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RESEARCH ARTICLE

Neutropenic Fever in Pediatric Patients with Cancer in South Egypt: A Report from a Single Institute

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ABSTRACT

Background: Fever and neutropenia (FN) is a potentially life-threatening complication of chemotherapy in children with cancer. **Aim:** Our objectives were to describe the characteristics of episodes of FN experienced by our patients and evaluate their outcomes and factors affecting them. **Material & Methods:** A prospective observational study was conducted at Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University. All pediatric patients ≤ 18 years with either hematological or solid tumors admitted with documented episodes of FN after receiving myelosuppressive chemotherapy were included in this study between February 2018 and February 2020. **Results:** 200 episodes of FN experienced by 125 pediatric cancer patients were included. The median age was six years; 60% of the patients were boys. FN was more prevalent among patients with hematological malignancies. Associated comorbidities were reported in 10.5%. Eighty percent of episodes were stratified as high-risk, with profound neutropenia reported in 47%. The focus of infection was documented in 82% of episodes. Blood-stream infections were 53.1% for Gram-negative and 24.4% for fungal isolates. Infection-related mortality was reported in 7% of episodes. Diagnosis, disease status, risk stratification, presence of comorbidity, and the grade of neutropenia significantly affected the outcome. **Conclusion:** Although satisfactory therapeutic interventions for neutropenic patients with fever, life-threatening resistant bacterial and fungal isolates were reported at high rates that mandate calling for an urgent review of infection control policy.

Keywords: Fever, Neutropenia, Pediatric, Oncology, South Egypt

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INTRODUCTION

Treatment advances in cytotoxic chemotherapy and immune-based therapies have increased patient survival rates (Ardura MI and Koh AY, 2021). The most frequent potentially fatal complication of chemotherapy in pediatric cancer patients is fever and neutropenia (FN). Patients who develop FN can be classified as low or high risk of complications considering some risk factors such as comorbidities, functional status, source of infection, or organ failure (Haro Acosta, 2019). FN can also lead to dose reductions, delays, or even discontinuation of chemotherapeutic agents, which may compromise treatment outcomes (Boada Burutaran et al., 2014). The advances in the management with emergency hospitalization and empirical administration of intravenous broad-spectrum antibiotics have decreased mortality to below 1% in pediatric FN episodes (Stergiotis et al., 2021).

In our institute, (South Egypt Cancer Institute (SECI), Assiut University, Assiut, Egypt), there is limited data concerning FN episodes in pediatric patients. So, in this study, we aimed to describe the characteristics of episodes of FN experienced by patients in our tertiary hospital and the pattern of blood-stream infections and evaluate their outcomes.

MATERIAL & METHODS

Material

This prospective study included 200 episodes of FN documented in 125 pediatric patients who were admitted to the Pediatric Hematology and Oncology Department, SECI, Assiut University, in the period from February 2018 to February 2020.

Inclusion criteria: All pediatric patients ≤ 18 years with either hematological or solid tumors admitted with documented episodes of FN after receiving myelosuppressive chemotherapy were included in this study.

Exclusion criteria: Patients who developed attacks of FN post bone marrow transplant (BMT) or radiotherapy (RTH) were excluded from the study.

Definitions: *Neutropenia* is defined as an absolute neutrophil count (ANC) <500 cells/microL or ANC <1,000 cells/microL expected to decrease to <500 cells/microL within a 48-hour period. *Fever* is defined as a single oral temperature of greater than 38.3°C or an oral temperature greater than 38°C sustained for 1 hour or occurring twice within a 24h period (Zimmer & Freifeld, 2019).

Methods

All patients were subjected to

- **Detailed history included:** demographic data: age, sex, diagnosis, disease status (denovo or relapsed), presence of intravascular catheters or other devices, and presence of co-morbid conditions.
- **Analysis of episodes of FN:** duration, grade of neutropenia (mild, moderate, severe, and profound) (Haro Acosta, 2019), associated fever and its duration, concomitant infection (bacterial, fungal, viral) or its complication, duration of antibiotics, and duration of hospitalization.
- **Assessment of the patients by complete physical examination and investigations:** complete physical examination and routine laboratory investigations [complete blood count (CBC), blood cultures, C-reactive protein (CRP), chemistry, electrolytes]. Radiological evaluation was done when indicated.

