Clinical Policy for Children Younger Than Three Years Presenting to the Emergency Department With Fever

See editorial, p. 546.

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INTRODUCTION

Fever is among the most common presenting complaints of children and infants presenting to the emergency department (ED).[1] Fever represents a normal physiologic response that may result from the introduction of an infectious pathogen into the body and is hypothesized to play a role in fighting and overcoming infections.[2,3] In some cases, fever is a response to a serious or potentially life-threatening infection. The challenge for emergency physicians is differentiating the vast majority of pediatric patients presenting with a fever who will have an uneventful course from the indeterminate few who have serious infections with the risk of long-term morbidity and mortality.

The evaluation and management of the febrile child is evolving at a rapid pace as a result of: (1) the amount of research conducted, (2) the introduction of *Haemophilus influenzae* type b (HIB) vaccine, (3) *Streptococcus pneumoniae* vaccine, and (4) ever-evolving diagnostic technology and therapies. The full extent of the impact of these ongoing changes, particularly of the introduction of the HIB and pneumococcal vaccines, is not yet known. However, there is a general consensus that the incidence of serious bacterial infections will likely decrease significantly over the next several years.

This policy is a revision of the 1993 American College of Emergency Physicians (ACEP) pediatric fever policy.[4] In an attempt to maximize the usefulness of this policy to the practicing emergency physician, this revision is organized into discrete "critical questions" that were believed by committee members to represent some of the most pressing and controversial issues faced when evaluating a child or infant with a fever. The scope of the policy has been broadened to include children aged 1 day to 3 years. Fever is defined as a rectal temperature greater than 38°C (>100.4°F).[4] The reliability of other methods of temperature measurements is lower and must be considered in the context of the clinical setting.

This policy is not intended to be all encompassing and is intended as a guideline. It represents evidence for answering important questions about these critical diagnostic and management issues. Recommendations in this policy are not intended to present

the only diagnostic and management options that the emergency physician can consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide strong support for answers to the critical questions addressed in this policy.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the peer-reviewed literature. A MEDLINE search of English-language articles published between 1985 and 2003 was performed using key words focused on in each critical question. Abstracts and articles were reviewed by subcommittee members, and pertinent articles were selected. These articles were evaluated, and those addressing the questions considered in this document were chosen for grading. Subcommittee members also supplied references from bibliographies of initially selected articles or from their own files.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[5] This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians; members of ACEP's Pediatric Emergency Medicine Committee and the Section of Pediatric Emergency Medicine; physicians from other specialties, such as pediatricians; and specialty societies, including individual members of the American Academy of Pediatrics and the American Academy of Family Physicians. Their responses were used to further refine and enhance this policy.

All publications were graded by at least 2 of the subcommittee members into 1 of 3 categories of strength of evidence. Some articles were downgraded on the basis of a standardized formula that considers the size of study population, methodology, validity of conclusions, and potential sources of bias (Appendix A).

During the review process, all articles were given a baseline "strength of evidence" by the subcommittee members according to the following criteria:

Strength of evidence Class I—Interventional studies including clinical trials, observational studies including prospective cohort studies, aggregate studies including meta-analyses of randomized clinical trials only.

Strength of evidence Class II—Observational studies including retrospective cohort studies, case-controlled studies, aggregate studies including other meta-analyses.

Strength of evidence Class III—Descriptive cross-sectional studies; observational reports including case series and case reports; consensus studies including published panel consensus by acknowledged groups of experts.

Strength of evidence Class I and II articles were then rated on elements the committee believed were most important in creating a quality work. Class I and II articles with significant flaws or design bias were downgraded on the basis of a set formula (Appendix B). Strength of Evidence Class III articles were downgraded if they demonstrated significant flaws or bias. Articles downgraded below Class III strength of evidence were given an "X" rating and were not used in formulating recommendations in this policy.

Recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on "strength of evidence Class I" or overwhelming evidence from "strength of evidence Class II" studies that directly address all the issues.)

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on "strength of evidence Class II" studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of "strength of evidence Class III" studies).

Level C recommendations. Other strategies for patient management based on preliminary, inconclusive, or conflicting evidence, or, in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This policy applies to previously healthy term infants and children between the ages of 1 day and 36 months.

