Management and Outcomes of Care of Fever in Early Infancy

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Management and Outcomes of Care of Fever in Early Infancy

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Context Fever in infants challenges clinicians in distinguishing between serious conditions, such as bacteremia or bacterial meningitis, and minor illnesses. To date, the practice patterns of office-based pediatricians in treating febrile infants and the clinical outcomes resulting from their care have not been systematically studied.

Objectives To characterize the management and clinical outcomes of fever in infants, develop a clinical prediction model for the identification of bacteremia/bacterial meningitis, and compare the accuracy of various strategies.

Design Prospective cohort study.

Setting Offices of 573 practitioners from the Pediatric Research in Office Settings (PROS) network of the American Academy of Pediatrics in 44 states, the District of Columbia, and Puerto Rico.

Patients Consecutive sample of 3066 infants aged 3 months or younger with temperatures of at least 38°C seen by PROS practitioners from February 28, 1995, through April 25, 1998.

Main Outcome Measures Management strategies, illness frequency, and rates and accuracy of treating bacteremia/bacterial meningitis.

Results The PROS clinicians hospitalized 36% of the infants, performed laboratory testing in 75%, and initially treated 57% with antibiotics. The majority (64%) were treated exclusively outside of the hospital. Bacteremia was detected in 1.8% of infants (2.4% of those tested) and bacterial meningitis in 0.5%. Well-appearing infants aged 25 days or older with fever of less than 38.6°C had a rate of 0.4% for bacteremia/bacterial meningitis. Frequency of other illnesses included urinary tract infection, 5.4%; otitis media, 12.2%; upper respiratory tract infection, 25.6%; bronchiolitis, 7.8%; and gastroenteritis, 7.2%. Practitioners followed current guidelines in 42% of episodes. However, in the initial visit, they treated 61 of the 63 cases of bacteremia/bacterial meningitis with antibiotics. Neither current guidelines nor the model developed in this study performed with greater accuracy than observed practitioner management.

Conclusions Pediatric clinicians in the United States use individualized clinical judgment in treating febrile infants. In this study, relying on current clinical guidelines would not have improved care but would have resulted in more hospitalizations and laboratory testing.

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FEBRILE INFANTS OFTEN LACK SUGgestive clinical symptoms or findings, making it difficult to distinguish between a minor febrile illness and one that is life-threatening. To avoid the consequences of failing to detect serious bacterial illness (SBI), such as bacteremia and bacterial meningitis, a variety of clinical strategies have been developed to identify infants at high and low risk, including policies that require extensive laboratory testing, hospitalization, and treatment with intravenous antibiotics.[1-10] Although these strategies guarantee treatment of all infants with SBI, the costs are high, including considerable iatrogenic morbidity for some infants.[10]

Many strategies were developed from infants cared for in inner-city emergency departments. Performance of such strategies in the general population has not been evaluated. Studies surveying responses to case scenarios suggest that a large proportion of office-based physicians do not routinely follow these guidelines.[11] Little is known about the actual management of cases of febrile infants in office practice.

See also p 1261 and Patient Page.

The purposes of this study were to (1) characterize the management, spectrum of diseases, and clinical outcomes of febrile infants aged 3 months or younger in pediatric practices in the United States; (2) develop a clinical prediction model for the identification of infants with bacteremia/bacterial men-

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Table 1. Practitioner and Patient Characteristics*

Characteristics	Participating	Nonparticipating
Practitioners		
No. of practitioners	573	781
Sex		
Male	300 (52)	378 (49)
Female	273 (48)	389 (51)
Age, y		
<45	307 (54)	433 (59)
≥45	266 (46)	303 (41)
Race		
White†	519 (91)	632 (81)
African American	3 (1)	17 (2)
Asian/Pacific Islander	36 (3)	50 (6)
Other/missing	15 (3)	82 (11)
Practice structure		
Group	386 (67)	493 (64)
Solo	46 (8)	46 (6)
University	32 (6)	91 (12)
Health maintenance organization	22 (4)	40 (5)
Other	87 (15)	105 (13)
Practice region		
Northeast	197 (34)	306 (39)
South	141 (25)	180 (23)
Central/Midwest	91 (16)	163 (21)
West	144 (25)	132 (17)
Practice setting		
Urban, inner city	42 (7)	108 (14)
Urban, not inner city	133 (23)	202 (26)
Suburban	259 (45)	329 (42)
Rural	131 (23)	101 (13)
Other/missing	8 (1)	41 (5)
Patients (n = 3066)		
Demographic characteristics		
Age		
Mean (SD), wk	7.0 (3.4)	
1-30 d	775 (25)	
31-60 d	1220 (40)	
>60 d	1071 (35)	
Female	1436 (47)	
Race/ethnicity		
White, non-Hispanic	2150 (70)	
Black	246 (8)	
Asian	67 (2)	
Hispanic	453 (15)	
Other/missing	150 (5)	
Medicaid insured	1074 (35)	
Clinical characteristics		
Temperature, °C		
Mean (SD)	38.7 (0.50)	
Maximum (home or office)		
<38.5	1361 (44)	
38.5-38.9	1049 (34)	
39.0-39.4	458 (5)	
≥39.5	198 (7)	
Appearance		
Very ill	50 (2)	
Moderately ill	767 (25)	
Well or minimally ill	2206 (73)	

