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The Prevalence of Serious Bacterial Infections in Neutropenic Immunocompetent Febrile Children

Rosy Hao[1,2], Mona Saleh[1,2], Tian Liang[1,2], Neh Molyneaux[1,2], Isaac Gordon[1,2], Chiemelie Anyachebelu[1,3], and Richard Sinert[1,2]

1 Department of Emergency Medicine, Kings County Hospital, New York City Health and Hospitals, USA
2 Department of Emergency Medicine, Downstate Health Sciences University, State University of New York, USA
3 Department of Pediatrics, Kings County Hospital, New York City Health and Hospitals, USA

***Corresponding author:** Rosy Hao

haor2@nychhc.org

Department of Emergency Medicine, Kings County Hospital, New York City Health and Hospitals, USA.

Tel: (214)-755-2589

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Abstract

Context: Febrile neutropenic immunocompromised children are at a high risk of Serious Bacterial Infections (SBI).

Objective: This systematic review and meta-analysis report the prevalence of SBI in healthy children with febrile neutropenia.

Data source: PubMed, EMBASE, and Web of Science from their inception to August 2020.

Study selection: Patients with an Absolute Neutrophil Count (ANC) <1000 cells/mm^3 up to 18 years of age presenting to the ED with a chief complaint of fever (temperature >38.0 C) and who had a workup for SBI as defined by each study.

Data abstraction: Data from individual studies was abstracted by a subset of the authors and checked independently by the senior author. Any discrepancies were adjudicated by the joint agreement of all the authors. We calculated the prevalence of SBI by using the number of SBI's as the numerator and the total number of febrile events in patients as the denominator. Bias in our studies was quantified by the Newcastle Ottawa Scale.

Results: We identified 2,066 citations of which five studies (2269 patients) met our inclusion criteria. None of our reviewed studies consistently tested every included patient for SBI. Spectrum bias in every study resulted in a wide range of the SBI prevalence of 1.9% (<0.01% - 11%) similar to non-neutropenic children.

Limitations: All of our studies were retrospective and many did not consistently screen all subjects for SBI.

Conclusion: If the clinical suspicion is low, the risk for SBI is similar between febrile healthy neutropenic and non-neutropenic children.

Keywords: Bacterial infection; X-ray; Neutropenic

Abbreviations: SBI: Serious Bacterial Infections; ANC: Absolute Neutrophil Count; IQR: Interquartile Range; ED: Emergency Department; PRISMA: Preferred Reporting Items for Systematic Review and Meta-analyses; ICC: The Intraclass Correlation Coefficient; CBC: Complete Blood Count; CXRs: Chest X-rays; CSF: Cerebral Spinal Fluid; UTI: Urinary Tract Infection.

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Introduction

Febrile neutropenia in a child who is immune-compromised is a medical emergency and management includes initiating empiric antibiotics upon the onset of fever [1]. Children with a depressed immune system are at higher risk of serious bacterial infection (SBI) [2]. In healthy children with isolated febrile neutropenia, studies have shown that the prevalence of SBI is between 2-8%

[3-7]. Although the data are limited, viral infections have been considered the most frequent etiology in isolated neutropenia in previously healthy children [7]. The lack of a unified consensus for management based on strong clinical evidence creates a challenge for the clinician treating these patients.

Identifying the prevalence of SBI and risk factors among healthy children with isolated febrile neutropenia would allow physicians to adopt a less aggressive approach to management. In healthy febrile children with isolated neutropenia, empiric treatment with antibiotics is potentially harmful [8]. Patients are at risk for iatrogenic complications which include but are not limited to allergic reactions, IV infiltrations, risk of exposure to other infectious agents in the hospital, an increase in resistance pattern, and an overall rise in healthcare costs [8,9].

The objective of this systematic review and meta-analysis is to determine the prevalence of SBI in children who are otherwise healthy presenting with isolated febrile neutropenia to further guide clinical practice.

