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## Evaluation and management of febrile infants in the emergency department

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As every emergency physician knows, management of fever in young infants is fraught with anxiety for both parents and medical personnel. No physician wants to send home a patient from the emergency department (ED) with a potentially life-threatening infectious illness. Because they lack the normal social cues of older babies and children (eg, smiling, playing), febrile infants who look well may nevertheless have frank sepsis and/or meningitis. In fact, evidence has shown that distinguishing “high risk” versus “low risk” for these patients based solely on examination findings is impossible, even for the most experienced clinician. And, of course, a bad outcome with an infant is particularly devastating for all concerned.

The practice of unnecessarily admitting large numbers of infants to the hospital to guard against sending one home with a serious illness must also be avoided, however. The resulting risks of hospitalization, and the financial strain on an already overburdened health care system, would likewise be a disservice to patients. Thus, the salient question for any physician in this situation is “When can a febrile infant be safely discharged from the ED?” The work of Doug Baker and others, which culminated in one of the most important and influential publications in emergency medicine, has greatly enhanced our ability to answer that question.

Aside from the addition of third-generation cephalosporins to the available treatment options, management of “ill-appearing” febrile infants has not changed significantly in the past 15 to 20 years. These babies undergo a complete sepsis work-up and receive intravenous (IV) antibiotics on an inpatient basis, regardless of laboratory results. In contrast, management of

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“well-appearing” febrile infants has changed dramatically during this same period of time, and these changes are the focus of this discussion.

Such basic concepts as how to define “fever” and “infant” have evolved—and continue to evolve—as physicians’ understanding of these young patients has progressively increased. Whereas the picture has become somewhat more complex, current management strategies are undoubtedly safer and more cost-efficient than those of the past. Emergency physicians can now follow a clearly defined, evidence-based approach to the evaluation and treatment of well-appearing febrile infants that is strongly supported by the medical literature.

### **Definition of terms**

For purposes of managing fever, pediatric patients were previously divided into two age groups: (1) younger than 3 months and (2) 3 to 36 months. Children in the 3- to 36-month age range were considered to be at increased risk for occult bacteremia (ie, well appearing but with bacteria in the bloodstream), and those younger than 3 months were defined as “infants.” Whereas the significance of occult bacteremia has never been fully delineated, fever in an infant has been recognized for many years as an important risk factor for serious bacterial illness. Over time, it became increasingly clear that patients in the 2- to 3-month age range should be grouped with the older (occult bacteremia) children and that patients in the 24- to 36-month age range were actually at low risk for occult bacteremia. Most authorities therefore currently agree that the two primary risk groups for managing fever in younger children are (1) those younger than 2 months (“febrile infant”) and (2) those aged 2 to 24 months (“occult bacteremia”), although the prior definitions can still be found in some published reports.

The next issue is the proper definition of “fever.” For adults, many physicians consider a fever to be a core temperature of 38.5°C or more. In at least one major study of infants, fever was defined as a temperature of 38.2°C or more. The most widely accepted definition of fever in the context of managing febrile infants, however, is a rectal temperature of 38.0°C or more. The question of what constitutes fever in an infant is complicated somewhat by the fact that infants have poor thermoregulation. Whereas an adult, like all mammals, maintains a relatively stable core temperature over a wide range of environmental temperatures, the core temperature of an infant may fluctuate by a degree or more. An infant bundled in multiple layers of clothing and blankets may therefore have a “fever” resulting entirely from inadequate cooling mechanisms rather than an infectious illness. Despite this, the prudent approach is to assume that any fever in an infant is caused by infection and not by environmental factors. The only way to prove that an infant does not have a fever is by taking a rectal temperature. Both otic and axillary thermometers are unreliable and should

not be used for this purpose. Certainly, if an infant has an otic or axillary temperature of 39°C, then the rectal temperature will also be elevated. But a “normal” otic or axillary temperature must not be taken as proof that an infant is truly afebrile.

## **Background**

In the past, a very conservative approach to the management of febrile infants was followed in most academic emergency centers. In general, any infant with a fever had a full sepsis work-up followed by admission to the hospital for IV antibiotic therapy until all cultures proved to be negative. This was true even if the patient looked well and the sepsis work-up was negative. The assumption was that infants with early sepsis could not be distinguished from those with a benign febrile illness based on physical examination findings or laboratory results. Many stories were recounted about infants with fever who “looked fine” and had “normal labs” yet who, after being discharged from the ED, later returned in fulminate septic shock or died outside the hospital. Consequently, the most conservative management plan became the standard of care.

