The Risk of Severe Bacterial Infection in Non-Immunocompromised Neutropenic Infants and Children from 3 Months to 18 Years of Age: A 5 Years Case-Control Study with Literature Review

Keywords: Severe Bacterial Infections (SBI), Methylmalonic Acid (MMA) and Homocysteine (HCY), Large Granular Lymphocytes (LGL), Absolute Neutrophil Count (ANC)

ABSTRACT

Only a few reports have looked into the risk of invasive bacterial infection in children with neutropenia that is not malignancy related. The objective of the current study was to determine the clinical significance of neutropenia as a predictor of serious bacterial infection (SBI) in immune-competent children. We conducted a retrospective case-control study including children 3 months to 18 years of age with fever > 38.1°C hospitalized or presenting to the emergency department, who had neutropenia < 1000ANC/mL and had a blood culture taken, were matched for age with the consecutive febrile patients for whom also a blood culture was taken. The main outcome was the rate of SBI. SBI’s were more prevalent among the control group than in the group of children with neutropenia, 14/40 and 5/40, respectively (P = 0.018). Acute-phase reactants including CRP and platelets were higher in the control group. We concluded that immune-competent patients with fever and moderate neutropenia do not carry a higher risk for SBIs compared with patients with fever who do not have neutropenia.
INTRODUCTION

Neutropenia in children above 1 year old is defined as an absolute neutrophil count (ANC) < 1500/mL. Neutropenia may be divided into mild (1000 to 1500 ANC/mL), moderate (500 to 1000 ANC/mL), and severe (< 500 ANC/mL). In children aged from 2 weeks to 1 year; neutropenia is defined as ANC < 1000ANC/mL. The presence of fever and newly documented neutropenia in a previously healthy child may cause concern. Fever and neutropenia can result from diverse etiologies. Marrow suppression caused by a viral infection is the most common cause of mild to moderate neutropenia. Neutropenia caused by viral infections begins in the first few days of the infection and is self-limited [1]. Severe bacterial infections are known to cause neutrophilia but may also cause neutropenia. Drugs including antibiotics and anticonvulsants may also cause neutropenia. Severe hereditary diseases such as Kostmann syndrome may cause neutropenia; the molecular basis of over 12 hereditary diseases causing neutropenia is known. Different ethnic origins may be associated with leukopenia and neutropenia. Finally, neutropenia may be the inadvertent presenting symptom of leukemia or cyclic neutropenia. Neutropenic fever is a common problem among oncological patients, especially that receiving chemotherapy. In this group of patients, a pathogen may be identified in 10% to 30% of cases. Management of fever in neutropenic cancer patients has remained relatively constant and includes broad-spectrum antibiotic treatment; this management has been decreased gram-negative bacterial sepsis mortality rate from 80% a few decades ago to its present rate of 1% to 3%. In contrast to a large amount of the literature on febrile neutropenia in the oncological setting, there is relatively little information regarding fever and non-malignancy associated neutropenia. Therefore, many clinicians have extrapolated from the data on chemotherapy-related febrile neutropenia to febrile neutropenia which is not malignancy related. Only a few reports have looked into the risk of invasive bacterial infection in children with neutropenia that is not malignancy related [11, 15]. So to determine the clinical significance of neutropenia as a predictor of serious bacterial infection (SBI) in immune-competent children we conducted a retrospective case-control study including children 3 months to 18 years of age with fever >38.1 °C (axillary) hospitalized or presenting to the emergency department. Patients who had neutropenia <1000ANC/mL and had a blood culture taken were matched for age with the consecutive febrile patients for whom a blood culture was taken. As overview of neutropenia in children the absolute neutrophil count (ANC) is equal to the product of the white blood cell count (WBC) and the fraction of polymorphonuclear cells (PMNs) and band forms noted on the
differential analysis: \( \text{ANC} = \text{WBC (cells/microliter)} \times \text{percent (PMNs + bands)} \div 100 \). Neutrophilic metamyelocytes and younger forms are not included in this calculation. An ANC < 1500/microliter (< 1.5 x 10^9/L) is the generally accepted definition of neutropenia for adults, as well as the threshold for neutrophil toxicity and infectious risk following chemotherapy. The normal range for the ANC varies somewhat with age. The lower limit of normal is 5000/microliter (5.0 x 10^9/L) for the first week of life, then falls to 1000/microliter (1.0 x 10^9/L) between two weeks and one year of age [17]. Neutropenia is often categorized as mild, moderate or severe, based upon the level of ANC. Mild neutropenia corresponds to an absolute neutrophil count between 1000 and 1500/microliter, moderate between 500 and 1000/microliter and severe with less than 500/microliter. The risk of infection begins to increase at an ANC below 1000/microliter. However, the risk is also dependent upon the adequacy of the marrow reserve pool of granulocytes. Leukopenia and granulocytopenia are generally used interchangeably with neutropenia, although they are somewhat different: First, leukopenia refers to a low total white blood cell count that may be due to any cause (e.g., lymphopenia and/or neutropenia); however, almost majority of leukopenic patients are neutropenic since the number of neutrophils is so much larger than the number of lymphocytes. Second, granulocytopenia refers to a reduced absolute number of all circulating cells of the granulocyte series (e.g., neutrophils, eosinophils, and basophils); however, almost majority of granulocytopenic patients are neutropenic since the number of neutrophils is so much larger than the number of eosinophils and basophils. Third, agranulocytosis medically means the absence of granulocytes, but the term is often incorrectly used to indicate severe neutropenia (i.e., ANC < 500/microliter). Effect of race and ethnic origin. The above definition of neutropenia (i.e., an ANC < 1500/microliter) is applicable for all ages and ethnic groups except newborn infants who have an elevated ANC for the first few days of life [18, 19] and certain populations (e.g., African Americans, Yemenite Jews, Ethiopians, and some Arabs), who normally have slightly lower WBC and ANC [20, 23].

