Febrile Neutropenia

1

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Contents

Abstract

Febrile neutropenia (FN) is a common, potentially life-threatening complication in pediatric oncology patients due to deficiencies in both innate and adaptive immunity usually secondary to treatment of the underlying malignancy. Although a majority of oncology patients experience FN, large randomized controlled trials to determine appropriate management strategies in pediatric FN are lacking and much of the decision-making process is based on extrapolation of adult guidelines, consensus pediatric guidelines, and institutional protocols. Here we review the relevant literature focusing on available models for risk stratification, appropriate diagnostic evaluations, applicable empiric therapies as well as proper location, timing, and duration of such therapies.

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1.1 Introduction

Febrile neutropenia (FN) is a life-threatening complication of cancer therapy. FN is a medical emergency that requires thorough patient evaluation and prompt initiation of broad-spectrum empiric antibiotics. Fever is defined as a single oral temperature ≥38.3 °C (101.0 °F) or an oral temperature ≥38.0 °C (100.4 °F) that is sustained for >1 h (Freifeld et al. 2011). Recent consumption of hot or cold beverages should not be a factor if these thresholds are met. Temperatures taken via alternate routes including axillary, otic, and temporal should be discouraged but all are considered real if fever is documented by these modes. Families should be advised against rectal temperatures due to the potential underlying neutropenia. Clinically significant neutropenia in the context of FN is an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L or ANC $<1.0 \times 10^9$/L that is expected to decrease to $<0.5 \times 10^9$/L over the subsequent 48 h. Profound neutropenia is defined as ANC $\leq 0.1 \times 10^9$/L, while prolonged neutropenia is defined as neutropenia lasting >7 days (Freifeld et al. 2011). Neutropenia decreases the patient's ability to resolve infection in the background of anticancer treatment, which may alter both innate (natural protection barriers such as the skin and mucous membranes) and adaptive (pathogen specific B and T cell) immunity, predisposing the child to common pathogens as well as opportunistic infections (Lehrnbecher et al. 1997).

Despite thorough investigation, pathogens are identified in only approximately 15–30 % of FN episodes (Rackoff et al. 1996; Baorto et al. 2001; Duncan et al. 2007; Bakhshi et al. 2008; Stabell et al. 2008; Wicki et al. 2008; Meckler and Lindemulder 2009). Bacteremia is the most common cause of microbiologically documented infection in pediatric oncology patients with FN, particularly in patients who have received intensive therapy for hematologic malignancies (Castagnola et al. 2007). Gram-positive bacteria like coagulase-negative *Staphylococci* are the most common isolates (Zinner 1999; Duncan et al. 2007). However, Gram-negative bacteria are also common, particularly in patients with significant mucositis, and are associated with higher mortality (Aledo et al. 1998). Fungi are isolated less frequently and occur most often in patients with prolonged and profound neutropenia (Freifeld et al. 2011). Although a majority of oncology patients experience FN, large randomized controlled trials to determine appropriate management strategies in pediatric FN are lacking and much of the decision-making process is based on extrapolation of adult guidelines, consensus pediatric guidelines, and institutional protocols. Here we review the relevant literature focusing on available models for risk stratification, appropriate diagnostic evaluations, applicable empiric therapies as well as proper location, timing, and duration of such therapies. A grading of evidence-based recommendations is presented in Table 1.1.

1.2 History and Physical Examination

Critical assessment of the child with FN begins by obtaining a complete medical history and performing a thorough physical examination. This initial assessment will direct initial risk stratification and subsequent diagnostic evaluations (Table 1.2). It is important to inquire about the characteristics and height of the fever as temperature >39.0 °C has been noted as an independent risk factor for serious bacterial infection, and children (mainly inpatient) with a median fever of 39.4 °C have been reported to be at significantly increased risk of viridans streptococcal shock syndrome with underlying viridans strep bacteremia (Klaassen et al. 2000; Gassas et al. 2004). Fever may be the only sign of infection given the blunted inflammatory response associated with neutropenia. One must inquire about the presence of rigors or chills with central line flushing, recent therapy (potential for prolonged neutropenia), current medications (including antibiotic

Table 1.1 Graded recommendations for management of pediatric febrile neutropenia

Clinical scenario	Recommendation	Level of evidence[a]
Risk stratification	Must be individualized at local institutions due to lack of evidence to support the needs of each individual treatment area	2C
Baseline laboratory recommendations	CBC/diff to assess level of neutropenia and monocytopenia in addition to other cytopenias; CMP for potential drug interactions; CVC culture or peripheral culture if no CVC; viral studies if symptomatic and appropriate season	1B
Utilization of DTP at FN presentation	Peripheral blood cultures in addition to CVC cultures can be done at the discretion of individual institutions but may not impact management	2C
Baseline imaging	Not recommended except CXR if with respiratory symptoms	1B
Antibiotic management at FN presentation in the clinically stable patient	Monotherapy with piperacillin/tazobactam, cefepime, or carbapenem; based on institutional preference, initial dual therapy with an antipseudomonal cephalosporin plus aminoglycoside (e.g., ceftazidime + tobramycin) can also be considered; aminoglycosides may be preferably administered once daily; initial antibiotic therapy should not include vancomycin unless there is concern for a Gram-positive infection due to such findings as sepsis, severe mucositis, skin infection, pneumonia or recent high-dose cytarabine administration	1A
Location of FN management	All patients should initially be managed as inpatients; if early discharge is considered, a multidisciplinary approach to determine appropriate risk stratification and outpatient therapy is required with IRB approval of such a prospective study to ensure safety and efficacy; patients identified as low risk may be discharged after 48 h per protocol if stable and without microbiologic-documented infection	1B
Management of low-risk patients	Empiric antibiotic therapy may be discontinued after 48 h if the patient is afebrile ≥24 h with signs of bone marrow recovery; patients may also be discharged after 72 h if afebrile ≥24 h even without signs of bone marrow recovery if close follow-up is ensured based on institutional preference	1B
Management of high-risk patients	Antibiotic therapy should be continued until resolution of FN episode	1A
FN ≥5 days	Empiric CT of the chest ± sinuses can be considered to rule out occult fungal infection; serial galactomannan can be considered	1C
FN ≥5 days in high-risk patients	Empiric antifungal therapy can be considered; appropriate empiric antifungal agent is unclear and must be chosen based on institutional preference; preemptive management may also be considered on a local basis as there is unclear evidence that prophylaxis prevents IFI	1C

CBC complete blood count, *CMP* complete metabolic panel, *CVC* central venous catheter, *DTP* differential time to positivity, *FN* febrile neutropenia, *CXR* chest radiography, *IRB* institutional review board, *CT* computed tomography, *IFI* invasive fungal infection

[a]Per Guyatt et al. (2006); see Preface

prophylaxis), and possible infectious exposures at home and school as well as recent travel (Orudjev and Lange 2002). Additional history should focus on community outbreaks of specific pathogens (i.e., respiratory viruses), prior history of fevers and documented infections, and pathogen colonization (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA],

Table 1.2 Diagnostic evaluation based upon organ system involvement and physical findings

