Abstract:
Fever in a patient with an underlying malignancy who has neutropenia is a relatively common event that requires urgent attention because of the risk of associated morbidity and mortality. Although a clinically suspected or microbiologically documented bacterial infection is present in up to half of such febrile neutropenia episodes, an etiology is not identified in the rest. In a neutropenic patient, signs and symptoms of inflammation can be blunted or atypical, and infections may progress unnoticed, resulting in a life-threatening complication. Often, fever is the only manifestation of infection. For these reasons, empirical intravenous broad-spectrum antibiotics in an inpatient setting have long been the mainstay of treatment for febrile neutropenic patients. However, not all febrile neutropenic patients are at the same risk for developing infection-related complications. Addressing this variability in associated risk, risk-stratified management approaches have been suggested to minimize hospital stay, improve patients’ quality of life, and decrease related health care costs. This article reviews some guiding principles of initial management of febrile neutropenic children with cancer with a focus on risk-stratified treatment approaches, including the use of inflammatory markers to discern risk.

Keywords:
fever; neutropenia; children; cancer; risk prediction; management

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Initial Management of Fever and Neutropenia in a Child With Cancer—The Past, the Present, and the Future

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Fever and neutropenia (FN) in patients with cancer is a major cause of increased morbidity, mortality, and costs. In 1966, Bodey et al.1 published their findings that risk of infection is related to severity and duration of neutropenia. A 60% to 70% mortality rate associated with FN was reported during the 1960s and 1970s. In 1971, Schimpff et al.2 reported a striking reduction in the mortality rate with the use of empirical antibiotics in febrile neutropenic patients. After this, there were 2 studies from the National Cancer Institute showing that continuation of antibiotics even after resolution of fever in a patient who remains neutropenic and empirical addition of antifungals in patients with persistent fever with neutropenia were associated with a better outcome.3,4 This started the era of empirical broad-spectrum antibiotic use in this patient population, which, for the most part, was limited to the use of intravenous antibiotics in
an inpatient setting. Although this approach was successful in reducing morbidity and mortality in this patient population, especially over the past decade, the recognition that not every febrile neutropenic patient is at the same risk for invasive bacterial infection and clinical complications has come. This heterogeneity in part comes from differences in host vulnerability to infection and related complications based on the patients’ underlying disease and the chemotherapy they receive and their impact on the degree and duration of neutropenia. This has prompted development of approaches to ascertain ways to stratify febrile neutropenic patients as being at high or low risk for invasive infections and clinical complications and tailored management approaches based on this. Alternative management approaches to the conventional hospitalization and empirical intravenous antibiotic approach that was the cornerstone of febrile neutropenia management have included management in the outpatient setting with oral or intravenous antibiotics. The ultimate goals of risk-stratified management are to avoid unnecessary hospitalization and prolonged broad-spectrum antibiotic use and to maintain quality of life without risking morbidity or mortality. Although such approaches have made their way from the research environment into clinical practice guidelines for management of adult patients with cancer and febrile neutropenia, similar guidelines applicable to pediatric patients with cancer are awaited. Summarized in Table 1 are the axioms when managing a pediatric patient with cancer with febrile neutropenia that should serve as the guiding principles for the frontline emergency department (ED) practitioner who initially evaluates such a patient. The sections that follow focus on the initial assessment and management in the ED or any frontline clinical care setting where such patients are initially seen.

**HOST CHARACTERISTICS AND RISK OF INFECTION**

Ascertaining risk of infection in a febrile neutropenic patient starts with understanding the host. Neutrophils are the first line of defense against infection provided by innate immunity. Therefore, the risk of infections proportionately increases as the absolute neutrophil count decreases because of chemotherapy-induced toxicity, particularly when the count is reduced to less than 500 cells/mm³, which defines severe neutropenia. Profound neutropenia (absolute neutrophil count [ANC] ≤ 100 cells/mm³), in particular, has been noted as an indicator of high risk for infectious complications and as an independent predictor of invasive bacterial disease. Not only is the quantitative number of neutrophils important but so is their qualitative attribute, that is, how functional they are. This point is important to remember when seeing a noncancer patient with neutropenia, for example, related to a viral infection, where the infection-related risk would not be the same as in a patient with cancer. Although the risk of bacterial infections in patients with neutropenia has long been recognized and drives the empirical management of febrile patients with low neutrophil counts, there is increasing recognition of the risk for viral infections such as respiratory syncytial virus and cytomegalovirus and related morbidity in patients who are lymphopenic. Breaches in natural barriers to infections

