The evaluation of the infant with fever can create anxiety among clinicians and parents. Understanding the utility, purpose, and yield of empiric testing and treatment will help the clinician make appropriate decisions for management.
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Update on the Management of the Febrile Infant

By Marvin B. Harper, MD
BOSTON, MASSACHUSETTS

VERY YOUNG INFANTS ARE in the highest risk period for invasive bacterial infections that will be experienced during childhood. Unfortunately, small infants possess very limited means with which to communicate with physicians. Physical examination will reveal clues which can lead to correct diagnosis in some young febrile infants, however, others with normal physical examinations or favorable scores in clinical assessment scales can have bacteremia, urinary tract infection, or even bacterial meningitis.[1,2] This has led to very conservative management of infants with fever, including empiric testing, antimicrobial therapy, and hospitalization for a large proportion of these children. Much has been learned in the last decade about the utility of such management. The focus of this paper is to review some of the recent literature pertaining to the evaluation of the well appearing febrile infant. The following definition will be used: an infant is defined as a child less than three months of age, and fever is defined as a rectal temperature of 38°C or higher. Remember, however, that the very young infant, especially under 2 weeks of age, can present without fever or with hypothermia as a sign of serious infection.

Recommendations most often proposed in the literature for the management of febrile infants come predominantly from three prospective studies. The so-called Boston,[2] Philadelphia,[3] and Rochester[4] criteria each demonstrate a safe and effective way of screening young febrile infants for a serious bacterial infection (SBI), defined specifically as bacteremia, urinary tract infection, or bacterial meningitis. Each management strategy involves empiric testing of all children of specific ages, empiric antimicrobial treatment, and hospitalization of a large proportion of these infants (Table 1). Readers unfamiliar with the specifics of these clinical criteria are referred to the original manuscripts.

With the knowledge gained from these studies, guidelines for the management of the febrile young infant were published in

From the Divisions of Emergency Medicine and Infectious Diseases, Children's Hospital Boston, Boston, Massachusetts.
Address reprint requests to Marvin B. Harper, MD, Division of Emergency Medicine and Division of Infectious Diseases, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115.
E-mail: harper@childrens.harvard.edu.
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TABLE 1. Published Strategies for Management of the Febrile Infant

Criteria	Boston[2]	Philadelphia[3]	Rochester[4]	Pittsburgh[25]	Data model[7]
Age (days)	28-89	29-56	0-60	0-60	0-90 days
Temperature (C)	≥38.0	≥38.2	≥38.0	≥38.0	≥38.0
Clinical appearance	Well	Well	Well	Well	NA
Peripheral blood WBC/mm^3	<20,000	<15,000	<20,000	<15,000	<20,000
	>5,000		>5,000	>5,000	>4,100
Peripheral blood bands	NA	<0.2 ratio band:pmn	<1,500	<1,500	NA
Urine screening by UA	<10 wbc/hpf	<10 wbc/hpf	<10 wbc/hpf	<10 wbc/mm3*	<5 wbc/hpf + neg LE/nitrite
Urine Gram's stain	NA	Yes	NA	Yes	NA
CSF screening	<10 wbc/mm^3	<8 wbc/mm^3	Not req'd	<6 wbc/mm^3	NA
Stool screen†	If diarrhea	If diarrhea	If diarrhea	If diarrhea	NA
CXR	If done	All	If done	For resp findings	NA
High risk age	<28 days	<29 days	NA	NA	<13 days
High risk temperature	NA	NA	NA	NA	>39.6°C
Sensitivity (%)	NA (All treated)	98	92	100	82
Specificity (%)	95	42	50	35	76

*"Enhanced urinalysis" with hemocytometer WBC count of unspun urine.
†Stool screen is indicated when >5 wbc/hpf are found on stool smear.
Abbreviations: NA, not applicable; neg LE/nitrite, negative leukocyte esterase and negative nitrite on urine dipstick; pmn, polymorphonuclear cell; UA, urinalysis; WBC, white blood cells; wbc/hpf, white blood cells per high powered field on microscopic examination of spun urine.

1993 by Baraff et al[5] which remain unchanged today.[6] Much has been learned since that time.

