Risk of Serious Bacterial Infection in Isolated and Unsuspected Neutropenia

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Abstract

Objectives: The objective was to determine the risk of serious bacterial infection (SBI) among children without underlying risk factors for SBI who present to the emergency department (ED) for evaluation and have unsuspected and isolated neutropenia.

Methods: This was a retrospective consecutive chart review from October 1995 through September 2003. All patients aged 0–21 years presenting to the ED of an urban tertiary children's hospital, who were documented to have neutropenia (defined as an absolute neutrophil count [ANC] of <1,000 cells/µL) without known underlying risk factor for SBI were eligible for inclusion. SBI was defined as growth of a pathogen from culture of blood, urine, or cerebrospinal fluid (CSF).

Results: There were 3,179 children with an ANC of <1,000/µL during the study period. Of these, 1,888 had no underlying immunodeficiency or central venous catheter (CVC). Fifteen of 453 (3.3%; 95% confidence interval [CI] = 1.9% to 5.4%) infants less than 3 months of age had SBI: seven with bacteremia, four with meningitis, and eight with urinary tract infections. SBI was rare among children over 3 months of age (18 of 1,435; 1.3%; 95% CI = 0.7% to 2.0%): one had bacteremia, none had meningitis, and 13 had urinary tract infections.

Conclusions: Children older than 3 months of age without underlying immunodeficiency or CVC presenting to the ED and unexpectedly found to have isolated neutropenia are not at high risk of SBI. Infants less than 3 months of age have similar risk of SBI as febrile infants of same age.

Keywords: neutropenia, sepsis, serious bacterial infection, bacteremia, absolute neutrophil count

Children with depressed immune function are known to be at increased risk of serious bacterial, viral, and fungal infections. Adults and children with chronic or immune-mediated neutropenia are susceptible to mucocutaneous and pyogenic infections.1–3 The risk of infection is known to be directly correlated with the duration and the extent of neutropenia among patients with cancer.4–6 The quantitative relationship of leukocytes to important infections among patients with leukemia has been well known since the mid 1960s,4 but to date there have been very few studies regarding the risk of infection in neutropenic children without underlying disease.7,8 These studies have had very few cases, and none of them have considered the presence of neutropenia on emergency department (ED) presentation, or many of the cases did not have neutropenia in the absence of other hematologic derangements.7,8

The identification of neutropenia may represent the initial presentation of an underlying new immune-mediated or congenital neutropenia syndrome.9,10 Neutropenia may also occur as a result of consumption of neutrophils or depletion of bone marrow response in the child with severe sepsis or septic shock, especially in the neonate.11 In addition, isolated neutropenia may occur as a result of intercurrent viral or postviral bone marrow suppression. Even though isolated neutropenia occurs commonly in children who are otherwise well,12 to the best of our knowledge there exist no data in the literature to suggest whether the identification of unexpected neutropenia represents an increased, diminished, or unchanged risk of serious bacterial infection (SBI), mainly bacteremia, as it does among those with underlying malignancy, bone marrow insufficiency, and/or indwelling foreign bodies, such as central...
venous catheters (CVC). The purpose of this study was to determine the prevalence of SBI for children presenting to a pediatric ED where a complete blood count (CBC) revealed neutropenia as part of their evaluation for any complaint.

METHODS

Study Design
This was a retrospective cohort study of all ED patients aged 0–21 years. The institutional review board of the Children's Hospital, Boston, approved the study, and the requirements for informed consent were waived.

Study Setting and Population
We included all children with blood sent from the ED of Children's Hospital, Boston, for a period of 8 consecutive years from October 1, 1995, to September 30, 2003, with an identified absolute neutrophil count (ANC) of less than 1,000 cells/µL. All of these patients had the medical record reviewed for demographic, historical, and laboratory data, such as the presence of fever, age at presentation, presence of presumed risk factors for SBI, total white blood cell count, ANC, and the results of urine, blood, and/or cerebrospinal fluid (CSF) culture, if they were sent as part of the ED evaluation.

Patients with moderate or severe neutropenia were selected for the purpose of our study based on the risk of bacterial infection as it occurs for patients with cancer and an ANC of <1,000. In the oncology population, the predominant risk of SBI with fever occurs when the ANC is less than 500. The CBC was obtained at the discretion of the treating provider. However, in our ED from 1995 to 2000, many of these were drawn as part of a management algorithm for febrile children less than 36 months of age. After the year 2000, a CBC was routinely recommended only for these febrile young children only if they had not received three doses of the conjugate pneumococcal vaccine.

