The management of the febrile illnesses in young infants has been a topic of debate for decades. In a large part, the concerns of the practitioner lie in the knowledge that not only is the risk of serious bacterial illness higher in young infants, but also the clinical clues that are often used to detect serious illness are not reliable. During the first 2 months of life, the infant’s immune system is relatively immature. Chemotactic responses such as opsonin activity, macrophage function, and neutrophil activity are decreased, making the infant more susceptible to bacterial illness. In addition, although recent vaccination for Haemophilus influenzae type b and Streptococcus pneumoniae has led to a decline in invasive illness from those organisms, the newborn is still exposed to maternally transmitted organisms. In particular, gram-negative bacilli, Listeria, Enterococcus, and group B Streptococcus remain frequent etiologies of disease at this age. These bacterial diseases constitute about 10% of discharge diagnoses for infants younger than 2 months [1-5]. Although urinary tract infection is the most common serious bacterial illness identified, 1% to 3% of febrile infants have bacteremia and/or bacterial meningitis. Furthermore, clinical illness indicators such as state variation and reaction to parent stimulation are not reliable predictors of serious bacterial illness at this age [2,3,6]. As many as 65% of febrile infants with serious bacterial illness appear well on initial examination [6]. These concerns led to a conservative management strategy that was extrapolated from the experience with febrile infants in the newborn nursery. Thus, in the 1980s, the “rules” for management of febrile infants younger than 2 months generally included an evaluation for sepsis (including urine, blood and spinal fluid examination), inpatient admission, and empirical antibiotic therapy pending culture results [1,7,8].

By the 1990s, several investigators developed a combination of clinical and laboratory criteria to be used as a way of stratifying these febrile infants by their risk of serious illness [2-4]. Most of these studies showed high sensitivities and negative predictive values. Although the data sets differed somewhat in the age group studied and the specific criteria used, they were all primarily based in large urban
hospitals. In addition, specific practice guidelines for the management of infants and children without a source of infection were published in the pediatric and emergency medicine literature [7]. By the turn of the century, these studies of risk stratification had a noticeable impact on patient management especially for the febrile infant between 1 and 2 months old. A survey of pediatricians, emergency medicine physicians, and family practitioners regarding their management of hypothetical children with fever without source was conducted in 1993 and then repeated in 1998 (Table 1) [9,10]. In particular, routine admission of the febrile 7-week old declined from 82% to 62% for pediatricians and from 96% to 70% for emergency medicine physicians. At the same time, although many practitioners embraced the possibility of managing selected low-risk febrile infants as outpatients, they often acted outside established guidelines or apart from developed low-risk criteria [11].

Although it is clear that selected febrile infants can be managed as outpatients, the specific criteria used to define this low-risk population remain in flux. Much of the debate centers on the delicate balance between minimizing testing (and accepting a very small risk of missing a serious bacterial illness) vs minimizing the risk and doing more testing. There are no hard and fast rules because these issues are dependent on the practitioner’s interpretation of the existing data, the ability to apply them to their specific practice setting, and the variations associated with specific clinical epidemiology. To that end, we will review the basis for the current controversies surrounding the management of the febrile infant and whether the age of the infant, the practice setting, and concurrent viral infection should affect management.

**Identification and Management of Infants at Low Risk for Serious Bacterial Illness**

Of the studies that have tested screening tools to identify low-risk infants, 2 that used prospective consecutive cohort designs [2-4] have the most compelling methodology. The first published was conducted at Children's Hospital, Boston, Mass, and tested the safety and efficacy of outpatient management with intramuscular ceftriaxone of fever in 1- to 3-month-old infants who had been judged by the investigators to be at low risk for having serious bacterial disease. In this study, 336 febrile infants aged 1 to 2 months and 167 febrile infants aged 2 to 3 months were enrolled. All of those infants were judged to be at low risk for having bacterial disease, according to screening criteria used. Even in this low-risk cohort, 27 (5%) had culture-positive bacterial diseases, including bacteremia, urinary tract infections, and gastroenteritis. All infants recovered uneventfully from their illnesses and seemed to have no complications attributable to initial outpatient management. Furthermore, all 9 infants with initial bacteremia had repeat blood cultures that were negative. When those who had bacterial disease were compared with those with nonbacterial disease, few differences in individual screening parameter results were detected. One difference that was noted was the significantly higher proportion of bands detected in those with bacterial disease, which is consistent with the findings of others [2,4,12,13].