Risk assessment and intervention

After the initial assessment, patients were classified according to the guidelines of The Infectious Diseases Society of America (IDSA) into low risk (LR) and high risk (HR) of complications (Freifeld et al., 2011). Then the standard treatment plan of FN according to our department policy was applied as the following:

HR group: Initial dual intravenous antibiotic therapy including an antipseudomonal beta-lactam in addition to amikacin, with modifications of initial antimicrobial regimens done according to Koh and Pizzo (Koh and Pizzo, 2016).

LR group: Third-generation cephalosporins (cefotaxime) as **monotherapy** as initial therapy, oral regimen ciprofloxacin plus amoxicillin-clavulanic acid as outpatient management was given to the patients if they are clinically stable and have adequate GIT absorption.

Outcome: We assessed the outcome of all patients regarding recovery, delay in subsequent chemotherapeutic doses or infection-related mortality, and prognostic factors affecting it.

Statistical analysis

Data entry and data analysis were done using SPSS version 24 (Statistical Package for Social Science). Data were presented as numbers, percentages, mean, and standard deviation. Chi-square test and Fisher Exact test were used to compare qualitative variables. An independent sample t-test was used to compare quantitative variables between groups. P-value considered statistically significant when $P < 0.05$. Using Paired T to compare variables in the same group.

Ethical considerations

This study was reviewed and approved by the Institutional Review Board of SECI, Assiut, Egypt (Approval No. 431). Informed consent was taken from the child's parents before including the patient in the study.

RESULTS

Patient characteristics

Table 1 shows demographic data and characteristics of patients included in the study. The median age was six years; 60% of patients were boys. Forty-nine patients (39.2%) diagnosed with hematological malignancies who experienced 85 (42.5%) episodes of FN {acute myeloid leukemia (AML) in 50 (25%) episode, non-Hodgkin lymphoma (NHL) 26 (13%) episodes and acute lymphoblastic leukemia (ALL) 5 episodes (2.5%) episodes}, while 76 of patients (60.8%) diagnosed to had

solid tumors who experienced 115 episodes of FN (57.5%) {neuroblastoma (NB) in 52 (26%) episodes, Ewing sarcoma in 16 (8%) episodes and Wilm's tumor in 9 (4.5%) episodes}. The majority (81.6%) were stratified as HR, and the remaining 23 patients (18.4%) had criteria of LR. Comorbidities were reported in 10.5% of patients, mainly fungal chest infections.

Analysis of neutropenic episodes

The onset of neutropenic episodes ranged between 5-14 days with a mean of 8.7 ± 1.9 and a median of 9 days of last chemotherapy. The amplitude was reported within a median of 10 days and recovery was achieved within a median of 16 days. Most of our patients (70%) had severe to profound neutropenia.

Table 2 demonstrates the criteria of neutropenic episodes that occurred in the study group. Gastrointestinal (GIT) infections were the most common documented focus of infection (73%) followed by respiratory tract infection (RTI) (31%); however, no focus of infection was documented in 18% of episodes. Invasive fungal diseases (IFDs) were documented as follows proven infection in 2 cases (1%), probable infection in 8 cases (4%), and possible infection in 16 cases (8%). 18 viral infections (9%) were clinically diagnosed.

Regarding blood cultures, positive isolates were reported in 49 (23.1%) episodes. As shown in Table 3, the pattern of blood-stream infections (BSI) with the predominance of gram-negative isolates (53.1%). The most common complications that occurred in the study group were hepatic cell failure in 5 (2.5%), renal failure in 4 (2%), respiratory failure in 4 (2%), cardiovascular in 3 (1.5%), and neurological complications in 2 (1%).

Intervention

The mean duration of antibiotic therapy was 8.41 ± 3.85 days (3-26), with a median of eight days.