Data from the 1999 to 2004 United States National Health and Nutritional Examination Survey (NHANES) indicated a prevalence of neutropenia for the following population groups [23]: Black participants 4.5%, white participants 0.79 %, and Mexican-American participants 0.38 %. This issue was also studied in a group of 261 healthy women of varying ethnicities recruited in New York City. The incidence of neutropenia (ANC < 1500) according to their country of origin was [24]: United States Black 10.5 %, Haiti 8.2 %, Barbados/Trinidad-Tobago 6.4 %, Jamaica 2.7 %, the Dominican Republic zero %, and the United States or
Europe White zero %. Neutropenia in African Americans has two reasons for a lower ANC in African Americans: those with an ANC below 2000/microL have defective granulocyte release from an otherwise normal bone marrow; the majority with ANC above 2000/microL have a compromised bone marrow reserve of PMNs as assessed by measuring the maximum ANC increment after the administration of hydrocortisone [20], or following endurance exercise [25]. However, bone marrow aspirates are normal and progenitor release is increased. Furthermore, there is no propensity to infections, indicating that the neutropenia is benign [20, 26, 27]. In some cases, neutropenia has been traced to a common West African allele, a single nucleotide polymorphism in the Duffy antigen/receptor chemokine gene (DARC), which acts as a receptor for certain pro-inflammatory cytokines [28, 29]. Presence of this Duffy null state protects against malaria and has been shown to provide a survival advantage in leukopenic HIV-infected persons of African ancestry [30]. Benign familial (ethnic) neutropenia in those patients with what has been called benign familial neutropenia or benign familial leukopenia may not generate a leukocytosis during infection but are otherwise normal; they generate a fever and tachycardia during infection similar to controls, do not have an increased incidence of infection, and do not have an increased risk for febrile neutropenia secondary to myelosuppressive therapy [21, 22, 26]. Given that benign familial neutropenia has been reported in several ethnic groups, including Yemenite Jews, Blacks of South African extraction, West Indians, and Arab Jordanians, this condition may not be distinct from that described above, and may best be termed & benign ethnic neutropenia [21,26]. The bone marrow reserves of these patients are normal [20, 26, 27]. The causes of isolated neutropenia can be classified by mechanism or by the etiologic agent. Neutropenia results from four basic mechanisms: first decreased production, second ineffective granulopoiesis, the third shift of circulating PMNs to vascular endothelium or tissue pools and forth enhanced peripheral destruction. Confirmation of one of these mechanisms requires leukokinetic studies employing bone marrow cultures, radionuclide tagging of blood PMNs, and other monitoring devices not readily available unless outside the research laboratory. The classification of neutropenia according to marrow reserve status is useful when thinking about the mechanism of neutropenia and propensity to infection.