Patients were included for analysis if they had isolated neutropenia, defined as neutropenia in a patient without a known previous episode of neutropenia, persistent or recurrent, due to any cause, and with otherwise normal age-appropriate platelet and hemoglobin counts. Exclusion criteria were those that presumably can place the patient at increased risk of an SBI. Excluded patients were those where the ED record documented that the patient had a disorder such as immunodeficiency; idiopathic or autoimmune neutropenia; chemotherapy-induced neutropenia; newly diagnosed, suspected, or known malignancies; or bone marrow failure of any etiology. Bone marrow failure was defined as the presence of two or more hematologic cell lines being below age-appropriate norms. If the patient later presented with one of these defined disorders, the initial visit was still considered for analysis, because this diagnosis was not known at the time of evaluation. Additionally, patients were excluded if the patient had a CVC or other implantable device that may be susceptible to colonization or infection, a congenital heart disease associated with an increased risk of bacterial endocarditis, or known genitourinary tract abnormalities.

Study Protocol
An SBI was defined as the growth of bacteria from urine, blood, and/or CSF. A urine culture was considered positive if there were greater than 10,000 colony-forming units (CFU) per milliliter of a single pathogen on a catheterized specimen, greater than 50,000 CFU of a single pathogen from a clean voided specimen, or greater than 1,000 CFU of a single pathogen from a suprapubic tap. A blood or CSF culture was considered positive if a single pathogen was isolated. Coagulase-negative staphylococci were not considered pathogens, as our study population did not include children with CVC or other implantable devices. Radiographically diagnosed pneumonia was not considered because it can be difficult to distinguish viral versus bacterial pneumonia with certainty.

Data Analysis
SPSS 14 (SPSS Inc., Chicago, IL) was used for all analyses of data except for calculation of the 95% confidence intervals (CIs), which was done using STATA 8.0 (Stata-Corp, College Station, TX).

RESULTS

During the study period, 3,204 patients presented to the ED for evaluation and were found to have an ANC of less than 1,000/µL. Twenty-five were excluded because of age greater than 21 years, and 1,291 were excluded because of an identifiable factor or condition (Table 1) that could predispose them to an SBI, leaving 1,888 patients who met study criteria. Of these, 1,112 (59%) were male. The median age was 0.7 years (10th, 90th percentile = 0.1, 5.2 years). At least one specimen was sent for culture in 1,317 of these patients during their ED evaluation. Blood was obtained for culture from 1,254 (66%). Urine and CSF were obtained for culture from 676 (36%) and 325 (17%), respectively. There was growth of a pathogen from eight blood cultures (0.6%; 95% CI = 0.3% to 1.3%), 23 urine cultures (3.4%; 95% CI = 2.1% to 5.1%), and four CSF cultures (1.2%; 95% CI = 0.3% to 3.1%). These 35 positive cultures occurred in a total of 31 patients, for a 2.4% (95% CI = 1.6% to 3.3%) prevalence of SBI. The age groups, numbers of cultures sent and numbers of positive cultures are shown in Table 2.

Of the 1,888 patients, 600 were less than 3 months of age, and 453 of these infants had at least one specimen sent for culture. Seven of the eight positive blood cultures, eight of 23 positive urine cultures, and four of four positive CSF cultures occurred in the 453 children less than 3 months of age who had at least one specimen sent. The rates of SBI among these infants less than 3 months of age were 1.6% (7 of 434; 95% CI = 0.7% to 3.2%) for blood culture, 2.2% (8 of 363; 95% CI = 1.0% to 4.3%) for urine culture, and 1.5% (4 of 274; 95% CI = 0.4% to 3.7%) for CSF culture. Overall, 15 infants had SBI for a 3.3% prevalence of SBI (15 of 453; 95% CI = 1.9% to 5.4%). Table 3 shows the pathogens that grew in these infants.