Organ system	Physical findings	Diagnostic evaluation based upon physical finding(s)
Head, ears, nose, and throat	Mucositis Thrush Oral lesions Pre-septal/orbital cellulitis Facial pain Rhinorrhea Otorrhea	HSV, VZV, *Enterovirus/Parechovirus* PCR/DFA/viral culture (PCR preferred) Biopsy unusual oral lesions (histology and microbiology) CT scan of the sinuses, orbits, temporal bones (obtain sample) Sinus drainage sample if able to perform and send for bacterial, fungal, and viral culture Nasopharyngeal secretions for respiratory viral culture/antigen panel and PCR
Respiratory	Cough/respiratory distress Hypoxemia Chest radiograph infiltrates	CT chest *Legionella* urine antigen PCP evaluation: BAL, (1,3)-β-D-glucan, LDH Sputum culture if able to perform *Aspergillus* galactomannan, (1,3)-β-D-glucan *Histoplasma* urine and serum antigen
Vascular access sites	Exit site/tunnel erythema or discharge	Blood culture from all ports (consider bacteria, fungus, mycobacteria) Gram stain and culture (bacteria, fungal) exit site discharge
Gastrointestinal	Diarrhea Perirectal pain Abdominal pain	*C. difficile* PCR Viral stool culture/PCR (adenovirus, norovirus, etc.) SSYC and/or O&P if exposure by history Ultrasound or CT abdomen/pelvis Liver function test, amylase, lipase
Skin	Rash Cellulitis	DFA/PCR/viral culture of vesicular lesion Dermatology evaluation and biopsy of cellulitis or undiagnosed rash/lesion and send for culture (bacterial, fungal, and atypical mycobacteria)
Musculoskeletal	Arthritis Limp/point tenderness Lower back pain	Arthrocentesis: fluid for cell count and differential, cultures for bacteria, fungus, and mycobacteria CT/MRI extremity or site Urine culture (bacteria, fungal, consider adenovirus, BK, CMV PCR)
Central nervous system	Change in mental status Headache	CT/MRI brain (consider MRA/V) Lumbar puncture: cell count, bacterial and fungal stain and culture, viral PCR (consider CMV, EBV, *Enterovirus*, HHV-6, HSV, VZV)

HSV herpes simplex virus, *VZV* varicella zoster virus, *DFA* direct fluorescence antibody, *CT* computed tomography, *PCR* polymerase chain reaction, *PCP Pneumocystis jiroveci* (*carinii*) pneumonia, *BAL* bronchoalveolar lavage, *LDH* lactate dehydrogenase, *SSYC Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *O&P* ova and parasites, *MRI* magnetic resonance imaging, *CMV* cytomegalovirus, *MRA/V* magnetic resonance arterio/venogram, *EBV* Epstein-Barr virus, *HHV-6* human herpesvirus-6

vancomycin-resistant *Enterococcus* [VRE]). A comprehensive review of each organ system is important to determine possible etiologies of the fever. The physical exam should be thorough and not focus only on common sites of infection unique to the febrile neutropenic child (i.e., oral and perirectal mucosa, central venous access sites), but rather on all sites of common childhood infection such as the ears, throat, and skin (Auletta et al. 1999). Information obtained from the review of systems and physical findings will direct laboratory and ancillary evaluations and influence the choice of antimicrobial therapy.

1.3 Defining the Risk for Serious Infection

Risk stratification for serious infection incorporates the following variables: presenting clinical signs and symptoms, underlying cancer diagnosis and remission status, type of antitumor therapy received, and medical comorbidities (Orudjev and Lange 2002; Paganini et al. 2007; Freifeld et al. 2011). Sepsis signs and symptoms, presence of a central venous access device (CVAD), mucositis, infant acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), induction or intensification chemotherapy, and leukemia in relapse have all been shown to increase infection-related morbidity and mortality in pediatric patients and should be regarded as high-risk features at initial FN presentation (Orudjev and Lange 2002; Wicki et al. 2008; Badiei et al. 2011). Social factors including history of noncompliance and distance >1 h from clinical facility must be considered high-risk conditions (Orudjev and Lange 2002; Paganini et al. 2007). Paganini et al. (2007) showed that advanced disease stage, bacteremia, and associated comorbities including persistent bleeding, refractory hypoglycemia, hypotension, altered mental status, renal insufficiency and hepatic dysfunction were independent risk factors for mortality.

The Multinational Association for Supportive Care in Cancer (MASCC) risk index has been prospectively validated in adults allowing for potential outpatient management of low-risk patients (Klastersky et al. 2000; Uys et al. 2004). Multiple risk prediction models for pediatric oncology patients have been presented in the literature and are reviewed by Orudjev and Lange (2002), Härtel et al. (2007), Phillips et al. (2010), and Lehrnbecher et al. (2012). No one system has been found superior, none have undergone rigorous prospective validation to ensure patient safety across populations, and no prospectively validated stratification for high-risk patients has been identified (Härtel et al. 2007; te Poele et al. 2009; Phillips et al. 2010; Lehrnbecher et al. 2012). With the lack of significant randomized prospective data, Härtel et al. (2007) strongly recommend against outpatient management of FN in pediatric patients outside of clinical trials. In the recent pediatric FN expert consensus guidelines, Lehrnbecher et al. (2012) recommend the use of local population-based stratification systems with careful prospective and continuous evaluation to ensure safety and efficacy.

In particular risk stratification schemata, initial laboratory values such as platelet count $<50\times10^9$/L and C-reactive protein (CRP) $\geq$90 mg/L have been noted to increase risk, while absolute monocytosis $\geq0.1–0.155\times10^9$/L (depending on study) has tempered risk (Rackoff et al. 1996; Baorto et al. 2001; Santolaya et al. 2002; Ammann et al. 2010). Multiple laboratory assessments including CRP, procalcitonin, IL-6, and IL-8 have all been studied in pediatric and adult oncology patients to potentially define high-risk patients but none has been uniformly shown as an effective marker (Santolaya et al. 1994; Lehrnbecher et al. 1999; Uys et al. 2007; Semeraro et al. 2010; Phillips et al. 2012). These studies have been recently reviewed by Phillips et al. (2012).

1.4 Diagnostic Evaluation

1.4.1 Initial Laboratory Evaluation

The diagnostic evaluation for the pediatric patient with FN should be guided by clinical history and physical findings to optimize detecting an etiology for the fever. Initial work-up includes a complete blood cell count (CBC), a comprehensive metabolic panel, and blood cultures from each port of a central catheter. The CBC will demonstrate the degree of neutropenia and monocytopenia, and the metabolic panel will evaluate renal and hepatic function, which could be affected by previous chemotherapeutic agents and may influence antimicrobial selection and dosing. For example, if the patient's creatinine is elevated,

antimicrobials like aminoglycosides, vancomycin or amphotericin B should be used with caution and appropriate trough levels followed (Fisher et al. 2010; Lahoti et al. 2010).

Peripheral blood cultures should be obtained if cultures are not or are unable to be obtained from the patient's central venous access device. Peripheral blood cultures in addition to central line cultures are recommended in infection guidelines but remains controversial as the yield for detection from peripheral cultures is <15 % and the utility of differential time to positivity (DTP) between central and peripheral cultures in treatment decision-making is unclear in FN (Gaur et al. 2003; Raad et al. 2004; Gaur et al. 2005; Mermel et al. 2009; Scheinemann et al. 2010; Lehrnbecher et al. 2012; Rodriguez et al. 2012; Carraro et al. 2013). To increase the blood culture yield, ≥1 mL of blood should be added to the culture bottles for children ≥1 month of age (Connell et al. 2007). Repeating blood cultures in patients who are persistently febrile has been shown useful in identifying bacteremia in a subset with initial negative cultures (Rosenblum et al. 2013). Most contemporary blood culture vials support the growth of *Candida* spp; however, other fungal species may not grow, so sending fungal blood cultures from all ports should be considered with persistent fever (i.e., ≥5 days) (Hennequin et al. 2002; Kosmin and Fekete 2008). If clinically suspected, acid-fast bacteria (AFB) cultures from the blood should also be sent to best isolate mycobacterial species.

Urinary tract infection (UTI) in the neutropenic patient may be subclinical given that patients may have minimal symptoms and pyuria may not be present in urinalysis (Klaassen et al. 2011). A recent study utilizing midstream urine samples reported UTI frequency of 8.6 % in 45 children with 58 episodes of FN, with all patients being asymptomatic and the majority having normal urinalyses, supporting the recommendation to obtain clean-catch bacterial urine cultures at the time of initial FN presentation (Lehrnbecher et al. 2012; Sandoval et al. 2012).