However, classification based on whether the neutropenia is acquired or congenital and grouped by known causes or associations provides a practical means to approach the differential diagnosis of these disorders in a clinical setting. That said, there is great overlap in the disorders listed, which is why we favor a classification based on marrow reserve. There
are several named disorders that lead to neutropenia with normal cellularity, late myeloid arrest, and little or no propensity to infection. These likely represent various interactions between subtle genetic differences and environmental factors. Apoptosis of marrow precursors is now recognized as a common mechanism for many acquired and congenital neutropenias. Acquired neutropenias have many causes such as infection, drugs, and immune disorders being the most common. As with all neutropenias, the danger to the patient depends on the marrow status. Post-infectious neutropenia; may represent the most common cause of acquired isolated neutropenia. A number of bacterial, viral, parasitic and rickettsia infections are responsible. In most instances, particularly with viral infections, the neutropenia is short-lived and rarely results in bacterial super-infection. Mechanisms include redistribution, sequestration and aggregation, and destruction by circulating antibodies. Hepatitis B virus, Epstein-Barr virus and human immunodeficiency virus can be associated with more severe and protracted neutropenia. Drug induced neutropenia and agranulocytosis occurs as an adverse idiosyncratic reaction and is the second most common cause of neutropenia. The true incidence of drug induced neutropenia is not known; the reported incidence of the rare, more severe, agranulocytosis ranges from approximately 1 to 10 cases per million populations per year. The usual definition excludes known cytotoxic agents and requires that the drug has been administered within four weeks of the onset of neutropenia. The drugs with the highest risk of inducing severe neutropenia include Clozapine, the Thionamides (Antithyroid drugs), and Sulfasalazine. These drugs appear to cause neutropenia either by immune mediated destruction of circulating neutrophils by drug dependent or drug induced antibodies or by direct toxic effects upon marrow granulocytic precursors. Nutritional neutropenia and marrow failure can be seen with severe vitamin B12 deficiency, folate deficiency, and copper deficiency. Vitamin B12 and folate deficiency, as well as inborn errors of B12 metabolism, are well known to be associated with neutropenia and anemia [31]. Dietary deficiency of these vitamins is relatively uncommon in children and adolescents. However, the diagnosis should be thought of in chronically ill children, especially if they have frequent or prolonged hospitalizations or have malabsorption syndromes including the short gut. The diagnosis should not be excluded simply because patients are receiving vitamins in parenteral nutrition solutions. The actual requirements for these vitamins are not known in critically ill patients, so it is best to monitor for a deficiency. B12 deficiency can also be seen in exclusively breastfed infants of mothers who have a B12 deficiency. Diagnosis of B12 deficiency is particularly important because severe developmental delay can occur if the severe B12 deficiency is not treated. B12 and folate deficiency are best detected by measuring
Methylmalonic Acid (MMA) and Homocysteine (HCY). Both are elevated with B12 deficiency, and HCY alone is elevated in folate deficiency. This is important because serum levels of B12 and folate can be normal in the face of deficiency as detected by MMA and HCY [32]. Copper deficiency and subsequent low ceruloplasmin are a well-recognized cause of isolated neutropenia as well as pancytopenia. While not often thought of, it is not uncommon in children with short gut syndromes receiving parenteral nutrition, patients with malabsorption, and post-gastric bypass surgery. It can cause a marrow picture indistinguishable from myelodysplasia. Particularly in young children completely supported via parenteral nutrition, copper is often removed from the intravenous solution and not reintroduced, leading to deficiency [33, 36]. Critically ill patients who have prolonged hospitalizations should be screened for these deficiencies if they present with neutropenia, even if they are receiving parenteral nutrition. Primary immune disorders; antineutrophil antibodies mediate neutrophil destruction either by splenic sequestration of opsonized cells or by complement mediated neutrophil lysis. Immune neutropenia can occur as a myeloid specific syndrome or in association with other cytopenias. Antineutrophil antibodies are involved in the pathophysiology of the neutropenia caused by some infections, drug exposure, and immune deficiencies. In addition, there are specific primary immune disorders characterized by neutropenia and antineutrophil antibody production. Assessment of immune neutropenias can be particularly problematic because the propensity to infection may be more related to the underlying immune disorder than to the neutropenia. Thus, while immune disorders may have antibody mediated neutropenia, they may also be associated with vasculitis, leading to mucosal ulcers. Isoimmune neonatal neutropenia; can occur in newborn infants secondary to transplacental passage of IgG antibodies directed against neutrophil-specific antigens inherited from the father. The pathogenesis of this disorder is similar to that of Rh hemolytic disease, except that it can occur with the initial pregnancy [37]. The neutropenia is usually noted in an otherwise healthy infant.

