The Appropriateness of Early Discharge of Hospitalized Children with Suspected Sepsis

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BACKGROUND. Febrile children with suspected sepsis are often hospitalized and empirically treated with parenteral antibiotics pending results of bacterial cultures. The question of just how long such children should be observed and treated following initial negative culture reports has not been adequately addressed. This study was designed to determine the appropriateness of discharging hospitalized culture-negative children with suspected sepsis at the end of 48 hours.

METHODS. All children admitted with a diagnosis of "suspected sepsis" over an 8-month period were prospectively evaluated. Based on initial culture data, children were divided into two groups: group A with positive bacterial cultures and group B with negative bacterial cultures. Clinical assessment and review of cerebrospinal fluid, blood, and urine culture data were made at 24 hours, 48 hours, and until discharge, and at 2 weeks following discharge of all group B patients.

RESULTS. Of the 83 children enrolled in the study, 8 (9.5%) patients had a culture positive for bacterial infection (group A): meningitis in two, bacteremia in six, and urinary tract infection in two. All cultures were positive within 48 hours. Cultures were negative at 48 hours in the remaining 75 (90.4%) children (group B), and remained negative until discharge and at 2-week follow-up. Eight (10.6%) patients had received antibiotics prior to admission. After the workup, 37 of 73 (50.6%) children received antibiotics for less than 48 hours, while 36 (49.4%) children did so for more than 48 hours. Clinical assessment was normal at 48 hours in 71 of the 75 children. Sixty-three (84%) children available for follow-up continued to do well after discharge. No statistical distinction could be made between those children who remained hospitalized after 48 hours and those children who were dismissed at 48 hours.

CONCLUSIONS. Although our study data suggest that culture-negative children hospitalized for suspected sepsis who meet the criteria for normal clinical assessment can be safely discharged at 48 hours, a stronger statistical validation of this approach can be made if a larger sample size is studied.

KEY WORDS. Sepsis; pediatrics; hospitals, pediatric; bacterial infections; diagnostic tests, routine. *(J Fam Pract 1997; 44; 91-96)*

Suspicion of sepsis in a febrile child is a common reason for hospitalizing a child.[1-8] This is especially so in a young infant in whom a focus of infection is not readily apparent. Once admitted, these children undergo a workup for sepsis, which includes blood, urine, and cerebrospinal fluid (CSF) culture studies. Most of these children are empirically treated with age-appropriate antibiotics until negative culture results are firmly established or the child's clinical condition is assessed as normal.[5-9] The duration of therapy and hospitalization generally varies from 2 to 3 days,[5,7,9] and up to an average of 7 days[2] even in those children with initial negative cultures at 24 to 48 hours. This cautionary approach reflects the physician's continued suspicion of the presence of an infection despite negative cultures and continued clinical improvement, particularly in the very young child.

This study was designed to determine the appropriateness of discontinuing the antibiotic treatment and discharging culture-negative asymptomatic children with suspected sepsis at the end of 48 hours.

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TABLE 1

Inclusion and Exclusion Criteria for Patient Enrollment

Inclusion criteria

Children with fever of more than 38°C and two or more of the following features:

- lethargy
- irritability
- inconsolable crying
- seizure
- clinical dehydration
- vomiting

Exclusion criteria

- Patients in whom a focus of infection is evident,eg, skin, soft tissue, skeletal and middle ear infections, urinalysis with WBC more than 10 per high power field
- Infants with chest roentgenographic or clinical findings indicating a respiratory source of infection

METHODS

All children admitted to the pediatric service of the Children's Hospital at the University Medical Center, Lubbock, Texas, between August 1992 and March 1993 with an admission diagnosis of "suspected sepsis" were enrolled in the study. Inclusion criteria used for the study are listed in Table 1. Children with an obvious focus of infection were excluded on the basis of defined exclusion criteria, which are also listed in Table 1. All children underwent routine workup for sepsis, which included complete blood count, urinalysis, and cultures of blood, urine, and CSF.