1.4.2 Radiographic Imaging

1.4.2.1 Chest Radiography (CXR)

A supine CXR may identify pleural effusions, allow for assessment of central line catheter position and detect pulmonary congestion. However CXR is less useful in identifying early pneumonia (Heussel 2011). CXR has not been found beneficial without the presence of respiratory symptoms and therefore should only be obtained in the symptomatic patient (Feusner et al. 1988; Roberts et al. 2012).

1.4.2.2 Computed Tomography (CT)

Institutional practice may recommend CT of the chest, abdomen and pelvis in neutropenic patients with ≥5 days of persistent fever although a recent pediatric study challenges this practice (Agrawal et al. 2011). Specifically, for 52 children with 68 episodes of FN for whom CT (sinuses, chest, abdomen and pelvis) was performed at day five of fever, minimal changes in clinical management occurred based upon results from imaging. The authors conclude that patients with prolonged FN (defined as >4 consecutive days of fever), in which occult fungal infections are being sought, should have CT imaging limited to the chest (Agrawal et al. 2011). Other pediatric studies have similarly found CT chest as well as sinuses to be most useful in prolonged FN (Archibald et al. 2001). CT of the sinuses can be performed in the context of pulmonary symptoms to rule out invasive fungal infections, as some patients with fungal sinusitis can present with minimal symptoms. Of note, patients with fungal sinusitis usually have positive findings on chest CT, and endoscopic biopsy of the sinuses has the highest yield for determining the microbiologic cause (Ho et al. 2011).

High-resolution chest CT with thin sections (1 cm slices) is the preferred imaging modality in patients with neutropenia and pulmonary symptoms, given its ability to characterize lesions and discriminate between infectious and noninfectious etiologies (Heussel 2011). In addition, CT imaging can be used for diagnostic purposes such

as CT-guided biopsy of lung lesions for histologic and microbiologic assessment. Importantly, radiologic findings of common molds in children may differ from those in adults. For example, pulmonary nodules are common findings in pediatric patients with *Aspergillus*, while the halo and crescent signs occur less frequently than in adult patients (Thomas et al. 2003; Burgos et al. 2008). Therefore, consultation with pediatric radiologists is critical when interpreting these studies. Providing the radiologist with information about the patient's clinical presentation, level of neutropenia, and current supportive therapy including specific antimicrobial and growth factor use increases the diagnostic utility of CT (Heussel 2011).

1.4.2.3 Magnetic Resonance Imaging (MRI)

MRI is advantageous over CT due to a lack of radiation exposure although at a much higher cost. MRI is also more affected by motion related to cardiorespiratory function increasing artifact incidence especially in the chest. Furthermore, given its increased imaging time, MRI usually requires sedation for pediatric patients, decreasing its convenience as a diagnostic tool. However, MRI remains the imaging of choice for assessing lesions in the liver, spleen, and central nervous system (CNS) (brain and spine) (Sahani and Kalva 2004; Luna et al. 2006).

1.4.2.4 Positron Emission Tomography (PET)

PET is now used frequently alongside CT for the diagnosis of cancer, but experience using PET/CT for FN is limited. A recent study from Australia compared diagnostic yields of PET/CT and conventional imaging in 20 adult patients with FN of >5 days duration (Guy et al. 2012). By using conventional imaging, the authors found 14 infections sites, 13 of which were also confirmed by PET/CT; in addition, PET/CT identified 9 more sites of infection (8 of which were subsequently confirmed as true infection), suggesting that PET/CT may be useful in the study of prolonged FN. However, more data are needed to support the use of this modality as first-line imaging in pediatrics given its inherent expense and associated radiation exposure (Xu et al. 2010; Haroon et al. 2012).

1.4.3 Biomarkers for Invasive Fungal Infection (IFI)

Early identification of infection in FN, especially IFI, critically affects patient survival. Biomarkers for IFI have proven useful in the adult population as adjuncts to clinical findings and imaging. Limited pediatric data suggest these biomarkers may also be used in children with similar sensitivities and specificities as defined in adults.

1.4.3.1 *Aspergillus* Galactomannan (GMN)

GMN is a cell-wall component of growing hyphae and can be detected by assay from the serum, urine and bronchoalveolar (BAL) fluid (Klont et al. 2004; Pfeiffer et al. 2006). The GMN assay has been shown effective in adult populations with hematologic malignancies and limited data in children suggest utility in pediatric oncology patients as well (Sulahian et al. 2001; Pfeiffer et al. 2006; Steinbach et al. 2007; Castagnola et al. 2010). A recent observational, prospective, multicenter study found the specificity of urine and serum GMN assays were 80 % and 95 %, respectively. This study found that the false-positive rate was lower than previously described (Fisher et al. 2012).

The GMN assay must be interpreted with caution, particularly in the context of a single positive value, and should be utilized in conjunction with corroborative clinical and radiologic findings. Serial repetition of the assay can be used as a surveillance marker either for potential IFI or disease response to antifungal therapy (Groll et al. 2014). The GMN assay may have false-positive results in patients receiving beta-lactam antimicrobials (especially piperacillin/tazobactam), although recent studies suggest the false-positive rate may not be as high as previously published (Zandijk et al. 2008; Metan et al. 2010; Mikulska et al. 2012).

1.4.3.2 (1,3)-β-D-glucan (BDG)

Serum BDG, an important cell-wall component of most fungi including *Pneumocystis jiroveci* (former *carinii*), has been measured in adult patients with IFI and hematologic malignancies (Marty and Koo 2009). Like GMN, studies using serum BDG in the pediatric population are limited. In fact, few studies performed to date even establish a normal value for children, which may be higher than the 60 pg/mL cutoff used in adult patients (Smith et al. 2007; Mularoni et al. 2010). In immunocompromised adult patients, serum BDG levels exceeding 500 pg/mL have been used to diagnose *P. jiroveci* (Del Bono et al. 2009; Koo et al. 2009; te Poele et al. 2009). One pediatric study found serum BDG potentially useful for *P. jiroveci* diagnosis in three patients with hematologic malignancies, one with BAL fluid confirmation (Gonzalez et al. 2011). The sensitivity of BAL for diagnosing *P. jiroveci* pneumonia is lower in non-HIV patients and in patients receiving aerosolized pentamidine. Therefore, serum BDG may be a useful adjunctive, noninvasive diagnostic tool (Levine et al. 1992; Azoulay and Schlemmer 2006; Jiancheng et al. 2009). More pediatric studies are needed to define serum BDG as a reliable indicator of IFI such as *P. jiroveci*.

Serum BDG does not detect *Cryptococcus* or *Zygomycetes* spp. (e.g., *Mucor*, *Rhizopus*, *Absidia*), which do not produce BDG. False positives also occur in patients receiving antimicrobial agents such as piperacillin/tazobactam in addition to hemodialysis with cellulose membranes, intravenous albumin and immunoglobulin (Marty and Koo 2009; Karageorgopoulos et al. 2011). Finally, the test may serve as a prognostic marker for invasive candidiasis when serial levels are measured, but data supporting this indication are limited (Ginocchio et al. 2012; Glotzbecker et al. 2012; Jaijakul et al. 2012).

1.4.3.3 Polymerase Chain Reaction (PCR)

Molecular methodology such as PCR testing may improve the detection of IFI as well as bacterial or viral organisms in children with FN (Santolaya et al. 2011; Kourkoumpetis et al. 2012). However, lack of standardization has limited its current use and more data are required to make firm recommendations.

1.4.4 Viral Studies

Viral infections may cause prolonged fevers in neutropenic patients. Seasonal viral infections such as influenza A/B and respiratory syncytial virus (RSV) in the winter and enterovirus in the summer must be considered (Lindblom et al. 2010; Ozdemir et al. 2011). In patients with mucositis, herpes simplex virus (HSV) should be considered. Viral PCR (whole blood and plasma, cerebrospinal fluid, stool) is commercially available and enables faster identification of viral etiologies at higher sensitivity and specificity compared to viral culture. In addition, direct fluorescent antibody (DFA) testing of cutaneous lesions may expedite diagnosis of herpetic skin infections (i.e., HSV, varicella).