Literature Review

Study design

We conducted a systematic review of studies that reported the prevalence of serious bacterial infections in febrile neutropenic otherwise healthy children without other risk factors. The systematic review was conducted using the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [10] The protocol for this systematic review can be accessed in PROSPERO with the registration number: CRD42020186862 [11]. **(Table 1)**.

Search strategy

The design and manuscript structure of this systematic review conforms to the recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [12]. In conjunction with a medical librarian, we searched the medical literature up to June 2020 in PUBMED, EMBASE, and Web of Science using the search terms “epidemiology, prevalence, bacteremia, neutropenia” (**Appendix-1**). We also searched the following online databases to avoid missing relevant unpublished articles and abstracts: Clinicaltrials.gov, open grey, OpenDOAR, BASE, WorldWideScience.org, Mednar, and HSO. We also completed a hand search of references of included studies. We limited studies to the English language only.

Data from individual studies were abstracted by RH, MS, TL, NM, IG, CA and checked independently by RS. Any discrepancies were adjudicated by the joint agreement of all the authors.

Patients

We included studies that examined patients with an ANC < 1000 cells/m^3 up to 18 years of age presenting to the ED with a chief complaint of fever (temperature >38.0 C) and those who had a workup for Serious Bacterial Infection as defined by each study.

Laboratory tests

Laboratory tests for bacteremia, meningitis, urinary tract infection included cultures of blood, CSF, and urine, which were collected before starting antibiotics as empiric treatment. We included studies with all types of cultures with no restriction with respect to the time the culture results were reported.

Outcomes

Serious Bacterial Infections were defined by each study, which meant the growth of a specific organism after a defined period of time.

Quality assessment

Table 2 indicates the results of each individual study quality assessment according to the Newcastle-Ottawa scale [13]. The included studies were not cohort-studies in design and therefore not every category and/or item included in the scale is applicable, but we have summarized the results of the applicable categories of Selection and Outcome. Two reviewers (TL, CA) rated the study quality according to the checklist and their responses were analyzed to quantify interrater reliability. A third reviewer was available in case there was a discrepancy in the selection of the articles. Intra class Correlation Coefficient (ICC)

Table 1 Description of reviewed studies.

Study	Design	Population	Definition of SBI
Bonadio et al. [4]	A retrospective chart review	**Inclusion**: Fever > °C Age: Not specified Neutropenia • ANC< 1000 cells/microliter	Not defined
		Exclusion: Antibiotic use within 72 hrs of evaluation with negative cultures Underlying malignancy or chronic systemic disease.	
		Sample Size: N=63	
		Median Age: N/A	

Study	Design	Population	Definition of SBI
Melendez et al. [5]	Retrospective Cohort	**Inclusion**: Fever: Not required Age: < 21 years old Neutropenia ● ANC< 1000 cells/microliter	Bacteraemia Urinary Tract Infection Meningitis
		Exclusion: Patients with increased risk of SBI: Known underlying immunosuppression Chemotherapy-induced neutropenia Newly diagnosed, suspected, or known malignancies Bone marrow failure of any etiology. CVC or any implantable device Congenital heart condition or genital urinary abnormalities with increased risk for bacterial	
		Sample Size: N=1,317	
		Median Age: 8.4 months	
Barg et al. [6]	Retrospective Case-control	**Inclusion**: Fever>38°C Age: 3 months-18 years old Neutropenia ● ANC< 1000 cells/microliter Well-appearing CBC and blood culture	Bacteraemia Urinary Tract Infection Pneumonia Meningitis Septic Arthritis Bacterial Gastroenteritis Mastoiditis Osteomyelitis
		Exclusion: Known underlying immunosuppressive condition Antibiotic use within 48 hrs. Known history of neutropenia Pancytopenia	
		Sample Size: N=71	
		Median Age: 14 months	
Pascual et al. [7]	Retrospective Chart review	**Inclusion**: Fever > 38°C Age: <18 years old Neutropenia ● ANC< 1000 cells/microliter	Bacteremia Urinary tract infection Pneumonia Meningitis Bacterial Synovitis Bacterial Pleural Effusion
		Exclusion: Known underlying immunosuppressive condition	
		Sample Size: N=190	
		Median Age: 8.5 months	
Wittman et al. [3]	Retrospective Chart review	**Inclusion**: Fever >38°C Age: 1.5 months - 36 months Neutropenia ● ANC< 500 cells/microliter	Bacteremia Urinary tract infection Pneumonia Meningitis Septic Arthritis Septicemia Abscess Bacterial Gastroenteritis Acute Mastoiditis Lymphadenitis Osteomyeolitis
		Exclusion: Chronic condition with increased bacterial infection risk Antibiotics within 48 hrs Severe anemia or thrombocytopenia	
		Sample Size: N=52	
		Median Age: 8 months	

