PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

REVIEW ARTICLE

Febrile neutropenia management in pediatri onco-hematologic patients: a systematic review

Manejo da neutropenia febril em pacientes pediátricos onco-hematológicos: uma revisão sistemática

Manejo de la neutropenia febril en pacientes pediátricos oncohematológicos: una revisión sistemática

https://doi.org/10.17058/reci.v1i1.14581

Received: *12/10/2019*
Accepted: *08/23/2020*
Available online: *03/02/2021*

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ABSTRACT

Background and Objectives: cancer cases are gradually increasing, and most treatments still cause several adverse reactions, such as myelosuppression. When neutrophils decline, febrile neutropenia (FN) can be triggered, considered an oncological emergency, leaving patients susceptible to infections. Therefore, it is necessary to determine the best treatment, seeking to reduce the risk of complications. The purpose of this review is to identify, in literature, randomized clinical studies that compare different treatments for FN in pediatric onco-hematological patients. **Content:** a systematic search was carried out on the PubMed database, for randomized clinical studies, from 2009 to 2019, in English, using "Febrile Neutropenia", "Pediatric", and "Therapeutics" as descriptors. A total of 233 articles were found, seven of which were selected for review. The most described antimicrobial for FN treatment was Piperacillin/Tazobactam (PIP/TAZ) and its use is justified by its spectrum of action to cover the most frequent microorganisms in patients with FN. The possibility of using oral antimicrobials may be an alternative and should be analyzed. The description of the risk classification criteria is essential to guide the therapy, and new tools, such as the stewardship, add safety to patient care. **Conclusion:** the most used antimicrobial to treat FN was PIP/TAZ, and the establishment of standardized risk classification scores in pediatric onco-hematological patients is essential to guide clinical management in FN treatment.

Keywords: *Febrile Neutropenia; Pediatrics; Therapy.*

RESUMO

Justificativa e objetivos: os casos de câncer estão aumentando gradativamente, e a maioria dos tratamentos

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ainda causa várias reações adversas, como a mielossupressão. Com o declínio dos neutrófilos, pode-se desencadear a neutropenia febril (NF), considerada uma emergência oncológica, deixando o paciente suscetível a infecções. Portanto, é necessário determinar o melhor tratamento, visando reduzir o risco de complicações. O objetivo desta revisão é identificar, na literatura, estudos clínicos randomizados que comparem diferentes tratamentos para NF em pacientes onco-hematológicos pediátricos. **Conteúdo:** foi realizada busca sistemática na base de dados PubMed, de estudos clínicos randomizados, no período de 2009 a 2019, na língua inglesa, utilizando como descritores "Febrile Neutropenia", "Pediatric" e "Therapeutics". Foram encontrados 233 artigos, dos quais sete foram selecionados para revisão. O antimicrobiano mais descrito para o tratamento com FN foi Piperacilina / Tazobactam (PIP / TAZ) e seu uso justifica-se por seu espectro de ação para cobrir os microrganismos mais frequentes em pacientes com FN. A possibilidade de uso de antimicrobianos orais pode ser uma alternativa e deve ser analisada. A descrição dos critérios de classificação de risco é essencial para orientar a terapia, e novas ferramentas, como o stewardship, agregam segurança ao atendimento ao paciente. **Conclusão:** o antimicrobiano mais utilizado para tratar FN foi o PIP / TAZ, e o estabelecimento de escores de classificação de risco padronizados em pacientes onco-hematológicos pediátricos é essencial para orientar o manejo clínico no tratamento de FN.