### *Clinical scoring*

In the 1980s, various attempts were made to devise an objective scoring system based on physical examination findings that could reliably discriminate between “high risk” and “low risk” pediatric patients, in the hope that such a scoring system might obviate the need for aggressive management. The most widely studied of these scoring systems is the Yale Observation Scale, which was developed by Paul McCarthy et al [1]. Six characteristics (ie, quality of cry, state of hydration, response to social overtures, color, and reaction to parents) were found to be independently predictive of serious illness in febrile patients aged 24 months and younger. Each characteristic was defined using a 5-point scale, with “1” being normal and “5” representing severe impairment. An overall score of 10 or less indicated a generally well-appearing patient, and an overall score of 16 or more indicated an ill-appearing patient.

One of the main problems with this type of scoring system is that to be a definitive management tool for febrile infants, it must have a negative predictive value near 100%. Sending home even 1 or 2 infants in 100 with a serious bacterial illness, although an admirable statistical accomplishment, is potentially disastrous from a clinical standpoint. The question that must be asked is this: “How many times in a career is it acceptable to discharge an infant from the ED with meningitis or sepsis?” In the current practice environment, for better or worse, the answer is “none.” Subsequent research indicated that when the Yale Observation Scale was applied to infants aged

younger than 2 months, not only was its negative predictive value well below 100%, it was in fact relatively poor. In 1990, Baker et al [2] found that of 91 febrile infants who were considered generally well appearing (Yale Observation Scale  $\leq 10$ ), 22% had serious bacterial illness. An unacceptably high likelihood of false negatives with even the best of the clinical scoring systems made it evident that these methods alone could not be used to determine the appropriate management of febrile infants.

### *Rochester criteria*

In 1988, Dagan et al [3] at the University of Rochester published a modified version of previously developed criteria designed for risk stratification in infants, which are known as the “Rochester criteria.” The factors proposed by these authors to identify high-risk infants were as follows: (1) soft tissue, skeletal, or ear infections; (2) peripheral white blood cell (WBC) count of less than 5000 cells/mm<sup>3</sup> or more than 15,000 cells/mm<sup>3</sup>; (3) total band count of 1500 cells/mm<sup>3</sup> or more; (4) urine WBC count of 10/hpf or more; and (5) stool WBC count of 25/hpf or more. No cerebrospinal fluid (CSF) results were included in the criteria because the authors believed that when none of these risk factors was found, a lumbar puncture (LP) was unnecessary.

Although this study opened a new area of investigation (ie, adding laboratory results to clinical findings in identifying high-risk infants), it had several major limitations. First, the older definition for infant ( $< 3$  months) was used, so that only 199 of the 250 patients enrolled fit the more widely accepted usage ( $< 2$  months). In addition, only 204 patients actually had a fever of  $\geq 38.0^{\circ}\text{C}$ . Patients without fever were included because they had symptoms such as vomiting or diarrhea which, at best, are nonspecific markers for possible sepsis or meningitis. There was also no breakdown of the results by either presence of fever or age of the subject, precluding any comparison of the effectiveness of the criteria for febrile versus afebrile subjects or for subjects aged younger than 2 months versus those aged 2 to 3 months. With no requirement for fever and an outdated definition of infant, it is difficult to imagine how these criteria could ever be appropriately applied in the management of febrile infants.

Perhaps most troubling of all was that no assessment of clinical appearance was included in the criteria. Patients with presentations such as “severe irritability,” “lethargy,” and “apnea” were enrolled in the study. It seems exceedingly unlikely that a patient with any of these findings could reasonably be considered an appropriate candidate for designation as “high risk” versus “low risk” —by definition they are all high risk. These problems prevented the Rochester criteria from gaining wide acceptance, and in fact, later data showed that the sensitivity of the Rochester criteria in detecting serious illness is relatively low [4,5].

### *Combining clinical and laboratory findings*

With the failure of clinical scoring systems and criteria from laboratory results to identify infants at risk for sepsis and meningitis, physicians were left with the costly and inefficient “shotgun” approach of admitting every patient to the hospital for treatment with IV antibiotics, a practice that was the standard of care for many years. It was clear that most well-appearing infants with fever had benign viral illnesses and that physicians were exposing them without benefit to the risks of parenteral antibiotics and hospitalization. Physicians simply had no reliable means of identifying the patients who were more likely to have a bad outcome. Yet the importance of the early studies on this subject, despite their limitations, should not be understated. By challenging the prevailing orthodoxy, McCarthy et al [1] and Dagan et al [3] provided the basis for more refined study questions, which led directly to many of the answers we have today. Specifically, investigators began to ask “If clinical scoring and laboratory results do not adequately predict the risk of serious illness in a febrile infant when used independently, how effective are they when combined?”