Abbreviations: SBI: Serious Bacterial Infection, °C: Degrees Celsius, ANC: Absolute Neutrophil Count, N/A: Not Available, CVC: Central Venous Catheter.

Table 2 Newcastle-Ottawa Rating Scale.

Selection					Comparability	Outcome		
Studies	**Representativeness of Exposed Cohort**	**Selection of non-exposed cohort**	**Ascertainment of Exposure**	**Outcome of Interest Not Present at the Start**	**Comparability of Cohorts**	**Assessment of Outcome**	**Follow-up**	**Adequacy of Follow up of Cohorts**
Bonadio et al. [4]	A*	N/A	A*	A*	N/A	A*	A*	A*
Melendez et al. [5]	A*	N/A	A*	A*	N/A	A*	A*	A*
Barg et al. [6]	A*	N/A	A*	A*	N/A	A*	A*	A*
Pascual et al. [7]	A*	N/A	A*	A*	N/A	A*	A*	A*
Wittmann et al. [3]	A*	N/A	A*	A*	N/A	A*	A*	A*
Selection:								
1) Representativeness of the exposed cohort—A=truly representative of the average number of febrile children in the community. B=somewhat representative of the average number of febrile patients in the community. C=selected group of users eg nurses, volunteers D=no description of the derivation of the cohort.								
2) Selection of the non-exposed cohort A=drawn from the same community as the exposed cohort. B=drawn from a different source. C=no description of the derivation of the non-exposed cohort.								
3) Ascertainment of exposure A= secure record (e.g., surgical records) B=structured interview C=written self report D=no description.								
4) Demonstration that outcome of interest was not present at start of study A=yes* B=no.								
Comparability:								
1) Comparability of cohorts on the basis of the design or analysis a=age B= study controls for any additional factor (geographic area).								
Outcomes								
1) Assessment of outcome a) independent blind assessment* B=record linkage* C=self report D=no description.								
2) Was follow-up long enough for outcomes to occur A=yes (select an adequate follow up period for outcome of interest) B=no.								
3) Adequacy of follow up of cohorts a) complete follow up-all subjects accounted for b) Small number of subjects lost to follow up unlikely to introduce bias c) No description of subjects lost d) No statement on loss to follow up.								

Data analysis

Data were reported as percentages with 95% Confidence Intervals (95% CI) and medians with InterQuartile Range (IQR 25, 75%). We calculated the prevalence of SBI by using the number of SBI's as the numerator and the total number of febrile events in patients with neutropenia as the denominator. Heterogeneity between prevalence estimates was assessed using the I^2 statistic, which describes the percentage of variation not because of sampling error across studies. An I^2 value above 75% indicates high heterogeneity [14,15].

We conducted the meta-analysis with prevalence estimates that had been transformed using the double arcsine method [16]. The final pooled result and 95% CIs were back-transformed for ease of interpretation. Meta-analysis was undertaken using a random-effects model (to account for heterogeneity) conducted using the MetaXL (www.epigear.com) add-in for Microsoft Excel. A pooled prevalence figure was calculated with 95% CI. Statistical package: IBM Corp. Released in 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Results

Selection of the included studies

The PubMed, Embase, and Web of Science searches identified 2,066 citations **(Figure 1).** 9 articles were evaluated for full-text review. The papers written by Husain, Alexandrapoulou, and Karavanaki were excluded after the whole text review because it included patients with mild neutropenia (ANC <1500) [17-19]. The paper written by Serwint was excluded because some patients in the study were diagnosed with an oncologic etiology for the neutropenia [20]. We included in our review 5 articles [3-7]. All 5 reviewed studies used a retrospective design with data extracted from medical records. In addition, Barg et al., conducted a case-control study with a matched group of non-neutropenic children; we did not review the control study, just their data from their cases.

