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Review

Update on Febrile Neutropenia in Pediatric Oncological Patients Undergoing Chemotherapy

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Abstract: Febrile neutropenia (FN) is a common complication of chemotherapy in oncological children and one of the most important causes of morbidity and mortality in these patients. The early detection of a bacteremia and the rapid therapeutic intervention are crucial to improve the outcome. We analyzed the literature in order to clarify the epidemiology of FN in children undergoing chemotherapy, the specific factors associated with a negative outcome, the most common etiology, and the value of biological markers as a tool to make an early diagnosis or to monitor the evolution of the infection. Several studies have tried to identify specific factors that could help the clinician in the detection of an infection and in its microbiological identification. However, due to the heterogenicity of the available studies, sufficient evidence is lacking to establish the role of these risk factors in clinical practice and future research on this topic appear mandatory. Determinations of risk factors, etiology, and markers of febrile episodes in these patients are complicated by the characteristics of the underlying illness and the effects of treatments received. Although some studies have tried to develop an evidence-based guideline for the empiric management of FN in pediatrics, validated predictive scores and algorithms are still lacking and urgently needed.

Keywords: bacteremia; chemotherapy; febrile neutropenia; pediatric oncology; sepsis

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1. Introduction

Over the last decades, the prognosis of pediatric malignancies has progressively changed due to many factors, including a better knowledge of the biology of the diseases and an impressive improvement in supportive care. Nevertheless, febrile neutropenia (FN) remains a common complication of chemotherapy in oncological patients and one of the most important causes of morbidity and mortality [1,2]. Several researchers have tried to identify specific factors that could help the clinician in the detection of an infection and in its microbiological identification to improve the outcome of these children [2]. We analyzed the literature in order to clarify the epidemiology of FN in oncological children undergoing chemotherapy, the specific factors associated with a negative outcome in these patients, the most common etiology, and the value of biological markers as a tool to make an early diagnosis or to monitor the evolution of the infection.

2. Epidemiology of Febrile Neutropenia

FN is a leading cause of infectious mortality for oncological children receiving cytotoxic chemotherapies. Approximately one third of children treated for cancer or who underwent hematopoietic stem cell transplantation (HSCT) experienced FN during the

neutropenic period [2]. Mortality associated with FN in these patients ranges from 2% to 6% [3]. The incidence and rate of febrile complications varies according to treatment intensity. In a prospective study, Castagnola et al. showed that the highest proportions of neutropenic periods with primary febrile episodes were observed after autologous HSCT (58%), aggressive treatment for acute leukemia (AL) or non-Hodgkin lymphoma (NHL, 48%), and allogeneic HSCT (44%); the lowest proportion (9%) was observed during maintenance chemotherapy for AL [2].

The most common causes of FN are bloodstream infections (BSIs). A large national study demonstrated that neutropenia was associated with BSIs in patients affected by AL in 84% of cases, in comparison with 47% of patients with solid tumor and 55% of patients who received bone marrow transplant [4]. Fever may also occur as part of the underlying diseases for a number of other causes, such as viral or fungal infections, drug or transfusion reactions or mucositis [5]. However, considering the importance of an early diagnosis in case of infectious etiology in order to decrease mortality [2], it is essential to consider pediatric oncological patients with FN as at high risk of infectious complications.

3. Predictive Factors for Sepsis Risk and Negative Outcomes in Children with Oncological Disease and Febrile Neutropenia

Several predictive factors have been evaluated in order to determine sepsis risk and negative in pediatric oncological patients. It has been demonstrated that previous episodes of FN and time from last chemotherapy ≤7 days increased the risk of BSI in febrile neutropenic children [6,7]. Bothra et al. observed that > 3 previous FN episodes were associated with adverse outcomes such as mortality, invasive infections, and hemodynamic instability [7]. Rondinelli et al. reported that central venous catheter was an independent risk factor for severe infectious complications, including bacteremia in FN patients, particularly in the first phases of AL treatment [8]. Positive growth cultures of central line catheter during the previous 3 months increased the risk of bacteremia [6].

