Evaluation of the Incidence of Occult Bacteremia Among Children With Fever of Unknown Origin

Eitan Naaman Berezin and Marco Antonio Iazzetti

Pediatric Infectious Disease division of the Pediatric Department of the Irmandade da Santa Casa de Misericória de São Paulo; São Paulo, SP, Brazil

We reviewed the incidence of occult bacteremia, to identify the most frequent etiological agents of bacteremias in otherwise healthy children from one month to 10 years old, who had fever of unknown origin attended at the emergency ward of an urban, university-affiliated pediatric referral center. This was a retrospective medical record review, evaluating children with fever. Data were collected from the initial visit, when blood cultures, hematological properties and hemosedimentation rates were examined. Fever was considered as the highest temperature assessed in the hospital or reported by the responsible adult. Occult bacteremia was discovered in 1.4% of the 1,051 children evaluated, and the most common etiologic agent was *Streptococcus pneumoniae.* Total leukocyte count and blood sedimentation rates greater than 30 mm^3 were not predictive factors for occult bacteremia. Fever greater than 39ºC was the most important factor for predicting occult bacteremia (P<0.001). The presence of occult bacteremia was significantly correlated with patient hospitalization.

Key Words: Fever, *Streptococcus pneumoniae*, occult bacteremia.

Although most fevers in children are caused by viral infections that can heal naturally, there are some cases of rare but severe bacterial infections [1]. The early identification and treatment of this condition in febrile children is one of the biggest challenges for pediatricians in outpatient services. Many such cases do not present symptoms and findings other than fever, and it is difficult to specify the causative pathogen. In some cases the symptoms manifest after a hospital visit and diagnosis of severe bacterial infection is made later [1-4].

Occult bacteremia is defined as the presence of potentially pathogenic microbes in the bloodstream of an individual who is in an apparently good clinical state and who presents fever without a known infectious process [4]. Previous studies have found that children 3 to 36 months of age with fever without a known origin are at risk for occult bacteremia, with rates of bacteremia in this population of between 1.6% and 7% [2-7].

Streptococcus pneumoniae currently causes 90% of occult bacteremias, after the introduction of the *Haemophilus influenzae* conjugate vaccine [7,8]. We undertook this study to review the incidence of occult bacteremia and to identify the most frequent etiological agents of bacteremias in otherwise well children between one month and 10 years old who had fever without a known origin and who were attended at the emergency ward of an urban, university-affiliated pediatric referral center.

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Address for correspondence: Dr. Eitan N Berezin. Av Roberto Lorenz 482. Zip code: 05611-050. São Paulo, SP, Brazil. Fax: (55+11) 37216688 Email – berezin@terra.com.br.

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Material and Methods

Santa Casa de São Paulo is one of the most active hospitals in Brazil. The pediatrics emergency unit receives over 144,000 patients each year, and approximately 400 children per day. We made a retrospective medical record review, evaluating children with fever. Data were collected from the initial visit, when blood cultures, hematological parameters and hemosedimentation rates were examined. Fever was considered as the highest temperature assessed in the hospital or reported by the responsible adult.

Our team reviewed blood cultures ordered by the pediatric unit from January 1, 2002 to December 31, 2003. Children having fever without localized signs were selected according to the following inclusion and exclusion criteria.

Inclusion criteria

- Age from one month to 10 years old;
- No localizing clinical features;
- Fever over 38ºC, assessed at the service or reported by the mother;
- No hospitalization 30 days prior to the initial evaluation.

Exclusion criteria

- Patients with Acquired Immunodeficiency Syndrome (AIDS);
- Patients exposed to chemotherapy or radiotherapy;
- Patients undergoing corticosteroid treatment for a period greater than five days;
- Patients with nephrotic syndrome;
- Patients with rheumatologic syndrome;
- Patients with hematological diseases.

All of the blood cultures were processed in the Microbiology Sector of the Central Laboratory of the Santa Casa de São Paulo. The hemograms and blood sedimentation

rate were processed in the Hematology Center of the Central Laboratory of the Santa Casa de São Paulo. After material collection, the blood cultures were immediately inoculated in the Hemobac Trifásico bacterial culture system (Probac®).

