Approach to febrile neutropenia in the general paediatric setting

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Febrile neutropenia is common in children with cancer and can also occur outside of the oncology setting. The present article provides an overview of febrile neutropenia from the general paediatric perspective.

In cancer patients, the principles of febrile neutropenia management have remained relatively constant. For neutropenic children with cancer, empirical antibiotics should be initiated at the onset of fever. There is insufficient evidence at this point to recommend exclusively outpatient management of the child with cancer-related febrile neutropenia.

Far less is known about febrile neutropenia in the noncancer setting. The approach to this condition should be influenced by the underlying condition and its associated risk of invasive infection and serious outcome in the absence of hospitalization and empirical antibiotic therapy.

Key Words: Cancer; Children; Empirical antibiotics; Febrile neutropenia

Febrile neutropenia is not uncommon in paediatric medicine, particularly within the cancer setting. While there continues to be ongoing research in this area, the basic principles of management have remained relatively unchanged over the past few decades.

The purpose of the present review is to provide an overview of febrile neutropenia in the general paediatric setting. While we suggest that management of these children with cancer occurs in concert with a paediatric oncologist, further understanding of the problem may enhance the general paediatrician's ability to play an active role in providing care for these children.

OVERVIEW OF FEBRILE NEUTROPENIA IN THE CANCER SETTING

The important role of empirical antibiotics in the management of the febrile neutropenic cancer patient was initially demonstrated over 30 years ago, when the introduction of empirical carbenicillin and gentamicin was associated with a dramatic reduction in Pseudomonas bacteremia mortality (1). Since that time, guidelines for the management of fever in neutropenic cancer patients have continued to evolve, but still include broad-spectrum antibiotic therapy at the onset of fever as outlined by the Infectious Diseases Society of America (2). In general, fever is defined as a single oral temperature of at least 38.3°C or a temperature of at least 38.0°C for 1 h. Neutropenia is defined as an absolute neutrophil count of 500 cells/μL or less (2). In addition to empirical antibiotic therapy, the management of febrile neutropenic children with cancer includes a thorough physical examination, blood cultures, including sampling from all lumens of a central venous line if present, and other investigations depending on presenting signs and symptoms (2). There is no single correct choice of empirical antibiotics; rather, a decision should be based on the patient's history and clinical findings, local antibiotic resistance patterns, and toxicity/cost profiles of antibiotics.

The duration of antibiotic therapy is influenced by the results of initial cultures, the ongoing clinical status of the child, and time to resolution of fever and neutropenia. In the child at low risk for infectious morbidity, antibiotics usually can be discontinued if the initial cultures are negative at 48 h, the child is clinically well, and there is evidence...
but rather based on positive cultures. It is likely that these delayed therapy if antibiotics are not initiated empirically, probability of serious infection and the consequences of chemotherapy-related febrile neutropenia to febrile neutropenia. Therefore, many clinicians and clinical care guidelines have extrapolated from the experience with information regarding fever and nonmalignancy-associated neutropenia in the cancer setting, there is relatively little data regarding either initial oral therapy or outpatient treatment for febrile neutropenia. Two large randomized controlled trials in adults demonstrated that initial in-hospital treatment of low-risk patients with febrile neutropenia, with oral ciprofloxacin plus amoxicillin-clavulanate, resulted in similar outcomes compared with intravenous ceftriaxone plus amikacin (10) or ceftazidime (11). Thus, the management of low-risk adults with cancer and febrile neutropenia now may include oral antibiotic therapy (12). However, there currently remains limited data regarding either initial oral therapy or outpatient treatment for febrile neutropenia in young children with cancer. Furthermore, specific concerns, such as adequate oral absorption of antibiotics for the initial treatment of a potentially bacteremic neutropenic child and parental preferences regarding location of treatment (13), remain unaddressed.

