abstract

CONTEXT: Fever without source (FWS) in children 3-36 months is a common presenting complaint. Because of changes in immunization practices and their effects on rates of bacteremia, older guidelines may no longer be applicable. We reviewed the literature regarding the necessity of obtaining a blood culture in non-toxic children in this age group with FWS.

DATA SOURCES: We conducted a MEDLINE search on the topic of bacteremia in febrile children 3-36 months from 2004-present.

RESULTS: Eight studies were included. Although the studies varied in terms of approach and analysis, all suggested a rate of bacteremia in a non-toxic, febrile child 3-36 months of age to be less than 1%.

CONCLUSIONS: Strong consideration should be given for foregoing blood culture in a non-toxic child 3-36 months of age with FWS.

Background

The extent of evaluation required by well-appearing febrile children (fever without localizing signs or “FWS”) has been controversial for many years. Roughly 20% of children 3-36 months of age presenting with fever have FWS. A 1993 practice guideline suggested that children 3-36 months of age with fever ≥ 39 degrees and a white blood cell count of 15,000 should have a blood culture obtained, but this recommendation preceded wide-scale vaccination against Haemophilus influenzae type B (1990) and Streptococcus pneumoniae (PCV7, 2000). Historically, these two organisms have represented the most common causes of bacteremia in young children. Prior to widespread use of PCV7, the rate of bacteremia in children with FWS was estimated at 2-6%. The American College of Emergency Physicians’ 2003 clinical policy statement unfortunately did not specifically address the impact of large-scale PCV7 vaccination on the decision to obtain blood cultures in children with FWS. No studies have yet investigated the impact on bacteremia of PCV13, a newly approved vaccine.

Bacteremia represents a risk to children because it may lead to focal infections, including meningitis. Though this likely occurs less frequently with S. pneumoniae than with other organisms causing bacteremia, meningitis carries a risk of permanent neurologic sequelae. A positive blood culture in a bacteremic patient can likely improve care by quickly mandating follow-up and further investigations.

PCV7 vaccination has led to a significant decrease in the rate of all types of invasive S. pneumoniae infections, including bacteremia. This leaves the question

Should blood cultures be obtained in all infants 3 to 36 months presenting with significant fever?
of risk versus benefit in obtaining a blood culture in a nontoxic child 3-36 months of age with FWS.

**Methods**

We performed a MEDLINE search on the subject of fever without source, bacteremia, and fever in this age group. We included articles which studied at least a group of children who received PCV7. Inclusion criteria included English language, original research studies in largely immunized populations.

**Results**

We included 8 studies in this review, 5 retrospective and 3 prospective cohorts.4,5,10-15 Table 1 provides the specific characteristics of the studies reviewed. Half of the studies reviewed included data from the pre-PCV7 era for comparison. Only two studies clearly specified FWS as the inclusion criterion, whereas the remainder evaluated febrile children who had blood cultures obtained.

**Retrospective Studies**

Waddle and Jhaveri4 retrospectively studied children 3-36 months with fever ≥ 39 degrees and no obvious source at a large academic medical institution. They observed a bacteremia rate of 0.36% in this cohort. Since the study was conducted before the introduction of PCV7, it provides a baseline for comparison with subsequent studies. Other studies included in this analysis varied in terms of inclusion criteria, age groups, and sample sizes, but all shared the common goal of assessing the risk versus benefit of obtaining blood cultures in febrile children.

