

Time to Detection of Positive Cultures in 28- to 90-Day-Old Febrile Infants

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ABSTRACT. *Objective.* To determine the time to detection of positive blood, urine, and cerebrospinal fluid (CSF) cultures among febrile 28- to 90-day-old infants.

Study Design. Retrospective cohort of consecutive 28- to 90-day-old infants presenting with a temperature of $\geq 38^{\circ}\text{C}$ to an urban pediatric emergency department. Positive cultures and times to detection were noted. Patients were categorized as being at high risk for serious bacterial illness (SBI) based on clinical and laboratory criteria.

Results. Of the 3166 febrile infants seen in the emergency department during the study, 2733 had blood (86%), 2517 had urine (80%), and 2361 had CSF (75%) specimens obtained for culture, and 2190 had all 3 cultures (69%) sent. There were 224 positive cultures in 214 patients; of these, 191 had all 3 cultures (89%) sent. Subsequent analyses were confined to those who had all 3 cultures sent. The detected rate of SBI was 8.7% (191/2190). There were 28 positive blood cultures (1.3%), 165 positive urine cultures (7.5%), and 8 positive CSF cultures (.4%). Median time to detection of positive cultures was 16 hours for blood, 16 hours for urine, and 18 hours for CSF. Four blood cultures (.1%), 20 urine cultures (.9%), and 0 CSF cultures were noted to have growth of a pathogen >24 hours after the specimen was obtained. All 4 blood cultures and 17 of 20 urine cultures with growth noted after 24 hours occurred among high-risk patients.

Conclusions. The risk of identifying SBI after 24 hours is 1.1% among all 28- to 90-day-old febrile infants and .3% in low-risk infants. *Pediatrics* 2000;106(6). URL: <http://www.pediatrics.org/cgi/content/full/106/6/e74>; *serious bacterial illness, febrile infants.*

ABBREVIATIONS. SBI, serious bacterial illness; CSF, cerebrospinal fluid; ED, emergency department; CI, confidence interval; CBC, complete blood cell count.

Up to 15% of 28- to 90-day-old febrile infants may have serious bacterial illness (SBI).¹⁻⁸ The patient's physical examination and laboratory evaluation may not detect all SBIs.⁹⁻¹⁹ No definitive data have been reported establishing the timing of detection of positive cultures. The practice guidelines by Baraff et al¹⁷ for the management of infants and children 0 to 36 months of age with fever without source include recommendations that were

made in the absence of these data. In 2 studies, low-risk infants were treated as outpatients with empiric antibiotics.^{9,15} Baskin et al¹⁵ showed that low-risk febrile infants 28 to 89 days of age can be managed safely with the administration of a parenteral dose of ceftriaxone and discharged from the hospital with a scheduled follow-up within 24 hours for clinical reevaluation and a second dose of ceftriaxone to provide antibiotic coverage while the blood, urine, and cerebrospinal fluid (CSF) cultures incubate. This strategy is based on the assumptions that most pathogens are identified within 48 hours and 2 doses of ceftriaxone will provide sufficient protection for those children whose pathogens are identified later. Other authors, using more stringent risk criteria, advocate outpatient management of low-risk febrile infants without antibiotic treatment, and inpatient management of the rest.^{10,18,19} We sought to determine the time to detection of positive cultures so that optimal strategies for management and follow-up can be devised and implemented.

METHODS

Design, Setting, and Subjects

The investigation was a retrospective cohort study. Subjects were febrile infants seen in the emergency department (ED) of an urban pediatric teaching hospital. To establish the cohort, an electronic database with ED visit information was queried to identify all patients who: 1) were 28 to 90 days old; 2) had an initial triage rectal temperature of 38°C or higher; and 3) were seen in the Children's Hospital ED from January 1, 1993 through December 31, 1997. The human subjects committee at Children's Hospital, Boston, approved this study.