### TABLE 1. Axioms of management of a patient with cancer who presents with FN.

1. Fever is assumed to be of infectious etiology until proven otherwise.
2. Characteristic signs and symptoms of infection such as focal swelling and redness at a site of infection can be absent; pain at an infection site maybe the only clue of a brewing infection.
3. Most patients with cancer have an indwelling temporary or permanent CVC, and by default, a CVC infection is always on the differential diagnosis.
4. Organisms such as coagulase-negative staphylococcus or enterococci, often disregarded as having low virulence or as potential contaminants in an immunocompetent host, can cause serious infections in a neutropenic host.
5. Untreated infections can rapidly disseminate and be fatal.
6. Co-infections with multiple organisms are not uncommon.
7. Prompt blood cultures and empirical broad-spectrum antibiotics remain the mainstay of the initial management.

CVC indicates central venous catheter.
provide portals of entry for infections. Factors that affect skin and mucosal integrity include chemotherapy-related gastrointestinal tract mucositis, skin graft-vs-host disease, and insertion of temporary or permanent indwelling central venous catheters (CVCs), which most patients with cancer have.

Finally, eliciting history of what chemotherapy the patient has received helps in understanding the components of the immune system affected, predilection to infection with certain pathogens, and organ systems at risk. For example, mucositis in recipients of high-dose cytosine arabinoside is well recognized to be associated with increased infection risk from oral/gastrointestinal pathogens such as viridans Streptococcus species. Although most chemotherapeutic agents are associated with some degree of neutropenia, some chemotherapeutic agents may also influence infection risk via other mechanisms, including lung fibrosis related to busulfan, lymphopenia with rituximab, and cyclophosphamide-induced hemorrhagic cystitis.

**SPECTRUM OF INFECTIONS AND ANTIBIOTIC RESISTANCE**

The past several decades have witnessed substantial changes in the microbial etiologies of infections identified in febrile neutropenic patients, with Gram-positive bacteria being the currently predominant isolates.\(^5\,9,10\) This change in epidemiology has been attributed to the increased use of indwelling CVCs and increased intensity of chemotherapy with resultant oral and intestinal mucositis, factors that can serve as a portal of entry for pathogens. The most commonly isolated organisms in febrile neutropenic patients with identified infections include coagulase-negative staphylococcus, Staphylococcus aureus, viridans group streptococci, Enterococcus species, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae.\(^5\)

Over the past decade, multidrug-resistant bacteria are causing an increasing number of infections in febrile neutropenic patients.\(^11,12\) The predominant resistant pathogens include extended-spectrum \(\beta\)-lactamase–producing Enterobacteriaceae, carbapenemase–producing Gram-negative bacteria such as K pneumoniae carbapenemase, methicillin-resistant S aureus (MRSA), and vancomycin-resistant Enterococcus species (VRE). The prevalence of these pathogens varies by region and center, making it essential for the treating physicians to be cognizant of resistance patterns of infections in their patient population. Risk factors for infection with a resistant pathogen include previous infection or colonization with the organism and having received care in a hospital with high rates of resistant pathogens. The empirical antibiotics regimen should provide coverage against resistant pathogens when clinically suspected. Clinicians in the ED should familiarize themselves with the choice of empirical antibiotics recommended by the infectious disease and oncology staff at their institution or call the primary institution where the patient receives his/her oncology care if different from the one where the ED is located. This also allows for the collection of additional information about the patient such as history of infections, prior organisms isolated, and other information that can further guide initial antibiotic therapy.

**THE INITIAL CLINICAL EVALUATION**

Although local signs of infection can be minimal to absent in neutropenic children, the importance of a thorough clinical evaluation by detailed history and physical examination cannot be overemphasized. A substantial proportion of FN episodes in children with cancer are characterized as fever of unknown origin (FUO), with reported rates of FUO ranging between 53 and 79%.\(^9,10,13,14\) In those with identified foci of infection, sites of infection reported included bacteremia (12 to 55%), upper respiratory tract infections (2 to 14%), gastrointestinal tract infections (5 to 8%), pneumonia (4 to 13%), and skin and soft tissue infections (1 to 13%).\(^9,10\) Therefore, initial evaluation should elicit information about any subtle changes in health that are suggestive of a brewing infection, in addition to any history of environmental exposure, contact with people with viral illnesses, and use of antimicrobial prophylaxis. In addition, the patient’s ill clinical appearance has been identified as an independent risk factor predicting development of infection-related morbidity and mortality.\(^6,15\) Measurement of rectal temperatures and rectal examination should be avoided in oncology patients because of the risk of introduction and translocation of infectious pathogens in the neutropenic host.

