Neutropenia in the Febrile Child

Brandon C. Ku, MD,†‡ Charles Bailey, MD, PhD,*,‡ and Fran Balamuth, MD, PhD, MSCE*†

Abstract: Fever in the pediatric population is a common chief complaint presenting to the emergency department and may be one of the first indications of a life-threatening infection, especially in patients with neutropenia. Given that pediatric patients with febrile neutropenia frequently present to emergency departments for emergent care, it is critical for emergency medicine physicians and pediatricians and family physicians working in the emergency department to know the key aspects of the clinical approach to these patients. This review of the clinical evaluation and treatment of the pediatric patient presenting with fever and confirmed or suspected neutropenia will provide health care providers with the necessary tools to effectively care for this patient population.

Key Words: fever, neutropenia, serious bacterial infection

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TARGET AUDIENCE

The target audience for this review includes pediatric emergency physicians, general emergency physicians, general pediatricians, and family physicians working in emergency departments (EDs).

LEARNING OBJECTIVES

After completion of this CME article, the reader should be better able to:
1. Obtain a detailed history and physical exam of a pediatric patient presenting with fever and neutropenia.
2. Know key evaluation aspects of a patient presenting with fever and neutropenia.
3. Determine initial management and treatment for febrile pediatric patients with either chemotherapy-induced neutropenia or nonchemotherapy-induced neutropenia.

BACKGROUND

Fever in the pediatric population is a common chief complaint presenting to the ED and may be one of the first indications of a life-threatening infection, especially in patients with neutropenia. Neutropenia can be the result of myelosuppressive chemotherapeutic regimens or hematopoietic stem cell transplantation in the pediatric oncologic population or the result of nonmalignant hematologic etiologies. In children with chemotherapy-induced neutropenia or recent hematopoietic stem cell transplant, febrile episodes occur in approximately one third of neutropenic episodes and may be the first indicator of a serious bacterial or fungal infection, which is a major cause of morbidity and mortality in oncology patients.1,2

DEFINITIONS

Normal ranges for absolute neutrophil count (ANC) vary by age with the lower limit of normal starting at 6000 cells/μL during the first 24 hours of life, with the ANC calculated as the proportion of segmented neutrophils and bands:

\[
\text{ANC} = \frac{\text{total white blood cell count (cells/μL)} \times \text{percent(segmented neutrophils + bands)}}{100}
\]

This lower limit gradually decreases during the first year of life, and neutropenia in children 1 year or older is defined as an ANC less than 1500 cells/μL.3 Categorization of neutropenia is defined by its degree: mild (ANC, 1000–1500 cells/μL), moderate (ANC, 500–1000 cells/μL), and severe (ANC < 500 cells/μL).4 In the absence of other predisposing factors, risk of invasive infection is minimally increased with ANC greater than 1000 cells/μL, and increases with greater severity of neutropenia, particularly below 200 cells/μL.

Fever in the neutropenic population is generally defined as a single oral temperature greater than 38.3°C (101°F) or 3 oral temperatures 38.0°C or greater (100.4°F) over at least 1 hour, and some institutions use at least a 2-hour interval between each temperature measurement.5 Rectal temperatures should be avoided due to the risk of intestinal mucosal injury and resulting bleeding or infection.

Although neutropenia most commonly occurs in pediatric oncology patients undergoing myelosuppressive chemotherapeutic regimens, other causes of neutropenia exist in the pediatric population. Specifically, patients can present with neutropenia due to nonmalignant hematologic etiologies, and this group can be divided into transient neutropenias (either induced by medications or viral infections) and cyclic/persistent neutropenias. The general ED approach and evaluation of a febrile child with chemotherapy-induced neutropenia and non-chemotherapy-induced neutropenia that is cyclic or persistent is similar, but the risk stratification and treatments may differ based on clinical presentation. Therefore, these areas will be presented in separate sections.