Neutropenia severity and duration relate directly to the development of sepsis in FN episodes, although the data from available studies are controversial. Kara et al. showed that neutrophil count < 100/ mm^3 and lower white blood cell counts (WBC) were associated with bacteremia [6]. In addition, Rondinelli et al. observed that neutrophil count lower than 500 cells/mm^3 represented a risk factor for severe complications in FN patients [8]. Freifeld and Pizzo observed that the risk to develop bacteremia and bacterial pneumonias were higher when neutrophil counts were < 100 cells/mm^3 [9]. They also reported that patients with long-term neutropenia were more susceptible to recurrent or new bacterial infections [9]. Similarly, Hughes et al. have demonstrated that neutrophil counts <100 cells/mm^3 were associated with high incidence of bacteremia [9,10]. However, Regazzoni et al. found no association between neutrophil count at admission and mortality in these children [11]. In addition to neutropenia, the absolute monocyte count may be useful in identifying children at high risk for bacteremia [12]. Monocytes counts lower than 100 cells/mm^3 represented an infection risk [8]. Madsen et al. showed that patients with high monocyte counts at admission presented a lower infection risk of bacteremia [13]. Other laboratory anomalies can represent a risk of infectious complications in FN pediatric patients, such as hemoglobin level < 7 g/dL and platelet counts < 20,000/mm^3 [8]. Badiei et al. showed a significant association between a platelet count < 20,000/mm^3 and life-threatening infections [14]. Thrombocytopenia works as a marker for marrow suppression and increased consumption in sepsis. Das et al. pointed out that platelet count < 20,000/mm^3 was an additional predictor for infections, while albumin < 2.5 g/dL and C reactive protein (CRP) > 90 mg/L were risk factors for infection-associated mortality in FN patients [15]. CRP > 90 mg/dL is one of the strongest predictive factors of infectious complications in children with FN and this assumption was confirmed by several studies. Santolaya et al. reported that CRP > 90 mg/L was associated with increased risk of invasive bacterial infection in children with cancer and FN [16]. An Indian research piece reported that CRP was useful to establish the diagnosis of infections, and serial CRP monitoring was

necessary in order to evaluate the response to antibiotic therapy in children with FN [17]. Furthermore, Asturias et al. identified a direct association between elevated CRP levels and the duration of FN, bacteremia, and mortality [18]. Moreover, it was observed that serum lactate > 3 mmol/L and serum bicarbonate < 17 mmol/L were associated with septic shock and mortality in neutropenic children [19].

Some authors observed a worse outcome in malnourished patients with cancer [20]. Low albumin level predicted worse outcome in many diseases including FN because hypoalbuminemia is a marker for malnutrition and inflammatory state [15,21]. The risk of bacteremia appeared higher in neutropenic cancer patients with fever > 39.0 °C [12,13,22]. Rondinelli et al. showed that temperature > 38.5 C in children with FN at admission was an independent predictive risk factor for septic shock [8]. Hypotension, tachycardia, and tachypnea were more often indicative of concurrent bacteremia in pediatric patients with FN. The National Institute for Health and Care Excellence (NICE) guidelines underline that hypotension and tachypnea were strong risk factors for septic complications [23]. In addition, Alberti et al. showed that heart rate > 120/min and systolic blood pressure < 110 mmHg were related to progression from sepsis to severe sepsis or septic shock [24].

The risk of sepsis in children with FN is different between hematological malignancies and solid tumors. Patients with hematological malignancies have higher risk for infection than patients with solid tumor. In fact, hematological diseases affect bone marrow and require more intensive myeloablative therapy, resulting in disruption of normal immune function [25]. Viscoli et al. observed that neutropenia was associated with bloodstream infections in patient affected by AL in 84% of cases, in comparison with 47% of patients with solid tumor and 55% of patients who received bone marrow transplant [4]. Furthermore, primary progressive or relapsed disease with bone marrow involvement in children < 5 years old appeared predictive of septic complications [6].

The state of the disease and its treatment are related with sepsis predisposition. Haupt et al. reported that patients receiving intense chemotherapy had infection rates six times higher than those receiving less intense therapies [7]. Ammann et al. showed that bone marrow involvement in patients with cancer was associated with double risk of bacteremia compared to children with cancer without bone marrow infiltrations [26].

The site of infection is also correlated with infectious prognosis. Reilly et al. observed that upper airway infections were more frequent in children with FN than adults [27]. It was also observed that an identified focus predicted higher risk of serious complications [28].

Studies on a predictive score for sepsis risk and outcome in oncological children with FN were performed. Green et al. tested the Ammann score based on hemoglobin ≥9 g/dL, white blood cell count (WBC) < 300/mm^3, platelet count < 50,000/mm^3 and intensive chemotherapy, although this score has not yet been prospectively validated [29]. In addition, Rondinelli et al. had suggested a score for predicting severe infection complications in patients with chemotherapy-induced FN and considered that severe bacterial infection was associated with bone marrow involvement, diagnosis of pre–B-cell leukemia, viral infection, CRP values, hemoglobin and leukocyte counts, and presence of central venous catheter [8]. Finally, Phillips et al. suggested the PICCNIC (predicting infections in children with cancer) predictive model was able to predict microbiologically documented infection: it included type of malignancy, maximum temperature, clinically severely unwell, hemoglobin, white cell count and absolute monocyte count [30].