It is clear from surveys of physicians, from self-reporting by pediatricians, and review of practice at academic pediatric centers that these guidelines are not followed for a substantial percentage of these children. Even one of the centers originating clinical criteria proposing intensive evaluation criteria deviates from its guidelines at times (Table 2). Practice varies by age and degree of fever, indicating that clinicians recognize young age and higher fever as risk factors.[7] Even more variance from the proposed guidelines is noted in the practice of pediatricians and family practitioners in the office setting.[8-11] It has also been made clear that even when a management protocol has been accepted and all testing is performed that there are instances where the treating clinician fails to recognize or act upon abnormalities in screening studies.[12] In this case, 7% (95% CI: 4, 10) of high risk patients were managed without antibiotic therapy out of accordance with the protocol. Conversely, 7% of low risk patients were unnecessarily hospitalized.

What each of the clinical screening criteria have in common is the use of multiple tests. When any test result is outside a specified range, the child is classified as "high risk" (or at least not low risk) for SBI. As is true for any set of tests utilized in succession, the sensitivity of the screening criteria improves with each additional test but the specificity will correspondingly decrease. This accounts for the very poor specificity of the screening criteria that are used. In practice, clinicians do not always obtain all of these tests and decisions for management are made with portions of the data. This has led to careful scrutiny of the performance for individual components of these screening criteriae in predicting clinically unsuspected SBI, which is discussed below.

TABLE 2. Proportion of Febrile Infants With Specimen of Urine, Blood, or Cerebrospinal Fluid Submitted for Culture by Age or Temperature[7]

Age (months)	Urine	Blood	CSF	Number of Infants
0-1	78%	94%	88%	1298
1-2	73%	89%	82%	2104
2-3	66%	84%	66%	1877
Total	72%	88%	78%	5279
Temp Group	**Urine**	**Blood**	**CSF**	**Number of Infants**
38-38.4°C	67%	85%	70%	2726
38.5-38.9°C	77%	92%	85%	1371
39-39.4°C	78%	94%	88%	857
≥39.5°C	77%	90%	86%	324
Total	72%	88%	78%	5279

NOTE: The data in the temp group portion of the table are unpublished but from same data set as the age in months data.
Abbreviations: Blood, blood submitted for culture; CSF, cerebrospinal fluid submitted for culture; Temp, temperature; Urine, urine submitted for culture.

What is the Risk of SBI by Age?

The detected rates of SBI have typically ranged from 6% to 9% throughout the first three months (Table 3).[7,13] It is clear, however, that the rate of detection for urinary tract infections, bacteremia, or bacterial meningitis is higher in the first month of life with a SBI rate of approximately 12% in the first month.[14,15] There is no significant difference in the rates of bacteremia or meningitis from the second to third month of life (Table 3). There is, however, a change in the pathogen profile with an increasing role of *S pneumoniae* and decreasing importance of group B streptococci in the third month of life. Whether the ability of clinicians to detect, by physical examination alone, which febrile infants have SBI changes over the first 3 months has not been studied. Clinical scoring scales, however, have not been helpful.[1]

Of the clinical guidelines commonly used, only the Rochester criteria include the neonate (infant in the first month of life) but do not examine the criteria in this subgroup alone. The Boston and Philadelphia criteria have been applied and do not reliably screen infants less than 1 month of age for the presence of clinically unsuspected SBI.[14,16] In fact, any febrile infant less than 4 weeks of age should be considered at high risk for SBI . In the first 2 weeks of life, the rate of SBI is still 5% among infants with a negative urinalysis, normal white blood cell (WBC) count, and fever of 39.5°C or less.[7] Among infants 2 to 4 weeks of age, there is a 4% rate of SBI with negative screening by clinical criteria including evaluation of urine, blood, and cerebrospinal fluid (CSF) parameters.[15] In addition, very young infants may have difficulty dealing with viral as well as bacterial infections, and may need supportive care regardless of the need for antimicrobial therapy. Particular attention should also be directed toward the possibility of Herpes simplex virus (HSV) infections in the first month of life. One should maintain a low threshold for sending viral cultures from any suspicious skin lesions, sending CSF for HSV PCR and then empirically administering acyclovir based on clinical concern and local epidemiology.

