The Use of Antimicrobial Agents in Children With Fever During Chemotherapy-induced Neutropenia

The Importance of Risk Stratification

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The Infectious Diseases Society of America recently published updated clinical practice guidelines for the management of neutropenic fever.1 Despite improvements in therapeutic strategies leading to better prognosis for most pediatric patients with malignancy, infection remains a significant cause of morbidity and mortality in those with neutropenia caused by chemotherapy.2-4 In neutropenic children with cancer and potentially life-threatening infection, fever may be the only initial manifestation of illness because other signs of systemic disease can be attenuated. Therefore, it is recommended that all children with fever and cancer-related neutropenia be assessed with a complete history and physical examination, undergo appropriate diagnostic studies, and promptly receive empirical antimicrobial therapy.

DEFINITIONS

Fever, generally, is defined as a single oral temperature of at least 38.3°C (101°F), or a temperature of ≥38°C (100.4°F) sustained over 1 hour. Axillary temperatures are discouraged and rectal temperatures are contraindicated in children with chemotherapy-induced febrile neutropenia (FN). Neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/mm³ or an ANC <100 cells/mm³, which is expected to decrease to <500 cells/mm³ in the next 48 hours. Profound neutropenia is defined as an ANC <100 cells/mm³, and prolonged neutropenia is that which lasts >7 days.

EPIDEMIOLOGY AND ETIOLOGY

Fever occurs in approximately 35% (range: 10%–60%) of episodes of neutropenia in children, and is most common in patients after hematopoietic stem cell transplantation (HSCT) or aggressive myeloablative treatment for acute leukemia or lymphoma.5 Documentation of an infectious etiology or focus of infection occurs in only 10% to 45% of febrile episodes.5-8 However, infection remains the most common potentially life-threatening complication of cytotoxic chemotherapy.5,6 The majority of infections is caused by bacterial pathogens, and bloodstream infection is the most common cause of microbiologically documented FN. Bacteremia, which often is catheter related, occurs in approximately 10% to 20% of febrile neutropenic patients after HSCT or aggressively treated acute leukemia or lymphoma.5,9-11 Other frequently involved sites of bacterial infection include the respiratory tract, gastrointestinal tract, and skin and soft tissues.

Enterobacteriaceae are common causes of documented infection in cancer-related FN due to translocation of organisms from the gastrointestinal tract into the bloodstream. Depending on local epidemiology, some of these pathogens can be multiply drug-resistant (eg, extended-spectrum beta-lactamase producers). However, although gram-negative pathogens were the predominant cause of infection in febrile neutropenic patients in past decades, gram-positive organisms now are equally, and in some studies more, responsible.5,8,12,13 The increased incidence of gram-positive pathogens as etiologic agents is the result of increased use of invasive devices, such as central venous catheters, and extensive use of broad-spectrum antimicrobials.1,14 Coagulase-negative staphylococci account for the majority of gram-positive organisms isolated, but Staphylococcus aureus (methicillin-resistant and -susceptible) and vancomycin-susceptible and vancomycin-resistant enterococci also occur.1 In patients with significant mucositis...
caused by aggressive chemotherapy, viri- 
dans streptococci are important and poten-
tially life-threatening pathogens.14 How-
ever, although gram-positive organisms are equally common in patients with FN, 
gram-negative pathogens, especially Pseu-
 domonas aeruginosa, are associated with 
greater mortality.4

Fungi (yeasts and molds) occur in less 
than 5% of patients with FN but are impor-
tant causes of morbidity and mortality.15,16 
These patients often have been treated with 
prolonged courses of broad-spectrum anti-
microbials and typically have neutropenic fever 
that persists beyond 4 to 7 days or recurs 
despite antibiotic therapy.16 Patients with 
acute myelogenous leukemia (AML) and 
those who have undergone HSCT are partic-
ularly at risk. Candida species are the most 
common pathogens causing invasive fungal 
infections (IFI) in febrile neutropenic chil-
dren.5,13 Invasive mold infections (aspergil-
losis, zygomycosis, fusariosis) are much less 
common and occur most often in children 
with profound neutropenia lasting more than 
10 days.

