TITLE: Guideline for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem Cell Transplantation (Long Version)

RUNNING HEAD: Pediatric fever and neutropenia guideline

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INTRODUCTION

Fever and neutropenia (FN) is a common complication in children who receive chemotherapy for cancer. Although several guidelines for the management of FN have been developed by organizations such as the Infectious Diseases Society of America (IDSA),[1] the European Conference on Infections in Leukemia,[2-5] the National Comprehensive Cancer Network[6] and others,[7] none are dedicated to children. FN guidelines specifically focused on children with cancer are important. We have previously described substantial differences between adults and children with cancer which may impact on risk stratification, evaluation, and treatment of patients with FN.[8]

To address this critical gap, we convened a panel of pediatric cancer and infectious diseases experts to develop an evidence-based guideline for the empiric management of pediatric FN. This guideline focuses on children and adolescents with cancer and/or undergoing hematopoietic stem cell transplantation (HSCT) who have FN, and is designed for healthcare professionals who care for these patients. Implementation will require adaptation to the local context and should consider organizational barriers such as available local infrastructure to support different models of care. This document is divided into three major sections: (1) Initial presentation of FN; (2) Ongoing management; and (3) Empiric antifungal treatment.

METHODS

We followed previously validated procedures for creating evidence-based guidelines[9] and used the Appraisal of Guidelines for Research & Evaluation II instrument as a framework.[10] The International Pediatric Fever and Neutropenia Guideline Panel was

first formed in October 2010. The group included representation from oncology, infectious disease, nursing, pharmacy, and a patient advocate from 10 different countries (Appendix 1). Members were divided into working groups that addressed each of the three major sections (initial presentation, ongoing management and empiric antifungal therapy). Each member completed conflict of interest forms (http://www.icmje.org/coi_disclosure.pdf) and no conflicts precluded involvement in the Panel. The guideline was editorially independent from the funding body (Canadian Institutes of Health Research).

Formulating Questions, Rating Importance of Outcomes and Development of Evidence Profiles

Each working group developed the key clinical questions to be addressed by the guideline and identified and rated the importance of outcomes relevant to the questions on a 9 point scale (Appendix 2). Ratings of 7–9 indicated that the outcome was critical for a decision or recommendation; 4–6 indicated that it was important, and 1–3 indicated that it was not important. The median ratings from working group members established the importance of the outcomes and guided recommendations.

For each question, systematic reviews of the published literature were conducted until March 2011 (available on request) and each working group compiled evidence summaries. Empiric treatments focused on pharmacological interventions and did not include therapies such as growth factors. A pragmatic, hierarchical approach was undertaken in the search. For all questions, systematic reviews of primary studies were sought and results in children were identified. In the event that there were little or no

pediatric data to inform recommendations on a specific health question, evidence from adult studies and combined adult and pediatric studies was considered. Lack of pediatric data was accounted for in the quality description of evidence (i.e. indirect evidence). Where there were no studies of the highest quality or where they were few in number, for example, few randomized controlled trials (RCTs), designs with a greater risk of bias such as observational studies were subsequently searched for and reviewed. Sample sizes were limited for some synthesized outcomes and thus, 95% confidence intervals (CIs) were provided to facilitate interpretation. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach was used to generate summaries and evidence was classified as high, moderate, low or very low based upon methodologic considerations.[11] The key methodological elements are in study design, consistency of the body of evidence, directness of the studies to the question under consideration, and limitations in the conduct of the studies. Based upon the evidence summaries, each working group then developed recommendations which considered health benefits, side effects, risks and costs.

Panel Meeting and Development of Recommendations

The first meeting of the Panel was held on October 21st, 2010 (Boston, MA) to plan guideline development. A second meeting was held on September 18th, 2011 (Chicago, IL) to discuss the results of the evidence summaries and each working group's preliminary recommendations. Following several conference calls, revised documents were then circulated. Once the group had approved the final version, review by seven external expert reviewers was undertaken. A final revised version was created on

February 17, 2012. A guideline update is planned in 3 years or sooner in the event of the publication of important new information.

RECOMMENDATIONS AND EXPLANATIONS

The summary of recommendations is listed in Table 1 and the associated evidence profiles are illustrated in Appendices 3 to 9. Considerations for implementation are presented where relevant. Identified research gaps and recommendations for future research are listed in Appendix 10.

SECTION 1: INITIAL PRESENTATION OF FN

Question: *What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?*

Recommendation: Adopt a validated risk stratification strategy (see Table 2) and incorporate it into routine clinical management (1C, strong recommendation, low-quality evidence).

Explanation: Risk stratification at the time of a child's presentation with FN may allow for intensification of therapy and monitoring for those at higher risk for serious infections and/or complications and, conversely, de-escalation of therapy for those at lower risk for severe FN outcomes.

Studies of risk prediction in children include retrospective and prospective observational cohort studies that varied in inclusion criteria, specific definitions of FN, and exact outcomes measured.[12-30] These studies used variable measures of outcomes including death, intensive care unit admission, serious infection and bacteremia to

derive, and in some instances, validate risk prediction rules. Studies of risk assessment in adult FN populations were not included in the development of these recommendations given age-related patient, disease and treatment differences.[8]

Studies of FN in pediatric patients identify a series of common elements that are informative for risk stratification. These include patient-specific factors (including age, malignancy type, and disease status); treatment-specific factors (type and timing of chemotherapy); and episode-specific factors, both clinical (including height of fever, hypotension and mucositis) and laboratory (such as blood counts and C-reactive protein (CRP)). The schemas uniformly exclude those with more severe myelosuppression and HSCT patients from low-risk definitions. These are consistent with the largely adult IDSA guideline,[1] but in pediatric studies, the depth of thrombocytopenia or leukopenia has been examined rather than anticipation of prolonged neutropenia in predicting patients at higher risk of experiencing complications.

Six low-risk stratification schemas have been validated in different pediatric populations (Table 2). Evaluation of these studies does not allow the recommendation of a single low-risk prediction rule as no single rule is clearly more effective or reliable than the others, nor do they allow us to convincingly recommend different rules for predicting specific outcomes.[31] It is important to recognize that the process of deriving prediction rules frequently overestimates their effectiveness in practice, and that geographical and temporal validation are important since differences in local practices, systems and approaches may alter how the rules perform.[32]

The Santolaya rule[28] derived in Chile was shown to be highly effective when used in the same population.[33] Similarly, the Alexander rule[13] from Boston has been

effectively used in England[34] and implemented in Canada. Consequently, clinicians in Chile would be justified in using the Santolaya rule, while those in England, Canada and the United States could reasonably implement the Alexander rule. Identification of a predominant risk stratification schema for use across clinical trials and in clinical practice (where appropriate) would optimize future research and patient care. It is important to note that there are no validated risk stratification schemas for defining those patients at high risk of developing complications from FN.

Implementation Considerations: Use of a risk stratification strategy is important, and individual institutional standards of care for risk assignment should be based on one of the six validated schemas (Table 2). The choice of strategy may be influenced by an institution's ability to implement more complex rules and the timeliness of receipt of test results such as CRP. Each institution should maintain records of which specific strategy was used and evaluate the performance of the chosen rule to ensure accuracy and safety within the specific clinical setting.

Question: *What clinical, laboratory and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?*

Recommendations: Obtain blood cultures at the onset of FN from all lumens of central venous catheters (CVCs) (1C, strong recommendation, low-quality evidence).

Consider peripheral blood culture concurrent with obtaining CVC cultures (2C, weak recommendation, low-quality evidence).

Consider urinalysis and urine culture in patients for whom a clean-catch, midstream specimen is readily available (2C, weak recommendation, low-quality

evidence).

Obtain chest radiography (CXR) only in symptomatic patients (1B, strong recommendation, moderate-quality evidence).

Explanation*:* The etiology of initial fever may be non-infectious, bacterial, viral or less commonly due to other pathogens. Viral pathogens are common and evaluation should be directed at specific signs and symptoms.

Blood Culture: Blood cultures obtained during the evaluation of FN are essential. The majority of children with cancer receiving chemotherapy have an indwelling CVC; for these children, obtaining a blood culture of an adequate volume from all lumens of the CVC is important. However, the utility of peripheral blood cultures in addition to CVC cultures is controversial. Seven studies evaluated concurrent peripheral and CVC cultures in adults and children with cancer and/or undergoing HSCT[35-41] (Appendix 3). Only two studies removed probable contaminants from the analysis. Overall, the proportion of bacteremia detected by peripheral blood cultures alone (in other words, CVC cultures were negative) was 13% (95% CI 8-18%). The designation of this recommendation as 'weak' arises from balancing increased yield of bacteremia against pain/inconvenience and contaminants associated with peripheral cultures. Peripheral cultures may also help to diagnose catheter-related infections although the clinical utility of the diagnosis is unclear and the issue was not specifically addressed in this guideline.[42]

Multiple variables can influence blood culture yield including blood culture volume, choice of media type, number of culture bottles inoculated and frequency of cultures.[43] Although an adequate volume of blood inoculated is important[44,45] and often

not consistently collected,[46] minimum volumes have not been established in pediatric patients. Manufacturer volume recommendations and weight based sliding scales[47] are two approaches to standardizing volume of blood collected.

Urinalysis and Urine Culture: Urinary tract infections (UTIs) are common in pediatric FN.[27] Routine urinalysis and culture at the initial evaluation of FN in children is controversial. Benefits may include the detection of an otherwise unsuspected source of fever and more directed antibiotic therapy; the disadvantages may include delay in treatment, invasive procedures to collect urine, and the possibility of false-positive results due to contamination.

Restricting urine culture to those with symptoms or abnormal urinalysis is probably not justified in children. Pyuria was found in only 4% of UTI episodes during neutropenia, compared to 68% in control patients with cancer without neutropenia ($P<0.0001$).[48] Nitrite testing in younger children (without cancer) is also known to be less effective than in older patients.[49]

Given the concerns regarding delay of therapy and possibly increased adverse events associated with invasive methods for urine collection in children with mucositis, thrombocytopenia and immunosuppression, the Panel recommended that where a clean-catch or midstream urine can be collected, urine should be obtained prior to commencing antibiotics. Urine collection should not delay treatment.

CXR: A CXR had been advocated as part of the routine, initial assessment of pediatric FN since the neutropenic child was believed to be less likely to exhibit signs and symptoms of pneumonia than the immunocompetent child.[50] Four studies that included 540 episodes of FN[51-54] examined the value of routine CXR; each of them found that the

frequency of pneumonia in an asymptomatic child was 5% or less.[55] Asymptomatic children who do not receive a CXR had no significant adverse clinical consequences[51] and thus, routine CXRs are not recommended in asymptomatic children.

Question: *What empiric antibiotics are appropriate for children with high-risk FN?*

Recommendations: Use monotherapy with an anti-pseudomonal *β*-lactam or a carbapenem as empiric therapy in pediatric high-risk FN (1A, strong recommendation, high-quality evidence).

Reserve addition of a second Gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (1B, strong recommendation, moderate-quality evidence).

Explanation: Initial management of pediatric FN will be influenced by many factors such as patient characteristics, clinical presentation, local infrastructure to support different models of care, drug availability and costs, and local epidemiology including resistance patterns. In general, coverage should include Gram-negative organisms in all patients as well as viridans group streptococci and *Pseudomonas aeruginosa* in high-risk FN. The overall goal of empiric therapy is to provide coverage for virulent organisms while minimizing exposure to unnecessary antibiotics as indiscriminant use of broad-spectrum antibiotics may accelerate antibiotic resistance rates.

Appendix 4 presents all published, English-language, prospective trials of pediatric FN that evaluated a homogeneous initial empiric antibiotic strategy that provides coverage appropriate for high-risk FN patients; combination regimens were

included. Outcomes deemed clinically important by the Panel were synthesized by antibiotic type; no particular regimen was superior to another.