What is the Risk of SBI by Fever?

Increasing height of fever is associated with an increasing risk of SBI. Of interest, the screening criteria use different entry thresholds for defining fever. The Philadelphia criteria require a temperature of 38.2°C or higher for entry, whereas the

TABLE 3. Rate of SBI by Age[7]

Age (months)	Blood	CSF	All SBI
0-1	2.1% (1.4, 3.1)	0.9% (0.4, 1.6)	8.8% (7.2, 10.6)
1-2	1.0% (0.6, 1.5)	0.2% (0.1, 0.5)	7.3% (6.2, 8.5)
2-3	0.8% (0.4, 1.5)	0.2% (0.1, 0.7)	7.1% (6.0, 8.4)
Total	1.4% (0.9, 1.6)	0.4% (0.2, 0.7)	7.6% (6.9, 8.3)

The All SBI group data was published,[7] however the specific rates of bacteremia and bacterial meningitis were unpublished but are derived from the same data set and are calculated as rate of positive cultures per total cultures obtained per group. Numbers in parentheses are the 95% confidence intervals.

Boston and Rochester use a threshold of 38.0°C. Data from Boston report a rate of detected SBI of 4% (95% confidence intervals: 3%, 5%) among infants zero to 3 months of age with a triage rectal temperature of 38.0°C or 38.1°C compared to 8% (95%CI: 7%, 9%) for those with fever of 38.2°C or higher.[7] Therefore the risk is clearly diminished but not trivial. Formal evaluation of infants with temperatures below 38.0°C have not been done but begin to overlap significantly with temperatures that occur in well infants as a result of normal physiologic variation.

Among infants with normal urinalysis and a WBC count of less than 20,000 cells/mm^3, a fever of greater than 39.6°C will increase the risk of SBI from 2% to 7%.[7]

Do Specific Identifiable Infections Predict Risk?

The identification of a specific infection on clinical examination will guide the diagnostic evaluation. It is only when no specific infection is found on examination that empiric testing and treatment strategies have been studied. It is not entirely clear, therefore, what empiric testing is prudent or justified when a specific identifiable infection is present. When the focus is suspected to be bacterial, the risk of unsuspected bacterial invasion or dissemination or additional foci should guide additional testing. Unfortunately there are little data available to evaluate the risk of SBI among febrile infants with infections such as impetigo, cellulitis, or otitis media. Additionally, there are nonspecific symptoms suggestive of viral etiologies such as rhinorrhea or watery diarrhea that are very common but do not exclude the infant from intensive evaluation as recommended in any of the published schemes.

There are growing data, involving hundreds of children, that now demonstrate the lack of need for routine blood or CSF testing of well appearing young febrile infants with lower respiratory tract physical examination findings suggestive of bronchiolitis with or without confirmatory testing for respiratory syncitial virus.[17-19]

While the presence of bronchiolitis is not protective against meningitis or bacteremia, and undoubtedly some cases will occur, the presence of clinical bronchiolitis provides a reasonable alternative source for the fever which reduces the risk of SBI sufficiently to no longer warrant the routinely obtained specimens for blood or CSF culture. Clinicians should be rigorous in the clinical assessment of the infant and the assignment of lower respiratory tract symptoms. In this population, a chest radiograph should be obtained to exclude pneumonia and attention should be paid to any new or high fever occurring during the course of the illness. Obtaining a specimen of urine for urinalysis or culture should still be considered, however, because 2% of these children will have significant bacteriuria.

What is the Utility of Specific Screening Tests?

Recently, progress has been made in the evaluation of the performance of specific laboratory tests used in screening infants by the Boston, Philadelphia, or Rochester guidelines. Unfortunately these tests, when used in isolation, do not have sufficient sensitivity to allow assignment of a child to a low enough risk group for SBI in order to obviate full screening as per one of these guidelines. Abnormal results, however, can categorize children as being at increased risk for SBI. The utility of specific tests varies and are discussed below.