**LABORATORY AND IMAGING EVALUATION**

Initial laboratory evaluation of febrile and neutropenic children should include complete blood count, serum levels of electrolytes, creatinine, blood urea nitrogen, hepatic transaminases, and total bilirubin.\(^5\) At least 2 sets of blood cultures should be simultaneously collected from each lumen of the CVC, if present, and from a peripheral vein to facilitate identification of CVC-related bloodstream
infection. The use of automated blood culture systems, maximizing the amount of blood inoculated in the culture media using weight-based guidelines, and using different culture media types have been shown to optimize the yield of blood cultures. Differential time to positivity of paired blood cultures from the CVC and a peripheral vein or from 2 lumens of a double-lumen CVC can help diagnose a CVC-related bloodstream infection and guide related management such as antibiotic lock therapy. Urine cultures should also be collected if the patient manifests signs and symptoms of urinary tract infection, if he or she has a urinary catheter in place, or if the results of a urinalysis are abnormal. Culture specimens from other sites should be obtained if an infection is suspected. A chest radiograph is indicated for patients with respiratory signs or symptoms. A normal chest radiograph does not exclude the possibility of pneumonia because neutropenia might attenuate any inflammatory changes.

Role of Inflammatory Markers

Several inflammatory markers such as acute-phase proteins (eg, C-reactive protein [CRP]), pro-inflammatory cytokines (tumor necrosis factor α, interleukin 1, interferon γ, interleukin 6, interleukin 8), and soluble adhesion molecules (soluble E-selectin, vascular cell adhesion molecule 1, intercellular adhesion molecule 1) have been investigated for their ability to identify infections as the cause of neutropenic fever. Candidate markers with good discriminative power include CRP and procalcitonin.

C-reactive protein is an acute-phase protein that is synthesized by hepatocytes in response to infection or inflammation. It is produced within 4 to 6 hours after the onset of tissue injury or inflammation, doubles every 8 hours, and peaks approximately 36 to 48 hours. Its normalization is also prolonged because of a long elimination half-life of 19 hours. Its level can be affected by the degree of tissue damage caused by the underlying malignancy and by radiotherapy. It has long been used as a sensitive marker of bacterial infections. It has been reported that 2 consecutive low serum levels of CRP have a high negative predictive value (NPV) for the presence of a bacterial infection. A serum CRP concentration of 90 mg/L or greater was identified as a significant independent factor in the model developed by Santolaya et al to predict invasive bacterial infections. However, because of its slower kinetics and the discovery of other inflammatory markers, CRP has been reevaluated as a marker of infections in febrile neutropenic patients. Compared with CRP, procalcitonin increases within 3 to 4 hours after the onset of systemic infection and plateaus within 8 to 24 hours. Its level decreases 48 hours after fever onset in those responding to antibiotic therapy. Procalcitonin concentrations peak and subsequently decline more rapidly than CRP levels. Several studies have confirmed the usefulness of procalcitonin as a sensitive (67 to 94%) and specific (48 to 97%) marker in the early diagnosis of severe bacterial infections in both immunocompetent and immunocompromised patients depending on the cutoff level used. A meta-analysis by Simon et al showed that procalcitonin levels were significantly more sensitive and specific than CRP levels for differentiating bacterial from noninfectious or viral causes of inflammation. On sequential analysis of procalcitonin levels for the whole duration of the febrile episode in patients with neutropenia and cancer, it was found that it markedly increased in serious systemic infections, particularly in bacteremia and severe sepsis, and to a lower level in viral or localized infections. The highest median levels of procalcitonin were observed in cases with Gram-negative bacteremia followed by Gram-positive bacteremia or pneumonia, whereas patients with FUO or localized infections showed low or slightly elevated median levels of procalcitonin on admission and throughout the FN episode until defervescence. Persistently low procalcitonin levels 3 days daily after the onset of fever indicated high NPV of 92 to 100% for the detection of subsequent infection-related complications.