Two meta-analyses compared monotherapy versus an aminoglycoside-containing regimen in FN[56] and in immunocompromised patients with sepsis;[57] patients were primarily adults. The meta-analyses demonstrated non-inferiority of monotherapy regimens and higher toxicity with combination regimens. The FN meta-analysis found fewer treatment failures with monotherapy (odds ratio (OR) 0.88, 95% CI 0.78-0.99) but this analysis included only 4 trials that enrolled patients younger than 14 years of age.[56] A pediatric meta-analysis found that aminoglycoside-containing combination treatment did not improve clinical outcomes in comparison to anti-pseudomonal penicillin monotherapy.[58]

Specific monotherapy regimens evaluated in children and presented in Appendix 4 include anti-pseudomonal penicillins (such as piperacillin-tazobactam and ticarcillin-clavulinic acid), anti-pseudomonal cephalosporins (such as cefepime) and carbapenems (meropenem or imipenem). No difference in treatment failure, mortality or adverse effects was seen when anti-pseudomonal penicillins were compared to anti-pseudomonal cephalosporins or carbapenems.[58,59] However, carbapenems may be associated with more pseudomembranous colitis in comparison to other *β*-lactam antibiotics.[60] In terms of anti-pseudomonal cephalosporins, a meta-analysis of RCTs found a statistically significant increase in all-cause mortality in cefepime-treated versus other *β*-lactam treated patients.[60] However, this finding was refuted in a FDA review[61] and increased mortality was not observed in a pediatric meta-analysis.[51] Consequently, cefepime may be an appropriate initial empiric therapy for children with FN if local

circumstances support its use. Ceftazidime monotherapy should not be used if there are concerns of Gram-positive (such as viridans group streptococcal) or resistant Gram-negative infections.[62]

The role of empiric glycopeptides in FN was examined in a predominantly adult meta-analysis of 14 RCTs.[63] Inclusion of a glycopeptide led to less frequent treatment modification, but if addition of glycopeptides in the control arm was not considered failure, no difference in treatment success was seen (OR 1.02, 95% CI 0.68-1.52). However, adverse effects were more common in the empiric glycopeptide group. Only three pediatric RCTs have compared glycopeptide and non-glycopeptide containing regimens.[64-66] None contained the same base regimen and thus, recommendations are based on the meta-analysis.

Implementation Considerations: Empiric antibiotic choices should be regularly reviewed in light of evolving institutional microbial resistance patterns, and rigorous epidemiological surveillance is critical. Monotherapy may not be appropriate for institutions with a high rate of resistance.

Question: *In children with low-risk FN, is initial or step-down outpatient management as effective and safe as inpatient management?*

Recommendation: In children with low-risk FN, consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (2B, weak recommendation, moderate-quality evidence).

Explanation: Outpatient management of children with FN is attractive given increased quality of life for children[67] and large reduction in costs[68] associated with ambulatory

management. Outpatient therapy can be initiated at the onset of FN or after a short period of inpatient treatment (step-down management). One meta-analysis of RCTs compared inpatient versus outpatient management of FN.[69] Six studies (4 adult and 2 pediatric) were included; 2 studies consisted of an entirely outpatient strategy while 4 consisted of an early discharge (step-down) strategy. Outpatient management was not associated with significantly higher treatment failure (rate ratio (RR) 0.81, 95% CI 0.55-1.28, P=0.28; N=738) where RR < 1 favored inpatient care. Failure was biased against outpatient care since readmission, a criterion for failure, is only applicable to outpatients. There was no difference in mortality (RR 1.11, 95% CI 0.41-3.05, P=0.83; N=742). In a stratified analysis of the two pediatric studies,[70,71] results were similar to the overall analysis.

Data from 16 prospective trials of pediatric low-risk FN based upon site of care within the first 24 hours are presented in Appendix 5. There was no increase in treatment failure (including modification) with outpatient relative to inpatient management (15% versus 27%, P=0.04; N=795). Importantly, there were no infection-related deaths among the 953 outpatients.[72]

Since outcomes appear similar between strategies, considerations such as feasibility and patient/family preferences should determine the site of care of low-risk patients.

Implementation Considerations: Safety of specific circumstances will need to be determined at the local level and a conservative approach should be taken for individual cases in which there are questions about suitability of outpatient management. The minimum frequency and type of follow-up has not yet been established for pediatric FN

patients managed as outpatients.

Question: *In children with low-risk FN, is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?*

Recommendation: In children with low-risk FN, consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (2B, weak recommendation, moderate-quality evidence).

Explanation: Oral antibiotics may be advantageous as they facilitate outpatient management and are generally less costly compared with parenteral antibiotics. However, oral medication administration may present major challenges in children. Issues include drug availability as an oral liquid, palatability, co-operation of young children, mucositis and impaired gastrointestinal absorption. Oral therapy may be started as initial therapy for FN or following a short period of intravenous administration (step-down management). There are two meta-analyses of RCTs that compared oral and parenteral antibiotics for FN; one included all settings (N=2,770)[73] while the other was restricted to the outpatient setting (N=1,595).[69] Both included all FN risk groups. They both showed no difference in treatment failure (including modification), overall mortality, or adverse effects of antibiotics either among all participants or when stratified among the pediatric subset. However, in the stratified analysis of 5 pediatric RCTs, oral outpatient management was associated with a higher rate of readmission compared with parenteral outpatient management (RR 0.52, 95% CI 0.24-1.09, P=0.08; N=639).[69]

Prospective pediatric trial data comparing parenteral and oral antibiotic therapy started within 24 hours of treatment initiation in low-risk FN are presented in Appendix

6. Oral antibiotics used were fluoroquinolone monotherapy (7 studies, N=581), fluoroquinolone and amoxicillin-clavulanate (3 studies, N=159), and cefixime (1 study, N=45). There were no differences in treatment failure (including modification) and no infection-related deaths among the 676 children given oral antibiotics.[72] Since outcomes appear similar between regimens, considerations such as ability of the child to reliability take and absorb oral antibiotics, costs, feasibility, and patient/family preferences should determine the route of antibiotic administration for low-risk pediatric FN.

SECTION 2: ONGOING MANAGEMENT OF FN EXCLUDING EMPIRIC ANTIFUNGAL THERAPY

The following section applies to children with FN who have already been started on empiric antibiotic therapy and observed for some period of time by either healthcare providers, parents or both.

Question: *When and how should the initial empiric antibiotic therapy be modified during the pediatric FN episode?*

Recommendations: In patients who are responding to initial empiric antibiotic therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (1B, strong recommendation, moderate-quality evidence).

Do not modify the initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable (1C, strong recommendation, low-quality evidence).

In children with persistent fever who become clinically unstable, escalate the

initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria (1C, strong recommendation, very low-quality evidence).

Explanation: Initial empiric antibiotics should be modified to include clinically or microbiologically documented infection. In patients who are responding to initial empiric antibiotic therapy in whom double Gram-negative coverage or empiric glycopeptide was initiated (for example, because of clinical instability or concern about resistance), these additional antibiotics should be discontinued 24 to 72 hours after treatment initiation if there is no specific microbiologic indication to continue combination therapy. Early discontinuation is based upon the rationale for initial monotherapy without the addition of aminoglycosides and empiric vancomycin as described earlier. Empiric antibacterials should not be modified solely based upon the persistence of fever in clinically stable patients; rather, modification should be based upon clinical and microbiological factors. For example, modification may occur on the basis of an evolving clinical site of infection, microbiology results including resistance profiles, or occurrence of hypotension or other signs of clinical instability. A double-blind RCT showed that the addition of vancomycin, compared to placebo, did not reduce the time to defervescence in neutropenic patients with cancer who had persistent fever 48-60 hours after the initiation of empiric piperacillin-tazobactam monotherapy.[74] However, only 9 of 165 patients were children.

There are no trials that evaluated the role of modifying initial empiric monotherapy in persistently febrile patients who become clinically unstable. The Panel recommended escalation of the initial empiric antibiotic regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria. In the clinically

unstable child, non-bacterial etiologies such as fungi and viruses should also be considered. Empiric antifungal treatment is addressed in a later section.

Question: *When can empiric antibiotics be discontinued in patients with low- and high-risk FN?*

Recommendation: Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours and who have evidence of marrow recovery (1C, strong recommendation, low-quality evidence).

Consider discontinuation of empiric antibiotics at 72 hours in low-risk patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured (2B, weak recommendation, moderate-quality evidence).

Explanation: Appropriate cessation of antimicrobials is important to minimize exposure to unnecessary antibiotics. Appendix 7 summarizes the pediatric observational and randomized trials that described outcomes with cessation of antibiotics.[75-94]

When pediatric studies were stratified by the status of bone marrow recovery at the time of antibiotic discontinuation, the pooled incidence of recurrent fever was 1% (95% CI 0.1-5%) in children with definite marrow recovery, 5% (95% CI 3-9%) where marrow recovery was not required, and 14% (95% CI 5-36%) where there was no evidence of marrow recovery. Consequently, empiric antibiotics should be discontinued in patients who are clinically well with negative blood cultures who have been afebrile for at least 24 hours and who have evidence of bone marrow recovery. The pediatric studies did not set threshold criteria for evidence of marrow recovery,[76,81,84,86,87] but the

Panel suggested that an absolute neutrophil count (ANC) ≥ 100/uL post nadir is reasonable.

Pediatric patients who had antibiotics discontinued irrespective of bone marrow recovery were more likely to demonstrate recurrent fever and less frequently bacterial infection (incidence 2%, 95% CI 0.1-5%). No bacterial infectious deaths were identified in low-risk patients. One RCT[78] randomized low-risk patients to either stop or continue antibiotics on day 3 irrespective of bone marrow status and found no difference in outcomes and no infectious deaths. However, *Enterobacter aerogenes* bacteremia occurred in one child in the group who stopped antibiotics early. Thus, discontinuation of empiric antibiotics in low-risk patients at 72 hours irrespective of bone marrow status may be appropriate as long as careful follow-up can be ensured.

The optimal duration of empiric antibiotics for high-risk patients with sustained bone marrow suppression is uncertain. In 1979, Pizzo et al. randomized 33 high-risk patients aged 1 to 30 years who were afebrile and neutropenic on day 7 to either continue or stop antibiotics.[77] Of the 17 patients who discontinued antibiotics, 7 developed infectious sequalae and 2 died as a result of *Escherichia coli* bacteremia.[77] Since this single study was conducted over 30 years ago, the optimal duration of antibiotic administration in high-risk patients is a research gap.

SECTION 3: EMPIRIC ANTIFUNGAL TREATMENT

Question: *What clinical parameters can classify pediatric patients with persistent FN as high risk or low risk for invasive fungal disease (IFD)?*

Recommendation: Patients at IFD high-risk are those with acute myeloid leukemia

(AML), relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and allogeneic HSCT recipients with persistent fever despite prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (>10 days). All others should be categorized as IFD low-risk (1B, strong recommendation, moderate-quality evidence).

Explanation: The risk stratification for IFD in children is based on underlying malignancy (higher risk in AML and relapsed acute leukemia) or type of HSCT (higher risk in unrelated cord blood and matched unrelated donor transplantation) as well as on certain clinical and laboratory factors (higher risk in patients with severe and prolonged neutropenia, mucositis, CVC, steroid exposure, and elevated CRP on day 4 of FN).[1,95-102] IFD low-risk patients include children with standard-risk acute lymphoblastic leukemia, lymphoma and most solid tumors,[96,103,104] although IFDs have been described in these patients.[105] Importantly, environmental factors such as climatic variables and proximity to construction work also influence the risk for invasive aspergillosis.[106,107]

Question: *What clinical features, laboratory tests, imaging studies and procedures (such as bronchoalveolar lavage (BAL) and biopsy) are useful to identify a fungal etiology for persistent/recurrent FN despite broad-spectrum antibiotics?*

Recommendations: Consider prospective monitoring of serum galactomannan (GM) twice weekly in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis (2B, weak recommendation, moderate-quality evidence).

In IFD low-risk patients, do not implement routine galactomannan screening (1C, strong recommendation, low-quality evidence).

Consider GM in BAL and cerebrospinal fluid (CSF) to support the diagnosis of pulmonary or central nervous system (CNS) aspergillosis (2C, weak recommendation, low-quality evidence).