White Blood Cell Counts

The WBC count is clearly associated with increased risk for bacteremia at values below 5,000 cells/mm^3 (likelihood ratio: 3.9) and above 15,000 cells/mm^3 (LR 2.0) or 20,000 cells/mm^3 (LR 3.5), but fully one-third of bacteremic children will have values of WBC between 5,000 and 15,000cells/mm^3 (55% of bacteremic children have WBC between 5,000 and 20,000 cells/mm^3). This limits the usefulness of the WBC to exclude bacteremia.[20]

Some clinicians argue that CSF examination can be reserved for infants with abnormal WBC or positive blood culture. Because bacterial meningitis is an infrequent event, clinical experience will reinforce the impression that any laboratory screening tool is helpful. In fact, because the rate of bacterial meningitis is less than one percent, the negative predictive value of assuming nobody has meningitis is 99%. This, however, would be a mistake for those unfortunate infants with bacterial meningitis. Unfortunately, when the WBC count is scrutinized for predicting bacterial meningitis, it does not perform any better than it does to identify children with bacteremia.[21] WBC counts of less than 5,000 cells/mm^3 are associated with a significant increase in the risk for bacterial meningitis. But, using a peripheral WBC count of less than 5,000 or greater than 15,000 cells/mm^3 as abnormal will identify only 59% of cases of bacterial meningitis (cutoffs of WBC using $<$5,000 or $>$20,000 cells/mm^3 will identify 36%).[21]

Band Counts or Band to Neutrophil Ratios

The band to neutrophil ratio was added to the Philadelphia criteria (with a positive result defined as >0.2) because of its ability to detect some children with group b streptococcal infections (bacteremia and meningitis) missed by the rest of the criteriae. Caution must be used in interpreting band counts and band to neutrophil ratios, however, as there is great variation between institutions in the interpretation of band forms on the peripheral smear.

Blood Culture

The sensitivity of a single blood culture versus multiple blood cultures or the effect of blood volume on the recovery of a pathogen has not been studied in this age group. The rate of positive blood culture among infants with bacterial meningitis is 47% (95% CI: 23, 72).[7] A negative blood culture therefore does not exclude the need for lumbar puncture.

Cerebrospinal Fluid

No screen other than lumbar puncture with CSF cell counts (or possibly the fully applied Rochester criteria) can reasonably exclude the possibility of bacterial meningitis among febrile infants. The overall rate of bacterial meningitis in this population is approximately 3 to 8 per thousand and the associated morbidity and mortality are high. Because of this, the CSF WBC count is used as one of the required screening labs in the Philadelphia and Boston criteria. Even this screen, however is imperfect. At our institution, in this age group, a CSF WBC cutoff of less than 8 WBC/mm^3 will miss 23% of bacterial meningitis cases (sensitivity 77%, specificity 79%) and a cutoff of 10 or more CSF WBCs/mm^3 will miss 26% (sensitivity 73%, specificity 84%). Not surprisingly, with increasing CSF WBCs the likelihood ratio for bacterial meningitis increases. The point to be noted here is that full sepsis evaluations are often initiated early in this age group and detect cases of bacterial meningitis early, which is good for our patients, but this also means a normal CSF WBC does not exclude the possibility of bacterial meningitis.[21]

Chest Radiographs

The role of the chest radiograph has been carefully evaluated and is a required component of the Philadelphia criteria. Studies demonstrate the value of ordering a chest radiograph if the infant has any one of the following: (1) a respiratory rate of 50 breaths per minute or greater; (2) exam findings of any one of coryza, cough, nasal flaring, grunting, stridor, rales, rhonchi, wheezing, or retractions; or (3) a peripheral blood WBC count of >20,000 cells/mm^3.[22] If any of these criteria are met, there is a 33% chance of a positive finding on chest radiograph, whereas if none of the criteria is met there is a 1% or less chance of a positive finding.[22]

