

Unpredictability of Serious Bacterial Illness in Febrile Infants From Birth to 1 Month of Age

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Background: A prior study (*N Engl J Med.* 1993;329:1437-1441) produced an effective screen to identify 1- to 2-month-old febrile infants (FIs) who are at low risk of having a serious bacterial illness (SBI). Because of anticipated differences in the epidemiological features of febrile illnesses, that Philadelphia protocol was not applied to FIs younger than 1 month.

Objectives: To describe the epidemiological features of febrile illness in neonates from birth to 1 month of age and to determine the applicability to this population of the Philadelphia screen for identifying FIs at low risk for SBI.

Design: A 36-month consecutive cohort study.

Setting: An urban pediatric emergency department.

Participants: Infants aged from 3 to 28 days old with temperatures of 38°C or higher.

Interventions: Following full evaluation for SBI, all FIs, pending results of bacterial cultures, were admitted to

the hospital and empirically administered antibiotics. After their illnesses resolved, the medical records of all FIs were reviewed. At that time, the Philadelphia protocol (originally developed for 1- to 2-month-old FIs) was applied and retrospectively judged for safety and efficacy.

Results: Of the 254 FIs enrolled, 32 (12.6%) had an SBI. The spectrum of bacterial and nonbacterial diseases closely approximated that described in 1- to 2-month-old FIs. When the Philadelphia protocol was applied to all 254 FIs, 109 (42.9%) would have been identified as at low risk for bacterial disease. Included in that group are 2 FIs with bacterial urinary tract infection, 2 FIs with bacteremia, and 1 FI with bacterial gastroenteritis.

Conclusions: The cause of febrile illnesses in neonates (infants younger than 1 month) approximates that of FIs 1 to 2 months of age. Unlike that for older 1- to 2-month-old FIs, however, the Philadelphia protocol lacks the sensitivity and negative predictive value to identify neonates at low risk for SBI.

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Editor's Note: Now we have more data that febrile infants younger than 1 month are different and that support current practice. I guess we keep the course.

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THE MANAGEMENT of febrile illnesses in infants younger than 2 months has been much debated in recent years.¹⁻¹³ Several reports^{4,9,12,13} have focused on the development of clinical screening tools to identify selected groups of febrile infants (FIs) who are at low risk for serious bacterial illness (SBI) and therefore safe to manage as outpatients. Among the studies were 2^{9,12} that used prospective consecutive cohort designs. Both limited their study populations to FIs older than 1 month, likely because of the perceived higher risk of SBI in FIs younger than

1 month.¹⁴⁻¹⁶ To date, no large prospective study has applied the principles of outpatient management to a consecutive series of neonates (infants from birth to 1 month old) with febrile illnesses.

The first purpose of our study was to describe the spectrum of febrile illnesses in infants from birth to 1 month of age and to compare it with that reported in 1- to 2-month-old FIs. Our second purpose was to determine the applicability to febrile neonates of an outpatient management protocol demonstrated to be safe and effective for use in 1- to 2-month-old FIs.

RESULTS

During the 36-month study, 254 febrile neonates between 3 and 28 days of age were treated in the emergency department. All of their medical records were available for re-

PATIENTS AND METHODS

From January 1, 1994, to December 31, 1996, we enrolled all neonates younger than 29 days who presented to the emergency department of the Children's Hospital of Philadelphia, Philadelphia, Pa, with rectal temperatures of 38.0°C or higher, as measured by an electronic digital thermometer. All infants underwent a standard evaluation for SBI. A complete history was taken from infants' parents, and a physical examination, including overall clinical appearance, was performed by the attending physician in the emergency department. The standard laboratory evaluation included a complete blood cell count with differential cell count, a microscopic urinalysis, a 2-view chest x-ray film, a lumbar puncture with standard analysis, and cultures of blood, urine, and spinal fluid specimens for bacteria. Stool specimens were obtained from infants with a history of diarrhea, tested for the presence of blood, and sent for white cell analysis and bacterial culture.

We considered the results of these tests to be normal if they met the following criteria: peripheral-blood white cell count, fewer than $15 \times 10^9/L$; band-to-neutrophil ratio, less than 0.2; urinalysis, fewer than 10 white cells per high-power field and no bacteria detected by bright-field microscopy (both in spun specimens collected by bladder catheterization); cerebrospinal fluid, fewer than 8 white cells per microliter in a nonbloody specimen and a negative Gram stain; and chest x-ray film, no evidence of a discrete infiltrate, as determined by the attending physician (and subsequently confirmed by an attending radiologist). Infants whose spinal fluid specimens were grossly bloody were considered to have uninterpretable specimens. Stool specimens were considered abnormal if they tested positive for blood using a commercial test (Hemocult; SmithKline Diagnostics, Inc, San Jose, Calif).