In children, do not use *β*-D-glucan (BG) testing for clinical decisions until further pediatric evidence has accumulated (1C, strong recommendation, low-quality evidence).

In IFD high-risk children with persistent FN beyond 96 hours, perform evaluation for IFD. Evaluation should include computerized tomography (CT) of the lungs and targeted imaging of other clinically suspected areas of infection (1B, strong recommendation, moderate-quality evidence). Consider CT of the sinuses in children 2 years of age or older (2C, weak recommendation, low-quality evidence).

Explanation: Early detection of IFD, especially in the case of invasive molds such as *Aspergillus*, can be difficult. Serum tests for fungal antigens and various radiographic modalities have been developed and improved over the last two decades; GM and BG assay results along with typical findings on chest CT are now included in the revised definitions for IFD from the European Organisation for Research and Treatment in Cancer/ Mycosis Study Group (EORTC/MSG).[108] In contrast to adult focused guidelines for the diagnosis and management of IFD,[109-112] no formal recommendations have previously been made for these tests in pediatric populations.

GM: A total of ten pediatric studies evaluated serum GM as a mycological criterion[108] of IFD,[113-119] mostly in the setting of serial screening for IFD high-risk patients (Appendix 8). These studies should be interpreted cautiously given the heterogeneity across studies such as different definitions of assay positivity. The combined sensitivity and

specificity of the 5 pediatric studies which included adequate information for individual patients and used EORTC/MSG criteria[114-117,120] were 0.76 (95% CI 0.62-0.87) and 0.86 (95% CI 0.68-0.95) respectively, which favorably compare with the results from a meta-analysis for GM testing in adults (0.73, 95% CI 0.46-0.61 and 0.90, 95% CI 0.88-0.92 respectively).[109] The Panel agreed upon the threshold of an optical density index 0.5 for GM in the serum, as suggested by the manufacturer. While the diagnostic properties of the GM assay are adequate in children, the designation of this recommendation as 'weak' arises from uncertainty about the overall effectiveness of routine GM screening in children, and whether implementation of this strategy improves clinical outcomes. In adults, the sensitivity of the GM assay may decrease with prophylactic antifungal administration.[121] It is not known if the same reduction in sensitivity occurs in pediatric patients. GM may also be useful in the non-neutropenic setting such as with graft-versus-host disease, but this use is outside the scope of this guideline.

A recent meta-analysis including 27 studies of patients with hematological cancer and proven or probable aspergillosis undergoing sequential GM testing suggested that serum GM results may be a reasonable proxy for aspergillosis control with antifungal therapy.[122] Although data in children are limited, reassessment of patient management should be considered in patients with persistent or increasing GM-antigenemia during antifungal therapy. The performance of the GM assay under non-surveillance conditions (such as in patients presenting with new pulmonary infiltrates) is unclear and is identified as a research gap. It is important to note that some specific antibacterial agents (such as piperacillin-tazobactam) may cause false-positive GM results in pediatric and adult patients.

In terms of GM testing in body fluids other than serum, a small pediatric study corroborated the results of a retrospective study of 99 adult IFD high-risk hematology patients,[123] and suggested that BAL-GM is a potentially valuable adjunctive diagnostic tool in addition to conventional microbiologic and radiologic studies.[124] Similarly, very limited data suggest that detection of GM in CSF can support the diagnosis of invasive aspergillosis in the CNS in both children and adults.[125,126] Adult guidelines recommend an optical density index threshold of 1.0 (BAL) and 0.5 (CSF).[127]

BG: In contrast to adults in whom BG testing has demonstrated good diagnostic accuracy for early diagnosis of IFD,[128] there are very limited data on BG testing in children.[129,130] Furthermore, the optimal threshold for positivity of BG testing in children is unknown. Mean BG levels are slightly higher in immunocompetent uninfected children than in adults. In a group of healthy children, 15% of tests were within the adult-derived positive range for IFD.[131] Thus, BG should not be used to guide pediatric clinical decision making.

Imaging Studies: Prospective adult studies have demonstrated that CTs detect pneumonia earlier than CXRs, and systematic CT scans allow earlier diagnosis of invasive pulmonary aspergillosis with a resultant improvement in prognosis.[132,133] The limited data on imaging studies in children with underlying malignancy and persistent FN[134-137] demonstrate that radiographic findings in immunocompromised children with proven pulmonary IFD are often non-specific.[134,135] In particular, in children <5 years of age, typical signs of pulmonary IFD (halo sign, air crescent sign, and cavities) are not seen in the majority of patients. Instead, multiple nodules or fluffy masses and infiltrates which look like mass lesions are more frequently reported in children. A single center

retrospective study of CT scans in pediatric patients with prolonged FN (≥ 96 hours) demonstrated the potential usefulness of repeated imaging studies.[136] However, the potential benefits of repeated CT scans should be balanced against the cumulative radiation exposure from this approach.

The role of routine sinus imaging (such as by CT) during prolonged FN is uncertain and data on the frequency of accompanying symptoms of sinonasal IFD in children are scarce.[138,139] Given that the sinuses may be involved, CT may be considered in the evaluation for IFD. MRI may also be considered instead of CT in order to reduce radiation exposure although experience in children has been limited. Notably, children younger than 2 years have not had sufficient pneumatization of the sinus cavities and thus sinus imaging is rarely informative in this age range. Similarly, the role of routine abdominal imaging is uncertain and imaging of abdominal lesions may be falsely negative in neutropenic children.[140]

Diagnostic Procedures in Patients with Positive Laboratory Studies and/or Imaging: In children with positive GM or imaging studies that suggest IFD, antifungal treatment with a mold-active agent should be initiated and further diagnostic investigation should be considered whenever possible. In the case of pulmonary lesions identified by CT, the diagnostic work-up may include BAL and trans-bronchial or trans-thoracic biopsy.[141] In this setting, there are no published pediatric data to identify the diagnostic procedure with the greatest yield relative to procedure-related risks.

Questions: *When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?*

Recommendations: In neutropenic IFD high-risk children, initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (≥ 96 hours) broad-spectrum antibacterial agents (1C, strong recommendation, low-quality evidence).

In neutropenic IFD low-risk children, consider empiric antifungal therapy in the setting of persistent FN (2C, weak recommendation, very low-quality evidence).

Use either caspofungin or liposomal amphotericin B (L-AmB) for empiric antifungal therapy (1A, strong recommendation, high-quality evidence).

Explanation: Three prospective trials evaluated empiric antifungal therapy in children with persistent FN (Appendix 9).[142-144] Caspofungin was as effective as L-AmB,[143] L-AmB was slightly more effective than amphotericin B deoxycholate (AmB-D),[142] and the efficacy of AmB-D was similar to amphotericin B colloidal dispersion (ABCD).[144] Caspofungin was better tolerated than L-AmB (less nephrotoxicity and less discontinuation of therapy due to side effects), and L-AmB was less nephrotoxic than AmB-D. ABCD demonstrated significantly less renal toxicity compared to AmB-D, whereas infusion-related toxicity were more frequent in the ABCD group (not statistically significant). Efficacy and safety in children were consistent with the much larger trials in adults.[145-147] Thus, either caspofungin or L-AmB should be used for empiric antifungal therapy in children. However, AmB-D may be considered as an alternative therapy in settings with limited resources. The optimal dosage of L-AmB in the empiric setting is uncertain. In one pediatric study, the efficacy of L-AmB at a dosage of 1 mg/kg/day was comparable to 3 mg/kg/day;[142] however, large trials comparing the two doses are lacking. In contrast, the 3 mg/kg/day pediatric dosage of L-AmB for empiric antifungal

therapy is supported by large adult studies.[145]

Adult guidelines recommend empiric antifungal therapy be initiated in IFD high-risk neutropenic patients after 96 hours of fever in the setting of broad-spectrum antibiotics.[1] Data specific to children are lacking and in the absence of additional data, it is reasonable to recommend a similar approach in children. Although there are almost no data to guide cessation of antifungal therapy, the Panel agreed that empiric antifungal therapy should be continued until resolution of neutropenia (ANC consistently rising and > 100-500/uL) in the absence of documented or suspected IFD.

Although data are insufficient to recommend a specific empiric antifungal agent for patients already receiving mold-active antifungal prophylaxis, the Panel agreed that switching to a different class of mold-active antifungal agent should be considered.

A pre-emptive antifungal therapy strategy uses clinical, laboratory and radiographic parameters and not merely persistence of fever to determine indication for anti-fungal therapy. This approach has been accepted as an alternative to empiric antifungal therapy in a subset of IFD high-risk adult neutropenic patients.[1] However, there are no studies that evaluated this approach in children. While the Panel believes that a pre-emptive approach may be feasible in centers with adequate experience and facilities, research describing the safety and effectiveness of this approach is needed.

References

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:e56-93, 2011
2. Bucaneve G, Castagnola E, Viscoli C, et al: Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients. EJC 5:5-12, 2007 (suppl)
3. Drgona L, Paul M, Bucaneve G, et al: The need for aminoglycosides in combination with β-lactams for high-risk, febrile neutropaenic patients with leukaemia. EJC 5:13-22, 2007 (suppl)
4. Cometta A, Marchetti O, Calandra T: Empirical use of anti-Gram-positive antibiotics in febrile neutropaenic cancer patients with acute leukaemia. EJC 5:23-31, 2007 (suppl)
5. Marchetti O, Cordonnier C, Calandra T: Empirical antifungal therapy in neutropaenic cancer patients with persistent fever. EJC 5:32-42, 2007 (suppl)
6. National Comprehensive Cancer Network: NCCN Guidelines™ for Supportive Care: Prevention and Treatment of Cancer-Related Infections (Version 2.2011), Fort Washington, PA: National Comprehensive Cancer Network, 2011 (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp)
7. de Naurois J, Novitzky-Basso I, Gill MJ, et al: Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol 21:v252-6, 2010 (suppl 5)
8. Sung L, Phillips R, Lehrnbecher T: Time for paediatric febrile neutropenia guidelines - children are not little adults. Eur J Cancer 47:811-3, 2011
9. Oxman AD, Fretheim A, Schunemann HJ: Improving the use of research evidence in guideline development: introduction. Health Res Policy Syst 4:12, 2006
10. Brouwers MC, Kho ME, Browman GP, et al: Development of the AGREE II, part 1: performance, usefulness and areas for improvement. CMAJ 182:1045-52
11. Brozek JL, Akl EA, Alonso-Coello P, et al: Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 64:669-77, 2009
12. Agyeman P, Aebi C, Hirt A, et al: Predicting bacteremia in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. Pediatr Infect Dis J 30:e114-9, 2011
13. Alexander SW, Wade KC, Hibberd PL, et al: Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol 24:38-42, 2002
14. Ammann RA, Aebi C, Hirt A, et al: Fever in neutropenia in children and adolescents: evolution over time of main characteristics in a single center, 1993-2001. Support Care Cancer 12:826-32, 2004
15. Ammann RA, Bodmer N, Hirt A, et al: Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. J Clin Oncol 28:2008-14, 2010
16. Ammann RA, Hirt A, Luthy AR, et al: Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. Med Pediatr Oncol 41:436-43, 2003
17. Baorto EP, Aquino VM, Mullen CA, et al: Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. Cancer 92:909-13, 2001

18. Hakim H, Flynn PM, Srivastava DK, et al: Risk prediction in pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J 29:53-9, 2010

19. Hann I, Viscoli C, Paesmans M, et al: A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). Br J Haematol 99:580-8, 1997

20. Jones GR, Konsler GK, Dunaway RP, et al: Infection risk factors in febrile, neutropenic children and adolescents. Pediatr Hematol Oncol 13:217-29, 1996

21. Klaassen RJ, Goodman TR, Pham B, et al: "Low-risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. J Clin Oncol 18:1012-9, 2000

22. Lucas KG, Brown AE, Armstrong D, et al: The identification of febrile, neutropenic children with neoplastic disease at low risk for bacteremia and complications of sepsis. Cancer 77:791-8, 1996