*Data are expressed as No. (%) unless otherwise noted.
†Includes 18 participating Hispanic practitioners and 23 nonparticipating Hispanic practitioners.

ingitis; and (3) compare the accuracy of practitioners' management with existing guidelines.

METHODS

Sites and Practitioner Participants

This study was conducted by the Pediatric Research in Office Settings (PROS) practice-based research network of the American Academy of Pediatrics (AAP). A total of 573 members of the PROS network (91% of whom were physicians) from 219 practices submitted data on eligible infants. Data were received from 44 states, the District of Columbia, and Puerto Rico. Participant and nonparticipant characteristics are shown in TABLE 1. Practitioners who declined to participate or who did not respond to recruitment efforts varied little from participating practitioners. In addition, compared with AAP members who listed patient care as their primary activity in a 1995 periodic survey, PROS practitioners were similar in age and sex, but fewer (7.3% vs 12%; $P<.001$) practiced in urban inner-city areas. Infants who were eligible but not enrolled also closely resembled enrolled infants with respect to temperature and on average were slightly older (4 days); hospitalization rates were similar.

Patient Participants

Infants were eligible for the study if they were aged 3 months or younger, had been discharged from the hospital as a newborn, had a temperature of 38°C or greater either at home or in the clinician's office, and had no other major comorbidities (eg, congenital anomalies, extreme prematurity, conditions associated with organ system failure). For analysis, we used the maximum rectal temperature taken in the office or reported by the parent in the past 24 hours, after adding 0.5°C for axillary temperatures. Data were collected for 3131 consecutive infants, 3066 of whom met eligibility requirements. The study was approved by the Committee on Human Research of the University of California, San Francisco.

Procedures

We used a prospective cohort study design to follow the episode of care for infants seen by PROS practitioners from February 28, 1995, through April 25, 1998. Demographic and clinical data were recorded by office staff and clinicians on standard forms. Practitioners recorded clinical signs and symptoms and an overall assessment of clinical appearance before ordering laboratory tests. They also answered questions about clinical appearance similar to those of the Yale Observation Scale,[12,13] with the addition of an item on respiratory distress. For clinical appearance, practitioners indicated whether the infant appeared well/minimally ill, moderately ill, or very ill. Initial management, changes in treatment strategies, and subsequent medical contacts were decided by individual clinicians and documented until resolution of illness, when they recorded final diagnosis. A variety of techniques were used to maximize patient enrollment and minimize selection bias and ensure data quality.

Laboratory testing was performed at the discretion of the clinician according to their usual and customary practice. Testing was performed at the usual laboratories of the practice sites; all clinicians were supplied with and asked to use urine dipsticks (Ames-Multistix, Miles Inc, Elkhart, Ind).

Clinical Diagnoses

A study manual was developed containing definitions of all clinical conditions and variables. While other studies have addressed SBI (ie, bacteremia, bacterial meningitis, urinary tract infection, and bacterial gastroenteritis) as the main outcome variable, this report focuses on occult infections that have generated the most uncertainty in developing clinical strategies; ie, bacteremia with pathogenic organisms and bacterial meningitis. We have reported elsewhere on urinary tract infections[14] and also report herein the frequency of other, less common serious bacterial illnesses, such as cellulitis and osteomylelitis. A pediatric infectious disease specialist reviewed all cases of bacteremia and excluded those not considered to be caused by pathologic bacteria. Similarly, all cases of meningitis were reviewed to ascertain the accuracy of the diagnosis and whether the meningitis was likely bacterial, partially treated bacterial, or viral in origin.