Most infants have only mild neutropenia with a mean duration of seven weeks, but moderate to severe neutropenia can also occur. Transient neutropenia in newborns is due to transplacental passage of antibodies of broad specificity from women with the past or present autoimmune neutropenia. The neutropenia is usually mild and disappears after a few weeks [38]. Chronic autoimmune neutropenia; occurs primarily in infants and children under age four and is also called chronic benign neutropenia of infancy and childhood. Most patients present with recurrent infections. Specific treatment of neutropenia is not required. Many
patients remain free of infections and maintain a normal lifestyle with no or minimal medical intervention. Spontaneous remission with the disappearance of autoantibodies is common. Chronic idiopathic neutropenia; also known as benign chronic neutropenia, is used to describe chronic neutropenia for which there is no obvious cause. In contrast to autoimmune neutropenia, which is primarily a disease of infants and young children, chronic idiopathic neutropenia tends to occur in late childhood or adulthood and does not undergo spontaneous remission. Serologic abnormalities and evidence of antibody production have been found in 30 to 40 percent. These patients most often have a benign course despite the degree of neutropenia. The presence of normal marrow reserve may explain the lack of significant infections. Pure white cell aplasia; is a rare disorder characterized by the complete disappearance of granulocytopoietic tissue from the bone marrow. It is often associated with thymoma and is due to the presence of antibody-mediated GM-CFU inhibitory activity. Such individuals have no marrow reserve and are at risk for infection because of the neutropenia. Other autoimmune disorders; that are associated with neutropenia include T-gamma lymphocytosis (large granular lymphocyte syndrome) and Felty's syndrome. In the former disorder, there is infiltration of the bone marrow with Large Granular Lymphocytes (LGL), most often due to a clonal expansion of cytotoxic T-cells and often associated with rheumatoid arthritis. LGL disease has markedly decreased marrow reserve as well as autoimmune vasculitic components. Complement activation; the exposure of blood to artificial membranes, as in dialysis and extracorporeal membrane oxygenation, may result in complement activation in vivo. The complement is typically produced by the classical complement activation pathway and induces neutrophil aggregation and adherence to endothelial surfaces, often in the lung. Neutropenia and cardiopulmonary symptoms typically occur shortly after exposure to the membrane. This complication can be prevented during hemodialysis by using biocompatible membranes. Hypersplenism; from any etiology can result in neutropenia, due to splenic trapping [23]. The severity of neutropenia is related to the size of the spleen and rarely is sufficient to result in severe infection. Anecdotal information is available indicating the ability of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage-colony-stimulating factor (GM-CSF) to improve absolute neutrophil counts in patients with severe hypersplenism-associated neutropenia [40, 41]. Bone marrow disorders; a number of diseases affecting the bone marrow is associated with neutropenia. In most cases, such as aplastic anemia, leukemia, myelodysplasia, and postchemotherapy, the neutropenia is not an isolated defect and is associated with varying degrees of anemia and thrombocytopenia. Examination of the peripheral smear and a bone