1.4.5 Invasive Procedures: Bronchoalveolar Lavage (BAL) and Tissue Biopsy

Tissue is necessary for diagnosis when physical examination or radiographic imaging is concerning for abscess formation or lesions of the skin, sinuses, or organ parenchyma but without corroborative microbiologic confirmation. Microbiologic evaluations should include proper sample collection for assessing AFB and other bacterial and fungal pathogens. For IFI such as chronic disseminated candidiasis or invasive *Aspergillus* spp., hepatic or splenic biopsy may be required (Masood and Sallah 2005).

In children with pulmonary lesions, BAL should be attempted first as it has a low complication rate and may yield an etiologic agent (Pattishall et al. 1988; Jain et al. 2004; Efrati et al. 2007). CT-guided lung biopsy or wedge resection may be necessary if BAL sampling is nondiagnostic in the patient with persistent fever and pulmonary nodules (Wingard et al. 2012). In addition to routine cultures, BAL samples should be analyzed by GMN assay (Wingard et al. 2012).

In patients with neutropenia, skin lesions may be a manifestation of localized or systemic infection (Mays et al. 2006). Ecthyma gangrenosum, a black eschar with surrounding erythema originally attributed to *Pseudomonas* spp., can be caused by many other bacterial as well as fungal and viral pathogens (Moyer et al. 1977; Reich et al. 2004; Son et al. 2009). Many invasive systemic fungal infections with high potential for dissemination like *Zygomycetes* spp., *Aspergillus* spp. and *Candida* spp. may present as nonspecific lesions that require prompt evaluation (Mays et al. 2006). Contaminated medical equipment such as adhesive tape has been associated with nosocomial outbreaks of *Zygomycetes* spp., so it is imperative to consider such infections in skin lesions found under dressings near tape (Everett et al. 1979; Lalayanni et al. 2012). Prompt punch biopsy and consideration for consultation with a dermatology specialist is advisable.

1.5 Empiric Management of Febrile Neutropenia (FN)

Management of FN in pediatric oncology is often based on institutional and consensus guidelines. To inform decision-making we review the appropriate literature regarding specific topics including the use of monotherapy versus combination antibiotic therapy, use of vancomycin, empiric utilization of antifungals, emergence of resistant pathogens, duration and location of therapy, and criteria for central venous catheter removal. Pediatric FN guidelines from one institution are provided as an example of how these concepts can be practically implemented.

1.5.1 Adult FN Guidelines for Empiric Therapy: Do They Apply to Children?

Infectious Diseases Society of America (IDSA) guidelines for empiric antimicrobial therapy for FN patients serve as the foundation for institutional protocols treating pediatric cancer patients (Freifeld et al. 2011). Notably, the International Pediatric Fever and Neutropenia Guideline Panel has also published guidelines for FN in pediatric oncology patients (Lehrnbecher et al. 2012). Recommendations from such practice guidelines are mostly based upon level III evidence (expert opinion) versus level I and II evidence (results from randomized clinical trials) (Lee and Vielemeyer 2011). Furthermore, no formal guidelines for FN have been published by the American Society of Pediatric Hematology/Oncology (ASPHO) or the Pediatric Infectious Diseases Society (PIDS) despite notable disparity among adult and pediatric cancer patients, including differences in underlying malignant diseases and associated therapies, immunity and susceptibility to pathogens, and antimicrobial pharmacodynamics (PD) and pharmacokinetics (PK) (Sung et al. 2011; Watt et al. 2011). Defining such PD/PK differences are critical, particularly in the cancer patient as cancer therapy can affect antimicrobial efficacy, promoting pathogen resistance (Theuretzbacher 2012). Whether such differences significantly impact infection-related morbidity and mortality in pediatric cancer patients remains largely unstudied.

The International Antimicrobial Therapy Cooperative Group (IATCG) published the largest series comparing FN episodes in adult ($n = 2{,}321$) and pediatric ($n = 759$) patients receiving standardized disease assessment and empiric therapy and noted significant differences in patient demographics and outcomes by age: (1) malignant diagnoses associated with FN episodes differed across patient age with ALL being most frequent in children and AML most frequent in adults; (2) adult patients more frequently received antibacterial and antifungal prophylaxes; (3) children tended to have lower ANCs at presentation but shorter durations of granulocytopenia; (4) children had less defined sites of infection and more fever of unknown origin; (5) children and adults had similar rates of Gram-positive and Gram-negative bacteremia, but children had more streptococcal bacteremia; and (6) children had lower infection-related mortality and overall mortality (3 % vs. 10 %) than adult FN patients (Hann et al. 1997). Together, these data suggest that children and adults with FN are indeed distinct both in presentation and outcome.

Additional studies are needed to investigate further these suggestive data. However, such clinical investigation is practically limited by the large numbers of patients required for accurate statistical analysis as well as by the inherent expense associated with large randomized clinical trials (RCTs) (Mullen 2012). Likewise, reproducible and accurate biomarkers of response to infection and clinical end points are needed to ensure sound clinical trials addressing antimicrobial efficacy and safety (Powers 2012). Given their limitations in study design and expense, RCTs comparing FN episodes and response to therapy among adult and pediatric cancer patients will likely not be performed. Yet, extensive pediatric literature incorporating antimicrobial agents used in adult FN demonstrates that empiric antibacterial and antifungal therapies are comparable in their efficacy. For these reasons, extrapolation of adult FN guidelines to the pediatric population is unavoidable.

1.5.2 Choice of Empiric Antimicrobial Therapy

As discussed, determination of initial risk stratification can help guide utilization of appropriate antimicrobial agents and specifically the route (oral vs. intravenous), setting (inpatient vs. outpatient), and duration of use. In general, antimicrobial choices for empiric pediatric FN are comparable in their efficacy in either high-risk or low-risk scenarios as serious medical complications remain low with use of contemporary treatments (Baorto et al. 2001; Luthi et al. 2012; Manji et al. 2012b, c). Therefore, institutional guidelines for empiric antimicrobial therapy should consider the following: (1) published experience with using the antimicrobial agent in the context of FN; (2) physician experience with using the proposed antimicrobial agent; (3) pathogen epidemiology and resistance patterns to the antimicrobial agent inherent to the institution and its surrounding community; and (4) the antimicrobial agent's toxicity profile, cost and availability. In essence, choice of empiric antimicrobial therapy should integrate the patient's clinical history and presentation with institutional experience of local microbial patterns and specific antimicrobial therapies.

1.5.2.1 Monotherapy Versus Combination Therapy

Pizzo et al. (1986) first showed that cephalosporin monotherapy is as effective as combination therapy in adult oncology patients. Since that time, institutional guidelines are slowly adopting the recommendation for monotherapy that is supported in both the IDSA as well as the recent pediatric guidelines (Freifeld et al. 2011; Lehrnbecher et al. 2012). In a Cochrane review of 71 published trials, monotherapy with broad-spectrum, antipseudomonal beta-lactams was found to be non-inferior to combination therapy with a trend toward improved survival and a significantly decreased risk of adverse events, specifically fungal infection and nephrotoxicity secondary to aminoglycosides as part of combination therapy (Paul et al. 2013). The observations of Paul et al. (2013) have been corroborated by a previous systematic meta-analysis by Furno et al. (2002). Specifically for pediatric oncology patients, Manji et al. (2012b) conducted a meta-analysis and found no significant difference between antipseudomonal penicillins and antipseudomonal cephalosporins either as monotherapy or when combined with an aminoglycoside. The authors therefore recommend choosing a regimen based on cost, availability and local factors such as institutional resistance patterns. Whether the increased utilization of a more broad-spectrum agent as monotherapy over a more narrow-spectrum antipseudomonal cephalosporin plus an aminoglycoside will lead to increased resistance for these agents is unknown.

