Time to Positivity of Blood Cultures for Children with *Streptococcus pneumoniae* Bacteremia

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We report on a 3-year (1 January 1996 through 31 December 1999) retrospective chart review of children with *Streptococcus pneumoniae* bacteremia to identify the time to identification of growth of *S. pneumoniae* in blood culture and to attempt to identify clinical predictors of early versus late growth of *S. pneumoniae* in culture. The time to detection of *S. pneumoniae* in blood culture for immunocompetent patients ranged from 4.4 to 25.9 hours (h), with a mean of 11.5 h (standard deviation, 2.8). There was no difference in the time to detection for immunocompromised versus immunocompetent patients. The 10th and 90th deciles for time to detection among immunocompetent patients were 9.2 and 14.0 h, respectively. There were no differences in white blood cell count, absolute neutrophil count, or height of fever between the lowest and highest decile groups. Ninety percent of blood cultures yielding *S. pneumoniae* are noted positive within 14 h, and no clinical or laboratory parameters accurately predicted early versus late growth of *S. pneumoniae* in blood culture.

*Streptococcus pneumoniae* is the most common cause of bacteremia in young febrile children [1–9]. Although some children recover from this infection without complications, others develop sequelae. Prevention of these sequelae and the judicious use of antibiotics require rapid identification of patients with bacteremia and prediction of those likely to progress to invasive disease. Prior studies on time to recovery of pathogen in blood culture for patients with *S. pneumoniae* bacteremia have shown that as few as 40% of specimens had growth detected within 24 h [10]. Newer culture methods and recent reports suggest a shorter time to detection of growth. Previous investigators have also demonstrated a correlation between the number of bacteria isolated per milliliter of blood by means of quantitative methods and the presence of focal infection such as pneumonia and meningitis [11, 12]. Thus, we sought (1) to establish the time to culture recovery of *S. pneumoniae* from pediatric patients, with use of new culture methods, and (2) to identify clinical predictors for early versus late growth of *S. pneumoniae* in culture.

**METHODS**

**Patient population** The investigation was a retrospective cohort study. During a 36-month period from 1 January 1996 through 31 December 1999, the charts of all patients whose blood cultures yielded *S. pneumoniae* at an urban tertiary care children’s hospital in Boston were reviewed. Cases were included for evaluation if *S. pneumoniae* was isolated as a single pathogen from a blood culture. We recorded the time to detection, age of the patient, underlying medical conditions, pretreatment with oral or parenteral antibiotic(s), triage or initial temperature and duration of fever, presence of meningitis, pneumonia, or other focal infection,
WBC count, absolute neutrophil count (ANC), treatment, and disposition. Clinical and laboratory parameters of patients with immunodeficiency or an oncologic disorder were compared with those of immunocompetent hosts and then excluded from further data analysis. Patients were then subgrouped by the time elapsed from incubation of cultures to detection of growth in culture to identify any intergroup differences. Patients whose time to detection was within the first decile (the most rapid time to detection) were compared with patients in the 10th decile, as well as those in the second through ninth deciles. Comparisons were also made between groups on the basis of prior use of antibiotic(s), initial diagnosis, and disposition.

Clinical and laboratory characteristics of patients with focal infections were compared with those of patients without a focus of infection. Focal infections were defined by the presence of pneumonia, meningitis, cellulitis, sinusitis, osteomyelitis, mastoiditis, or an abscess. Meningitis among those patients with *S. pneumoniae* bacteremia was defined by (1) a CSF leukocyte count of at least 10 WBCs/mm³, (2) the presence of gram-positive diplococci on Gram stain of CSF, or (3) growth in culture of CSF. Pneumonia was defined by a lobar infiltrate on chest radiography. Clinical sepsis was defined as hemodynamic instability requiring admission to the intensive care unit. Patients who received an oral antibiotic prior to blood culture, as well as those with either meningitis or septic shock at initial presentation, were included in the data analysis and subsequently analyzed separately. This study was approved by the human subjects committee at our facility.