Table 1 summarizes main risk factors associated with sepsis risk and negative outcomes in children with oncological disease and FN.

Table 1. Main risk factors associated with sepsis risk and negative outcomes in children with oncological disease and febrile neutropenia (FN).

Data	Negative Risk Factor
Clinical history	Previous history of FN

	Time from last chemotherapy ≤ 7 days
	Central venous catheter
Laboratory exams	Neutropenia severity (<100/mm^3) and duration
	Monocyte count < 100/mm^3
	Hemoglobin level < 7 g/dL
	Platelet count < 20,000/ mm^3
	Albumin < 2.5 g/dL
	C reactive protein > 90 mg/L
	Serum lactate > 3 mmol/L
	Serum bicarbonate < 17 mmol/L
Clinical data	Malnutrition
	Fever > 39 °C
	Hypotension
	Tachycardia
	Tachypnea
Type of cancer	Hematological malignancies
	Bone marrow involvement
	Requirement of intensive chemotherapy
	Bone marrow transplantation

4. Etiology of Infections in Febrile Episodes

Over the last few decades, the etiology of microbial-related FN episodes has changed. In the 1960s and 1970s, the principal agents responsible of bacteremia in febrile neutropenia were Gram-negative bacteria (GNB), mainly *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. In the 1980s bacteremia caused by Gram-positive cocci increased with the use of central line catheters, introduction of fluoroquinolone prophylaxis and use of intensive chemotherapy, causing severe mucositis [31]. However, bacteremia due to GNB increased again in the following years probably in correlation with the increase of fluoroquinolone-resistant GNB resulting from fluoroquinolone prophylaxis, and prevalence of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, multidrug-resistant (MDR) *P. aeruginosa* and *Acinetobacter baumannii* [30]. Lee et al. observed that the proportion of GNB in bacteremia cases in children with FN increased in parallel with the developing of antibiotic-resistant (AR) [32]. They showed that AR GNB infections caused worse prognosis compared with non-AR bacterial infections [32]. In addition, Akova et al. reported that the incidence of Gram-positive bacterial infections raised with the use of central venous catheters, quinolone prophylaxis and broad-spectrum empirical antibacterial therapy, although Gram-negative pathogens remained predominant [33]. Oberoi et al. pointed out that *Staphylococcus aureus* and *E. coli* were the most common Gram-positive and Gram-negative identified bacteria in children with febrile neutropenia, respectively [34]. Instead, Jeddi et al. found that *K. pneumoniae* and *S. aureus* were the predominant Gram-negative and Gram-positive bacteria, respectively [35].

Currently, the rate of GNB in pediatric onco-hematological patients with FN is increasing, and *E. coli* is the predominant pathogen [36]. In the last years, the emergence and diffusion of MDR *E. coli* have been observed. In a trial performed in children with onco-hematological disorders, Wang et al. reported that the frequency of septic shock was 51.1%, higher than the average rate of 5%–30% in studies of patients of all ages [37]. Despite the advent of potent antibiotics, *P. aeruginosa* infection is one of the most serious nosocomial infections related with high mortality in patients with immunosuppression or comorbidities, including FN [38,39].

Although bacteria are the most common agents involved in children with FN, fungal infections are an emerging concern. According to several studies, incidence of invasive fungal infection (IFI) varies from 2 to 36.5% [7,40]. Kumar et al. showed that Aspergillus

sp. was the most common fungal isolate, followed by *Candida* species [41]. Accordingly, Lehrnbecher et al. observed that *Aspergillus* was the most common species of fungi followed by Candida in children with FN [42]. On the contrary, Gupta et al. [40] and Villarroel et al. [43] showed that *Candida* was the most frequently isolated fungal species from blood cultures in children with FN. Lai et al. showed that prolonged neutropenia >30 days, prolonged steroids therapy, relapsed malignancy and bone marrow transplant were significantly associated with IFI risk [44]. Moreover, Villarroel et al. showed found that hypotension or shock within 24 h, fever, Absolute monocyte count (AMC) < 100/mm^3 and C reactive protein CRP > 90 mg/L were significant risk factors for IFI [43]. Several studies reported that death by fungal infection is relevant and deserves early intervention for prevention as well as treatment in pediatric FN [40,42,45].

The etiological diagnosis of FN in patients differ from those described in adults. A prospective multicenter study documented that in many FN episodes (78%), no microbiologically defined infection (MDI) was detected [46]. In addition, lack of MDI detection was related to shorter duration of fever and hospitalization, less need of intensive care and less intensive antimicrobial therapy compared with FN episodes with MDI [46]. The concept that infections can be observed only in a minority of pediatric cancer patients with FN has been challenged by studies relying on systematic identification of viral infections by molecular methods. In another two research studies, MDIs were reported in 67% and 60% of FN episodes, with respiratory virus infections detected by molecular methods in 57% and 46% of FN episodes, respectively [47]. The difference of MDI frequency is explained by different diagnostic procedures used for the detection of respiratory virus infections or by prevalence of non-infectious fever in these patients.

