150 mg/kg/day	Success Rate: 65% vs 60%. Mortality: Similar (no values). Adverse events: Similar.
Corapcioglu *et al.* Turkey 2006 (16)	RCT	27 pacients. Age: 8.4 (0.7-18) yo.	50	PTZ 320 mg/kg/day FEP 150 mg/kg/day	Success Rate: n=14 (56%) vs n=12 (48%). p. 0.78. Mortality: 0% Adverse Reactions: Similar. Modification of Treat-ment: n=1 (4%) vs n=9 (36%). p. 0.01
Sano *et al.* 2015 (17)	RCT	53 pacients. Age: 6 (0-22) yo.	213	PTZ 337.5 mg/kg/day FEP 100 mg/kg/day	Success rate: n=64 (62%) vs n=65 (59%). p. 0.65. Mortality: n=1 (1%) vs n=0 (0%). p. 0.30 Adverse reactions: Similar.
Aamir *et al.* 2015 India (18)	RCT	40 pacients. Age: 6.42 yo.	50	PTZ 300 mg/kg/day FEP 150 mg/kg/day	Success rate: n=15 [75%] vs n=16 [80%]. p. 0.71. Mortality: n=4 [20%] vs n=2 [10%]. p. 0.38. Adverse Reactions: Similar.

Tabla 1. Studies comparing initial empirical monotherapy with PTZ vs FEP in pediatric patients with FN.
Abbreviation: PTZ: Piperacilin Tazobactam. FEP: Cefepime. RCT: Randomized Controlled Trial.

Databases PubMed, Cochrane Library, Scielo and Science Direct with the keywords Mesh [Piperacillin tazobactam AND Cefepime AND febrile neutropenia AND pediatric] were reviewed, and 4 articles were found with 343 episodes included, comparing PTZ vs FEP therapy through randomized controlled clinical trials (RTC).[15-18]

The purpose of this study is to describe the empirical antibiotic therapy used in a Hospital in Bucaramanga, Colombia in pediatric patients with hematological cancer and FN during a period of 5 years, and to compare the experience with the main empirical first-line antibiotics used in this institution: PTZ and FEP.

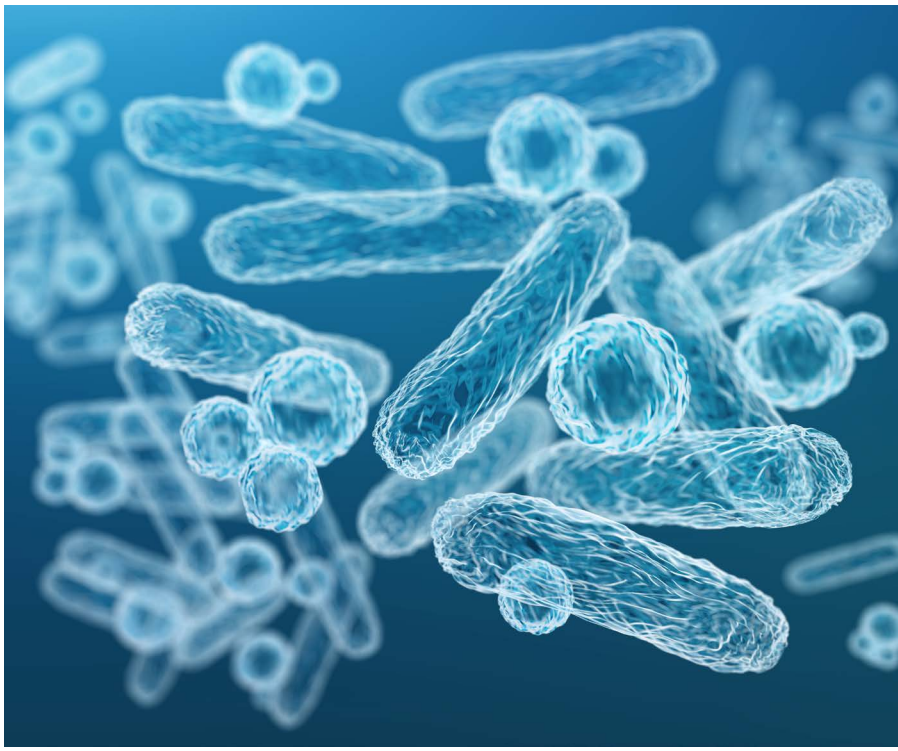
Methodology

Inclusion criteria

All hospitalized patients with age between 1 month and 18 years with hematological cancer, susceptible to presenting FN with fever (axillary temperature> 38° C) and absolute neutrophil counts less than 500 cells/mm^3, which had initial empirical antibiotic therapy were selected. All newborns and those patients whose FN was secondary to non-hematological or oncological pathologies were excluded.