Exclusion Criteria. This policy excludes high-risk children such as those with congenital abnormalities, serious illnesses preceding the onset of a fever, those born prematurely, and those in an immunocompromised state.

CRITICAL QUESTIONS

I. Are there useful age cutoffs for different diagnostic and treatment strategies in febrile children?

Historically, physicians caring for children with a fever have long recognized the importance of a child's age when making decisions regarding diagnostic testing and treatment options. Infants in the first few months of life have decreased opsonin activity, macrophage function, and neutrophil activity.[6] Furthermore, common pathogens vary by age group, and children's physical and behavioral response to illness varies with their age, as evidenced by the failure of observation scales in infants aged 1 to 2 months.[7] More recently, prospective clinical research has substantiated the age grouping and, at the same time, has led to changes and, in some cases, uncertainty as to what are the most appropriate age cutoffs.

Three large, prospective studies have focused on management strategies for children younger than 90 days.[8-10] The success of these trials led to the dissemination of "Rochester"[10] and "Philadelphia"[8] criteria for identifying infants with fever at low risk for developing serious bacterial infections and, in the process, gave strength to the notion that infants aged younger than 90

days with a fever form a succinct age group for diagnostic and treatment purposes. Subsequently, confirmatory studies have been undertaken to further validate these treatment strategies.[11,12] Additionally, studies have assessed the applicability of the Rochester and Philadelphia criteria specifically to infants aged 1 to 28 days.[13-16] All of these studies found an increase in the number of serious bacterial infections missed in infants aged 1 to 28 days indicating that a sepsis evaluation and admission is more appropriate in this group, and adding evidence for an age cutoff between the first and second months of life.

Children aged 3 to 36 months have tended to be studied as a group, although this is thought to be arbitrary.[17] Three large randomized trials of outpatient antibiotic therapy have been conducted in this age group,[18-20] as well as other studies. Regardless of an age cutoff chosen, the astute physician recognizes that no age cutoff is absolute, but rather is a point on a continuum as the child grows and his or her physiology and behavior mature.

Patient Management Recommendations: Are there useful age cutoffs for different diagnostic and treatment strategies in febrile children?

Level A recommendations. Infants between 1 and 28 days old with a fever should be presumed to have a serious bacterial infection.

Level B recommendations. None specified.

Level C recommendations. None specified.

II. Does a response to antipyretic medication indicate a lower likelihood of serious bacterial infection in the pediatric patient with a fever?

It has been suggested that response to antipyretic medication may enhance the evaluation of a febrile infant.[21] Some physicians may rely on a decrease in fever with antipyretic therapy to indicate a lower likelihood of serious bacterial infection. A number of trials have been conducted over the past 20 years to address this and have consistently found no correlation between fever reduction with antipyretic medication and the likelihood of serious bacterial infection.[22-27] These studies are summarized in Table 1.

Patient Management Recommendations: Does a response to antipyretic medication indicate a lower likelihood of serious bacterial infection in the pediatric patient with a fever?

Level A recommendations. A response to antipyretic medication does not change the likelihood of a child having serious bacterial infection and should not be used for clinical decisionmaking.

Level B recommendations. None specified.

Level C recommendations. None specified.

III. What are the indications for a chest radiograph during the workup of pediatric fever?

The decision to include a chest radiograph in the evaluation of an infant or child with fever without a source can be a difficult one for the emergency physician. Seven percent of all febrile children aged younger than 2 years with temperature greater than 38°C (>100.4°F) will have pneumonia.[28] Furthermore, it has recently been reported that occult pneumonia, defined as a definite radiographic infiltrate on the chest radiograph of a child lacking clinical evidence of pneumonia, may be present in up to 26% of children with fever without a source and a WBC count greater than 20,000/mm³.[29] However, it has also been determined that the majority of lower res-

piratory tract infections in children have a viral etiology.[30-32] In addition, multiple studies have shown that, even among pediatric radiologists, there is poor interobserver reliability for determining when bacterial pneumonia truly exists on a chest radiograph.[33-35]

Therefore, it is important to carefully consider the clinical features of the evaluation of the febrile child and infant when determining when a chest radiograph is indicated.

