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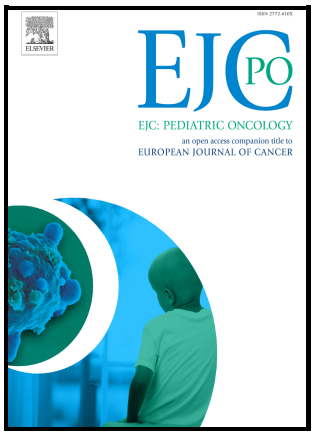

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Diagnostics and Therapy of Paediatric Patients with Febrile Neutropenia

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Abstract

Febrile neutropenia is a common infectious complication in children and adolescents receiving chemotherapy for cancer, requiring immediate hospitalisation and empirical antibacterial therapy. The risk for a severe infection increases with lower neutrophil counts, but other factors such as underlying malignancy, remission state or the genetic background might also impact on the risk and severity of infection. Initial antibacterial treatment as well as modification and cessation of therapy depends on clinical performance, microbiological findings and haematological recovery. Although paediatric specific guidelines have been developed in the last decade, a number of questions are still unsolved. This article gives an overview on diagnostics and management of paediatric patients presenting with febrile neutropenia, on research gaps and will speculate on future perspective.

Key words: Child – febrile neutropenia – risk group – diagnostics – antibacterial therapy – antifungal therapy

Introduction

Over the last decades, we could witness a dramatic improvement of the outcome of paediatric cancer. For example, the cure rates in paediatric acute

lymphoblastic leukaemia (ALL), the most common malignancy in childhood and adolescence, now exceeds 90% [1], and treatment-related mortality is now almost the same as the rate of deaths due to refractory disease and relapse [2]. Febrile neutropenia is a common infectious complication, which occurs, depending on the myelosuppressive intensity of chemotherapy, in up to 30% of neutropenic episodes at a rate of 0.15 per month of chemotherapy exposure time [3, 4]. In an immunocompromised patient, all infectious episodes are potentially life-threatening. Current paediatric specific guidelines recommend that febrile neutropenic patients will be hospitalised, thus decreasing the quality of life [5, 6]. In addition, febrile neutropenic patients will receive empirical broad-spectrum antibiotics, which are potentially associated with adverse events, and the use of these drugs may further increase the rates of resistant pathogens.

This article gives and overview on the current concepts of diagnostics and management of children and adolescents presenting with febrile neutropenia, on research gaps and will also speculate on future perspectives.

Definitions for neutropenia and fever

As detailed below, chemotherapy-induced neutropenia is the major risk factor for life threatening infections, both in children and adults. Therefore, fever during a neutropenic episode is managed as an emergency. Unfortunately, until to date, no common consensus regarding the definition of neutropenia exists [7]. Although in many studies, neutropenia is defined as an absolute neutrophil count of less than 0.5×10^9/L, or of less than 1.0×10^9/L with the expectation to decline to values below 0.5×10^9/L within the next 48-72 hours, this definition reached only 51% agreement in a survey among international experts of paediatric haematology and oncology [7].

The situation is even more complex for the definition of fever. Importantly, the threshold for the temperature that is used to define fever, directly influences the likelihood whether a neutropenic patient is diagnosed with febrile neutropenia, which in turn, results in hospitalisation and the immediate administration of broad-spectrum antibiotics. Ultimately, the threshold for the temperature defining fever impacts on quality of life, costs, and potentially treatment-related morbidity and mortality. Using higher thresholds of temperatures will decrease the number of patients being hospitalised and reduce unnecessary antibiotic therapy. This might be beneficial in particular in those patients, in whom the elevated temperature decreases

spontaneously. On the other hand, high and very high temperatures were associated with adverse events in some risk prediction studies [8-10], and a higher threshold for temperature may delay diagnosis of febrile neutropenia and the start of empirical antibiotics, which could result in poorer outcome. Conversely, a lower threshold for the temperature defining fever may reduce adverse events in febrile neutropenic patients, but at the same time, increases the number of patients with unnecessary therapy and therapy-associated adverse events. Nevertheless, despite these important implications in the clinical setting, the threshold for the temperature defining fever varies substantially between different paediatric haematology and oncology institutions, even within the same country. In that respect, a survey which was conducted in the United Kingdom in 2007 demonstrated that the definitions for fever ranged from a persisting temperature of ≥37.5°C to a single measurement of ≥39.0°C [11]. However, the definition has become more uniform over time, and an updated survey from 2017 revealed that 96% of participating centres in the United Kingdom use a definition of >38.0°C for fever, according to the NICE CG151 guidelines [12, 13]. Similar results were observed in an assessment of 51 institutions in Austria, Germany and Switzerland in 2016 [14], which revealed that a temperature >38.5°C or >38.0°C with a repeated measurement after one hour was the most commonly used definition for fever. The mostly used corresponding definition using the Fahrenheit scale is an oral temperature of 101°F (which equals 38.3°C) or consecutive readings of >100.4°F (which equals 38.0°C) [15]. The survey additionally demonstrated that 41% of the participating paediatric oncology centres did not have a standard method for temperature measurement in outpatients, and methods for inpatients varied [14]. Results of ear temperature measurements are estimated to be around 0.6°C higher than results of axillary measurements [16]. Therefore, the threshold of temperature used for defining fever should directly depend on the method of taking temperature.

