Ruling Out Bacteremia and Bacterial Meningitis in Infants Less Than One Month of Age: Is 48 Hours of Hospitalization Necessary?

abstract

OBJECTIVE: The appropriate duration of hospitalization for infants ≤ 30 days admitted for fever or other concerns for a serious bacterial infection is an understudied area. We sought to determine the risk of a positive, pathogenic bacterial culture of blood or cerebrospinal fluid (CSF) in this population beyond 24 hours after collection.

METHODS: This study was a retrospective review of 1145 infants aged ≤ 30 days who had a blood or CSF culture from 1999 to 2010 at Santa Clara Valley Medical Center, a county health system in San Jose, California. Time to notification and the probability of a positive culture result after 24 hours were calculated. Infants were considered high risk if they had either a white blood cell count < 5000 or > 15000 per µL, a band count > 1500 per µL, or an abnormal urinalysis.

RESULTS: We identified 1876 cultures (1244 blood, 632 CSF) in 1145 infants aged ≤ 30 days; 901 (79%) of 1145 were hospitalized and 408 (45%) of 901 hospitalizations were for fever without source (FWS). Thirty-one (2.7%) of the 1145 infants had pathogenic cultures; 6 of 1145 infants (0.5% [95% confidence interval: 0.2–1.1]) had a time to notification > 24 hours. All 6 patients had FWS (1.5% of hospitalized FWS sample) and met high-risk criteria on presentation. None of the low-risk patients had a time to notification > 24 hours. Low-risk characteristics were found in 57% (232 of 408) of the entire hospitalized FWS population.

CONCLUSIONS: Low-risk infants hospitalized for FWS or other concerns for serious bacterial infection may not need hospitalization for a full 48 hours simply to rule out bacteremia and bacterial meningitis.

Given the inability of clinical prediction models to accurately predict serious bacterial infections in infants aged ≤ 30 days,1,2 common practice for this age group is hospitalization for a sepsis evaluation and administration of intravenous antibiotics.3,4 As a recent review demonstrated,5 the appropriate length of hospitalization for well-appearing infants presenting with fever remains an area without definitive guidance from commonly used sources.6–8

A recent study suggested a low prevalence (2.8%) of bacteremia and bacterial meningitis in infants 7 to 28 days old, although this study did not specifically address appearance, fever at presentation, or time to positivity.9 Reports of time to positivity of blood and cerebrospinal fluid (CSF) cultures in neonates suggest that a 48-hour period is necessary to capture an acceptable percentage (generally 95%–99%) of cases,10,11 and at least 1 investigation has recommended as long as 72 hours.12 However, these studies included infants in ICUs, increasing estimates...
of time to positivity due to inclusion of organisms such as coagulase-negative staphylococci and yeasts as pathogens often drawn from central lines. A recent survey of pediatric hospitalists showed that 84% favored a period of hospitalization >36 hours for infants aged <30 days. The practice in our hospital has been to provide intravenous antibiotics until culture results are negative at 48 hours.

Recently, a large study in Utah demonstrated the effectiveness of an evidence-based care protocol for discharge at 24 to 36 hours for well-appearing febrile infants ≤28 days old presenting as outpatients, although this study did not specifically address time to positivity of cultures. One study examined time to positivity in infants aged ≤3 months, specifically excluding cultures drawn from central lines but did not stratify according to age.

The aims of the current study were to determine the probability of positive pathogenic blood and CSF cultures after 24 hours in infants aged ≤30 days hospitalized outside of an ICU setting for suspected serious bacterial infections and to assess whether stratifying infants into high- and low-risk categories based on presentation modifies that probability.

METHODS
This was a retrospective cohort study using a microbiology database from Santa Clara Valley Medical Center (SCVMC) and accompanying medical records of identified patients within this database. The study was approved by the institutional review board at SCVMC. Based in San Jose, California, SCVMC is the county hospital for Santa Clara County, with 1800 to 2200 annual admissions to the pediatric ward.

We first identified all infants ≤30 days old who had blood and/or CSF cultures performed at SCVMC between January 1, 1999, and December 31, 2010. Infants with cultures sent from the pediatric clinics, emergency department, or pediatric ward were included. Outpatients are generally not admitted to the NICU in our institution. In addition, ill-appearing infants are generally admitted to the PICU. As such, infants with cultures sent from the NICUs and PICUs were excluded.