Statistical Analyses

STATA software, version 6 (CRC Inc, College Station, Tex) was used for statistical analyses. For multivariate analyses of bacteremia/bacterial meningitis that included laboratory data as predictors, we included only patients for whom a blood culture was obtained. For these models, the white blood cell (WBC) count was considered to be abnormal if it was less than 5000/μL or at least 15000/μL and the urinalysis was considered abnormal if the dipstick test was positive for leukocyte esterase or nitrite or if more than 5 WBCs per high-powered field were reported on microscopic examination. We used a backward stepwise logistic regression model, with a P value of .02 to predict ordering of WBC counts and blood cultures and a P value of .10 to predict bacteremia/bacterial meningitis. Standard errors for all logistic models were adjusted for clustering by practitioner and models tested for goodness of fit by the method of Hosmer and Lemeshow. Tree-structured analyses were conducted using S-PLUS, version 3.4 (MathSoft, Seattle, Wash).[15,16]

Clinical Prediction Models

To compare the accuracy of various clinical prediction models, we analyzed several alternative scenarios. For model 1, we used patient appearance alone as a predictor of bacteremia/bacterial meningitis. Two additional models were created by adding WBC count and WBC count with urinalysis, respectively. For the fourth model, we relied on current guidelines. Current guidelines[6,17] and protocols[5,7,18,19] differ slightly in specific lower limits of age to be considered "low risk" (28-30 days), definition of abnormal WBC count (>15000/μL to >20000/μL), urinalysis performance, whether stool WBC count should be performed in infants with diarrhea, whether a lumbar puncture is required in all infants regardless of appearance and screening test results, and whether screening should be done in all febrile infants or only in those without a source of infection. We blended these guidelines so that infants aged 30 days or younger and ill-appearing infants required a WBC count, blood culture, urinalysis, urine culture, cerebrospinal fluid analysis and culture, hospitalization, and antibiotics; well-appearing infants aged 31 days or older required a WBC count and urinalysis as the basis for proceeding with further management. For the fifth model, we used the decision tree derived from applying tree-structured analysis to our sample. We compared the sensitivity and specificity of the 5 clinical prediction models described herein with the actual management and outcomes of the PROS practitioners. Sensitivity was calculated as the number of infants with bacteremia/bacterial meningitis who would have been treated in each strategy or, for study infants, were actually treated with antibiotics at the initial visit divided by the number with bacteremia/bacterial meningitis (n=63). The concept of specificity, defined as the percentage of patients without the condition (bacteremia/bacterial meningitis) who were not treated, does not strictly apply, since other diseases require antibiotics. However, to reflect the trade-off between sensitivity and specificity, we calculated a specificity in which the denominator used represents all infants without bacteremia/bacterial meningitis and other conditions requiring antibiotics (ie, otitis media, urinary tract infection, pneumonia), while the numerator represents children not treated at the initial encounter with an antibiotic. "Specificity" in this context does not infer unnecessary treatment but is used as an indicator of the relative frequency of antibiotic use in different strategies.

RESULTS

Management Practices of PROS Practitioners

Of the 3066 infants, 1975 (64%) were managed exclusively outside of the hospital. Only 125 episodes of care were managed with a single office visit without other medical contacts (eg, telephone). A single visit was recorded for 909 infants, while 761 infants had 2 visits and 305 had 3 or more visits to the hospital. In addition, 1014 episodes were accompanied by a single follow-up telephone call, 325 received more than 1 telephone encounter. Of infants managed outside of the hospital, 68 were seen in emergency departments following the initial office visit.

Testing and management strategies did not vary by practitioner age, sex, or region but varied with certain infant demographic and clinical variables. Compared with older infants, those younger than 1 month were significantly more likely to have a WBC count or blood culture (83.0 vs 71.4%; $P<.001$), have a lumbar puncture (54.8 vs 25.6%; $P<.001$), begin antibiotic treatment at the time of the initial examination (68.2% vs 53.7%; $P<.001$), and be hospitalized (60.1% vs 27.3%; $P<001$). Adjusted odds ratios for independent predictors of blood testing (WBC count and/or blood culture) are documented in TABLE 2. Prediction was fair, with the area under the receiver operating characteristic curve (AUROC)=0.735. Coding temperature and age as continuous variables improved the fit slightly with AUROC=0.746. Patients seen outside of typical office hours were significantly more likely to receive laboratory testing and to be treated with antibiotics and admitted to the hospital. Infants receiving Medicaid had more testing and hospitalizations.

Nearly one quarter of infants had no blood, urine, or cerebrospinal fluid tested during their evaluation (n=726), and slightly more than half had their urine tested (n=1666). Actual management strategies varied considerably from suggested approaches to febrile infants. TABLE 3 compares PROS practitioners' management with recommended strategies.

Table 2. Multivariate Predictors of Blood Testing

Clinical Features	Odds Ratio (95% CI)	*P* Value
Age, d*		
<31	2.86 (2.19-3.72)	<.001
31-60	2.31 (1.88-2.84)	<.001
Temperature, °C†		
38.5-38.9	1.40 (1.17-1.68)	<.001
39.0-39.4	1.60 (1.22-2.10)	.001
≥39.5	1.81 (1.22-2.71)	.004
Appearance		
Moderately ill vs well	1.92 (1.55-2.38)	<.001
Very ill vs well	2.63 (0.99-7.00)	.05
Unattentive	1.81 (1.36-2.48)	<.001
No smile	1.55 (1.24-1.93)	<.001
Decreased social interaction	1.35 (1.05-1.74)	.02
Received care after hours	2.32 (1.70-3.18)	<.001
Medicaid insured	1.39 (1.12-1.72)	.003
Source of fever known	0.63 (0.52-0.76)	<.001

Abbreviation: CI, confidence interval.
*Comparison group: aged >60 days.
†Comparison group: temperature <38.5°C.