Description of included studies

The five studies [3-7] in our review included a total of 2269 individual patients **(Table 1).** Inclusion criteria of having a fever (>38C) was required for four studies [3-7] and the study by Melendez et al., did not explicitly require a fever for subject inclusion. As stated in the paper by Melendez et al., patients were selected if a complete blood count (CBC) was sent from their ED with an ANC <1,000 cells/mm^3. It does not appear that all subjects in the study by Melendez et al. had a fever. Between 1995 to 2000, many but not all of Melendez's subjects had CBC's as part of a febrile workup of children < 36 months. After 2000, a CBC was recommended in Melendez's cohort only for febrile young children if they did not receive three doses of conjugate pneumococcal vaccine. Melendez et al does not provide the exact number of febrile as opposed to non-febrile neutropenic children in their sample.

This difference in sampling by Melendez et al may explain why their study had a significantly larger size (n = 1888) compared to

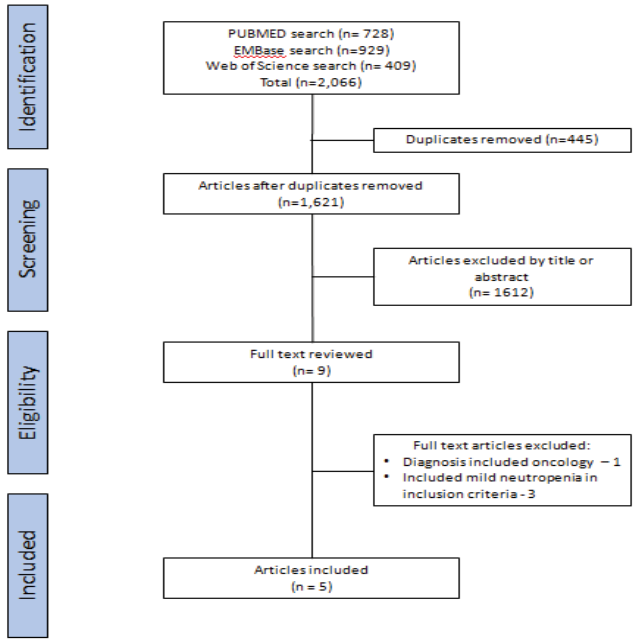

Figure 1 Study selection process.

the range (n=52) [3] to (n=190) [7] of sample sizes in the other four studies which required a fever for study inclusion.

Age as an inclusion criterion varied widely among the studies from an upper limit of 21 years [5] to only 36 months [3]. Lower age limits were from birth in [5,7] and to 1.5 months [3]. Age as inclusion was not specified by Bonadio et al., [4].

Neutropenia was defined similarly by four studies [4-7] as ANC < 1000 cells/mm^3. Wittman et al., used a lower limit of ANC < 500 cells /mm^3 as their inclusion criteria.

All of our studies generally excluded patients because of comorbid immunosuppressive diseases. Three of our studies [3,4,6] also, excluded patients recently on antibiotics.

Finally, the definitions of Serious Bacterial Infections (SBI) varied widely across our studies. Besides the study Bonadio et al., which did not clearly define SBI, all the other four studies included bacteremia, meningitis, and urinary tract infections in their definition of SBI. In addition, Barg et al., and Wittman et al., included septic arthritis, mastoiditis, gastroenteritis, and osteomyelitis in their definitions of SBI.