As with other parameters that have been studied regarding febrile children without a source of infection, the literature evaluating predictors for pneumonia divides patients into 2 age groups: infants younger than 3 months, and infants and children aged 3 months to 3 years.

Multiple studies have examined the use of the chest radiograph in the evaluation of the febrile infant aged younger than 3 months without respiratory symptoms.[36-38] In a meta-analysis of these studies, a combined group of 361 febrile (>38.0°C [>100.4°F]) infants, all without clinical evidence of pulmonary disease on history or physical examination, had normal chest radiographs as determined by 2 or more radiologists.[39] The clinical findings considered as potential for pul-

Table 1.

Studies in children of the oral temperature response of bacteremic versus nonbacteremic infections to antipyretic agents. Reprinted with permission from: Plaisance KI, Mackowiak PA. Antipyretic therapy. Physiologic rationale, diagnostic implications, and clinical consequences. Arch Intern Med. 2000;160:449-456. Copyright © 2000, American Medical Association. All rights reserved.[121]

| | | | | | Temperature Response | | | | | |
| | | | | | Bacteremic | | | Nonbacteremic | | |
Authors	Year	Study Design	Antipyretic Agent	Age of Subjects, y	No.*	T,† °C (°F)	↓T‡	No.*	T,† °C (°F)	↓T‡	P§
Torrey et al[22]	1985	Prospective/observational	Acetaminophen/aspirin	≤2	16	40.1 (104.2)	1.3	239	39.9 (103.8)	1.05	.14
Weisse et al[23]	1987	Prospective/observational	Acetaminophen	≤17	11	NG	1.4	16	NG	1.2	.37
Baker et al[24]	1987	Prospective/observational	Acetaminophen	≤6	10	40.1 (104.2)	1.5	225	39.6 (103.3)	1.0	NG
Mazur et al[25]	1989	Retrospective/case control	Acetaminophen	≤6	34	39.8 (103.6)	1.0	68	39.8 (103.6)	1.5	<.001
Baker et al[26]	1989	Prospective/observational	Acetaminophen	≤2	19	40.1 (104.2)	1.7	135	40.0 (104)	1.6	>.05
Yamamoto et al[27]	1987	Prospective/observational	Acetaminophen	≤2	17	40.5 (104.9)	1.6	216	40.4 (104.7)	1.6	.85

NG, Not given.
*Number of subjects studied.
†Mean initial temperature (T) (ie, T just before administration of antipyretic agent).
‡Mean decrease in T 60 to 120 minutes after treatment with antipyretic agent.
§Comparison of ↓T in "bacteremic" vs "nonbacteremic" subjects by *t* test.

monary disease included tachypnea more than 50 breaths/min, rales, rhonchi, retractions, wheezing, coryza, grunting, stridor, nasal flaring, or cough. Conversely, a total of 256 infants in this analysis did have at least 1 of these clinical findings of pulmonary disease. Of these infants, 85 (33.2%) had positive chest radiograph results for pneumonia. Therefore, this evidence supports only ordering chest radiographs in febrile infants younger than 3 months with a temperature greater than 38°C (>100.4°F) who manifest at least 1 clinical sign of pulmonary disease.

Taylor et al[28] studied 572 children aged younger than 2 years with a temperature of 38°C or greater (≥100.4°F). Pneumonia, determined on chest radiograph by pediatric radiologists, was diagnosed in 42 (7%) patients. In this study, tachypnea was defined as a respiratory rate greater than 59 breaths/min in infants younger than 6 months, greater than 52 breaths/min in those aged 6 to 11 months, and greater than 42 breaths/min in those aged 1 to 2 years. Respiratory rates were counted for a full 60 seconds, which has been shown to be the most accurate method of determining respiratory rate.[40] In this group, tachypnea as a sign of pneumonia had a sensitivity of 73.8% (95% confidence interval [CI] 60.5% to 87.1%), a specificity of 76.8% (95% CI 73.2% to 80.4%), a positive predictive value of 20.1% (95% CI 13.8% to 26.4%), and a negative predictive value of 97% (95% CI 95.9% to 98.9%). Other studies have shown similar results. However, the definition of tachypnea varies from study to study.