Research about fever limits in paediatric cancer patients is limited, and most studies were performed from one group in Switzerland [3, 17, 18]. Not surprisingly, an observational single-centre study demonstrated that compared to a fever limit of 39.0°, lower temperatures resulted in a lower number of febrile neutropenia diagnoses [3]. A multicentre, cluster-randomised, multiple-crossover, non-inferiority trial investigated safety and efficacy of a fever limit of 39.0°C ear temperature compared to a limit of 38.5°C [18]. The trial was conducted in six paediatric oncology centres in Switzerland, and temperature was measured with the same kind of ear thermometer throughout the

trial. In a total of 269 patients and 360 episodes of febrile neutropenia, non-inferiority of safety for the higher fever limit of 39.0°C was observed. In 20% of the episodes, a safety relevant event occurred: 16 intensive care unit (ICU) admissions, 22 episodes of septic shock, 56 bacteraemia, but no deaths. Importantly, the distribution of safety relevant events was not higher in patients with a fever limit of 39°C (15%) compared to 38.5°C (24%), and the authors conclude that it is safe to use 39.0°C ear temperature as fever limit for paediatric patients with chemotherapy induced neutropenia. Due to the low numbers of included patients, children with acute myeloid leukaemia and patients after allogeneic cell transplantation were excluded from this conclusion [18]. Although the data were convincing, a sufficient and wide clinical implementation of the new, higher fever limit did not occur due to a number of reasons such as centre specific habits, personal experiences and caution.

Recent studies were investigating the feasibility of continuous fever monitoring in paediatric oncology patients with wearable devices [19] or skin patches [20, 21]. A preliminary case series presented three episodes in neutropenic paediatric cancer patients, where fever was detected earlier or only by such patches [22]. Irrespective of the fever limit used, such devices and patches monitoring vital signs may be useful in the future not only to detect fever at an earlier time point, but to identify vital sign patters predicting imminent fever or infection. They may show to be useful in risk prediction models.

It is important to note that current paediatric specific guidelines on the management of paediatric febrile neutropenia do not address the issue of a fever limit [5, 6]. However, prior to a consensus definition which is widely accepted, the choice for a local fever limit has to consider the method of temperature assessment used, and should be the same for both in- and outpatients.

Infection risk in the immunocompromised host

Since the 1960s, it has become clear, that severe neutropenia is a risk factor for infectious complications in patients receiving myelosuppressive therapy for cancer. The risk for a severe infectious episode increases with lower neutrophil counts as well as with longer duration of neutropenia [23]. In addition, the outcome of infection depends on neutrophil recovery, with poorest outcome in patients in whom the neutrophil count does not increase during infection [23]. These observations were first made in adult patients, but were later confirmed in the paediatric population, resulting

in the introduction of empiric antibiotic therapy in febrile neutropenic patients [24]. The strategy of empiric therapy is based on the observation that fever in the neutropenic patient may indicate an infection, and as infectious complications may have a fulminant clinical course associated with high mortality. Therefore, antibiotics covering a broad spectrum of pathogens including *Pseudomonas aeruginosa* are started in a neutropenic patient at the first sign of fever before the results of blood cultures are available.

However, it was also recognized that, in addition to the degree and duration of neutropenia, other factors have an impact on the risk for an infection. For example, the risk for an infectious complication depends on both the underlying malignancy and the remission state, as the risk differs between patients with ALL compared to those with acute myeloid leukaemia (AML), and between patients in remission and those suffering from a refractory or relapsed malignancy [23]. Although the risk for a bloodstream infections seems to be higher in children treated for AML compared to those with ALL or solid tumour, the incidence rates vary widely across the literature [25-27]. In addition, tTIn addition, the risk for a specific infection also depends on the affected part of the immune system: whereas neutropenia is associated with an increased risk for bacterial and fungal infection (the latter in patients with prolonged neutropenia, e.g., with an absolute neutrophil count of less than 0.5 x 10^9/L for longer than 10 days), lymphopenia is associated with viral and fungal infection [28].