This question was addressed by Baskin et al [5] in 1992. These authors published the first major study of risk stratification in febrile infants to use clinical appearance combined with a complete sepsis work-up (including CSF results). Subjects who were well appearing and had negative laboratory findings were discharged from the ED with arrangements made for close outpatient follow-up. Appropriately, this study was designed to take the first step in redefining the management of febrile infants by evaluating only patients aged 28 days and older. Without question, the decision to discharge an infant with fever, contrary to accepted practice, was associated with potential risk, and the best way to minimize that risk was to begin by studying the population for whom success was most likely. If outcomes were good, then the approach could later be assessed for infants younger than 28 days old. The main strengths of this study are that the authors used a broader and more sophisticated set of criteria in identifying a low-risk population and that they penetrated the longstanding barrier of mandatory hospital admission for all patients. A few serious weaknesses in the study have limited its applicability to clinical practice, but it warrants a detailed discussion, not only for its scientific merit but because it has proved over the years to be a source of ongoing confusion for clinicians.

The Baskin et al [5] study was a prospective trial involving the evaluation and treatment of 503 infants aged 28 to 89 days with a temperature of 38.0°C or greater (in the ED or at home). Subjects were well appearing with no source of fever identified on physical examination and had the following characteristics: (1) CSF leukocytes of less than 10 cells/mm<sup>3</sup>; (2) peripheral WBC count of less than 20,000 cells/mm<sup>3</sup>; (3) microscopic urinalysis with less than 10 leukocytes per hpf or negative leukocyte esterase on urine dipstick; (4) no pneumonia on chest radiograph, if obtained; (5) no

antibiotics or immunizations within 48 hours; (6) reliable caretakers; (7) no other reasons for admission (eg, dehydration); and (8) no allergies to B-lactam agents. Subjects received an intramuscular (IM) injection of ceftriaxone (50 mg/kg) prior to discharge. Telephone follow-up was performed at 12 hours and reexamination was performed at 24 hours, at which time a second dose of IM ceftriaxone was given. Additional telephone follow-up was performed at 48 hours and 7 days. Subjects with positive blood culture results (N = 9) and/or positive urine culture results (N = 8) were treated with “a full course of appropriate antimicrobial therapy,” presumably IV antibiotics on an inpatient basis, although this is not specified. Of infants with positive stool cultures, 9 of 10 were treated as outpatients; the other patient was hospitalized for increasing bloody diarrhea. All of the patients with positive blood or urine cultures had sterile cultures when recalled to the ED for reevaluation. No complications associated with the use of IM ceftriaxone were reported.

Although these results might initially be interpreted as supporting outpatient management of febrile infants with presumptive administration of IM ceftriaxone, there are significant methodologic problems that undermine that conclusion. First, the older definition of infant (< 3 months) was used at a time when the current usage (< 2 months) was virtually universal. Therefore, only 336 of the 503 patients in this study were aged 60 days and younger. In addition, the decision to permit a urine dipstick test to be substituted for a standard urinalysis in determining a “negative sepsis work-up” seems questionable. Although there have been a few studies published suggesting that the negative predictive value of a urine dipstick is high (and others that have refuted this contention), the use of a urine dipstick as part of the sepsis work-up for febrile infants has never been a widely accepted practice. The authors also reported that differences between infants with serious bacterial illness versus those without serious bacterial illness were statistically significant for both percentage of band cells and absolute band cell count in the peripheral blood. Despite this, they did not recommend incorporating these variables into the decision-making process in management of these patients.

The most problematic aspect of the Baskin et al [5] study, which the authors acknowledge, is the failure to have controls (ie, a group of infants who did not receive ceftriaxone). Without controls, the presumption must be accepted on faith that IM ceftriaxone is an appropriate therapy for infants with fever, because this was not demonstrated in any prior study. It was certainly possible (and was shown by later data) that infants in the placebo group would have the same good outcomes as those in the ceftriaxone group. Therefore, the findings from this study do not justify that the absence of any significant complications from bacterial illness can be attributed to the use of IM ceftriaxone. These results showed, however, that about 95% of the patients who were presumptively treated with a parenteral third-generation cephalosporin did not have positive blood, urine, or stool

cultures. The approach outlined in this study is an improvement over admitting every patient to the hospital for IV antibiotics, but it certainly could not be considered an optimal mode of therapy unless it proved to be the only option. Furthermore, such as with the debate over occult bacteremia, there is an important downside to presumptive treatment. The emerging resistance to third-generation cephalosporins among community-acquired *S pneumoniae* has made overuse of ceftriaxone an issue of increasing concern. In many areas, IV vancomycin is now used to treat children with pneumococcal meningitis until antibiotic sensitivity results are available. This ominous and unwelcome development is a direct result of selective pressures exerted on bacteria in the community by widespread presumptive administration of IM ceftriaxone as a treatment for possible occult bacteremia.