23. Macher E, Dubos F, Garnier N, et al: Predicting the risk of severe bacterial infection in children with chemotherapy-induced febrile neutropenia. Pediatr Blood Cancer 55:662-7, 2010

24. Paganini HR, Aguirre C, Puppa G, et al: A prospective, multicentric scoring system to predict mortality in febrile neutropenic children with cancer. Cancer 109:2572-9, 2007

25. Rackoff WR, Gonin R, Robinson C, et al: Predicting the risk of bacteremia in childen with fever and neutropenia. J Clin Oncol 14:919-24, 1996

26. Rondinelli PI, 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 28:665-70, 2006

27. Santolaya ME, Alvarez AM, Aviles CL, et al: Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever, and neutropenia. Clin Infect Dis 35:678-83, 2002

28. Santolaya ME, Alvarez AM, Becker A, et al: Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. J Clin Oncol 19:3415-21, 2001

29. Tezcan G, Kupesiz A, Ozturk F, et al: Episodes of fever and neutropenia in children with cancer in a tertiary care medical center in Turkey. Pediatr Hematol Oncol 23:217-29, 2006

30. West DC, Marcin JP, Mawis R, et al: Children with cancer, fever, and treatment-induced neutropenia: risk factors associated with illness requiring the administration of critical care therapies. Pediatr Emerg Care 20:79-84, 2004

31. Phillips B, Wade R, Stewart LA, et al: Systematic review and meta-analysis of the discriminatory performance of risk prediction rules in febrile neutropaenic episodes in children and young people. Eur J Cancer 46:2950-64, 2010

32. Toll DB, Janssen KJM, Vergouwe Y, et al: Validation, updating and impact of clinical prediction rules: A review. J Clin Epidemiol 61:1085-1094, 2008

33. Phillips R, Lehrnbecher T, Alexander S, et al: Updated systematic review and meta-analysis of the performance of risk prediction rules in children and young people with febrile neutropenia. PLoS One 7:e38300, 2012

34. Dommett R, Geary J, Freeman S, et al: Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. Eur J Cancer 45:2843-9, 2009

35. Scheinemann K, Ethier MC, Dupuis LL, et al: Utility of peripheral blood cultures in bacteremic pediatric cancer patients with a central line. Support Care Cancer 18:913-9, 2010

36. DesJardin JA, Falagas ME, Ruthazer R, et al: Clinical utility of blood cultures drawn from indwelling central venous catheters in hospitalized patients with cancer. Ann Intern Med 131:641-7, 1999

37. Chen WT, Liu TM, Wu SH, et al: Improving diagnosis of central venous catheter-related bloodstream infection by using differential time to positivity as a hospital-wide approach at a cancer hospital. J Infect 59:317-23, 2009

38. Adamkiewicz TV, Lorenzana A, Doyle J, et al: Peripheral vs. central blood cultures in patients admitted to a pediatric oncology ward. Pediatr Infect Dis J 18:556-8, 1999

39. Raad I, Hanna HA, Alakech B, et al: Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med 140:18-25, 2004

40. Handrup MM, Moller JK, Schroder H: Catheter-related bloodstream infections in children with cancer admitted with fever, 42nd Congress of the International Society of Pediatric Oncology (SIOP). Boston, MA, Pediatr Blood Cancer, 2010

41. Barriga FJ, Varas M, Potin M, et al: Efficacy of a vancomycin solution to prevent bacteremia associated with an indwelling central venous catheter in neutropenic and non-neutropenic cancer patients. Med Pediatr Oncol 28:196-200, 1997

42. O'Grady NP, Alexander M, Burns LA, et al: Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 39:S1-34, 2011

43. Wilson ML, Mitchell M, AMorris AJ, et al: Principles and Procedures for Blood Cultures; Approved Guideline. CLSI document M47-A. Wayne, PA, Clinical and Laboratory Standards Institute, 2007

44. Isaacman DJ, Karasic RB, Reynolds EA, et al: Effect of number of blood cultures and volume of blood on detection of bacteremia in children. J Pediatr 128:190-5, 1996

45. Kellogg JA, Manzella JP, Bankert DA: Frequency of low-level bacteremia in children from birth to fifteen years of age. J Clin Microbiol 38:2181-5, 2000

46. Connell TG, Rele M, Cowley D, et al: How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics 119:891-6, 2007

47. Gaur AH, Giannini MA, Flynn PM, et al: Optimizing blood culture practices in pediatric immunocompromised patients: evaluation of media types and blood culture volume. Pediatr Infect Dis J 22:545-52, 2003

48. Klaassen IL, de Haas V, van Wijk JA, et al: Pyuria is absent during urinary tract infections in neutropenic patients. Pediatr Blood Cancer 56:868-70, 2011

49. Mori R, Yonemoto N, Fitzgerald A, et al: Diagnostic performance of urine dipstick testing in children with suspected UTI: a systematic review of relationship with age and comparison with microscopy. Acta Paediatr 99:581-4, 2010

50. Sickles EA, Greene WH, Wiernik PH: Clinical presentation of infection in granulocytopenic patients. Arch Intern Med 135:715-9, 1975

51. Renoult E, Buteau C, Turgeon N, et al: Is routine chest radiography necessary for the initial evaluation of fever in neutropenic children with cancer? Pediatr Blood Cancer 43:224-8, 2004

52. Korones DN, Hussong MR, Gullace MA: Routine chest radiography of children with cancer hospitalized for fever and neutropenia: Is it really necessary? Cancer 80:1160-1164, 1997

53. Feusner J, Cohen R, O'Leary M, et al: Use of routine chest radiography in the evaluation of fever in neutropenic pediatric oncology patients. J Clin Oncol 6:1699-702, 1988

54. Katz JA, Bash R, Rollins N, et al: The yield of routine chest radiography in children with cancer hospitalized for fever and neutropenia. Cancer 68:940-3, 1991

55. Phillips R, Wade R, Riley R, et al: Systematic review and meta-analysis of the value of clinical features to exclude radiographic pneumonia in febrile neutropenic episodes in children and young people. J Paediatr Child Health, 2011

56. Furno P, Bucaneve G, Del Favero A: Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis. Lancet Infect Dis 2:231-42, 2002

57. Paul M, Soares-Weiser K, Leibovici L: Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. BMJ 326:1111, 2003

58. Manji A, Lehrnbecher T, Dupuis LL, et al: A systematic review and meta-analysis of anti-pseudomonal penicillins and carbapenems in pediatric febrile neutropenia. Support Care Cancer, 2011 (in press)

59. Manji A, Lehrnbecher T, Dupuis LL, et al: A Meta-Analysis of Anti-Pseudomonal Penicillins and Cephalosporins in Pediatric Patients with Fever and Neutropenia. Pediatr Infect Dis J 31:353-8, 2012

60. Paul M, Yahav D, Bivas A, et al: Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. Cochrane Database Syst Rev:CD005197, 2010

61. Kim PW, Wu YT, Cooper C, et al: Meta-analysis of a possible signal of increased mortality associated with cefepime use. Clin Infect Dis 51:381-9, 2010

62. Marron A, Carratala J, Alcaide F, et al: High rates of resistance to cephalosporins among viridans-group streptococci causing bacteraemia in neutropenic cancer patients. J Antimicrob Chemother 47:87-91, 2001

63. Vardakas KZ, Samonis G, Chrysanthopoulou SA, et al: Role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomised controlled trials. Lancet Infect Dis 5:431-9, 2005

64. Riikonen P: Imipenem compared with ceftazidime plus vancomycin as initial therapy for fever in neutropenic children with cancer. Pediatr Infect Dis J 10:918-23, 1991

65. Shenep JL, Hughes WT, Roberson PK, et al: Vancomycin, ticarcillin, and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. N Engl J Med 319:1053-8, 1988

66. Viscoli C, Moroni C, Boni L, et al: Ceftazidime plus amikacin versus ceftazidime plus vancomycin as empiric therapy in febrile neutropenic children with cancer. Rev Infect Dis 13:397-404, 1991

67. Speyer E, Herbinet A, Vuillemin A, et al: Agreement between children with cancer and their parents in reporting the child's health-related quality of life during a stay at the hospital and at home. Child Care Health Dev 35:489-95, 2009

68. Teuffel O, Amir E, Alibhai SM, et al: Cost-effectiveness of outpatient management for febrile neutropenia in children with cancer. Pediatrics 127:e279-86, 2011

69. Teuffel O, Ethier MC, Alibhai SM, et al: Outpatient management of cancer patients with febrile neutropenia: a systematic review and meta-analysis. Ann Oncol 22:2358-65, 2011

70. Ahmed N, El-Mahallawy HA, Ahmed IA, et al: Early hospital discharge versus continued hospitalization in febrile pediatric cancer patients with prolonged neutropenia: A randomized, prospective study. Pediatr Blood Cancer 49:786-92, 2007

71. Santolaya ME, Alvarez AM, Aviles CL, et al: Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. J Clin Oncol 22:3784-9, 2004

72. Manji A, Beyene J, Dupuis LL, et al: Outpatient and Oral Antibiotic Management of Low-Risk Febrile Neutropenia are Effective in Children - a Systematic Review of Prospective Trials. Support Care Cancer 20:1135-45, 2012

73. Vidal L, Paul M, Ben-Dor I, et al: Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. Cochrane Database Syst Rev:CD003992, 2004

74. Cometta A, Kern WV, De Bock R, et al: Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. Clin Infect Dis 37:382-9, 2003

75. Oude Nijhuis C, Kamps WA, Daenen SM, et al: Feasibility of withholding antibiotics in selected febrile neutropenic cancer patients. J Clin Oncol 23:7437-44, 2005

76. Aquino VM, Buchanan GR, Tkaczewski I, et al: Safety of early hospital discharge of selected febrile children and adolescents with cancer with prolonged neutropenia. Med Pediatr Oncol 28:191-5, 1997

77. Pizzo PA, Robichaud KJ, Gill FA, et al: Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med 67:194-200, 1979

78. Santolaya ME, Villarroel M, Avendano LF, et al: Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clin Infect Dis 25:92-7, 1997

79. Wacker P, Halperin DS, Wyss M, et al: Early hospital discharge of children with fever and neutropenia: a prospective study. J Pediatr Hematol Oncol 19:208-11, 1997

80. Cohen KJ, Leamer K, Odom L, et al: Cessation of antibiotics regardless of ANC is safe in children with febrile neutropenia. A preliminary prospective trial. J Pediatr Hematol Oncol 17:325-30, 1995

81. Bash RO, Katz JA, Cash JV, et al: Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. Cancer 74:189-96, 1994

82. Hodgson-Viden H, Grundy PE, Robinson JL: Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. BMC Pediatr 5:10, 2005

83. Lehrnbecher T, Stanescu A, Kuhl J: Short courses of intravenous empirical antibiotic treatment in selected febrile neutropenic children with cancer. Infection 30:17-21, 2002

84. Griffin TC, Buchanan GR: Hematologic predictors of bone marrow recovery in neutropenic patients hospitalized for fever: implications for discontinuation of antibiotics and early discharge from the hospital. J Pediatr 121:28-33, 1992

85. Kaplan AH, Weber DJ, Davis L, et al: Short courses of antibiotics in selected febrile neutropenic patients. Am J Med Sci 302:353-4, 1991

86. Mullen CA, Buchanan GR: Early hospital discharge of children with cancer treated for fever and neutropenia: identification and management of the low-risk patient. J Clin Oncol 8:1998-2004, 1990

87. Aquino VM, Tkaczewski I, Buchanan GR: Early discharge of low-risk febrile neutropenic children and adolescents with cancer. Clin Infect Dis 25:74-8, 1997

88. Slobbe L, Waal L, Jongman LR, et al: Three-day treatment with imipenem for unexplained fever during prolonged neutropaenia in haematology patients receiving fluoroquinolone and fluconazole prophylaxis: a prospective observational safety study. Eur J Cancer 45:2810-7, 2009

