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Frequency of Low-Level Bacteremia in Children from Birth to Fifteen Years of Age

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A single blood culture inoculated with a small volume of blood is still frequently being used for the diagnosis of bacteremia in children because of the continued belief by many that bacteria are usually found in high concentrations in the blood of pediatric patients with sepsis. To determine the importance of both blood volume cultured and the number of culture devices required for the reliable detection of pathogens in our pediatric population, blood from children from birth to 15 years of age and with suspected bacteremia at York Hospital (a 500-bed community hospital) was inoculated into at least a Pediatric Isolator (Wampole Laboratories; 1.5 ml of blood) or a standard Isolator (10 ml of blood) and a bottle of ESP anaerobic broth (Trek Diagnostic Systems; 0.5 to 10 ml of blood). The use of a second Isolator and additional aerobic and anaerobic bottles and the total blood volume recommended for cultures (2 to 60 ml) depended on the weight and total blood volume of each patient. One hundred forty-seven pathogens were recovered from the blood of 137 (3.6%) of 3,829 children for whom culturing was done. Of 121 septic episodes for which the concentration of pathogens in the blood could be determined using Isolators, 73 (60.3%) represented low-level bacteremia (<10 CFU/ml of blood), including 28 pathogens (23.1%) which were detected at concentrations of only <1.0 CFU/ml. Of 144 septic episodes for which two or more culture devices (Isolators and/or bottles) were inoculated, 85 (59%) were associated with false-negative results from one or more of the culture devices. Of the 128 children for whom antibiotic therapy records were complete, therapy was either started or changed for 88 (68.8%) following notification of positive blood cultures. Low-level bacteremia was common in our pediatric population, requiring the culturing of up to 4 or 4.5% of a patient’s total blood volume for the reliable detection of pathogens and appropriate, timely changes in empiric therapy.

In two well-documented studies, only 25 to 26% of pediatric patients who were admitted to intensive care units with clinical evidence of sepsis had blood cultures from which pathogens were recovered (16, 29). Previous studies which have based a diagnosis on a single small-volume blood culture have underestimated the prevalence of bacteremia in children (15). Blood volumes traditionally used for cultures for infants and older children are frequently inadequate for the comprehensive and rapid detection of pathogens which may be present in relatively low concentrations in the blood (15, 17, 24, 30). As little as 1 ml of blood has been routinely cultured for pediatric patients (8), and a recent report suggests that 0.2 ml of blood provided 95% sensitivity, compared to 2 ml of blood, for infants from birth to 12 months of age (32). In another recent study, only 1 to 3 ml of blood was cultured in a single aerobic bottle for children between 3 and 36 months of age and at risk for occult bacteremia (22).

Low-level bacteremia (<10 CFU/ml) may be more common in pediatric patients than has been previously thought and has been reported in up to 38% of culture-positive children, as previously reviewed (20). Reasons for culturing small volumes of blood from pediatric patients have included concern about the small blood volumes of younger patients (11, 13, 21, 30, 31), difficulties frequently encountered in obtaining blood from children (15, 30), desires both to avoid the need for blood transfusions after repeated phlebotomies (24, 30, 31, 39) and to start antibiotics without delay (10–13, 39), and the common belief throughout the 1990s that bacterial concentrations are often greater (“far greater” [32]) in the blood of younger patients than in that of adults (26, 28, 39, 40). However, the advantages of culturing larger volumes of blood from children and inoculating two or more culture devices (bottles and/or Isolators) include an increase in the number of children from whom pathogens are detected (8, 9, 15, 17, 24, 30, 35, 39), a decrease in detection times (15, 35), an improved ability to differentiate pathogens from contaminants (1, 5, 25, 34, 37, 39), assistance either with the selection of more specific antimicrobial agents when a pathogen is detected and identified or with the discontinuation of unnecessary therapy when a sensitive blood culture system remains negative for pathogens (2, 6, 12, 14, 25, 33, 37, 39), reduction of both overall costs (6, 7, 36) and selection of resistant microorganisms (6) when empiric therapy is changed to specific therapy following the report of positive blood cultures, and additional reimbursement when pathogens are detected (4).

A recent study at York Hospital determined both that 68% of our infants up to 2 months of age had low-level bacteremia and that culturing of up to 6 ml of blood (up to 4.5% of an infant’s total blood volume) was required for the detection of pathogens from those infants (19). It seems appropriate that the volume of blood cultured from a pediatric patient should directly depend on the patient’s weight (and total blood volume) and age (17, 20, 27). The current study was undertaken to determine the frequency of low-level bacteremia in the York Hospital general pediatric population as well as the importance of blood volume cultured for the detection of pathogens and the impact of positive blood culture reports on appropriate changes in empiric therapy.