Blood for culture was drawn by using the Isolator 1.5 tube (E.I. duPont de Nemours & Co, Wilmington, Del) with a holding time of not more than 4 hours prior to direct plating. Cerebrospinal fluid was sent directly for culture in solid media (trypticase soy agar with 5% sheep blood [TSA II 5% SB P21239 Rev.04 BBL] and chocolate agar [CHOCII P21169 Rev.04 BBL])[10] and enriched thioglycolate broth medium (T21741 Rev.03 BBL).[11] Urine culture was directly cultured on TSA II 5% SB and MacConkey agar (II P21172 Rev.04 BBL).[10] Clinical evaluation and review of the culture results reported on blood, urine, and CSF were performed at 24, 48, and 72 hours and until discharge on every patient.

After completion of workup, all except two patients were empirically started on age-appropriate antibiotics: ampicillin and cefotaxime for children under 3 months and ceftriaxone for children over 3 months. The length of antibiotic treatment was determined by the attending pediatrician.

Patients were divided into two groups: group A in whom a culture for a bacterial infection proved positive within 48 hours, and group B in whom a culture for a bacterial infection was negative within 48 hours. Group A children received full antibiotic treatment based on clinical diagnosis and were excluded from further consideration for the study. Group B children with normal clinical assessments as evidenced by normal temperature, activity, alertness, feeding, and hydration were discharged after variable lengths of hospital stay and antibiotic treatment. Follow-up clinical assessment using the same criteria was done at 2 weeks by the authors. All final culture results were reviewed at the time of standard incubation periods: 5 days for blood culture, 3 days for CSF culture plate, 5 days for CSF culture broth, and 3 days for urine culture.[12,25]

The objective of the statistical analysis used for the study was threefold. The first objective was to estimate the true percentage of the population that might test positive for sepsis after 48 hours. The second objective was to estimate the maximal expected number of patients that might test positive for sepsis in a random sample drawn from our population and thus obtaining an estimate of the risk involved in sending children home at 48 hours. The third objective was to statistically compare the outcomes of those patients dismissed at 48 hours with those who were held for more than 48 hours. The true percentage of the first objective was estimated by using the binomial distribution. Based on the percentage thus derived, data for the second objective were calculated. The third objective was accomplished by using an estimate obtained by binomial distribution and by standard comparison of proportion tests.

RESULTS

Of the 2254 medical admissions made during the study period, 83 (3.7%) patients satisfied criteria for enrollment in the study (Table I). The age groups of study children and results of initial sepsis workup are shown in Table 2. Eight of 83 (95%) patients had positive cultures identified within 48 hours (group A). Seven of these patients were under 1 month of age. Culture profiles for group A patients were as follows: two patients had positive CSF cultures: one

TABLE 2

Analysis of Children with Suspected Septis Admitted to Hospital During Study Period, by Age

	Age				
	1 mo	1-3	3 mo-1 y	1-3 y	More than 3 y*
No. of admissions of children with suspected sepsis (N=83)	28	20	20	12	3
No. with positive cultures (group A) (n=8)†	7	0	1	0	0
No. with negative cultures (group B) (n=75)	21	20	19	12	3

*Oldest child, 4 years old.
†Meningitis: 2 (1 of *Streptococcus pneumoniae*: and 1 case of Group B streptococci).
Bacteremia: 6 (2 of *Streptococcus pneumoniae*, 3 of Group B streptococci, and 1 of *Salmonella Infantis*).
Urinary tract infection: 2 (1 of enterococci: and 1 of *Citrobacter amalonaticus*).

for group B streptococci and the other for *Streptococcus pneumoniae* (both cultures were positive within 24 hours); six patients had positive blood cultures: three for group B streptococci, two for *S pneumoniae*, and one for *Salmonella infantis* (all blood cultures were positive within 48 hours); and urine samples from two children were positive: one for enterococci and the other for *Citrobacter amalonaticus* (both were positive within 48 hours). All group A patients were treated with age-appropriate antibiotics and were clinically well at discharge.