The observation that risk and clinical course of infectious complications vary widely across children receiving identical treatment for a malignancy implied, that genetic factors might have an additional impact on the infection risk. In fact, it has been demonstrated that variants in genes (polymorphisms) coding for proteins of the innate immune system and altering either the function or the circulating level of these molecules may modify the individual risk and outcome of infection [29]. This has been shown for the mannose-binding protein (MBL) (e.g., affecting the risk of febrile neutropenia), for pro- and anti-inflammatory cytokines (e.g., affecting the risk of infection or sepsis caused by Gram-negative bacteria) and other molecules involved in the immune system such as the DNA repair gene XRCC1 and chitotriosidase (e.g., affecting febrile neutropenia or Gram-negative infection) [30-33]. However, it is important to note that most of these results have not necessarily validated thereafter and are currently not included in any risk prediction strategy.

Risk prediction rules

Risk prediction rules are increasingly developed and validated to classify paediatric cancer patients presenting with febrile neutropenia in being at high or low risk for poor outcomes [34-37]. This would allow to stratify the management, e.g., the choice and duration of antibiotic treatment. In the first international paediatric specific clinical practice guideline for febrile neutropenia, six risk prediction rules were analysed, all of them excluding patients undergoing hematopoietic cell transplantation [38]. Depending on the risk prediction rule, the classification included information on patient-specific factors such as age, underlying malignancy or disease status, treatment specific factors such as time and type of last chemotherapy given as well as episode specific factors such as blood count, or the presence or absence of mucositis and hypotension. None of the rules were clearly superior than others, and the clinical practice guideline recommended that institutions should adopt a validated risk stratification strategy and incorporate it into their routine clinical management.

Using relevant data from an existing data set of 650 episodes in children with febrile neutropenia, five clinical decision rules were found to have high reproducibility [39]. Unfortunately, these rules are limited either by inadequate sensitivity or as they were unable to identify a clinically meaningful number of low risk patients. Importantly, the authors found that the observation time of 24 hours exhibits the best balance between sensitivity and specificity. The same group also analysed variables which have been demonstrated to be significant predictors of infection and/or adverse outcome in at least two clinical decision rules [40]. These analyses were performed by logistic regression, and the rules were recalibrated by re-evaluation of beta-coefficients (logistic model) or recursive-partition analysis (tree-based models). Recalibration increased sensitivity and specificity, and external validation showed reproducibility, which makes recalibration to a novel way to improve diagnostic performance of clinical decision rules and maintain their relevance. Their final model, including decreasing platelets, temperature and clinical presentation, was sensitive for the prediction of likely bacterial infection, but had poor specificity.

In a prospective multicentre trial performed in the UK, a new protocol of risk stratification was evaluated in 405 paediatric patients with 729 episodes of febrile neutropenia [41]. All patients received intravenous antibiotics at the time of presentation, and the risk stratification according to the **A**ustralian – **U**K - **S**wiss (AUS) rule determined which patients could be eligible for discharge on oral antibiotics. The

risk stratification variables were a) preceding chemotherapy with a higher intensity than ALL maintenance therapy (yes = 1; no = 0); b) total white cell count <0.3 x 10^9/L (yes = 1; no = 0); and platelet count <50 x 10^9/L (yes = 1; no = 0). In clinically stable patients who fulfilled homecare criteria, the minimum observation period depended on the score, and was 4 - 8 hours, 4 – 24 hours, 24 hours, and 48 hours in children with a total score of 0, 1, 2, and 3, respectively. The risk prediction rule was originally developed in a prospective study, then validated and combined with homecare criteria [40, 42, 43]. In a pilot study performed in Melbourne, the strategy not only proved to be safe, but also reduced costs [44]. In the current study in the UK, the scores positively correlated with blood stream infections, the admission to the ICU, and death. One fifth of patients were eligible for homecare with oral antibiotics, and 55% of these patients were low risk patients, defined by a score of 0 and 1, respectively. Overall, 48% of home care eligible patients at low-risk were discharged within 24 hours, compared with 2% low risk patients who were homecare ineligible. A total of 14% of discharged patients were readmitted, but no patients eligible for homecare were admitted to the ICU or died.

Role of biomarkers

Another attractive strategy to predict the severity of an infection includes cytokines and other inflammatory parameter in the initial evaluation of a paediatric patient presenting with fever and neutropenia, as the increased serum level of these molecules are apparent at an early stage of infection. An early monocentric study in febrile neutropenic paediatric patients demonstrated that elevated serum levels of interleukin (IL)-6 and IL-8 assessed at presentation could indicate severe infection, but unfortunately, sensitivity and specificity of these biomarkers were disappointing in a follow-up multicentre study [45, 46]. In turn, low levels of plasma IL-8 combined with clinical parameters could identify febrile neutropenic patients in whom withholding antibiotics was safe, but this strategy never has been adopted for routine clinical practice [47]. An 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 included 30 biomarkers such as TNF-alpha, IL-1ß, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12/23p40, IL-17, IL-21, macrophage inflammatory protein (MIP) 1a and 1b, monocyte chemoattractant protein (MCP), Granulocyte colony stimulating factor (G-CSF), C-reactive protein (CRP) or procalcitonin [48]. The fact that a multitude