HR group: 93 (46.5%) episodes treated with initial double intravenous antibiotic in form of: cefepime +amikacin (n=40, 43%), piperacillin-tazobactam+amikacin (n=30, 32.3%), 23 (24.7%) received meropenem + amikacin, and 70 (35%) episodes received triple therapy (after addition of vancomycin). Regarding antifungal therapy, fluconazole was used in 30 episodes (15%), 40 (20%) with liposomal amphotericin, 9 episodes (4.5%) treated with caspofungin, voriconazole used only in 5 (2.5%) episodes.

LR group: among the 37 episodes stratified as a low risk, only 17 (8.5%) episodes received IV monotherapy in the hospital.

Outcome: Chemotherapy delay was reported in 41 (20.5%) episodes with a mean duration of 4.60 ± 2.35 days (1-15). Recovery was reported in 186 (93%) of episodes of FN, while infection-related mortality was reported in 14 (7%) of episodes. Type of malignancy ($P<0.05$), disease status ($P<0.01$), presence of comorbidity ($P<0.01$), grade of neutropenia ($P<0.04$), and risk stratification ($P<0.001$), were significantly affecting the outcome Table 4.

DISCUSSION

Neutropenia is a common complication of myelosuppressive chemotherapy, often causing hospitalization to manage a febrile patient who has an increased risk of sepsis and infection-related mortality (Mack et al., 2019). FN remains a life-threatening medical condition, despite the wide availability of effective antimicrobial therapies (Innocenti et al., 2019).

In our institution, no sufficient studies are available regarding the management of FN in those pediatric populations. Only one previous study was carried out to assess neutropenic enterocolitis (NE) in patients diagnosed with leukemias (Fouad et al., 2020). We aimed to describe the characteristics of episodes of FN developed by patients diagnosed to have either hematological or solid tumors and their outcome.

This study was conducted on 125 patients who experienced 200 episodes of FN. The mean age was 6.9 years, this is nearly the same as the study reported in National Cancer Institute (NCI) in Egypt but less than that reported in Turkey, with the mean age was 7.5 years (El-Mahallawy et al., 2015; Kara et al., 2019). The male gender was predominant (60%), this was comparable to national and international

Table 1. General characteristics of 125 pediatric oncological patients who experienced fever neutropenia.

Variable	N (%)
Age (years)	
Mean ±SD (Range)	6.91± 3.9 (0.75- 16)
Median	6
Gender:	
Boys	75 (60)
Girls	50 (40)
Diagnosis:	
Hematological malignancies	49 (39.2)
Solid tumors	76 (60.8)
Disease status	
Denovo	113 (90.4)
Relapse	12 (9.6)
Risk Stratification	
Low Risk	23 (18.4)
High risk	102 (81.6)
Presence of co-morbid illness	21 (8)
Fungal chest infection	8 (6.4)
Seizures	5 (4)
Hypertension	4 (3.2)
Congestive heart failure	1 (0.8)
Diabetes Mellitus	1 (0.8)

Table 2. The criteria of neutropenic episodes in the study group (N =200).

Variable	N (%)
Grade of neutropenia*	
Mild	15 (7.5)
Moderate	45 (22.5)
Severe	46 (23)
Profound	94 (47)
Fever	152 (76)
Duration (mean± SD)	4.66 ± 2.1
Focus of infection	**164 (82)**
GIT infection	146 (73)
Oral mucositis	*90 (45)*
Typhlitis	*40 (20)*
Esophagitis	*16 (8)*
Respiratory tract infection	62 (31)
Soft tissue infection	43 (21.5)
Catheter-related infection	19 (9.5)
CNS infection	2 (1)
Duration of hospitalization (mean± SD)	9.03 ± 2.04
< 5 days	34 (17)
5-10 days	114 (57)
> 10 days	52 (26)

* Mild neutropenia, 1000-1500cells/µl; Moderate neutropenia, 500-1000 cells/µl; Severe neutropenia, < 500/µl; Profound neutropenia, < 100 cells/µl.