In summary, with reported high NPV, selected markers such as procalcitonin and CRP have a promising role in the early prediction of severe bacterial infections or clinical complications in febrile neutropenic episodes in children with cancer. However, until their role is further established, the Infectious Diseases Society of America (IDSA) does not recommend routine use of these tests in guiding decisions about antimicrobial use. The addition of inflammatory markers to clinical risk assessment rules needs to be further investigated for their ability to discriminate between low-risk and high-risk neutropenic patients.

Management of the Febrile Neutropenic Child

Fever in the setting of neutropenia in a child with cancer is considered a medical emergency that warrants prompt evaluation and initiation of
<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Outcome</th>
<th>Independent Predictors</th>
<th>Time of Risk Assessment</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rackoff, USA 54</td>
<td>Bacteremia</td>
<td>AMC, temperature</td>
<td>Presentation</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Cross-validation</td>
</tr>
<tr>
<td>Klaassen, Canada 15</td>
<td>Significant bacterial infection</td>
<td>AMC, temperature, bone marrow disease, general appearance</td>
<td>Presentation</td>
<td>74</td>
<td>46</td>
<td>25</td>
<td>88</td>
<td>Prospective validation</td>
</tr>
<tr>
<td>Alexander, USA 49</td>
<td>Bacteremia, other microbiologically defined infections, serious medical complications, or death</td>
<td>Anticipated duration of neutropenia, outpatient, comorbidity</td>
<td>Presentation</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No validation</td>
</tr>
<tr>
<td>Santolaya, Chile 26</td>
<td>Invasive bacterial infection</td>
<td>Serum CRP level, hypotension, relapse of leukemia, platelet count, duration since last chemotherapy leukemia</td>
<td>Presentation</td>
<td>92</td>
<td>76</td>
<td>90</td>
<td>82</td>
<td>Prospective validation</td>
</tr>
<tr>
<td>Ammann, Switzerland 51</td>
<td>Severe bacterial infection: bacteremia, UTI, pneumonia, or unexpected death from infection</td>
<td>Bone marrow involvement, clinical signs of viral infection, CRP, hemoglobin, leukocyte count, CVC, diagnosis of pre-B cell leukemia</td>
<td>Within 2 h of presentation</td>
<td>96</td>
<td>26</td>
<td>43</td>
<td>91</td>
<td>Cross-validation, scoring system</td>
</tr>
<tr>
<td>Ammann, Switzerland 52</td>
<td>Bacteremia</td>
<td>Temperature, comorbidity, leukocyte count, remission of malignancy</td>
<td>Within 2 h of presentation</td>
<td>95</td>
<td>37</td>
<td>32</td>
<td>96</td>
<td>Cross-validation</td>
</tr>
<tr>
<td>Rondinelli, Brazil 55</td>
<td>Severe infection complications (sepsis, shock, bacteremia or fungemia, or death from infection)</td>
<td>Age, CVC use, temperature, hemoglobin, clinical focus of infection, upper respiratory tract infection</td>
<td>Presentation</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No validation, scoring system</td>
</tr>
<tr>
<td>Paganini, Argentina 53</td>
<td>Mortality</td>
<td>Stage of cancer, comorbidity, bacteremia</td>
<td>Presentation</td>
<td>84</td>
<td>83</td>
<td>89</td>
<td>99</td>
<td>Cross-validation, scoring system</td>
</tr>
<tr>
<td>Wicki, Switzerland 57</td>
<td>Bacteremia</td>
<td>Intensity of chemotherapy, time since diagnosis, bone marrow involvement, central venous access device, prior FN</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Cross-validation</td>
</tr>
</tbody>
</table>
empirical intravenous antibiotics therapy. Management of the febrile neutropenic child still consists of hospitalization for intravenous empirical antipseudomonal antibiotic therapy such as cefepime, a carbapenem, or piperacillin-tazobactam. Other antimicrobials (aminoglycosides, fluoroquinolones, or vancomycin) may be added to the initial regimen in the presence of complications (such as hypotension and pneumonia) or if antimicrobial resistance is suspected or proven. Vancomycin is only indicated for suspected CVC-related infection, skin or soft-tissue infection, pneumonia, hemodynamic instability, Gram-positive bacteremia, colonization with MRSA, VRE, or penicillin-resistant *Streptococcus pneumoniae*, or for severe mucositis in the setting of fluoroquinolone prophylaxis and empirical therapy with ceftazidime. Modifications to initial empirical therapy may be considered for patients at risk for infection with antibiotic-resistant organisms. For example, extended spectrum β-lactamase–producing Enterobacteriaceae are resistant to β-lactam antibiotics and are often only susceptible to carbapenems such as imipenem or meropenem. Early addition of vancomycin or linezolid should be considered if an infection with MRSA is suspected. Linezolid or daptomycin is the agent of choice to treat infections with VRE.