**Table 1: Studies included in this analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Age</th>
<th>Temperature</th>
<th>Inclusions</th>
<th>Exclusions</th>
<th>Pre-PCV7</th>
<th>Post-PCV7</th>
<th>Bacteremia Rate Post-PCV7</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waddle4</td>
<td>Retrospective</td>
<td>3-36 mos</td>
<td>≥ 39</td>
<td>FWS only</td>
<td>Otitis media</td>
<td>x</td>
<td>x</td>
<td>0.36%</td>
<td>Individual immunization status unknown, small sample</td>
</tr>
<tr>
<td>Herz5</td>
<td>Retrospective</td>
<td>3-36 mos</td>
<td>Not defined</td>
<td>Any child with blood culture</td>
<td>Immunocompromised CVL</td>
<td>x</td>
<td>x</td>
<td>0.25% (est)</td>
<td>All patients with E coli also had UTI</td>
</tr>
<tr>
<td>Sard10</td>
<td>Retrospective</td>
<td>1-36 mos</td>
<td>≥ 38</td>
<td>Fever + blood culture obtained</td>
<td>Not reported</td>
<td>x</td>
<td>x</td>
<td>0.44%</td>
<td>5/9 patients with bacteremia were under 2 months</td>
</tr>
<tr>
<td>Wilkinson11</td>
<td>Retrospective</td>
<td>3-36 mos</td>
<td>≥ 39</td>
<td>FWS (included otitis media)</td>
<td>Admitted patients, Immunocompromised CVL</td>
<td>x</td>
<td>x</td>
<td>0.25%</td>
<td>Immunization status or pneumococcal serotype not reported</td>
</tr>
<tr>
<td>Stoll12</td>
<td>Retrospective</td>
<td>2-36 mos</td>
<td>≥ 39</td>
<td>Fever + blood culture obtained</td>
<td>Admitted patients, prior antibiotics, immunodeficiency, CHD, VP shunt, CVL</td>
<td>x</td>
<td>x</td>
<td>0.91%</td>
<td>Two positive cultures in same unimmunized patient; pneumonia and UTI excluded</td>
</tr>
<tr>
<td>Carstairs13</td>
<td>Prospective</td>
<td>0-36 mos</td>
<td>≥ 38</td>
<td>Fever + blood culture obtained</td>
<td>Immunization status unknown</td>
<td>x</td>
<td>x</td>
<td>2.4% (unimmunized) 0 (immunized)</td>
<td>60% of eligible pts did not have blood culture drawn</td>
</tr>
<tr>
<td>Rudinsky14</td>
<td>Prospective</td>
<td>0-24 mos</td>
<td>≥ 38 (0-3 mos), ≥ 39 (3-24 mos)</td>
<td>Fever + blood culture obtained</td>
<td>None</td>
<td>x</td>
<td>x</td>
<td>0.7%</td>
<td>WBC and height of fever did not correlate with bacteremia; urine culture not done in 4 of 5 patients with bacteremia</td>
</tr>
<tr>
<td>Craig15</td>
<td>Prospective</td>
<td>0-5 yrs</td>
<td>≥ 38 or &quot;felt hot&quot;</td>
<td>Fever</td>
<td>Previous illness, immunocompromised, oncology, abuse</td>
<td>x</td>
<td>x</td>
<td>0.4%</td>
<td>Did not report bacteriology or immunization rates in bacteremic patients</td>
</tr>
</tbody>
</table>
These authors indicated that only 26% of patients with bacteremia also had urinary tract infections. Though all patients with vaccine serotypes of streptococcus and E. coli were included, 10 (0.36%) were true pathogens. None were positive for S. pneumoniae. This decline was highly statistically significant (p<0.001). This study also reported the results of urine testing; urine culture positivity was not affected by vaccination: 10 positive urine cultures (6.8%) were found pre-vaccine and 21 positives found post-vaccine (7.6%, p=0.9). Since the study included only patients who had blood and/or urine cultures drawn, it may have been biased towards sicker-appearing patients. This study also did not report individual patients’ PCV7 vaccination status.

Herz5 used a retrospective case series design to study children 3-36 months of age who had a blood culture obtained as an outpatient or in the emergency department from 1998-2003. Of 37,133 blood cultures obtained, 352 (0.95%) were deemed to be true positives. This study did not exclude patients with specific symptoms like focal pain, respiratory distress, or febrile seizures, nor ill-appearing patients from those with FWS. They found that the rate of pneumococcal bacteremia dropped between 78% and 85% in 2000-2003 compared to 1998. Most common causes of bacteremia were non-vaccine serotypes of S. pneumoniae and E. coli, though all patients with E. coli bacteremia also had urinary tract infections. These authors indicated that only 26% of patients with bacteremia could be classified as FWS; they estimated a “true occult bacteremia rate” of 0.25%.