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marrow aspirate with biopsy are indicated when more than one cell line is involved. Congenital neutropenias; rare primary neutropenias occur and when associated with severe recurrent infections as in the severe congenital neutropenias, can be treated successfully with hematopoietic growth factors. These syndromes include severe infantile agranulocytosis, myelokathexis, Shwachman-Diamond-Oski syndrome, Chediak-Higashi syndrome, and reticular dysgenesis. The diagnosis is made by examination of the bone marrow, which reveals myeloid hypoplasia (Genetics) Congenital neutropenia can also be seen with certain inborn errors of metabolism such as glycogen storage disease and with some of the primary immune deficiency states. Cyclic neutropenia is characterized by recurrent mouth infections and regular oscillations in the numbers of blood neutrophils, monocytes, eosinophils, lymphocytes and reticulocytes at approximately 21 day intervals. It usually presents in childhood, as a familial syndrome, but there is a subset of patients with onset in adulthood. Treatment is largely supportive and G-CSF has been effective in preventing infection and reducing symptoms. Myeloperoxidase deficiency; in many clinical laboratories, neutrophils are identified on the white blood cell differential by virtue of their positivity for myeloperoxidase. Patients with myeloperoxidase deficiency may then be erroneously considered as having severe neutropenia. The propensity of infection; most studies evaluating the significance of the degree of neutropenia on the risk of infection have been in cancer patients, in whom an increased risk of infection becomes apparent at an ANC < 1000/microliter, is greater at < 500/microliter, and greatest at < 100/microliter [3]. In addition to the ANC, factors that influence a patient's susceptibility to infection include: first; duration of neutropenia, second; a function of the neutrophils, the third; ability of the bone marrow to respond to an infectious insult and forth; the function of other components of the immune system. These factors contribute to the differences in infectious complications that are observed among hematology patients with neutropenia and cancer patients with therapy-induced neutropenia. For example, neutropenia in the oncology patient is related to cytotoxic therapy and generally is self-limited, whereas, in the patient with severe aplastic anemia, neutropenia may be prolonged for months to years. However, the neutropenic oncology patient often has defects in several arms of the immune system because of the underlying disease and/or chemotherapeutic agents used, and these defects may not exist in the hematology patient. So the lack of literature in healthy children led us consider starting our study.

Citation: Bassem Abou Merhi MD et al. Ijsrm.Human, 2017; Vol. 7 (3): 11-25.
MATERIALS AND METHODS

A retrospective case control study over 5 years conducted case control study including children 3 months to 18 years of age in the pediatric emergency department and ward at Rafik Hariri University Hospital, Beirut, Lebanon between January 1, 2010 and December 31, 2015 with fever (>38.1 °C) (Axillary) who had a complete blood count and blood culture performed as part of their evaluation and whose ANC was 1000/mL or less were included. The study protocol was approved by the Hospital Ethics Committee and IRB Lebanese University-Faculty of Medical Sciences. Exclusion criteria were those children who suffered from a known underlying chronic condition that placed them at an increased risk of bacterial infections (e.g., malignancy or primary immunodeficiency), children known as neutropenic, children who had received a course of antibiotics within 48 hours before taking their blood count and blood culture, and children with pancytopenia. We studied what we collect mainly: CBCD, CRP, Platelets, Gender, Age, investigations such as X-rays, CT, U/S, cultures, duration of admission, special symptoms as diarrhea, rash, URI symptoms (sneezing, cough). The following infections were considered SBIs for the purpose of this study: bacteremia, bacterial meningitis, bacterial gastroenteritis, pyelonephritis, pneumonia, mastoiditis, osteomyelitis, and septic arthritis.