**Blood cultures.** At our institution the microbiology laboratory recommends that a volume of 1–3 mL of blood be obtained in a sterile fashion and inoculated directly into Bactec aerobic Peds-Plus bottles (Becton Dickinson) [13]. The volume of blood inoculated is not generally recorded. The Bactec culture bottles contain a sensor, which detects increases in CO₂ produced by the growth of microorganisms. The sensor is monitored by the use of a Bactec 9240 instrument (Becton Dickinson) every 10 min for an increase in fluorescence, which is proportional to the amount of CO₂ produced. The elapsed time used in our study was the time from placement of the culture bottle into the fluorescent sensor instrument to the time growth was first detected.

Specimens are delivered hourly to our laboratory by courier and are placed shortly after arrival into the sensor, 24 h per day. When bacterial growth is detected, a specimen is withdrawn from the culture bottle, plated on chocolate and blood agar, and placed on slides for Gram stain analysis. A Quellung reaction is performed on all gram-positive specimens, and the findings concerning culture growth, Gram staining, and Quellung reactions are reported to the clinical staff.

**Statistical analysis.** Univariate and multivariate analysis were performed with SPSS for Windows, version 9.0 (SPSS). Continuous variables such as WBC count, ANC, height of fever, and time to detection of positive culture were compared between the 2 groups with use of independent-samples t tests. Categorical variables such as admission rates were compared with χ² analysis or Fisher’s exact test. Factorial analysis of var-
### RESULTS

During the 36-month period, 187 blood culture specimens yielded growth of *S. pneumoniae*. The time to first detection of growth was available for 178. Three patients had duplicate positive culture specimens drawn at the time of evaluation. For each of these 3 patients, the difference in the time to detection of growth between paired specimens ranged from 0.2 to 1.0 h; only the first blood culture specimen received by the microbiology laboratory was used for further data analysis.

Of the 175 patients, 102 (58%) were male. Ages ranged from 5 weeks to 18 years, with a median age of 17 months (interquartile range, 10–23 months). Diagnoses made at the initial evaluation included fever without obvious focus of infection (123 patients), pneumonia (27), meningitis (7), cellulitis (4), septic shock (3), suspected appendicitis (2), sinusitis (1), suspected intussusception (1), mastoiditis (1), abscess (1), and diagnosis not specified (5). Both patients with suspected appendicitis underwent exploratory laparotomies and had no evidence of inflammation or perforation of the appendix. The time to detection of growth ranged from 4.4 h to 25.9 h (figure 1). The median time to detection was 11.1 h (mean ± SD, 11.5 ± 2.8 h).

Eleven patients had some degree of recognized immunocompromise, which was due to chemotherapy in 5 patients with malignancies, immunosuppressive therapy following organ transplantation in 3 patients, and HIV infection in 3 patients. When immunocompromised patients were compared with immunocompetent hosts, there was no significant difference in mean time to detection of growth in culture (10.9 vs. 11.6 h; *P* = .33) or in triage temperature (39.0°C vs. 39.3°C; *P* = .53). Immunocompromised patients did have lower WBC counts (10,100 cells/mm³ vs. 19,600 cells/mm³; *P* = .001) and lower ANCs (8300 cells/mm³ vs. 19,800 cells/mm³; *P* = .005) than patients without recognized immunocompromise. Immunocompromised patients were excluded from further analysis.