5. Markers of Infections in Febrile Neutropenia

Early diagnosis of patients at low risk of infections in FN allows to avoid antibiotics reducing cost as well as antibiotic resistance, whereas the precocious detection of children at high risk permits a prompt antimicrobial therapy that permits to reduce complications and mortality [2]. Neutropenia significantly changes the inflammatory response of the host and several markers have been evaluated as markers of infections. Many cytokines have been studied to identify a marker which could stratify infectious risk in children with FN, but their role is still evolving. The most studied markers are procalcitonin (PCT), CRP, interleukin (IL)-6, IL-8, and IL-10, which are usually involved in the inflammatory mechanisms [48–51]. Interestingly, lactate was not explored as a diagnostic biomarker, although it represents a risk factor for septic shock and mortality [52].

PCT has a higher specificity for bacterial infections than other acute phase reactants and it is produced in multiple organ tissues during infection [53], with no influence caused by an alteration in the number and function of leukocytes. It was found that at diagnosis and also at the beginning of neutropenia, PCT concentrations were similar to basal levels in healthy controls, whereas CRP concentrations were moderately elevated [53]. Nevertheless, both PCT and CRP were significantly higher at fever onset although, in the case of CRP this increase was independent of the etiology of fever [53]. Fleischhack et al. showed that PCT was superior to CRP, IL-8 and IL-1β for distinguishing between bacterial and viral infections among patients with AL on the first day of FN [54]. They also observed that at admission PCT level could predict FN outcome [54].

Cytokines resulted to be less specific in detecting bacterial infections despite the precocity of their elevation. IL-6 and IL-8 have been shown to increase much earlier than CRP [55]. Narendra et al. demonstrated that CRP, IL-6, and IL-8 at admission were not useful to differentiate the infectious etiology in FN, but they confirmed the importance of rise in CRP and not of IL-6 or IL-8 in monitoring the response to treatment [56].

Regarding the specific etiology, Ruokonen et al. found that PCT has a poor sensitivity in patients with FN and Gram-positive infections [57]. In IFI, the role of PCT is still debated. One research study that analyzed recent literature, concluded that in the early phase of IFI PCT was elevated in fewer than half of invasive candidiasis episodes and in

only one patient with invasive aspergillosis [58]. In addition, the role of serum PCT as a marker of prognosis in IFI has not been clarified. Studies of PCT levels in IFI have included a limited number of patients and the results are contradictory [59]. Christofilopoulou et al. found a significant PCT peak at around Day 10 associated with clinical complications [60]. This observation means that, according to their findings, the diagnostic role of PCT in IFI at onset is of limited value.

6. Conclusions

FN is a relevant cause of morbidity and mortality in pediatric oncological patients receiving chemotherapy. Early detection of an infectious etiology and the rapid therapeutic intervention are crucial to improve the outcome of these children. Several researchers have tried to identify specific factors that could help the clinician in the detection of an infection and in its microbiological identification. However, due to the heterogenicity of the available studies, sufficient evidence is lacking to establish the role of these risk factors in clinical practice and future research on this topic appear mandatory. Determinations of risk factors, etiology, and markers of febrile episodes in these patients are complicated by the characteristics of the underlying illness and the effects of treatments received. Although some studies have tried to develop an evidence-based guideline for the empiric management of FN in pediatrics [61–63], validated predictive scores and algorithms are still lacking and urgently needed.