Study design

Descriptive, retrospective cohort study carried out at the CMISL (Bucaramanga, Colombia). The medical records for the period 2013-2017 were reviewed according to the ICD-10 code, demographic and clinical data of the underlying disease, and episodes of FN and microbiological characteristics were collected in REDCap®. The use of empirical antibiotics in the institution was described for those episodes in which PTZ and FEP were used. The need for antibiotic stepping was determined by the persistence or recurrence of fever after 72 hours from the start of treatment, clinical and hemodynamic complications. Bivariate analysis was performed to establish statistical association.



Ethical aspects

The study was considered risk-free, and was approved by the CMISL research committee. There are no conflicts of interest.

Statistical analysis

The variables were described by percentages, proportions, ratios, and in the continuous quantitative variables, the median was calculated with the respective interquartile range, since they were all non-parametric. The bivariate analysis was performed in Stata 14.0, Pearson's chi2 test was used for categorical variables, Fisher's exact test for categorical variables with low sample number, and Mann-Whitney test for continuous quantitative variables. In all analyses, a P value <0.05 was considered statistically significant, with a 95% confidence interval.

The purpose of this study is to DESCRIBE THE EMPIRICAL ANTIBIOTIC THERAPY used in a Hospital in Bucaramanga, Colombia IN PEDIATRIC PATIENTS WITH HEMATOLOGICAL CANCER

Results

130 patients were obtained for 315 episodes of FN, with a median of 2.42 episodes per patient. The main causes were hematolymphoid neoplasms (n=108 [83.08%, 95% CI 75.52-88-65]), the most frequent being ALL (n=77 [59.23%, 95% CI 50.48-67.44]). 51.54% (n=67) corresponded to male patients. The ages ranged from 1 month to 16 years, with a median of 6 years and 3 months (IQR 3-10).

All episodes of high-risk FN received empirical inpatient antibiotic therapy. **Figure 1** shows the way in which antibiotics were used during the treatment of the episodes, being monotherapy regimen the most frequent management. The starting treatment with a single antibiotic was administered in 64.13% of the episodes.

The most used single empirical antibiotics were PTZ and FEP (n=91 [45.05%], n=84 [41.58%], respectively). The most used antibiotics both in monotherapy and in association for empirical therapy were PTZ (n=154, 48.89%), FEP (n=119, 37.77%), VAN (n=68, 21.59%), Amikacin (n=29, 9.20%), MEM (n=18, 5.71%), Metronidazole (n=17, 5.40%), Ampicillin Sulbactam (n=17, 5.40%), among others.

Regarding combined therapy, biconjugate treatment was employed in 26.67% of the cases, and the most frequent association was PTZ-VAN, followed by FEP-VAN (n=28 [33.34%], n=24 [28.57%], respectively); more than two antibiotics were used in 9.21% of the episodes.

In the cases that required stepping therapy, it was performed in 33.33% (n=105, 95% CI 28.32-38.76) of the episodes, being MEM (n=50, 45.45%) and VAN (n=53, 48.18%) the most added. Fluconazole was