Measures and Data Collection

SBI was defined as growth of a pathogen in a blood, urine, or CSF culture from specimens collected during the ED visit. The following organisms were classified as pathogens: *Streptococcus pneumoniae*, *Streptococcus pyogenes*, group B streptococci, enterococci, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* sp, *Citrobacter* sp, *Enterobacter* sp, *Proteus* sp, *Neisseria meningitidis*, *Salmonella*, and *Pseudomonas aeruginosa*. The following organisms were classified as contaminants: nonaureus staphylococci, viridans streptococci, *Micrococcus* sp, and *Corynebacterium* sp. A urinary tract infection was defined as a urine culture with ≥ 10 000 colony-forming units/mL of a single organism in urine obtained by bladder catheterization or suprapubic aspiration. The main outcome variable was time to detection of positive cultures. Time to detection was defined as the time elapsed between specimen collection and the time the culture was first recorded as positive in the microbiology laboratory; the laboratory called a physician as soon as a positive blood or CSF culture was detected. A report of positive urine cultures was generated every afternoon and sent to the ED; results could be checked 24 hours a day by the clinician providing follow-up. The database was queried and the following

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data elements extracted: age; sex; temperature; peripheral white blood cell count; urinalysis results; CSF cell counts; blood, urine, and CSF culture results; and disposition from the visit at which the cultures were drawn. For patient specimens with growth in culture, the organism(s) isolated, the time to detection, and the presence of significant preexisting medical conditions were recorded.

All patients were classified as being at high or low risk for SBI based on clinical and laboratory criteria.¹⁵ Infants were considered to be at high risk by clinical criteria if they had an identified focal bacterial infection or preexisting illness or were judged by the treating clinician to be ill appearing or to require hospital admission. Patients were categorized as high risk for SBI by laboratory criteria if they had any of the following laboratory findings: 1) peripheral leukocyte count of $\geq 20\,000/\text{mm}^3$, 2) urinalysis demonstrating ≥ 10 leukocytes per high-powered field, or 3) CSF leukocyte count ≥ 10 white blood cells/ mm^3 . Patients with missing laboratory data or bloody CSF specimens (CSF red blood cell count $\geq 10\,000/\text{mm}^3$) were considered to be at high risk. The presence of any clinical risk factors was determined by chart review for the patients with growth of a pathogen in culture(s). Analyses were performed with *SPSS for Windows, Release 9.0* (SPSS, Chicago, IL).

Culture Technique

All cultures were handled by the bacteriology laboratory of the Children's Hospital (Boston, MA). Becton Dickinson (Mountain View, CA) Bactec Peds Plus blood culture bottles were inoculated with blood obtained by peripheral venipuncture. From January 1993 through October 1995, blood cultures were evaluated for growth with the Bactec model NR660 analyzer. With this system, blood cultures were evaluated twice daily for the first 2 days and daily thereafter for 7 days. After October 1995, blood cultures were read with the Bactec model 9240, a continuous monitoring system. Urine and CSF cultures were checked twice daily for growth, once in the early morning and once in the late afternoon. Urine cultures were kept for at least 48 hours and CSF cultures for 7 days.

RESULTS

The Cohort

During the 5-year study, 3166 infants 28 to 90 days of age presented to the ED with a rectal temperature of 38.0°C or higher. Of these, 2733 had blood (86%), 2517 had urine (80%), and 2361 had CSF specimens (75%) obtained for culture, and 2190 had all 3 cultures (69%) sent. Analysis was confined to patients who had all 3 cultures sent.

Positive Cultures

There were 224 specimens from 214 infants that exhibited growth of a pathogen in culture; 191 of these patients had all 3 cultures sent. The detected rate of SBI was 8.7% (95% confidence interval [CI]: 7.7–10.0) among infants who had all 3 cultures sent. In this group there were 28 positive blood cultures (1.3%; 95% CI: .9–1.8), 8 positive CSF cultures (.4%; 95% CI: .2–.7), and 165 positive urine cultures (7.6%; 95% CI: 6.5–8.8). Organisms isolated from blood were group B streptococci (12), *E coli* (9), *S pneumoniae* (3), *S pyogenes* (2), *Salmonella* (1), and *Enterobacter cloacae* (1). Pathogens isolated from the culture of CSF included group B streptococci (4), *E coli* (3), and mixed growth of *Klebsiella pneumoniae* and enterococcus in 1 patient with a bloody sample. Of the urine cultures, 141/165 (86%) grew *E coli*. Other organisms included *Enterobacter cloacae* (5), *K pneumoniae* (5), *K oxytoca* (2), enterococcus (2), and 1 each of the following: group B streptococci, *Proteus sp*, *P aeruginosa*, *Citrobacter freundii*, *Citrobacter diversus*, and *Enterobacter aerogenes*. Four patients had the

same pathogen identified from CSF and blood culture. One infant had growth in CSF and urine cultures. Five patients had a pathogen isolated from blood and urine cultures.