The second large prospective consecutive cohort study was published by the investigators at Children's Hospital of Philadelphia in Pennsylvania [2]. Those investigators tested the efficacy and safety of outpatient management without antibiotics of fever in a selected group of 1- to 2-month old infants who were prospectively judged to be at low risk for bacterial disease. Of the 747 infants who presented with fever during the 5-year study period, 287 (39.4%) were, according to the screening tool used, judged to be low risk for bacterial disease. In addition, no infant classified by those criteria as low risk had bacterial disease. Thus, these authors concluded that fever in carefully selected infants could be managed safely without antibiotics on an outpatient basis, provided that a complete evaluation for bacterial disease was performed and that follow-up within 24 hours could be assured.

<table>
<thead>
<tr>
<th>Year of survey</th>
<th>Pediatrics</th>
<th>Family Medicine</th>
<th>Emergency Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted (%)</td>
<td>82</td>
<td>62</td>
<td>64</td>
</tr>
<tr>
<td>Treated empirically (%)</td>
<td>65</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Observed (%)</td>
<td>17</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Sent home (%)</td>
<td>19</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Treated empirically (%)</td>
<td>9</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Observed (%)</td>
<td>10</td>
<td>10</td>
<td>23</td>
</tr>
</tbody>
</table>
Another group of investigators (Jaskiewicz et al [4]) used the screening criteria developed in Rochester, NY, to prospectively study fever in infants younger than 60 days old. They too sought to determine the reliability of low-risk criteria in infants with fever. Of the 931 well-appearing febrile infants included in the study, 437 (47%) were classified as low risk for serious bacterial illness. Five of those low-risk infants had a serious bacterial illness. Although the negative predictive value was 98.9% (95% CI, 83.2%-97.4%), the sensitivity of their criteria was only 92.4% (95% CI, 83%-97%). In addition, there were several important limitations to their findings. Unlike the other studies from Boston and Philadelphia, there was no uniform sepsis evaluation; 97% had spinal fluid cultures and 75% had urine cultures. There were multiple observers, and the assessment of the infant’s general appearance was poorly specified. Finally, empirical treatment with antibiotics was inconsistent.

The reason for the difference in predictive values of low-risk criteria for bacterial illness among the 3 studies lies in the differences in the composition of their screening evaluations (Table 2). In particular, the Philadelphia group chose a slightly higher temperature cutoff, chose a lower peripheral white blood cell (WBC) count, included the band-to-total neutrophil ratio, and used a tested clinical appearance score. Unlike the other studies, the Rochester criteria did not include spinal fluid analysis as a routine part of their low-risk criteria, based the attainment of urine cultures upon the results of urinalyses, and included infants younger than 1 month. All the studies had high negative predictive values largely related to the overall low incidence of serious bacterial illness in febrile infants. When applied, useful criteria should also yield a very high sensitivity, thereby assuring that the risk of misclassifying an infant with serious bacterial illness as low risk is very unlikely. The Philadelphia criteria demonstrated both high negative predictive value and high sensitivity. The Boston group, which had a relatively low negative predictive value, supports the routine use of ceftriaxone in their outpatient low-risk group. The Philadelphia and Rochester groups, who used criteria that led to higher negative predictive values, do not recommend routine antibiotic use.