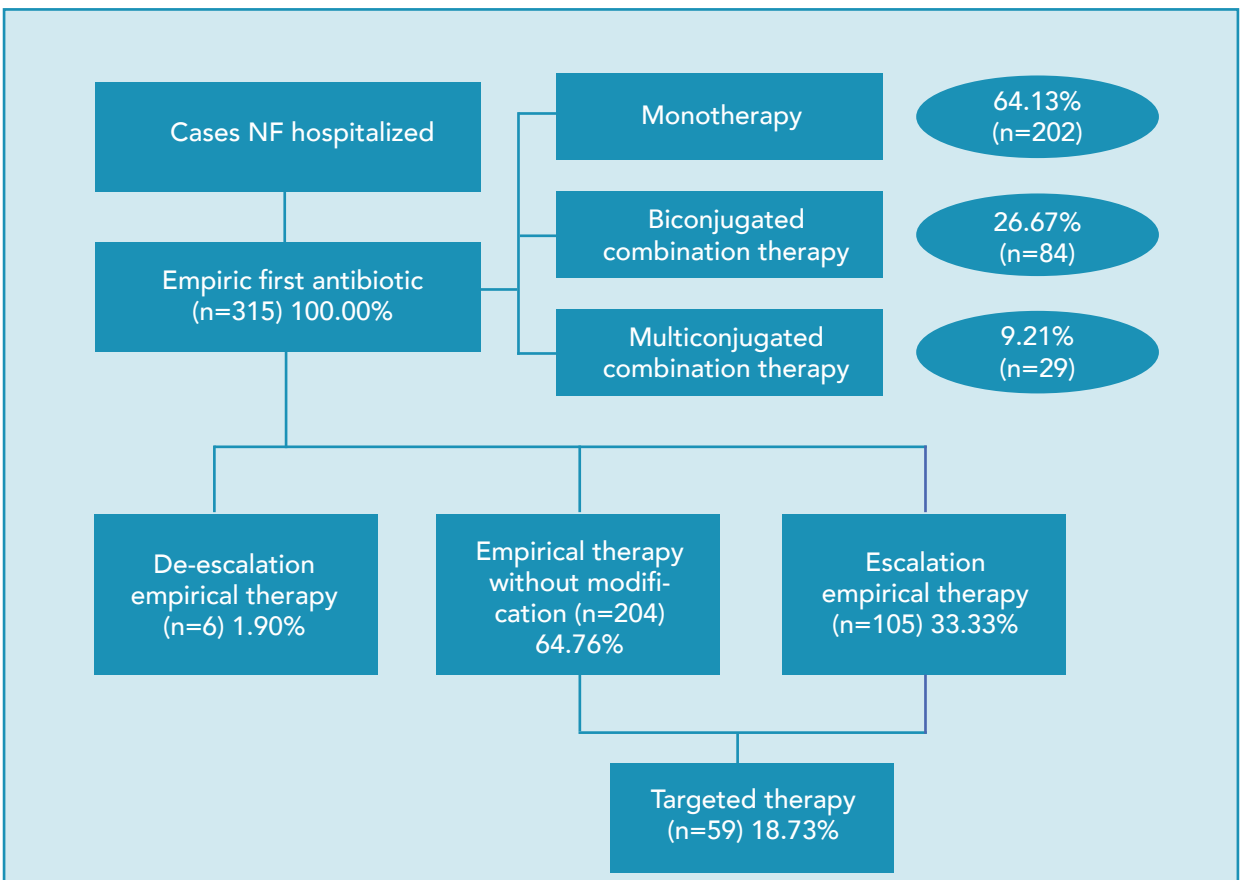


Figure 1. Diagram of the use of antibiotics during episodes of FN in pediatric patients of the pedi-atric hemato-oncology service of the CMISL, 2013-2017

the main antifungal added. Other used antimicrobials were Voriconazole (n=25, 22.73%), Metronidazole (n=19, 17.27%), PTZ (n=19, 17.27%), Amphotericin B (n=17, 15.45%), TMP SMX (n=15, 13.64%), and FEP (n=14 , 12.73%).

For the cases that achieved targeted therapy, the most relevant were PTZ (n=15, 25.42%), MEM (n=13, 22.03%), NPV (n=11, 18.64%), Amikacin (n=8, 13.56%), and Voriconazole (n=6, 10.17%). **Table 2** outlines the type of antibiotic used in empirical, stepping and targeted therapy.

In 274 episodes, PTZ or FEP were used as the initial empirical antibiotic, with PTZ doses of 300 mg/kg/day divided into 3 doses and 100 mg/kg/day of FEP divided into 2 doses. A comparison was made between these antibiotics, discriminating according to the monotherapy and combined therapy regimen. The clinical and microbiological characteristics are described in **Table 3.**

Discussion

In this study, the main empirical therapy was monotherapy and the most commonly used antibiotics were FEP or PTZ.