SOURCES OF FEVER/EVALUATION

Potential sites of serious bacterial infection include blood, the upper and lower respiratory tract, urinary tract, gastrointestinal tract, and skin and soft tissue.6 The rates of documented infection in pediatric oncology patients presenting with fever and chemotherapy-induced neutropenia ranges from 10% to 40% in the literature and varies based on underlying malignancy, chemotherapeutic regimens and specific characteristics of the
chemotherapy used, and institution.1,6–9 Bacteremia is the most common serious bacterial infection with rates ranging from 15–25% in febrile neutropenic episodes, with both gram-positive and gram-negative organisms.6–8,10,11 The most common organisms isolated from blood cultures in children with fever and chemotherapy-induced neutropenia are listed in Table 1.6

The rates of serious bacterial infection in pediatric patients presenting with fever and non–chemotherapy-induced neutropenia vary based on the anticipated timeframe of neutrophil recovery and the degree of neutropenia (mild, moderate, or severe). Limited studies have shown that febrile pediatric patients with transient moderate neutropenia who are otherwise well-appearing do not have increased risk of serious bacterial infection when compared with febrile patients without neutropenia.12–14 However, comparative studies of treatment of these patients is limited, and many centers continue to treat these patients with antibiotics and hospital admission, absent either a known rapid response to G-CSF treatment, or an established history of no serious infections despite neutropenia.

**Initial Evaluation**

**History**

A detailed focused history is key to the initial assessment of a febrile neutropenia patient. For the chemotherapy-induced neutropenia patient, chemotherapeutic agents last used and timing of last chemotherapy, type of indwelling central venous catheter (implantable central venous access device, tunneled central venous catheter, or peripherally inserted central catheter), history of bone marrow transplant or stem cell transplant, and history of prior invasive infection are important considerations to assess to determine the patient's risk for life-threatening infections. For the non–chemotherapy-induced neutropenia patient, specific attention should be dedicated to the history and duration of neutropenia, prior infections, medication exposure, any recent infections or current broad-spectrum antibiotic use, and in patients with autoimmune neutropenia, history of response to G-CSF. Family history should also be assessed for family members with neutropenia or other hematologic abnormalities.

**Physical Examination**

A complete physical examination can aid in diagnosing the etiology of a fever in a neutropenic patient. Specific attention should be placed at common sites of infection including the oropharynx and mucosa, central venous catheter site (if applicable), pulmonary and abdominal examination, and general skin examination including the perineum and perianal region. It is necessary to recall that in the neutropenic patient, localizing signs of infection may be reduced or absent due to inability to generate an adequate inflammatory response.

**Laboratory and Radiographic Evaluation**

In all patients with fever and suspected or presumed neutropenia, blood cultures and complete blood count with manual differential to determine degree of neutropenia should be obtained.15,16 For patients with central venous catheters, blood cultures should be obtained from all lumens of the catheters.15,16 The utility of concurrent peripheral blood cultures is controversial. The proportion of bacteremia detected by peripheral culture alone with negative cultures from central venous catheters is about 13% in the literature. These potential benefits have to be weighed against the possibility of contaminants and patient discomfort/inconvenience, as well as the potential for localized infection at venipuncture sites.15,17–23

Serum electrolytes, levels of creatinine and blood urea nitrogen, and liver transaminases and bilirubin should also be obtained, when an extended course of antibiotics is anticipated.15 Urinalysis and urine culture can be considered as clinically indicated and readily available but should not delay antibiotic administration.16 A systematic review and meta-analysis of frequency of pneumonia in an asymptomatic child with febrile neutropenia was less than 5%, hence routine chest radiographs are not recommended in asymptomatic children and should be obtained only as clinically indicated.24 Additional studies, such as abdominal radiographs, lumbar punctures, stool cultures, and viral testing, should also be obtained as clinically indicated.

**FEVER AND CHEMOTHERAPY-INDUCED NEUTROPENIA**

Patients with fever and neutropenia can be further stratified based on their risk of developing severe infection. Multiple studies have developed validated pediatric risk stratification guidelines to identify low-risk patients but no single consensus low-risk rule specific to pediatric patients has been identified.10,25–29 Guidelines designed primarily for adults such as the Infectious Diseases Society of America (IDSA) 2010 guidelines define high-risk as profound neutropenia (ANC ≤ 100 cells/μL) anticipated to last more than 7 days.15 High-risk stratification should also be considered in patients with significant comorbid conditions, including hepatic or renal insufficiency, hemodynamic instability, neurologic changes, history of central venous catheter infection, or a recent hematopoietic stem cell transplant.15 Although the Multinational Association for Supportive Care in Cancer scoring system was developed based on patients older than 16 years, the IDSA guidelines support formal risk stratification using this system.15,30 In this scoring system, patients are assigned points based on burden of illness, age, cancer type, history of fungal infection, outpatient status and presence of hypotension, dehydration or COPD, and patients with a Multinational Association for Supportive Care in Cancer score less than 21 should be considered high-risk and patients with a score of 21 or greater should be considered low risk.15,30

**CHOICE OF ANTIBIOTICS**

Infectious Disease Society of America (2010) and International Pediatric Fever and Neutropenia (2012) guidelines provide recommendations for initial antibiotic therapy for high-risk febrile chemotherapy-induced neutropenia patients.15,16 Both guidelines highlight that individual treatment regimens should be based on the patient's risk stratification for development of infection.

