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Bacteriological Profile of Febrile Neutropenia in the Pediatric Oncology Department of the Mother-Child Hospital of Bingerville (Ivory Coast)

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Abstract

Febrile neutropenia is a serious complication of cancer treatment. It reduces the body's defenses and opens the door to infections. It constitutes a therapeutic emergency due to the major risk of morbidity and mortality. Antibiotic treatment is probabilistic, broad-spectrum and synergistic. It should be adapted to the bacterial ecology specific to each center. The objective of our study was to describe the epidemiological and clinical profile of cases of febrile neutropenia, identify the causative organisms and establish the antibiotic resistance profile of these organisms. A prospective observational descriptive study was carried out at the Mother and Child Hospital in Bingerville over a 2-year period, including patients in the pediatric oncology department admitted for or presenting on admission febrile neutropenia meeting the criteria of the international definition issued by the IDSA following chemotherapy treatment. It involved 25 episodes of febrile neutropenia with 20 patients. Patients with neutropenia were predominantly aged between 5 and 12 years, with a mean age of 8.9 ± 3.6 years and a male predominance (sex ratio = 1.8). Acute Lymphoblastic Leukemia (ALL) was common in 35% of cases, followed by osteosarcoma as a solid tumour in a further 30%. Half of our patients presented profound neutropenia with neutrophils below 100 elements/mm^3, with a strong expression of the nose and throat (ENT)-Stomatological signs (25%) dominated by mucositis. Blood cultures were positive in 36% of cases and identified a germ, the most common was *Escherichia coli* (33.3%), followed by *Staphylococcus aureus* (22.2%) and *Klebsiella pneumoniae* (22.2%). The combination of ceftriaxone and gentamicin has been shown to be effective, with a

20% failure rate. The occurrence of febrile neutropenia with children remains a problem, but identification of the germs and their resistance profile allows for selecting an adapted antibiotic therapy.

Keywords

Bacteriological Profile, Febrile Neutropenia, Pediatric Oncology

1. Introduction

Febrile neutropenia (FN) is defined by IDSA (Infectious Diseases Society of America) as: a rate of neutrophils < 500 el/mm^3 or between 500 and 1000 el/mm^3 and soon (within 24 h) < 500 el/mm^3 (likely to become <500 el/mm^3 within 24 h) [1]. The febrile nature of neutropenia is defined as a temperature equal to 38.3˚C or higher on a single visit or 38˚C or higher measured twice within an hour without the use of antipyretics [1].

Febrile neutropenia (FN) is a medical emergency in pediatric oncology. It is the main infectious complication in children treated with chemotherapy. Its severity depends on the depth and duration of immunosuppression, associated co-morbidities and the quality of management. This situation requires parenteral antibiotic therapy to be administered empirically, in accordance with commonly accepted recommendations and adapted to the bacterial ecology of the hospital setting. To date, there are no studies describing the bacterial ecology of chemo-induced febrile neutropenia in our working context. The objective is therefore to obtain the most frequent trends so that treatment can be adapted to our environment.

The objective of our study was to investigate the bacterial ecology of febrile neutropenia in our Pediatric Oncology Department by identifying the causative germs and their resistance profile.

2. Materials and Method

This was a prospective, descriptive, observational study conducted at the Mother and Child hospital from June 2021 to June 2023. The study population consisted of all children and adolescents hospitalized for febrile neutropenia during the study period. Sociodemographic, clinical and paraclinical data were entered on a survey form.

The various paraclinical tests were carried out in accordance with the department's protocol, which was based on the following principles: systematic assessment (blood count, two sets of consecutive blood cultures, cytobacteriological examination of urine CBEU) and assessment according to the evolution of the disease (abdominal ultrasound if fever persisted for more than 5 days, thoracic Xray or CT scan if fever persisted for more than 7 days).

Blood cultures were taken before initiating empirical therapy. Failure was defined as persistence of fever under well-administered antibiotic therapy for 5 days

and required the administration of a second line of treatment, which was either a third-generation cephalosporin, carbapenems, antifungals or antivirals.

The same patient could be included several times for different episodes. The data were analyzed using EPI info software.

The confidentiality of the data was respected. We obtained verbal agreement from the families to participate in the study and they did not express any opposition.

3. Results

Table 1. Sensitivity profile of isolated germs to beta-lactam antibiotics.