At the conclusion of the Philadelphia study, the febrile infant management protocol was established there as the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Common strategies for the management of febrile infants.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rochester Criteria [4]</strong></td>
<td><strong>Philadelphia Criteria [2]</strong></td>
</tr>
<tr>
<td>Age</td>
<td>• 60 d</td>
</tr>
<tr>
<td>Temperature</td>
<td>• 38°C</td>
</tr>
<tr>
<td>History</td>
<td>Term infant</td>
</tr>
<tr>
<td></td>
<td>No perinatal antibiotics</td>
</tr>
<tr>
<td></td>
<td>No hospitalization longer than the mother</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Well appearing</td>
</tr>
<tr>
<td></td>
<td>Unremarkable examination</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td>WBC &gt;5000 and &lt;15 000/mm³</td>
</tr>
<tr>
<td></td>
<td>Absolute band count &lt;1500/mm³</td>
</tr>
<tr>
<td></td>
<td>UA &lt;10 WBC/mm³</td>
</tr>
<tr>
<td></td>
<td>&lt;5 WBC/mm³ stool smear</td>
</tr>
<tr>
<td></td>
<td>with diarrhea</td>
</tr>
<tr>
<td>Fail low-risk criteria</td>
<td>Hospitalize + empirical antibacterial agent(s)</td>
</tr>
<tr>
<td>Meet low-risk criteria</td>
<td>Home</td>
</tr>
<tr>
<td></td>
<td>No antibacterial therapy</td>
</tr>
<tr>
<td></td>
<td>Follow-up required</td>
</tr>
<tr>
<td>Reported statistics</td>
<td>Sensitivity 92% (83%-97%)</td>
</tr>
<tr>
<td></td>
<td>Specificity 50% (47%-53%)</td>
</tr>
<tr>
<td></td>
<td>Positive predictive value 12.3% (10%-16%)</td>
</tr>
<tr>
<td></td>
<td>NPV 98.9% (97%-100%)</td>
</tr>
</tbody>
</table>

Data from **Consensus in Pediatrics.** 2005;1(7):1. UA, urinalysis; hpf, high power field; NPV, negative predictive value.
The Practice Setting and the Pediatric Research in Office Settings Experience

One of the criticisms of the large prospective studies of febrile infants was that the patient samples were generally drawn from urban hospital emergency departments (EDs). To be sure, the low incidence of serious illness necessitated a large sample size, which was most likely generated from a busy academic pediatric ED. However, this led to an apparent disconnection between the practice in academic hospitals and that in a private practitioner’s office. This disparity was evident since the early 1980s when surveys of practitioners in the office setting showed that they ordered fewer tests and less routine hospitalization of the febrile infant when compared with the general practice in academic hospitals [14]. Perhaps the office practitioners believed that the practice guidelines were developed from studies that could not be generalized to the patient populations they cared for. In particular, office practitioners touted better follow-up abilities and a stronger connection to ongoing care of their patients.

In 2004, a study that was specifically designed to address this patient population was published. The Pediatric Research in Office Settings (PROS) practice-based research network of the American Academy of Pediatrics, consisting of 573 members from 219 practices representing 44 States, the District of Columbia, and Puerto Rico, conducted the study [5]. A consecutive sample of 3066 febrile infants younger than 3 months was studied, 63 (2.1%) of whom had bacteremia/bacterial meningitis. Clinical appearance was judged as well/minimally ill, moderately ill, or very ill; laboratory testing was at the discretion of the practicing clinician. Thirty-six percent of the infants were hospitalized, 75% had some laboratory testing, and 57% were initially treated with antibiotics. Of particular importance, only 125 (4%) had just single office visit and no other contact.

Of the 2249 infants who looked well/minimally ill on initial presentation, 27 (1.2%) had bacteremia/bacterial meningitis. When stratified by age, infants younger than 25 days had a bacteremia/bacterial meningitis rate of 3.4% compared with only 0.8% of those infants 25 days and older. The authors also noted that PROS practitioners’ actual management practice had greater accuracy than the existing established management guidelines. Although on the surface, this study seemed to support individualized clinical judgment by office practitioners, there were important limitations. Specifically, not all practitioners in the network participated, not all febrile infants were enrolled, and standard laboratory testing was not done on all infants. The lack of standard evaluation of these infants prohibits conclusive identification of all infants with bacterial illness, and therefore, the true incidence of disease is unknown. It is possible that the sickest febrile infants bypassed the office to go to the ED, thus, leading to lower incidence rates of serious bacterial illness in the office setting [15]. However, it is also possible that the perspective of an office practitioner is limited by the number of febrile infants seen in their office compared with a busy ED. Using the PROS data, an office practitioner would evaluate a febrile infant once every 214 days, and, if the bacteremia/bacterial meningitis incidence was 1%, that practitioner would see a febrile infant in the office with bacteremia/bacterial meningitis once every 58 years. Therefore, one must exercise extreme caution in feeling secure with an individualized management strategy when the incidence of serious disease is so low.