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**TABLE 1. Most Commonly Isolated Organisms From Blood Cultures in Patients With Fever and Chemotherapy-Induced Neutropenia**

**Gram-Positive Organisms**

| Coagulasenegative staphylococci |
| Viridans streptococci |
| Staphylococcus aureus (including methicillinresistant S. aureus) |
| Gram-negative organisms |
| Escherichia coli |
| Klebsiella spp. |
| Pseudomonas spp. |
| Enterobacter spp. |

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history of prior bacterial colonization, renal or hepatic dysfunction, medication allergies, drug availability and cost, and local epidemiology of bacterial isolates and resistance patterns.\textsuperscript{3,15} In general, the guidelines recommend initial antibiotic coverage for gram-negative organisms in all febrile neutropenia patients with additional coverage for viridans group streptococci and Pseudomonas aeruginosa in high-risk patients.\textsuperscript{13,16} With these considerations, the guidelines recommend initial monotherapy with broad-spectrum antipseudomonal penicillin, cephalosporin, or carbapenem antibiotic, listed in Table 2.\textsuperscript{13,16} For patients with a history of type I immediate hypersensitivity reaction to penicillins, combination therapy that avoids β-lactams and carbapenems is recommended, and options include ciprofloxacin plus clindamycin or aztreonam plus vancomycin.\textsuperscript{15,16}

A consensus exists that empiric antibiotic therapy is warranted for febrile episodes in the setting of severe neutropenia (ANC < 500 cells/μL), but variability exists among centers, with actual cutoffs for initiation of antibiotic therapy with ANC less than 200 cells/μL to ANC less than 500 cells/μL. In addition, if present, the type of indwelling central venous catheter should be considered when determining empiric antibiotic coverage as percutaneous central venous catheters (eg, tunneled central venous catheters and peripherally inserted central catheters) are associated with a higher incidence of central-line associated bloodstream infections when compared with implantable central venous access device).\textsuperscript{31,32} As a result, many institutions consider oncology patients with percutaneous central venous catheters at a higher risk of invasive infections and will treat with empiric antibiotics regardless of ANC. For patients who have an implantable central venous access device and have only mild or moderate neutropenia, one may consider empiric therapy with ceftriaxone with discharge and outpatient follow-up pending culture results.

A pediatric meta-analysis found no difference in clinical outcome when aminoglycoside-containing combination treatment was compared with antipseudomonal penicillin monotherapy and carbapenem monotherapy.\textsuperscript{33} Therefore, an additional gram-negative antibiotic should be reserved for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant organisms.\textsuperscript{16}

Vancomycin and other antimicrobial agents for aerobic gram-positive cocci are not recommended for routine empiric antibiotic coverage for fever and neutropenia and should be added as clinically indicated for specific conditions, including suspected catheter-related infection, which may include tracking erythema, swelling, or tenderness around central venous catheter site. Other potential indications include skin or soft tissue infection, pneumonia, hemodynamic instability, or previous infection or colonization with antibiotic-resistant organisms.\textsuperscript{13} They may also provide benefit for specific populations at risk for infection with viridans streptococci, such as patients receiving high-dose cytarabine, or other resistant gram-positive organisms.

Recent research has focused on improving timeliness of antibiotic administration to pediatric febrile neutropenic patients. One recent study suggests improved outcomes as measured by length of stay and adverse events composite of mortality, intensive care unit admission, and fluid resuscitation with antibiotic administration within 60 minutes of presentation in febrile neutropenic children with an oncologic diagnosis undergoing myelosuppressive chemotherapy regimens.\textsuperscript{32} Additional studies are needed to further determine the effects of timeliness of antibiotics on patient outcomes.

**Antifungal Therapy**

Empiric antifungal therapy should be reserved for children if they have persistent fever unresponsive to initial broad-spectrum antibiotics (≥96 hours), or physical examination or radiographic findings, such as tree-in-bud, nodules, and so on, suggestive of invasive fungal infection. Initial empiric antifungal therapy options include caspofungin, a second- or third-generation azole, or liposomal amphotericin B.\textsuperscript{16}

**Antiviral Therapy**

In the setting of high incidence of influenza, neutropenic patients presenting with influenza-like illness should receive empiric treatment with neuraminidase inhibitors. Specific antiviral treatment for herpes simplex virus and varicella-zoster virus infections is only indicated for clinical or laboratory evidence of active viral infection.\textsuperscript{13} The threshold for empiric antiviral therapy is lower in subsets of patients at particularly high risk due to impaired cellular immunity, including infants, patients who have undergone blood or marrow transplant in the past 6 months, and children with congenital immunodeficiencies.