CLINICAL AND RISK ASSESSMENT

Assessment of risk for severe infec-
tion is crucial in determining the appropriate 
antimicrobial, route (intravenous vs. oral), 
venue (inpatient vs. outpatient), and duration 
of empirical antimicrobial therapy. The type of 
malignancy and associated chemothera-
pies, medical comorbidities, relevant history, 
and presenting signs and symptoms must be 
considered. In children, studies have sought to 
stratify risk for serious infection and its 
complications in febrile neutropenic patients, 
with varying results.6,9,10,17–19

High Risk

High-risk patients are those who have 
an increased risk for severe infection or its 
sequelae. Studies have found that children are 
at greater risk of life-threatening infec-
tion if they have fever ≥39°C, prolonged 
neutropenia, recent intensive chemotherapy, 
underlying diagnosis of AML, bone marrow 
involve ment, relapsed malignancy or second 
tumor, “sick” clinical appearance (hypoten-
sion, respiratory distress, hypoxemia, new-
onset abdominal pain, neurologic changes), 
medical comorbidities (eg, renal or hepatic 
sufficiency), or evidence of focal infection 
(mucositis, pneumonia, cellulitis, perianal 
tenderness, presence of a central venous ac-
cess device).1,6,10,19 Laboratory abnormali-
ties associated with a high risk of infection 
include profound neutropenia, a C-reactive 
protein ≥90 mg/L, platelet count <20,000 to 
50,000 cells/mm3; these factors and an abso-
lute monocyte count <100 cells/mm3 also 
predict a high risk for mortality.4,6,17

Low Risk

Patients are categorized as low risk for 
infec tion if they are clinically stable without 
medical comorbidities and have neutropenia 
expected to resolve within 7 days.1,20 Pa-
tients with solid tumors generally have lower 
risk for infection than those with leukemia or 
lymphoma. Any patient who does not clearly 
fulfill criteria for being at low risk of infec-
tion should be evaluated and treated accord-
ing to high-risk guidelines.1

EMPIRIC ANTIBIOTIC THERAPY

High-risk Patients

Febrile neutropenic patients at high 
risk of infection should be hospitalized and 
administered broad-spectrum, empirical in-
travenous antibiotic therapy.1,4 Choice of 
initial antimicrobial therapy should be based 
on history and physical examination findings 
as well as local (and the patient’s own) 
epidemiology and antimicrobial susceptibil-
ity data. Numerous clinical studies have not 
established a single best therapeutic regi-
men for the empiric treatment of patients 
with FN.1 Optimal empirical antibiotic 
therapy should include an agent(s) with 
bactericidal activity, especially against 
Pseudomonas aeruginosa, and have a fa-
 vorable toxicity profile.

Monotherapy with an antipseudomonal 
beta-lactam agent has been shown to be 
as effective and as combination therapy in 
patients who are hemodynamically stable with-
out evidence of skin or soft tissue infection, 
pneumonia, or concern for catheter-related 
infection.21–23 Current evidence supports the 
empirical use of piperacillin-tazobactam or 
cefeime in locations where antimicrobial 
susceptibility data do not warrant empirical 
carbenemen (meropenem or imipenem-cila-
statin) use.23,25,26 Aztreonam can be used in 
children with a life-threatening beta-lactam 
al lergy but lacks activity against viridans streptococci (and thus should be used in 
combination with an agent active against 
these microbes in patients with severe mu-
cositis). Routine initiation of an aminoglyco-
side in combination with a beta-lactam agent 
should be avoided because it offers no 
 survival advantage and is associated with 
increased toxicity and a higher treatment 
failure rate.21 Ceftazidime is no longer 
recommended for empiric monotherapy in 
high-risk patients with fever and neutrope-
nia due to its decreasing activity against 
many gram-negative pathogens.26 Ceftazi-
dime also offers only weak activity against 
viridans streptococci.