In addition to tachypnea, other clinical examination findings have been shown in well-conducted studies to be predictive of pneumonia. Singal et al[41] identified crackles as the only univariate predicator of infiltrates in a population of 78 children aged younger than 18 years, 24 (30.7%) with pneumonia. In addition, Leventhal[42] suggested that a cluster of pulmonary findings including respiratory distress, tachypnea, rales, or decreased breath sound was a good index for pneumonia. Furthermore, Zukin et al[43] reported that, in addition to fever and tachypnea, all chest examination findings other than wheezing, cough, prolonged expirations, or rhonchi significantly increased the likelihood of

pneumonia on chest radiograph. Therefore, on the basis of multiple clinical trials it can be reasonably concluded that, in the evaluation of the febrile child aged younger than 3 years, the presence of any clinical findings of lower respiratory tract infection on chest examination significantly increases the likelihood of pneumonia. However, no single finding by itself can be used to accurately diagnose pneumonia. More importantly, the lack of all clinical signs or symptoms of lower respiratory tract infection obviates the need for a chest radiograph.

Despite the aforementioned work, Bachur et al[29] recently reported that occult pneumonia was discovered in 26% of children aged younger than 5 years with a triage temperature of 39°C or greater (≥102.2°F) and leukocytosis greater than 20,000/mm^3. This study included 225 febrile patients who received chest radiographs because of respiratory findings suggestive of pneumonia (79 patients), or because of leukocytosis (WBC count >20,000/mm^3) and no source of infection (146 patients). Pneumonia was found in 40% (95% CI 20% to 52%) of those with findings suggestive of pneumonia and 26% (95% CI 19% to 34%) of those without clinical evidence of pneumonia. They concluded that a chest radiograph should be considered as a routine diagnostic test in highly febrile children (temperature >39°C [>102.2°F]) with leukocytosis (WBC count >20,000/mm^3). It should be noted that none of the infants aged younger than 3 months with these clinical parameters included in this analysis had chest radiograph findings consistent with pneumonia.

The results of this well-designed study have been questioned for several reasons. First, the patients included were risk-stratified in the ED where the study was conducted on the basis of clinical findings. Only 43% of all febrile infants (>38°C [>100.4°F]) had a WBC count performed, as did only 72% of those with a temperature greater than 39°C (>102.2°F). In addition, residents rather than attending physicians performed the majority (56%) of the clinical assessments. More importantly, no interobserver reliability data between radiologists determining the diagnosis of pneumonia were reported. Furthermore, the question has been

raised as to the true utility of determining occult pneumonia in patients without clinical findings. However, 2 other researchers have independently reported preliminary data collaborating similar rates of occult pneumonia.[44,45] Therefore, in highly febrile (>39°C [>102.2°F]) children aged older than 3 months without clinical evidence of lower respiratory tract infection and a WBC count greater than 20,000/mm^{3}, a chest radiograph should be considered to help determine the radiographic diagnosis of pneumonia.

Patient Management Recommendations: What are the indications for a chest radiograph during the workup of pediatric fever?

Level A recommendations. None specified.

Level B recommendations. A chest radiograph should be obtained in febrile children aged younger than 3 months with evidence of acute respiratory illness.

Level C recommendations. There is insufficient evidence to determine when a chest radiograph is required in a febrile child aged older than 3 months. Consider a chest radiograph in children older than 3 months with a temperature greater than 39°C (>102.2°F) and a WBC count greater than 20,000/mm^{3}.

A chest radiograph is usually not indicated in febrile children aged older than 3 months with temperature less than 39°C (<102.2°F) without clinical evidence of acute pulmonary disease.