Table 3. PROS Practitioner Adherence to Guidelines

Age/Appearance	Recommendation	Cases in Which Guideline Was Followed, %
<31 days	Complete sepsis workup/hospitalization/ antibiotics	45.7
31-90 days/moderately or very ill	Complete sepsis workup/hospitalization/ antibiotics	35.8
31-90 days/minimally ill	White blood cell count/urinalysis	41.6

Abbreviation: PROS, Pediatric Research in Office Settings.

Final Diagnoses of Febrile Episodes

TABLE 4 lists the primary final diagnoses at the end of the illness episodes. Most febrile episodes were due to benign illnesses, while bacteremia was present in 2.4% of infants with blood cultures and bacterial meningitis in 0.5% of the entire sample of infants. Other causes of "serious" bacterial illness were documented but many (eg, cellulitis) were not occult.

The 54 cases of bacteremia represent cases reviewed by an infectious disease consultant and diagnosed as having pathogenic organisms; 18 other cases originally classified as bacteremic by clinicians were recoded to either the next listed diagnostic category or to an unidentified source. Of 16 infants originally classified as having bacterial meningitis by clinicians, the external reviewer confirmed 14 cases, including some cases in which the culture was sterile because of prior antibiotics but the cerebrospinal fluid and clinical findings were consistent with bacterial meningitis. Five of the infants with bacterial meningitis also had bacteremia. The bacterial organisms in infants with bacteremia/bacterial meningitis are identified in TABLE 5. Much of the bacteremia/bacterial meningitis occurred in the first month after birth, when 4.1% of febrile infants had bacteremia/bacterial meningitis compared with 1.9% in the second month and 0.7% in the third month (TABLE 6).

We also examined the frequency of bacteremia/bacterial meningitis and other bacterial illnesses by temperature. Because fever of at least 38.0°C at home was an eligibility criteria, some infants included were afebrile at the time of office visit. The frequency of bacteremia/bacterial meningitis found in infants who were afebrile in the office as well as those who had higher temperatures is documented in TABLE 7.

Developing a Clinical Prediction Model

We used logistic regression analyses to identify the best clinical predictors of bacteremia. The analysis in TABLE 8 is for the entire sample of 3066 infants. In this analysis, we exclude laboratory results to identify which clinical features are potentially useful in initially identifying infants at high risk. We allowed for entry of variables with $P<.10$ because of the small number of cases of bacteremia. Age and very ill appearance emerged as the strongest predictors (AUROC=0.820). To evaluate the predictive value of laboratory testing, we first performed a logistic regression on the 1746 infants who had both WBC counts and blood cultures but excluded WBC results. Without WBC count, the AUROC was 0.767. By adding abnormal WBC count (as a dichotomous variable with abnormal counts considered to be $<5000/\mu L$ or $\geq 15000/\mu L$), the AUROC increased to 0.803. The resulting model is summarized in TABLE 9. By adding abnormal urinalysis, the AUROC increased to 0.806, but the coefficient for an abnormal urinalysis was not statistically significant.

Finally, we used recursive partitioning analysis with tree-structured analysis to develop a classification tree to identify low- and high-risk groups. The classification procedure initially dichotomizes on the single variable that best separates low- and high-risk groups using internal split sampling into tenths. It then continues to select the best variable for separating the remaining patients into low- and high-risk groups. In the model (FIGURE), infants who are moderately or severely ill appearing have a bacteremia/bacterial meningitis rate of 4.4%, while those who appeared well/minimally ill have a 1.2% occurrence. Of this latter group, 3.4% of those younger than 25 days had bacteremia/bacterial meningitis while 0.8% of those aged 25 days or older had bacteremia/bacterial meningitis. Finally, for infants who appeared well/minimally ill, were at least 25 days old, and had a temperature of 38.6°C or higher, bacteremia/bacterial meningitis was found in 1.2%, while those with these characteristics but temperature of less than 38.6°C had a 0.4% chance of bacteremia/bacterial meningitis, or a negative predictive value of 99.6%.