In an additional Cochrane review of anti-Gram-positive antibiotics (often vancomycin) in FN, Paul et al. (2005) showed that the addition of such therapy does not improve outcomes without a documented Gram-positive infection. Use of vancomycin as initial empiric FN therapy is not recommended in consensus guidelines as it does not significantly affect survival or length of stay (Freifeld et al. 2011; Lehrnbecher et al. 2012). Furthermore, imprudent use of vancomycin has been associated with emergence of resistant

pathogens (e.g., VRE) and nephrotoxicity. Clinical indications for empiric vancomycin include skin/soft-tissue and catheter-related infection, hemodynamic instability, severe mucositis, and pneumonia. In these situations, targeted vancomycin trough levels and renal function surveillance are recommended (Rybak et al. 2009). If susceptible bacteria are not recovered or if concern for Gram-positive infection abates, vancomycin should be discontinued within 72 h (Lehrnbecher et al. 2012).

Consensus guidelines recommend combination therapy be reserved for specific clinical indications including patient instability, concern for resistant pathogens (e.g., extended spectrum β-lactamase [ESBL]-producing *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, *Enterobacter* and *Klebsiella* spp.), and need for synergism to treat specific pathogens (e.g., *Enterococcus*, *Mycobacterium* spp., MRSA) or infections (e.g., endocarditis, cryptococcal meningitis) (Freifeld et al. 2011; Lehrnbecher et al. 2012). Of note, if combination therapy is required, meta-analyses in pediatrics recommend utilization of once rather than multiple daily doses of aminoglycosides due to trends toward improved efficacy and decreased nephrotoxicity (Sung et al. 2003; Contopoulos-Ioannidis et al. 2004).

1.5.2.2 Which Monotherapy to Choose

A Cochrane review of antipseudomonal beta-lactams for initial management of FN compared studies with ceftazidime, cefepime, piperacillin/tazobactam, meropenem and imipenem (Paul et al. 2010). Cefepime monotherapy was shown to have a significantly higher all-cause mortality which had been previously reported (Yahav et al. 2007). The Cochrane meta-analysis reported a nonsignificant higher rate of bacterial superinfection with cefepime which has been a reported concern due to its limited anaerobic profile and poor coverage for skin infections (Yahav et al. 2007; Paul et al. 2010; Kalil 2011). A follow-up meta-analysis did not find a statistically significant increased mortality with cefepime and current pediatric consensus guidelines consider cefepime a reasonable choice for monotherapy (Kim et al. 2010; Lehrnbecher et al. 2012). Ceftazidime is not a good first-line choice for monotherapy due to reduced Gram-positive coverage as well as induction of β-lactamase production leading to subsequent emergence of resistant pathogens and inferior clinical outcomes in pediatric patients (Mebis et al. 1998; Ariffin et al. 2000; Greenberg et al. 2005). Paul et al. (2010) additionally noted that carbapenem monotherapy had similar all-cause mortality as other monotherapy regimens but was associated with higher rates of antibiotic- and *Clostridium difficile*-associated diarrhea. Pediatric meta-analyses have shown similar effectiveness between antipseudomonal cephalosporins, antipseudomonal penicillins and carbapenems as monotherapy but without the noted increase in *Clostridium difficile*-associated diarrhea (Manji et al. 2012b, c).

1.5.2.3 Alterations in Initial Empiric FN Antibiotic Management

Once empiric therapy has been initiated, alterations in FN antibiotic management may be required to optimize treatment; these changes occur at the discretion of the practitioner or institution without significant evidence basis. For instance, Lehrnbecher et al. (2012) recommend discontinuing combination therapy (if initiated at presentation) after 24–72 h in the stable patient without microbiologic evidence to continue both agents. Similarly, patients who are stable but with persistent fever should not have their initial regimen escalated. Those who become unstable should have additional coverage for potential resistant Gram-negative, Gram-positive and anaerobic causes initiated with consideration for fungal and viral etiologies.

1.5.2.4 Outpatient Management of FN

Although there remains a lack of one uniform pediatric oncology risk stratification system, many institutions have begun to utilize outpatient management of low-risk FN which can include outpatient oral or parenteral therapy as either initial management or as step-down to outpatient treatment after initial inpatient management; such options and the evidence

surrounding them are reviewed by Chisholm and Dommett (2006). This differs from previous studies in which low-risk patients were discharged early (ANC $<0.5 \times 10^9$/L) but only after defervescence (Mullen and Buchanan 1990; Aquino et al. 1997; Wacker et al. 1997). Meta-analyses of efficacy and safety from adult and pediatric studies found no significant difference in treatment failure in the inpatient versus outpatient setting and no significant difference in the efficacy of outpatient oral versus parenteral therapy in low-risk FN (Teuffel et al. 2011b). Studies were extremely heterogenous in terms of choice of antibiotics (both oral and parenteral) as well as timing of step-down making generalizations difficult. A recent Cochrane review of randomized controlled trials comparing oral versus intravenous antibiotic therapy for FN found no significant difference in treatment failure or mortality (Vidal et al. 2013).

The utilization of outpatient oral therapy specifically for pediatric patients either at FN presentation or as step-down after initial inpatient management was most recently reviewed by Manji et al. (2012a). Sixteen prospective trials were reviewed in the meta-analysis with no significant difference between oral and parenteral regimens and no outpatient infection-related mortality. None of the trials were randomized controlled trials specifically comparing inpatient versus outpatient management and outcomes of low-risk FN (Manji et al. 2012a). The types of oral agents utilized in pediatric studies are quite heterogenous and include amoxicillin/clavulanate, cefixime, fluoroquinolones (ciprofloxacin, gatifloxacin) and combination therapy (ciprofloxacin plus amoxicillin) (Mullen et al. 1999; Aquino et al. 2000; Paganini et al. 2000, 2001; Shenep et al. 2001; Park et al. 2003; Petrilli et al. 2007; Dommett et al. 2009; Brack et al. 2012). Ciprofloxacin plus amoxicillin/clavulanate is recommended as the oral regimen of choice in adult patients (Freifeld et al. 2011). Brack et al. (2012) recently reported on an RCT comparing continued inpatient treatment versus oral outpatient management and found non-inferiority for efficacy but lack of power to prove non-inferiority for safety.

Many centers are continuing to initially admit all pediatric oncology FN patients with the potential for early discharge with or without continued antibiotic support depending on the clinical context (Gibson et al. 2013). The United Kingdom recommends such a management strategy after 48 inpatient hours in patients >1 year of age, without medical or social comorbidities, not receiving extremely intensive therapy, appearing clinically well without a source of infection, with some marrow recovery (i.e., ANC $>0.1 \times 10^9$/L), and with fever improvement (but not full defervescence necessary), for outpatient oral antibiotics to complete a 5-day course (Gibson et al. 2013). A recent survey of Canadian pediatric oncology centers found heterogenous treatment strategies from full inpatient care, to step-down care, to full outpatient care exemplifying the perceived lack of sufficient data to uniformly modify practice (Boragina et al. 2007). Sung et al. (2004) reported in a survey of parents that only 53 % supported initial FN outpatient management (as compared to 71 % of practitioners) due to perceived increased fear and anxiety balanced with increased comfort, while early discharge and outpatient intravenous management are reportedly associated with improved health-related quality of life (Cheng et al. 2011). Finally, Teuffel et al. (2011a) calculated that the most cost-effective model is one in which low-risk FN patients are treated entirely at home but through a parenteral rather than oral route. The risk of nosocomial infection (NI) with inpatient management must also be considered and was reported to be 5.2 NI per 100 admissions by one group (Simon et al. 2000). The recent pediatric FN expert consensus guidelines allow for consideration of initial or step-down outpatient management for the low-risk patient in the appropriate setting although as a weak recommendation (Lehrnbecher et al. 2012).