of parameters was tested is not surprising, as modern laboratory techniques allow the assessment of multiple biomarkers simultaneously, but unfortunately, the number of patients included is often too small to allow a solid conclusion. The authors found that procalcitonin at a threshold of 0.5 ng/ml appears to be the most suitable biomarker at the time of admission in order to predict adverse outcomes, and serial measurements may offer additional benefit. Biomarkers such as preseptin, pancreatic stone protein and adrenomedullin have shown usefulness in other patient populations but data are lacking in the paediatric cancer setting [49-51]. Newer techniques such as gene expression profiling, which aims to discover biomarkers for the early detection of specific infections, are promising and preliminary studies suggest the potential value in invasive aspergillosis or tuberculosis [52, 53]. Similarly, it has been demonstrated that the assessment of specific T-cell responses might be helpful in the diagnosis of infection [54]. Unfortunately, these elegant strategies have not been tested in larger populations of paediatric cancer patients.

Antimicrobial prophylaxis

The use of primary antibacterial and antifungal prophylaxis may impact on both diagnostics and therapeutic strategy (see below). Several randomised studies evaluated antibacterial prophylaxis, mostly in ALL, AML, relapsed leukaemia, and in paediatric patients undergoing allogeneic hematopoietic cell transplantation and demonstrated the following: antibacterial prophylaxis 1) did not reduce mortality, but mortality rates in children were very low in controls of these studies; 2) reduced the rate of bloodstream infections in patients with AML and in those with relapsed acute leukaemia, but the baseline rate of bloodstream infections in controls of these studies was high and the rate of resistance to fluoroquinolones of colonising bacteria was low; 3) did not reduce the rate of bloodstream infections in transplant recipients; and 4) fluoroquinolones, but not amoxicillin/clavulanate reduced the rate of febrile neutropenia. Based exclusively on the data of these randomized studies, an international clinical practice guideline gave a weak recommendation for systemic antibacterial prophylaxis in paediatric patients on intensive therapy for AML and relapsed ALL, and a weak recommendation against the routine use of systemic antibacterial prophylaxis in patients with ALL or those undergoing hematopoietic cell transplantation [55]. Levofloxacin seemed to be superior compared to the other antibacterial compounds. In contrast, the panel of the European Conference of

Infections in Leukaemia (ECIL) 8 included in their decision also non-randomised observational studies which demonstrated that 1) the use of fluoroquinolones resulted in a rapid and dramatic increase of resistance rates, 2) that a poor outcome was often seen in bloodstream infections with resistant Gram-negative pathogens, and 3) that fluoroquinolones caused three more times adverse events of the central nervous system than any other antimicrobial drug [56-58]. Therefore, the panel recommended not to routinely use any antibacterial prophylaxis in paediatric patients with cancer [5]. Models predicting the risk for adverse outcome of febrile neutropenia for children and adolescents during chemotherapy may help to decide in which patients prophylaxis is effective [59, 60].

Mold-active antifungal prophylaxis is indicated for both paediatric and adult patients in whom the risk for invasive fungal disease (IFD) without prophylaxis is at least 10%, e.g., for children with AML, relapsed acute leukaemia or allogeneic hematopoietic cell transplant recipients [5]. Although the overall incidence of IFD in paediatric ALL is less than 5%, there are subpopulations of patients such as those older than 12 years of age or those with poor response to therapy on day 15 in which the risk for IFD approaches 10% as recently shown in a large international trial [61]. The broad-spectrum triazoles voriconazole and posaconazole, both available as intravenous and oral formulation, are approved for antifungal prophylaxis in the paediatric setting, but their use is limited in particular in ALL patients due to their multiple drug-drug interactions and contra-indication in children concomitantly receiving vincristine, a cornerstone in ALL therapy. Liposomal amphotericin B is often used in different dosages and schedules in the prophylactic setting, although the compound is not licensed for this indication and clear efficacy data are lacking [62]. In contrast, a randomised study in paediatric AML has demonstrated that caspofungin significantly reduced all IFD and invasive aspergillosis, but echinocandins such as caspofungin and micafungin have to be administered intravenously at a daily basis [63]. To this end, the best mold-active antifungal prophylactic strategy has not been determined in children, but new compounds such as echinocandins with a longer half-life such as rezafungin could be interesting options [64].