Palavras-chave: *Neutropenia febril; Pediatria; Terapia.*

RESUMEN

Antecedentes y objetivos: los casos de cáncer están aumentando gradualmente y la mayoría de los tratamientos aún causan varias reacciones adversas, como la mielosupresión. Cuando los neutrófilos disminuyen, se puede desencadenar la neutropenia febril (FN), considerada una emergencia oncológica, dejando a los pacientes susceptibles a infecciones. Por tanto, es necesario determinar el mejor tratamiento, buscando reducir el riesgo de complicaciones. El propósito de esta revisión es identificar, en la literatura, estudios clínicos aleatorizados que comparen diferentes tratamientos para la FN en pacientes pediátricos oncohematológicos. **Contenido:** se realizó una búsqueda sistemática en la base de datos PubMed, de estudios clínicos aleatorizados, de 2009 a 2019, en inglés, utilizando como descriptores "Febrile Neutropenia", "Pediatric" y "Therapeutics". Se encontraron un total de 233 artículos, siete de los cuales fueron seleccionados para revisión. El antimicrobiano más descrito para el tratamiento de FN fue Piperacilina / Tazobactam (PIP / TAZ) y su uso se justifica por su espectro de acción para cubrir los microorganismos más frecuentes en pacientes con FN. La posibilidad de utilizar antimicrobianos orales puede ser una alternativa y debe analizarse. La descripción de los criterios de clasificación de riesgo es fundamental para orientar la terapia, y nuevas herramientas, como la rectoría, añaden seguridad a la atención al paciente. **Conclusión:** el antimicrobiano más utilizado para tratar la FN fue la PIP / TAZ, y el establecimiento de puntuaciones estandarizadas de clasificación de riesgo en pacientes pediátricos oncohematológicos es fundamental para orientar el manejo clínico en el tratamiento de la FN.

Palabras llave: Neutropenia febril; Pediatría; Terapia.

INTRODUCTION

It is estimated that 420 thousand new cases of cancer will occur in Brazil for the 2018-2019 biennium, excluding non-melanoma skin cancer from this number. Considering that the median percentage of childhood and juvenile tumors observed is 3%, it is expected that 12,500 new cases of cancer will occur in children and adolescents (up to 19 years old). The Southeast and Northeast regions are those with the highest numbers, 5,300 and 2,900, respectively, followed by the Center-West (1,800), South (1,300) and North (1,200).[1]

Despite advances in cancer treatment, the main drugs used to treat neoplasms, hematology and solid tumors still cause numerous adverse reactions. One of the main ones that competes at great risk to patients is myelosuppression, characterized by a decrease in the elements of the immune system, leaving patients exposed to various infections. When there is a decline in neutrophils, the first line of defense against some pathogens, it can trigger febrile neutropenia (FN), considered an oncological emergency.[2]

The severity of FN can vary due to the type and cycle of therapy, type of cancer, sex and clinical conditions of patients. The incidence of FN in the United States is estimated at 60,294 cases per year, 7.83 cases per 1,000 cancer patients, and 43.3 cases per 1,000 hematological tumor patients. The epidemiology of FN is related to some factors, which may be responsible for 50% of deaths in patients receiving chemotherapy for solid tumors and 75% for leukemias. In relation to Brazil, there are no general data; however, we can use as a basis the results of a study carried out in a hospital in northeastern Brazil with onco-hematological children and adolescents, which out of 180 occurrences, 87 were FN, giving rise to the 74 cases of infection reported in the study.[2-4] According to the guideline published by the European Society for Medical Oncology (ESMO) in 2016, FN is defined as oral temperature > 38.3ºC or two consecutive measurements > 38.0ºC for 2h and absolute neutrophil count (ANC) of

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500 cells/mm^3, or an expectation that it will decrease to below 500 cells/mm^3.[5] When FN is detected, the rapid onset of broad-spectrum empirical antibiotics is necessary, as the permanence of patients with FN can lead to delay in treatment, which directly or indirectly affects morbidity and mortality.[6]

Cancer patients have a higher risk of infection, not only due to chemotherapy treatment that induces immunosuppression and neutropenia, but also due to hypogammaglobulinemia and loss of normal physiological barriers. This increases the risk of infections by bacteria, viruses, fungi and parasites, as well as complications or spread of common pathogens from normal flora and latent viral infections. [7]

The clinical identification of infections can contribute to the diagnosis in more than 30% of the cases of FN and thus guide the treatment. However, a relevant portion (10-60%) of FN in patients is treated due to fever of unknown origin, without elucidating the pathogen.[8]

The purpose of this review is to identify, in the literature, randomized clinical trials that compare different treatments for FN in pediatric onco-hematological patients.

METHODS

The question used to guide the research was: what is the most used therapy to treat FN in pediatric onco-hematological patients?

This is a literature review based on PICO strategy. The population consisted of pediatric patients with solid or hematological tumors who developed FN and who needed treatment with antimicrobial or antifungal agents. They were randomized to studies that aimed to compare the effectiveness of each treatment and, with that, to define the best conduct for this population.