Risk Status

Of the 2190 patients, 1146 (52%) met low-risk criteria and 1044 (48%) were categorized as high-risk. Of the 191 patients with a positive culture, 169 (88%; 95% CI: 83–93) met high-risk criteria and 157 (82%) were admitted from the initial encounter. Twenty-two of 28 positive blood cultures (79%; 95% CI: 59–92), 148 of 165 positive urine cultures (90%; 95% CI: 84–94) and all of the 8 positive CSF cultures (100%; 95% CI: 63–100) occurred in patients who were classified as being at high risk for SBI. Forty-two patients (2%) did not have complete blood cell count (CBC) results available, and 246 (11%) did not have urinalysis results available. All patients had CSF samples sent for cell counts. One patient with positive blood and CSF cultures did not have a CBC but was categorized as high-risk based on CSF pleocytosis and on clinical grounds. Among patients with a positive urine culture, 6 did not have a CBC and 12 did not have urinalysis results available; of these, only 1 patient was categorized as high-risk based on missing data alone.

Time to Detection

Blood cultures were reported to have growth in a median of 16 hours (range: 6–50; 90th percentile: 30), urine cultures in a median of 16 hours (range: 1–34; 90th percentile: 25) and CSF cultures in a median of 18 hours (range: 3–24; 90th percentile: 24). The times to detection of positive cultures are illustrated in Fig 1. Among low-risk infants, all 6 of the blood cultures (100%; 95% CI: 54–100), and 14 of 17 urine cultures (82%; 95% CI: 57–96) were noted to be positive within 24 hours. No low-risk patient had a positive CSF culture.

Prolonged Time to Detection

Twenty-four of the 201 positive cultures (12%; 95% CI: 10–17), or 24 of the 6570 specimens (.4%; 95% CI: .3–.6) had a pathogen detected in culture after 24 hours. This led to detection of SBI after 24 hours in 24 of 2190 (1.1%; 95% CI: .8–1.6) patients. Four of 2190 (.2%; 95% CI: .1–.5) blood cultures, 20 of 2190 (.9%; 95% CI: .7–1.4) urine cultures, and 0 of 2190 (.0%; 95% CI: .0–.1) CSF cultures were first noted to have

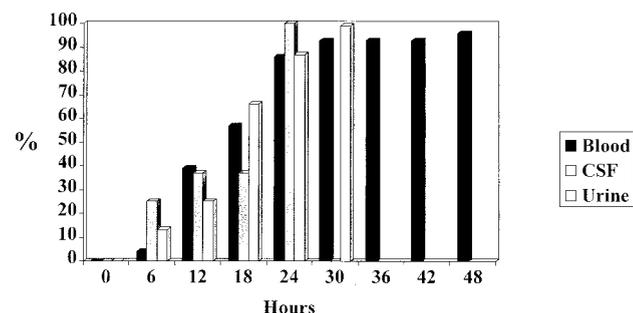


Fig 1. Times to detection of positive cultures. Percentage of positive cultures detected plotted against time in hours.

growth of a pathogen >24 hours after the specimen was obtained. SBI was detected after 24 hours in 3 of 1146 low-risk patients who had all 3 cultures sent (.3%; 95% CI: .1–.8). Four blood cultures became positive after 24 hours: 1 with *E coli* at 28 hours in a patient with a urine culture positive at 5 hours, 1 with *Salmonella* at 26 hours in a patient with enteritis, 1 with *S pneumoniae* at 48 hours, and 1 with *Enterobacter cloacae* in 51 hours in a patient with a urine culture noted to have growth at 7 hours. Overall, 26 of 28 (93%; 95% CI: 82–100) of positive blood cultures were detected within 28 hours.

The 4 blood cultures and 17 of 20 urine cultures with growth first noted after 24 hours occurred among patients considered to be at high risk of SBI based on laboratory screening, clinical evaluation, or preexisting illness.

All patients with positive cultures not initially admitted were called to return and subsequently admitted to the hospital for parenteral antibiotic therapy. All patients with positive cultures did well, and no untoward clinical outcomes were observed.