Accuracy of Diagnostic Strategies

We compared the sensitivity of different approaches to identify infants with bacteremia/bacterial meningitis. The results are displayed in TABLE 10 for infants with WBC counts and blood cultures. Only 58.1% with bacteremia/bacterial meningitis appeared clinically ill; the "specificity" as defined for this analysis was 68.1% (model 1). Adding abnormal WBC count as a predictor increases sensitivity to 83.9% but decreases "specificity" to 54.0% (model 2). The addition of a urinalysis increases the sensitivity to 87.1%, with a small decrement in specificity. Current guidelines (model 4) call for treating all infants with high-risk criteria while giving options for treating low-risk infants. Using this approach, 3 of 62 with bacteremia/bacterial meningitis would have been classified as low risk (1 infant with bacteremia/bacterial meningitis did not have clinical appearance recorded initially and is

Table 4. Final Primary Diagnoses

Primary Diagnosis	No.	Percentage
Upper respiratory tract infection	785	25.6
Unidentified source	655	21.4
Otitis media	375	12.2
Bronchiolitis	239	7.8
Gastroenteritis	222	7.2
Urinary tract infection		
Total	167 (18)*†	5.4/10.3‡
Girls	107	7.5/13.4‡
Boys, uncircumcised	41	11.5/20.8‡
Boys, circumcised	15	1.3/2.6‡
Boys, circumcision status not specified	4	4.0/9.1‡
Pneumonia	102	3.3
Viral syndrome, nonspecific	85	2.8
Viral meningitis (nonherpes)	82	2.7
Noninfectious	76	2.5
Well child	69	2.3
Bacteremia	54	1.8/2.4‡
Influenza	41	1.3
Exanthematous illness	39	1.3
Pharyngitis	29	1.0
Viral syndrome, specific	21	0.7
Bacterial meningitis	14 (5)*	0.5
Cellulitis	6	0.2
Sinusitis	5	0.2
Conjuctivitis	4	0.1
Candidiasis	4	0.1
Pertussis	3	0.1
Other infectious	2	0.1
Peritonitis	2 (1)*	0.1
Cervical adenitis	2	0.1
Osteomyelitis, omphalitis, mastitis, salmonella enteritis, renal abscess, herpes meningitis (1 case each)	6	0.3
Total	**3066**	100

*Numbers in parentheses represent cases of bacteremia occurring simultaneously. These are included in the total number with bacteremia.
†Of the 167 cases of urinary tract infection, 18 were bacteremic (17 with same organism) and 1 had renal abscess.
‡Percentage when denominator included only those who had blood cultures performed.

excluded from this analysis). Therefore, we estimate that 59 of 62 with bacteremia/bacterial meningitis would have received appropriate antibiotics.

For model 5, tree-structured analysis (Figure), the sensitivity closely resembles current guidelines but the model is less specific. The PROS practitioners (model 6) initially treated 61 of the 63 infants with bacteremia/bacterial meningitis on the initial visit; all but 1 received parenteral antibiotics; 36% initially received ceftriaxone, 34% ampicillin plus cephalosporin, 22% ampicillin plus gentamycin, and 8% other antibiotic combinations. The sensitivity of PROS practitioners in treating bacteremia/bacterial meningitis was 96.8%. The 2 infants not treated initially included a 26-day-old infant who appeared well, had an initial WBC count of 13 000/μL, and had a blood culture positive for group B streptococci on the following day; the infant was treated and had an uneventful recovery. The other child was a 4-week-old infant who appeared well and had a WBC count of 15 300/μL with 8% bands. The infant was sent home without antibiotics, became progressively more irritable the next day, and was diagnosed as having pneumococcal meningitis; reports over the following year indicated that the infant achieved normal developmental milestones.

Among children without bacteremia/bacterial meningitis, otitis media, urinary tract infection, or pneumonia, clinicians treated 64.5%, for a "specificity" of 35.5%. Practitioners also hospitalized 309 fewer infants younger than 1 month of age and conducted fewer diagnostic tests (Table 3) than they would have had they followed current guidelines.

Table 5. Bacteria Identified

Organisms	Bacteremia Cases, No.	Bacterial Meningitis Cases, No.
Escherichia coli	16	2*
Group B *Streptococcus*	14	1*
Staphylococcus aureus	5	0
Enterococcus faecalis	3	0
Streptococcus pneumoniae	3	2
Enterobacter cloacae	2	0
Staphylococcus (other)	3	0
Group A *Streptococcus*	2	0
Streptococcus bovis	1	1*
Klebsiella pneumoniae	1	0
Listeria monocytogenes	1	1*
Yersinia enterocolitica	1	0
Proteus mirabilis	1	1*
Gram-negative rod	1	0
Pseudomonas stutzeri	0	1
Neisseria meningitides	0	1

*Cases with simultaneous bacteremia.