	Staphylococcus aureus	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
Amoxicillin	0	0	0	0
Ampicillin	_	0	0	_
Ticarcilin	0	0	0	_
Pipercillin_Tazobactam	50%	100%	100%	100%
Cefalexin	50%	_	_	0
cefuroxim	50%	33.33%	_	0
Cefoxitin	50%	100%	100%	_
Cefpodoxim	50%	_	50%	0
Cefotaxim	50%	33.33%	50%	_
Ceftriaxon	50%	_	_	0
Ceftazidim	0	33.33%	_	100%
Imipenem	50%	100%	100%	100%
Meropenem	50%	100%	100%	100%
Ertapenem	50%	100%	100%	_

We followed 181 patients during the study period. Our study involved 25 episodes of febrile neutropenia, occurring in 20 patients, over a 2-year period (June 2021-June 2023) with an incidence of 11%. Patients with febrile neutropenia ranged in age from 5 to 12 years with a mean age of 8.9 ± 3.6 years and were predominantly male (sex ratio = 1.8). The type of underlying cancer was hematological, dominated by acute lymphoblastic leukemia (ALL) in 35% of cases; Burkitt's lymphoma in 25% of cases, followed by osteosarcoma as a solid tumor in 33% of cases and soft tissue sarcomas (3%), neuroblastoma (2%), malignant germ cell tumors (2%). During episodes of neutropenia, half of our patients presented neutrophils between 100 and 500 elements, with a strong expression of the ENT-Stomatological signs (25%), dominated by mucositis (20%), followed by digestive signs (35%), which may constitute the most frequent gateway of infection. No central venous catheter had been inserted in any of our patients. Antibiotic treatment had been

received prior to blood cultures in 44% of cases, consisting of amoxicillin clavulanic acid 100 mg/kg/d (45.5%) and ceftriaxone 100 mg/kg/d (54.5%). Blood cultures were taken during each episode and came back positive in 36% of cases, with *Escherichia coli* (33.3%) the most common germ, followed by meticillin-resistant *Staphylococcus aureus* (22.2%) and *Klebsiella pneumoniae* (22.2%). X-rays were taken in 40% of cases, with 16% showing radiographic abnormalities (dullness). Cytobacteriological Examination of Urine (CBEU) were carried out in 60% of cases, with a positive rate of 6.6%, isolating a *Staphylococcus hemolitycus*. *Escherichia coli* showed sensitivity to piperacillin-tazobactam, carbapenems, aminoglycosides and ofloxacin (Table 1, Table 2). The combination of ceftriaxone and gentamicin (5 mg/d for 5days) had a favorable outcome. The mean duration of treatment was 10.3 days, with extremes ranging from 03 to 16 days. The duration of treatment from 07 to 10 days was the most frequent at 44%. Treatment failure occurred in 20% of cases, leading to treatment with carbapenems (15 - 25 mg/kg/6 h), antifungals (fluconazole 12 mg/kg/d) or antivirals (acyclovir 10 - 20 mg/kg/d). The average hospital stay was 30.42 days, with extremes ranging from 06 to 72 days.

Table 2. Sensitivity of isolated germs to aminoglycosides, quinolones, cyclins, glycopeptides, macrolides, lincosamides, oxazolidinone and sulphonamides.

	Staphylococcus aureus	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
Gentamicin	100%	66.66%	0	100%
Amikacin	_	100%	100%	100%
Netilmicin	100%	66.66%	_	100%
Tobramycin	_	66.66%	0%	100%
Ofloxacin	0%	0	100%	_
Ciprofloxacin	_	_	100%	100%
Levofloxacin	0%	_	100%	_
Norfloxacin	0%	_	_	_
Moxifloxacin	0%	_	_	_
Doxycyclin	50%	_	_	_
Tetracyclin	50%	_	_	_
Teicoplanin	50%	_	_	_
Vancomycin	50%	_	_	_
Erythromicin	50%	_	_	_
Clindamycin	50%	_	_	_
Linezolide	100%	_	_	_
sulfamethoxazol-trimethopim	100%	_	100%	_

The death rate was 15%. These were 3 patients suffering from acute leukemia in induction phase. The deaths occurred in a context of acute anemia with unavailability of blood transfusion.