Sard10 performed a retrospective chart review of all children 1-36 months of age with temperature ≥38 degrees who had a blood culture obtained in a community hospital emergency department from 1997 to 2005. The study was designed to determine which characteristics were associated with true positive blood cultures as opposed to contaminants. In the post-PCV7 group, they found 9 true positive blood cultures (of 2060; 0.44%) compared to 65 false positives (3.16%). Of the 9 true positives, 4 were S. pneumoniae with one each of Group B Streptococcus, M. catarrhalis, S. aureus, E. coli, and Enterococcus. Whether any of these patients had urinary tract infections was not reported. Of these true positives, only 5 were reported as being over 2 months of age without focal physical findings. The authors reported that mean white blood cell count and time to positivity were statistically significantly associated with true positive blood cultures.

Wilkinson11 performed a retrospective study at a large children’s hospital in the post-PCV7 era of all children 3-36 months of age presenting with FWS of ≥ 39 degrees. Patients who were admitted were assumed not to be well-appearing and were therefore excluded. Immunodeficient patients and those with indwelling catheters were also excluded, though those diagnosed with acute otitis media were included. Of 8,413 patients, 159 were deemed contaminants, while 21 were true positives (true positive rate of 0.25% with 95% CI of 0.16 to 0.37). When divided into first, second, or third year of life, the highest rate was found in the 24-36 month age range, though this was not statistically significant. By far the most common cause of true bacteremia was S. pneumoniae (14/21). Since these were not serotyped and immunization status of these children not reported, these cases may represent inadequate vaccination, vaccine failures, or non-vaccine serotypes. The authors did not report either an association with otitis media or the incidence of urinary tract infection. They argued that in this population blood cultures should not be routinely obtained.

Stoll and Rubin12 conducted a retrospective cohort study of children ages 2-36 months with temperature ≥ 39 degrees who had blood cultures obtained in an emergency department or urgent care center and were then discharged. They excluded patients with focal bacterial infections except otitis media, while including patients with a clinical presentation suggestive of a viral process, such as those with croup, bronchiolitis, and gastroenteritis. Of 329 patients studied, they found 3 positive blood cultures; all grew S. pneumoniae (0.91%), two of which were found in the same, unimmunized patient. Importantly, patients who were ultimately diagnosed with urinary tract infections or pneumonia were excluded; how many of these may have presented with FWS is unknown. This study also did not include patients with FWS who did not have blood cultures drawn.

Prospective Studies

Carstairs13 performed a non-concurrent, prospective, observational cohort study from November 2000 through October 2002, noting that by late 2001 widespread use of PCV7 was established.
This study investigated all febrile children less than 36 months of age, including neonates, with temperature \( \geq 38 \) degrees, regardless of symptoms, who had a blood culture done. The study noted PCV7 immunization status as indicated by the electronic medical record. Patients were excluded if their vaccination status was unknown. Of 1,383 patients eligible for the study, 833 had received PCV7 while 550 had not. The unimmunized group had a bacteremia rate of 13/550 (2.4%); all positive cultures were with \( S. pneumoniae \) (no other organisms were found). Of these 13, 7 had a diagnosis of pneumonia. In the immunized group, the rate of bacteremia with \( S. pneumoniae \) was 0/883 (0%) while the rate of bacteremia with other pathogens was 2/883 (0.23%; both patients also had urinary tract infections). This study did not differentiate FWS from sicker appearing children, but this offers further evidence that the rate of bacteremia in immunized children is very low.

Rudinsky\(^{14} \) performed a prospective cohort study of children 0–3 months of age with temperatures of \( \geq 38 \) and 3-24 months with temperatures of \( \geq 39 \) regardless of symptoms. Vaccination records were available in the electronic medical record. The study enrolled 985 children, of whom 690 had blood cultures, and 129 were found to have serious infections (defined as pneumonia, urinary tract infection, or bacteremia; there were no cases of meningitis). Of these, 5 (0.7%) had bacteremia, of which one was \( S. pneumoniae \). The four others had bacteremia caused by \( Enterococcus \) (2), Group B \( streptococcus \) (1), and \( E. coli \) (1). Of these four, one had a urine culture performed and this was positive.