FEBRILE NEUTROPENIA OUTSIDE OF THE CANCER SETTING

In contrast with the large amount of literature on febrile neutropenia in the cancer setting, there is relatively little information regarding fever and nonmalignancy-associated neutropenia. Therefore, many clinicians and clinical care guidelines have extrapolated from the experience with chemotherapy-related febrile neutropenia to febrile neutropenia in other settings. The management of noncancer-related febrile neutropenia should be guided by the probability of serious infection and the consequences of delayed therapy if antibiotics are not initiated empirically, but rather based on positive cultures. It is likely that these factors differ depending on the underlying cause of neutropenia. For example, some conditions are associated with more generalized immunodeficiency, such as severe congenital neutropenia, while other conditions appear to leave the other components of the immune system relatively intact, such as neutropenia related to viral suppression. In addition, some conditions, such as aplastic anemia, are treated using immunosuppressive therapies, increasing the susceptibility of the host to invasive infections. Therefore, a single approach cannot be taken for all patients with noncancer-related neutropenia and fever. Tables 1 and 2 illustrate the groups of children likely to be at higher and lower risk for invasive infections, as well as factors that affect this risk.

For children without cancer at lower risk of invasive infection, several reports (14-17) have demonstrated a very low risk of infection if there is a short history of neutropenia and well appearance, and if the evaluation does not suggest an underlying cause for the neutropenia. This group includes most children with viral infection-associated neutropenia. Thus, it has been suggested that admission to hospital and empirical antibiotics are not necessary in this group (15-17). Those at lower risk for invasive infection but with prolonged neutropenia (for example, more than 30 days) are at increased risk for infection relative to other low-risk children, although these infections tend to be superficial (16). Some clinicians will admit these children for empirical antibiotics during febrile neutropenia. Unfortunately, controlled studies are lacking to determine the optimal strategy in this setting.

At least two groups of children with febrile neutropenia outside of the cancer setting are at high risk for infectious morbidity and mortality – namely, those with aplastic anemia and severe chronic neutropenia (a group of rare hematological disorders in which the patient’s absolute neutrophil count falls to 500 cells/μL or below, typically due to underproduction of neutrophils). Those with aplastic anemia appear to be at particular risk for invasive bacterial infection (similar in spectrum to cancer patients) and fungal infection (particularly Aspergillus species) (18). Similarly, the clinical course of severe congenital neutropenia is marked by early and severe episodes of infection, which are frequently lethal in the absence of cytokine therapy (19). Therefore, we would suggest, at the onset of fever during neutropenia, that both of these groups be assessed.

**TABLE 1**

<table>
<thead>
<tr>
<th>Lower-risk conditions</th>
<th>Higher-risk conditions</th>
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<tbody>
<tr>
<td>• Familial benign neutropenia</td>
<td>• Severe congenital neutropenia (Kostmann syndrome)</td>
</tr>
<tr>
<td>• Autoimmune neutropenia</td>
<td>• Cyclic neutropenia</td>
</tr>
<tr>
<td>• Chronic benign neutropenia</td>
<td>• Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>• Viral infection-associated neutropenia</td>
<td>• Reticular dysgenesis</td>
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<tr>
<td></td>
<td>• Myelokathexis</td>
</tr>
<tr>
<td></td>
<td>• Aplastic anemia</td>
</tr>
</tbody>
</table>

**TABLE 2**

Factors that increase the risk of invasive bacterial infection in febrile neutropenia

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Mucositis</td>
</tr>
<tr>
<td>Intravascular devices</td>
</tr>
<tr>
<td>Depression of other immune function</td>
</tr>
<tr>
<td>Abnormal neutrophil function</td>
</tr>
<tr>
<td>Longer duration of neutropenia (eg, &gt;30 days)</td>
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<tr>
<td>Lower absolute neutrophil count (eg, &lt;100 cells/μL)</td>
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<tr>
<td>Concurrent immunosuppressant therapy</td>
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</tbody>
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and receive empirical antibiotic therapy similar to that received by patients with cancer-related febrile neutropenia.

CONCLUSIONS
The principles of febrile neutropenia management have remained relatively constant. For children with cancer, empirical antibiotics should be initiated at the onset of fever. There is insufficient evidence at this point to recommend exclusively outpatient management of the child with cancer-related febrile neutropenia. Far less is known about febrile neutropenia in the noncancer setting. The approach to this condition should be influenced by the underlying disease and its associated risk of invasive infection and serious outcome in the absence of hospitalization and empirical antibiotic therapy.

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