There were 898 children 3 months to 2 years of age among whom 663 had at least one specimen sent for culture. The overall rate of SBI was 2.0% (13 of 663;
Patients were stratified into three groups according to degree of neutropenia, and there was no increased rate of SBI in patients who had an ANC of <500 versus those with an ANC of 501–1000. Because only one patient over 3 months of age had bacteremia and none had meningitis, we evaluated the subgroup of children less than 3 months of age specifically. Eleven patients had an ANC of <200 cells/µL; 73 had an ANC of 200–499 cells/µL, and 516 had an ANC from 500 to 999 cells/µL. Of the 15 patients with any positive culture, two (2.7%, 95% CI = 0.8% to 9.5%) had an ANC between 200 and 499 cells/µL, and 13 (2.5%, 95% CI = 1.5% to 4.3%) had an ANC between 500 and 999 cells/µL. There was still no association in regards to the ANC and risk of SBI in those children less than 3 months, with overlapping CIs.

Among the 600 infants less than 3 months of age, four did not have a temperature recorded in the medical record, which included one of the infants with a positive culture. Of 380 infants who were neutropenic and afebrile, 68% had at least one culture done, in contrast to 98% of infants who were neutropenic and either febrile or hypothermic. Five infants less than 3 months of age with a recorded temperature of >38.0°C had no cultures sent to our laboratory. As expected, the absence of fever was associated with a decrease in the overall risk of SBI, with one of 247 (0.4%, 95% CI = 0.1% to 2.3%) of the afebrile neutropenic infants who had a culture sent having a pathogen identified from culture, compared to 13 of 211 (6.2%, 95% CI = 3.6% to 10.3%) of the febrile/hypothermic neutropenic infants (0.4% vs. 6.2%, p < 0.0005).

**DISCUSSION**

Clinical practice regarding management of children with isolated neutropenia is unclear and thus subject to variable styles of practice. Physicians may find themselves extrapolating from the oncology or neonatal literature, or from their own experience with patients with clinically evident septic shock, and struggle to apply this experience to the otherwise well-appearing child found to have neutropenia in the process of the child’s evaluation for any illness. This may result in unnecessary studies, empiric antibiotic therapy, or even hospital admission, each of these with attendant risk. This analysis was undertaken to assess for the prevalence of SBI among children who presented to the ED.

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Table 1: Potential Risk Factors for SBI

<table>
<thead>
<tr>
<th>Potential Risk Factor*</th>
<th>Percent, N = 1,291</th>
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<tbody>
<tr>
<td>Bone marrow failure†</td>
<td>76</td>
</tr>
<tr>
<td>CVC</td>
<td>61</td>
</tr>
<tr>
<td>Chronic neutropenic syndrome†</td>
<td>10</td>
</tr>
<tr>
<td>Immunodeficiency§</td>
<td>8</td>
</tr>
<tr>
<td>Congenital heart disease with risk of SBE</td>
<td>1.2</td>
</tr>
<tr>
<td>Urogenital foreign body or abnormality</td>
<td>1.2</td>
</tr>
<tr>
<td>VP shunt or intrathecal catheter</td>
<td>0.9</td>
</tr>
<tr>
<td>Other†</td>
<td>0.4</td>
</tr>
</tbody>
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CVC = central venous catheter; SBE = spontaneous bacterial endocarditis; VP = ventriculoperitoneal.

*Some patients had more than one factor.
†Bone marrow failure defined as chemotherapy induced, infiltrative, or aplastic.
‡Cyclic, autoimmune, or idiopathic neutropenia; Kostmann’s; Schwannman-Diamond; etc.
§Immunodeficiency = HIV, DiGeorge, immunoglobulin deficiencies, or medication related, etc.
||One HbSC disease, two HbSS disease, one recent postop, one asplenia.

95% CI = 1.0% to 3.3%). The specific rates of SBI were 0.2% (1 of 640; 95% CI = 0 to 0.9%) for blood culture, 4.8% (12 of 249; 95% CI = 2.5% to 8.3%) for urine culture, and 0% (0 of 41; 95% CI = 0 to 8.6%) for CSF culture. No patient had a positive culture from more than one site. The pathogens identified in the urine in these patients are shown in Table 3.

The single child identified with bacteremia in the 3-month to 2-year age group was a 9-month-old female who presented to the ED febrile to 38.2°C, with obvious clinical evidence of septic shock including tachypnea, retractions, tachycardia, poor perfusion, and a metabolic acidosis. She was admitted to the intensive care unit with a diagnosis of septic shock, and *Streptococcus pneumoniae* was recovered from the blood culture.