4. Discussion

The average age of a patient with febrile neutropenia was 8.9 years, with a majority in the 5 to 12 age group, as in the series of Salhi S in 2018 in Marrakech, where the average age was 9.14 years, with a majority in the 5 to 11 age group [2]. A difference in age was observed with the studies of Al Omar in Jordan in 2013 and Özdemir in Turkey in 2016 which found a mean age of 7.14 years [3] [4]. This could be assimilated to the variation in patient selection and recruitment methods, although age does not appear to be a factor influencing the occurrence of febrile neutropenia, just like sex. However, there are similarities in the predominance of males and the sex ratio with the study of Özdemir in Turkey in 2016 (sex ratio = 1.3) and Le Carrer in France in 2014 (sex ratio = 1.03) [4] [5]. The incidence and severity of febrile neutropenia increase with the management of hematological pathologies, particularly with the treatment of ALL or lymphoma, which explains the predominance of hematological malignancies representing most underlying tumors. These results are consistent with several studies, including those of Salhi S in Marrakech in 2018 (61.5% hematological malignancies and 33.3% solid tumors), and Mahmud in Pakistan in 2004 (60% hematological malignancies and 40% solid tumors) [2] [6]. These findings could be due to several factors: hematological malignancies are more common in children, febrile neutropenia in hematological malignancies is not caused solely by chemotherapy but can also be seen in the context of medullary invasion by blasts. Furthermore, the corresponding chemotherapy targets hematological cells and more frequently leads to neutropenia [2]. In the field of hematological malignancies, there has been a strong trend in favor of ALL, which is the most common hematological tumors, according to studies carried out in France, Morocco, India and Pakistan. The results of Le Carrer in France in 2014 expressed 27.7% of ALL, 19.4% of lymphomas and 6.2% of Acute Myeloblastic Leukemia (AML) and those of Mohib S, Morocco, 2013 expressed 26.1% of ALL against 25% of Lymphomas [5] [7]. However, the predominance between ALL and lymphoma varies with higher rates of ALL as in the study by Mahmud in Pakistan (in 2004) finding 44% of ALL, 8% of AML and 8% of lymphoma and the study by Das (India, 2017) with 74.2% of ALL, 9.2% of AML and 5.2% of lymphoma [6] [8]. In Pakistan, leukemia (31%) and lymphoma (20%) are the main childhood cancers according to the Karachi Cancer Registry in Pakistan [9]. Data from the Punjab Cancer Registry showed that lymphoma (31%) was relatively more common than leukemia (23%) [10]. In India, common childhood malignancies include leukemia (the most common, 30% - 40%), brain tumors (20%) and lymphoma (12%), followed by neuroblastoma, retinoblastoma and tumors of the soft tissues, bones and gonads [11]. During FN, fever was associated with other clinical signs of several systems, of which the ENT-Stomatolog-

ical system was the most expressive and even with significant proportions as in the study of Al Omar, with 62% ENT signs and the study of Le Carrer, which expressed 69% [3] [5]. Our series also shows a predominance of these signs, with a proportion of 26% of ENT signs in the study of Salhi S in Morocco in 2018 [2]. In addition to the atypical presentation and the rarity of clinical signs, the neutropenic febrile child is also unusual in the presence of clinical signs of several systems, which cannot be assimilated to a single infection; these clinical associations are sometimes individualized and sometimes not considered [2]. We frequently found an association of several systems in the expression of clinical signs, *i.e.* 41% in our series and 37% in the series of Salhi S [2]. Fever remains the most constant sign of febrile neutropenia, and sometimes the only one. The clinical presentation of neutropenic children is usually poor [12] [13]. Cytobacteriological examinations of urine were carried out in 60% of cases, due to difficulties in collecting urine from some children. Our blood cultures were positive in 36% of cases, enabling us to isolate Gram-negative bacilli in 66.6% of cases and Gram-positive cocci in 33.3% of cases. These results are in line with the study of Safia Masmoudi in Tunis in which Gram-negative bacilli (GNB) represented most organisms isolated from different samples in 66.6% of cases, Gram-positive cocci (GPC) were found in 24.2% of cases [14]. Similarly, in a study of chemo-induced neutropenia in children in Morocco in 2013 by Mohib S, the germs isolated regardless of the site were mainly GNB (58%), and less frequently GPC (22%) [7]. Adel A Hagag in Egypt in 2016 studied the bacterial and fungal pathogens in children with hematological tumors during febrile neutropenia and found a significantly higher rate of Gram-negative bacterial growth [14]. However, several recent epidemiological studies of adult and pediatric patients worldwide have confirmed the predominance of Gram-positive organisms over Gram-negative bacilli in microbiologically documented infections in neutropenic patients. This predominance is due in part to the almost universal use of central venous catheters with these patients, to antimicrobial prophylaxis directed mainly against gram-negative enteric bacilli, and to the frequent administration of chemotherapy which produces significant oral mucositis [15]. The germs most frequently found in the GNB category are *Escherichia coli*, followed by *Klebsiella* spp. and *Pseudomonas aeruginosa*. *Escherichia coli* ranks as the most isolated germ in several studies, such as those by Özdemir in Turkey, and Lam in Singapore, but at 25% in the Le Carrer study in France which is close to our series (33.3%) [5] [6] [9]. *Escherichia coli*, the most common GNB in our series of neutropenic patients, is naturally sensitive to all beta-lactam antibiotics. *Escherichia coli* resistance to amino-penicillin is primarily linked to the production of TEM-1 penicillinase, an enzyme present in other bacterial genera [16]. The presence of beta-lactamases confers resistance to all beta-lactam antibiotics. This is consistent with our series, in which *Escherichia coli* shows resistance to penicillin and ofloxacin, and increasing resistance to cephalosporins, particularly 2nd (cefuroxime) and 3rd generation cephalosporins (cefotaxime, ceftazidime), but remains sensitive to piperacillin-tazobactam, carbapenems and amikacin.