The 2010 IDSA clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with fever recommend that assessment of the patient’s risk for complications of severe infection should be undertaken at presentation of fever to determine the type and route of empirical antibiotic therapy, setting of treatment (inpatient vs

<table>
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<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammann, Switzerland and Germany</td>
<td>Adverse events: serious medical complication, microbiologically defined infection, or radiologically confirmed pneumonia</td>
<td>Chemotherapy more intensive than ALL maintenance, hemoglobin, leukocyte count, platelet count</td>
<td>Within 24 h of presentation</td>
<td>92</td>
<td>45</td>
<td>39</td>
<td>93</td>
<td>Cross-validation, scoring system</td>
</tr>
<tr>
<td>Hakim, USA</td>
<td>Clinical complications</td>
<td>Clinical appearance, relapse of malignancy, race, underlying malignancy</td>
<td>Within the first hour of presentation followed by 24 h of observation</td>
<td>78</td>
<td>73</td>
<td>29</td>
<td>96</td>
<td>Cross-validation, scoring system</td>
</tr>
<tr>
<td>Hakim, USA</td>
<td>Proven invasive bacterial infection or culture-negative sepsis</td>
<td>Underlying malignancy, clinical appearance, temperature, ANC</td>
<td>Within the first hour of presentation followed by 24 h of observation</td>
<td>75</td>
<td>77</td>
<td>36</td>
<td>95</td>
<td>Cross-validation, scoring system</td>
</tr>
<tr>
<td>Semeraro, France and Belgium</td>
<td>Unfavorable outcome defined as persistence or reappearance of fever at day 3 or later or occurrence of secondary clinical or microbiological infection</td>
<td>PCT PCT at presentation, risk assessment at 48 h of presentation</td>
<td></td>
<td>80</td>
<td>64</td>
<td>60</td>
<td>82</td>
<td>Cross-validation</td>
</tr>
<tr>
<td>Agyeman, Switzerland and Germany</td>
<td>Bacteremia</td>
<td>Hemoglobin, platelet count, shaking chills, other need for inpatient care</td>
<td>At presentation and reassess after 8-24 h of inpatient management</td>
<td>100</td>
<td>15</td>
<td>18</td>
<td>100</td>
<td>Cross-validation, scoring system</td>
</tr>
</tbody>
</table>

AMC indicates absolute monocyte count; NR, not reported; PCT, procalcitonin; UTI, urinary tract infection.
outpatient), and duration of antibiotic therapy.\textsuperscript{5} Risk assessment can be done by using clinical criteria of high risk that include prolonged (>7 days) and profound (ANC \textless 50,000/mm\textsuperscript{3}) neutropenia and the presence of comorbid conditions such as hemodynamic instability or by a formal risk classification using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system.\textsuperscript{5,47} The MASCC score was developed and validated in adults and assigns weighted scores to the following characteristics: burden of febrile neutropenia with no or mild symptoms (5 points), no hypotension (5 points), no chronic obstructive pulmonary disease (4 points), solid tumor or hematologic malignancy with no previous fungal infection (4 points), no dehydration requiring parenteral fluids (3 points), burden of febrile neutropenia with moderate symptoms (3 points), outpatient status (3 points), and age younger than 60 years (children not included) (2 points).\textsuperscript{5,47} Based on this classification, high-risk patients require hospitalization for intravenous empirical antibiotic therapy. On the other hand, low-risk patients may be treated using oral and/or outpatient empirical antibiotic therapy. It is clear, however, that some of these criteria are not applicable to the pediatric population. Therefore, the IDSA guidelines, which were based on adult literature, might not be directly applied to pediatric oncology patients with FN.