Craig\(^{15} \) performed a very large, prospective cohort study looking at clinical signs and diagnosis of SBI in children 0–5 years in Australia. This study developed a clinical prediction model and asked physicians to estimate the probability that a patient had an SBI (urinary tract infection, pneumonia, or bacteremia). The clinical prediction model was found to outperform physician clinical judgment. There was no study-mandated investigation or algorithm, so many children with FWS may not have had blood cultures done, though they were closely followed. This study found that urinary tract infections (3.4%) and pneumonia (3.4%) occurred much more commonly than bacteremia (0.4%). In addition, this study found that of 26 clinical criteria, only two—tachycardia and ill appearance—were associated with a statistically significant increased risk of bacteremia. In this study, 52 of 64 (81%) patients with bacteremia received antibiotics on presentation. Bacteriology of infections in patients with bacteremia was not reported. Lack of immunization against \( S. pneumoniae \) showed a trend toward an increased rate of bacteremia in the analysis, but the number of patients with bacteremia who were unimmunized was not reported.

**Discussion**

Healthcare providers do not wish to miss cases of children with fever who have bacteremia because these children are at risk for focal infections including meningitis. Identifying a true positive blood culture early in the disease course may prevent these developments.\(^7 \) The risk of developing meningitis among children with bacteremia is probably about 10%; of these, perhaps 20–30% will have neurologic sequelae.\(^16-19 \) However, this rate likely differs significantly among organisms, as \( S. pneumoniae \) bacteremia causes focal infections less commonly than \( N. meningitidis \), for example. Bacteremia with \( S. pneumoniae \) also may clear spontaneously without antibiotics in 25–30% of cases.\(^20 \)

Obtaining a blood culture carries risk. The published, accepted rate of contaminated blood cultures (3-4%) is well higher than true positives in any of the reviewed studies, so unnecessary procedures and hospitalizations may occur and costs incurred.\(^3-5 \) The cost of hospitalization due to a contaminated specimen—generally including intravenous antibiotics and often lumbar puncture—has been estimated at $6,200 per patient.\(^21 \)

The studies described in this paper differ significantly in study design and may underestimate or overestimate the rate of bacteremia in children with FWS. For example, the studies by Sard, Stoll, and Carstairs included patients with clinical symptoms suggestive of viral illnesses who had blood cultures drawn.\(^10,12-13 \) These are not true FWS patients and their inclusion may lead to underestimation of the FWS bacteremia rate. On the other hand, many of these studies included patients who were “ill-appearing,” so they may have overestimated the rate of bacteremia in well-appearing children with FWS.

While recognizing these limitations, the data presented here consistently suggest that PCV7 has significantly reduced the incidence of bacteremia in children 3–36 months of age with FWS. The impact of PCV7 (and now PCV13) may change over time, but currently the rate of bacteremia in this population is less than 1%.

More recent reviews and guidelines have integrated this data. The 2007
UK NICE guidelines emphasize the diagnosis of urinary tract infections in this population and de-emphasize blood cultures. Other recent reviews also support not obtaining blood cultures in children ages 3–36 months with FWS.

Further studies will evaluate the impact of PCV13 vaccination on the epidemiology of bacteremia in children with FWS in this age group over time. Specifically the impact of non-vaccine serotypes will require monitoring. The risk of developing a complication of bacteremia (such as meningitis) is based on older studies; whether different strains of S. pneumoniae will behave similarly is not known.

**Conclusion**

Children 3–36 months present commonly with FWS. Clinical guidelines generally predate or do not consider the impact of wide-scale pneumococcal vaccination. Newer data suggest that the risk of bacteremia in this population is less than 1%. Strong consideration should be given for not routinely performing blood cultures in the well-appearing subset of this population.

**References**