Table 6. Patients With Bacteremia/Bacterial Meningitis by Age

Age, mo	Total No. of Patients	Cases of Bacteremia Only, No.	Cases of Bacterial Meningitis, No.	Total No. (%) With Bacteremia/Bacterial Meningitis
0-1	775	23	9*	**32** (4.1)
>1-2	1220	18	5	**23** (1.9)
>2-3	1071	8	0	**8** (0.7)
Total	**3066**	**49**	**14**	**63** (2.1)

*Five of these 9 cases of bacterial meningitis also had bacteremia.

Table 7. Office Temperature of Patients With Bacteremia/Bacterial Meningitis

Temperature, °C	Total No. (%) of Patients	No. (%) With Bacteremia/ Bacterial Meningitis
<38.0	835 (27)	6 (0.7)
38.0-38.4	1141 (37)	18 (1.6)
38.5-38.9	604 (20)	27 (4.5)
≥39.0	304 (10)	10 (3.3)
Missing data	182 (6)	2 (1.1)

COMMENT

Fever in young infants has generated substantial interest, research, and controversy over the past 30 years. A number of factors in the 1970s contributed to concerns about the appropriate treatment of febrile infants, including emerging awareness of late-onset group B β-hemolytic streptococcal sepsis and occult bacteremia due to *Streptococcus pneumoniae*.[20-22] In response, many academic centers encouraged extensive diagnostic testing, hospitalization, and antibiotic treatment of all infants younger than 60 or 90 days. This approach had considerable costs and morbidities[10] and was followed by efforts to identify methods to distinguish infants at high and low risk of serious bacterial illness. Different strategies were developed and tested in emergency departments in urban centers (Boston, Mass,[18] Philadelphia, Pa,[7] Rochester, NY,[4,5] and Pittsburgh, Pa[19]), and guidelines were also promulgated.[5,17] Subsequent experience revealed good sensitivity and negative predictive value but less so in infants younger than 1 month.[23-26] The generalizability of these strategies to office practice has not been studied, and there are indications that these guidelines do not seem to have been widely adopted[11,27] and were imperfectly applied in institutions where they were generated.[6,28]

This is the first nationwide study of febrile infants treated in community-based pediatric practices in the United States. We have developed a portrait of how febrile infants are cared for and the

types of illnesses seen in office practice. It is clear that the PROS practitioners in our sample do not follow existing guidelines for treating febrile infants, even for those younger than 1 month. While use of less-invasive testing such as WBC count and urinalysis occurs in the majority of cases, more invasive testing, such as lumbar punctures and hospitalizations, occurrs less frequently, especially in older infants, than called for by published strategies or documented in series from emergency departments.

Our results suggest that clinical characteristics of febrile infants have a strong association with both diagnostic evaluation and management strategies. Younger infants, those appearing more ill, and those with higher fever were significantly more likely to receive laboratory evaluations, receive antibiotics, or be hospitalized. A few patient characteristics unrelated to clinical appearance predicted management. Medicaid-insured infants were more likely to receive laboratory tests and be hospitalized after adjusting for other factors, likely due to perceived barriers in obtaining adequate follow-up care. Because testing was less selective in infants with Medicaid, they had a lower rate of bacteremia.

The majority of febrile infants in this study had benign and self-limited illnesses; our sample size permits reasonable estimates of the risk of bacteremia/bacterial meningitis as well as other serious illnesses, including urinary tract infection. The frequency of urinary tract infections was 5.4% in the total sample of 3066 infants and 9.7% in the 1666 infants who had urine testing at the initial visit. The detection of bacterial meningitis in 0.5% of patients is less than that in an analysis of 14 studies from 1972 to 1991, in which 0.8% of 1703 infants had bacterial meningitis.[29] Most of these studies were conducted in urban emergency departments. More recent studies found 2 cases of bacterial meningitis in a series of 394 (0.5%),[19] 17 of 5279 (0.3%),[25] and 5 of 422 (1.2%).[6] We detected bacteremia in 1.8% of our population of 3066 infants (2.4% of those who had blood cultures performed) compared with.7%[19] and 1.2%[25] in other contemporary series. An earlier meta-analysis documented a bacteremia/bacterial meningitis rate in febrile infants younger than 1 month of 3.7% and 1.6% in infants aged 1 to 3 months.[30] The sample size and geographic diversity of this study helps provide accurate estimates of the risk of various illnesses. These estimates may be helpful in discussions with parents about management strategies commensurate with the estimated level of risk. Along with parents' individual preferences,[31] these could enhance collaborative decision making.