The identification process was in accordance with pre-established central norms, utilizing the standards of the National Committee for Clinical Laboratory Standards (NCCLS). Based on the definition of occult bacteremia, our study considered two types of bacteria, pathogenic bacteria and the group of bacteria that is considered potentially contaminating, based on published reports. We considered potentially contaminating bacteria to be coagulase-negative *Staphylococcus* and *Bacillus* spp. [9,10].

For analysis, the children were divided into three groups
- § Between 0 and 3 months;
- § Between 3 and 36 months;
- § Older than 36 months.

The temperatures considered as a risk for occult bacteremia were ≥ 39ºC measured in the hospital or reported by the responsible adult.

The total leucocyte count (WBC) that was considered as a risk for occult bacteremia was ≥ 15×10^9/L. The hemosedimentation rate considered to be a risk for occult bacteremia was ≥ 30 mm^3/hour, based on published standards [4].

For statistical analysis, data were calculated with the EPI-Info program version 6.1. Univariate analysis was performed with the chi-square test, with Yates correction, in order to look for significant differences between the groups of colonized and non-colonized children. P values less than 0.05 were considered significant. Fisher's exact test was used where expected cell values were < 5. The study was approved by the Ethics Committee for Research of the Santa Casa de São Paulo, Faculty of Medical Sciences.

Results

Within a two-year period, from January 2002 to December 2003, we evaluated 1,051 blood cultures that had been solicited by the pediatrics emergency unit . Among these children, 61% were male and 39% were female.

Pathogenic bacteria were isolated from 15 patients (1.4 %), and the patients were considered to have a diagnosis of occult bacteremia. In 175 patients, bacteria were considered as potentially contaminating and the blood culture was considered as contaminant . In the remaining 681 patients, the bacterial cultures were negative (Table 1).

In the division according to age groups, 102 children were between 0 and 3 months, 439 were between 3 and 36 months and 335 were over 36 months of age. The detection rate of bacteremia did not differ between the age groups (Table 2).

Table 1. Distribution of bacteria in children two months to 10 years of age with fever ≥ 39ºC, n = 190

Bacteria	Frequency	(%)
Streptococcus pneumoniae	9	5
Salmonella sp.	2	1
Coagulase-positive staphylococci	2	1
Neisseria meningitides	1	0.5
Haemophilus influenzae type B	1	0.5
Coagulase-negative staphylococci	167	78
Bacillus sp.	8	4

Table 2. Rate of occult bacteremia (OB) and contaminated cultures (CC) by age group

Age group (months) N (%)	Number in age group	OB N (%)	CC N (%)
1-3	54 (34.0)	156	2 (1.2)
3-36	88 (16.6)	527	7 (1.3)
>36	33 (12.1)	368	6 (1.6)
N	175	1,051	15

Table 3 presents the rate of patients with temperatures ≥ 39ºC, leucocytes ≥ 15×10^9/L or hemosedimentation rate ≥ 30 mm^3/hour.

Table 3. Distribution of occult bacteremia in children two months to 10 years of age related to temperature (T) ≥ 39ºC leucocytes (WBC) count above 15 × 109/L and hemosedimentation rate (HS) above 30

	N	OB N =15	RR	P
≥ 39	213	11	8.37	<0.001
T < 39	648	4	2.69-26.0	
WBC ≥ 15 × 109/L	419	7	1.21	0.7
WBC < 15 × 109/L	442	8	0.44-3.31	
HS ≥ 30	452	9	1.00	0.07
HS < 30	409	6	0.98-1.02	

RR = relative risk.

Temperatures ≥ 39ºC were significantly associated with bacteremia (Fisher's test, P < 0.001, Table 3). The absence of high fever (temperature < 39ºC was negatively associated with bacteremia relative risk (RR) = 0.12 (95% confidence interval = 0.04-0.37, P<0.0001), especially in children over three months of age. This relation was not found for children younger than three months of age.

Table 4 presents the outcomes for patients evaluated for occult bacteremia. Among the 1,051 children evaluated, 59

were hospitalized at reevaluation, 10 with a positive blood culture for pathogenic bacteria, 15 with a contaminated culture and 34 with negative blood cultures. The distribution based on the etiological agent of the patients with positive blood cultures who were hospitalized was as follows: eight cases of *Streptococcus pneumoniae*, onecase of *Salmonella* and one case of *Neisseria meningitidis*.