1.5.2.5 Choice of Empiric Antifungal Therapy

The use of empiric antifungal therapy in neutropenic children is also based upon limited data (Pizzo et al. 1982). Despite the low incidence of

IFI in pediatric FN, cost of associated antifungal therapy and supportive care and IFI-related mortality are high (Zaoutis et al. 2006; Kim et al. 2011; Mor et al. 2011; Steinbach 2011). Therefore, recent emphasis has been placed on defining risk factors for IFI and providing empiric antifungal therapy only to high-risk FN patients (Cordonnier et al. 2009; Caselli et al. 2012; Lehrnbecher et al. 2012). Notable risk factors for IFI include hematologic malignancy, especially AML and relapsed disease, prolonged and profound neutropenia and lymphopenia, and adolescent age (Groll et al. 1999; Rosen et al. 2005; Castagnola et al. 2006; Mor et al. 2011).

The number of antifungals has increased dramatically over the last decade but efficacy data in prevention of IFI in pediatric oncology are very limited (Blyth 2011; Steinbach 2011). Meta-analyses on the utilization of empiric antifungal therapy has shown mixed benefit in decreasing all-cause mortality (Gøtzsche and Johansen 2002; Goldberg et al. 2008). Similarly, one small prospective pediatric study showed no benefit with antimycotic prophylaxis as compared to early therapeutic treatment (Uhlenbrock et al. 2001). Additional meta-analyses of limited trial data mainly from adult oncology patients have shown that intravenous liposomal amphotericin B and potentially caspofungin (2 trials) are the most effective empiric agents (Johansen and Gøtzsche 2000; Jørgensen et al. 2006; Goldberg et al. 2008). Voriconazole was reported to be non-inferior to liposomal amphotericin B as empiric antifungal therapy by Walsh et al. (2002), but this was refuted by a subsequent Cochrane review and not approved by the US Food and Drug Administration (FDA) for this indication (Jørgensen et al. 2006). Clinical trials incorporating empiric antifungal therapy in pediatric FN are extremely limited. Maertens et al. (2010) report that liposomal amphotericin B and caspofungin are comparable in their efficacy and safety although patient numbers were small and it is unclear if the study was powered to make this conclusion (Sekine et al. 2010). Generalizability in regard to the efficacy of other echinocandins is unknown. Consensus guidelines recommend initiation of empiric antifungal therapy in high-risk patients with persistent FN without a source while receiving broad-spectrum antibiotics for ≥4 days (Freifeld et al. 2011; Lehrnbecher et al. 2012). Pediatric guidelines recommend either liposomal amphotericin B or caspofungin while the adult IDSA guidelines admit there is insufficient evidence to recommend any one particular agent beyond ensuring for anti-mold coverage (Freifeld et al. 2011; Lehrnbecher et al. 2012; Groll et al. 2014). Due to unclear efficacy of empiric antifungal prophylaxis in the prevention of IFI, the IDSA guidelines also suggest consideration for "preemptive antifungal management" (i.e., withholding empiric therapy) as an alternative strategy in patients who remain febrile >4 days but are clinically stable and have no clinical, radiographic (CT sinus and chest), laboratory (negative fungal serology screens), or microbiologic (positive culture from sterile site) evidence of fungal infection (Freifeld et al. 2011).

1.5.3 Duration of Antimicrobial Therapy: Empiric Versus Therapeutic Intent

In the absence of documented or clinical concern for infection, empiric antimicrobial therapy is often continued until resolution of FN in both low- and high-risk patients. As mentioned, in low-risk pediatric patients, discontinuing antibiotics prior to attaining an ANC $>0.5 \times 10^9$/L has been shown safe if afebrile ≥24 h and with negative cultures ≥48 h (Mullen and Buchanan 1990; Aquino et al. 1997; Wacker et al. 1997; Lehrnbecher et al. 2002; Hodgson-Viden et al. 2005; Lehrnbecher et al. 2012). Risk stratification in these studies was heterogenous with no set ANC threshold for early discharge; therefore, consensus pediatric guidelines recommend evidence of bone marrow recovery (i.e., post nadir ANC $\geq 0.1 \times 10^9$/L) prior to antimicrobial discontinuation (Lehrnbecher et al. 2012). Santolaya et al. (1997) have also shown in a small low-risk carefully selected pediatric cohort that antimicrobials can be discontinued on day 3 of hospital admission prior to defervescence or neutrophil

recovery; thus, consensus guidelines suggest discontinuation of antimicrobials after 72 h of intravenous antibiotic therapy in the patient who is afebrile ≥24 h even without evidence of bone marrow recovery as long as close follow-up is ensured (Lehrnbecher et al. 2012). Again, the data to support this practice comes from small prospective trials with no uniform risk stratification system. In high-risk patients, empiric antifungal therapy is usually discontinued once fever has resolved for ≥48 h with an ANC $>0.5 \times 10^9$/L. If the patient remains afebrile and clinically stable, antibiotic therapies are discontinued. Although definitive evidence is lacking, the usual clinical practice is to remove one antimicrobial agent per 24 h time interval to observe for fever recrudescence if the patient is on combination antimicrobial therapy. No pediatric studies address the appropriate management strategy in high-risk pediatric FN patients and specific management of these patients is not addressed in the pediatric consensus guidelines (Lehrnbecher et al. 2012).

For documented infection, duration of therapy is determined by the site, pathogen and clinical response to therapy. Most bacterial infections (with notable exceptions including CNS infection, abscess formation and endovascular focus) require 10–14 days of appropriate therapy, assuming complete clinical and microbiologic response. In general, duration of antimicrobial therapy should be continued through a time of neutrophil recovery (i.e., at least 5 days beyond ANC $>0.5 \times 10^9$/L), although there is little evidence to support the efficacy of this practice. For established IFI, prolonged therapy (4–6 weeks) is necessary and concomitant immune recovery is critical for favorable outcomes (Nucci et al. 2003). The role for combination antifungal therapy, particularly in the context of mold infection, requires further investigation; potential utilization of combination therapy must balance the significant drug interactions and potential side effects with questionable benefit (Vazquez 2008; Spellberg et al. 2012). The interested reader is directed to recently published IDSA guidelines for a more extensive discussion of infections due to *Aspergillus*, *Candida* and *Cryptococcus* (Walsh et al. 2008; Pappas et al. 2009; Perfect et al. 2010).

1.5.4 Endovascular Sources of Infection: Catheter Removal

Any central venous access device (CVAD) can cause central line-associated bloodstream infection (CLABSI), including a peripherally inserted central catheter (PICC) (Advani et al. 2011). As mentioned, although DTP between peripheral and central cultures can allow for determination of line infection versus bacteremia, such information rarely changes management. Rather, CVAD removal is necessary in the following clinical contexts: any bloodstream infection in which the CVAD is no longer required, tunneled catheter site infection, hemodynamic instability/sepsis, endocarditis or other endovascular infection (e.g., thrombophlebitis), persistent positive blood culture despite appropriate antimicrobial therapy for >72 h, and CLABSI due to highly resistant pathogens (e.g., MRSA, ESBL Gram-negative bacilli, VRE) or pathogens that are difficult to eradicate, particularly due to adhesive biofilm production (e.g., fungi, *Propionibacterium* spp., *Bacillus* spp. *Mycobacterium* spp.) (Mermel et al. 2009). Delay in catheter removal for less virulent pathogens increases the risk for recurrent CLABSI (Raad et al. 2009). Antibiotic lock therapy, instilling high concentrations of susceptible antibiotic or ethanol into the CVAD lumen, has been successfully used in combination with systemic antimicrobial therapy to both eradicate and prevent CLABSI and should be considered when the CVAD cannot be removed (e.g., limited access sites in the patient) (Fortun et al. 2006; Flynn 2009).