89. Cornelissen JJ, Rozenberg-Arska M, Dekker AW: Discontinuation of intravenous antibiotic therapy during persistent neutropenia in patients receiving prophylaxis with oral ciprofloxacin. Clin Infect Dis 21:1300-2, 1995

90. de Marie S, van den Broek PJ, Willemze R, et al: Strategy for antibiotic therapy in febrile neutropenic patients on selective antibiotic decontamination. Eur J Clin Microbiol Infect Dis 12:897-906, 1993

91. Joshi JH, Schimpff SC, Tenney JH, et al: Can antibacterial therapy be discontinued in persistently febrile granulocytopenic cancer patients? Am J Med 76:450-7, 1984

92. Bjornsson S, Preisler H, Henderson ES: A study of antibiotic therapy in fever of unknown origin in neutropenic cancer patients. Med Pediatr Oncol 3:379-85, 1977

93. Mahendra P, Jacobson SK, Ager S, et al: Short-course intravenous antibiotics with oral quinolone prophylaxis in the treatment of neutropenic fever in autologous bone marrow or peripheral blood progenitor cell transplant recipients. Acta Haematol 96:64-7, 1996

94. Tomiak AT, Yau JC, Huan SD, et al: Duration of intravenous antibiotics for patients with neutropenic fever. Ann Oncol 5:441-5, 1994

95. Groll AH, Kurz M, Schneider W, et al: Five-year-survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long-term survival. Mycoses 42:431-42, 1999

96. Zaoutis TE, Heydon K, Chu JH, et al: Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. Pediatrics 117:e711-6, 2006

97. Leahey AM, Bunin NJ, Belasco JB, et al: Novel multiagent chemotherapy for bone marrow relapse of pediatric acute lymphoblastic leukemia. Med Pediatr Oncol 34:313-8, 2000

98. Mor M, Gilad G, Kornreich L, et al: Invasive fungal infections in pediatric oncology. Pediatr Blood Cancer 56:1092-7, 2011

99. Rosen GP, Nielsen K, Glenn S, et al: Invasive fungal infections in pediatric oncology patients: 11-year experience at a single institution. J Pediatr Hematol Oncol 27:135-40, 2005

100. Castagnola E, Cesaro S, Giacchino M, et al: Fungal infections in children with cancer: a prospective, multicenter surveillance study. Pediatr Infect Dis J 25:634-9, 2006

101. Hovi L, Saarinen-Pihkala UM, Vettenranta K, et al: Invasive fungal infections in pediatric bone marrow transplant recipients: single center experience of 10 years. Bone Marrow Transpl 26:999-1004, 2000

102. Villarroel M, Aviles CL, Silva P, et al: Risk factors associated with invasive fungal disease in children with cancer and febrile neutropenia: a prospective multicenter evaluation. Pediatr Infect Dis J 29:816-21, 2010

103. Afzal S, Ethier MC, Dupuis LL, et al: Risk factors for infection-related outcomes during induction therapy for childhood acute lymphoblastic leukemia. Pediatr Infect Dis J 28:1064-8, 2009

104. Haupt R, Romanengo M, Fears T, et al: Incidence of septicaemias and invasive mycoses in children undergoing treatment for solid tumours: a 12-year experience at a single Italian institution. Eur J Cancer 37:2413-9, 2001

105. Grigull L, Beier R, Schrauder A, et al: Invasive fungal infections are responsible for one-fifth of the infectious deaths in children with ALL. Mycoses 46:441-6, 2003

106. Panackal AA, Li H, Kontoyiannis D, et al: Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. Clin Infect Dis 50:1588-1597, 2010

107. Haiduven D: Nosocomial aspergillosis and building construction. Med Mycol 47:S210-6, 2009 (suppl 1)

108. De Pauw B, Walsh TJ, Donnelly JP, et al: Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46:1813-21, 2008

109. Pfeiffer CD, Fine JP, Safdar N: Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 42:1417-27, 2006

110. Morrissey CO, Bardy PG, Slavin MA, et al: Diagnostic and therapeutic approach to persistent or recurrent fevers of unknown origin in adult stem cell transplantation and haematological malignancy. Intern Med J 38:477-95, 2008

111. Maschmeyer G, Beinert T, Buchheidt D, et al: Diagnosis and antimicrobial therapy of pulmonary infiltrates in febrile neutropenic patients--guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 82:S118-26, 2003 (Suppl 2)

112. Maertens J, Marchetti O, Herbrecht R, et al: European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 Update. Bone Marrow Transpl 46:709-18, 2010

113. Rohrlich P, Sarfati J, Mariani P, et al: Prospective sandwich enzyme-linked immunosorbent assay for serum galactomannan: early predictive value and clinical use in invasive aspergillosis. Pediatr Infect Dis J 15:232-7, 1996

114. El-Mahallawy HA, Shaker HH, Ali Helmy H, et al: Evaluation of pan-fungal PCR assay and Aspergillus antigen detection in the diagnosis of invasive fungal infections in high risk paediatric cancer patients. Med Mycol 44:733-9, 2006

115. Hovi L, Saxen H, Saarinen-Pihkala UM, et al: Prevention and monitoring of invasive fungal infections in pediatric patients with cancer and hematologic disorders. Pediatr Blood Cancer 48:28-34, 2007

116. Steinbach WJ, Addison RM, McLaughlin L, et al: Prospective Aspergillus galactomannan antigen testing in pediatric hematopoietic stem cell transplant recipients. Pediatr Infect Dis J 26:558-64, 2007

117. Hayden R, Pounds S, Knapp K, et al: Galactomannan antigenemia in pediatric oncology patients with invasive aspergillosis. Pediatr Infect Dis J 27:815-9, 2008

118. Armenian SH, Nash KA, Kapoor N, et al: Prospective monitoring for invasive aspergillosis using galactomannan and polymerase chain reaction in high risk pediatric patients. J Pediatr Hematol Oncol 31:920-6, 2009

119. Castagnola E, Furfaro E, Caviglia I, et al: Performance of the galactomannan antigen detection test in the diagnosis of invasive aspergillosis in children with cancer or undergoing haemopoietic stem cell transplantation. Clin Microbiol Infect 16:1197-203, 2010

120. Challier S, Boyer S, Abachin E, et al: Development of a serum-based Taqman real-time PCR assay for diagnosis of invasive aspergillosis. J Clin Microbiol 42:844-6, 2004

121. Marr KA, Laverdiere M, Gugel A, et al: Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis 40:1762-9, 2005

122. Miceli MH, Grazziutti ML, Woods G, et al: Strong correlation between serum aspergillus galactomannan index and outcome of aspergillosis in patients with hematological cancer: clinical and research implications. Clin Infect Dis 46:1412-22, 2008

123. Maertens J, Maertens V, Theunissen K, et al: Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis 49:1688-93, 2009

124. Desai R, Ross LA, Hoffman JA: The role of bronchoalveolar lavage galactomannan in the diagnosis of pediatric invasive aspergillosis. Pediatr Infect Dis J 28:283-6, 2009

125. Roilides E, Pavlidou E, Papadopoulos F, et al: Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. Pediatr Nephrol 18:450-3, 2003

126. Viscoli C, Machetti M, Gazzola P, et al: Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 40:1496-9, 2002

127. Verweij PE, Maertens J, Lehrnbecher T, et al: ECIL guidelines: Non-culture based diagnostic procedures for Aspergillus infections. Juan-les-Pins, France, European Conference on Infections in Leukemia, 2010

128. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, et al: beta-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis 52:750-70, 2011

129. Mularoni A, Furfaro E, Faraci M, et al: High Levels of beta-D-glucan in immunocompromised children with proven invasive fungal disease. Clin Vaccine Immunol 17:882-3, 2010

130. Zhao L, Tang JY, Wang Y, et al: Value of plasma ß-Glucan in early diagnosis of invasive fungal infection

in children. Chin J Contemp Pediatr 11:905-908, 2009

131. Smith PB, Benjamin DK, Jr., Alexander BD, et al: Quantification of 1,3-beta-D-glucan levels in children: preliminary data for diagnostic use of the beta-glucan assay in a pediatric setting. Clin Vaccine Immunol 14:924-5, 2007

132. Heussel CP, Kauczor HU, Heussel GE, et al: Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. J Clin Oncol 17:796-805, 1999

133. Caillot D, Casasnovas O, Bernard A, et al: Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 15:139-47, 1997

134. Taccone A, Occhi M, Garaventa A, et al: CT of invasive pulmonary aspergillosis in children with cancer. Pediatr Radiol 23:177-80, 1993

135. Burgos A, Zaoutis TE, Dvorak CC, et al: Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics 121:e1286-94, 2008

136. Archibald S, Park J, Geyer JR, et al: Computed tomography in the evaluation of febrile neutropenic pediatric oncology patients. Pediatr Infect Dis J 20:5-10, 2001

137. Agrawal AK, Saini N, Gildengorin G, et al: Is routine computed tomographic scanning justified in the first week of persistent febrile neutropenia in children with malignancies? Pediatr Blood Cancer 57:620-4, 2011

138. Sorensen J, Becker M, Porto L, et al: Rhinocerebral zygomycosis in a young girl undergoing allogeneic stem cell transplantation for severe aplastic anaemia. Mycoses 49:31-6, 2006 (suppl 1)

139. Rassi SJ, Melkane AE, Rizk HG, et al: Sinonasal mucormycosis in immunocompromised pediatric patients. J Pediatr Hematol Oncol 31:907-910, 2009

140. Flynn PM, Shenep JL, Crawford R, et al: Use of abdominal computed tomography for identifying disseminated fungal infection in pediatric cancer patients. Clin Infect Dis 20:964-70, 1995

141. Bochennek K, Abolmaali N, Wittekindt B, et al: Diagnostic approaches for immunocompromised paediatric patients with pulmonary infiltrates. Clin Microbiol Infect 12:199-201, 2006

142. Prentice HG, Hann IM, Herbrecht R, et al: A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. Br J Haematol 98:711-8, 1997

143. Maertens JA, Madero L, Reilly AF, et al: A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. Pediatr Infect Dis J 29:415-20, 2010

144. Sandler ES, Mustafa MM, Tkaczewski I, et al: Use of amphotericin B colloidal dispersion in children. J Pediatr Hematol Oncol 22:242-6, 2000

145. Walsh TJ, Teppler H, Donowitz GR, et al: Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 351:1391-402, 2004

146. White MH, Bowden RA, Sandler ES, et al: Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 27:296-302, 1998

147. Walsh TJ, Finberg RW, Arndt C, et al: Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med 340:764-71, 1999

148. Madsen K, Rosenman M, Hui S, et al: Value of electronic data for model validation and refinement: bacteremia risk in children with fever and neutropenia. J Pediatr Hematol Oncol 24:256-62, 2002

149. Miedema KG, de Bont ES, Oude Nijhuis CS, et al: Validation of a new risk assessment model for predicting adverse events in children with fever and chemotherapy-induced neutropenia. J Clin Oncol 29:e182-4; author reply e185, 2011

150. Corapcioglu F, Sarper N, Zengin E: Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. Pediatr Hematol Oncol 23:177-86, 2006

151. Petrilli AS, Cypriano M, Dantas LS, et al: Evaluation of ticarcillin/clavulanic acid versus ceftriaxone plus amikacin for fever and neutropenia in pediatric patients with leukemia and lymphoma. Braz J Infect Dis 7:111-20, 2003

152. Uygun V, Karasu GT, Ogunc D, et al: Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. Pediatr Blood Cancer 53:610-4, 2009

153. Vural S, Erdem E, Gulec SG, et al: Imipenem-cilastatin versus piperacillin-tazobactam as monotherapy in febrile neutropenia. Pediatr Int 52:262-7, 2009

154. Aksoylar S, Cetingul N, Kantar M, et al: Meropenem plus amikacin versus piperacillin-tazobactam plus netilmicin as empiric therapy for high-risk febrile neutropenia in children. Pediatr Hematol Oncol 21:115-23, 2004

155. Bolton-Maggs PH, van Saene HK, McDowell HP, et al: Clinical evaluation of ticarcillin, with clavulanic acid, and gentamicin in the treatment of febrile episodes in neutropenic children. J Antimicrob Chemother 27:669-76, 1991