Related to this ongoing need, many studies have been conducted in pediatric oncology patients to identify risk prediction models for febrile neutropenia. However, these studies used different designs, methods, time of risk assessment, definitions, and outcomes.\textsuperscript{6,15,26,27,48-56} Table 2 summarizes the published risk prediction models in pediatric febrile neutropenic patients. In contrast to the adult risk prediction studies that consistently evaluated the patients’ risk for clinical complications, most of the pediatric studies assessed their risk for microbiologically proven or clinical infections. For example, in a prospective multicenter study, Santolaya et al\textsuperscript{27} proposed and validated a risk prediction rule for pediatric patients with “invasive” bacterial infection. The identified independent risk factors were collected at the time of initial evaluation of FN and included serum CRP levels of 90 mg/L or greater, hypotension, relapsed leukemia, thrombocytopenia of less than 50,000 platelets/mm\textsuperscript{3}, and receipt of chemotherapy within 7 days of presentation with FN. Invasive bacterial infection was defined as bacteremia, positive results of bacterial culture of a specimen obtained from a usually sterile site (e.g., indwelling catheter, blood, urine, or cerebrospinal fluid), severe sepsis, or focal organ involvement in a child with hemodynamic instability, and severe malaise. This prediction rule took into account not only the type of risk factors but also the number. For example, the absence of risk factors was associated with invasive bacterial infection in 2% of the FN episodes. Two or more risk factors at the time of presentation with FN were associated with a risk greater than 48%. Based on this model, a child with an FN episode can be considered at high risk for invasive bacterial infection if he or she has 2 or more risk factors or a serum CRP level of 90 mg/L or greater, hypotension, or relapse of leukemia as sole factors; the child can be considered at low risk if he or she has an absence of risk factors, a platelet count of 50,000/mm\textsuperscript{3} or less, or recent chemotherapy as sole factors. This prediction rule performed with a sensitivity of 90%, specificity of 65%, and positive predictive value (PPV) and NPV of 75% and 87%, respectively. A prospective multicenter validation of this risk assessment rule, which was applied within the first 24 hours after presentation with FN, showed a sensitivity of 92%, specificity of 76%, PPV of 82%, and NPV of 90%.\textsuperscript{26} This model misclassified 11% of the febrile neutropenic patients as low-risk patients while they developed invasive bacterial infections.\textsuperscript{26}

Unfortunately, not all the developed risk prediction models have been prospectively validated. Attempts to validate various predictive rules in different clinical settings have failed to show a reproducible discriminatory power.\textsuperscript{58-60} Therefore, awaiting development of guidelines for the risk-stratified management of pediatric febrile neutropenia, the common practice continues to consist of hospitalization for empirical broad-spectrum intravenous antibiotics therapy.

Risk-Stratified Management Approaches There are several selective management strategies suggested for febrile neutropenic patients: (1) early discharge with the use of oral antibiotics after initial treatment in the hospital with oral\textsuperscript{61-63} or intravenous antibiotics\textsuperscript{54-71} and (2) outpatient treatment only with oral antibiotics.\textsuperscript{72-79}

Oral vs Intravenous Empirical Antibiotics The first report of treatment for febrile cancer patients with oral antibiotics was published in 1991 after adults with lymphoma were instructed to initiate oral pefloxacin plus amoxicillin-clavulanic acid at home at the onset of fever.\textsuperscript{80} Since then,
several studies have confirmed the successful role of oral antibiotics as a treatment option for neutropenic febrile patients who are at low risk for morbidity and mortality. In a recent systematic review and meta-analysis of 15 clinical trials, initial oral or sequential intravenous followed by oral antibiotics therapy was a safe and effective management option for carefully selected low-risk febrile neutropenic patients. Ciprofloxacin alone or in combination with amoxicillin-clavulanate acid or penicillin was the most frequently evaluated oral regimens. Oral therapy has the advantages of reduced cost, facilitation of outpatient management, and avoidance of catheter use, hence reducing the possibility of CVC-related infection. Therefore, the 2010 IDSA guidelines for the treatment for febrile neutropenic patients recommend the use of ciprofloxacin plus amoxicillin-clavulanate for empirical treatment for patients who are classified as low risk using the criteria described previously. However, it is important to emphasize that the evidence supporting this recommendation is vastly derived from adult studies. Similar data that support initial outpatient empirical oral therapy in febrile neutropenic children remain insufficient. Hence, initiation of empirical intravenous antibiotic therapy in an inpatient setting for this population remains the prevalent standard of care, and it is not recommended that ED providers discharge children with FN on oral antibiotics unless there are local institutional guidelines developed specifically for this purpose. The outpatient oral empirical antibiotic therapy approach was investigated by Petrielli et al. One hundred sixteen febrile neutropenic episodes in children with solid tumors or non-Hodgkin lymphomas were randomized to receive either oral ciprofloxacin or intravenous ceftriaxone, both given on an outpatient basis. More than half of FN episodes were attributed to clinically documented infections. Only 1 case of bacteremia was noted. The successful responses to treatment were similar in the 2 groups (83% vs 75%), as was the need for readmission (7% vs 4%). In another study by the same group of investigators, empirical oral ciprofloxacin in an outpatient setting was found to be a successful treatment option in 75% of the pediatric FN episodes. However, most of these episodes were described as being caused by urinary tract infections. The published pediatric data provide a more supportive role for the use of oral antibiotic therapy as a continuation to an initial observation period of treatment with intravenous antibiotics followed by early discharge.