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References

1. Cecinati, V.; Principi, N.; Brescia, L.; Esposito, S. Antibiotic prophylaxis in children with cancer or who have undergone hematopoietic cell transplantation. *Eur. J. Clin. Microbiol. Infect. Dis*. **2014**, *33*, 1–6.
2. Castagnola, E.; Fontana, V.; Caviglia, I.; Caruso, S.; Faraci, M.; Fioredda, F.; Garrè, M.L.; Moroni, C.; Conte, M.; Losurdo, G.; et al. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. *Clin. Infect. Dis.* **2007**, *45*, 1296–1304.
3. Basu, S.K.; Fernandez, I.D.; Fisher, S.G.; Asselin, B.L.; Lyman, G.H. Length of stay and mortality associated with febrile neutropenia among children with cancer. *J. Clin. Oncol*. **2005**, *23*, 7958–7966.
4. Girmenia, C.; Bertaina, A.; Piciocchi, A.; Perruccio, K.; Algarotti, A.; Busca, A.; Cattaneo, C.; Raiola, A.M.; Guidi, S.; Iori, A.P.; et al. Incidence, Risk Factors and Outcome of Pre-engraftment Gram-Negative Bacteremia After Alloge-neic and Autologous Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey. *Clin. Infect. Dis.* **2017**, *65*, 1884–1896.
5. Donnelly, J.P.; Chen, S.C.; Kauffman, C.A.; Steinbach, W.J.; Baddley, J.W.; Verweij, P.E.; Clancy, C.J.; Wingard, J.R.; Lockhart, S.R.; Groll, A.H.; et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the Eu-ropean Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Re-search Consortium. *Clin. Infect. Dis*. **2020**, *71*, 1367–1376.
6. Kara, S.S.; Tezer, H.; Polat, M.; Yayla, B.C.C.; Demirdağ, T.B.; Okur, A.; Fettah, A.; Yüksek, S.K.; Tapisiz, A.; Kaya, Z.; et al. Risk factors for bacteremia in children with febrile neutropenia. *Turk. J. Med. Sci.* **2019**, *49*, 1198–1205.
7. Bothra, M.; Seth, R.; Kapil, A.; Dwivedi, S.N.; Bhatnagar, S.; Xess, I. Evaluation of predictors of adverse outcome in febrile neutropenic episodes in pediatric oncology patients. *Indian J. Pediatr*. **2013**, *80*, 297–302.
8. Rondinelli, P.I.; Ribeiro Kde, C.; de Camargo, B. A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *J. Pediatr. Hematol. Oncol*. **2006**, *28*, 665–670.
9. Freifeld, A.; Pizzo, P.A. The outpatient management of febrile neutropenic in cancer patients. *Oncology* **1996**, *10*, 599–616.