"Serious bacterial illness" was defined as the growth of a known bacterial pathogen in cultures of specimens of blood, spinal fluid, urine, or stool. Infants with obvious cellulitis or abscess were considered to have SBI. "Pneumonia" was defined as a new discrete infiltrate on the chest film that was confirmed by an attending radiologist. Pneumonia was considered to be an SBI only if an infant's culture of blood or of respiratory secretions grew a known respiratory bacterial pathogen. "Aseptic meningitis" was defined as pleocytosis (≥ 11 white cells per microliter in a nonbloody specimen)¹⁷ and an absence of bacterial pathogens in cerebrospinal fluid specimens obtained from

infants who had not previously received antibiotic treatment.

Cultures of specimens of blood and spinal fluid that were free of bacterial pathogens at 72 hours were considered negative. A blood specimen for culture was considered to be contaminated if the patient's symptoms resolved without appropriate treatment (in a patient with coagulase-negative staphylococcus) or if the bacteria located were not pathogens (eg, diphtheroids, nonpathogenic *Neisseria* species, and α -streptococci).

All urine specimens were obtained by bladder catheterization. The results of urine cultures were considered positive if the cultures grew bacteria of 10^3 or more colony-forming units per milliliter of known urinary pathogens. These specimens were considered contaminated or the culture results negative if fewer than 10^3 colony-forming units of a single organism per milliliter were recovered. Urine specimens for culture were also considered contaminated if 10^3 colony-forming units or more were isolated, with multiple colony types present and none predominant.

Following their initial diagnostic evaluation in the emergency department, all infants were treated in accordance with the existing standard of care at the Children's Hospital of Philadelphia for neonates, with hospital admission and the administration of intravenous antibiotics chosen by the infants' physicians. Infants were usually discharged from the hospital after 72 hours if they appeared well and cultures were negative for bacteria.

After the patients' illnesses resolved, all medical records were reviewed by the investigators, and information on the inpatient management, laboratory test results, and final diagnosis was noted. At that time, the Philadelphia protocol for identifying FIs at low risk for SBI, which was developed for FIs 29 to 56 days of age,¹² was applied. The Philadelphia protocol used the same definitions of normal for laboratory tests as was stated earlier for our study sample. Infants whose laboratory values fell within the defined reference ranges, who appeared clinically well, and who had no recognized bacterial infection on physical examination were considered to be at (protocol-identified) low risk for SBI. The identification of low risk for SBI did not alter in any way the management of the infants' illnesses.

The data were analyzed by the χ^2 technique for categorical variables, with Yates correction for 2×2 tables. When the expected number of patients in any cell was less than 5, the Fisher exact test was used.

The study protocol was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

view. Most (n = 145 [57.1%]) were boys. Most (n = 222 [87.4%]) did not have SBI. The final diagnoses of all the infants are listed in the following table:

Diagnostic Category	No. (%)
Viral syndrome	166 (65.4)
SBI	32 (12.6)
Nonbacterial gastroenteritis	22 (8.7)
Aseptic meningitis	20 (7.9)
Bronchiolitis	11 (4.3)
Viral encephalitis	2 (0.8)
Pneumonia	1 (0.4)

Serious bacterial illnesses are listed in **Table 1**. All febrile neonates were treated as inpatients, and all recovered uneventfully from their diseases.

When the Philadelphia protocol was retrospectively applied to 254 febrile neonates, 109 (42.9%) were identified as at low risk for SBI. These were infants who appeared well to the emergency department attending physician, who had no focus of bacterial disease apparent on physical examination, and whose initial screening laboratory test results were entirely within our defined reference ranges. Of these 109 infants at (protocol-identified) low risk for SBI, 104 (95.4%) had nonbacterial diseases, and 5 had bacterial diseases. Of the 104 febrile neonates with nonbacterial diseases, 87 had a viral syndrome, 14 had gastroenteritis, 1 had bronchiolitis, and 2 eventually demonstrated findings consistent with viral encephalitis. The 5 neonates with bacte-

Table 1. Bacterial Diseases Diagnosed in 254 Study Infants

Disease	Infants, No. (%)
Urinary tract infection	17 (6.7)
<i>Escherichia coli</i>	13
Enterococcus	1
Klebsiella	1
Corynebacterium	1
<i>Enterobacter cloacae</i>	1
Bacteremia	8 (3.1)*
Group B streptococcus	2
<i>E cloacae</i>	1
<i>Listeria monocytogenes</i>	1
Enterococcus	1
Klebsiella	1
<i>Streptococcus pneumoniae</i>	1
<i>E coli</i>	1
Meningitis	4 (1.6)
Klebsiella	2
<i>L monocytogenes</i>	1
Group B streptococcus	1
Gastroenteritis	2 (0.8)
<i>Clostridium difficile</i>	1
<i>Salmonella</i> serogroup Y	1
Other	5 (2.0)
Pertussis	1
Peritonitis†	1
Osteomyelitis†	1
Cellulitis†	1
Bullous impetigo†	1

*Four infants with bacteremia had other concomitant bacterial diseases: meningitis (n = 3) and urinary tract infection (n = 1).