Management of febrile neutropenic episodes

Initial presentation of the febrile neutropenic child

The presentation of each paediatric cancer patient with febrile neutropenia or as being “unwell” has to be considered as a potential emergency, and this patient has to undergo rapid and complete physical examination. According to the clinical condition, the physical examination has to be repeated regularly, even several times per day, as clinical deterioration can occur rapidly in immunocompromised patients. There are a number of early warning signs (“red flags”) for septic shock, which include the changes in behaviour (e.g., irritable, lethargic, no response to pain), of the cardiovascular system (e.g., tachycardia without fever, prolonged capillary refill, grey or mottled skin), and of the respiratory system (e.g., tachypnea, dyspnea, reduced oxygen saturation) (Figure 1). Scoring systems for the early detection of sepsis have been developed and validated, and may improve outcome in these patients [65, 66]. In addition, special attention needs to be placed at common sites of potential infection in immunocompromised patients, which includes skin and mucosa (in particular oropharynx due to mucositis, central catheter site, and perineal and perianal region), lungs and abdomen [67, 68]. Importantly, clinical signs of severe infection may be subtle or even missing in immunocompromised patients.

In addition to laboratory parameters including full blood count, electrolytes, parameters of liver and kidney function, paediatric specific guidelines strongly recommend to obtain blood cultures from each lumen of a central venous line [6]. The utility of simultaneous additional blood cultures from peripheral veins remains controversial. Although these cultures increase the proportion of bacteraemia by approximately 10%, it has to be balanced against the discomfort of the child with caner and potential contaminants [38]. It is important to note that manufacturers´ recommendations, in particular regarding blood volume collected, have to be followed in order to optimize the yield of positive blood cultures. Positive cultures need to be tested for resistance of the pathogen, which will guide the escalation, change or de-escalation of empirical antibacterial therapy. Whereas techniques such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) from briefly incubated sub-cultures to rapidly identify pathogens of positive blood cultures are commonly used in the daily routine [69], other technologies such as next generation sequencing (NGS) based approaches including cell-free DNA NGS (cfNGS) and metagenomic NGS (mNGS) are promising for the culture-independent identification of pathogens and may increase the yield of positive results, but have not been validated to date in the routine clinical setting [70, 71].

Additional diagnostics should be led by clinical symptoms. The usefulness of urine analysis and culture in a non-symptomatic febrile neutropenic child is controversial, and should only be considered if urine collection does not delay antibiotic treatment [38]. Similarly, a routine chest radiograph for asymptomatic children is not recommended, as studies have demonstrated that this investigation does not decrease the risk of adverse events in the febrile neutropenic paediatric patient [38].

Time to antibiotics

The rapid institution of empirical antibiotic therapy is standard of care for all patients presenting with febrile neutropenia, as it influences the outcome of patients with bacteraemia or sepsis [72, 73], and guidelines in adult patients with cancer recommend the administration of antibiotics within 60 min from admission ("golden hour") [74, 75]. The time to antibiotics, in most cases defined as the time period between arrival at the hospital and administration of antibiotic [76], is also used for the evaluation of quality of care [77]. Several approaches to successfully reduce the time to antibiotics have been described, including guidelines, checklists, algorithms and training of staff [78].

Current data suggest that aiming for a time to antibiotics of less than one hour may not be needed for all patients, and that a more patient specific approach could be useful [79]. An analysis of prospectively collected data from Switzerland indicates that the time to antibiotics influences the clinical outcome only in patients presenting with severe disease, such as a reduced clinical condition or with clinical signs of shock [79]. Therefore, warning signs such as reduced vigilance, low blood pressure, reduced oxygen saturation, signs of dehydration, reduced skin perfusion or skin abnormalities should urge the treating team to administer antibiotic therapy immediately (Figure 1). In contrast, the time to antibiotics seems less important in patients presenting without warning signs, which is most likely due to the fact that fever is not caused by a bacterial infection. In these patients the treating team can wait for withe blood cell count results before the start of an empiric antibiotic treatment. With this approach, unnecessary intravenous broad-spectrum antibiotics may be spared (e.g., in non-neutropenic patients without other sings of a bacterial infection or sepsis), but the clinical relevance has to be evaluated in future studies.

Primary empirical antibacterial treatment

The initial empirical antibacterial therapy should ideally cover all virulent bacteria which might have infected the immunocompromised host. It is important to note that also pathogens, which are normal commensals in an immunocompetent individual may cause a life-threatening infection in the immunocompromised state. The most common pathogens identified in febrile neutropenia patients are coagulase negative staphylococci (23%), Enterobacterales (23%), viridans streptococci (13%) and *Pseudomonas aeruginosa* (9%) [80]. At the same time, however, one has to consider resistant pathogens the patient is colonised with and the local epidemiology [81], as many studies have shown differences in resistances and pathogens between different countries [82].

