The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–5, 2017

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2017.10.022

ELSEVIER

Brief Report

OUTCOMES OF IMMUNOCOMPETENT CHILDREN PRESENTING WITH FEVER AND NEUTROPENIA

Osnat Wittmann, MD,* Ayelet Rimon, MD,* Dennis Scolnik, MB, CHB,† and Miguel Glatstein, MD*

*Division of Pediatric Emergency Medicine, Department of Pediatrics, Dana-Dwek Children Hospital, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel and †Divisions of Pediatric Emergency Medicine and Clinical Pharmacology and Toxicology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Reprint Address: Miguel M. Glatstein, MD, Pediatric Emergency Medicine, Dana-Dwek Children Hospital, Sackler School of Medicine, Tel Aviv University, 6 Weizman Street, Tel- Aviv 64239, Israel

☐ **Abstract—Background: Neutropenia may alarm clinicians and prompt extensive evaluation in children with fever, even in immunocompetent patients. Objective: Our aim was to determine outcomes in previously healthy febrile children presenting to the emergency department with severe neutropenia. Methods: We reviewed data from infants and children aged 3–36 months with fever and severe neutropenia, defined as a peripheral neutrophil count <500 × $10^3/\mu$L, at our institution between January 1, 2012 and December 31, 2015. We compared our results to those from a similar study of children with a peripheral neutrophil count of 500–1000 × $10^3/\mu$L. Results: Severe neutropenia was recorded in 52 patients; severe bacterial infection (SBI) was found in 1 (1.9%), but none had a positive blood culture. Incidence of SBI was not different from that found in a study of similar patients with moderate neutropenia. Conclusions: Immunocompetent patients with fever and severe neutropenia do not carry a higher risk for SBI compared to patients with fever and moderate neutropenia. Such patients could potentially be followed closely with serial blood counts to ensure bone marrow recovery, without the use of antibiotics.**

☐ **Keywords—neutropenia; severe bacterial infection; bacteremia; pneumococcal vaccine**

INTRODUCTION

Children and adults with a chronically suppressed immune system are at increased risk for developing septicemia or a serious focal infection (1). Neutropenia is usually defined as an absolute neutrophil count (ANC) < 1.5 × $10^3/\mu$L, but when the ANC falls below 0.5 × $10^3/\mu$L, patients manifest an increased susceptibility to infections caused by normal skin, respiratory, or gastrointestinal tract flora (2). With an ANC of 0.5–1.0 × $10^3/\mu$L, susceptibility to infection is less significant, although the host's ability to combat more typical infections is impaired (3). Neutropenic fever is commonly encountered among oncology patients, especially those receiving chemotherapy (3,4). In this group of patients, a pathogen can be identified in 10%–30% of cases, and management is relatively well defined (5). Management of febrile neutropenic children cannot be based on the ANC alone because other factors contribute to the severity of the clinical course (1). Isolated neutropenia is also relatively common in febrile children who were previously well, and pediatricians often become concerned that these children may be presenting in an immune-compromised state (6–9). In contrast to the large amount of literature on febrile neutropenia in the oncology setting, there is a dearth of information regarding fever and neutropenia in otherwise well children (7). Some physicians admit these patients for treatment and administer empirical antibiotics, even though controlled studies determining optimal strategy in this setting are lacking (5). Recent evidence has suggested that immunocompetent patients with fever and moderate neutropenia (0.5–1.0 × $10^3/\mu$L) do not carry a higher risk for severe bacterial infections (7). In most instances, both the fever

RECEIVED: 12 July 2017; FINAL SUBMISSION RECEIVED: 23 October 2017;
ACCEPTED: 26 October 2017

and the neutropenia are the result of viral illness, serious secondary bacterial infection is unlikely, and admission to the hospital for antibiotic therapy is probably unnecessary (1). However, because the neutropenia cannot usually be attributed with certainty to a viral illness, other causes of neutropenia have to be carefully sought.