Empiric antibiotic therapy	Total number (n)	Percentage according to therapy type (%)	Percentage according to total episodes (%)
Monotherapy	202	100.00	64.13
Piperacillin Tazobactam	91	45.05	28.89
Cefepime	84	41.58	26.67
Ampicillin Sulbactam	16	7.92	5.07
Meropenem	4	1.98	1.27
Others	7	3.47	2.22
Biconjugated combination therapy	84	100.00	26.67
Piperacillin Tazobactam + Vancomycin	28	33.34	8.89
Cefepime + Vancomycin	24	28.57	7.62
Piperacillin Tazobactam + Amikacin	17	20.24	5.40
Meropenem + Vancomycin	9	10.71	2.86
Cefepime + Amikacin	3	3.57	0.95
Others	3	3.57	0.95
Multiconjugated combination therapy	29	100.00	9.21
Piperacillin Tazobactam + others	18	62.10	5.71
Cefepime + others	6	20.69	1.90
Meropenem + others	5	17.24	1.59

Table 2. Diagram of the use of antibiotics during episodes of FN in pediatric patients of the pedi-atric hemato-oncology service of the CMISL, 2013-2017
Abbreviation: FN: Febrile neutropenia. CMISL: Materno Infantil San Luis Clinic.

Variables	Monotherapy			Monotherapy and combination therapy		
	PTZ n=91 n (%)	FEP n=84 n (%)	p. Value ($IC_{95\%}$)	PTZ n=154 n (%)	FEP n=119 n (%)	p. Value ($IC_{95\%}$)
Gender						
Female	46 (50.55)	43 (51.19)	0.93	75 (48.70)	58 (48.74)	0.99
Male	45 (49.45)	41 (48.81)		79 (51.30)	61 (51.28)	
Age (Years)[a]	6 (3-8)	6 (2-9)	1.00	6 (3-8)	6 (2-9)	1.00
Cancer type						
ALL	57 (62.64)	47 (55.95)	0.37	93 (60.39)	70 (58.82)	0.79
AML	15 (16.48)	23 (27.38)	0.08	23 (14.94)	26 (21.85)	0.15
Lymphomas	6 (6.59)	7 (8.33)	0.66	11 (7.14)	14 (11.76)	0.21
Solid tumors	10 (10.99)	5 (5.95)	0.23	20 (12.99)	7 (5.88)	0.07
Others	3 (3.30)	2 (2.38)	0.72	7 (4.55)	2 (1.68)	0.31
Use of implantofix	28 (30.77)	41 (48.81)	**0.02**	62 (40.26)	61 (51.26)	0.07
Comorbidities	20 (21.98)	23 (27.38)	0.69	43 (27.92)	38 (31.93)	0.47
Previous AB[b]	48 (52.75)	44 (52.38)	0.65	79 (51.30)	61 (51.26)	0.93
AB prophylaxis[c]	57 (62.64)	58 (69.05)	0.0.37	97 (62.99)	82 (68.91)	0.31
AN count at start[a]	50 (10-251)	95 (20-225)	0.48	59 (10-284)	80 (17-190)	0.56
Days of severe neutropenia	6 (3-10)	6 (4-9)	0.64	.5 (4-10)	6 (4-9)	0.15
CRP at start[b]	96 (24-192)	36 (24-48)	**<0.01**	96 (48-192)	48 (24-96)	**<0.01**
Clinical infectious focus						
ORL	10 (10.99)	9 (10.71)	0.95	18 (11.69)	10 (8.40)	<0.01