1.5.5 Adjunctive Treatment Modalities

Additional treatment modalities such as granulocyte transfusion and hematopoietic growth factors are of unclear benefit in pediatric FN and are discussed in detail in Chaps. 2 and 15 respectively.

1.5.6 Emergence of Resistant Pathogens: Dwindling Antimicrobial Options and Focus on Prevention

Judicious use of antimicrobial therapy is imperative to curb emergence of resistant pathogens which have been shown to negatively affect clinical outcomes in pediatric FN patients (El-Mahallawy et al. 2011). In particular, prevalence of highly resistant ESBL- and carbapenemase-producing organisms is increasing while development of novel effective antimicrobial therapy is both limited and associated with significant side effects (Prasad et al. 2012). Institutional prevention through implementation of surveillance and antimicrobial stewardship programs is vital, particularly for heavily exposed patient populations like cancer patients (Rolston 2005). Similarly, establishing guidelines for resistant pathogens and their associated therapies is also imperative (Rybak et al. 2009; Liu et al. 2011).

1.6 Summary: Building Institutional FN Guidelines

It is clear that without sufficient data guiding uniform treatment strategies, institutional guidelines addressing FN in pediatric oncology are critical in effective clinical management for this life-threatening complication and in monitoring institutional trends in resistance and infectious sequelae. A multidisciplinary team approach is required to create comprehensive and critically reviewed guidelines that are supported at all levels of the hospital, from primary patient managers including hematology/oncology physicians to consultants such as infectious disease specialists and pediatric surgeons to additional caregivers such as emergency medicine physicians and pediatric intensivists. Cooperation between all care providers will ensure uniformity and successful treatment of this patient population. In a recent survey of time to antibiotic delivery for presenting FN in the emergency department, Burry et al. (2012) note many factors to improve care including administrative barriers, communication between oncology and emergency department staff, and patient education. As noted, implementing potential practices such as early discharge will require multidisciplinary discussion, institutional review board (IRB) approval, and prospective study and ongoing analysis to ensure patient safety as well as efficacy of the treatment strategy.

Here we provide examples of institutional guidelines incorporating the various diagnostic and management concepts throughout this chapter and compiled into a practical algorithm to illustrate a standard supportive care approach for FN in pediatric oncology patients (Figs. 1.1, 1.2, and 1.3). These guidelines should be regarded as quality of evidence level III recommendations as they are based mainly on expert opinion and published reports from expert committees due to the lack of randomized clinical trials in pediatrics; additionally, the reader should refer back to the text for full details as many reasonable treatment options are equally valid. As discussed, institutional guidelines must incorporate local microbial prevalence and incidence and local clinical expertise which may not necessarily be equal across institutions. Lastly, available guidelines assist with decision-making but an individualized approach must be taken when evaluating and treating each episode of FN in pediatric oncology patients.

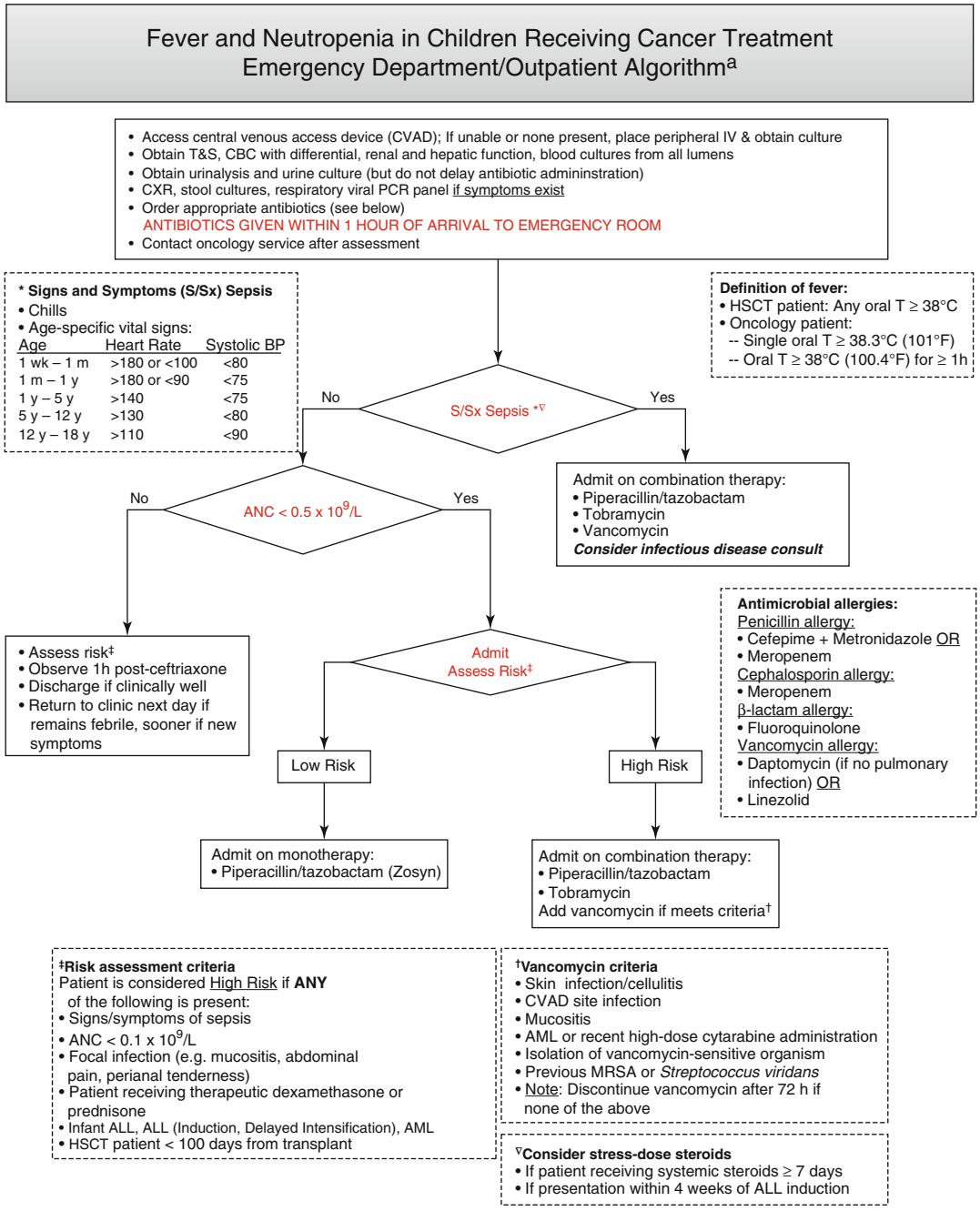

Fig. 1.1 Emergency room algorithm for fever and neutropenia in pediatric oncology patients
[a]see text for full detail as other treatment algorithms are equally justifiable
T&S type and screen, *CBC* complete blood count, *PCR* polymerase chain reaction, *HSCT* hematopoietic stem cell transplant, *ANC* absolute neutrophil count, *ALL* acute lymphoblastic leukemia, *AML* acute myelogenous leukemia, *MRSA* methicillin resistant *S. aureus*