The search was carried out in literature through combination of "Febrile Neutropenia", "Pediatric" and "Therapeutics" descriptors using the Boolean operators (OR and AND) and limited to the English language. These criteria were defined after a search for articles was carried out in other databases, such as Scielo and LILACS, in Brazilian Portuguese, English and Spanish, not finding studies that fit the defined criteria, so it was decided to include only the articles found on PubMed.

Articles published from 2009 to 2019, a randomized clinical trial comparing treatments for FN in pediatric onco-hematological patients (maximum age up to 18 years) were included. Review articles, guidelines, case reports, non-pediatric population (over 18 years old), duplicate articles, which addressed FN prophylaxis or which did not address the comparison of treatments for FN were excluded. The search was limited to pediatric onco-hematological patients, as information on treatment and management of FN in this population is scarce when compared with adult patients, with no standard risk classification score.

After selecting the articles by two reviewers screened using the keywords, the titles and abstracts were read, focusing on their methodology. The data of the selected articles were compiled and presented in a table, according to the objectives of this review.

RESULTS AND DISCUSSION

The search in the database resulted in a total of 233 articles that met the descriptors used. Of these, 217 were excluded after reading the summary. A total of 16 articles were selected for detailed analysis. Nine articles were excluded because they did not address the comparison between treatments for FN in randomized controlled trials. Thus, seven articles presented information relevant to the research objective for this review, as described in figure 1.

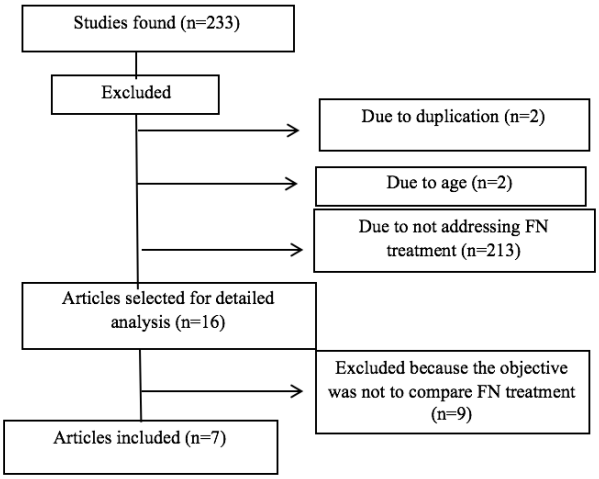

Figure 1. Flowchart of articles selected for review.

Of the seven articles selected, five sought to compare antimicrobial regimens, an antifungal regimen and a treatment for viral infections.[9-15] In clinical practice, most infections that affect patients with FN are caused by bacteria and because of this, studies mainly seek to define the best antimicrobial scheme (ATB) to be used in this clinical situation. Only one article used a different definition for FN, characterized by ANC of ≤ 1000 cells/mm^3, the others used the ESMO criterion.[10] The most frequent ATB in the regimens was piperacillin/tazobactam (PIP/TAZ) and amoxacillin/clavulanate (AMOX/CLAV).[9-13] Only two articles described the chemotherapeutic drugs used in the treatment of pediatric onco-hematological patients.[9,13] The most frequent neoplasm in the cases of FN in the articles assessed was acute lymphoid leukemia, with a high prevalence of other hematological neoplasms compared to solid tumors. Three articles described the FN classification criteria, but they were not the same criteria.[10,13-14] There was evidence of infection in the seven articles.[9-15]

FN is a clinical condition originated by chemotherapy, which can make an individual susceptible to infections.

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Patients' characteristics (age, neoplasia, treatment, type of infection, performance status) need to be considered when choosing the best therapy.

Bacterial infections are generally associated with FN in onco-hematological patients, and the identification of the pathogen causing the infection is important for choosing the appropriate ATB. The use of empirical PIP/TAZ in the management of patients with FN is explained by its spectrum of action, which includes the microorganisms most associated with FN in pediatric patients (*Enterobacteriaceae* (30%) and Coagulase-negative *staphylococci* (24%), and *Pseudomonas aeruginosa* (5%)).[16,17]

No statistically significant differences were found in clinical outcomes when compared to therapy with PIP/TAZ versus cefepime, drugs routinely used in bacterial infections in neutropenic patients. However, an increase in mortality was observed in the PIP/TAZ group, when patients have a previous history of treatment with etoposide, a chemotherapy used in several protocols for childhood and juvenile neoplasms. This reinforces the importance of knowing patients' history and assessing the medications they use so that the choice of ATB is adequate, as this information may interfere with patients' clinical evolution.[9,18]