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RESULTS

From 1 June 1995 until 13 June 1999, blood cultures were done for 3,829 pediatric patients. The age range was newborn to 15 years (mean, 2.3 years; median, 1.0 year). Contaminants were recovered from one or more devices in 267 (3.4%) of the 7,930 cultures from these patients, including 165 (21.1%) of 7,916 Isolators, 64 (2.0%) of 3,219 aerobic bottles, and 67 (1.2%) of 5,763 anaerobic bottles. During the 4-year interval, 137 patients (or 3.6% of the total) had 140 episodes of bacteremia or fungemia involving 147 pathogens. The age range of these patients was newborn to 15 years (mean, 2.2 years; median, 0.6 year). One patient had three separate septic episodes with different pathogens over a 6-week interval, and another had two episodes, 3 months apart. Of the 137 patients with significant isolates, 82 (60%) were male and 55 (40%) were female. The mortality rate for these patients was 5.1% (7 of 137).

Although a wide variety of pathogens were recovered from the patients, Streptococcus pneumoniae and the Enterobacteriaceae accounted for 86 (58.5%) of the 147 isolates (Table 2). As expected, Escherichia coli and Streptococcus agalactiae accounted for more than half (29; 50.9%) of the 57 pathogens detected from infants up to 2 months old but were infrequently recovered from older children. Although S. pneumoniae was isolated from the blood of children of all ages, it was detected most frequently and was the predominant pathogen in patients 2 months to 1 year old. Polymicrobial bacteremia occurred in 5 (3.6%) of the 140 septic episodes, and yeasts were recovered in only 3 (2.1%) of the episodes. Anaerobes were detected in 3 (3.5%) of the 86 episodes for which anaerobic culture bottles were inoculated.

Of the 121 patients whose pathogen concentration in blood could be determined because of positive Isolator cultures, 73 (60.3%) had low-level bacteremia (≤10 CFU/ml) and 28 (23.1%) had extremely low pathogen concentrations (≤1.0 CFU/ml), including 38% of those with Staphylococcus aureus and over one-third of those with Enterobacteriaceae (Table 3). Concentrations of ≤10 CFU/ml for one or more pathogens were found in the blood of four of five children with polymicrobial bacteremia and five of seven who died. The average detection times were 23.2 h (range, 10 to 61 h) for low-level bacteremia and 17.5 h (range, 8 to 48 h) for high-level bacteremia. These differences in detection times were not significant. Detection times when only bottles were positive ranged up to 91 h.

From one 2-year-old patient, only a single colony of Streptococcus pyogenes was recovered from 1 ml of blood (1 CFU/ml) on one Isolator-inoculated culture plate. Two bottles and another Isolator inoculated with a total of 7 ml of blood from this child were all culture negative. From another child (1 month old), only two colonies of S. pyogenes (1.3 CFU/ml) were recovered from one Isolator, which contained 1.5 ml of blood, while two other culture devices (another Isolator and an anaerobic bottle) inoculated with a total of 11.5 ml of additional blood also failed to recover the pathogen. False-negative results for Isolators or bottles were very common for our young patient population. Of 144 pathogens re-
covered when two or more culture devices were inoculated, 85 (59.0%) failed to grow from one or more of the culture devices, which were often inoculated with as much as 5 to 10 ml of blood each. For example, of pathogens recovered when only two culture devices were inoculated, 10 (43.5%) of 23 failed to grow from one of the devices. Of pathogens detected when three blood culture devices were used, 13 (20.6%) and another 21 (33.3%) of 63 failed to be recovered from one and two of the devices, respectively. When four blood culture devices were inoculated, all within 20 min. These devices consisted of two aerobic bottles of the six devices inoculated, and the detection time was 91 h. No other sites were cultured for this patient. A 2-day-old patient from whom the Salmonella species was recovered with blood cultured within 4 days of birth) had been pretreated within 4 days of blood sample collection. Seven of the 10 pretreated children had been given antibiotics, either alone or in combination, which were later determined to be appropriate for the recovered pathogens; 5 (71.4%) of those 7 had low-level bacteremia. Of the 128 children for whom antibiotic therapy records were available, 10 (7.4%) of the children (or their mothers, if infants were bacteremic within 4 days of birth) had been pretreated within 4 days of blood sample collection. Seven of the 10 pretreated children had been given antibiotics, either alone or in combination, which were later determined to be appropriate for the recovered pathogens; 5 (71.4%) of those 7 had low-level bacteremia. Of the 128 children for whom antibiotic therapy records were available, 10 (7.4%) of the children (or their mothers, if infants were bacteremic within 4 days of birth) had been pretreated within 4 days of blood sample collection. Seven of the 10 pretreated children had been given antibiotics, either alone or in combination, which were later determined to be appropriate for the recovered pathogens; 5 (71.4%) of those 7 had low-level bacteremia. Of the 128 children for whom antibiotic therapy records were complete (7 patients died soon after blood sample collection), therapy was either started or changed following notification of positive blood cultures for 88 (68.8%), including 1 of 3 patients with anaerobes, 2 of 4 (for whom records were complete) with polymicrobial bacteremia, 53.7% (22 of 31), and 89.3% (25 of 28) of the pathogens when 0.1 to 1.0, 1.1 to 10, and >10 CFU, respectively, of the pathogens per ml of blood were recovered with the Isolators. Similarly, anaerobic bottles detected 46.4% (13 of 28), 71.0% (22 of 31), and 89.3% (25 of 28) of the pathogens when 0.1 to 1.0, 1.1 to 10, and >10 CFU, respectively, of the pathogens per ml of blood were detected with the Isolators.