Table 3. The pattern of blood-stream infections (BSI) among the study group (N=49)

Variable	N (%)
Gram-negative organism	**26 (53.1%)**
ESBL	6 (12.2%)
E. Coli	6 (12.2%)
K. pneumoniae	5 (10.2%)
S. paucimobilis	5 (10.2%)
Acinetobacter	4 (8.2%)
Gram-positive organism	**11 (22.4%)**
CoNS	2 (4.1%)
MRSA	4 (8.2%)
VRSA	5 (10.2%)
Fungal isolates	**12 (24.5%)**
Candida Species	6 (12.2%)
C. albican	3 (6.1%)
C. non albican	3 (6.1%)
C glabrata	*1 (2%)*
C dubliniensis	*1 (2%)*
C parapsilosis	*1 (2%)*
Aspergillus fumigatus	4 (8.2%)
Rhizopus	2 (4.1%)

ESBL; Extended-spectrum beta-lactamase, E. coli; Escherichia coli, K. pneumoniae; Klebsiella pneumoniae, S. paucimobilis; Sphingomonas paucimobilis, CoNS; Coagulase-negative Staphylococcus aureus, MRSA; Methicillin-resistant Staphylococcus aureus, VRSA; Vancomycin-resistant Staphylococcus aureus.

Table 4. Prognostic factors affecting the death rate of patients with febrile neutropenia (N=200)

Variable	Recovery "n=186"	Death "n=14"	*P-value*
Diagnosis			
Hematological malignancies	75 (40.9%)	10 (71.3%)	**P<0.05***
Solid tumors	111(59.6%)	4 (28.3%)	
Disease status			
Denovo	173(93%)	8(57.1%)	**P<0.01***
Relapse	13(7%)	6(42.9%)	
Grade of neutropenia			
Mild	15(8 %)	0	
Moderate	45(24.2 %)	0	**P<0.01***
Severe	40(21.5%)	6(42.9%)	
Profound	86(46.2%)	8(57.1%)	
Risk stratification			
Low risk	35(18.8%)	2(14.3%)	**P<0.04***
High risk	151(81.2%)	12(85.7%)	
Associated fever			
Yes	140(75.3%)	12(85.7%)	P=0.268
No	46(24.7%)	2(14.3%)	
Presence of comorbidity			
Yes	14(7.52%)	7(50.0%)	**P<0.001***
No	172(92.47%)	7(50.0%)	

**P-value* < 0.05 is statistically significant

studies with results reported as 62%, 54.5%, and 55%, respectively (El-Mahallawy et al., 2015; Fouad et al., 2020; Israels et al., 2021). Thirty-nine percent of patients who experienced 85 episodes of neutropenia were diagnosed to have hematological malignancies with the majority (25%) of them having AML followed by NHL (13%), while 60.8% of patients who experienced 115 episodes of neutropenia had solid tumors, mainly (26%) NB. This agrees with the study of Koçak et al. On the contrary, Mohammed et al. showed that 67% of episodes in their study were reported among patients with hematological malignancy mainly ALL (52%) followed by AML (7.4%), while 33% had solid tumors, mainly NB and sarcomas (Koçak et al., 2002; Mohammed et al., 2019).

The neutropenic episodes were recorded mainly in denovo cases (90.5%), this coincides with the study of Haro Acosta (Haro Acosta, 2019). According to risk stratification, 81.6% of the episodes were stratified to be HR. This is in similarity to the study of Miedema et al with HR episodes were (80%) (Miedema et al., 2016).

As a result of the predominance of AML cases in the current study, fungal chest infection was reported as the most common associated co-morbidity followed by seizures, this differs markedly from the study of Mohammed et al, in Ethiopia, whose patients show a higher incidence of cardiovascular affection with a predominance of hypertension (7.4%) and congestive heart failure (4.4%) as associated co-morbidity may be due to predominance of ALL cases who exposed to long periods of steroids among their patients (Mohammed et al., 2019).

Fifty-seven percent of the episodes required hospitalization between 5 to 10 days with a median time of 9 days. This duration is less than the study of Haro Acosta whose patients had a median time of hospitalization of 12 days but more than the study of Omar et al, who had a median time of hospitalization of 7 days (Haro Acosta, 2019; Omar et al., 2013).

On analysis of the neutropenic episodes, the median time of onset of neutropenia occurred after nine days of last chemotherapy and persisted for a median of seven days; this is in agreement with the study of Vathana et al who reported a median time of onset of eight days and persisted for a median of 7 days (Vathana et al, 2017).