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Age and Weight Parameters</th>
<th>Dose</th>
<th>Maximum Dose</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipseudomonal penicillins</strong></td>
<td></td>
<td></td>
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<tr>
<td>Piperacillin-tazobactam</td>
<td>&lt;9 mo</td>
<td>80 mg/kg piperacillin IV every 8 h</td>
<td>16 g piperacillin/d</td>
<td>Adjust for renal impairment</td>
</tr>
<tr>
<td></td>
<td>≥9 mo and &lt;40 kg</td>
<td>100 mg/kg piperacillin IV every 8 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥40 kg</td>
<td>3000 mg piperacillin IV every 6 h</td>
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<td></td>
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<tr>
<td>Ticarcillin-clavulanic acid</td>
<td>50 mg/kg ticarcillin IV every 4 h</td>
<td>2 g ticarcillin/dose</td>
<td></td>
<td>Adjust for renal impairment</td>
</tr>
<tr>
<td><strong>Antipseudomonal cephalosporins</strong></td>
<td></td>
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<tr>
<td>Cefepime</td>
<td>50 mg/kg IV every 8 h</td>
<td>2 g/dose</td>
<td></td>
<td>Adjust for renal impairment</td>
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<tr>
<td><strong>Carbapenems</strong></td>
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<tr>
<td>Meropenem</td>
<td>≥3 mo</td>
<td>20 mg/kg IV every 8 h for non-CNS infections</td>
<td>2 g/dose</td>
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<tr>
<td></td>
<td></td>
<td>40 mg/kg IV every 8 h for CNS infections</td>
<td></td>
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<tr>
<td>Imipenem-cilastatin</td>
<td>≥1 mo</td>
<td>25 mg/kg IV every 6 h</td>
<td>1 g/dose</td>
<td></td>
</tr>
<tr>
<td><strong>Lower-risk patients</strong></td>
<td></td>
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</tbody>
</table>
| Ceftriaxone | ≥1 mo | 75 mg/kg every 24 h | 2 g/dose | | }

IV, intravenous
Hematopoietic Growth Factors

The 2010 IDSA guidelines recommend consideration of prophylactic use of hematopoietic growth factors (G-CSF or GM-CSF) for patients who have an anticipated risk of febrile neutropenia of 20% or greater. However, the guidelines do not recommend general use of hematopoietic growth factors for the treatment of established febrile neutropenia because studies have only found small, although significant, reduction in hospital length of stay and duration of antibiotic use.15,35,36

DISPOSITION

In general, patients with fever and chemotherapy-induced severe neutropenia should be admitted to the hospital for administration of parental antibiotics, results of cultures and cell count trends, and ongoing reassessments. In patients with low-risk febrile neutropenia, guidelines support consideration of outpatient oral antibiotic administration if the local institution and infrastructure can ensure close monitoring and follow-up and if the patient can tolerate oral antibiotic administration reliably. This recommendation is based on a review of 16 mostly small single-center prospective trials of pediatric low-risk febrile neutropenia that found no increase in treatment failure and when outpatient treatment was compared with inpatient management and found no infection-related deaths in patients that were treated as outpatients. In addition, research comparing parental and oral antibiotic therapy in low-risk febrile neutropenia patients found no difference in treatment failure and no infection-related deaths.37 Oral antibiotics used in these studies were either fluoroquinolone monotherapy, fluoroquinolone and amoxicillin-clavulanate, or cefixime monotherapy. The research suggests that there may be certain subpopulations of low risk febrile neutropenia oncology patients in whom early discharge off antibiotics is safe, but ongoing research needs to be performed. For patients who have fever and only mild or moderate neutropenia and no percutaneous central venous catheter, one may consider empiric therapy with ceftriaxone with discharge and outpatient follow-up pending culture results.