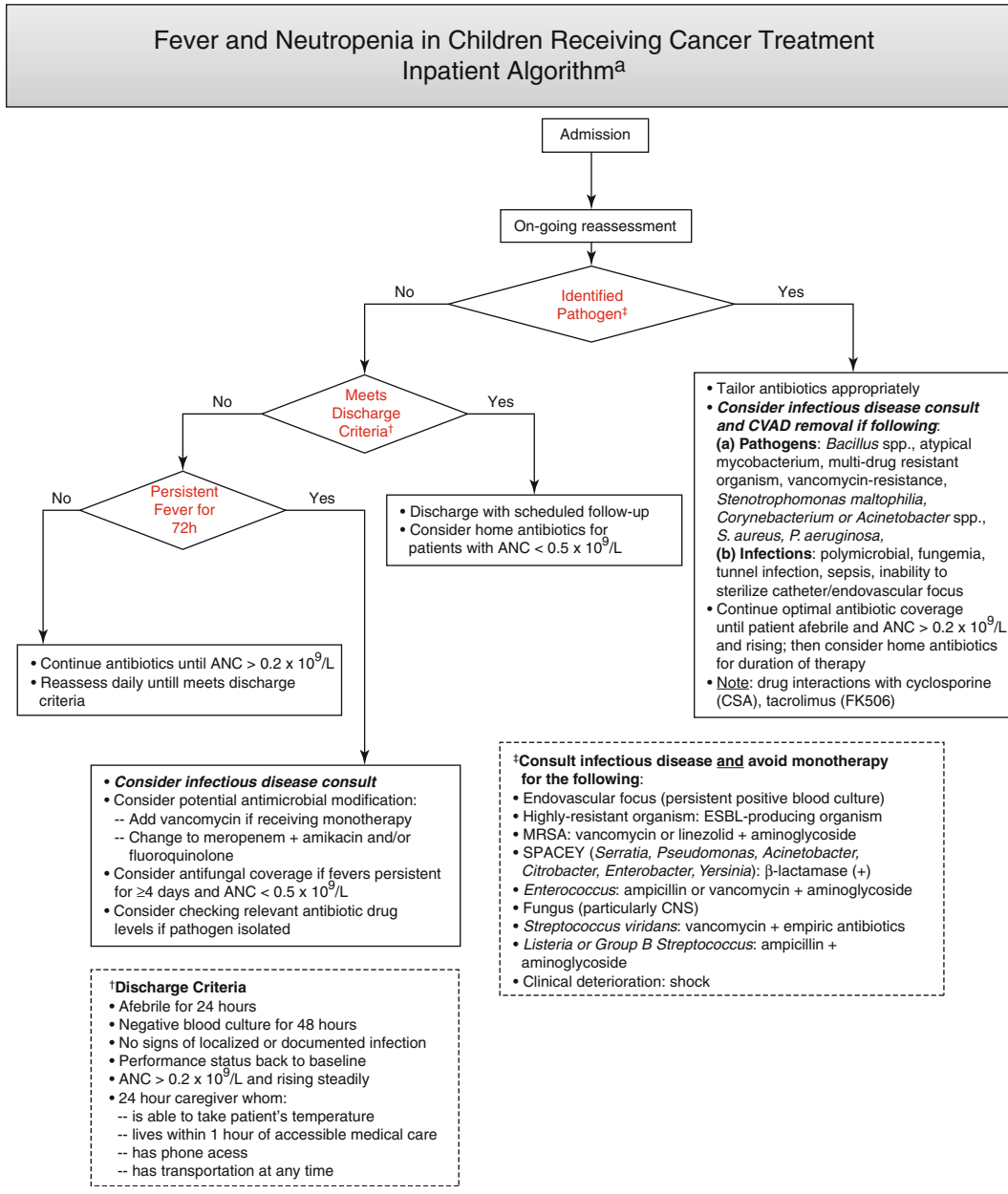

Fig. 1.2 Inpatient algorithm for fever and neutropenia in pediatric oncology patients
[a]see text for full detail as other treatment algorithms are equally justifiable
CVAD central venous access device, *ANC* absolute neutrophil count, *MRSA* methicillin resistant *S. aureus*

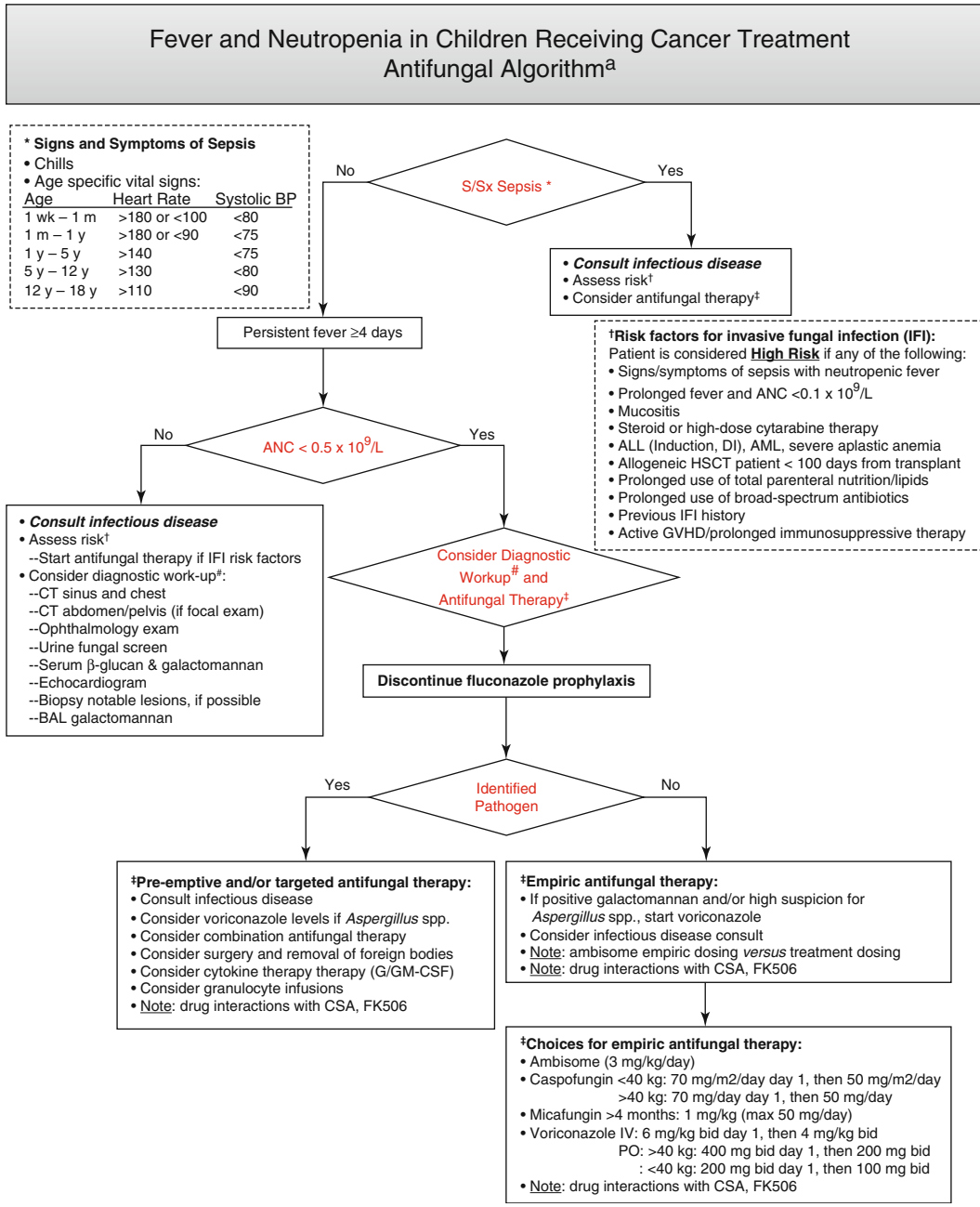

Fig. 1.3 Antifungal algorithm for fever and neutropenia in pediatric oncology patients
[a]see text for full detail as other treatment algorithms are equally justifiable
ANC absolute neutrophil count, *ALL* acute lymphoblastic leukemia, *DI* delayed intensification, *AML* acute myelogenous leukemia, *HSCT* hematopoieic stem cell transplant, *GVHD* graft-versus-host disease, *CT* computed tomography, *BAL* bronchoalveolar lavage, *CSA* cyclosporine, *FK506* tacrolimus, *bid* twice daily

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