Thus, it appears that in the absence of additional data, management of febrile infants in the office setting should be similar to that in the ED. However, the ability of an office practitioner to have reliable and consistent follow-up is an important decision modifier when deciding among different outpatient management criteria.

Applicability of Screening Criteria to Infants Younger Than 1 Month

Although the current screening criteria can be applied to febrile infants 1 to 2 months old, there remain insufficient data to generalize this approach to younger infants. This is largely due to reported higher rates of bacterial disease in this age group [12,16,17] and the limited abilities of young infants to portray ill appearance [6]. Rates of bacteremia and/or bacterial meningitis have been reported between 1.5% and 4% in this age group, which is more than twice that of febrile infants 1 to 2 months old [5,18]. Furthermore, clinical parameters remain unreliable; the development of a social smile, one of the most common
clinical signs of well appearance, is generally not present until after 1 month old. Justifiably, these concerns formed the basis for many investigators [2,3,18,19] to exclude febrile infants younger than 1 month from outpatient management schemes.

Others, such as the proponents of the Rochester criteria, have included infants younger than 1 month in their study sample and have provided some preliminary insight into this issue [4]. In one group of 227 infants younger than 1 month who, by Rochester criteria, were at low risk for bacterial disease, 2 had bacterial disease. Unfortunately, the group studied was not one of consecutively presenting eligible infants, which makes questionable the applicability of the results to the population as a whole.

Two studies [18,20] have shown that the published Philadelphia and Boston protocols, which were designed for use in infants older than 1 month, are not applicable to infants younger than 1 month. In a retrospective study conducted in Salt Lake City, Utah, 45 of 372 febrile 0- to 1-month-old infants were proven to have serious bacterial illnesses [20]. Of those, 13.3% by Philadelphia criteria and 17.8% by Boston criteria would have been identified as low risk for bacterial disease. In a similar prospective study of 254 febrile 0- to 1-month-old infants in Philadelphia, 5 (15.6%) of 32 who had serious bacterial illnesses would have been identified as low risk for bacterial disease according to the Philadelphia criteria [18]. Viewing that data from a different perspective, applying the screening criteria in the Philadelphia protocol to febrile neonates younger than 1 month would falsely identify them as low risk for serious bacterial illness in as many as 10 per 100 neonates with fever.

Thus, for infants younger than 1 month, risk stratification criteria are unreliable, and therefore, these infants should have a sepsis evaluation, including a lumbar puncture, hospitalization, and empirical antibiotic treatment pending culture results.

Meningitis (and the Issue of the Lumbar Puncture)

Although the prevalence of aseptic meningitis in infants with fever may be relatively high (up to 13% during seasonal outbreaks of enterovirus [2,11]), the prevalence of bacterial meningitis is quite low. The combined results of the investigations from Philadelphia reported that 1.2% of all 1- to 2-month-old infants studied had bacterial meningitis. Common experience suggests that the occurrence is less than that today, in part, because of the decline in H influenzae type b and S pneumoniae in the older infants. In a study from Boston conducted from 1992 to 1999, the prevalence of bacterial meningitis in infants younger than 2 months was approximately 0.5% [21]. Data from the PROS network corroborate these findings [5].