The combination of PIP/TAZ with other ATBs can help to improve the clinical condition of patients with FN, however, it is essential to define the best association. One study found that sulbactam/ampicillin associated with aztreonam (62.5%) is equivalent to or higher than PIP/TAZ associated with ceftazidime, (57.1%), with fewer cases of new infections and deaths.[11] However, another study that assessed the association of cefoperazone/sulbactam and amikacin, found no statistical difference between the groups (47.5% versus 52.6%, respectively). The search for different combinations of ATB is essential, especially in cases of microbial resistance or non-response to PIP/TAZ, requiring the use of other effective alternatives, such as schemes with broad-spectrum ATB that are not routinely used.[12]

In practice, the concern with the rapid evolution of the infection, makes the use of ATB often occur empirically. In this context, the use of PIP/TAZ for the empirical treatment of FN is of great value, as demonstrated in a study, in which the results found showed that the decrease in body temperature in patients occurred in 62.5% on the fourth day, 57.1% on the seventh day and 75.0% at the end of treatment, suggesting that the applicability of the empirical form of PIP/TAZ is satisfactory for the resolution of FN.[19]

Comparing the use of oral ATB with intravenous ATB in patients with FN can be an effective alternative, especially for those who have a low risk of infection and with the opportunity to perform treatment at home. The use of oral ATB can facilitate treatment in pediatrics, allowing greater autonomy for family members and patients, decreasing the number of punctures, in addition to being also considered the alternative of hospital discharge, reducing the possibility of exposure to nosocomial infection and providing reduction of hospitalization costs.[13,17,20–22]

However, it is important to classify the severity of the risk of infection for this patient, considering several factors that directly affect the conduct to be taken. There is no internationally accepted risk stratification, requiring each hospital to choose a validated stratification and adapt to its reality. Risk score for children with FN was validated in a hospital in India and compared with other models already published. The authors concluded that this model demonstrated applicability, however, a multicenter study is needed to verify the possibility of employment in practice in developed countries, in which health conditions differ from those in development, such as malnutrition.[23-25]

Despite the fact that most infections in FN patients are of microbial origin, other etiologic agents such as fungi and mycobacteria can also be the cause, especially in more severe and prolonged episodes of neutropenia, in a period longer than 10 days of hospitalization.[26]

Fungi can be considered responsible for 30-40% of infections after the fifth day of neutropenia, the most common being *Candida albicans* and *Aspergillus*, but there is an increase in documentation related to *Non-albicans candida*. A study compared the effectiveness of two antifungals, caspofungin and amphotericin B liposomal in patients divided into low and high-risk groups. The results found, demonstrated that both treatments are effective for management of fungal infections in patients with FN. However, it is important to develop studies that compare broad-spectrum antifungals with those of minors, most used in routine.[14,27]

In addition to bacterial or fungal infections, viral infections, especially respiratory infections, appear as potential pathogens in this specific population. Viral respiratory infections can induce morbidity and mortality, being detected in more than 57% of FN episodes in children with cancer. [28,29]

It is essential to determine the type of pathogen that causes the infection for the appropriate choice of therapy, since ATBs are ineffective in viral infections and their indiscriminate use can induce antimicrobial resistance. The suspension of ATB after confirming the results of negative cultures, does not interfere in the final outcome, with the resolution rates in both groups without significant difference (97% in the group with ATB and 95% in the group without ATB). [15]

The use of adjuvant therapies to decrease patients' neutropenia time can be considered a useful tool, such as the use of granulocyte growth stimulating factors (G-CSF), adopted in the onco-hematological routine. Its use contributes to the increase of ANC and, with that, it decreases the time that patients would be susceptible to opportunistic infections, also reducing the time of use of ATB.[30,31]

The guidelines for initial management of FN in children and adolescents with cancer, published by the Brazilian Society of Pediatrics, indicate the initial empirical use of monotherapy with B-lactam antipseudomonal, fourth-generation cephalosporin or carbapenem.[32] These indications corroborate the studies included in this review, in which most studies used PIP/TAZ and/or

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Chart 1. Distribution of articles included in this literature review, according to the reference, type of study, study description, neoplasia, chemotherapy, therapy used, results and limitations, PubMed, 2009-2019.