The aim of this study was to determine outcomes in previously healthy febrile children presenting to the emergency department with severe neutropenia. We were particularly interested in investigating whether patients with severe neutropenia represented a population with more severe outcomes than those with a moderate neutropenia. We review our experience and compare outcomes with previous studies.

METHODS

A retrospective chart review was performed in the pediatric emergency department of a university-affiliated hospital. The study was approved by the hospital's Research Ethics Board. We included children aged 1.5–36 months, admitted to the pediatric emergency department of our institution between January 1, 2012 and December 31, 2015, with fever > 38°C, who had a complete blood count and blood culture performed as part of their evaluation, and whose ANC was $< 0.5 \times 10^3/\mu$L. Patients younger than 1.5 months were excluded because many of these infants will undergo a full sepsis workup and empiric antibiotic therapy without regard to results of their blood count. Outcomes of patients 1.5–3 months of age were compared to those of older patients to assess whether there was any observable effect on outcomes of neutropenic infants who were still very young. Children were also excluded if they suffered from a known underlying chronic condition that placed them at an increase risk of bacterial infection, for example, malignancy, sickle cell disease, cyclic neutropenia, primary immunodeficiency, cystic fibrosis, steroid therapy, or chronic neutropenia, if they had received a course of antibiotics within the 48 h before blood sampling, or had severe anemia or thrombocytopenia. Demographics; clinical and laboratory findings, including blood and urine culture results; C-reactive protein, leukocyte count; and differential were recorded, as well as the radiology report, if pneumonia was diagnosed.

A complete blood count and differential were performed 2–4 months later on all patients and none had recurrent neutropenia. No patient developed cyclic neutropenia during a follow-up of 12 months.

DEFINITIONS

1. Occult bacteremia: The presence of pathogenic bacteria in the blood of a well-appearing febrile infant in the absence of an identifiable focus of infection.
2. The following infections were considered serious bacterial infections (SBIs): pneumonia, meningitis, septicemia, urinary tract infection, abscess, bacterial gastroenteritis, acute mastoiditis, lymphadenitis, bacteremia, septic arthritis, and osteomyelitis (10).
3. Pathogenic bacteria: These included *Streptococcus pneumonia, Staphylococcus aureus, group A Streptococcus, Enterococcus* spp*, Neisseria meningitis, Enterobacteriae, Salmonella* spp*, Pseudomonas* spp*, Haemophilus influenzae, Campylobacter*, and *Escherichia coli.*
4. Bacterial contaminants: coagulase-negative *Staphylococcus*, α-hemolytic streptococci, *Micrococcus, Corynebacterium*, and *Neisseria* other than *Neisseria meningitis* or *Neisseria gonorrhea.*
5. Pneumonia was diagnosed if the pediatric radiologist reported lobar or segmental airspace consolidation representing consolidative pneumonia, or patchy reticulonodular infiltrates representing bronchopneumonia.

Clinical and laboratory data were analyzed and compared to data from a retrospective case–control study conducted in a pediatric population with the same routine immunization coverage in the same geographical area as ours; they analyzed patients with moderate neutropenia of ANC of 500–1000 $\times 10^3$/mL aged 3–36 months (7).

Categorical and continuous variables were analyzed using *t*-test and Fisher's exact test the Mann-Whitney U test as appropriate. A p value < 0.05 was considered statically significant. Statistical analysis was performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

RESULTS

One hundred and ninety-nine patients presented with severe neutropenia during the study period; 124 had a chronic underlying condition and an additional 23 had received antibiotics within the preceding 48 h or did not have a blood culture performed, leaving 52 immunocompetent patients with fever and severe neutropenia for inclusion in the study. Most had fever < 39°C for < 5 days (Table 1). Mean age ± standard deviation was 9.96 ± 1.59 months (range 1.5–36 months; median 8 months), and 25 (48%) were boys. The majority of the patients were 3–36 months of age (37 of 52 [71.2%]), and 39 (75%) were hospitalized with a mean stay of 5.1 days. No patients were admitted to the intensive care unit and there were no fatalities.

Blood test results are shown in Table 2. Twenty-two patients (42%) underwent chest radiography, but only