Though infrequent, bacterial meningitis still occurs in these infants and can be difficult to detect by means other than analysis of cerebrospinal fluid (CSF). Bonsu et al [21] studied the use of peripheral WBC counts as a screen for need for lumbar puncture in infants 3 to 89 days old. They analyzed 3353 CSF samples of consecutive infants evaluated for presence of bacterial disease in the ED at Children’s Hospital, Boston, Mass. Of the 22 cases of bacterial meningitis, 41% had peripheral WBC counts between 5000 and 15 000 (low risk according to Philadelphia and Rochester criteria), and 64% had peripheral WBC counts between 5000 and 20 000 (low risk according to Boston criteria). They concluded that lumbar punctures of febrile infants should not be omitted based on the results of peripheral WBC counts. However, the study examined the use of the WBC alone and not as part of a more comprehensive set of clinical and laboratory criteria. Furthermore, they did not attempt to use other WBC count indices such as the absolute band count or the band to total neutrophil ratio that has been used as part of other predictor sets of serious bacterial illness in febrile infants. Perhaps, most importantly, there was no stratification by clinical appearance. Thus, it is possible that many febrile infants with bacterial meningitis looked clinically ill and therefore would have qualified for a lumbar puncture on that basis.

Many continue to advocate routine lumbar puncture as part of the evaluation of febrile infants younger than 2 months [2,11], regardless of clinical appearance, whereas a minority, notably those who use the Rochester low-risk criteria, does not [4,5]. To be sure, infants who are younger than 1 month have higher rates of bacteremia and bacterial meningitis and also lack many of the clinical clues necessary to make a reliable global assessment of appearance. The issue is whether a well-defined selected group of older febrile infants between 4 and 8 weeks old can have risk stratification based on clinical appearance and blood and urine studies without the routine spinal fluid analysis. To that end, one must realize that the term febrile infants is not a homogenous group. Infants, even at this young age, develop at different rates. Some 6-week olds are relatively immature in terms of their clinical state, ability to smile, and quality of reaction to parent stimulation, whereas others appear clinically closer to older infants. These factors should be considered when evaluating these infants and planning management strategies. There are no conclusive data to support omission of the lumbar puncture from routine evaluation of fever in infants between 4 and 8 weeks old. Nevertheless, for a selected group of older well-appearing febrile infants who meet all low-risk criteria (both clinical assessment and diagnostic testing), some experienced clinicians will elect to delay or omit the lumbar puncture, provided that reliable follow-up can be arranged and that the healthcare provider is confident that parents have appropriate observational skills. However, one must
Infants Who Test Positive for Viruses

Because viral disease is the most common reason for fever in infants, it is not surprising that rapid testing for viruses will at times be positive. In that setting, physicians often question the need for further evaluation of fever. Although viral polymerase chain reaction testing is available for a wide variety of viral pathogens, the most common rapid viral tests used in the ED are for influenza and respiratory syncytial virus (RSV).

The issue of a positive rapid test for influenza is discussed in depth elsewhere in this journal. Although the effects of rapid influenza testing have lead to a reduction of tests obtained in the evaluation of febrile infants and toddlers, the key question is whether there is an association between influenza and serious bacterial illness. Most studies show a significantly lower risk of serious bacterial illness in children older than 2 to 3 months [22-24]. However, there is, of yet, no data showing a similar result for infants younger than 2 to 3 months. Thus, in the absence of new data, febrile infants who test positive for influenza should be managed similar to those who do not.

Febrile infants who have concurrent bronchiolitis have been the subjects of several investigations. Many studies have shown that febrile infants younger than 2 to 3 months with bronchiolitis had significantly lower rates of serious bacterial illness, and when present, these illnesses were all urinary tract infections [25-27]. However, these studies were retrospective, and few had a defined control group.

In 2004, as part of the Pediatric Emergency Medicine Collaborative Practice Committee, a large prospective study involving 8 pediatric EDs enrolled 1248 infants younger than 60 days with temperatures 38°C or higher [28]. All infants had undergone blood, urine, and spinal fluid studies as well as an RSV rapid test. The overall rates of serious bacterial infection (11.4%), bacteremia (2%), and bacterial meningitis (0.7%) were similar to prior studies. Twenty-two percent of the infants were RSV positive. Overall, RSV-positive infants were less likely to have a serious bacterial illness than RSV-negative infants (7% vs 12.5%). Urinary tract infection represented most cases of serious bacterial illness in both groups (5.4% vs 10.1%). Respiratory syncytial virus–positive infants also had lower rates of bacteremia, but the differences were not statistically significant. When the results were stratified by age, the risk of serious bacterial illness was substantial in infants younger than 28 days old and not altered by being RSV positive or RSV negative (10.1% vs 14.2%). However, for infants 29 to 60 days old, 5.5% had urinary tract infections but none had bacteremia or bacterial meningitis. Thus, for these infants, urine testing should continue to be routine. Although the rates of bacteremia and bacterial meningitis appear to be lower in RSV-positive infants, to be more data is required before the other laboratory tests for risk stratification can be modified.