However, resistance to other aminoglycosides (gentamicin, netilmicin and tobramycin) is gradually emerging. *Staphylococcus aureus* is the most common Gram-positive cocci, resistant to penicillin and fluoroquinolones but moderately sensitive to piperacillin-tazobactam, cephalosporins, carbapenems, glycopeptides and macrolides. But remains sensitive to aminoglycosides. *Pseudomonas aeruginosa* is resistant to all beta-lactam antibiotics except ceftazidime. It is also sensitive to piperacillin-tazobactam, carbapenems, all aminoglycosides and ciprofloxacin, which is in line with the study by Mahmud *et al. Pseudomonas aeruginosa* was 100% sensitive to amikacin and ciprofloxacin and 66.7% sensitive to piperacillin, ceftazidime and cefotaxime. Several treatment regimens for febrile neutropenia have been proposed in the literature. Despite extensive clinical studies since the 1970s, no single empirical regimen for the initial treatment of febrile neutropenic patients has been recommended. The choice of a specific antibiotic regimen should, however, depend on the local epidemiology, the type and sensitivity profiles of bacterial isolates in the institution, as well as the experience of the physician and the type of patients being treated. The use of some antibiotics may be limited by special circumstances, such as drug or organ allergy (e.g. renal or hepatic) [17]. Several studies have shown no striking difference between monotherapy and multiple-drug combinations for the empirical treatment of uncomplicated febrile episodes with neutropenic patients [18] [19]. In our series, the empirical protocol most used for febrile neutropenia was a combination of Ceftriaxone and Gentamicin. This therapy proved effective, with thermal defervescence in less than 48 hours. In the series of Faten F, 62% of febrile neutropenia episodes treated with parenteral dual therapy (third generation cephalosporin and Aminoside) progressed well according to the IHS definition [12]. In the study by Mahmud in Pakistan, a combination of ceftazidime and amikacin was used as empirical antibiotic therapy with a response rate of 61.3% [6]. However, 3rd or 4th generation cephalosporins (ceftazidime or cefepime, imipenem-cilastatin or meropenem) can be used successfully as monotherapy [20] [21]. Analysis of the resistance found and the results of our study, together with those of other studies, have enabled us to develop a management protocol for febrile neutropenia aimed at reducing the spectrum and limiting the duration of antibiotic therapy (**Table 3**).

Table 3. Guidelines for the management of febrile neutropenia.

Situation	Conduct
Febrile neutropenia	1rst line: 3GC (ceftriaxone/cefotaxime/ceftazidime)
Febrile neutropenia + severe sepsis	third generation cephalosporin + Aminoglycosides
Failure (persistence of fever after 3 days of well-administered antibiotic therapy)	2nd line: piperacillin-tazobactam or carbapenems
Failure	3rd-line: antifungals and/or antivirals

5. Conclusion

Patients with ALL, lymphoma and osteosarcoma are the most likely to develop febrile neutropenia. The most important investigations are a blood culture, a CBEU and a chest X-ray to identify the causative organism. However, as bacteriological documentation is found in few cases, probabilistic antibiotic therapy is required, with administration of 3rd generation cephalosporins in the first line and piperacillin-tazobactam or carbapenem in the 2nd line if the fever persists. We recommend this because of the observed bacterial resistance of *E coli*. It remains essential to consider antifungal or antiviral treatment as a 3rd-line option. In our work context, mortality is affected by systemic healthcare challenges in addition to infection management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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