Infants hospitalized with fever without source (FWS) were identified by examining the pediatric ward admission logbooks for admission and discharge diagnoses consistent with fever (eg, “fever,” “fever without source,” “rule-out sepsis,” “rule-out serious bacterial infection,” “hyperthermia”). All infants with logbook entries consistent with fever underwent a comprehensive review. The purpose of this review was: (1) to confirm the admission diagnosis of FWS; and (2) to gather clinical and laboratory characteristics of the infants with confirmed fever to classify them as low or high risk at presentation. In addition, the charts of all infants with pathogenic blood or CSF cultures were reviewed to determine whether the infant was admitted with FWS. Subjects were excluded from the FWS population if they did not have a reported or documented temperature ≥38°C taken by any method, if they had an indwelling central venous catheter at the time of presentation, or if patients received their initial evaluation or treatment outside of our system (eg, a referring emergency department). Multiple hospitalizations of the same infant were considered as separate events.

Bacterial Growth and Time to Notification
Bacteremia and bacterial meningitis were defined as growth of a pathogen in a blood culture or a CSF culture, respectively. A pediatric infectious disease specialist (Dr Hong) retrospectively assessed whether positive culture results represented pathogens or contaminants, based on whether the isolated organism was a known pathogen that could cause a serious bacterial infection in otherwise healthy infants, independent of the specific clinical history or time to notification. Cultures that only isolated typical skin contaminants such as coagulase-negative staphylococci or viridans-group streptococci were considered nonpathogenic and were classified as negative.

The time to notification was determined for each case of bacteremia and bacterial meningitis. Time to notification was defined as the time elapsed between sample collection and initial notification of the medical staff of a positive culture result. All cultures drawn in any of our inpatient or outpatient settings are processed by the microbiology laboratory. A single BacT/ALERT (bioMérieux, Inc, Durham, NC) SA (aerobic media) 40-mL bottle is used for blood culture. Hospital policy is to draw 1 to 2 mL of blood for infants aged ≤30 days, although volume data are inconsistently reported for individual cultures. The BacT/ALERT 3D Blood Culture instrument continuously monitors blood cultures for growth. If growth is detected by the instrument during the day (8 AM–5 PM), a Gram stain is performed by the microbiology clinical laboratory scientist, and the ward staff is called immediately with the positive result and the preliminary morphology. If growth occurs...
overnight (5 PM–8 AM), the ward staff is called the following morning (generally 8 AM–9 AM). Time to notification can therefore be longer (but not shorter) than the true time to positivity, and it reflects the actual practice in our institution. CSF samples are cultured on standard agar media and enrichment broth, and they are examined by a microbiology clinical laboratory scientist once per day. Mean and median time to notification were calculated for both pathogenic cultures and contaminants, and values were compared by using a Wilcoxon rank sum test.

To describe the risk of detecting bacteremia and bacterial meningitis after 24 hours, the proportion and corresponding 95% confidence intervals (CIs) of infants with pathogenic cultures and time to notification >24 hours were calculated. Two denominators were used: all patients for whom a blood and/or CSF culture was obtained and all patients who were hospitalized with FWS. The proportion of FWS infants with bacteremia or bacterial meningitis who had positive culture results at >24 hours was also calculated. All patients hospitalized for FWS and all patients with bacteremia and/or bacterial meningitis underwent a comprehensive medical records review to identify clinical and laboratory characteristics upon presentation.

Risk criteria were chosen that closely mirror published Rochester criteria, with the exception of an expanded definition of what constitutes a negative urinalysis (UA). Infants were classified as low risk if they met the following characteristics: a nontoxic initial appearance (absence of “toxic,” “lethargic,” or “septic” in the medical record), a white blood cell (WBC) count of 5000 to 15000 per µL, an absolute band count ≤1500 per µL, and a negative UA (≤10 WBCs per high-power field, leukocyte esterase <2+, and negative nitrites). The percentage of high- and low-risk infants was calculated for the infants with bacteremia or bacterial meningitis and for infants with negative culture results. Infants were determined to have a urinary tract infection (UTI) if they had urine cultures showing growth of >50000 CFU/mL of a pathogenic organism from a catheterized specimen or >100000 CFU/mL from a bag or clean-catch specimen. Because medical staff are not contacted directly with positive
TABLE 1 True Pathogens in Infants Aged ≤30 Days (N = 1880 Cultures)