Regarding grades of neutropenia, most of the episodes were recorded as profound and severe (47% and 23% respectively). This percentage is much lower than that was reported by Mohammed et al (88% profound neutropenia, 6% severe neutropenia) (Mohammed et al., 2019). This can be explained by a higher percentage of solid tumors reported in our study compared to hematological malignancies.

Associated fever during the episodes was recorded in 76% of episodes that persisted for a median of 4 days, this is nearly the same as the studies of (Badr et al., 2016; Vathana et al, 2017).

Fever of unknown origin (FUO) was reported in 18% of episodes, this is in agreement with the study of Haro Acosta, but much lower than the results of Boada Burutaran et al (Boada Burutaran et al., 2014; Haro Acosta, 2019). The most common focus of infection reported in the episodes was GIT 73% (oral mucositis in 45%, typhlitis in 20%, and esophagitis in 8%) followed by RTI at 31% then soft tissue infection at 21.5%. This approaches what was reported by the study of Mohamed et al. that oral mucositis was more prevalent (54.9%) followed by RTI (45.1%) and soft tissue infections (23.9%) during neutropenic episodes among their patients (Badr et al., 2016). On the other hand, Koçak et al reported the predominance of RTI and central venous catheter infections in their patients (Koçak et al., 2002). The higher percentage of GIT infection, mainly oral mucositis and typhlitis reported in our study can be explained by the predominance of cases of AML and NHL who received high dose cytarabine in the hematological malignancies' subgroup. IFDs were categorized as proven, probable, and possible in 1, 4, and 8% of episodes respectively; this is nearly the same as reported by Linke et al (Linke et al., 2019).

In the current study, hepatic cell failure and renal failure were reported in (2.5%) and (2%), respectively. However, renal failure (4.8%) and respiratory failure (3.8) were the most common complications reported by the study of Haro Acosta (Haro Acosta, 2019).

Similar to the literature, 49 (23.13%) of the blood cultures were drawn in this study showed positivity for BSI (Kara et al., 2019). Gram-negative isolates (53.1%) predominated over the gram-positive organisms (22.4%); this is in agreement with the studies of El-Din et al and Thacker et al (El-Din et al., 2011; Thacker et al., 2014). However, the reverse was reported in the studies of El-Mahallawy et al and Mvalo et al with the predominance of gram-positive isolates (El-Mahallawy et al., 2015; Mvalo et al., 2018). This may be due to high rates of insertion of indwelling central venous catheters in both centers.

Extended-spectrum beta-lactamase (ESBL) accounted for (12.2%) of isolates, E-coli (12.2%), and Klebsiella (10.2%), which differ from those mentioned by Thacker et al. who reported 24% for ESBL, 28.4% for E-coli and 22.1% for Klebsiella (Thacker et al., 2014). Although the rate of gram-positive organisms was the lowest, the rate of VRSA was (45.5%) which is higher than El-Din et al., who reported 42%, El-Mahallawy et al., who reported 7.6%, and Amer et al., who reported no VRSA among their patients (Amer et al., 2017; El-Din et al., 2011; El-Mahallawy et al., 2015).

Furthermore, we reported a high rate of fungal isolates (24.5%) of blood cultures, 12.2% candida species (3 were candida albican and 3 were non-albican), 8.2% aspergillus-fumigatus, and 4.1% Rhizopus compared to that reported in the studies as Thacker et al. and Mvalo et al.; with 4.7% and 9.3%, respectively reported with colonization only by candida species (Mvalo et al., 2018; Thacker et al., 2014). This mandate calls for an urgent review of institutional antibiotic and antifungal usage, as well as infection control policy.

Unlike Mohammed et al who reported that 7.4% of the patients received monotherapy and 92.6% received combination antibiotics (75% with double therapy, 17.6% with triple therapy) (Mohammed et al., 2019), monotherapy was used only in (8.5%) of patients, versus 81.5% received combination antibiotic (46.5% double therapy and 35% triple therapy) with a higher rate of vancomycin use in this study. This may be due to the high rates of VRSA infections recorded among our patients. A combination of meropenem and amikacin was used in about 24.7% of episodes which is quite less than reported by Benanti et al who found that meropenem plus amikacin was used in 28.4 % of episodes (Benanti et al., 2019). This might be explained by less documented ESBL infections in our unit than in other studies.