Quality assessment

Table 2 indicates the results of each individual study quality assessment according to the Newcastle-Ottawa scale. Of the included studies, all were not cohort-studies in design except Melendez et al., and therefore not every category and/or item included in the scale is applicable, but we have summarized the results of the applicable categories of Selection and Outcome. Two reviewers rated the study quality according to the checklist and their responses were analyzed to quantify inter rater reliability. The Intra class Correlation Coefficient (ICC) was 1.0.

All our reviewed studies were retrospective chart reviews. Gilbert et al., have defined eight criteria for retrospective chart reviews to improve accuracy and minimize inconsistencies in data acquisition: 1) training, 2) case selection, 3) definition of variables, 4) abstraction forms, 5) meetings, 6) monitoring, 7) blinding, and 8) testing of interrater agreement. None of our studies utilized these precautions to prevent inaccuracies and potential bias in their reviews of their subjects' medical records [14].

Prevalence of serious bacterial infections

In reviewing the prevalence of SBI across our reviewed papers we discovered as a consequence of their retrospective design and the lack of pre-study testing protocols none of our studies had all their subjects simultaneously cultured for bacteremia, meningitis, urinary tract infection (UTI), or had chest x-rays (CXRs) to evaluate for pneumonia. The wide variety of testing in febrile neutropenic children in our studies reflects individual hospital management patterns at the time of their study.

From **Table 3**, we have documented the actual number of cultures obtained from blood, cerebrospinal fluid (CSF), urine, and the number of CXRs for each study. Blood cultures were the most consistently cultured source and were obtained in 100% of subjects for Bonadio et al., Barg et al., and Wittman et al., [3,4,6] as compared to only 76% of Pascual's subjects and 95% of Melendez's subjects. Urine cultures were also obtained in all our studies ranging from 18% [6] to 61% [7]. CSF cultures were only obtained by Bonadio et al., (48%), Melendez et al., (25%), and Pascual et al., (10%). CXRs were the least commonly ordered test only by Wittman et al., (42%) and Barg et al., (55%).

We reproduced in **Table 3**, the prevalence of SBI as reported by all of our studies in the fourth column, which varied from 1.9% [3] to 8.5% [6]. The reported SBI prevalence in each study represents the number of positive cultures or cases of pneumonia on CXR divided by the total sample size of each study. Since not all patients received the full complement of cultures or CXR to rule-out these sources of infection, the true SBI prevalence in each study is suspect. To give a more granular view of each study's prevalence of individual elements of their definition of SBI we recalculated in column 5 of **Table 3**, the culture results of each study's blood, CSF, and urine tests, and CXR. Since the denominator of each culture result is generally smaller than the study's sample size the confidence intervals are mostly much larger than the stated SBI prevalence for each study. We had questions about the biases in determining which subjects were tested for SBI in each study so we decided to forgo our planned meta-analysis of the prevalence of SBI across our studies.

Discussion

Although we planned to do a meta-analysis for a pooled estimate of the prevalence of SBI in healthy appearing febrile neutropenic children, our literature search failed to find any article(s) that screened all their subjects with a consistent set of test modalities for SBI (blood cultures, CSF cultures, CXRs, and urine cultures). When we recalculated these studies' prevalence using only those patients with definite cultures or CXRs, we found their data were incalculable or that the confidence intervals for SBI were much larger than was stated in their respective studies [3-7].

Table 3 Comparison of prevalence of serious bacterial infection by study and by cultured specimens.