Statistical Analysis

Data analysis of the studied population was described through categorical and continuous variables. Categorical variables of cases and controls were compared using the K2 test Continuous variables of the 2 groups were compared using the Student t-Test.

RESULTS

A total of 40 patients with fever and neutropenia were compared with the randomized patients matched for age, for which a complete blood count and blood culture were dropped. Demographic and clinical data of the 2 groups (Table 1) showed that there was no significant difference in age and sex between the groups. Duration of fever before the presentation was shorter in the control group and the rash was more prevalent in the neutropenic group of patients. No difference was found in the rest of the parameters examined.
Table 1: Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Neutropenic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>23 males</td>
<td>22 males</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean = 29.725</td>
<td>Mean 29.61</td>
<td>0.4936</td>
</tr>
<tr>
<td>Max Time</td>
<td>Mean = 39.365</td>
<td>Mean 39.5</td>
<td>0.0159</td>
</tr>
<tr>
<td>Duration of fever</td>
<td>Mean 1.475 days</td>
<td>Mean 3.075 days</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Rash</td>
<td>2/40</td>
<td>10/40</td>
<td>0.012249</td>
</tr>
<tr>
<td>URI</td>
<td>18/40</td>
<td>16/40</td>
<td>0.65103</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11/40</td>
<td>9/40</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Blood tests including hemoglobin level, platelet count, results of blood smear, CRP values, and WBC differential counts, significant statistical differences were observed in the median platelet count, which was higher in the control group than the group of children with neutropenia, 377.45 and 280.1, respectively (P < 0.0001). CRP values were also higher in the control group than in the group of patients with neutropenia, 79.875 and 31.225 mg/mL, respectively (P < 0.0001). As expected, the total white blood count and the absolute neutrophil number were significantly higher in the control group. Absolute monocyte count was also higher in the control group (Table 2).

Table 2: Blood Tests

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (Mean)</th>
<th>Neutropenic (Mean)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Mean 11.3405</td>
<td>Mean 11.62875</td>
<td>0.4618</td>
</tr>
<tr>
<td>WBC</td>
<td>Mean 15945</td>
<td>Mean 5297.85</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Mean 10750</td>
<td>Mean 779.25</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Mean 1380</td>
<td>Mean 689.15</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Mean 3659.75</td>
<td>Mean 3796</td>
<td>0.015</td>
</tr>
<tr>
<td>Platelets</td>
<td>Mean 377.45</td>
<td>Mean 280.1</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>CRP</td>
<td>79.875</td>
<td>31.225</td>
<td>&lt; 0.00001</td>
</tr>
</tbody>
</table>

SBIs were found in 14/40 patients in the control group and 5/40 patients in the neutropenic group of patients (P = 0.018). Although all types of infections, including bacteremia, pneumonia, and pyelonephritis were more common in the control group, no statistically
significant difference was found among the groups when examining each subtype of infection separately (Table 3).

Table 3: Blood, Urine Cultures, and Pneumonia, SBI

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Neutropenic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>2/40 positive</td>
<td>0/40</td>
<td>0.152</td>
</tr>
<tr>
<td>Urine culture</td>
<td>5/40 positive</td>
<td>2/40</td>
<td>0.235</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7/40</td>
<td>3/40</td>
<td>0.1762</td>
</tr>
<tr>
<td>SBI</td>
<td>14/40</td>
<td>5/40</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Concerning the type of bacteria, it was found that control group had more positive cultures versus the neutropenic group but with no significant P-Value (Table 4).