Systemic antifungal therapy was used in 42% of the episodes with liposomal amphotericin B was the most common agent that was used in 20% of patients followed by fluconazole in 15%. This is unlike what was reported by Mohammed et al where systemic antifungal was given in 38.5% of episodes with the majority treated by fluconazole 31% followed by liposomal amphotericin 2.3% (Mohammed et al., 2019). This difference may be due to a high percentage of fungal isolates of Candida non-albican and other filamentous fungi in our patients.

Infection-related mortality was 7% which was lower than many studies (Al-Tawfiq et al., 2019; Israels et al., 2021). Regarding factors affecting the outcome, our study showed that many factors can adversely affect it such as patients who had hematological diseases, disease in relapse, presence of co-morbidities, HR criteria for FN, and severe to profound grades of neutropenia. These were in agreement with many international studies (Ahn et al., 2011; Assefa et al., 2017; Basu et al., 2005; Hartmann et al., 1997).

FN is a frequent side effect in pediatric cancer patients. Although a high incidence of profound neutropenia among our patients, the recovery rate was high indicating satisfactory supportive care provided to them. However, high incidence rates of VRSA and fungal isolates were reported that mandate calling for an urgent review of infection control policy.

CONFLICT OF INTEREST

The authors declare that no conflict of interest to disclose.

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REFERENCES

Ahn, S., Lee, Y. S., Chun, Y. H., Kwon, I. H., Kim, W., Lim, K. S., Kim, T. W., & Lee, K. H. (2011). Predictive factors of poor prognosis in cancer patients with chemotherapy-induced febrile neutropenia. Supportive Care in Cancer, 19(8), 1151–1158. https://doi.org/10.1007/s00520-010-0928-4

Al-Tawfiq, J. A., Hinedi, K., Khairallah, H., Saadeh, B., Abbasi, S., Noureen, M., Raza, S., & Alkhatti, A. (2019). Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study. Journal of Infection and Public Health, 12(3), 364–366. https://doi.org/10.1016/j.jiph.2018.12.006

Amer, W., Elrifaey, S., & Sharaby, R. (2017). Blood Stream Infections in Children with Malignancies: A Single-Center Experience Risk Factors, Microbiological Isolates, and Sensitivity Pattern. Microbiology Research Journal International, 18(3), 1–12. https://doi.org/10.9734/mrji/2017/30595

Ardura MI and Koh AY. (2021). Infectious Complications in Children with Underlying Malignancies. In Principles and Practice of Pediatric Oncology (8th ed, pp. 2875–3009). Lippincott Williams & Wilkins, a Wolters Kluwer business.

Assefa, S., Alemayehu, T., & Abebe, W. (2017). Factors Associated With Treatment Outcome of Pediatric Cancer Patients Admitted With Febrile Neutropenia in Tikuranbessa Specialized Teaching Hospital, Addis Ababa, Ethiopia. Ethiopian Medical Journal, 55(1), 43–47.

Badr, M., Hassan, T., Sakr, H., Karam, N., Rahman, D. A., Shahbah, D., Zakaria, M., & Fehr, S. (2016). Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences. Molecular and Clinical Oncology, 5(3), 300–306. https://doi.org/10.3892/mco.2016.957

Basu, S. K., Fernandez, I. D., Fisher, S. G., Asselin, B. L., & Lyman, G. H. (2005). Length of stay and mortality associated with febrile neutropenia among children with cancer. Journal of Clinical Oncology, 23(31), 7958–7966. https://doi.org/10.1200/JCO.2005.01.6378

Benanti, G. E., Brown, A. R. T., Shigle, T. L., Tarrand, J. J., Bhatti, M. M., McDaneld, P. M., Shelburne, S. A., & Aitken, S. L. (2019). Carbapenem versus cefepime or piperacillin-tazobactam for empiric treatment of bacteremia due to extended-spectrum-lactamase-producing Escherichia coli in patients with hematologic malignancy. Antimicrobial Agents and Chemotherapy, 63(2), 1–10. https://doi.org/10.1128/AAC.01813-18