10. Hughes, W.T.; Armstrong, D.; Bodey, G.P.; Brown, A.E.; Edwards, J.E.; Feld, R.; Pizzo, P.; Rolston, K.V.; Shenep, J.L.; Young, L.S. Guidelines for the use of antimicrobial agents in neutropenic pa-tients with unexplained fever. *J. Infect. Dis*. **1997**, *25*, 551–573.
11. Regazzoni, C.J.; Khoury, M.; Irrazabal, C.; Myburg, C.; Galvalisi, N.R.; O'Flaherty, M.; Sarquis, S.G.; Poderoso, J.J. Neutropenia and the development of the systemic inflammatory response syndrome. *Intensive Care Med.* **2003**, *29*, 35–138.
12. Tamburro, R. Pediatric cancer patients in clinical trials of sepsis: Factors that predispose to sepsis and stratify outcome. *Pediatr. Crit. Care Med.* **2005**, *6*(Suppl. S3), S87–S91.
13. Madsen, K.; Rosenman, M.; Hui, S.; Breitfeld, P.P. Value of electronic data for model validation and refinement: Bactere-mia risk in children with fever and neutropenia. *J. Pediatr. Hematol. Oncol*. **2002**, *24*, 256–262.
14. Badiei, Z.; Khalesi, M.; Alami, M.H.; Kianifar, H.R.; Banihashem, A.; Farhangi, H.; Razavi, A.R. Risk factors associated with lifethreatening infections in children with febrile neutropenia: A data mining approach. *J. Pediatr. Hematol. On-Col.* **2011**, *33*, e9–e12.
15. Das, A.; Trehan, A.; Bansal, D. Risk Factors for Microbiologically-documented Infections, Mortality and Prolonged Hospital Stay in Children with Febrile Neutropenia. *Indian Pediatr.* **2018**, *55*, 859–864.
16. Santolaya, M.E.; Alvarez, A.M.; Becker, A.; Cofré, J.; Enríquez, N.; O'Ryan, M.; Payá, E.; Pilorget, J.; Salgado, C.; Tordecilla, J.; et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia and fever. *J. Clin. Oncol.* **2001**, *19*, 3415–3421.
17. Avabratha, K.S.; Rau, A.T.; Venkataravanamma, P.; Rau, A. Significance of C-reactive protein during febrile neu-tropenia in pediatric malignancies. *Indian Pediatr.* **2009**, *46*, 797–799.
18. Asturias, E.J.; Corral, J.E.; Quezada, J. Evaluation of six risk factors for the development of bacteremia in children with cancer and febrile neutropenia. *Curr. Oncol.* **2010**, *17*, 59–63.
19. Ramzi, J.; Mohamed, Z.; Yosr, B.; Karima, K.; Raihane, B.; Lamia, A.; Hela, B.A.; Zaher, B.; Balkis, M. Predictive factors of septic shock and mortality in neutropenic patients. *Hematology* **2007**, *12*, 543–548.
20. Alexandre, J.; Gross-Goupil, M.; Falissard, B.; Nguyen, M.L.; Gornet, J.M.; Misset, J.L.; Goldwasser, F. Evaluation of the nutritional and inflammatory status in cancer patients for the risk assessment of severe haematological tox-icity following chemotherapy. *Ann. Oncol.* **2003**, *14*, 36–41.
21. Lehrnbecher, T.; Averbuch, D.; Castagnola, E.; Cesaro, S.; Ammann, R.A.; Garcia-Vidal, C.; Kanerva, J.; Lanternier, F.; Mesini, A.; Mikulska, M.; et al., 8th European Conference on Infections in Leukaemia: 2020 guidelines for the use of antibiotics in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol*. **2021**, *22*, e270-e280.
22. West, D.C.; Marcin, J.P.; Mawis, R.; He, J.; Nagle, A.; Dimand, R. Children with cancer, fever, and treatment-induced neutropenia: Risk factors associated with illness requiring the administration of critical care therapies. *Pediatr. Emerg. Care* **2004**, *20*, 79–84.
23. Bate, J.; Gibson, F.; Johnson, E.; Selwood, K.; Skinner, R.; Chisholm, J. Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients (NICE Clinical Guideline CG151). *Arch. Dis. Child.* **2013**, *98*, 73–75.
24. Alberti, C.; Brun-Buisson, C.; Chevret, S.; Antonelli, M.; Goodman, S.V.; Martin, C.; Moreno, R.; Ochagavia, A.R.; Palazzo, M.; Werdan, K.; et al. Systemic inflammatory response and progression to severe sepsis in critically ill infected patients. *Am. J. Respir. Crit. Care Med*. **2005**, *171*, 461–468.
25. Viscoli, C.; Castagnola, E.; Giacchino, M.; Cesaro, S.; Properzi, E.; Tucci, F.; Mura, R.; Alvisi, P.; Zanazzo, G.; Surico, G.; et al. Bloodstream infections in children with cancer: A multicentre surveillance study of the Italian Association of Paediatric Haematology and Oncology. Supportive Therapy Group-Infectious Diseases Section. *Eur. J. Cancer* **1999**, *35*, 770–774.
26. Ammann, R.A.; Hirt, A.; Lüthy, A.R.; Aebi, C. Predicting bacteremia in children with fever and chemotherapy-induced neutropenia. *Pediatr. Infect. Dis. J.* **2004**, *23*, 61–67.
27. Reilly, A. Infections in children with cancer—old approaches and new. *Eur. J. Cancer* **2003**, *39*, 652–653.
28. Paganini, H.R.; Aguirre, C.; Puppa, G.; Garbini, C.; Javier, R.G.; Ensinck, G.; Vrátnica, C.; Flynn, L.; Iacono, M.; Zubizarreta, P.; et al. A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. *Cancer* **2007**, *109*, 2572–2579.
29. Green, L.L.; Goussard, P.; van Zyl, A.; Kidd, M.; Kruger, M. Predictive Indicators to Identify High-Risk Paediatric Febrile Neutropenia in Paediatric Oncology Patients in a Middle-Income Country. *J. Trop. Pediatr*. **2018**, *64*, 395–402.
30. Phillips, R.S.; Sung, L.; Ammann, R.A.; Riley, R.D.; Castagnola, E.; Haeusler, G.M.; Klaassen, R.; Tissing, W.J.; Lehrn-becher, T.; Chisholm, J.; et al. Predicting microbiologically defined infection in febrile neutropenic episodes in children: Global individual participant data multivariable meta-analysis. *Br. J. Cancer* **2016**, *114*, 623–630.
31. Blennow, O.; Ljungman, P. The challenge of antibiotic resistance in hematology patients. *Br. J. Haematol*. **2016**, *172*, 497–511.
32. Lee, J.H.; Kim, S.K.; Kim, S.K.; Han, S.B.; Lee, J.W.; Lee, D.G.; Chung, N.-G.; Cho, B.; Jeong, D.C.; Kang, J.H.; Kim, H.K. Increase in Antibiotic-Resistant Gram-Negative Bacterial Infections in Febrile Neutropenic Children. *Infect. Chemother*. **2016**, *48*, 181–189.
33. Akova, M.; Alp, S. Management of febrile neutropenia in the era of bacterial resistance. *Ther. Adv. Infect. Dis*. **2013**, *1*, 37–43.
34. Oberoi, S.; Das, A.; Trehan, A.; Ray, P.; Bansal, D. Can complications in febrile neutropenia be predicted? Report from a developing country. *Support. Care Cancer* **2017**, *25*, 3523–3528.
35. Jeddi, R.; Achour, M.; Ben Amor, R.; Aissaoui, L.; Bouterâa, W.; Kacem, K.; Ben Lakhal, R.; Ben Abid, H.; BelHadjAli, Z.; Turki, A.; et al. Factors associated with severe sepsis: Prospective study of 94 neutropenic febrile episodes. *Hematology* **2010**, *15*, 28–32.