156. Duzova A, Kutluk T, Kanra G, et al: Monotherapy with meropenem versus combination therapy with piperacillin plus amikacin as empiric therapy for neutropenic fever in children with lymphoma and solid tumors. Turk J Pediatr 43:105-9, 2001

157. Fleischhack G, Schmidt-Niemann M, Wulff B, et al: Piperacillin, beta-lactam inhibitor plus gentamicin as empirical therapy of a sequential regimen in febrile neutropenia of pediatric cancer patients. Support Care Cancer 9:372-9, 2001

158. Gonzalez M, Clavell LA: Piperacillin and gentamicin as non toxic empirical therapy in pediatric patients with fever and neutropenia. P R Health Sci J 6:13-5, 1987

159. Haddad AMA: Comparison of cefoperazone-sulbactam versus piperacillin plus amikacin as empiric therapy in pediatric febrile neutropenic cancer patients. Curr Ther Res 56:1094-1099, 1995

160. Hamidah A, Rizal AM, Nordiah AJ, et al: Piperacillin-tazobactam plus amikacin as an initial empirical therapy of febrile neutropenia in paediatric cancer patients. Singapore Med J 49:26-30, 2008

161. Hemsworth S, Nunn AJ, Selwood K, et al: Once-daily netilmicin for neutropenic pyrexia in paediatric oncology. Acta Paediatr 94:268-74, 2005

162. Heney D, Lewis IJ, Ghoneim AT, et al: Aztreonam therapy in children with febrile neutropenia: a randomized trial of aztreonam plus flucloxacillin versus piperacillin plus gentamicin. J Antimicrob Chemother 28:117-29, 1991

163. Kosmidis H, Varvoutsi M, Kafetzis D, et al: Efficacy and safety of azlocillin and ticarcillin in febrile neutropenic children with cancer: a comparative study. Chemioterapia 6:396-8, 1987

164. Miranda-Novales MG, Belmont-Martinez L, Villasis-Keever MA, et al: Empirical antimicrobial therapy in pediatric patients with neutropenia and fever. Risk factors for treatment failure. Arch Med Res 29:331-5, 1998

165. Morgan G, Duerden BI, Lilleyman JS: Ceftazidime as a single agent in the management of children with fever and neutropenia. J Antimicrob Chemother 12:347-51, 1983 (suppl A)

166. Smith L, Will AM, Williams RF, et al: Ceftriaxone vs. azlocillin and netilmicin in the treatment of febrile neutropenic children. J Infect 20:201-6, 1990

167. Yildirim I, Aytac S, Ceyhan M, et al: Piperacillin/tazobactam plus amikacin versus carbapenem monotherapy as empirical treatment of febrile neutropenia in childhood hematological malignancies. Pediatr Hematol Oncol 25:291-9, 2008

168. Zulfikar B, Devecioglu O, Anak S, et al: The efficacy of mezlocillin-amikacin combination in febrile neutropenic children with oncologic disease. J Chemother 3:250-4, 1991

169. Chuang YY, Hung IJ, Yang CP, et al: Cefepime versus ceftazidime as empiric monotherapy for fever and neutropenia in children with cancer. Pediatr Infect Dis J 21:203-9, 2002

170. Fleischhack G, Hartmann C, Simon A, et al: Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer. J Antimicrob Chemother 47:841-53, 2001

171. Granowetter L, Wells H, Lange BJ: Ceftazidime with or without vancomycin vs. cephalothin, carbenicillin and gentamicin as the initial therapy of the febrile neutropenic pediatric cancer patient. Pediatr Infect Dis J 7:165-70, 1988

172. Jacobs RF, Vats TS, Pappa KA, et al: Ceftazidime versus ceftazidime plus tobracycin in febrile neutropenic children. Infection 21:223-228, 1993

173. Kebudi R, Gorgun O, Ayan I, et al: Randomized comparison of cefepime versus ceftazidime monotherapy for fever and neutropenia in children with solid tumors. Med Pediatr Oncol 36:434-41, 2001

174. Mullen CA, Petropoulos D, Roberts WM, et al: Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. Cancer 86:126-34, 1999

175. Mustafa MM, Carlson L, Tkaczewski I, et al: Comparative study of cefepime versus ceftazidime in the empiric treatment of pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J 20:362-9, 2001

176. Ariffin H, Arasu A, Mahfuzah M, et al: Single-daily ceftriaxone plus amikacin versus thrice-daily ceftazidime plus amikacin as empirical treatment of febrile neutropenia in children with cancer. J Paediatr Child Health 37:38-43, 2001

177. Charnas R, Luthi AR, Ruch W: Once daily ceftriaxone plus amikacin vs. three times daily ceftazidime plus amikacin for treatment of febrile neutropenic children with cancer. Writing Committee for the International Collaboration on Antimicrobial Treatment of Febrile Neutropenia in Children. Pediatr Infect Dis J 16:346-53, 1997

178. Corapcioglu F, Sarper N: Cefepime versus ceftazidime + amikacin as empirical therapy for febrile neutropenia in children with cancer: a prospective randomized trial of the treatment efficacy and cost. Pediatr Hematol Oncol 22:59-70, 2005

179. Hung KC, Chiu HH, Tseng YC, et al: Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empirical therapy for neutropenic fever in children with malignancy. J Microbiol Immunol Infect 36:254-9, 2003

180. Laoprasopwattana K, Pruekprasert P, Laosombat V, et al: Clinical outcome of febrile neutropenia in children with cancer using ceftazidime and aminoglycosides. Pediatr Hematol Oncol 24:595-606, 2007

181. Maltezou HC, Baka M, Gombakis N, et al: Comparison of isepamicin with amikacin for the empirical treatment of febrile neutropenic children with malignancies. Int J Antimicrob Agents 18:383-6, 2001

182. Cagol AR, Castro Junior CG, Martins MC, et al: Oral vs. intravenous empirical antimicrobial therapy in febrile neutropenic patients receiving childhood cancer chemotherapy. J Pediatr (Rio J) 85:531-5, 2009

183. Chastagner P, Plouvier E, Eyer D, et al: Efficacy of cefepime and amikacin in the empiric treatment of febrile neutropenic children with cancer. Med Pediatr Oncol 34:306-8, 2000

184. Hamidah A, Lim YS, Zulkifli SZ, et al: Cefepime plus amikacin as an initial empirical therapy of febrile neutropenia in paediatric cancer patients. Singapore Med J 48:615-9, 2007

185. Kutluk T, Kurne O, Akyuz C, et al: Cefepime vs. Meropenem as empirical therapy for neutropenic fever in children with lymphoma and solid tumours. Pediatr Blood Cancer 42:284-6, 2004

186. Gupta A, Swaroop C, Agarwala S, et al: Randomized controlled trial comparing oral amoxicillin-clavulanate and ofloxacin with intravenous ceftriaxone and amikacin as outpatient therapy in pediatric low-risk febrile neutropenia. J Pediatr Hematol Oncol 31:635-41, 2009

187. Paganini H, Gomez S, Ruvinsky S, et al: Outpatient, sequential, parenteral-oral antibiotic therapy for lower risk febrile neutropenia in children with malignant disease: a single-center, randomized, controlled trial in Argentina. Cancer 97:1775-80, 2003

188. Paganini H, Rodriguez-Brieshcke T, Zubizarreta P, et al: Oral ciprofloxacin in the management of children with cancer with lower risk febrile neutropenia. Cancer 91:1563-7, 2001

189. Bartolozzi S, Clerico A, Properzi E, et al: Ceftriaxone as a single agent in empirical therapy of unexplained fever in granulocytopenic children with solid tumors. J Chemother 9:227-31, 1997

190. Shrestha PN, Sah KP, Rana R: Emperical oral antibiotic therapy for children with low risk febrile neutropenia during cancer chemotherapy. J Nepal Paediatr Soc 29:22-25, 2009

191. Abbas AAH, Felimban SK, Cittana BA, et al: Once daily ceftriaxone and amikacin for outpatient treatment of neutropenic fever in children with acute lymphoblastic leukaemia. Haema 6:501-506, 2003

192. Aquino VM, Herrera L, Sandler ES, et al: Feasibility of oral ciprofloxacin for the outpatient management of febrile neutropenia in selected children with cancer. Cancer 88:1710-4, 2000

193. Kaplinsky C, Drucker M, Goshen J, et al: Ambulatory treatment with ceftriaxone in febrile neutropenic children. Isr J Med Sci 30:649-51, 1994

194. Malik IA: Out-patient management of febrile neutropenia in indigent paediatric patients. Ann Acad Med Singapore 26:742-6, 1997

195. Mustafa MM, Aquino VM, Pappo A, et al: A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. J Pediatr 128:847-9, 1996

196. Petrilli A, Altruda Carlesse F, Alberto Pires Pereira C: Oral gatifloxacin in the outpatient treatment of children with cancer fever and neutropenia. Pediatr Blood Cancer 49:682-6, 2007

197. Petrilli AS, Dantas LS, Campos MC, et al: Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients: randomized prospective trial. Med Pediatr Oncol 34:87-91, 2000

198. Sulahian A, Boutboul F, Ribaud P, et al: Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. Cancer 91:311-8, 2001

199. Herbrecht R, Letscher-Bru V, Oprea C, et al: Aspergillus galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol 20:1898-906, 2002

Table 1. Overall Summary of Recommendations*

	Risk Stratification	Evaluation	Treatment
INITIAL PRESENTATION OF FN	Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C).	Obtain blood cultures at the onset of FN from all lumens of central venous catheters (1C). Consider peripheral blood culture concurrent with obtaining central venous catheter cultures (2C). Consider urinalysis and urine culture in patients where a clean-catch, midstream specimen is readily available (2C). Obtain chest radiography only in symptomatic patients (1B).	**High-Risk FN** Use monotherapy with an anti-pseudomonal *β*-lactam or a carbapenem as empiric therapy in pediatric high-risk FN (1A). Reserve addition of a second Gram-negative agent or a glycopeptide for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens (1B). **Low-Risk FN** In children with low-risk FN, consider initial or step-down outpatient management if the infrastructure is in place to ensure careful monitoring and follow-up (2B). In children with low-risk FN, consider oral antibiotic administration if the child is able to tolerate this route of administration reliably (2B).
		Modification of Treatment	**Cessation of Treatment**
ONGOING MANAGEMENT OF FN: 24 to 72 hours or more after initiation of empiric antibacterial treatment		In patients who are responding to initial empiric antibiotic therapy, discontinue double coverage for Gram-negative infection or empiric glycopeptide (if initiated) after 24 to 72 hours if there is no specific microbiologic indication to continue combination therapy (1B). Do not modify the initial empiric antibacterial regimen based solely on persistent fever in children who are clinically stable (1C). In children with persistent fever who become clinically unstable, escalate the initial empiric antibacterial regimen to include coverage for resistant Gram-negative, Gram-positive, and anaerobic bacteria (1C).	**All Patients** Discontinue empiric antibiotics in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours and who have evidence of marrow recovery (1C). **Low-Risk FN** Consider discontinuation of empiric antibiotics at 72 hours in low-risk patients who have negative blood cultures and who have been afebrile for at least 24 hours, irrespective of marrow recovery status, as long as careful follow-up is ensured (2B).