DISCUSSION

We report here on a series of over three thousand 28- to 90-day-old infants evaluated for febrile illness in our ED over a 5-year period. Our data show that 87% of SBIs are evident within 24 hours of specimen collection including all of our cases of meningitis and 86% of those with bacteremia. Only 1.1% of all patients evaluated for fever would be expected to have a blood, urine, or CSF culture first exhibit growth after 24 hours. There were 191 patients with SBI identified, of which 24 had growth of a pathogen first noted after 24 hours. Twenty-one of these 24 pathogens (including all positive blood cultures) occurred in patients classified as high-risk according to previously established criteria.¹⁵ One might expect that high-risk patients have a heavier bacterial load or more virulent organism and are less likely to have delayed growth. However, this was not the case and is likely attributable to the fact that most of the cultures that took >24 hours to identify were urine cultures, and most patients with urinary tract infections had a positive urinalysis classifying them as high-risk. Three low-risk patients with SBI, all with urinary tract pathogens, had growth detected after 24 hours. Therefore, if the clinician chooses to administer empiric antibiotics to low-risk febrile infants 28 to 90 days of age, 24 hours of antibiotic coverage should be sufficient.

The approach to the 28- to 90-day-old febrile infant varies. Several management protocols have been published.^{9,10,15,17–19} Some studies have shown that selected febrile infants may safely be managed as outpatients without the use of antibiotics.^{10,18,19} Those infants had to meet more stringent risk criteria than ours to qualify for outpatient management, and 75% of the most recent study population of infants 29 to 60 days old using this strategy were admitted.¹⁹ In our population, the strategy of Baskin et al¹⁵ was used, so all children were treated with antibiotics but only 39% (42% of 28- to 60-day-old infants and 34% of 61- to 90-day-old infants) were admitted. This

approach treats more infants but reduces the proportion hospitalized, which may decrease the cost and potential morbidity associated with hospitalization. Most patients with SBI met high-risk criteria and were admitted at the initial encounter. The outpatient use of parenteral ceftriaxone proved to be safe among those patients later identified to have SBI. This protocol included a second dose of ceftriaxone, and our data suggest that the second dose of ceftriaxone can be safely omitted. Such a reduction can potentially decrease the cost and adverse events associated with antibiotic use.

Our results have implications for the inpatient management of febrile infants. If the clinician chooses to admit infants at the initial evaluation because they do not meet low-risk criteria, most could safely be discharged after 24 hours if all culture specimens are sterile. A dose of ceftriaxone at discharge to provide antibiotic coverage beyond 24 hours may be prudent because these children are at higher risk for SBI. The cost and morbidity associated with longer hospitalizations might be reduced.

Although this study had a retrospective design, all eligible patients were included in the cohort. Because patients were included only if they had all 3 cultures sent, it was not truly a consecutive sample. Detailed data from the clinical database were available on all patients in the cohort; however, only the charts of patients with SBI were reviewed for the presence of chronic or underlying illness, preexisting bacterial illness, or clinical ill appearance. Patients with negative cultures were considered high-risk if they were admitted, because detailed clinical history was not available. Patients with missing laboratory data were considered high-risk as well. Both of these factors may have artificially increased the proportion of high-risk patients. However, only 1 patient with a positive urine culture was categorized as high-risk solely based on missing data, and the urine culture was positive in 12 hours. Clinical follow-up was generally conducted at the primary care provider's office rather than the ED; therefore, details regarding final diagnosis and clinical outcomes were not always available for children managed as outpatients. However, all patients with positive cultures were hospitalized in follow-up and outcomes for these were known.

It should also be noted that microbiology laboratory practices might vary in terms of time of plating and reading of cultures, so the applicability of these results will depend on specific laboratory protocols. Two different methods for reading blood cultures were used during the study. Before November 1995, cultures were read twice daily. This may have led to cultures taking longer to be detected, compared with those that were read by the continuous monitoring system. Because this would only prolong the apparent time to detection, the strength of the results should not be lessened.

CONCLUSION

We conclude that the probability of identifying SBI in febrile infants 28 to 90 days of age after 24 hours in our population was 1.1% among all patients and .3%

among low-risk patients. If the treating clinician chooses to use antibiotics for low-risk infants, 24 hours of coverage should generally be adequate. For some practitioners, this recommendation may result in a reduction in antibiotic use.

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