The relative risk of hospitalization was higher when there was a positive culture for pathogenic bacteria in comparison with contaminant bacteria (Table 4). The relative risk of hospitalization when comparing blood cultures positive for contaminant bacteria with negative blood cultures was of 1.05 (95% CI, 1.0-1.1) with P =0.015 (Table 4).

Table 4. Outcomes for patients evaluated for occult bacteremia. Rate of hospitalization at reevaluation (Hosp.) of patients with occult bacteremia due to pathogenic bacteria (OB), with contaminated blood culture (CC) or with negative blood culture (BCN)

Blood cultures	N (%)	Hosp.	P	RR
BCN	861 (81)	34		1
OB	15 (1.4)	10	<0.001	2.88
				1.41 -5.90
CC	175 (16.5)	15	0.01	1.05
				1.00-1.10

Discussion

One-thousand-fifty-one children between the ages of one month and 10 years with an undefined fever source were evaluated in our pediatric emergency unit. The rate of occult bacteremia was 1.4% .The prevalence of occult bacteremia in our study was lower than rates reported before the use of the HIB vaccine (2.8%-11.6%), but similar to values reported in the post-HIB vaccine era [2,3,11,12].

In 1987, Jaffe et al. [13] evaluated children between the ages of 3 and 36 months and discovered a 2.87% rate of bacteremia and an important presence of type-b *H. influenzae*. In 1993, Bass et al. also evaluated children between 3 and 36 months and discovered occult bacteremia in 11.5% of the patients, with 10% having infection by type-b *H. influenzae* [14]. In our study, *H. influenzae* was only found in one patient (Table 1); this low rate was probably due to universal vaccination for this bacterium [15].

Evaluation of a child with fever should be carefully done. The main objective is to try to define if there is a localized infectious process or determine if there is an undefined fever source [4,5]. We evaluated children having a fever of unknown origin that were treated in the Pediatric Emergency Service of the Santa Casa de Sao Paulo based on recommendations in the international literature, based on total leukocyte count, blood sedimentation rate and body temperature parameters [6,7].

Different from other studies, we also considered the temperature reported by the parents. This is important because frequently the child is medicated with an antipyretic prior to arrival at the service, making a real assessment difficult [16,17].

We applied the established parameters from the international literature to determine that coagulase-negative *Staphylococcus* and *Bacillus* sp. growth in blood culture indicate non-pathogenic bacteria, even though in very young infants, less than 30 days of age, they could have clinical significance [8,9]. The laboratory parameters followed were the same used by Baraff et al. [4]. The rate of contaminated blood cultures in our study was 16.5%. This contamination rate is greater than most reports from first world countries. Segall and Cahamberlain reported 2.9% of contaminated blood cultures from Washington (USA) [9]. Another study from Philadelphia (USA) reported 2.08%contaminated blood cultures [3]. Lieu et al., in the cost-effectiveness portion of their study, estimated that for each 1% increase in the contamination rate (or decrease in the specificity of the blood culture), an additional 1,303 dollars would be spent in treating patients or repeating blood cultures [12].

The main agent responsible for occult bacteremia was *Streptococcus pneumoniae* in our study, consistent with most previous studies [3,17-19]. *Streptococcus pneumoniae* was associated with the rate (89%) of hospitalization (Table 4).

High fever (temperature ≥ 39ºC) was a predictive factor for occult bacteremia, especially in children over three months of age (Table 3). The leukocyte counts were not a predictive factor for occult bacteremia data, which is similar to what is known from the literature, even though Kupperman [18] proposed the use of total neutrophil count as a predictive parameter for occult bacteremia, using as the cutoff line a count of 10,000 /mm^3. Lee proposed an 18,000 /mm^3 leukocyte count cutoff line as a predictive parameter for occult bacteremia [6]. These two studies were directed at occult bacteremia due to *Streptococcus pneumoniae* and not bacteremia.

The total leukocyte count is also useful for determining bacteremia by *Neisseria meningitidis*. Kupperman, evaluating children with meningococcal disease and without a known fever source also did not find significant differences in total neutrophil count; however, there was a low positive predictive factor since meningococcemia is not common for this age group [7].

There are several limitations to our study. We did not know the number of children who were seen during that time who were at risk for occult bacteremia, both those who did and did not have blood cultures.

Based on the data and analysis from our study, we conclude that the incidence of occult bacteremia in our service was similar to that found in published reports. The

finding of positive blood cultures for pathogenic bacteria gave objective information on patients hospitalized with fever without a known motive.

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