	Risk Stratification	Evaluation	Treatment
EMPIRIC ANTIFUNGAL TREATMENT: 96 hours or more after initiation of empiric antibacterial treatment	Patients at IFD high-risk are those with AML, relapsed acute leukemia, those receiving highly myelosuppressive chemotherapy for other malignancies, and allogeneic hematopoietic stem cell transplant recipients with persistent fever despite prolonged (≥ 96 hours) broad-spectrum antibiotic therapy and expected prolonged neutropenia (>10 days). All others should be categorized as IFD low-risk (1B).	**All Patients** Consider galactomannan in bronchoalveolar lavage and cerebrospinal fluid to support the diagnosis of pulmonary or central nervous system aspergillosis (2C). In children, do not use ß-D-glucan testing for clinical decisions until further pediatric evidence has accumulated (1C). **IFD High Risk** Consider prospective monitoring of serum galactomannan twice per week in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis (2B). In IFD high-risk children with persistent FN beyond 96 hours, perform evaluation for IFD. Evaluation should include CT of the lungs and targeted imaging of other clinically suspected areas of infection (1B). Consider CT of the sinuses in children 2 years of age or older (2C). **IFD Low Risk** In IFD low-risk patients, do not implement routine galactomannan screening (1C).	**All Patients** Use either caspofungin or liposomal amphotericin B for empiric antifungal therapy (1A). **IFD High Risk** In neutropenic IFD high-risk children, initiate empiric antifungal treatment for persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (≥ 96 hours) broad-spectrum antibacterial agents (1C). **IFD Low Risk** In neutropenic IFD low-risk children, consider empiric antifungal therapy in the setting of persistent FN (2C).

*Parenthesis indicates the GRADE strength of recommendation (1=strong, 2=weak) and quality of the evidence (A=high, B=moderate, C=low or very-low).

Abbreviations: AML – acute myeloid leukemia; CT – computed tomography; FN – fever and neutropenia; GRADE – Grades of Recommendation Assessment, Development and Evaluation; IFD – invasive fungal disease; CNS –central nervous system

Table 2: Validated Pediatric Risk Stratification Strategies for Low-Risk Patients

	Rackoff (1996)[25]	Alexander (2002)[13]	Rondinelli (2006)[26]	Santolaya (2001)[28]	Ammann (2003)[16]	Ammann (2010)[15]
Patient and disease related factors	None	AML, Burkitt lymphoma, induction ALL, progressive disease, relapsed with marrow involvement	2 points for central venous catheter, 1 point for age ≤5 years	Relapsed leukemia, chemotherapy within 7 days of episode	Bone marrow involvement, central venous catheter, pre-B-cell leukemia	4 points for chemotherapy more intensive than ALL maintenance
Episode specific factors	Absolute monocyte count	Hypotension, tachypnea/hypoxia <94%, new CXR changes, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason for in-patient treatment	4.5 points for clinical site of infection,2.5 points for no URTI, 1 point each for fever >38.5°C, hemoglobin ≤70g/L	CRP ≥90 mg/L, hypotension, platelets ≤50 g/L	Absence of clinical signs of viral infection, CRP >50 mg/L, white blood cell count ≤500/uL, hemoglobin >100 g/L	5 points for hemoglobin ≥90 g/L, 3 points each for white blood cell count <300/uL, platelet <50 g/L
Rule formulation	Absolute monocyte count ≥ 100/uL= low risk of bacteremia HSCT = high risk	Absence of any risk factor = low risk of serious medical complication HSCT = high risk	Total score <6 = low risk of serious infectious complication HSCT =high risk	Zero risk factors or only low platelets or only <7 days from chemotherapy = low risk of invasive bacterial infection	Three or fewer risk factors = low risk of significant infection HSCT = high risk	Total score <9 = low risk of adverse FN outcome HSCT = high risk
Demonstrated to be valid*	USA Madsen 2002[148]	United Kingdom Dommett 2009[34]	Brazil Rondinelli 2006[26]	South America Santolaya 2002[27]	Europe Ammann 2010[15], Macher 2010[23]	Europe Miedema 2011[149]

Abbreviations: USA – United States of America; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; URTI – upper respiratory tract infection; CXR – chest radiograph; CRP – C-reactive protein; FN – fever and neutropenia

*"Valid" refers to clinically adequate discrimination of a group at low risk of complications

Appendix 1. Composition of the International Pediatric Fever and Neutropenia Working Group Panel

Name	Country	Profession	Discipline
Sarah Alexander	Canada	Physician	Oncology
Frank Alvaro	Australia	Physician	Oncology
Fabianne Carlesse	Brazil	Physician	Infectious disease
Elio Castagnola	Italy	Physician	Infectious disease
Bonnie Davis	Canada	Patient advocate	
Lee Dupuis	Canada	Pharmacist	Oncology
Brian Fisher	US	Physician	Infectious disease
Faith Gibson	UK	Nurse	Oncology
Andreas Groll	Germany	Physician	Oncology, infectious disease
Aditya Gaur	US	Physician	Infectious disease
Ajay Gupta	India	Physician	Oncology
Hana Hakim	US	Physician	Infectious disease
Rejin Kebudi	Turkey	Physician	Oncology
Thomas Lehrnbecher	Germany	Physician	Oncology
Sérgio Petrilli	Brazil	Physician	Oncology
Bob Phillips	UK	Physician	Oncology
Maria Santolaya	Chile	Physician	Infectious disease
William Steinbach	US	Physician	Infectious disease
Lillian Sung	Canada	Physician	Oncology, infectious disease
Milena Villarroel	Chile	Physician	Oncology
Theo Zaoutis	US	Physician	Infectious disease

Abbreviations: US – United States; UK – United Kingdom

Appendix 2. Outline of Sections, Clinical Questions and Median Importance Ratings for Outcomes

The following presents the specific clinical questions for guideline development. Italics illustrate how these clinical questions may be translated into practical questions relevant to clinical care.

SECTION 1: INITIAL PRESENTATION OF FEVER AND NEUTROPENIA (FN)

Initial presentation and evaluation of pediatric patients with FN

Specific Questions:

1. What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?

Can we select patients who need higher or lower degrees of observation and aggressiveness of antibiotic therapy?

2. What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?

What tests should be routinely performed to identify the etiology of an episode? For example, should urine culture and chest radiography be conducted in children who do not have symptoms or signs localized to those sites?

Outcomes:

Outcomes	Importance
Death	Critical
Persistent fever / time to resolution of fever	Important
Sepsis syndrome	Critical
Intensive care unit admission	Critical
Serious medical complication	Critical
Microbiologically documented infection (e.g. bacterial, viral or fungal infection)	Critical
Clinically documented focal infection (included radiologically documented e.g. pneumonia)	Critical

Initial management of FN including drug choice, location of treatment, and route of administration

Specific Questions:

3. What empiric antibiotics are appropriate for children with high-risk FN?

4. In children with low-risk FN, is initial or step-down outpatient management as effective and safe as inpatient management?

5. In children with low-risk FN, is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?

For patients who are predicted to have a low risk of an adverse outcome with this episode of FN, can they be managed as out-patients, and can they be managed with oral antibiotics?

Outcomes:

Outcomes	Importance
Death	Critical
Sepsis syndrome	Critical
Intensive care unit admission	Critical
Serious medical complication	Critical
Persistent fever / time to resolution of fever	Important
Secondary infection including breakthrough bacteremia	Critical
Re-admission	Important
Recurrence of infection/fever	Important
Modification of initial empiric antibiotics	Important
Quality of life	Important

SECTION 2: ONGOING MANAGEMENT OF FN EXCLUDING EMPIRIC ANTIFUNGAL THERAPY

Treatments including modification of therapy (excluding empiric antifungal therapy) and cessation of therapy in pediatric patients with FN who have been receiving antibiotic therapy

Specific Questions:

6. When and how should the initial empiric antibiotic therapy be modified during the pediatric FN episode?

How should the initial antibiotics be modified in those who are responding to initial treatment, those who remain persistently febrile and those who clinically deteriorate?

7. When can empiric antibiotics be discontinued in patients with low- and high-risk FN?

When can antibiotics be discontinued in those who become afebrile and are clinically stable in low and high risk FN?

Outcomes:

Outcomes	Importance
Death	Critical
Re-hospitalization	Critical
Resolution of fever and neutropenia without modification of therapy	Critical
Resolution of fever and neutropenia with modification of therapy	Important
Quality of life	Important
Toxicity	Critical

SECTION 3: EMPIRIC ANTIFUNGAL TREATMENT

Risk stratification and evaluation of patients with persistent or recurrent FN despite broad-spectrum antibiotics

Specific Questions:

8. What clinical parameters can classify pediatric patients with persistent FN as high-risk or low-risk for invasive fungal disease (IFD)?

What clinical or laboratory features can indicate whether a child is at higher or lower risk of developing an IFD, which may impact on whether a child receives more or less aggressive antifungal therapy?

9. What clinical features, laboratory tests, imaging studies, and procedures (such as bronchoalveolar lavage and biopsy) are useful to identify a fungal etiology for persistent/recurrent FN despite broad-spectrum antibiotics?

What tests should be performed to identify or exclude IFD? What is the appropriate timing of these tests?

Outcomes:

Outcomes	**Importance**
Death	Critical
Breakthrough fungal infection (proven or probable mold infection)	Critical
Breakthrough fungal infection (proven or probable yeast infection)	Critical
Development of pulmonary infiltrates	Critical
Fever unresponsive to antibiotic treatment	Important
Serious medical complication	Critical

Management of persistent or recurrent fever in neutropenic children despite broad-spectrum antibiotics: empiric antifungal therapy

Specific Questions:

10. When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?

What are the empiric antifungal regimens that have been evaluated in children and which ones have better efficacy and fewer toxicities?

Outcomes:

Outcomes	**Importance**
Death (overall)	Critical
Death attributable to invasive fungal disease	Critical
Breakthrough fungal disease (mold, yeast)	Critical
Clinical deterioration / intensive care unit admission	Critical
Development of pulmonary infiltrates	Critical
Resolution of fever and neutropenia with or without modification of empiric antifungal treatment	Important
Toxicity	Critical

Appendix 3. Pediatric and Adult Studies that Evaluated the Proportion of Positive Blood Cultures Identified only by Peripheral Culture

Study	Pediatric or Adult	Number of Paired Blood Cultures	Contaminates Deleted	Proportion Positive Only in Peripheral Culture (%)
Handrup 2010[40]	Pediatric	68	No	7/51 (13.7)
Scheinemann 2010[35]	Pediatric	318	Yes	28/228 (12.3)
Chen 2009[37]	Adult	2775	No	68/533 (12.8)
Raad 2004[39]	Both pediatric and adult	6138	No	191/1010 (18.9)
Adamkiewickz 1999[38]	Pediatric	176	No	6/21 (28.6)
DesJardin 1999[36]	Adult	552	Yes	5/46 (10.9)
Barriga 1997[41]	Both pediatric and adult	143	No	7/44 (15.9)

Appendix 4. Efficacy and Safety of Initial Empiric Antibiotic Regimens in Children with Fever and Neutropenia Reported in All Prospective Trials*

	APP ± BLI Monotherapy	APP ± BLI and Aminoglycoside	Ceftazidime Monotherapy	Ceftazidime and Aminoglycoside	FGC Monotherapy	FGC and Aminoglycoside	Carbapenem
Citations	[150-153]	[65,154-168]	[165,169-175]	[66,164,172,176-181]	[66,147,149,168,170, 173,175,181-185]	[183,184]	[61,65,150,152,166,167,176,182,183,186-188]
Number of Studies***	4	13	7	10	11	2	10
Number of Patients***	210	1092	406	805	517	167	572
Percentage treatment failure including modification (95% CI)	34 (27,41)	41 (32, 50)	43 (28, 58)	32 (19, 45)	39 (35, 44)	40 (27, 52)	36 (26, 45)
Percentage infection-related mortality (95% CI)	2 (0, 3)	1 (0, 2)	1 (0, 2)	2 (1, 3)	1 (0, 2)	1 (0, 2)	1 (0, 1)
Percentage overall mortality (95% CI)	2 (0, 4)	4 (2, 7)	1 (0, 2)	3 (2, 4)	2 (0, 3)	1 (0, 2)	1 (0, 2)
Mean days of fever (95% CI)	3.1 (2.8, 3.5)	3.5 (2.9, 4.2)	2.8 (1.7, 3.9)	3.1 (2.3, 3.9)	3.0 (2.4, 3.7)		3.5 (2.7, 4.3)
Percentage recurrent infection** (95% CI)		12 (8,16)	3 (0, 5)	2 (0, 6)	12 (0, 24)	5 (0, 10)	3 (0, 8)
Percentage sepsis (95% CI)		3 (1, 6)	4 (0, 7)	2 (0, 6)	16 (0, 39)		5 (0, 10)
Percentage secondary infection** (95% CI)	10 (3, 18)	5 (2, 8)	4 (2, 6)	4 (2, 6)	4 (1, 7)		2 (0, 4)
Percentage adverse events causing antibiotic discontinuation (95% CI)	1 (0, 3)	0 (0, 1)	1 (0, 3)	1 (0, 2)	1 (0, 2)	1 (0, 3)	1 (0, 3)

Abbreviations: APP – anti-pseudomonal penicillin; BLI – beta lactamase inhibitor; FGC – fourth generation cephalosporin, CI – confidence interval

* If outcome is missing, no studies reported on that outcome.
** Recurrent infection defined as reappearance of fever or infection after initial resolution; secondary infection defined as development of a new infection during ongoing treatment.
*** Maximum number of studies and patients reporting any outcome. Not all outcomes were reported for each study.