We documented a wide array of organisms responsible for bacteremia/bacterial meningitis. Given the low frequency of pneumococcal disease,

Table 8. Multivariate Predictors of Bacteremia/Bacterial Meningitis Before Laboratory Testing (n = 3066)

Demographic/Clinical Features	No. of Patients	Unadjusted Odds Ratio	Adjusted Odds Ratio (95% CI)	*P* Value
Age, d*				
≤30	775	5.72	5.56 (2.50-12.36)	<.001
31-60	1220	2.55	3.03 (1.35-6.81)	.007
Medicaid insured	1074	0.68	0.56 (0.32-0.99)	.05
Appearance†				
Moderately ill	767	2.89	1.79 (0.95-3.38)	.07
Very ill	50	20.1	8.90 (3.34-23.69)	<.001
URTI diagnosed	785	0.18	0.27 (0.06-1.15)	.08
Ill family member(s)	1512	0.47	0.51 (0.30-0.89)	.02
Temperature, °C‡				
38.5-38.9	1049	2.63	2.37 (1.22-4.63)	.01
39.0-39.4	458	2.59	1.84 (0.84-4.37)	.12
≥39.5	198	4.51	3.61 (1.40-9.25)	.008
Inner-city clinic	42	1.82	2.23 (0.97-5.13)	.06
Abnormal cry	251	5.16	2.23 (1.16-4.29)	.02

Abbreviations: CI, confidence interval; URTI, upper respiratory tract infection.
*Comparison group: aged >60 days.
†Comparison group: well or minimally ill.
‡Comparison group: temperature <38.5°C.

Table 9. Multivariate Predictors of Bacteremia, Including Laboratory Data*

Demographic/Clinical Feature	Adjusted Odds Ratio (95% CI)	*P* Value
Age, d†		
≤30	4.03 (1.74-9.37)	.001
31-60	2.39 (1.00-5.71)	.06
Medicaid insured	0.54 (0.30-0.97)	.04
Appearance‡		
Moderately ill	1.31 (0.69-2.48)	.41
Very ill	5.26 (1.89-14.63)	.001
Ill family member(s)	0.61 (0.34-1.08)	.09
Temperature, °C§		
38.5-38.9	2.03 (1.03-4.02)	.04
39.0-39.4	1.79 (0.78-4.09)	.17
≥39.5	2.90 (1.09-7.74)	.03
Abnormal cry	2.40 (1.20-4.96)	.01
Abnormal white blood cell count‖	3.62 (2.13-6.15)	<.001
Abnormal urinalysis result¶	1.67 (0.90-3.13)	.10

Abbreviation: CI, confidence interval.
*Includes only those with complete blood cell counts and blood cultures; n = 1746.
†Comparison group: aged >60 days.
‡Comparison group: well or minimally ill.
§Comparison group: temperature <38.5°C.
‖Defined as <5000/μL or ≥15 000/μL.
¶Defined as positive or negative esterase or ≥5 white blood cells per high-powered field.

introduction of the pneumococcal vaccine subsequent to this study will not appreciably change the epidemiology reported. Of interest was the frequency of *Escherichia coli* infections, which was greater than group B β-hemolytic streptococcal infections. The greater use of intrapartum antibiotics may have decreased the risk of group B β-hemolytic *Streptococcus* and increased the risk of *E coli*.

This study also provides data on how well current guidelines would perform in infants seen in clinicians' offices. We found that the current guidelines are very sensitive in detecting bacteremia/bacterial meningitis. Practitioners relying on their clinical judgments were at least as sensitive in treating bacteremia and bacterial meningitis, missing only 2 cases of bacteremia/bacterial meningitis while sparing many infants unnecessary hospitalization and tests. (At least 1 protocol calls for lumbar puncture in all children, while only a third of patients in this study had lumbar punctures.) Using recursive partitioning analysis, we were able to approximate the performance of current guidelines without the need for laboratory tests. While this model did not perform quite as well as practitioners in this study, it identified patients at very low risk of bacteremia/bacterial meningitis. Only 4 in 1056 infants aged 25 days or older who appeared minimally ill and had temperatures of less than 38.6°C had bacteremia/bacterial meningitis. Many such infants might be spared unnecessary laboratory testing. This is of practical importance in situations in which laboratory testing might not be immediately available.

The variation of the strategies of PROS practitioners from established guidelines may reflect the changing frequency of serious illnesses accompanying febrile illness in infants. With bacterial meningitis in 0.5% and no bacterial meningitis in more than 1000 infants aged 2 to 3 months, it is not surprising that clinicians used fewer laboratory tests than suggested in published guidelines.

Also noteworthy is that a majority of infants had more than 1 office visit and frequent telephone contacts. The ability to achieve this level of follow-up was an important element in this group of primary care patients and may also explain the low frequency of hospitalization. The cost of 2 to 3 follow-up visits is substantially less than a hospitalization and was safe in this population. Any new guidelines for the management of fever in infants should consider a strategy of watchful waiting with repeat observations for infants who, in the judgment of the clinician, can be safely observed at home and have continuing access to care.