Testing for Urinary Tract Infections

Urinary tract infections are by far the most prevalent infection in this age group. Because of this, screening of the urine by urinalysis is the single best screening test to apply. A positive urinalysis—when defined as either a positive urine dipstick nitrite or leukocyte esterase, or on microscopic examination of spun urine more than 5 WBCs per high powered field—will identify a subgroup with a 32% (95%CI: 29, 36) risk of having SBI.[7] When defined as above, the standard urinalysis has a sensitivity of 82% and specificity of 93% among infants,[23] which is virtually identical to the results obtained by the "enhanced urinalysis" (defined as a quantitative hemocytometer WBC count of unspun urine [sensitivity 82%, specificity 94%] when abnormal is defined as >10 WBCs per microliter).[24] Another group suggests a better sensitivity (96%) for the "enhanced urinalysis" but with broad confidence intervals (95%CI: 79, 100).[25] Either of these definitions of a positive urinalysis is preferable to the > 10 cells/hpf originally used by the Boston, Philadelphia, and Rochester criteria because of improved sensitivity with minimal loss in specificity. The routine addition of a Gram's stain of the urine is also helpful in identifying urinary tract infection among some infants with negative urinalysis and can guide initial therapy. (For further discussion regarding testing and diagnosis for urinary tract infections in the infant, please see the article by Bachur in this issue). Urinary tract infections will be complicated by bacteremia in 3% (95%CI: 2, 6) and meningitis in 0.3% (95%CI: 0, 2) of infants in this age group.[7]

Stool Tests

The specific role of stool testing for blood, WBCs, or lactoferrin has not been specifically evaluated in the very young infant. However, these tests should be routinely considered in the infant with fever and diarrhea. Stool specimens should be submitted for Salmonella culture when appropriate given the potential for meningitis and other complications caused by this organism.

Microbiology Studies: Time for Pathogen Detection in Cultures

In a study of 2,190 infants (0-3 months of age) with blood, urine, and CSF submitted for culture, 9% had a pathogen detected. The great majority of cultures with growth of a pathogen were noted to be positive in less than 24 hours. Overall 1.1% of all infants evaluated had a pathogen detected in culture after 24 hours. Blood cultures had growth after 24 hours in 0.2%, urine in 0.9% of infants tested, and none had growth of a pathogen from CSF after 24 hours (but there were only 8 positive CSF specimens).[26] This information can be used in combination with clinical and laboratory factors locally to help determine the optimal duration of empiric antimicrobial coverage and even for the duration of inpatient care. Some have therefore adopted a strategy utilizing a single dose of ceftriaxone (using the Boston criteria) for infants older than 4 weeks that screen into the "not at high risk" for SBI group.[27] In addition, high risk and 2- to 4-week-old infants can be discharged after only 24 hours of inpatient admission (with a second dose of ceftriaxone) with negative cultures if there is no CSF pleocytosis and the infant is clinically improved.[28] This requires knowledge that appropriate specimens have been handled in a timely manner by the laboratory.[29] In the absence of additional data, we continue to keep infants aged 0 to 14 days hospitalized for two days awaiting cultures and undergoing observation of clinical status.

Management

Antimicrobial Recommendations

Antibiotic recommendations by age are listed in Table 4. The use of ampicillin in addition to ceftriaxone or cefotaxime is required when there is concern for a possible enteroccal or *Listeria monocytogenes* infection. Enterococci need not be empirically covered unless there is evidence suggesting a urinary tract infection (and Gram's stain does not reveal gram negative rods) or meningitis. *L monocytogenes* typically presents as sepsis (with or without meningitis) in the first two weeks of life or as meningitis (with or without sepsis) at two weeks to two months. Therefore, it is good practice to include ampicillin for all infants receiving empiric antimicrobial coverage under 2 weeks of age. Ampicillin should be used for all infants with evidence of urinary tract infection or meningitis on screening studies unless there is compelling evidence for a pathogen other than enterococci or *L monocytogenes*. A review of available published literature supports this approach and recommends ampicillin for all febrile infants in the first month of life because of the increased prevalence of these infections in this group.[30]

A third generation cephalosporin or meropenem in addition to an aminoglycoside must be considered for all infants with meningitis when a gram negative rod is suspected. Vancomycin should be considered if methicillin resistant *Staphylococcus aureus* is a concern or *Streptococcus pneumoniae* meningitis is likely.