36. Montassier, E.; Batard, E.; Gastinne, T.; Potel, G.; de La Cochetiere, M.F. Recent changes in bacteremia in patients with cancer: A systematic review of epidemiology and antibiotic resistance. *Eur. J. Clin. Microbiol. Infect. Dis*. **2013**, *32*, 841–850.
37. Wang, H.; Liu, J.; Huang, Z.; Tao, X.; Li, J.; Hu, Y.; Dou, Q.; Zou, M.; Yan, Q.; Liu, W.E. Clinical characteristics and risk factors for shock and death from E. coli bacte-remia in pediatric hematological patients. *J. Infect. Dev. Ctries*. **2019**, *13*, 365–373.
38. Kuo, F.C.; Wang, S.M.; Shen, C.F.; Ma, Y.J.; Ho, T.S.; Chen, J.S.; Cheng, C.N.; Liu, C.C. Bloodstream infections in pediat-ric patients with acute leukemia: Emphasis on Gram-negative bacteria infections. *J. Microbiol. Immunol. Infect*. **2017**, *50*, 507–513.
39. Vidal, F.; Mensa, J.; Almela, M.; Martı´nez, J.A.; Marco, F.; Casals, C.; et al. Epidemiology and outcome of Pseudo-monas aeruginosa bacteremia, with special emphasis on the influence of antibiotic treatment. Analysis of 189 episodes. *Arch. Intern. Med*. **1996**, *156*, 2121–2126.
40. Gupta, A.; Singh, M.; Singh, H.; Kumar, L.; Sharma, A.; Bakhshi, S.; Raina, V.; Thulkar, S. Infections in acute myeloid leukemia: An analysis of 382 febrile episodes. *Med. Oncol*. **2010**, *27*, 1037–1045.
41. Kumar, J.; Singh, A.; Seth, R.; Xess, I.; Jana, M.; Kabra, S.K. Prevalence and Predictors of Invasive Fungal Infections in Children with Persistent Febrile Neutropenia Treated for Acute Leukemia—A Prospective Study. *Indian J. Pediatr*. **2018**, *85*, 1090–1095.
42. Lehrnbecher, T.; Varwig, D.; Kaiser, J.; Reinhardt, D.; Klingebiel, T.; Creutzig, U. Infectious complications in pediat-ric acute myeloid leukemia: Analysis of the prospectivemulti-institutional clinical trial AML-BFM 93. *Leuke-Mia* **2004**, *18*, 72–77.
43. Villarroel, M.; Avilés, C.L.; Silva, P.; Guzmán, A.M.; Poggi, H.; Alvarez, A.M.; Becker, A.; O'ryan, M.; Salgado, C.; Topelberg, S.; et al. Risk factors associated with invasive fungal disease in children with cancer and febrile neutropenia: A prospective multicenter evaluation. *Pediatr. Infect. Dis. J*. **2010**, *29*, 816–821.
44. Lai, H.-P.; Chen, Y.-C.; Chang, L.-Y.; Lu, C.-Y.; Lee, C.-Y.; Lin, K.-H.; Huang, L.-M. Invasive fungal infection in children with persistent febrile neutropenia. *J. Formos Med. Assoc. Taiwan Yi Zhi.* **2005**, *104*, 174–179.
45. Bakhshi, S.; Padmanjali, K.S.; Arya, L.S. Infections in childhood acute lymphoblastic leukemia: An analysis of 222 febrile neutropenic episodes. *Pediatr. Hematol. Oncol*. **2008**, *25*, 385–392.
46. Agyeman, P.; Kontny, U.; Nadal, D.; Leibundgut, K.; Niggli, F.; Simon, A.; Kronenberg, A.; Frei, R.; Escobar, H.; Kühne, T.; et al. A Prospective Multicenter Study of Microbiologically Defined Infections in Pediatric Cancer Patients With Fever and Neutropenia: Swiss Pediatric Oncology Group 2003 Fever and Neutropenia Study. *Pediatr. Infect. Dis. J*. **2014**, *33*, e219–e225.
47. Torres, J.P.; Labraña, Y.; Ibañez, C.; Kasaneva, P.; Farfán, M.J.; De la Maza, V.; Villarroel, M.; Vergara, I.; Piemonte, P.; Zubieta, M.; et al. Frequency and clinical outcome of respiratory viral infections and mixed viral-bacterial infections in children with cancer, fever and neutropenia. *Pediatr. Infect. Dis. J*. **2012**, *31*, 889–893.
48. Urbonas, V.; Eidukaitė, A.; Tamulienė, I. Increased interleukin-10 levels correlate with bacteremia and sepsis in febrile neutropenia pediatric oncology patients. *Cytokine* **2012**, *57*, 313–315.