In clinically stable patients presenting with febrile neutropenia, monotherapy with an antipseudomonal beta-lactam or a fourth-generation cephalosporin is recommended as initial empirical antibacterial therapy, and no specific regimen for primary empirical antibacterial treatment has been shown to be better than another [6, 81]. Initial dual-therapy may be indicated in institutions with high resistance rates, although a meta-analysis demonstrated that, compared to an aminoglycoside-containing regimen, monotherapy with an antipseudomonal penicillin (such as piperacillin-tazobactam), a fourth generation cephalosporine (such as cefepime) or a carbapenem (meropenem or imipenem) did not significantly differ regarding therapy failure, infection-related mortality, overall mortality, days of fever or days of antibacterial therapy [6, 83]. Despite the fact that one guideline includes carbapenems in their recommendations for monotherapy [6], carbapenem should be considered as reserve compounds, as they are associated with an increased risk of adverse events (e.g., pseudomembranous colitis) and with the development of resistance, which is dramatically increasing [84, 85]. In this respect, the importance of antibiotic stewardship has to be underlined, as studies have shown that antimicrobial stewardship programs were associated with a lower likelihood of inappropriate therapy and that the establishment of individualized antibiotic plans resulted in the reduction of overall antibiotic use without increase in rate of blood stream infections [86, 87]. Glycopeptides should be included in initial empirical therapy only if the patient is in an unstable clinical condition, has received high dose of cytarabin, which is associated with the infection with viridans streptococci [88, 89], or if Gram-positive pathogens are suspected (e.g., in suspected central venous line associated infections). Importantly, glycopeptides should be stopped as early as possible.

In a clinically unstable patient, current paediatric specific guidelines recommend a carbapenem combined with a second anti-Gram negative antibiotic and/or glycopeptide [81].

In a febrile neutropenic patient colonised or previously infected with resistant pathogens, initial empirical antibacterial therapy should be adjusted accordingly, in particular for Gram-negative pathogens [90]. When an agent has been chosen by a centre, it is important to regularly evaluate local epidemiology, and evolving institutional microbial resistance patterns should be regularly reviewed.

Ongoing management

Escalation or de-escalation of antibacterial therapy should not be guided by fever alone, but by the patients' initial and ongoing clinical condition, the initial choice of antibiotics, microbiological findings and susceptibility testing using minimum inhibitory concentrations. In patients in whom initial blood cultures were negative, optimal timing and usefulness of repeated blood cultures is unclear, but in patients with proven blood stream infection with *Staphylococcus aureus* or candidemia it is needed, in order to demonstrate the effectiveness of antimicrobial therapy. Escalation of antibiotic therapy without microbiologic indication is only necessary if the clinical condition deteriorates, e.g., if a child becomes instable and develops signs of a septic shock. In this situation, treatment escalation should include coverage for resistant Gram-negative, Gram-positive and anaerobic bacteria. In clinically stable, mainly adult patients without microbiological finding, who were still febrile after 48 to 60 hours, one randomized trial investigated the addition of vancomycin versus placebo to the initial empirical regimen, but did not find a significant difference in time to defervescence [91].

When a causative pathogen is identified, it is recommended that treatment should be modified to an antimicrobial regimen with a narrower-spectrum, adapted to the pathogen and its resistance profile [81]. Although this approach seems plausible, there is not much evidence supporting this strategy [92-95], and prospective studies on safety and efficacy are missing. Discontinuation of double coverage for Gram-negative infections or receiving an empirical glycopeptide is recommended in patients that are responding to initial treatment after 24 to 72 hours, as long as there is no specific microbiological or clinical indication to continue combination therapy [6].

With increasing awareness for the importance of quality of life and patient satisfaction as well as due to the emergence of resistance, re-evaluation of treatment

at home and oral treatment has come again into focus. Several paediatric randomized trials investigated safety of switching intravenous to oral antibiotics, with [96-98] or without [99] hospital discharge. A Cochrane Review included eight randomized paediatric studies, investigating intravenous versus oral antibacterial therapy, with either oral cefixime or a quinolone (ofloxacin or ciprofloxacin) with or without adding amoxicillin-clavulanic acid [100]. According to the review, oral treatment is considered to be safe in patients with solid tumours who do not have a central venous line, who are hemodynamically stable, without organ failure, pneumonia, or severe soft-tissue infection [100]. Another meta-analysis in paediatric cancer patients with low-risk febrile neutropenia, found a pooled risk of failure of 11.2% for outpatient therapy and 10.5% for oral antibiotics [101]. Analysis included data from randomized trials as from observational cohorts. Seven studies that changed from an intensive regimen to a reduced regimen at 48 hours had lower treatment failure (2.2%) compared to 16 studies with reduced regimens from presentation with febrile neutropenia (14%) [101]. The approach to re-evaluate patients during the course of febrile neutropenia seems to be reasonable and safe. However, to date, this strategy has not routinely be implemented in paediatric febrile neutropenia.

Irrespective of antibacterial treatment, additional diagnostic should be considered when new symptoms arise, e.g. ultrasound, chest radiograph and repetition of laboratory parameters.