Of 135 patients from whose blood pathogens were recovered and for whom antibiotic pretreatment records were available, only 10 (7.4%) of the children (or their mothers, if infants were bacteremic within 4 days of birth) had been pretreated within 4 days of blood sample collection. Seven of the 10 pretreated children had been given antibiotics, either alone or in combination, which were later determined to be appropriate for the recovered pathogens; 5 (71.4%) of those 7 had low-level bacteremia. Of the 128 children for whom antibiotic therapy records were complete (7 patients died soon after blood sample collection), therapy was either started or changed following notification of positive blood cultures for 88 (68.8%), including 1 of 3 patients with anaerobes, 2 of 4 (for whom records were complete) with polymicrobial bacteremia, 53.7% (22 of 41) with Streptobacillus moniliformis (1); and Enterobacter cloacae (2); Enterobacter aerogenes (1); Enterobacter agglomerans (1); and Serratia marcescens (1). Covering when two or more culture devices were inoculated, 85 (59.0%) failed to grow from one or more of the culture devices, which were often inoculated with as much as 5 to 10 ml of blood each. For example, of pathogens recovered when only two culture devices were inoculated, 10 (43.5%) of 23 failed to grow from one of the devices. Of pathogens detected when three blood culture devices were used, 13 (20.6%) and another 21 (33.3%) of 63 failed to be recovered from one and two of the devices, respectively. When four blood culture devices were inoculated, all within 20 min. These devices consisted of two aerobic bottles of the six devices inoculated, and the detection time was 91 h. No other sites were cultured for this patient. A 2-day-old patient from whom the Salmonella species was recovered with blood cultured within 4 days of birth) had been pretreated within 4 days of blood sample collection. Seven of the 10 pretreated children had been given antibiotics, either alone or in combination, which were later determined to be appropriate for the recovered pathogens; 5 (71.4%) of those 7 had low-level bacteremia. Of the 128 children for whom antibiotic therapy records were complete (7 patients died soon after blood sample collection), therapy was either started or changed following notification of positive blood cultures for 88 (68.8%), including 1 of 3 patients with anaerobes, 2 of 4 (for whom records were complete) with polymicrobial bacteremia, 53.7% (22 of 41) with Streptobacillus moniliformis (1); and Enterobacter cloacae (2); Enterobacter aerogenes (1); Enterobacter agglomerans (1); and Serratia marcescens (1).
TABLE 3. Relative concentrations of Isolator-recovered pathogens from septic episodes in children