Table 4: Type of Infection

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Neutropenic</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>E. Coli 1/2</td>
<td>None</td>
<td>0.15078</td>
</tr>
<tr>
<td>Strep Pneum 1/2</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine culture</td>
<td>Klebsiella 1/5</td>
<td>E. Coli 1/2</td>
<td>0.235222</td>
</tr>
<tr>
<td>Proteus 1/5</td>
<td>Klebsiella 1/2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

In the current study, we have demonstrated that neutropenic fever among previously healthy nonimmunocompromised children is not a risk factor for the development of an SBI. Even more so, the risk of an SBI was lower in the group of children with neutropenia than in the group of patients with fever without neutropenia. Studies regarding the prevalence of SBI among neutropenic patients have thus far been conducted mostly on oncological patients treated with chemotherapy. Data regarding SBIs in nonimmunocompromised patients is scarce. A prospective study of 161 previously healthy children aged 3 months to 14 years (mean age 3 years) with febrile neutropenia sought to determine the clinical course, complications, and outcomes. The majority of patients had mild to moderate transient neutropenia (most resolved in < 30 days) associated with viral infections. Twenty-five (15.5 percent) of 161 patients had chronic neutropenia (>180 days); an infectious agent was
associated with the initial diagnosis in only five children. Two years after the diagnosis of febrile neutropenia, 6 of 143 children (4.2 percent) available for evaluation remained neutropenic without a cause identified. Three of these patients suffered infectious complications: periorbital cellulitis, *Pseudomonas* sepsis with labial abscess, and a severe bacterial infection in a patient diagnosed with myelodysplastic syndrome. Another retrospective study examined the outcomes of patients presumed to be immunocompetent who presented to a pediatric primary care clinic or pediatric emergency department with fever and newly identified moderate to severe neutropenia, leukopenia, or both [7]. This study found that leukopenia and neutropenia did not necessarily occur together. The prevalence of bacteremia was 5.5 %, and while neither the degree of neutropenia nor leukopenia predicted bacteremia, nearly all bacteremia children were toxic-appearing at presentation. The prevalence of other infections was 14 %, and the most common of these was pneumonia. In contrast to the pre-mentioned studies, our study included only neutropenic patients; we excluded patients for whom a blood culture was not drawn and patients who were on previous antibiotic treatment, and offered an age-matched control group. All types of bacterial infections (bacteremia, pneumonia, urinary tract infection, and dysentery) were much more common in the control group compared with the group of neutropenic patients. However, when we examined each group of infections separately, no statistically significant difference was found. We believe this disparity can be explained by the small number of patients that were formed when separating each group of infections. Hardly any differences in the clinical and demographical characteristics were found between the 2 study groups. The only differences were the length of disease before medical examination and the finding of rash on physical examination. In the group of patients with neutropenia, the number of days with the fever before medical evaluation in the hospital was significantly higher than in the control group. A possible explanation is that the patients in this group suffered from milder, more trifle illnesses and therefore medical evaluation by a physician was sought at a later stage. This is strengthened by the higher prevalence of rash among the neutropenic patients, possibly explained by the commonness of viral exanthemas. Platelet count was significantly higher in the control group. A possible reason is that thrombocytes are an acute phase reactant and therefore were higher in the group of patients in which bacterial infections were indeed more prevalent. We presume that the higher CRP levels in the control group states for the same reason.
These combined findings, that is, rash and a longer period of fever in the neutropenic group versus higher platelet counts and CRP levels in the control group, support our main finding of more SBIs in the control group compared with the neutropenic group.

CONCLUSION

Our study results support the conclusion that the risk of an SBI in patients with mild to moderate neutropenia who are presumed to be healthy is low. Accordingly, it is doubtful whether such patients should be treated empirically with antibiotics, considering normal initial workup (such as urinalysis and chest X-rays). We consider the risk of serious infection in otherwise healthy children with isolated transient neutropenia (e.g. in the setting of a viral illness or in association with drugs such as antibiotics or anticonvulsants) is reflected in the general appearance of the child. Ill appearing children are at greater risk for serious infection. The well appearing child can be managed safely with an age appropriate treatment of any minor acute illness and frequent follow-up. The ill-appearing child should receive empiric intravenous antibiotic therapy if necessary.

REFERENCES

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