Appendix 5. Prospective Studies that Compared Initial or Step-down Outpatient Management with Inpatient Management in Children with Low-Risk Fever and Neutropenia*

Number of Regimens	Number of Patients and Effect** (95% CI)		Comparison	Quality	Importance
	Inpatient [156,182,185,189,190]	Outpatient [174,186-188,191-197]			
Treatment Failure Including Modification					
8 inpatient: 7 outpatient	317 27% (17, 38)	478 15% (10, 20)	P=0.04	Moderate	Critical
Infection-related Mortality					
6 inpatient: 16 outpatient	227 1% (0, 3)	953 0%	P=0.49	Moderate	Critical
Overall Mortality					
6 inpatient: 14 outpatient	227 1% (0, 3)	837 0%	P=0.48	Moderate	Critical
Days of Fever					
1 inpatient: 12 outpatient	33 2.6 (2.4, 2.8)	642 2.3 (1.9, 2.6)	P=0.12	Low	Important
Adverse Events - Antibiotic Discontinuation					
3 inpatient: 6 outpatient	124 2% (0, 5)	253 1% (0, 2)	P=0.39	Moderate	Important

Abbreviation: CI – confidence interval
* Based upon all prospective trials conducted in pediatrics including randomized controlled trials (RCTs).
** Effect is percentage for all outcomes except duration of fever where the mean is presented.

Limitations refer to factors that decrease the quality of evidence supporting a recommendation. Directness refers to whether the trials studied the same population, intervention and outcomes. All estimates are limited by a lack of RCTs and indirect comparisons. For quality, observational studies can provide moderate or strong evidence in unusual circumstances. Importance refers to whether the outcomes are crucial to decision making.

Appendix 6. Prospective Studies that Compared Initial or Step-down Oral with Parenteral Antibiotic Management in Children with Low-Risk Fever and Neutropenia*

Number of Regimens	Number of Patients and Effect** (95% CI)		Comparison	Quality	Importance
	Parenteral [156,174,182,185-187,189,191,193,195,197]	Oral [174,182,186-188,190,192,194,196,197]			
Treatment Failure Including Modification					
9 parenteral: 6 oral	385 22% (14, 31)	410 20% (11, 29)	P=0.68	Moderate	Critical
Infection-related Mortality					
11 parenteral: 11 oral	504 1% (0, 2)	676 0%	P=0.71	Moderate	Critical
Overall Mortality					
10 parenteral: 10 oral	447 1% (0, 2)	617 0%	P=0.70	Moderate	Critical
Days of Fever					
6 parenteral: 7 oral	289 2.5 (1.9, 3.0)	386 2.1 (1.6, 2.7)	P=0.39	Moderate	Important
Recurrent Infection					
2 parenteral: 3 oral	69 3% (0, 8)	138 0%	P=0.31	Low	Important
Sepsis					
5 parenteral: 7 oral	267 0%	528 1% (0, 2)	P=0.73	Moderate	Critical
Secondary Infection					
1 parenteral: 4 oral	19 0%	339 4% (0, 8)	P=0.90	Low	Critical
Adverse Events - Antibiotic Discontinuation					
5 parenteral: 4 oral	201 1% (0, 3)	176 2% (0, 3)	P=0.73	Moderate	Important
Readmission					
6 parenteral: 9 oral	324 8% (2, 15)	672 7% (4, 11)	P=0.80	Moderate	Important

Abbreviation: CI – confidence interval

* Based upon all prospective trials conducted in pediatrics including randomized controlled trials (RCTs).

** Effect is percentage for all outcomes except duration of fever where the mean is presented.

Limitations refer to factors that decrease the quality of evidence supporting a recommendation. Directness refers to whether the trials studied the same population, intervention and outcomes. All estimates are limited by few RCTs and mainly indirect comparisons. For quality, observational studies can provide moderate or strong evidence in unusual circumstances. Importance refers to whether the outcomes are crucial to decision making.

Appendix 7. Pediatric Studies that Evaluated Fever and Neutropenia Outcomes of Antibiotic Discontinuation by Bone Marrow Recovery Requirements

Number of Studies by Design N=10	Number of Episodes	Marrow Recovery Requirements among All Studies (Not Stratified by Design)*	Proportion of Patients with Recurrent Fever (95% CI)
Randomized trial (n=1)[78]	1,167	Requirement for evidence of marrow recovery explicitly stated (n=2)	1% (0.1 to 5)
Prospective cohort studies (n=3)[79-81]		Requirement for marrow recovery not clear (n=7)	5% (3 to 9)
Retrospective cohort studies (n=6)[76,82-86]		No requirement for evidence of marrow recovery explicitly stated (n=4)	14% (5 to 36)**

Abbreviation: CI – confidence interval
* Discontinuation rules all required negative blood cultures (48 – 72 hours incubation), and patients to be afebrile between 24 and 48 hours.
**Significant heterogeneity

Appendix 8. Studies Evaluating Serum Galactomannan for Diagnosis of Invasive Fungal Disease

Author	Number of patients	Number of samples	Median Age in Years (range)	Number							Sensitivity	Specificity	Quality
				Proven IFD	Probable IFD	Controls	True positive	False positive	True negative	False negative			
Steinbach [116]	64	826	8 (0.8-19.5)		1	63	0 (0%)	8 (13%)	55 (87%)	1 (100%)	98%	87%	Low
Hayden [117]	56	990	NR (0.25-18)	17		39	11 (65%)	5 (13%)	34 (87%)	6 (35%)	65%	87%	Moderate
Armenian [118]	68	1086	11.1 (0.4-22.2)	0	3	45	NR						Low
Castagnola [119]	119 (195 episodes)	1798	9.5 (0.1-20)	NR									Moderate
Rohrlich [113]	37	413	8.5* (0.4-18)		10	27	10 (28%)	0 (0%)	2 (100%)	25 (72%)	29%	100%	Low
Challier [120]	20	NR	not specified	4	8	8	11 (92%)	0 (0%)	8 (100%)	1 (8%)	92%	100%	Low
Sulahian [198]	347	2376	14.5 (6-25) for IA	9		338	9 (100%)	34 (10%)	304 (90%)	0 (0%)	100%	90%	Moderate
Herbrecht [199]	48 episodes	NR	<18	NR									Low
Hovi [115]	98 (117 episodes)	932	6.5* (1-16.5)	2		97	1 (100%)	6 (6%)	91 (94%)	0 (0%)	100%	94%	Low
El-Mahallawy [114]	91	NR	6 (2-18)	15	13	63	22 (78%)	32 (51%)	31 (49%)	6 (22%)	79%	49%	Low

Abbreviations: IFD – invasive fungal disease; IA – invasive aspergillosis; NR – not reported
*Mean and not median reported

Appendix 9. Prospective Trials Evaluating Empiric Antifungal Therapy in Persistently Neutropenic Children with Fever

Author	Composite Endpoint for Efficacy	Results by Endpoint	Overall efficacy	Safety
Maertens[143]		Caspofungin vs LAmB		Caspofungin vs LAmB
	Successful treatment of any baseline invasive fungal disease	0/1 vs 0/0	Caspofungin 46%	Serious adverse events: 2% vs 12% Discontinuation of study drug due to adverse events: 4% vs 12%
	Survival 7 days after antifungal treatment	56/56 (100%) vs 25/25 (100%)	LAmB 32%	Clinical adverse events: 48% vs 46%
	No premature discontinuation of study drug	51/56 (91%) vs 21/25 (84%)		
	Resolution of fever >48 hours during neutropenia	27/56 (48%) vs 9/25 (36%)		
	No breakthrough invasive fungal disease	56/56 (100%) vs 24/25 (96%)		
Sandler[144]		ABCD vs AmB-D		ABCD vs AmB-D
	Survival 7 days after last dose of study drug		ABCD 18/26 (69%)	Renal toxicity*: 3/25 (12%) vs 11/21 (52%) (P<0.003)
	No breakthrough invasive fungal disease	24/25 (96%) vs 19/21 (90%)		Serum creatinine change from baseline to day 7: 0.1 vs 0.19 mg/dL (P<0.001)
	No premature discontinuation of study drug		AmB-D 9/22 (41%)	Serum creatinine change from baseline to end of therapy: 0.07 vs 0.28 mg/dL (P<0.001)
	Defervescence	Time to defervescence similar (data not reported; P=0.65)	(P=0.051)	Infusion-related chills: 78% vs 50% Hypoxia: 4% vs 0% Hypokalemia: 52% vs 55%
Prentice[142]		AmB-D vs LAmB1** vs LAmB3**		AmB-D vs LAmB1 vs LAmB3
	Minimum of 3 consecutive days without fever (<38°C) which continued until study end (recovery of neutrophils)	26/61 (43%) vs 18/70 (26%) vs 24/71 (34%)	AmB-D 31/61 (51%) LAmB1 45/70 (64%)	Severe adverse event related to drug: 8% vs 1% vs 1% (P=0.06) Nephrotoxicity***: 21% vs 8% vs 11% (P=0.1)
	No addition of antifungal therapy other than AmB	59/61 (97%) vs 66/70 (94%) vs 70/71(99%)	LAmB3 45/71 (63%)	Hypokalemia: 26% vs 10% vs 11% (P=0.02)
	No breakthrough invasive fungal disease	60/61 (98%) vs 67/70 (96%) vs 70/71(99%)	(P=0.22)	

Abbreviations: LAmB - liposomal amphotericin B, Ambisome®; ABCD – Amphotericin B Colloidal Dispersion, Amphotec®; AmB-D – amphotericin B deoxycholate
*Defined by a doubling of baseline serum creatinine, an increase of creatinine by 1 mg/dL, or a 50% decrease of calculated creatinine clearance;
**Dosage of 1 mg/kg/d (LAmB1) or 3 mg/kg/kg (LAmB3); ***Defined as 100% increase of baseline creatinine

Appendix 10. Research Gaps in Pediatric Fever and Neutropenia

Identification of a validated high-risk stratification schema for pediatric fever and neutropenia
Determination of the incremental value of a peripheral blood culture in addition to central venous catheter cultures of an adequate volume in children with fever and neutropenia
Identification of the optimal type and frequency of re-evaluation (for example, daily or every second day telephone contact or clinic visit) for pediatric outpatients with low-risk fever and neutropenia
Determination of the optimal treatment regimen for microbiologically documented sterile site infections during fever and neutropenia
Identification of the optimal frequency of blood culture sampling in persistently febrile pediatric patients with neutropenia who are either clinically stable or unstable
Determination of the optimal duration of antibiotic therapy for patients with high-risk fever and neutropenia without bone marrow recovery for prolonged periods
Determination of whether a strategy of routine galactomannan screening in IFD high-risk children is cost-effective and results in better clinical outcomes compared to a strategy without screening
Determination of the clinical utility and optimal cut-off of ß-D-glucan testing in IFD high-risk children
Determination of the clinical utility of routine sinus imaging in children being evaluated for IFD
Determination of the safety and efficacy of a pre-emptive antifungal approach in IFD low-risk and IFD high-risk children
Identification of the optimal investigation and treatment for viral infections in children with fever and neutropenia

Abbreviation: IFD – invasive fungal disease