Reference	Type of study	Description of study	Neoplasm	Chemotherapy	Therapy used	Result	Limitations
Aamir, M., et al, 2015, India.[9]	Randomized, prospective, open-label clinical study (n=40)	Patients aged ≤18 years, receiving CT, who did not receive ATBs in 1 week.	ALL (n=18), osteosarcoma (n=10), Ewing's sarcoma (n=4), NHL (n=4), AML (n=4)	Antibiotics (36), vinca alkaloids (26), folic acid analogs (22), steroids (18), alkylating agents (18), enzymes (18), epipodophyllotoxins (12), platinum complexes (10), analogues of pyrimidines (8).	Group 1: PIP/TAZ 100mg/Kg/dose 8h/8h IV; Group 2: CEF 50mg/Kg/dose 8h/8h IV	Success rate: Group 1: 75%; Group 2: 80% There was no significant difference between the two groups (P=0.705). Mortality rate doubled in the PIP/TAZ group when patients used Etoposide.	Small sample, schematics should be assessed in a larger sample.
Caselli, D. et al, 2012, England.[14]	Clinical, randomized, prospective, multicenter study (n=110).	Patients aged ≤18 years, with CT-induced neutropenia or HSCT, persistent fever after 96h even after ATB use. Patients were divided into low or high-risk groups, according to criteria.	ALL (n=29), AML (n=32). CML (n=1), lymphoma (n=13), brain tumor (n=15), other solid tumors (n=19), severe aplastic anemia (n=1).	Not described.	Arm A: control group (low-risk patients without receiving antifungal); Arm B: 3mg/Kg/day IV; Arm C 50mg/m^2/day, with an attack dose of 70mg/m^2/day. IV;	Patients classified as high risk: Arm B: 88%; Arm C: 83% (P=0.72). Patients classified as low risk: Arm A: 87.5%, Arm B: 80%, Arm C: 94.1% (P=0.41). The three experimental arms provided complete response (i.e., survival), disappearance of fever and no evidence of fungal infection.	There was evidence of fungal infection in only 9 of the 110 patients. It would be important to have isolation of the fungus greater sample. One of the arms could be composed of antifungal slower spectrum of action, such as fluconazole, routinely used.
Gupta, A. et al, 2009, India.[13]	Prospective, randomized, open study (n=88).	Patients aged between 2 and 15 years, with low-risk FN, who did not need hospitalization.	ALL (n=41)*, primitive neuroectodermic tumor (n=26)*, rhabdomiosbraçooca (n=25)*, osteosarcoma (n=17)*, Others (n=14)*. Number of episodes*	Cis/adria: cisplatin, adriamycin (n=8); ECI: ifosfamide, carboplatin, etoposide (n=4); Ifos/adria: ifosfamide, adriamycin (n=4); Ifos/etop: ifosfamide, etoposide (n=21), VAC: vincristine, actinomycin D, cyclophosphamide (n=25), VadrC: vincristine, adriamycin, cyclophosphamide (n=14), others (n=6), indicated for ALL (n=41).	Group 1: OFL OR 7.5 mg/Kg 12/12h and AMOX/CLAV OR 12.5 mg/Kg 8h/8h; Group 2: CEF EV 75mg/Kg and AMK IV 15mg/Kg IV 1 time daily.	Success rate: Group 1: 90.32%; Group 2: 93,44%. No statistical difference (P=0.56).	Parents checked the temperature. Although there is no statistical difference between the groups, due to convenience and fewer invasive procedures, the use of oral therapy could be highlighted.
Santolaya, M.E. et al, 2017, Chile.[15]	Prospective, randomized, multicenter study (n=176).	Patients aged 18 ≤ and FN were treated with 4th generation cephalosporins. After 48 hours, patients with a positive sample for respiratory virus and negative culture for bacteria were randomized for the study.	Leukemia/lymphoma (n=104), leukemia recurrence (n=11), solid tumor (n=61).	Not described.	Group 1: Permanence of AtB until the end of the febrile episode; Group 2: ATB withdrawal.	The median duration of ATBs was 7 days (group 1) versus 3 days (group 2) (P=<0.0001), with similar frequency of uncomplicated resolution (97% versus 95%, respectively) (P=0.41) and a similar number of fever days (2 versus 1), hospitalization days (6 versus 6) and bacterial infections throughout the episode (2% versus 1%). There were no deaths.	It does not clearly demonstrate the outcome between the groups. They use as conclusion the incorporation of techniques to determine viral infections in the routine, not highlighting the result. This study could have highlighted the result that the withdrawal of ATB when it is not necessary, does not decrease the success of solving the problem, and may contribute to the reduction of microbial resistance.