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Bacteremia (n = 1248)</th>
<th>Bacterial Meningitis (n = 632)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E coli</td>
<td>18</td>
<td>3a</td>
</tr>
<tr>
<td>S aureusb</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28 (2.2%)</td>
<td>5 (0.8%)</td>
</tr>
</tbody>
</table>

* Two cases of simultaneous bacteremia and bacterial meningitis.

b Includes 1 case of methicillin-resistant S aureus.

statistical analysis was performed by using Stata version 11 (StataCorp, College Station, TX).

RESULTS

We identified 1876 cultures (1244 blood, 632 CSF) in 1145 infants ≤30 days old. Five hundred eighty (50.7%) infants had both blood and CSF cultures. Of the 1145 infants, 19 presented twice in their first 30 days of life, for a total of 1164 patient encounters involving bacterial blood and CSF cultures (Fig 1). Four hundred eighty infants had admission and/or discharge diagnoses in the admission logbook consistent with FWS, representing 484 hospitalizations. Four infants were admitted twice. Further medical records review of the 484 hospitalizations revealed that 408 (84%) of these were confirmed to be for FWS, 71 (15%) were for other causes, and 5 (1%) had missing or incomplete data.

Bacterial Growth and Time to Notification

In the overall sample, bacterial growth was present in 196 cultures from 189 (16.5%) of 1145 infants. Thirty-three cultures in 31 (2.7%) of 1145 infants were determined by a pediatric infectious disease specialist to represent true pathogens (Table 1). The following organisms were classified as contaminants: Bifidobacterium species, diphtheroids, coagulase-negative staphylococci, Propionibacterium species, and viridans-group streptococci. The majority of contaminants (74%) were coagulase-negative staphylococci.

Contaminants comprised 10.9% (135 of 1244) of the blood cultures and 4.4% (28 of 632) of the CSF cultures. Mean ± SD and median (interquartile range) time to notification were 24.5 ± 17.1 and 19 (16.5–22) hours for pathogens and 45.3 ± 30.7 and 35.8 (30.3–37.1) hours for contaminants, respectively (P < .001).

Six of the 1145 (0.5% [95% CI: 0.2–1.1]) infants in the overall sample had pathogenic culture results with a time to notification >24 hours (Table 2). All 6 were hospitalized for FWS, accounting for 6 of 408 (1.5% [95% CI: 0.5–3.2]) FWS hospitalizations. Of the 25 patients with positive culture results and a time to notification <24 hours, 20 were hospitalized for FWS and 5 were hospitalized for other reasons (1 apnea, 1 bullous impetigo, 1 osteomyelitis, 1 apparent life-threatening event, and 1 necrotizing enterocolitis). One infant hospitalized with FWS and bacteremia was noted to be ill-appearing on admission. Thus, 6 (24%) of 25 well-appearing infants hospitalized for FWS with bacteremia and/or bacterial meningitis had cultures with time to notification >24 hours.

Clinical Characteristics

Clinical characteristics of the 6 infants with time to notification >24 hours are presented in Table 3. Three of these infants had a time to notification between 24 and 48 hours, and all 3 of these notifications occurred in the morning (between 8 AM and 10:30 AM), indicating that the true time to positivity for these infants may have actually been <24 hours. The 6 cases included 5 cases of bacteremia (2 infants with Escherichia coli UTI and bacteremia, 1 infant with enterococcus UTI and bacteremia, 1 infant with Staphylococcus aureus, and 1 infant with Staphylococcus aureus with other pathology).
aureus UTI and bacteremia, and 1 infant with group B streptococcus bacteremia) and 1 case of enterococcus meningitis. All 6 infants looked well but had at least 1 high-risk laboratory value.