The following limitations of our study should be noted. While not all febrile infants were enrolled during the study period, infants eligible but not enrolled were slightly older, suggesting that the true frequency of SBI, including bacteremia/bacterial meningitis, may be less than that reported. The distribution of illness found in the sample of infants is likely representative of infants seen in community-based practice but is not broadly generalizable to infants seen in emergency department settings. Our methods differed from most studies by

Figure. Classification Tree for Detecting Bacteremia and Bacterial Meningitis in Infants

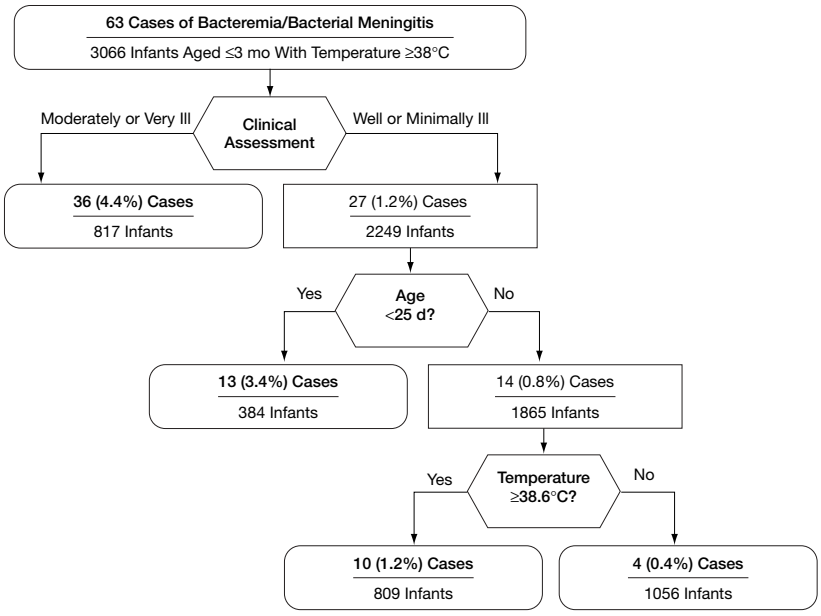

Table 10. Performance of Clinical Prediction Models

Clinical Prediction Models	Patients With White Blood Cell Counts and Blood Cultures (n = 1746)	
	Sensitivity, %	Specificity, %*
Clinical appearance	58.1	68.1
Clinical appearance; abnormal white blood cell count†	83.9	54.0
Clinical appearance; abnormal white blood cell count and urinalysis†	87.1	50.7
Guidelines model (Table 2)	95.2	35.2
Tree-structured analysis model (Figure)	93.6	27.3
PROS practitioners' actual experience: initial treatment with antibiotics	97.1	35.5

Abbreviation: PROS, Pediatric Research in Office Settings.
*See "Methods" section of text for definition of specificity used in this analysis.
†See Table 9 footnotes for definitions of abnormal results.

including children with normal temperatures in the office but febrile at home. However, we documented 6 cases of bacteremia/bacterial meningitis in this group, suggesting that these infants should not be ignored. Finally, this study included few African American, Hispanic, or inner-city infants. The PROS network has subsequently made efforts to recruit practices to reflect the current demographic portrait of the United States.

While this report focuses on the success of clinicians in addressing 2 of the most serious underlying causes of fever in infancy, we are not suggesting that the quality of care could not be further improved. As reported in detail elsewhere,[14] urinary tract infections in tested infants were documented in 19% of uncircumcised boys, 13% of girls, and 17% of infants with prolonged illness. Yet only slightly more than 50% of infants had a urine test, including uncircumcised boys, among whom 41% did not have urine evaluations. This discrepancy represents a potential opportunity to improve practice. However, obtaining urine tests in all infants may not be necessary; the selective approach by PROS practitioners did not result in detected adverse outcomes.

In summary, we have documented strategies for managing fever in infants by community practitioners and the frequency of illnesses diagnosed. The large sample size has allowed us to precisely assess the frequency and factors associated with high risk of bacteremia/bacterial meningitis in infants (age ≤30 days, higher temperatures, ill appearance, abnormal cry, and abnormal WBC count); and we have identified a group with a risk of bacteremia/bacterial meningitis of 0.4% (well appearing, aged 25 days or older, and temperature <38.6°C). Despite lack of adherence to guidelines, PROS clinicians detected as many cases of bacteremia/bacterial meningitis while performing fewer tests and hospitalizing fewer infants than would have occurred if strictly adhering to practice parameters. The findings suggest that if close follow-up care is attainable, the management of selected cases by experienced clinicians using clinical judgment may be more appropriate than strict adherence to published recommendations, with the potential benefit of reducing considerable costs and iatrogenic morbidity. While guidelines have an important role in ensuring the quality of care for many clinical issues, their performance in complex clinical situations, such as the management of febrile illnesses, should be analyzed to evaluate whether the guidelines actually optimize care.

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