The median time to detection of growth of *S. pneumoniae* in culture among the 164 immunocompetent children was 11.1 h (11.6 ± 2.9 h). The 10th and 90th deciles for time to detection were 9.2 h and 14.0 h, respectively. There were no significant differences among patients in the first, second to ninth, and 10th deciles with respect to height of fever, WBC count, or ANC (0.25, and 0.14 respectively, *P* > .20; table 1). There was a small but not statistically significant difference between the mean age of patients among the three groups; patients with

### Table 2. Characteristics of immunocompetent patients, as related to diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Temp., °C</th>
<th>WBCs (×1000 cells/mm³)</th>
<th>ANC (×1000 cells/mm³)</th>
<th>TTD, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult bacteremia (n = 116)</td>
<td>39.3 ± 1.0</td>
<td>19.8 ± 6.7</td>
<td>13.4 ± 6.5</td>
<td>11.6 ± 2.6</td>
</tr>
<tr>
<td>Pneumonia (n = 27)</td>
<td>39.3 ± 1.0</td>
<td>22.0 ± 7.2</td>
<td>16.0 ± 5.9</td>
<td>11.3 ± 1.4</td>
</tr>
<tr>
<td>Meningitis (n = 7)</td>
<td>39.3 ± 1.6</td>
<td>15.8 ± 10.3</td>
<td>11.1 ± 7.7</td>
<td>14.1 ± 7.5</td>
</tr>
</tbody>
</table>

**NOTE.** All comparisons were not significant at the .05 level of significance. ANC, absolute neutrophil count; Temp., temperature; TTD, time to detection.
Table 3. Individual characteristics of patients with sepsis and meningitis.

<table>
<thead>
<tr>
<th>Category and patient no.</th>
<th>Age</th>
<th>Temp., °C</th>
<th>WBCs (x1000 cells/mm³)</th>
<th>ANC (x1000 cells/mm³)</th>
<th>CSF cells/mm³</th>
<th>Time to detection, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 months</td>
<td>39.0</td>
<td>10.0</td>
<td>7.2</td>
<td>—</td>
<td>9.6</td>
</tr>
<tr>
<td>2</td>
<td>8 months</td>
<td>38.2</td>
<td>1.8</td>
<td>0.3</td>
<td>—</td>
<td>4.6</td>
</tr>
<tr>
<td>3</td>
<td>13 months</td>
<td>39.6</td>
<td>24.3</td>
<td>19.5</td>
<td>—</td>
<td>11.1</td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 months</td>
<td>41.6</td>
<td>26.9</td>
<td>10.5</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>12 months</td>
<td>39.5</td>
<td>21.0</td>
<td>16.5</td>
<td>108</td>
<td>220</td>
</tr>
<tr>
<td>3</td>
<td>5 years</td>
<td>39.9</td>
<td>20.9</td>
<td>25.7</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5 months</td>
<td>37.8</td>
<td>6.3</td>
<td>3.0</td>
<td>714</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>8 years</td>
<td>36.5</td>
<td>9.4</td>
<td>8.3</td>
<td>279</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>2 years</td>
<td>39.5</td>
<td>10.0</td>
<td>8.6</td>
<td>84</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>18 months</td>
<td>40.0</td>
<td>6.3</td>
<td>5.1</td>
<td>368</td>
<td>22</td>
</tr>
</tbody>
</table>

NOTE. ANC, absolute neutrophil count; Temp., temperature.

the most rapid time to detection had a mean age of 1.0 ± 0.5 years, vs. 1.7 ± 1.5 years for patients in the middle group and 2.1 ± 1.9 years for patients with the longest time to detection (P = .11). Of the 150 patients seen in the emergency department, 52 (31%) were admitted to the hospital. Patients in the first decile were significantly more likely to be admitted to the hospital than were patients in the 10th decile (10 [67%] of 15 patients vs. 5 [31%] of 16 patients; P = .02).

There was no difference in the mean time to detection for immunocompetent patients receiving an oral antibiotic prior to culture (n = 8) and patients who did not receive an antibiotic (13.8 h vs. 11.5 h; P = .25). There was no difference in the time to detection between immunocompetent patients with a focal infection (n = 38) and those without a focus of infection (11.8 h vs. 11.1 h; P = .6). No differences were seen for the time to detection, height of fever, WBC count, or ANC between groups of patients with occult bacteremia, pneumonia, and meningitis (table 2). Clinical and laboratory characteristics of the 3 immunocompetent patients who presented in septic shock and seven patients with meningitis are shown in table 3.