FEVER AND NON–CHEMOTHERAPY-INDUCED NEUTROPENIA

Neutropenia in the pediatric patient not due to myelosuppressive chemotherapy or hematopoietic stem cell transplantation is often due to primary hematologic etiologies and can be classified as either transient or chronic. An otherwise healthy pediatric patient, neutropenia can be the result of viral infection and subsequent suppression of neutrophil production, which is usually benign, resulting in mild or moderate neutropenia, and transient, resolving within 1 month.38 Transient neutropenia can also be the result of medications, such as analgesics and anti-inflammatory agents, antibiotics, anticonvulsants, antidepressants and antipsychotics, antithyroid, and cardiac medications, and resolves after discontinuation of inciting medication.39 Chronic neutropenia is defined as lasting longer than 2 months and can have multiple causes including autoimmune and alloimmune neutropenia, chronic idiopathic neutropenia, cyclic neutropenia, severe congenital neutropenia, Shwachman-Diamond syndrome, and bone marrow failure syndromes, such as aplastic anemia and Fanconi anemia.4 Autoimmune neutropenia can occur when host immune response to infectious antigens cross-reacts with host cells forming antineutrophil antibodies.4 Alloimmune neutropenia occurs in newborns to circulating maternal antineutrophil IgG antibodies results in neonatal neutropenia which often resolves by 2 to 3 months of age.4 Cyclic neutropenia is an inherited neutropenia when fluctuating rates of cellular production within the bone marrow results in neutropenia in cycles of every 21 days. Severe congenital neutropenia (eg, Kostmann syndrome) is due to gene mutations leading to bone marrow neutrophil precursor arrest and lack of peripheral neutrophil production.4

CHOICE OF ANTIBIOTICS

Unlike for patients with fever and chemotherapy-induced neutropenia, no formal guidelines have been established for the empiric treatment of patients with fever and non–chemotherapy-induced neutropenia. Many of the recommendations are based on guidelines for the treatment of fever and chemotherapy-induced neutropenia and limited studies involving this patient population. Individual treatment regimens should be based on the patient's risk for development of infection, history of prior bacterial infection, response to growth factors, renal or hepatic dysfunction, medication allergies, drug availability and cost, and local epidemiology of bacterial isolates and resistance patterns. It is also important in assessing an individual child's risk to have information available about their baseline ANC, because conditions, such as benign ethnic neutropenia, are not generally associated with increased risk of serious infection.40,41

For patients who are at high risk of serious bacterial infection based on underlying etiology and duration of neutropenia (conditions associated with chronic neutropenia such as aplastic anemia, severe congenital anemia, and bone marrow failure disorders), treatment typically follows recommendations for children with chemotherapy-induced neutropenia: initial monotherapy with broad-spectrum antipseudomonal penicillin, cephalosporin, or carbapenem antibiotic is recommended. For patients with a history of type I immediate hypersensitivity reaction to penicillins, combination therapy that avoids β-lactams and carbapenems is recommended, and options include ciprofloxacin plus clindamycin or aztreonam plus vancomycin. Addition of an aminoglycoside or of vancomycin should be reserved for patients who are clinically unstable, when a resistant infection is suspected, for centers with a high rate of resistant organisms.4 For patients with transient neutropenia, there are few general guidelines supported by strong evidence. Studies suggest that transient neutropenia, that is either mild or moderate, often resolves spontaneously without severe complication of invasive infections. A careful evaluation for signs and symptoms of serious bacterial infection is warranted, which in most cases includes a blood culture and other diagnostic testing as indicated by history and physical examination. In deciding whether to initiate empiric antibiotics, and the duration of empiric therapy, the clinical appearance of the patient, severity of neutropenia, and the patient's infection history, especially at similar levels of neutropenia, are all important considerations. For patients with transient neutropenia that is only mild or moderate in severity, consideration may be given for outpatient observation and follow-up without empiric antibiotics or with a single dose of ceftriaxone depending on degree of clinical concern. Given studies suggesting severe neutropenia being more associated with a chronic course and complications, consideration may be given for empiric antibiotic coverage, which is typically similar to that used for high-risk patients.

DISPOSITION

Similar to pediatric oncology patients with high-risk chemotherapy-induced neutropenia, children with fever and high-risk non–chemotherapy-induced neutropenia should be admitted to the hospital for administration of parental antibiotics, results
of cultures and cell count trends, and ongoing reassessments. Pediatric patients with transient mild or moderate neutropenia due to viral suppression or medication side effects who are otherwise well can be discharged home with appropriate primary care provider follow-up, although many centers continue to treat these patients more conservatively with admission and empiric antibiotics.

**CONCLUSIONS**

Fever in the neutropenic child may be one of the first indicators of a life-threatening infection, and successful ED management depends on prompt and thorough assessment and reassessments, testing, and antibiotic administration to reduce morbidity and mortality. Future directions for research should be focused on pediatric risk stratification models to further tailor individual therapies.

**REFERENCES**