The reason that the Baskin et al [5] study has been a cause of confusion is that its results are sometimes mistakenly “merged” with the results of the much more rigorous and convincing Baker et al [6] study. Although the Baker et al study was also designed to evaluate outpatient management of febrile infants, it did not involve the use of IM ceftriaxone at any point in its protocol. It is not uncommon, however, to encounter physicians-in-training (and occasionally attending physicians) who suggest that a febrile infant being discharged from the ED should receive an injection of ceftriaxone because “that was the approach used in the Baker study.” As discussed in the following section, any such statement is untrue.

### *Landmark study*

The large-scale study of febrile infants by Baker et al [6], from 1993, which appeared as the lead article in the *New England Journal of Medicine*, is one of those rare investigations that profoundly changed clinical practice for the better. It was a superbly designed and executed study that definitively answered several important questions. The “Philadelphia Protocol,” as it is known, is directly responsible for a dramatic reduction in unnecessary treatment and hospitalization, while resulting in significant cost savings. Achieving both of these goals at once—better care at a lower cost—is a major accomplishment in the current practice environment.

The Baker et al [6] study was a prospective trial of 747 consecutive infants aged 29 to 56 days old (4–8 weeks) with a temperature of 38.2°C or more. Every patient who was eligible for entry during the 5-year study period was enrolled. As in the Baskin et al [5] study, these authors excluded patients younger than 4 weeks, opting to first evaluate the proposed screening criteria in older infants because this population had the greatest likelihood of success. But unlike the prior study, the more clinically relevant definition of infant (< 2 months) was used. A full sepsis work-up was performed for each patient, which included a complete blood count (CBC), urinalysis, LP, and cultures of the blood, urine, and CSF. As appropriate from clinical findings, a chest radiograph and stool sample for fecal leukocyte and culture analysis were also obtained. Patients with a Yale Observation Score of 10 or

less and normal laboratory results were randomized into one of two groups: inpatient observation without antibiotics (N = 148) or outpatient observation without antibiotics (N = 139). Patients with an infant observation score of more than 10 or abnormal laboratory results were admitted for standard treatment with IV antibiotics (N = 460). Normal laboratory results were defined as follows: (1) peripheral WBC count of less than 15,000 cells/mm<sup>3</sup>; (2) urinalysis (by bladder catheterization only) with less than 10 WBC per hpf and few bacteria or none; (3) nonbloody CSF with less than 8 WBC and a negative gram stain; (4) normal chest X ray, if obtained; and (5) no evidence of soft tissue infection or abscess. During the third year of the study, two additional screening criteria were added: (1) band/neutrophil ratio in the peripheral blood of less than 0.2 and (2) no recognizable immunodeficiency syndrome. Subjects who were randomized to the outpatient group had to live within 30 minutes of the hospital, have a working phone, and their parents had to be willing to return for re-evaluation on each of the following 2 days. At the conclusion of the study, the modified screening criteria were found to be 100% sensitive in identifying patients with serious bacterial illness with a negative predictive value of 100%. With a 95% confidence interval, the sensitivity and negative predictive value were at least 92% and 98%, respectively. When compared with the traditional approach of inpatient management with presumptive IV antibiotic therapy, outpatient management without antibiotics resulted in a savings of approximately \$3000 per patient. Overall, the savings generated by this study were \$435,000.

One of several impressive aspects of this study is that it was actually two well-designed studies in one: (1) inpatient therapy with IV antibiotics versus inpatient observation without antibiotics and (2) inpatient observation without antibiotics versus outpatient management without antibiotics. Had outpatient management proved to be too risky, this study would also have shown whether inpatient observation without IV antibiotics was an acceptable alternative. This alone saved about \$600 per patient and would have been a significant achievement in its own right. As it turned out, not only was inpatient observation without antibiotics found to be acceptable using these screening criteria, outpatient management without antibiotics was also shown to be a valid approach. The key feature of this study that makes it superior to the Baskin et al [5] study, and it took courage for the authors to do this, is that the effectiveness of no antibiotic treatment at all was assessed, which is a critically important issue. The crucial question that was not addressed by the Baskin et al study—that is, what would happen if febrile infants were managed on an outpatient basis without parenteral ceftriaxone—was definitively answered by this study.