Ten patients found to have pneumococcal bacteremia received no antibiotic therapy at their initial visit. The median time to detection of growth for these patients was 12.0 h (range, 10.1–13.2 h). Nine of the 10 patients had a second blood culture performed at a follow-up visit after notification of the culture positivity. The median interval from obtainment of the first and follow-up blood culture specimens was 24 h (range, 22–42 h). Seven of the nine patients had no detectable growth in the second blood culture, despite lack of antibiotic therapy. A total of 2 of the 9 patients had detectable growth in the second blood culture. The matched times to detection of growth were 10.1/9.1 h and 12.2/13.6 h, respectively. None of the patients who were treated with either oral or parenteral antibiotics and returned for reevaluation had S. pneumoniae detected in the second blood culture.

**DISCUSSION**

We have addressed the time to culture positivity for children with S. pneumoniae bacteremia and have evaluated whether readily available clinical or laboratory parameters can predict early or late growth. Using the Bactec 9240 blood culture system, we found a rapid time to detection of growth of S. pneumoniae, with a mean time of 11.5 h (%2.8 h). Ninety percent of isolates were detected within 14 h, and all but 3 were detected within 24 h. Alpern et al. [14] similarly described a rapid time to detection, with a mean of 14 h (%2.4 h) when similar culture methods were used, but their population was limited to well-appearing children without focal infection. In 1998, using quantitative culture methods, Teach et al. [15] found the mean time to detection of growth of S. pneumoniae in blood culture to be 18.4 ± 6.7 h (range, 9.0–66.0 h). In contrast, Meadow and Schwartz [10], using radiometric detection methods, noted that only 38% of S. pneumoniae isolates were detected within 24 h, 94% by 48 h, and 99% by 72 h.

Previous investigators have demonstrated that children with identified focal infections such as pneumonia and meningitis have a significantly higher magnitude of bacteremia, i.e., quantitative blood culture methods identify higher numbers of cfu per milliliter of blood [11–12, 15]. Based on these studies, our hypothesis was that patients with more severe disease or invasive disease would have higher magnitudes of bacteremia and thus more rapid detection of growth in culture. Although we found that significantly more patients in the group with the most rapid detection were admitted to the hospital than were those in the other groups, we failed to show a difference in
time to detection when stratified by diagnosis. We also hypothesized that these patients would have clinical or laboratory correlates reflecting an increased inflammatory response such as higher temperatures, WBC counts, and ANCs.

Similar to Teach et al. [15], we failed to show a relationship between time to detection and age, level of fever, WBC count, or ANC. In addition, rapid detection was not associated with focal or invasive disease. Therefore, the time to detection of growth should not be used to predict the presence of focal infection. Nonetheless, a higher proportion of patients with the most rapid time to detection were admitted to the hospital, perhaps because they were somewhat younger or appeared to be more ill to the treating clinicians in a way not evident by chart review.

The time to detection of blood culture positivity may depend on multiple factors, including the amount of blood inoculated, the time from specimen collection to receipt in the laboratory, and the concentration of organism within the blood. The major limitation is that because of the retrospective nature of our study, we were unable to control for the quantity of blood inoculated into the culture bottles, which may have had an effect on our results [13]. Perhaps what was most notable in our study is that despite these variables, we found that the time to blood culture positivity was clustered within a narrow interval. Eighty percent of blood cultures became positive within a 5-h interval of 9–14 h.

In conclusion, we have been able to demonstrate that (1) current culture methods allow for rapid identification of growth of S. pneumoniae in blood cultures for patients with bacteremia, (2) the time to detection of growth in culture is independent of the patient’s age, level of fever, or WBC count, and (3) the time to detection cannot be used to predict the presence of pneumonia or meningitis.

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References