49. Arif, T.; Phillips, R.S. Updated systematic review and meta-analysis of the predictive value of serum biomarkers in the assessment and management of fever during neutropenia in children with cancer. *Pediatr. Blood Cancer* **2019**, *66*, e27887.
50. Mian, A.; Becton, D.; Saylors, R.; James, L.; Tang, X.; Bhutta, A.; Prodhan, P. Biomarkers for Risk Stratification of Febrile Neutropenia Among Children With Malignancy: A Pilot Study. *Pediatr. Blood Cancer* **2012**, *59*, 238–245.
51. Aggarwal, R.; Bansal, D.; Bansal, F.; Nanda, N.; Ray, P.; Trehan, A.; Marwaha, R. Interleukin-5, interleukin-6, interleukin-8 and tumour necrosis factor-alpha levels obtained within 24-h of admission do not predict high-risk infection in children with febrile neutropenia. *Indian J. Med. Microbiol*. **2013**, *31*, 226–229.
52. Levy, M.M.; Evans, L.E.; Rhodes, A. The surviving sepsis campaign bundle. *Crit. Care Med*. **2018**, *46*, 997–1000.
53. Müller, B.; White, J.C.; Nylen, E.S.; Snider, R.H.; Becker, K.L.; Habener, J.F. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. *J. Clin. Endocrinol. Metab*. **2001**, *86*, 396–404.
54. Fleischhack, G.; Kambeck, I.; Cipic, D.; Hasan, C.; Bode, U. Procalcitonin in pediatric patients: Its diagnostic relevance is superior to C-reactive protein, interleukin-6, interleukin-8, soluble interleukin 2 receptor and soluble tumor necrosis factor II. *Br. J. Haematol*. **2000**, *111*, 1093–1102.
55. Stryjewski, G.R.; Nylen, E.S.; Bell, M.J.; Snider, R.H.; Becker, K.L.; Wu, A.; Lawlor, C.; Dalton, H. Interleukin-6, interleukin-8, and a rapid and sensitive assay for calcitonin precursors for the determination of bacterial sepsis in febrile neutropenic children. *Pediatr. Crit. Care Med.* **2005**, *6*, 129–135.
56. Chaudhary, N.; Kosaraju, K.; Bhat, K.; Bairy, I.; Borker, A. Significance of Interleukin-6 (IL-6) and C-reactive Protein (CRP) in Children and Young Adults With Febrile Neutropenia During Chemotherapy for Cancer: A Prospective Study. *J. Pediatr. Hematol. Oncol.* **2012**, *34*, 617–623.
57. Ruokonen, E.; Nousiainen, T.; Pulkki, K.; Takala, J. Procalcitonin concentrations in patients with neutropenic fever. *Eur. J. Clin. Microbiol. Infect. Dis.* **1999**, *18*, 283–285.
58. Ortega, M.; Rovira, M.; Filella, X.; A Martinez, J.; Almela, M.; Puig, J.; Carreras, E.; Mensa, J.; A Mart, J. Prospective evaluation of procalcitonin in adults with non-neutropenic fever after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. **2006**, *37*, 499–502.
59. Beaune, G.; Bienvenu, F.; Pondarré, C.; Monneret, G.; Bienvenu, J.; Souillet, G. Serum procalcitonin is only slight in two cases of disseminated aspergillosis. *Infection* **1998**, *26*, 168–169.
60. Christofilopoulou, S.; Charvalos, E.; Petrikkos, G. Could procalcitonin be a predictive biological marker in systemic fungal infections? Study of 14 cases. *Eur. J. Intern. Med*. **2002**, *13*, 493–495.

61. Lehrnbecher, T.; Phillips, R.; Alexander, S.; Alvaro, F.; Carlesse, F.; Fisher, B.; Hakim, H.; Santolaya, M.; Castagnola, E.; Davis, B.L.; et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J. Clin. Oncol*. **2012**, *30*, 4427–4438.
62. Robinson, P.D.; Lehrnbecher, T.; Phillips, R.; Lee Dupuis, L.; Sung, L. Strategies for Empiric Management of Pediatric Fever and Neutropenia in Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients: A Systematic Review of Randomized Trials. *J. Clin. Oncol*. **2016**, *34*, 2054–2060.
63. Lehrnbecher, T.; Robinson, P.; Fisher, B.; Alexander, S.; Ammann, R.A.; Beauchemin, M.; Carlesse, F.; Groll, A.H.; Haeusler, G.M.; Santolaya, M.; et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. *J. Clin. Oncol*. **2017**, *35*, 2082–2094.