Boada Burutaran, M., Guadagna, R., Grille, S., Stevenazzi, M., Guillermo, C., & Diaz, L. (2014). Results of high-risk neutropenia therapy of hematology-oncology patients in a university hospital in Uruguay. Revista Brasileira de Hematologia e Hemoterapia, 37(1), 28–33. https://doi.org/10.1016/j.bjhh.2014.11.012

El-Din, S. S. S., El-Rehewy, M. S., Ghazaly, M. M., & Abd-Elhamid, M. H. (2011). Biofilm Formation by Blood Stream Staphylococcal Isolates from Febrile Pediatric Cancer Patients at South Egypt Cancer Institute. Journal of American Science, 7(1), 674–686.

El-Mahallawy, H. A., Hassan, S. S., El-Wakil, M., Moneer, M. M., & Shalaby, L. (2015). Update on Healthcare-Associated Blood Stream Infections in Febrile Neutropenic Pediatric Oncology Patients. Journal of Cancer Therapy, 06(06), 504–510. https://doi.org/10.4236/jct.2015.66054

Fouad, E. R., Morsy, A. M., Kamel, H. E. M., & Ali, A. M. (2020). Neutropenic enterocolitis in pediatric leukemia patients treated with intensive chemotherapy in Upper Egypt. Pediatric Investigation, 4(1), 5–10. https://doi.org/10.1002/ped4.12174

Freifeld, A. G., Bow, E. J., Sepkowitz, K. A., Boeckh, M. J., Ito, J. I., Mullen, C. A., Raad, I. I., Rolston, K. V., Young, J. A. H., & Wingard, J. R. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases, 52(4). https://doi.org/10.1093/cid/cir073

Haro Acosta, M. E. (2019). Management of febrile neutropenia in pediatric cancer patients. Journal of Pediatrics & Neonatal Care, 9(1), 22–26. https://doi.org/10.15406/jpnc.2019.09.00369

Hartmann, L. C., Tschetter, L. K., Habermann, T. M., Ebbert, L. P., Johnson, P. S., Mailliard, J. A., Levitt, R., Suman, V. J., Witzig, T. E., Wieand, H. S., Miller, L. L., Moertel, C. G., Grendahl, D. C., & Herrera, D. M. (1997). Granulocyte Colony-Stimulating Factor in Severe Chemotherapy-Induced Afebrile Neutropenia. New England Journal of Medicine, 336(25), 1776–1780. https://doi.org/10.1056/nejm199706193362502

Innocenti, R., Rigacci, L., Restelli, U., Scappini, B., Gianfaldoni, G., Fanci, R., Mannelli, F., Scolari, F., Croce, D., Bonizzoni, E., Perrone, T., & Bosi, A. (2019). Lenograstim and filgrastim in the febrile neutropenia prophylaxis of hospitalized

patients: Efficacy and cost of the prophylaxis in a retrospective survey. Journal of Blood Medicine, 10, 21–27. https://doi.org/10.2147/JBM.S186786

Israels, T., Afungchwi, G. M., Klootwijk, L., Njuguna, F., Hesseling, P., Kouya, F., Paintsil, V., Landman, L., Chitsike, I., Chagaluka, G., Sung, L., & Molyneux, E. (2021). Fever and neutropenia outcomes and areas for intervention: A report from SUCCOUR - Supportive Care for Children with Cancer in Africa. Pediatric Blood and Cancer, 68(9), 1–6. https://doi.org/10.1002/pbc.29224

Kara, S. S., Tezer, H., Polat, M., Cura Yayla, B. C., Bedir Demirdağ, T., Okur, A., Fettah, A., Kanik Yüksek, S., Tapisiz, A., Kaya, Z., Özbek, N., Yenicesu, İ., Yarali, N., & Koçak, Ü. (2019). Risk factors for bacteremia in children with febrile neutropenia. Turkish Journal of Medical Sciences, 49(4), 1198–1205. https://doi.org/10.3906/sag-1901-90

Koçak, Ü., Rolston, K. V. I., & Mullen, C. A. (2002). Fever and neutropenia in children with solid tumors is similar in severity and outcome to that in children with leukemia. Supportive Care in Cancer, 10(1), 58–64. https://doi.org/10.1007/s005200100277

Koh and Pizzo. (2016). Infectious Complications in Pediatric Cancer Patients. In Principles and Practice of Pediatric Oncology (7th ed, pp. 1190–1242). Lippincott Williams & Wilkins, a Wolters Kluwer business.