Despite the prevalence of gram-posi-
tive organisms in the etiology of FN, routine 
use of vancomycin or another agent active 
against gram-positive pathogens is not rec-
ommended as it offers no survival advantage 
and fails to decrease the length of fever in 
most patients.27 However, in communities 
with a high incidence of infections caused by 
meticillin-resistant staphylococci and in pa-
tients with hemodynamic instability, radio-
graphically documented pneumonia, skin or 
soft tissue infection, or concern for serious 
catheter-related infection, addition of vanco-
mycin to the empirical antimicrobial regimen 
is reasonable. Its addition may not be neces-
sary in patients with mucositis who are re-
ceiving monotherapy with piperacillin-tazo-
bactam, cefepime, or a carbenemen, since 
these drugs provide adequate coverage 
averidans streptococci. In patients in 
whom vancomycin is warranted, if no patho-
gens have been identified in cultures and no 
focus of infection is obvious, empirical ther-
apy should be reassessed after 48 to 72 
hours. Vancomycin should be discontinued 
if no obvious indication for ongoing treat-
ment is found.

Low-risk Patients

A large meta-analysis in adults found 
that oral quinolone therapy alone or in com-
bination with other antibiotics was an accept-
able alternative to intravenous therapy in 
select patients with FN.28 There was no dif-
fERENCE in either mortality or treatment fail-
ure rates in febrile neutropenic adults with 
cancer (other than acute leukemia) who were 
hemodynamically stable without organ fail-
ure, pneumonia, catheter-related infection, or 
severe soft-tissue infection. In adults, oral 
levofloxacin is the preferred fluoroquinolone 
for monotherapy, because it has better activ-
ity against gram-positive organisms than cip-
rofloxac in. Selected low-risk adult patients, 
who can be followed closely and in whom 
prompt access to appropriate medical care is 
ensured, are candidates for outpatient man-
agement of FN with oral antibiotic therapy.

Few studies exist in low-risk children 
with FN to support initial therapy with an 
oral agent.29 Considerable variation in prac-
tice exists, but initial inpatient or emergency 
center management of low-risk patients with 
FN remains routine in many (but not all) 
centers. A prospective, randomized, single-
institution trial of 135 children with low-risk 
FN, most of whom had leukemia, found 
outstanding clinical outcomes and no differ-
ence in treatment failure in children who 
received oral ciprofloxacin versus intrave-
rous ceftriaxone after a single dose of 
ceftriaxone and amikacin.30 In the United 
States, the use of oral fluoroquinolones 
empirically in low-risk children with FN and 
cancer is an off-label use.

A recent study from Switzerland of 
more than 400 episodes of FN among 206 
children reported that 8% of bacteremic epi-
isodes were identified only after inpatient
reassess at 8 to 24 hours; prediction of bacteremia at the reassessment was better than that at presentation of FN. Hakim et al[19] also highlighted the importance of both the initial clinical assessment and 24 hours of close observation in detecting invasive bacterial infection or a clinical complication in low-risk patients. Often, outpatient management of low-risk children with FN is not feasible because of nonmedical barriers, including transportation issues, language barriers, and lack of parent or physician comfort with care outside of the hospital.31

Duration of Antibiotic Therapy
In a child with a documented focus of infection, the duration of therapy is determined by the site of the infection, the clinical response (including resolution of fever) and the pathogen identified. In general, directed antimicrobial therapy should continue at least until the ANC exceeds 500 cells/mm3 (bone marrow recovery). When the source of the fever remains unknown, the initial choice of antibiotic therapy should be continued until bone marrow production of granulocytes has recovered.

ANTIFUNGAL THERAPY

High-risk Patients
Initiation of antifungal therapy is recommended in high-risk children with chemotherapy-induced neutropenia when fever persists or recurs at 4 to 7 days.1 Candida (yeast) and Aspergillus (mold) are the most common pathogens causing IFI, although infection due to mold is most common in patients with profound neutropenia and fever lasting beyond 7 to 10 days.1,32

Limited data are available comparing antifungal agents in children with suspected IFI.3,34 Important considerations in choosing an antifungal agent include type of antifungal prophylaxis (if any) and local epidemiology of Candida isolates. In patients who have not been given fluconazole prophylaxis and lack risk factors for mold infection, fluconazole may be an appropriate empiric therapy. For those in whom there is concern for IFI caused by fluconazole-resistant Candida species (Candida krusei or Candida glabrata) or mold, amphotericin B, echinocandins (eg, caspofungin), and newer azoles (voriconazole or posaconazole) are options. One should consider choosing an empirical antifungal (preferably intravenous) agent that is in a different class from that used for prophylaxis.