Herpes Simplex Virus Infections in Young Infants

Although most of the emphasis on management of fever infants centers on the identification of serious bacterial illness, one must not forget that certain viruses, in particular, herpes simplex virus (HSV), may cause high morbidity and mortality.

Herpes simplex virus is an uncommon cause of infection in infants younger than 2 months [29,30]. In the United States, incidence varies from 1 in 2000 to 1 in 5000 live births (approximately 1500 new cases per year). The 2 causative agents are HSV-2 (70%-75%) and HSV-1 (25%-30%). Most congenital infections are transmitted via direct contact with the infected birth canal during labor, but transplacental infection can also occur. Most (60%-80%) of the mothers of HSV-positive babies have no known history of HSV infection. The incubation period of congenital herpes infections ranges from 2 to 30 days after exposure. Signs and symptoms of these infections usually manifest between 10 and 20 days after birth.

There are 3 equally prevalent types of clinical presentations of congenital HSV infections: SEM (skin, eyes,

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Decision modifiers used in the evaluation and management of febrile infants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Practice setting</td>
<td>2. Experience of practitioner</td>
</tr>
<tr>
<td>3. Ease and reliability of follow-up</td>
<td>4. Patient demographics</td>
</tr>
</tbody>
</table>
mouth), central nervous system, and disseminated (increased levels of liver transaminases are seen in this group). The clinical manifestations of congenital HSV infections are diverse and vary by type [30]. In general, more than 50% of infected neonates (regardless of type) present with skin findings. The skin lesions may present as single or grouped vesicles, pustules, bullae, or denuded skin, and are often mistakenly identified as impetigo. However, between 32% and 39% of infants with congenital HSV central nervous system infection or disseminated disease do not have skin lesions on presentation [30]. Thus, the clinician must be acutely aware of secondary symptoms including hypothermia, poor feeding, irritability, lethargy, and vomiting.

Acyclovir (60 mg/kg per day, given in divided doses via intravenous infusion) should be empirically administered to all children with suspected congenital HSV infection. Early administration has been shown to reduce both morbidity and mortality associated with this disease [29]. One should suspect congenital HSV infection in full-term infants younger than 4 weeks and in premature infants (increased levels of liver transaminases are seen in this group) younger than 28 days of age with intramuscular administration of ceftriaxone. J Pediatr 1992;120:22-7.


Summary

Fever in young infants often accompanies bacterial disease. Approximately 10% of febrile infants younger than 2 months will have associated bacteriuria, bacteremia, or other bacterial disease. In spite of assertions to the contrary, “well” physical appearance does not reliably rule out the presence of bacterial disease in this population. Accordingly, the presence of fever in infants younger than 2 months demands immediate and comprehensive management. All such infants require complete evaluation for bacterial disease. Those younger than 1 month require empirical administration of antibiotics and careful observation, pending the results of their blood, urine, and CSF cultures.

The care of febrile infants between 1 and 2 months old can be individualized, based on the results of their physical examination and diagnostic tests. There are a variety of testing and management strategies each with defined risks and benefits. Most of these strategies include examination of the complete blood count and differential, urinalysis, chest radiograph (if respiratory symptoms), and CSF studies. The management strategy chosen should be based on a variety of decision modifiers, some of which are listed in Table 4. Once the laboratory tests are reviewed, final decisions can be made regarding administration of antibiotics and need for hospitalization. To qualify for outpatient management, the infant must appear well, must have complete results of all diagnostic tests clearly interpreted as acceptable, and must have competent caretakers at home who are confident in their ability to observe the infant and who will return with the infant for reevaluation both 24 and 48 hours later.

References