Linke, C., Tragiannidis, A., Ahlmann, M., Fröhlich, B., Wältermann, M., Burkhardt, B., Rossig, C., & Groll, A. H. (2019). Epidemiology and management burden of invasive fungal infections after autologous hematopoietic stem cell transplantation: 10-year experience at a European Pediatric Cancer Center. Mycoses, 62(10), 954–960. https://doi.org/10.1111/myc.12968

Mack, J. M., Spray, B. J., Mack, D., Mason, K., & Becton, D. (2019). Pegfilgrastim Administration Timing and its Effect on Febrile Neutropenia in Pediatric Cancer Patients. 6, 37–41. https://doi.org/10.15436/2377-0902.19.2546

Miedema, K. G. E., Tissing, W. J. E., Abbink, F. C. H., Ball, L. M., Michiels, E. M. C., Van Vliet, M. J., De Vries, W. Y., Kamps, W. A., Norbruis, O. F., Fiocco, M., De Groot-Kruseman, H. A., Van De Wetering, M. D., & De Bont, E. S. J. M. (2016). Risk-adapted approach for fever and neutropenia in pediatric cancer patients - A national multicentre study. European Journal of Cancer, 53, 16–24. https://doi.org/10.1016/j.ejca.2015.10.065

Mohammed, H. B., Yismaw, M. B., Fentie, A. M., & Tadesse, T. A. (2019). Febrile neutropenia management in pediatric cancer patients at Ethiopian Tertiary Care Teaching Hospital. BMC Research Notes, 12(1), 1–6. https://doi.org/10.1186/s13104-019-4569-5

Mvalo, T., Eley, B., Bamford, C., Stanley, C., Chagomerana, M., Hendricks, M., Van Eyssen, A., & Davidson, A. (2018). Bloodstream infections in oncology patients at Red Cross War Memorial Children's Hospital, Cape Town, from 2012 to 2014. International Journal of Infectious Diseases, 77, 40–47. https://doi.org/10.1016/j.ijid.2018.09.012

Omar, S. Al, Nazer, L., & Alkayed, K. (2013). A prospective study of febrile neutropenia in pediatric cancer patients in Jordan. Journal of Pediatric Hematology/Oncology, 35(8), 614–617. https://doi.org/10.1097/MPH.0b013e31829f3480

Stergiotis, M., Ammann, R. A., Droz, S., Koenig, C., & Abayie Agyeman, P. K. (2021). Pediatric fever in neutropenia with bacteremia—Pathogen distribution and in vitro antibiotic susceptibility patterns over time in a retrospective single-center cohort study. PLoS ONE, 16(2 February), 1–14. https://doi.org/10.1371/journal.pone.0246654

Thacker, N., Pereira, N., Banavali, S. D., Narula, G., Vora, T., Chinnaswamy, G., Prasad, M., Kelkar, R., Biswas, S., & Arora, B. (2014). Epidemiology of blood-stream infections in pediatric patients at a Tertiary Care Cancer Centre. Indian Journal of Cancer, 51(4), 438–441. https://doi.org/10.4103/0019-509X.175311

Vathana, N., Buaboonnam, J., & Thitipolpun, S., (2017). Prevalence Of Pathogens In Pediatric Cancer Patients With Febrile Neutropenia. Southeast Asian Journal Tropical Medical Public Health, 48(2), 151–160.

Zimmer, A. J., & Freifeld, A. G. (2019). Optimal management of neutropenic fever in patients with cancer. Journal of Oncology Practice, 15(1), 19–24. https://doi.org/10.1200/JOP.18.00269