Children and adults are less likely to develop nephrotoxicity or infusion-related effects with liposomal amphotericin B than other amphotericin formulations.32,34 One randomized, multicenter study of 82 children aged 2 to 17 years with persistent fever and neutropenia compared empiric caspofungin and liposomal amphotericin B and found no difference in safety, tolerability, and efficacy between the treatment groups.35 The use of 2 antifungals from different classes of mold-active agents (combination therapy) can be considered in patients with documented IFI who are clinically unstable or worsening, but this approach is controversial and no supportive efficacy data exist from well-controlled trials.

Low-risk Patients
Empirical antifungal therapy is not recommended for low-risk patients with chemotherapy-induced FN.

Duration of Antifungal Therapy
The duration of antifungal therapy in a child with a documented focus of infection is determined by the site of the infection, the clinical response (including resolution of fever and results of imaging studies and serum fungal assays) and the pathogen identified. In general, directed antifungal therapy should continue at least until bone marrow recovery. When the source of the fever is unknown, antifungal therapy should continue until resolution of fever and bone marrow recovery. Longer durations of therapy may be warranted when there is evidence of persisting fungal infection after marrow recovery and neutropenia is likely to recur soon due to the next chemotherapy cycle.

ANTIMICROBIAL PROPHYLAXIS

Antibiotics
The Infectious Diseases Society of America recommends considering fluoroquinolone prophylaxis for high-risk febrile adult patients with anticipated prolonged and profound neutropenia, although some controversy remains regarding precisely which patients are most appropriate for prophylaxis.1 However, no clear recommendation is found for children since high-quality clinical trials assessing the safety and efficacy of prophylaxis are lacking, and concern regarding increases in infections due to fluoroquinolone-resistant pathogens exists. In general, antibiotic prophylaxis (with fluoroquinolones) in children is considered only in very high-risk situations (eg, allogeneic HSCT, aggressive myeloablative therapy for leukemia).

Antifungals
Antifungal prophylaxis (eg, fluconazole, itraconazole, voriconazole, posaconazole, caspofungin) against Candida species is recommended in those patients most at risk for IFI, such as allogeneic HSCT recipients and patients undergoing intensive chemotherapy for acute leukemia. Prophylaxis against Aspergillus is recommended in patients with a prior history of IFI, neutropenia anticipated to last beyond 2 weeks, or prolonged neutropenia prior to HSCT.36 Posaconazole prophylaxis is recommended specifically for patients aged more than 12 years undergoing induction chemotherapy for AML or intensive chemotherapy for myelodysplastic syndrome.1 Posaconazole absorption is variable, and drug interactions with chemotherapeutic agents are a potential concern.1 The duration of antifungal prophylaxis is uncertain; however, patients with acute leukemia generally are treated until myeloid reconstitution, and HSCT recipients through day 75 posttransplantation or cessation of immunosuppression.1

Antivirals
Patients who are seropositive for herpes simplex virus undergoing induction therapy for leukemia or allogeneic HSCT warrant acyclovir prophylaxis. Prophylaxis generally is continued until bone marrow recovery. However, in patients with recurrent herpes simplex virus infections or graft-versus-host disease, prolonged antiviral prophylaxis may be necessary. All patients with cancer and their household contacts should be immunized annually with influenza vaccine. Further, neutropenic patients exposed to influenza should receive prophylaxis with a neuraminidase inhibitor (eg, zanamivir, oseltamivir). Neutropenia is not a risk factor for reactivation of other herpes viruses such as cytomegalovirus and human herpes virus 6. No other antiviral prophylaxis regimens have been proven effective for patients with chemotherapy-induced FN.

SUMMARY
Children with fever and chemotherapy-induced or cancer-associated neutropenia should be assessed with complete history and physical examinations, undergo appropriate diagnostic studies, and promptly receive broad-spectrum empirical antimicrobial therapy. Assessment of risk for severe infection is crucial in determining the appropriate antimicrobial, route, venue, and duration of empirical antimicrobial therapy and need for prophylactic antimicrobial agents.

REFERENCES