There were 390 patients aged 2 to 21 years, of whom 201 had at least one specimen sent for culture. The specific rates of SBI were 0% (0 of 180; 95% CI = 0 to 2.0%) for blood culture, 4.7% (3 of 64; 95% CI = 1.0% to 13.1%) for urine culture, and 0% (0 of 10; 95% CI = 0 to 31%) for CSF culture. The overall rate of SBI was 1.5% (3 of 201; 95% CI = 0.3% to 4.3%). Table 3 shows the pathogens in the urine in these patients.
and had a blood count for any reason that revealed an unexpected neutropenia.

Neutropenic infants less than 3 months of age did experience a similar rate of bacteremia (1.6%) and meningitis (1.5%), but interestingly a lower rate of urinary tract infection (2.2%), when compared to previously published data from the same ED, which showed the rates at 1.3, 0.3, and 8.3%, respectively, in infants 0–89 days of age. While this study does not evaluate the cause of neutropenia for these children, it does identify the relatively common nature of this finding and that neutropenia in this population, even in the presence of fever, should not by itself prompt any further empiric testing for infection or empiric antimicrobial therapy. Any diagnostic testing and treatment should be directed toward specific symptoms or signs that may point to a focus of infection, as it would for any child without neutropenia.

To the best of our knowledge, there has been no previous study that has looked specifically at the risk of SBI in patients with isolated neutropenia. Very few studies have evaluated patients who present with neutropenia and bacteremia. Leibovici et al. reported in her review a higher mortality in these patients, presumed by her to be secondary to failure of bone marrow to mount an appropriate neutrophil response to infection. Bonadio et al. found that in 68 children with neutropenia and fever, those who looked well on presentation had a negative blood culture, while 30% of the ill-appearing children had positive blood or CSF cultures. Three of these patients were less than 3 months of age, while two with group B streptococcal disease and one with Haemophilus influenzae type B, while the other two were less than 1 year of age with H. influenzae type B. Serwint et al. described 91 cases in children with leukopenia (<5,000/µL) and/or neutropenia (ANC < 1,000/µL). Of the five with positive blood cultures, one was clinically septic, one had leukemia, one did not have ANC performed, and those with an ANC of <1,000/µL also had platelets counts of <150,000.

Vlacha and Fekete described 143 cases of neutropenia where only 26% had neutropenia on presentation. In addition, isolated neutropenia was not always present, and bacterial infection was presumed in the cases without mention of microbial culture data.

We believe that our study demonstrates that neutropenia among children without risk factors for an SBI, who present with isolated neutropenia, are not at an increased risk of bacteremia. A urine culture may have utility in the child older than 3 months, as it does in the febrile child without neutropenia.

### LIMITATIONS

This was a retrospective review, which relies on documented information, which may not always be complete. As a result, the true prevalence of SBI in children who present to the ED with isolated neutropenia cannot be accurately known, because not all patients had cultures sent. It is indeed likely that the true prevalence is lower, but in fact, it could also be higher, since data regarding pretreatment with antibiotics or results of cultures obtained at an outside hospital prior to arrival at our institution may not have been recorded in the medical record. In addition, it is possible that the rate of fever is underestimated from review of the medical record. We did not apply any illness severity scoring and would not want to extend our results to the ill-appearing child, who by the nature of the presentation will warrant further diagnostic and therapeutic intervention. Chest radiographs with findings of pneumonia were not considered in this review, and thus, it is possible that some children will have pneumonia associated with neutropenia. However, presumably, the chest x-ray was indicated by a clinical concern. Previous antibiotic exposure, which may affect culture results, was not recorded and can affect true prevalence. Finally, follow-up data were not available for these children as to whether they presented to another institution later and were found to have an underlying immune or blood disorder.

This study does not address the potential causes of neutropenia, and it is likely prudent to obtain another CBC within 1 to 2 weeks in follow-up of children found to have neutropenia, to document marrow recovery or initiate further diagnostic evaluation if the neutropenia persists.

### CONCLUSIONS

Our study is the first to review the risk of serious bacterial infection with isolated moderate or severe neutropenia on presentation to the ED. Neutropenia is associated with bacteremia and meningitis in infants less than 3 months of age, but not to a larger extent than otherwise febrile infants of the same age. Conversely, there is a very low yield from culture of blood or cerebrospinal fluid from the neutropenic child older than 3 months of age without known predisposing risk factors for serious bacterial infection. In the absence of an identifiable bacterial source, children with isolated neutropenia do not have an increased risk of serious bacterial infection.