Cultures that were negative at 48 hours from 75 (90.4%) group B patients remained negative until the time of discharge. Forty-one of the 75 patients were under 3 months of age; 60 were under 1 year of age; and the oldest child was 4 years old. Eight of the 75 (10.7%) patients had received antibiotics prior to admission, and all except two patients were started on age-appropriate intravenous antibiotics, following admission and workup. Thirty-seven of the 73 (50.7%) patients received an antibiotic for 48 hours or less. The remaining 36 (49.3%) patients did so for longer than 48 hours (Table 3). Clinical evaluation at 48 hours was determined as normal in 71 of 75 (94.6%) patients. The four children whose clinical assessment was judged as not normal belonged to the group that received antibiotics for more than 48 hours. All children were determined to be clinically normal at time of discharge. No patient was discharged on an antibiotic. The average length of hospital stay for all of the study patients was 4.36 days, and for group B patients, 3.2 days. The average length of hospital stay at Children's Hospital was 4.66 days. All 63 (84%) patients available for follow-up evaluation at 2 weeks continued to do well after discharge. Of the 12 children lost to follow-up, four belonged to the culture-negative group that took antibiotics for less than 48 hours, and eight belonged to the culture-negative group that took antibiotics for more than 48 hours. All negative cultures from group B patients remained negative during the follow-up period.

Our statistical analysis showed that even though none of the patients from the study group of 75 tested positive for sepsis after 48 hours, we might still expect, at the 90% confidence level, as many as 3.2% of children to test positive after 48 hours in any large sample. Based on this percentage, the calculated probability that there would be 5 or fewer patients from a sample of 75 who would test positive for sepsis was .974. We can therefore be assured with very high probability that fewer than 6.7% (5 of 75) of the patients would test positive after 48 hours. Based on the same methodology for the age group under 3 months old, the probability that there would be 5 or fewer patients from a sample of 41 who would test positive for sepsis was .977. Again, we can be assured with very high probability that fewer than 12.5% (5 of 41) of the patients in this age group would test positive after 48 hours.

The statistical comparison between the group of 37 that was dismissed at 48 hours with the group of 36 that was retained for more than 48 hours showed no significant difference between the two groups at the 95% confidence level.

DISCUSSION

The incidence of serious bacterial infection in febrile and ill-looking children varies from 4% to 17%, and that of bacteremia from 1% to 15%.[1-8] Such children

TABLE 3

Duration of Antibiotic Treatment, by Study Group

	≤48 hours			>48 hours						
Study Group	**1 d**	**2 d**	**Total**	**1 d**	**2 d**	**3 d**	**4 d**	**5 d**	**>5 d**	**Total**
Group A (n=8) (culture positive)	0	0	0/8	0	0	0	0	0	8	8/8
Group B (n=75)* (culture negative)	2	35	37/73	0	0	25	5	2	4	36/73

* Two children from group B did not receive any antibiotics.

are often hospitalized and empirically treated with parenterally administered antibiotics pending results of bacterial cultures. The question of for just how long these children with suspected sepsis should be observed and treated following initial negative culture reports has not been adequately addressed. The present practice of managing such children varies from institution to institution. Generally, the physician takes a cautious approach because of doubts concerning the initial bacterial culture data, especially in regard to blood culture, and to some extent the CSF culture, because of the ambiguity of initial findings. The question is how valid is this concern, particularly in regard to those children who are doing clinically well.

Although there is considerable controversy about the time required to identify and isolate common pathogens from children's blood, it is increasingly becoming clear that by using the lysis direct-plating technique or the Bactec radiometric system the majority of common pathogens can be identified and isolated within 48 hours.[12-19] Many other studies have reported that the time for detection of *S pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus,* and other gram-negative pathogens is in the range from 19.8 to 28.9 hours.[13-15] Pichichero and Todd[21] found that of 105 blood cultures, 101 cultures became positive within 48 hours, two at 49 to 72 hours, and two at more than 72 hours. Klein has stated that 70% of positive blood cultures will be positive in 24 hours and 90% within 48 hours.[3] Dunne[12] has also found that up to 85% of positive cultures were confirmed at first 48 hours and 95% within 60 hours. Roberts[22] has reported that more than 94% of pathogens identified by 72 hours could be recognized within 48 hours. Thus only a small number of cultures (5% to 8%)[12,23] can be expected to take longer than 48 hours to become positive.