Medical records review of the 408 hospitalizations for FWS revealed that 232 (57%) were low risk and 176 (43%) were high risk at presentation (Table 2). Of the low-risk infants with negative culture results at 24 hours, 0 of 224 (0% [97.5% CI: 0–1.6]) had positive culture results with a time to notification >24 hours. At first glance, this percentage is seemingly high. However, in the context of whether to discharge an infant with FWS at 24 hours, the more clinically meaningful proportion to consider is the absolute risk of a positive culture result beyond 24 hours (6 of 388 [1.5%]). This proportion enables a calculation of number-needed-to-treat (NNT), a useful metric to interpret the results of our study.

A total of 66 (16.1%) of 408 FWS hospitalizations had urine culture findings meeting our definition of UTI. Of these, 58 (88%) of 66 had a positive UA. Of the 8 infants with UTI and a negative UA, 3 had at least 1 other high-risk criterion (elevated WBC or band count) or had documentation of urine growth in the medical chart within 24 hours of hospitalization. Therefore, a total of 5 low-risk patients would not have been diagnosed with a UTI until after 24 hours of hospitalization. Of note, in 3 of these 5 patients, the primary team did not treat the urine culture results as a true UTI.

**DISCUSSION**

Over a 12-year period in our institution, a very small percentage of blood and/or CSF cultures in infants aged ≤30 days had a time to notification >24 hours, and no culture results were positive after 24 hours in febrile infants who appeared well and had laboratory values at presentation that put them at low risk according to previously published criteria. However, the overall number of infants with FWS and positive culture results was low (n = 26), and 24% (6 of 25) of the positive culture results in well-appearing infants had a time to notification >24 hours. At first glance, this percentage is seemingly high. However, in the context of whether to discharge an infant with FWS at 24 hours, the more clinically meaningful proportion to consider is the absolute risk of a positive culture result beyond 24 hours (6 of 388 [1.5%]). This proportion enables a calculation of number-needed-to-treat (NNT), a useful metric to interpret the results of our study.

For infants aged ≤30 days who present with FWS, a high NNT is acceptable given the potentially devastating consequences of untreated bacteremia and/or bacterial meningitis. In our entire FWS sample, −6% of infants had a positive blood or CSF culture result, corresponding to an NNT of 17. In other words, −17 infants need to be hospitalized and treated with intravenous antibiotics to prevent missed or delayed treatment in 1 infant. For infants with negative culture results at 24 hours, 1.5% of infants in our sample ultimately had a positive culture result, corresponding to an NNT of −67, meaning that 67 infants would need to remain in the hospital beyond 24 hours to prevent 1 from being discharged with a partially treated infection. In the event that a culture becomes positive after 24 hours in a partially treated infant who has been discharged, the consequence in some cases may simply be readmission to the hospital, suggesting that the number of infants who need to be hospitalized beyond 24 hours to prevent a truly bad outcome (beyond readmission) may in fact be higher than 67. The outcomes of untreated or partially treated bacteremia and bacterial meningitis have not been adequately studied, but clearly such considerations are necessary when assessing the risks and benefits of ongoing hospitalization.

Although 6 infants developed positive blood or CSF culture results after 24 hours, all 6 had at least 1 high-risk characteristic, suggesting that in infants who have negative culture results at 24 hours, initial laboratory values (particularly a positive UA) might be used to modify the probability that a blood or CSF culture will turn positive. Although many previous investigations have used risk stratification to modify the probability of serious bacterial infection at the time of initial presentation,1−3 only 1 has examined time to positivity data in conjunction with risk criteria to update the risk of serious bacterial infection subsequent to the infant’s initial presentation.16 However, the study evaluated infants

### TABLE 3 Clinical and Laboratory Characteristics of Infants With TTN >24 Hours (n = 6)

<table>
<thead>
<tr>
<th>Age (d)</th>
<th>TTN</th>
<th>Organism</th>
<th>Site of Infection</th>
<th>High-Risk Characteristics</th>
<th>Other Laboratory Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>36 h</td>
<td>Enterococcus</td>
<td>Blood, urine</td>
<td>↑ WBCs; ↑ ABC; +UA</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>62 h</td>
<td>E. coli</td>
<td>Blood, urine</td>
<td>↑ ABC</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>77 h</td>
<td>S. aureus</td>
<td>Blood, urine</td>
<td>↑ WBCs; +UA</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>84 h</td>
<td>Enterococcus</td>
<td>CSF</td>
<td>↑ WBCs; ↑ ABC</td>
<td>CSF WBCs 18/HPF; C-reactive protein 4.1</td>
</tr>
<tr>
<td>25</td>
<td>28 h</td>
<td>E. coli</td>
<td>Blood, urine</td>
<td>+UA</td>
<td>CSF WBCs 36/HPF; C-reactive protein 16.3</td>
</tr>
<tr>
<td>27</td>
<td>29 h</td>
<td>Group B streptococcus</td>
<td>Blood</td>
<td>↑ WBCs; ↑ ABC</td>
<td>Chest radiograph with infiltrate</td>
</tr>
</tbody>
</table>