Close Clinical Follow-up

The role and utility of clinical follow-up for the infants managed as outpatients has not been specifically studied or precisely defined. In addition, the clinical follow-up utilized in some studies is difficult to replicate in practice. While almost universally required by guidelines, clinician initiated or scheduled clinical follow-up has not been compared to follow-up initiated by the parent. The optimal location, timing, and duration of follow-up have not been studied. Nonetheless, in the absence of data demonstrating the safety of alternative approaches, it is prudent to maintain once or twice daily contact with the parents of very young febrile infants managed as outpatients until the illness resolves.

The impact of testing, empiric therapy, and hospitalization of these infants must also be considered. The heightened parental anxiety and the financial stress caused by these evaluations and hospitalizations are real.[31] In one study, done more than 20 years ago, 8% (95%CI: 3, 17) of infants with fever as the sole indication for admission suffered some iatrogenic complication or nosocomial infection.[32] Surprisingly, the mean duration of hospitalization was 5 days, which would not be likely today. Further work is necessary to more precisely define the risk of direct complications, nosocomial infections, financial and emotional stress, and how to minimize their impact. In addition, these issues must be considered in formal analyses to help determine the best overall management strategies for the febrile infant.

Recommendations for management for any given patient must take into consideration many intangible items. These include the ability the clinician to adhere to a protocol (which will vary by clinician(s), the complexity of the protocol and available resources) but also to be flexible. When circumstances dictate, it may be necessary to go beyond or do less than the guidelines require. Another intangible includes the need to know the patient and/or patient population being treated,

TABLE 4. Age-specific Management Recommendations

0-2 weeks	Full septic work-up and hospitalization until afebrile
	ampicillin and gentamicin
	consider vancomycin, acyclovir, cefotaxime (if meningitis)
2-4 weeks	Full septic work-up and hospital admission
	ceftriaxone (if urine and CSF screens negative)
	or ampicillin/gentamicin if UTI suspected
	or ampicillin/ceftriaxone if CSF pleocytosis (add gentamicin if gram negative rod suspected)
	consider acyclovir
	Only 24 hours hospitalization unless CSF pleocytosis, persistent fever, or slower culture methods employed
4-8 weeks	Full septic work-up and screening criteria negative
	outpatient: consider single ceftriaxone dose
	At least one screening test positive
	no CSF pleocytosis: 24 hours hospitalization and empiric ceftriaxone
	urine screen positive: admit × 24 hours pending other cultures on ampicillin/gentamicin
	CSF pleocytosis: admit × 48 hours on ampicillin/ceftriaxone consider vancomycin and/or aminoglicoside based on Gram's stain
8-12 weeks	Full septic work-up and screening criteria negative by all criteria
	outpatient: consider single ceftriaxone dose
	Full septic work-up with screening positive
	no CSF pleocytosis: 24 hours hospitalization and dose ceftriaxone
	urine screen positive: admit × 24 hours pending other cultures on ampicillin/gentamicin
	CSF pleocytosis: admit × 48 hours on ceftriaxone consider ampicillin, vancomycin and/or aminoglycoside based on Gram's stain

Abbreviations: CSF, cerebrospinal fluid; UTI, urinary tract infection.

their resources, and their ability to care for a small infant at home. All recommendations assume close clinical follow-up, regardless of other management, until the illness resolves. Having a stated policy or protocol for management and follow-up is likely to improve the care of these infants and has been demonstrated to decrease median time to administration of antibiotics (if indicated).[33]

While the focus of this manuscript has been on the identification of clinically unsuspected bacterial infections, the importance of inpatient management of some infants with viral infections must also be considered. Poor feeding, vomiting, and diarrhea can all result in the rapid development of dehydration in this group. Viral sepsis, viral pneumonia, and viral meningitis can also result in significant illness requiring supportive care.

Summary

The well-appearing febrile infant remains a challenge for clinicians. The goal is to safely identify and promptly treat the small proportion with clinically unsuspected urinary tract infection, bacteremia, or bacterial meningitis. To accomplish this goal, the practitioner will need to carefully examine and perform invasive testing on most of these young children. Improved understanding of the individual components used in screening will result in appropriate interpretation of these studies and should minimize the number infants who suffer sequelae as a result of a delay in the treatment of SBI. In addition, careful application of this knowledge can maximize the proportion of febrile infants without SBI that are able to remain as outpatients and min-

imize the duration of hospitalization for those admitted.

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