Newer blood culture techniques provide pathogen identification even faster than conventional blood culture techniques.[14,17] Perhaps the single exception noted to this observation is coagulase-negative *Staphylococcus,* an important pathogen in the neonate, which usually takes a longer time to grow in culture media.[24]

In our study we used the Isolator 1.5 tube, which is recommended for culturing blood volume less than 1.5 mL. This lysis directing-plating technique permitted rapid removal of the microorganism from microbicidal serum factors and serum antibiotics, the selection of optimal culture media and atmosphere for incubation, and rapid recovery of an isolate. In our study all positive cultures were positive within 48 hours, and all 48-hour negative cultures remained negative throughout the study period. A 48-hour negative blood culture, except in circumstances where infection due to unusual organisms is a consideration, can be relied on for making a discharge decision on a child with suspected sepsis. These circumstances include infections in high-risk neonates and immunocompromised children.

The majority of positive CSF cultures on solid media will also be detected within 48 hours[12,13,25] with broth culture providing a backup system for detecting infection with low colony count bacteria. For example *Escherichia coli, Klebsiella pneumoniae, Listeria monocytogenes, Staphylococcus aureus,* and *Streptococcus agalactiae* all demonstrate growth by turbidity after 24 hours of incubation in the test broths. *H influenzae, Neisseria meningitidis,* and *S pneumoniae* grow well after 1 or 2 days of incubation in special broth media such as supplemented peptone broth and minced beef heart medi-

um.[25] In the two cases of meningitis in our series, cultures were positive within 24 hours. We therefore believe that it is highly unlikely for any new CSF growth beyond 48 hours, especially if the initial CSF cytology and rapid studies (eg, CIE, latex agglutination) are also within normal limits.

Finally, more than 80% of urine cultures will be positive at approximately 24 hours and almost all within 48 hours.[12] In our study all positive cultures were positive within 48 hours and all negative cultures remained negative throughout the follow-up period. Thus a negative 48-hour urine culture report can be safely accepted as a dependable guideline for making discharge planning decisions.

Prior antibiotic treatment is known to influence culture results, especially that of blood and urine. This obviously is an important consideration in the evaluation of negative culture reports. In our study, however, the vast majority of children (90%) had not received any antibiotics.

Clinical assessment of the hospitalized child may be equally or more important than that of culture data in determining the appropriateness of discontinuing antibiotic treatment and discharging a child. Ninety-four percent of the study children were clinically normal at 48 hours, and all children had a normal examination at the time of discharge. Clearly those children with abnormal clinical assessments should be observed carefully irrespective of culture reports and continue to receive treatment, if necessary. Those who were available for follow-up continued to do well throughout the follow-up period. Although there is considerable debate as to what constitutes "normal assessment," the criteria used in our study are generally consistent with those reported in the literature.[1,26,27]

The study design did not require discontinuation of antibiotics at 48 hours in every patient with a negative culture. Approximately one-half the number of children continued to receive antibiotics beyond 48 hours, usually up to 72 hours, and the other half did so for less than 48 hours. Did the longer duration of antibiotic treatment influence the overall outcome? That a majority of both groups were already assessed as doing well at 48 hours and that there was no outcome difference between the groups during the follow-up period strongly suggests that had the treatment been discontinued at 48 hours for all patients, the outcome would not have been any different.

The merits of discharging children expeditiously from a hospital setting are obvious. Not only does it lessen the potential for iatrogenic complications related to hospitalization but it will also lessen the family financial burden. If all the asymptomatic group B children in our study had been discharged at 48 hours, a saving of nearly 90 hospital days could have been achieved.

Although our study data suggest that culture-negative hospitalized children with suspected sepsis and normal clinical assessments can be safely discharged at 48 hours, a stronger statistical validation of this approach can be made if a larger sample size is studied.

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