†The pathogen was unidentified.

rial diseases included 2 with urinary tract infection, 2 with bacteremia, and 1 with bacterial gastroenteritis (**Table 2**), all of whom were born at term. The negative predictive value for detecting bacterial illness in febrile neonates with the Philadelphia protocol was 95% (95% confidence interval, 90%-99%) (**Table 3**). Of 109 febrile neonates who were identified by the Philadelphia protocol to be at low risk for SBI, however, 5 proved to have SBI.

COMMENT

The management of febrile illnesses in young infants varies considerably among physicians.^{1,2,7,11} This likely reflects individual physicians' training, personal experiences and practice setting, and the opinions reported in pediatric publications.¹⁻¹⁰ Several investigators^{4,9,12,13} have conducted clinical trials designed to demonstrate the safety and efficacy of outpatient management of FIs. Two of these included FIs younger than 29 days in their study samples.^{4,13} Inconsistencies in the initial evaluation or follow-up in 1 study⁴ and in enrollment omissions of eligible FIs in the other¹³ limit the interpretation of those data.

Prior investigations^{9,12} of prospective design that have studied consecutive cohorts of FIs have limited their study populations to FIs older than 28 days. The reported rate of bacteremia was thought to be considerably higher in febrile neonates (younger than 1 month) compared with FIs older than 1 month.¹⁴⁻¹⁶

Table 2. Bacterial Diseases in 5 Infants Who Were at Low Risk for Serious Bacterial Illness According to the Philadelphia Protocol

Gestation, wk	Sex/Age, d	Disease	Pathogen
40	M/4	Urinary tract infection	Enterococcus
41	F/5	Bacteremia	<i>Streptococcus pneumoniae</i>
37	M/9	Bacteremia	<i>Escherichia coli</i>
40	F/18	Urinary tract infection	<i>E coli</i>
40	M/20	Bacterial gastroenteritis	<i>Salmonella</i> serogroup Y

Table 3. Performance of Philadelphia Screening Protocol in Identifying Serious Bacterial Illness (N = 254)*

Classification	Serious Bacterial Illness, No.	No Serious Bacterial Illness, No.	Total, No.
Screening			
Positive	27	118	145
Negative	5	104	109
Total	32	222	254

*The positive predictive value was 18.6% (27/145) (95% confidence interval [CI], 12-25); the negative predictive value was 95.4% (104/109) (95% CI, 90-99). The sensitivity was 84.4% (27/32) (95% CI, 67-95); the specificity was 46.8% (104/222) (95% CI, 40-53).

For that reason, the investigators in Philadelphia¹² excluded febrile neonates from eligibility for outpatient management.

Our data demonstrate that, in fact, the incidence of SBI in febrile neonates appears to be similar to that observed in FIs 29 to 60 days of age who presented to the same emergency department during the same interval.¹⁸ Of the 254 febrile neonates in the present study, 32 (12.6%) had SBI, whereas 43 (10.2%) of 422 FIs aged 29 to 60 days had SBI.¹⁸ Kadish et al¹⁹ found the rate of SBI to be 13.7% in febrile neonates aged 1 to 29 days. The spectrum of bacterial diseases was also similar in each of these groups. Urinary tract infections accounted for the largest proportion of bacterial diseases in all FIs younger than 2 months. Bacteremia was detected in 3.1% of febrile neonates, which is comparable to the 2.1% reported in 1- to 2-month-old FIs.¹⁸

Unlike the situation with "older" 1- to 2-month-old FIs, our data indicate that for febrile neonates, the Philadelphia protocol is not completely accurate in identifying those who are at low risk for SBI. In our study sample, 5 of 109 febrile neonates identified by the Philadelphia protocol as at low risk for SBI proved to have bacterial diseases. With 95% confidence, as many as 10% of febrile neonates who are identified by the Philadelphia protocol to be at low risk for SBI actually could have SBI (Table 3). A similar rate of inaccuracy of the Philadelphia protocol and of the screen developed by Baskin et al⁹ has been observed in a retrospective study by Kadish et al.¹⁹

CONCLUSIONS

The epidemiological features of febrile illnesses in neonates (infants younger than 1 month) are similar to those in infants between 1 and 2 months of age. Unlike the case in older FIs, however, SBI in febrile neonates cannot be anticipated using the Philadelphia protocol. Applying the screening criteria in the Philadelphia protocol to febrile neonates would falsely identify as at low risk for SBI as many as 10 per 100 neonates with bacterial diseases. For that reason, we recommend that the initial management of febrile illnesses in infants younger than 1 month should include a complete evaluation for SBI and the empirical administration of antibiotics.

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