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Cagol, A.R., et al, 2009, Brazil.[10]	Prospective, randomized, double-blind, placebo-controlled study (n=58).	Patients aged 18 ≤, with neutropenia episode, classified as low risk for bacterial invasion, treated with CT.	Osteosarcoma (n=10), primitive neuroecctodemic tumor of the central nervous system (n=7), T=Willm's tumor (n=7), rhabdomyosarcoma (n=6), soft tissue sarcoma (n=7), leukemia (n=7), hepatoblastoma (n=2), neuroblastoma (n=6), lymphoma (n=1), gonadal tumor (n=1), Ewing's sarcoma (n=2), retinoblastoma (n=2).	Not described.	Group A: Ciprofloxacin 30mg/Kg/day 12h/12h OR + AMOX/CLAV 30mg/Kg/day 8h/8h OR + placebo IV. Group B: Cefepime 150mg/Kg/day 8h/8h IV and placebo OR.	Group A: ineffectiveness rate was 51.2%, with an average length of hospitalization of 8 days. Group B: ineffectiveness rate was 45.8%, with an average length of hospitalization of 7 days. No statistical difference (P= 0.77). Number of episodes in which patients remained with fever after 72h: Group A: 7 episodes; Group B: 14 episodes.	The way of classification of patients with FN was different from the other studies. It could have been highlighted the fact that there was no significant difference between the groups, saying that if patients had the OR preserved, it would be the preferred route for treatment, avoiding unnecessary punctures. .
Kobayashi, R. et al, 2009, Japan.[11]	Prospective, randomized study (n=53).	Pediatric patients aged 17 ≤ 17 years, with FN in CT or who received HSCT.	ALL (n=46)*, AML (n=44)*, other leukemias (n=6)*; neuroblastoma (n=17)*, retinoblastoma (n=5)*, hepatoblastoma (n=4)*, calf sac tumor (n=3)*, Ewing's sarcoma (n=2)*, LH (n=2)*, NHL (n=2)*, rhabdomyosarcoma (n=2)*, Wilms' tumor (n=1)*. Number of episodes*	Not described.	Group 1: PIP/TAZ 125mg/Kg/day 6h/6h IV + CAZ 100mg/Kg/day 6h/6h IV; Group 2: SBT/ABPC 150mg/Kg/day IV + AZT 150mg/Kg/day 6h/6h IV.5	Success rate Group 1: 57,1%; Group 2: 62,5%. Success rate considered equivalent (P>0.05). Length of neutropenia, treatment, and days of fever were similar in both groups, but there were fewer new infections and deaths due to infection in Group 2.	In the "Patients and Methods" topic, it is described that the sample is composed of 54 patients, but in the description of the results, it is changed to 53. Neoplasms are not mentioned by number of patients, but by episodes of FN. There was evidence of infection in only 14 episodes in group 1 and 8 episodes in group 2, out of a total of 134 episodes.
Demirkaya, M. et al, 2013, Turkey.[12]	Prospective, randomized, open study (n=46).	Patients from 0-18 years with FN, diagnosed with lymphoma or other solid tumor, without antibiotic prophylaxis.	NHL (n=10), LH (n=1), neuroblastoma (n=4), medulloblastoma (n=4), astrocytoma (n=1), ependymoma (n=1), germinoma (n=1), tumor atypical teratoid rhabdoid (n=1), Ewing's sarcoma (n=4), osteosarcoma (n=3), fibrosarcoma (n=2), rhabdomyosarcoma (n=1), Wilms' tumor (n=1), rhabdoid tumor of the kidney (n=1), clear cell sarcoma of the kidney (n=1), retinosarcoma (n=1), nasopharyngeal carcinoma (n=2), hepatocarcinoma (n=2).	Not described.	Group 1: PIP/TAZ 360mg/Kg/day 6h/6h plus AMK 15mg/Kg/day 8h/8h; Group 2: CS 100mg/Kg/day 8h/8h plus AMK 15mg/Kg/day 8h/8h.	Success rate: Group 1: 47,5%; Group 2: 52,7%. No statistical difference in length of neutropenia, fever and hospitalization (P=>0.05)	From a total of 116 episodes of NDF, they needed treatment modification (adding other ATBs and/or antifungals) in 31 episodes in group 1 and 27 in group 2, characterizing half of episodes, which can interfere in the success rate, generating an unreliable result.

