

Occult Bacteremia: Should We Look for the Needle in the Haystack?

Neta Baram MD¹, Orli Megged MD¹ and Giora Weiser MD²

Departments of ¹Pediatrics and ²Pediatric Emergency Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

ABSTRACT: **Background:** Once a well-recognized entity, occult bacteremia (OB) is no longer a significant serious bacterial infection. First following the introduction of the *Haemophilus influenzae* type B vaccine and now with the implementation of the conjugate pneumococcal vaccine (PCV), the number of cases has declined significantly. This has led to a change in many published guidelines to avoid taking blood cultures in fully vaccinated children presenting with fever. In Israel, the introduction of the PCV13 is now widespread.

Objectives: To assess the incidence and outcome of OB, specifically by *Streptococcus pneumoniae*, in a single large pediatric medical center.

Methods: We conducted a retrospective review of all cases of pneumococcal bacteremias in the years 2008–2013 and specifically those considered occult.

Results: Of 355 cases of bacteremia diagnosed during the study period, 164 were caused by *S. pneumoniae* and 20 (12.8%) were considered occult. None of the OB cases had any complications. OB was not found in children over the age of 36 months. There was a change in the serotypes involving pneumococcal OB.

Conclusions: OB is uncommon in the PCV-vaccinated population and the serotypes involved have changed.

IMAJ 2016; 18: 649–651

KEY WORDS: bacteremia, *Pneumococcus*, fever, blood culture, conjugate vaccine

Occult bacteremia (OB) is defined as a bacterial growth in blood cultures in a well-appearing child with a fever without source (FWS) [1]. The common ages for OB are 3–36 months. In Israel, the conjugated pneumococcal vaccination was introduced in 2009 as the PCV7, and in 2010 children started receiving as part of their routine vaccinations the PCV13. Due to its rarity, it is no longer recommended to take blood tests or cultures in a well-appearing child with FWS and no signs of distress [2]. There are still no validated laboratory markers for identifying those at risk. The historical markers introduced by Baraff in 1993 [3] have long since been questioned. Newer

biological markers such as C-reactive protein (CRP) and procalcitonin are being utilized more frequently. The consequences of OB have also not been fully explored, with “watchful waiting” considered an option [4].

In the Pediatric Emergency Department (PED) at Shaare Zedek Medical Center blood cultures are routinely taken in febrile children of all ages. Among other reasons this includes the attempt to avoid additional venous sampling and lack of data on the prevalence of occult bacteremia in the era of PCV13 in our medical center. Generally, all febrile children have blood cultures drawn. By examining OB prevalence in all febrile children in the PED, we attempted to better identify these cases and their characteristics throughout the introduction of PCV13 in order to change decisions on future culture sampling. An additional outcome examined was the serotypes involved in OB before and after the introduction of PCV.

PATIENTS AND METHODS

A retrospective cohort study was performed using the Shaare Zedek computerized database. All true bacteremias were identified and verified by the Infectious Disease Unit. The files of pneumococcal bacteremias were reviewed in order to identify those fitting the diagnosis of OB (a well-appearing child with fever without source, regardless of laboratory findings). Contaminants were determined based on an evaluation of such cases by an infectious disease specialist. At Shaare Zedek all cases of pneumococcal bacteremia are further assessed for specific serotyping.

The files included children aged 3 months–18 years who had blood cultures drawn in the PED. In the event of positive cultures and specifically *Streptococcus pneumoniae*, the files were reviewed by two of the researchers to determine the bacteremia as occult.

The pneumococcal bacteremias were divided into OB, bacteremias with a source, and bacteremias in ill-appearing children with fever and no obvious source. The investigators reviewed each case and agreed on the final allocation of each case. This study was approved by the hospital's ethics committee. Statistical analysis was based on Microsoft Excel (Microsoft inc.) and McCallum-Layton & Co. (UK).