In general, caution should be exercised when comparing the results of various studies because the definitions of the evaluated outcomes and the criteria used to assess the response to therapy vary considerably.

**Inpatient vs Outpatient Setting**

Outpatient treatment with oral antibiotics has many advantages: reduced cost, avoidance of catheter use and secondary infection, improved quality of life, and low risk of infection with resistant nosocomial pathogens. However, this management approach should be cautiously used because of the potential risk of life-threatening complications, such as septic shock, away from the hospital. Early discharge of children while receiving oral antibiotic treatment after an initial period of in-hospital observation of treatment with intravenous broad spectrum antibiotics has been extensively investigated in carefully selected low-risk patients. The children evaluated in these studies were discharged (whether randomized or not) on oral antibiotic immediately after initial evaluation or after a certain period of observation that ranged from 3 to 16 hours to as long as 48 to 120 hours if they were classified as “low risk.” In addition, the oral antibiotic regimens varied and included ciprofloxacin, cloxacillin plus cefixime, cefixime alone, ofloxacin plus amoxicillin-clavulanate, and ciprofloxacin plus amoxicillin. The success rate of oral outpatient therapy ranged from 72 to 98%. Definitions of “successful therapy” included resolution of the FN episode without modification of therapy, resolution of fever without rehospitalization, or absence of recurrent fever or newly documented bacterial infection. Whether using intravenous or oral antibiotics, outpatient therapy after an initial inpatient management of febrile neutropenic children has been shown to be the most cost-saving while maintaining the same high level of safety and efficacy standards. However, up to 28% of patients have been reported to fail outpatient therapy as defined previously. Emergency department practitioners are the front line medical care providers for those who fail outpatient therapy. Hospitalization and diagnostic studies such as blood cultures and other symptom-directed diagnostic tests to identify the etiology of infection, including the possibility of a nonbacterial etiology or bacterial infections resistant to or not covered by the antibiotics being given on an outpatient basis, should be done.

All of the studies used different low-risk definition criteria selected by clinical judgment. Santolaya et al. were the first group of pediatric investigators to incorporate a prospectively validated risk prediction rule into clinical decision making. After 24 to
36 hours of in-hospital observation, 149 febrile neutropenic children with cancer classified at low risk for invasive bacterial infection were randomly assigned either to early discharge and outpatient management or to continued hospitalization until resolution of the FN episode. There was no difference between the 2 groups in the percentage of patients who developed invasive bacterial infection. A favorable outcome was reported for 95 and 94% of the outpatients and inpatients, respectively.

SUMMARY

Prompt administration of empirical broad-spectrum intravenous antibiotic therapy in an inpatient setting at the onset of fever has been and still remains the standard management approach for children with cancer presenting with FN. Published experience on the use of less aggressive approaches that includes oral antibiotic therapy or management in the outpatient setting has guided the use of the same in clinical practice and inclusion in clinical practice guidelines applicable to adult patients with cancer. Differences in study design, including definitions of outcome measures, the lack of consistent prediction variables that have emerged as common themes across models, and the absence of a prediction model that has been cross-validated in different sites/settings remain some of the reasons why risk-stratified management approaches in children with cancer are still not the standard of care. Pending further studies and development of guidelines for risk-stratified initial management of FN, frontline management of fever with neutropenia remains based on the axioms outlined in Table 1.

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