Study	Sample Size	Cultured Specimens	SBI Prevalence by Study (n, %, 95%CI)	SBI Prevalence by Sensitivity Analysis (n, %, 95%CI)
Bonadio et al. [4]	n=63	BC (n=63)	5, 8% (3% -18%)	2, 3% (0.2% - 11.5%)
		CSF (n=30)		3, 10% (3% - 26%)
		U C&S (n=33)		0
		CXR (n=?)		?
Melendez et al. [5]	n=1317	BC (n=1254)	31, 2.4% (1.6% - 3.3%)	8, 0.6% (0.3% - 1.3%)
		CSF (n=325)		4, 1.2% (0.3% - 3.1%)
		U C&S (n=676)		23, 3.4% (2.1% - 5.1%)
		CXR (n=?)		?
Barg et al. [6]	n=71	BC (n=71)	6, 8.5% (4% - 18%)	0
		CSF (n=?)		?
		U C&S (n=13)		1, 8% (<0.01% - 35%)
		CXR (n=39)		5,13% (5% - 27%)
Pascual et al. [7]	n=190	BC (n=145)	4, 2.1% (0.6% - 5.5%)	0
		CSF (n=19)		0
		U C&S (n=116)		2, 1.2% (<0.01% - 6.5%)
		CXR (n=?)		2, 1.2% (<0.01% - 6.5%)
Wittman et al. [3]	n=52	BC (n=52)	1, 1.9% (<0.01% - 11%)	0
		CSF (n=?)		?
		U C&S (n=19)		0
		CXR (n=22)		1, 5% (<0.01% - 24%)

Abbreviations: SBI: Serious bacterial infection, BC: Blood Culture, CSF: Cerebrospinal Fluid, UC & S: Urine Culture & Urinalysis, CXR: Chest X-Ray, CI: Confidence Interval

Notes:

Melendez: Positive urine culture ≥ 1000 Colony Forming Units suprapubic, >10000 catheterized, >50000 clean void.
No mention of urinalysis results. 31 patients with SBI, total of 35 positive cultures.

We can infer that in all these retrospective studies clinical judgment must have been used by the subjects' primary caregivers to choose which test modality was most likely to diagnose their source of fever. This we feel explains why blood culture, CSF culture, urine culture, and CXR were ordered as the febrile workup only in select patients. The number of patients who received blood cultures were 66% [5], 75% [7], 92% [4], and 100% [3,6]. Lumbar punctures for CSF cultures were obtained in 0% [3,6] 17% [5], 19% [7], and 44% [4] of patients. Urine cultures were ordered in 18% [6], 36% [3,5], 49% [4], and 61% [7] of patients. CXR were obtained in 0% [4,5,7], 42% [3], and 55% [6] of patients. This represents a significant risk of spectrum bias in each of our 5 studies, which falsely increases the sensitivity and specificity of these tests [21,22]. Spectrum bias was also responsible for the wide SBI prevalence which varied from 1.9% [3] to 8.5% [6] among our studies [3-7].

Still, blood cultures and urine cultures were commonly ordered in these previously healthy neutropenic patients, and the prevalence of these cultures is similar to that of febrile immunocompetent children. The reported prevalence of occult bacteremia in febrile, previously immunocompetent healthy children is 1.9% [23]. As can be seen in **Table 3**, a similar prevalence of bacteremia is seen in febrile neutropenic patients in our reviewed studies, ranging from 0% [3,6,7], 0.6% [5], to 3% [4]. The prevalence of UTI in both populations is also similar; in immunocompetent children, it is 7% [24]. In our reviewed studies, UTI prevalence ranged from 0% [3,4], 1.2% [7], 3.4% [5], to 8% [6]. However, there again is the spectrum bias inherent in retrospective reviews. Tests were ordered when the clinician had a higher suspicion for bacteremia or UTI, yet prevalence is the same as that of the general population. Though Bonadio et al., [4] had a prevalence of 3% for bacteremia in their neutropenic patients versus 1.9% in the general pediatric population [23], our studies comment on the clinical presentations of the two infants with positive blood cultures [4]. Both were less than 9 months old, had apnea, and signs of shock, which were clinically concerning for sepsis [4].

When we compared the prevalence of bacterial pneumonia and meningitis in immunocompetent versus incidental neutropenic patients that had CXR and CSF obtained, both SBIs are more common in neutropenic patients. The annual incidence of pneumonia of general pediatric children in resource-rich countries is estimated to be between 0.1%-0.3% [25,26]. CXRs were not obtained in Bonadio et al., and Melendez et al., but were positive in 1.2%, 5%, and 13% of patients tested [3-7].