Empirical antifungal treatment and diagnostics for invasive fungal disease

There is no need to modify antibacterial therapy in persistently febrile neutropenic patients, who are in stable clinical condition and there are no new microbiological results. However, it is standard of care to institute empirical antifungal therapy in patients at high risk for IFD (e.g., those with an absolute neutrophil count of less than 500/µl for at least 10 days) after 3 to 5 days of persistent fever despite broad-spectrum antibiotics or recurrent fever [5, 6]. This strategy can be considered as antifungal prophylaxis in highest risk situations or as early antifungal treatment of occult infections. The paediatric specific guidelines strongly recommend to use either liposomal amphotericin B or caspofungin in this situation, both of which have a paediatric label for this indication and have been validated in much larger adult cohorts [5, 6]. Importantly, when starting empirical antifungal therapy, diagnostic procedures for IFD should be considered, which may have an impact on further therapy.

Galactomannan is a cell-wall antigen released by various fungi including *Aspergillus* species, and can be detected in the blood or in the broncho-alveolar lavage. False-positivity of the galactomannan test can be observed in various situations, such as with the concomitant use of some batches of beta-lactam antibiotics, whereas in patients receiving mold-active prophylaxis, the assay is often false-negative [102]. In contrast to beta-D-glucan, the galactomannan assay is included in the recently revised and updated consensus definitions for invasive fungal infections by the European Organization for Research and Treatment of Cancer Mycoses Study Group (EORTC/MSG) [103]. In addition to biomarkers, imaging is another cornerstone in the early diagnosis of IFD. It has been shown in adults that pulmonary computerised tomography (CT) can detect pulmonary aspergillosis earlier than X-ray, and earlier treatment is associated with better outcome [104]. Unfortunately, typical signs of pulmonary aspergillosis, such as the halo or the air-crescent sign, are often not found in the paediatric population [105]. There is considerable effort in improving the diagnostic tools for IFD, which includes improvement of Polymerase Chain Reaction (PCR)-techniques for various fungal pathogens, the evaluation of the host response to fungi such as the fungal-induced release of T-cellular signature cytokines, or the use of fungal-specific labelled antibodies for imaging, but all these techniques have not been introduced in the routine clinical setting [106-108].

Cessation of Treatment

For clinically stable patients, presenting with low or high risk febrile neutropenia, recommendations suggest to stop intravenous empirical antibacterial treatment when the patient defervesced, blood cultures remained negative at 48 hours and if there is evidence of bone marrow recovery [6]. One randomized trial [109] as well as several prospective observational studies [110-112] suggest that this approach is safe, and that patients have a low risk for recurrent fever [113]. However, the criteria for bone marrow recovery are ill-defined, but in the clinical setting, a neutrophil count of ≥0.1 x 10^9/L with rising counts seems reasonable.

In low risk patients, cessation of antibacterial treatment should also be considered with the preconditions above (clinically stable and afebrile, no positive microbiological results after 48 hours), even if there is no evidence of bone marrow recovery [6]. This approach has been studied in several randomized paediatric trials

[109, 114, 115]. One study was performed in Chile and investigated safety of stopping antibiotics on day three of treatment in 75 febrile neutropenic episodes in haemodynamic stable patients without focus of bacterial infection and serum CRP levels of ≤40 mg/L [109]. Outcomes were the same in patients that stopped antibiotic therapy, compared to those that continued. Occurrence of *Enterobacter aerogenes* bacteraemia in one patient in whom antibiotics were stopped highlights the importance of a close follow-up after early cessation of antibiotics. Another study randomized 75 low risk patients after they became afebrile for at least 24 hours to receive either oral treatment with amoxicillin-clavulanic acid or levofloxacin versus no antibiotics [114]. A low risk patient was defined as a patient with either a solid tumour or a haematological malignancy in remission, without clinical signs or microbiological evidence of an infection, an anticipated neutrophil count recovery within 10 days, normal renal and hepatic function and haemodynamically stable. There was no difference between both arms regarding success rate and patients remaining afebrile until neutrophil count recovery, but again, these studies included only low risk patients, whereas data in high risk patients are lacking.

Another third trial included both low and high risk patients, but required the detection of a respiratory virus and a favourable clinical evolution after 48 hours [115]. Patients were randomized to either continue or to stop antimicrobial therapy. The study showed a reduction of media antimicrobial use of 4 days, and no differences in days of fever and uneventful resolution of febrile neutropenia.