Caption: PIP/TAZ: Piperacillin-Tazobactam; CEF: Cefepime; ALL: Acute Lymphoid Leukemia; AML: Acute Myeloid Leukemia; CML: Chronic Myeloid Leukemia; NHL: Non-Hodking Lymphoma; HL: Hodking lymphoma; Arm A: without antifungal treatment; Arm B; Liposomal Amphotericin B; Arm C: Caspofungin; CT: Chemotherapy; G-CSF: Granulocyte Colony-Stimulating Factor; FN: Febrile Neutropenia; OR: Oral route; IV: Intravenous; HSCT: Hematopoietic Stem Cell Transplantation; CAZ: Ceftazidime; SBT/ABPC: Sulbactam/Ampicillin; AZT: Aztreonam; AMK: Amikacin; CS: Cefoprazone + Sulbactam; OFL: Ofloxacin; AMOX/CLAV: Amoxicillin + Clavulanate; CEF: Ceftriaxone; GEM: Gentamicin

Please cite this article as: *BERTELLA, Tatiane; HAHN, Siomara Regina. Febrile neutropenia management in pediatric onco-hematologic patients: a systematic review. Revista de Epidemiologia e Controle de Infecção, [S.l.], v. 11, n. 1, mar. 2021. ISSN 2238-3360. Available at: <https://online.unisc.br/seer/index.php/epidemiologia/article/view/14581>. Date accessed: 13 sep. 2021. doi:https://doi.org/10.17058/reci.v1i1.14581.*

cefepime as ATB compared to other ATB.

Although the empirical use of PIP/TAZ is widespread in the treatment of FN in pediatric onco-hematological patients, it is necessary to consider the infectious focus and modify the therapy as necessary. For this, it can be considered that the stewardship program, a term used to describe an integrated strategy that seeks to reduce the irrational use of ATB, helps in choosing the best treatment. This program has acquired some objectives over the years, including cost reduction, optimization of therapeutic results and reduction of antimicrobial resistance, associated with tools that are characterized by the restrictions of ATB classes, rotation in the use of ATB, support in clinical decisions, education of the team of prescribers.[33,34]

Recent systematic reviews and meta-analysis on stewardship differ in some points, however they converge in the fact that the application of this tool reduces the occurrence of nosocomial infections caused by drug-resistant bacteria. Moreover, it increases control and reduces the time of using ATB, without increasing the mortality rate, reducing hospital length of stay.[35,36]

Establishing protocols of the stewardship program in pediatric onco-hematological patients with FN, can be a useful resource for decreasing microbial resistance and the unnecessary use of broad-spectrum ATB. As they are patients who often use protocols that cause severe myelosuppression, when they have neutropenia, they seek to protect themselves from serious infections, but that can often be treated simply, and in some cases, on an outpatient basis.

CONCLUSION

Treatment with ATB was the most used, with PIP/TAZ being the most frequent in the regimens, followed by AMOX/CLAV. There was no statistically significant difference between treatment outcomes. However, length of stay, ANC, presence of fever and other clinical conditions must be taken into account when choosing the most appropriate ATB. Viral and fungal infections need to be considered to determine treatment with the correct class of drugs, and to avoid the irrational use of ATB. The establishment of standardized risk classification scores in pediatric onco-hematological patients is essential to guide clinical management in FN treatment.

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AUTHORS' CONTRIBUTIONS

Tatiane Bertella contributed to the conception, design, analysis and writing of the article;

Siomara Regina Hahn contributed to the planning, design, review and final approval of the article.

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

Please cite this article as: *BERTELLA, Tatiane; HAHN, Siomara Regina. Febrile neutropenia management in pediatric onco-hematologic patients: a systematic review. Revista de Epidemiologia e Controle de Infecção, [S.l.], v. 11, n. 1, mar. 2021. ISSN 2238-3360. Available at: <https://online.unisc.br/seer/index.php/epidemiologia/article/view/14581>. Date accessed: 13 sep. 2021. doi:https://doi.org/10.17058/reci.v1i1.14581.*