ABC, absolute band count; HPF, high-power field; TTN, time to notification.
28 to 90 days of age. The authors concluded that the risk of identifying serious bacterial infection after 24 hours was 0.3% in low-risk infants. Our data suggest that the risk is similarly low in infants <1 month of age.

Although we focused primarily on FWS hospitalizations, we also demonstrated that none of the infants who had blood and/or CSF cultures obtained for reasons other than FWS had pathogenic growth between 24 and 48 hours. Therefore, continued hospitalization of these infants for 48 hours may be unnecessary if the patient has otherwise been deemed ready for discharge.

Discharge before 48 hours may also be considered for high-risk infants with negative culture results at 24 hours. Although 48 hours of observation is an understandable approach for these infants, only a small percentage of these children will have bacterial growth between 24 and 48 hours (3 of 164 [1.8%] in our study). Our study did not address the role of nasopharyngeal viral testing, as this modality was used inconsistently in our patient sample. However, viral testing results may be able to further modify risk of bacterial infections and reduce length of stay, even in patients with high-risk laboratory characteristics.

Some limitations to our study should be noted. First, the sample size of well-appearing infants hospitalized for FWS with bacteremia and/or bacterial meningitis was low, leading to wide CIs around the proportion of infants who do not have a skin or soft tissue infection or pneumonia.

Contaminated cultures were more common in our sample than reports from previous studies would predict. Our hospital surveillance of contamination rates is done by unit, not by age, so the high rates in this subgroup of patients (≤30 days) had gone unnoticed and have since led to several interventions that have resulted in an overall reduction in blood culture contamination. As demonstrated by this investigation and previous studies, a positive blood or CSF culture result beyond 24 hours after presentation is most likely to be a contaminant, and the clinician must decide how to respond to the culture result based on available information, especially the bacterial morphology on Gram stain. Notification of a positive culture result on a recently discharged infant adds a potential burden to outpatient pediatricians, especially in institutions with high contaminant rates.

Our study did not use positive urine culture results for the preliminary identification of infants or in the time to notification analysis. Some infants with UTI may not develop urine culture growth within 24 hours of admission. If these low-risk patients (defined in part as a negative UA) with negative culture results at 24 hours are discharged at that time point, a small percentage (5 of 66 UTIs or 5 of 408 FWS hospitalizations in our study) may eventually be diagnosed with a UTI. However, these patients will have received at least 24 hours of intravenous antibiotics. Although a prolonged course...
of intravenous antibiotics is generally warranted for bacteremia and bacterial meningitis, it is less clear that long courses of intravenous antibiotics are necessary to treat UTIs. A recent retrospective investigation of the Pediatric Health Information System database found that ∼30% of infants <1 month of age with a UTI received ≤3 days of intravenous antibiotics, with no statistically significant effect on treatment failure. In addition, Byington et al have recently shown that discharge at 24 to 36 hours can be implemented for low-risk infants without increasing the risk of missed UTI. A practitioner’s general approach to UTI management in this age group will dictate to what degree the risk of a delayed diagnosis of UTI should influence the timing of hospital discharge. Ultimately, clinical judgment, risk tolerance, and family preferences should drive the decision-making for all infants with FWS, including those with possible UTI.

CONCLUSIONS

Our study supports previously published data that bacteremia and bacterial meningitis are rare in febrile but well-appearing infants. Although nearly 25% of infants with bacteremia or bacterial meningitis will not turn positive until >24 hours, the absolute risk of a positive culture result beyond 24 hours is low (1.5%), and even lower (0%) in infants with normal laboratory values on presentation.

REFERENCES

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