#### *Age limitations*

Once the Philadelphia Protocol was shown to be an effective screening tool for febrile infants between the ages of 1 and 2 months, the next obvious

step was to investigate the possibility of using this approach for infants younger than 1 month. The news here is less encouraging. In 1999, Baker and Bell [7] published results of a prospective study involving 109 infants younger than 29 days old with a temperature 38.0°C or more who met the “low risk” criteria of the Philadelphia Protocol (ie, they were well appearing and had a negative sepsis work-up as previously defined). Rather than being managed as outpatients, however, these subjects were admitted to the hospital for treatment with IV antibiotics in accordance with existing practice. After the subjects were released from the hospital, the authors reviewed the medical records to obtain final culture results and discharge diagnoses. They found that five infants who were identified as “low risk” from the initial ED evaluation in fact had bacterial illnesses: two with urinary tract infections, two with bacteremia, and one with bacterial gastroenteritis. Whereas patients with negative culture results were generally discharged within 72 hours, these five patients all required a full course of IV antibiotics as inpatients. From their results, the authors concluded that the Philadelphia Protocol is ineffective when applied to infants younger than 29 days old and should not be used to identify potential candidates for outpatient management in this age group. Of note, at least one study is currently underway assessing the possibility of observing these younger infants on an inpatient basis, without presumptive administration of IV antibiotics, as a potential alternative to current therapy.

### **Overview of management**

As has always been the case, management of any febrile infant with signs or symptoms of possible sepsis, meningitis, or other serious bacterial illness (eg, lethargy, irritability, cyanotic spells) should include a sepsis work-up and inpatient treatment with an appropriate regimen of IV antibiotics. The minimum sepsis work-up in this situation is generally considered to be the following: peripheral blood for CBC with differential, LP, urinalysis, and cultures of the blood, CSF, and urine. As indicated by history and physical findings, a chest radiograph and a stool specimen for fecal leukocytes and culture may also be appropriate. Deviating from the “standard” sepsis work-up may be necessary if a patient is unstable (eg, an immediate LP may be contraindicated because the infant is hypotensive or has respiratory failure). Furthermore, empiric administration of antibiotics, prior to obtaining cultures, may also be required for unstable patients. Although the ideal antibiotic therapy for an ill-appearing febrile infant is debated, most sources agree that either ampicillin and cefotaxime or ampicillin and gentamycin are acceptable choices.

For purposes of ED management, febrile infants younger than 1 month old are still considered a “black box.” Even if they are completely well and have an entirely negative sepsis work-up, the current recommendation is that they nonetheless be admitted to the hospital and treated with IV antibiotics, at least

until the final culture results are known to be negative. Physicians simply do not yet have the capability to discern which of these infants is likely to have a serious bacterial illness using current diagnostic modalities. Perhaps in the future a new laboratory test will be developed that will allow physicians to make this determination with confidence, or as mentioned previously, an intermediate level of care, such as inpatient observation without antibiotics, may prove to be acceptable management for these young infants. Until then, physicians are left with the current aggressive and costly approach.

The major change that has occurred in the last few years is that febrile infants aged 1 to 2 months old who are well appearing can now be discharged with close outpatient follow-up if they have a normal sepsis work-up as defined by the Philadelphia Protocol. Although a stricter definition of fever was used in the 1993 study by Baker et al [6] to ensure an “at risk” population, the generally accepted definition of fever for these patients is a temperature 38.0°C or greater. Clinicians can and should use clinical scoring systems such as the Yale Observation Scale if desired, but, in general terms, these infants should look and act completely well. Moreover, most physicians would agree that an additional factor to consider is whether the patient has had any unusual or concerning behavior during the hours prior to arrival at the hospital, such as “crying all night,” “refusing to feed,” or “sleeping all the time and not waking up for regular feedings.” Even when this type of behavior is not obvious in the ED, such descriptions should usually tip the balance toward a more conservative management plan.

In making the determination of “well” versus “ill” for a febrile infant, take the example of a 6-week-old baby, perfectly normal in appearance and behavior, brought to the ED for evaluation of a benign rash, but incidentally noted to have a fever of 38.2°C. In this situation, the available evidence strongly supports performing an appropriate sepsis evaluation and, if the work-up is negative, discharging the patient without administering IM ceftriaxone with a plan for follow-up reexamination in 12 to 24 hours. When considering outpatient management of an infant with fever, it is always advisable to contact the primary care provider, both to ensure that the patient will have proper follow-up and that the patient’s physician is comfortable with the proposed management plan. If the primary care provider feels that the patient should be admitted to the hospital, then this wish should be honored. It may be possible at a later time to discuss the available literature on this subject with the other physician in the interest of improving the overall care these patients receive.

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