RESULTS

BACTEREMIAS

During the years 2008–2013 a total of 43,650 blood cultures were taken from febrile children. Of these, 354 cases were determined to be true bacteremias, of which 163 were caused by *S. pneumoniae* (46%). Other common causes were *S. aureus* (14%), *Haemophilus influenzae* (all types) (7%), *Escherichia coli* (6%) and group A *Streptococcus* (5%). Compared to other bacteremias, pneumococcal bacteremias showed the greatest decline.

OCCULT BACTEREMIAS [Table 1]

Of 26 cases considered as occult, 20 were caused by *S. pneumoniae* (77.7%). The other causes were *Salmonella* spp. (2 cases), *H. influenzae* non-typable (2 cases), *Neisseria meningitidis* (1 case) and *Brucella melitensis* (1 case). The children with *S. pneumoniae* OB met the criteria originally set by Baraff [3] with white blood cell counts (WBC) above 15,000 cells and

elevated absolute neutrophil counts. There were 12 males and 8 females with an average age of 22.2 months [SD ± 8.77, 95% confidence interval (95%CI) 13.4–30.9]. An interesting finding was associated febrile seizures (FS) in 7 cases (33%). All cases of OB were discharged from the Emergency Department (ED). The majority of children were discharged with oral antibiotics (19/20) with one child receiving no treatment and one who received two doses of ceftriaxone and was then continued on oral antibiotics. Amoxicillin was the most commonly prescribed antibiotic (14/18) and four others received oral cefuroxime due to a suspected penicillin allergy. Two cases required admission. One was a 15 month old male who in addition had signs of glomerulonephritis and a 5 year old female who on readmission was described as “still looking ill to the parents.” Only two cases were over the age of 36 months. One was later diagnosed with a lobar pneumonia and the second child, as mentioned previously, may not have met the standard of “well appearing.” None of the pneumococcal OB cases developed complications [Table 2].

Table 1. Bacteremia and occult bacteremia in the Department of Pediatrics at Shaare Zedek

Non-pneumococcal bacteremias	Pneumococcal bacteremias: OB/non-occult (%)	Year
25	6/29 (20)	2008
28	9/39 (23)	2009
46	1/24 (4)	2010
30	3/33 (9)	2011
29	1/17 (5)	2012
27	0/13 (0)	2013

PNEUMOCOCCAL BACTEREMIA SEROTYPES

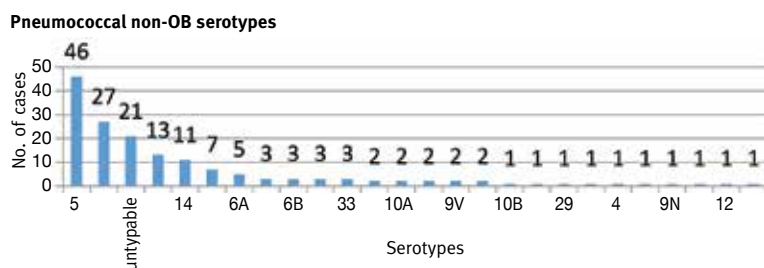
The distribution of serotypes was different between the bacteremia and OB groups. The OB group showed only single cases caused by serotypes 5 and 1, which accounted for approximately half of identified serotype bacteremias [Figure 1]. This may represent a direct effect of the coverage achieved by the PCV.

DISCUSSION

This study shows the relative paucity of pneumococcal bacteremias in general and OB specifically. This may help in focusing the use of blood cultures and less as a sampling aid for febrile children. Although the number of cases of OB in this study is too small to draw statistical conclusions, it would seem that OB is rare in vaccinated febrile patients in the PED. By sampling all febrile children our results are more likely to avoid possible biases.