Respiratory	21 (23.08)	24 (28.57)	0.41	47 (30.52)	32 (26.89)	0.51
Gastrointestinal	23 (25.27)	14 (16.67)	0.16	48 (31.17)	22 (18.49)	**0.02**
Skin	10 (10.99)	4 (4.76)	0.13	18 (11.69)	7 (5.88)	0.14
Unknown	38 (41.76)	42 (50.00)	0.27	54 (35.06)	54 (45.38)	0.08
Microbial isolation	25 (27.47)	16 (19.05)	0.18	55 (35.71)	33 (27.73)	**0.03**
GPC	3 (3.30)	3 (3.57)	1.00	12 (7.79)	(9.24)	0.31
GNB	22 (24.18)	13 (15.48)	0.19	49 (31.82)	22 (18.49)	**0.01**
PTZ-resistance	7 (7.69)	3 (3.57)	0.33	17 (11.04)	9 (7.56)	0.41
FEP-resistance	8 (8.79)	1 (2.3)	**0.04**	12 (7.79)	6 (5.04)	0.46
Unusual resistances[d]	9 (9.89)	1 (2.3)	0.11	12 (7.79)	7 (5.88)	0.70
Bacteremia[e]	12 (13.19)	9 (10.71)	0.65	25 (16.23)	23 (19.33)	0.73
Antibiotic escalation	30 (32.97)	27 (32.14)	0.33	53 (34.42)	35 (29.41)	0.33
Inotropics requirement	5 (5.49)	5 (5.95)	1.00	7 (4.55)	8 (6.72)	0.44
ICU admission	3 (3.30)	4 (4.76)	0.71	21 (13.64)	18 (15.13)	0.73
ICU stay (days)[a]	5 (3-5)	2 (1-3)	0.06	5 (4-10)	4 (2-9)	0.30
G-CSF use	24 (26.37)	27 (32.14)	0.14	48 (31.17)	22 (18.49)	**0.02**
Hospital stay (days)[a f]	9 (5-15)	9 (6-19)	0.69	11 (6-16)	9 (5-21)	0.89
Infection-related mortality	3 (3.30)	3 (3.57)	1.00	12 (7.79)	12 10.08)	0.53

Table 3. Diagram of the use of antibiotics during episodes of FN in pediatric patients of the pedi-atric hemato-oncology service of the CMISL, 2013-2017

[a]Median (RIQ). [b]Last 3 months. [c]Trimethoprim Sulfamethoxazole. [d]GNB producers of extended spec-trum betalactamases (ESBL), with a suggestive pattern of Carbapenemase production, a suggestive pattern of multi-drug resistance, Gram positive vancomycin resistant cocci. [e]CDC Criteria 2018. [f]Hospi-tal stay only due to FN.

Abbreviation: ALL: Acute Lymphoid Leukemia, AML: Acute Myeloid Leukemia, AB: Antibiotic, AN: Ab-solute Neutrophils, CRP: C-Reactive Protein, ORL otorhinolaryngological, GPC: Gram-Positive Cocci, GNB: Gram-Negative Bacilli. PTZ: Piperacillin Tazobactam, FEP: Cefepime, ICU: Intensive care unit, G-CSF: Granulocyte colony-stimulating factor, CI: Confidence interval.

Although MEM has been reported to have high efficacy and safety in this population, overuse of these drugs can lead to an increased prevalence of drug-resistant bacterial strains such as EPC

When comparing the groups (PTZ vs FEP) in any therapy modality, no differences were observed between the patients according to age, sex, and underlying hemato-oncological diseases, suspected infectious source at the beginning, bacterial isolates in cultures, and microorganisms with unusual resistance. The group that used PTZ had a greater suspicion of gastrointestinal focus (n=48 [31.17%] vs n=22 [18.49%], p. 0.02), more bacterial isolates (n=55 [35.71%] vs n=33 [27.73%], p. 0.03), predominance of GNB in the isolates (n=49 [31.82%] vs n=22 [18.49%], p. 0.01), greater need for the use of granulocyte colony stimulants (n=48 [31.17%] vs n=22 [18.49%], p. 0.02) and CRP at the beginning of the episode was shown to be higher (n=96 [IQR 24-192] vs n=36 [IQR 24-48], respectively, p. <0.01).

According to the outcomes in the monotherapy groups, there were no differences regarding the presence of bacteremia (n=12 [13.19%] vs n=9 [10.71%], p. 0.56), need for antibiotic stepping (n=30 [32.97 %] vs n=27 [32.14%], p. 0.33), need for inotropics (n=5 [5.49%] vs n=5 [5.95%], p. 1.00), need for ICU (n=3 [3.30 %] vs n=4 [4.76%], p. 0.71), stay in ICU (5 days [IQR: 3-5] vs 2 days [IQR: 1-3], p. 0.06), need for colony stimulants granulocytes (n=24 [26.37%] vs n=27 [32.14%], p. 0.14), hospital stay (9 days [IQR: 5-15] vs 9 days [IQR: 6-19], p. 0.69) and mortality associated with infection (n=3 [3.30%] vs n=3 [3.57], p. 1.00).