<table>
<thead>
<tr>
<th>Pathogen (no. of septicepisodes)</th>
<th>No. (%) of Isolator-recovered pathogens detected at the following CFU/ml of blood*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤1.0</td>
</tr>
<tr>
<td>Corynebacterium spp. (2)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>3 (33)</td>
</tr>
<tr>
<td>S. aureus (13)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>S. epidermidis (6)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Coagulase negative, other (2)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>1 (33)</td>
</tr>
<tr>
<td>S. agalactiae (9)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>S. pneumoniae (41)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>S. pyogenes (3)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Viridans group (1)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Enterococcus spp. (4)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Cappnoclostridium spp. (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Escherichia coli (22)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Other (5)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Flavobacterium meningosepticum (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Haemophilus influenzae (3)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Moraxella catarrhalis (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Neisseria meningitidis (1)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Candida spp. (3)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Total (121)</td>
<td>28 (23.1)</td>
</tr>
</tbody>
</table>

* If multiple Isolator cultures were positive for any one septic episode, the Isolator culture with the highest recovery in CFU per milliliter was recorded. A total of 121 patients had one or more Isolators with significant microbial isolates.

(35.2%) of the patients. The average total, inclusive cost per case per day at York Hospital is $1,237.00.

**DISCUSSION**

In our community hospital’s population of children from birth to 15 years of age, low-level bacteremia was quite common, occurring in 60% of those whose culture results could be quantified using Isolators. Four of five with polymicrobial bacteremia, and five of seven who died. Pathogens from 23% of the children with bacteremia were detected as only a single colony (<1 CFU/ml of blood) from Isolators inoculated with up to 10 ml of blood. The frequency of low-level bacteremia in our pediatric population is higher than that (up to 38%) in other similar populations, as previously reviewed (20), and our pediatric population is higher than that (up to 38%) in our younger patients, along with the frequent occurrence of low-level bacteremia in the current study than in previous reports may be due to the blood volumes cultured, the combination of Isolators and bottles used, or patient population differences.

The sensitivities of Isolators and bottles for microbial pathogens were not compared in the current study due to the different blood volumes frequently inoculated into the culture devices making up a set. However, neither Isolators, aerobic bottles, nor anaerobic bottles allowed for the detection of more than 75% of the pathogens when other blood culture devices used for the same patients during the same septic episodes were positive. This finding again illustrates the importance of both blood volume cultured and the routine use of two or more types of culture devices. Despite the frequently larger volumes of blood inoculated into bottles than into Isolators, the higher the concentration of pathogens in the blood (as determined with Isolators), the greater the likelihood of detection of the pathogens in the bottles. False-negative blood culture bottles were more common for patients with low-level bacteremia than for those with high concentrations of pathogens in the blood. The relative concentration of microorganisms in the blood is due to various factors, including antibiotic pretreatment, the severity of disease, and species and strain variations (3, 20, 37). While up to 48% of pediatric patients have been reported to be receiving antibiotics at the time when blood cultures are collected (2, 20, 24), only 7.4% of patients from whom pathogens were detected in the current study had been given antibiotics immediately prior to culture collection. Therefore, factors in addition to antibiotic pretreatment accounted for the majority of our cases of low-level bacteremia.

Culturing larger volumes of blood from our pediatric patients is expensive in terms of both material and labor. However, in addition to potentially improving patient outcomes, such an aggressive approach may result in substantial short- and long-term savings for hospitals, related to a reduction in the use of unnecessary empiric antibiotics once pathogens are detected (or ruled out [14]), a decrease in the duration of hospital stays, and a reduction in the emergence of antibiotic-resistant pathogens within the hospital environment. In addition, documentation of pathogens in the blood associated with another (primary) focus of infection may result in additional reimbursement to the hospital. In the current study, of the children for whom antibiotic therapy following notification of positive blood cultures could be determined, empiric therapy was changed for 64.8%, including reduced antibiotic costs for 53.9% and reduced spectra of activity for 59.4%. The cost of unnecessary antibiotic therapy has been reported to range from $158 to $716 per patient (2, 36). The average savings for York Hospital if a patient’s stay can be reduced by only 1 day is $1,237. Boschman et al. have reported that there has been an average of a $3,819 (range, $2,467 to $13,497) increase in
reimbursement following the isolation of a bloodstream pathogen associated with a respiratory, gastrointestinal, cardiovascular, renal, or skin infection (4).

Low-level bacteremia is common in our pediatric patient population. Its detection has been optimized by culturing up to 4 or 4.5% of a patient’s total blood volume. Potential advantages of such an approach have included increased detection of pathogens, a reduction in detection times, an improved ability to differentiate pathogens from saprophytes, assistance in the selection of specific antibiotics when a pathogen is detected, and both a reduction of hospital costs (due to appropriate antibiotic changes and reduced duration of hospital stays) and an increase in reimbursement associated with the increased detection and identification of pathogens.

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