The incidence of bacterial meningitis in the general pediatric population is <1% [27]. CSF was not obtained in Barg et al., and Wittman et al., but was positive in 0% [7], 1.2% [5], and 10% [4] of patients tested. However, the Bonadio paper describes the three patients out of 30 who had positive CSF culture all three were ill-appearing and lethargic [4]. This highlights spectrum bias--CSF culture and CXRs had a higher prevalence, sensitivity, and specificity because the clinicians used their judgment of pre-test

probability of SBI to order the tests which preferentially explained their fever [3-7].

We found three prospective studies that reviewed the prevalence of SBI in patients with mild to severe neutropenia (ANC<1500) [17-19]. We rejected these studies from our systematic review because the ANC was above our inclusion criteria of ANC<1,000 and did not comment on the degree of neutropenia in relation to positive bacterial cultures. Sixty-one percent [19] and 94% [17] of children had ANC<1000, and in Alexandropoulou et al., [18] 24% had ANC <500 and 76% had ANC between 501-1500. These prospective studies obtained blood and urine culture on all patients. The prevalence of bacteremia among these three studies ranged from 0% [17], 1.5% [19], to 4.4% [18], which mirrored the range of bacteremia 0% [3-7]-3% [4] in our reviewed studies [3-7]. Urinary tract infections varied among these three studies from 6.6% [18], 7% [17], and 10% [19]. This, again, is very similar to our reviewed neutropenic studies (0% [3,4] to 8% [6].

When we reviewed studies that also obtained viral testing in addition to blood and urine culture, we saw that the majority of positive tests were viral (47% [18]-50% [17]). For those patients who tested bacterial culture-negative and viral test negative, one can assume their infection was from a virus that was not detected. Thus, a large percentage of these neutropenic patients will be either viral positive or bacterial culture-negative (79% [18]-98% [19]).

There are limitations. These studies were all done in other countries (Greece and Kuwait) [17-19]. None of these studies describe the clinical picture of each child. In Alexandropoulou et al., there is a higher prevalence of bacteremia (4.4%) than the immunocompetent population quoted, 1.9% [18,23]. However, three of the positive blood cultures in the Alexandropoulou paper were rare bacterial pathogens in the US (*Rickettsia* and *Brucella*) [18]. The other bacteria growing from blood cultures were *Pneumococcus* (2) and *Pseudomonas* (1) making the prevalence of bacteremia 2.2% [18]. This is similar to the USA bacteremia prevalence in immunocompetent children of 1.9% [23-27].

Limitations

Limitations of our analysis include that all studies reviewed were retrospective chart reviews. Each study was dependent on documentation by healthcare professionals and recorded laboratory data, which is subject to error. Not all of the studies did each test or imaging study on every patient to screen for SBI. The true prevalence of SBI of each study could not be ascertained.

Conclusion

This systematic review could not conduct a meta-analysis given the limitations of our retrospective studies. However, there is spectrum bias inherent in retrospective reviews; clinicians clearly used their judgment in choosing which tests to confirm their diagnosis. It would be unethical and unrealistic to conduct a prospective review where every neutropenic child receives a lumbar puncture and CXR if clinical suspicion for bacterial meningitis or pneumonia is low, given the harms and risks of the tests. When examining each of the tests individually, the prevalence of bacteremia and urinary tract infections was similar in incidentally neutropenic patients compared to immunocompetent patients. Prevalence of bacterial meningitis and pneumonia was higher in neutropenic patients in our reviewed studies, but the spectrum bias we identified falsely increases the prevalence, sensitivity, and specificity of these tests.

If a febrile child is found to be incidentally moderately to severely neutropenic, and clinical suspicion for bacterial pneumonia or meningitis is low, their risk for SBI is similar to that of immunocompetent patients. It seems most causes of incidental neutropenia are viral related, and most of these patients are bacterial culture-negative and/or viral test positive. Antibiotics can cause allergic reactions, reduce the growth of normal intestinal flora, and increase antimicrobial resistance. It is worthwhile to risk-stratify moderate to severely neutropenic pediatric patients presenting with fever who were previously healthy; empiric antibiotic treatment can cause harm and is oftentimes unnecessary in these patients.

Conflict of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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