Research Gaps

- Integrating the genetic background to better define risk groups for infectious complications
- Evaluation of new diagnostic tools (biomarkers (e.g., host response molecules, vital sign monitoring, artificial intelligence) in the early detection and characterisation of an infectious episode
- Evaluation of new diagnostic tools for early detection and identification of bacterial and fungal pathogens (biomarkers, imaging techniques etc.)
- Assessment of new antifungal compounds in the prophylactic setting
- Assessment of prediction rules for the early and safe stop of empirical antibiotic therapy in special subgroups of children with cancer

- Assessment of safety and efficacy of antibiotic therapy at home in low risk patients with febrile neutropenia

Summary and perspectives

Febrile neutropenia is a common complication of chemotherapy, but with the current management strategies, mortality in neutropenic febrile children and adolescents is less than 5%. Still, hospitalisation affects quality of life, and antimicrobial therapy is associated with potential adverse events. Although risk prediction rules have been evaluated in different clinical settings and biomarkers have been assessed to predict a severe course of infection, empirical antibiotic therapy has to be initiated immediately according to current paediatric specific guidelines. Unfortunately, both bacterial and fungal diagnostics lack of sensitivity and specificity and need to be improved. There is a growing interest to decrease duration of antimicrobial therapy in paediatric patients presenting with febrile neutropenia without decreasing safety. Despite the improvement of supportive care, future studies have to address the implementation of risk prediction rules and biomarkers in the daily clinical setting in order to minimise the use of antimicrobial agents without decreasing safety, and to evaluate antibacterial and antifungal compounds in both prophylactic and therapeutic approaches.

Competing Interests

CK does not have to declare any competing interests. TL has received grants from Gilead Sciences, has served as consultant to Gilead Sciences, Merck/MSD, Pfizer, Astellas, AstraZeneca and Roche, and served at the speaker´s bureau of Gilead Sciences, Merck/MSD, Astellas, Pfizer and GSK.

Author contributions

Koenig Christa: Conceptualization, writing of the manuscript, visualization. CK agreed to the final version of the manuscript.

Lehrnbecher Thomas: Conceptualization, writing of the manuscript, visualization. TL agreed to the final version of the manuscript.

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Figure caption

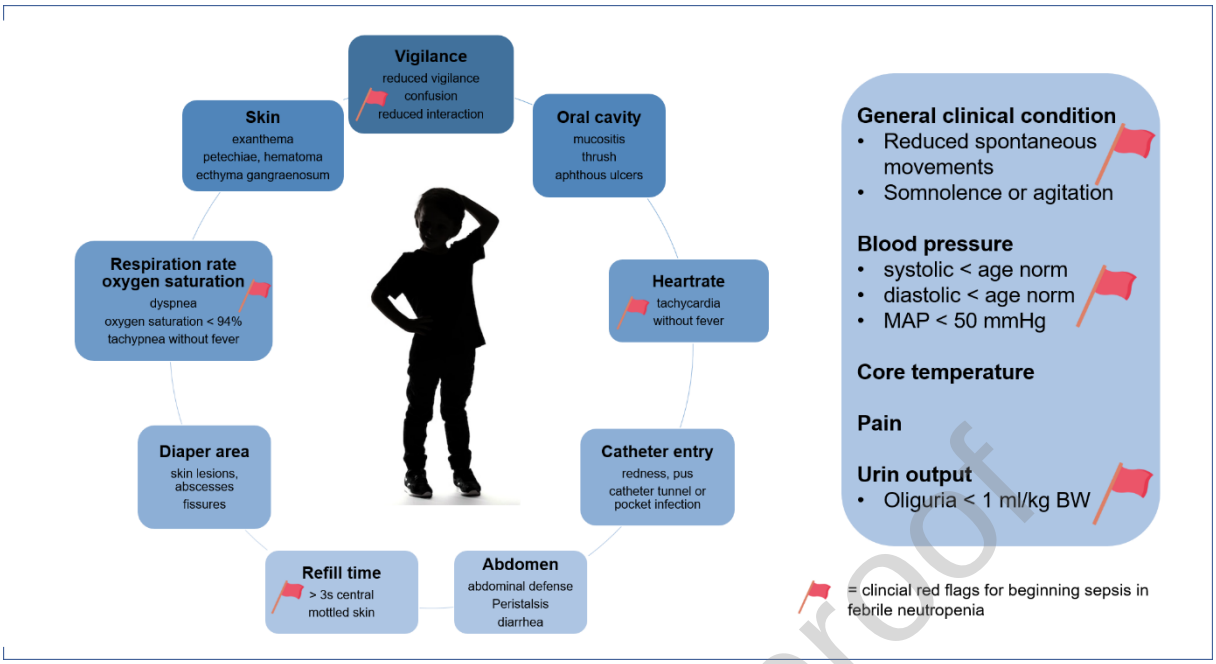

Figure 1: Clinical examination and red flags for beginning sepsis in paediatric patients with febrile neutropenia. Abbreviations: BW, body weight; MAP, mean arterial pressure. Adapted from “Fieber während der Granulozytopenie bei krebskranken Kindern und Jugendlichen” by Bochennek et al, 2021, *Manatsschr Kinderheilkd.*

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Highlights

- Febrile neutropenia is a common infectious complication of chemotherapy.
- Overview on diagnostics and management of children with febrile neutropenia.
- Highlighted are some research gaps and we speculate on future perspectives.