Our results show, as has been previously published, that introduction of the PCV led to a sharp decline in pneumococcal OB. This decline can be seen even though none of the patients with pneumococcal OB received PCV13, and only five were given at least one dose of PCV7. However, only partial information regarding vaccinations was available and in only 14 cases. In addition, cases of OB were managed orally with no significant

Figure 1. Pneumococcal serotypes



Pneumococcal OB serotypes

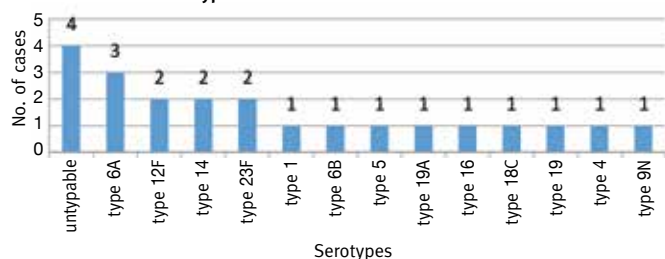


Table 2. Characteristics of occult bacteremia

Occult pneumococcal bacteremia (n)	20
Age (mean)	22.2 (SD ± 8.77, 95%CI 13.4–30.9)
Gender (F/M)	8/12
Discharge/Admission	18/2
Antibiotics (IV/oral/none)	1/18/1
Complications	0

complications. This was described recently by Vaillancourt et al. [5] who showed no immediate complications in children who returned to the ED with a final diagnosis of bacteremia or meningitis compared to children with the same diagnosis who were admitted on their first visit.

Since cases of OB are rare today, the use of additional markers beyond the traditional WBC, such as CRP or procalcitonin, may have a greater role than ever. Several studies have shown improved diagnosis incorporating additional biomarkers (e.g., CRP, procalcitonin, and interleukin-6) into the workup of FWS [6,7]. At Shaare Zedek these markers were not readily available and thus were under-utilized in the evaluation of febrile children.

In our study the distribution of pneumococcal serotypes in OB was different to that described in southern Israel [8]. The dominant serotypes in our center were 6A, 12F, 14 and 23F, compared to the results in southern Israel which consisted mostly of serotypes 19A, 1, 6B and 9V. The number of cases is relatively small so it may be hard to conclude the significance of this finding within the same country.

In this single-center retrospective study, the decline in OB by *Pneumococcus* is strongly reiterated. In Israel there has been a continued decline since the introduction of PCV7 followed by PCV13 [9]. The balance between the fear of missing bacteremia with severe complications compared to what seems a very high number needed to treat is a continuing challenge in the ED setting [10].

The presentation of a third of the cases of OB with a febrile seizure was unexpected. It has long been demonstrated that febrile seizures do not convey a higher risk for bacteremia than any other febrile child [11,12]. This was demonstrated even before PCV was fully implemented. Previous reviews, including in Israel, already showed that a febrile seizure was not associated with bacterial meningitis [13].

This study has several limitations. Its retrospective nature is an inherent limitation. In addition, we were unable to find the number of febrile children discharged with antibiotics and no growth in their cultures. Since treating empirically is common at our institute when OB is suspected, it may be assumed that the number far exceeds its need. Our total number of cultures is likely to include some of the repeated cultures.

CONCLUSIONS

The number of OB cases in the age of PCV13 continues to decline in our center, as has been described in other stud-

ies. This calls for more accurate consideration based both on the history (vaccination status) and laboratory results (CRP, procalcitonin, etc.). The serotypes involved in OB at our center are different than those described in other regions in Israel, yet still show a serotype shift from the pre-PCV period.

Correspondence

Dr. G. Weiser

Dept. of Pediatric Emergency Medicine, Shaare Zedek Medical Center, Jerusalem 94342, Israel

Phone: (972-2) 655-5781

Fax: (972-2) 655-5783

email: gioraweiser@gmail.com

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“The opposite of love is not hate, it’s indifference. The opposite of art is not ugliness, it’s indifference. The opposite of faith is not heresy, it’s indifference. And the opposite of life is not death, it’s indifference”

Elie Wiesel (1928-2016), Romanian-born American Jewish writer, professor, political activist, Nobel Laureate and Holocaust survivor. He was the author of 57 books, written mostly in French and English, including *Night*, a work based on his experiences as a prisoner in the Auschwitz and Buchenwald concentration camps