Similar findings were obtained in the four reviewed articles with 343 episodes included (**Table 4**) that compared PTZ vs FEP therapy in the pediatric population, where no significant differences were observed in success rates, duration of FN episodes, rates of new infections, and mortality, so they are considered equally effective and safe as empirical therapy.[15-18]

In 2017, Horita *et al*.[19] published a meta-analysis comparing the effectiveness and safety of empirical antipseudomonal beta-lactam monotherapy in adult and pediatric patients with FN (50 studies, 17 articles in children, 10,872 patients were included), and suggests IC, PTZ and MEM as the first-line antibiotics. Treatment with IC showed the highest probability of success, as well as the lowest probability of deaths from any cause. When comparing IC with FEP, the latter showed a lower success rate and a higher risk of death.

With the emergence of Cefozopran (CZOP), a fourth-generation cephalosporin, studies have proven its usefulness in pediatrics. In 2011, Ichikawa *et al*.[20] conducted a study of 49 patients (119 episodes), and compared PTZ (375 mg/kg/day) and CZOP (100 mg/kg/day) with similar success rate (n=34 [59.6 %] vs n=33 [53.2%], p. 0.58) and mortality in the two groups. Similarly, in 2014 Sarashina *et al*.[21] compared FEP with CZOP and obtained a similar success rate (n=63 [56.3%] vs n=71 [64%], p. 0.27), without significant differences in adverse events. This suggests that this molecule could be another useful option as empirical monotherapy in children with high-risk FN.

Although MEM has been reported to have high efficacy and safety in this population, overuse of these drugs can lead to an increased prevalence of drug-resistant bacterial strains such as EPC, so it should be used reasonably.[12,22] In support of the above, when comparing PTZ and MEM therapy, the success and mortality rates have been similar. Sano *et al*.[22] described in 2017 that the success rates of the PTZ and MEM groups were 62.4 vs 65.9% (p. 0.48) and the mortality rates were 0.8 vs 0%, respectively (p. 0.50). Similar data were obtained in the study by Sezgin *et al*. in 2014, and more recently by Kobayashi *et al*.,

who compared MEM and PTZ in association with immunoglobulin as a second-line treatment in pediatric patients with FN, and found that PTZ is as effective and safe as MEM.[23, 24]

Additionally, some studies have shown greater antibiotic susceptibility of isolated microorganisms to aminoglycosides, fluoroquinolones, and colistin.[25] However, the use of these drugs should be cautious to avoid an increase in the rate of antimicrobial resistance since, as in the case of aminoglycosides, they are not effective as single agents against Gram-negative bacterial infections; instead, they are third-line options in combined therapies for MDR microorganisms. In addition, they register severe adverse effects such as nephrotoxicity and neurotoxicity. Consequently, combined therapy with aminoglycosides and beta-lactams is proposed only in institutions with increased circulation of MDR strains, to improve empirical coverage and clinical response in patients.[3,6]

Other strategies that have emerged with the purpose of reducing the abuse of antibiotics and reversing the emergence of multi-drug resistance are cycled antibiotic therapy[26] and antimicrobial administration programs in a restrictive and audited manner, which seem to show cost-effective results.[27]

In our study, in one third of the cases an empirical antibiotic stepping was required, in almost two thirds of the cases the same antibiotic scheme was maintained, while in only 2% of the cases it was de-escalated. Furthermore, targeted therapy with specific antibiotics was performed in only 18.73% (n=59) of the episodes; PTZ, MEM, and VAN were the most used.

The clinical evaluation of the patient is determined according to the severity of the condition. Initial empirical treatment should be reviewed 72 to 96 hours after initiation, unless there is a condition that determines its early modification, such as the identification of a microorganism or the clinical deterioration of the patient.[28-30] Finally, when the pathogen is identified, specific treatment should be performed based on the susceptibility test, the minimum inhibitory concentration (MIC) and guided by the pediatric infectious disease specialist.[26]

Conclusion

In the studied population, there was no difference between PTZ or FEP in the need for escalation, mortality or adverse reactions. No evidence was found about the superiority of one of the treatments in terms of effectiveness or safety in patients with FN.

In the studied population, there was NO DIFFERENCE BETWEEN PTZ OR FEP in the need for escalation, mortality or adverse reactions

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