URINARY TRACT INFECTIONS IN YOUNG CHILDREN WITH FEVER

Urinary tract infection is an important cause of fever in young children. Fever, bacteriuria, and pyuria in children without other definitive sources of infection should be presumed to be symptoms of urinary tract infections. Using renal nuclear scans, it is estimated that 75% of children aged younger than 5 years with a febrile urinary tract infection have upper tract disease or pyelonephritis.[46-51] On the basis of limited data, it is estimated that renal scarring can occur in 27% to 64% of children after pyelonephritis.[50,52,53] Children most at risk for renal scarring as a result of pyelonephritis in-

clude young children, especially those aged younger than 1 year,[47,52,54,55] those with significant vesicoureteral reflux or obstruction,[56] or those with a delay in therapy for the urinary tract infection.[57] Recurrent urinary tract infections in young children also place a child at higher risk for renal scarring.[57-59] Some studies show that early renal scarring may lead to renal failure and a risk of hypertension later in life.[46] These studies have shown that there may be a 10% to 20% risk of hypertension and 10% risk of end-stage renal disease due to pyelonephritis-induced renal scarring.[60]

Although diagnosing urinary tract infections in infants and young children can be challenging, accurate diagnosis is important to avoid unnecessary treatment with antibiotics, as well as additional medical visits and imaging studies.

IV. Which children are at risk for urinary tract infection?

The prevalence of a urinary tract infection in young children aged 2 months to 2 years who have no identifiable source for fever on history or physical examination is approximately 3% to 7%.[57,61-64] The prevalence rate for girls aged younger than 1 year (6.5%) is twice that in boys (3.3%). For girls aged between 1 and 2 years, the rate increases to 8.1%; and for boys, it decreases to 1.9%.

Uncircumcised boys are also at an increased risk for urinary tract infections.[65-71] This increased risk appears to decrease somewhat with age. One study of febrile, mostly uncircumcised male infants aged younger than 8 weeks found a urinary tract infection prevalence rate of 12.4%.[72] Another study found a prevalence rate of 8% in uncircumcised and 1.2% in circumcised male infants aged younger than 1 year.[73]

Young children with unequivocal sources of fever such as varicella, pneumonia, meningitis, or herpes gingivostomatitis have a low overall prevalence of urinary tract infection (1.6%).[46] Young children with common but nondefinitive sources of fever such as acute otitis media, gastroenteritis, and upper respiratory tract infections have a prevalence of urinary tract infections of up to 4%.[46,61,62,73,74] Infants with higher fevers (≥39°C [≥102.2°F]) may also have a higher prevalence of urinary tract infection.[73] In an office setting, 10% of

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infants who underwent urine testing with a fever without a source were found to have a urinary tract infection.[75] All of these estimates of urinary tract infections must be understood in light of a background prevalence of asymptomatic bacteriuria estimated to be 1% to 1.5% of all children.[71]

Classic signs of urinary tract infection may be present but are difficult to recognize in young children. Symptoms of urinary tract infection in young children are generally nonspecific and include vomiting, diarrhea, irritability, or poor feeding. None of these have high sensitivity or specificity for urinary tract infections.[46] Fever, however, is the most common symptom in young infants.[76] A history of foul-smelling urine or crying during urination may increase the likelihood of a urinary tract infection.[73] A change in the urinary voiding pattern of a young child may be an indication of a urinary tract infection.

A clinical decision rule based on the results of a larger study was developed to identify febrile children at very low risk for urinary tract infection in whom further testing is not warranted. For females aged 2 to 24 months, the decision rule is based on 5 variables: (1) temperature of 39°C (102.2°F) or more, (2) fever for 2 days or more, (3) white race, (4) age younger than 1 year, and (5) absence of another potential source of fever. The presence of 2 or more of these risk factors had a sensitivity of 95% and specificity of 31% for detecting urinary tract infection.[77] Therefore, females with 1 or none of these risk factors are at lower risk for urinary tract infection. Because of fewer numbers of urinary tract infections in male infants, clinical risk factors are harder to identify. In one study, all boys with urinary tract infections had at least 1 of the following risk factors: (1) age younger than 6 months, (2) uncircumcised, or (3) absence of another potential source of fever. Urinary tract infection should also be considered in any child with prolonged, unexplained fever or known urinary tract anatomic abnormality.

Patient Management Recommendations: Which children are at risk for urinary tract infection?

Level A recommendations. Children aged younger than 1 year with fever without a source should be considered at risk for urinary tract infection.

Level B recommendations. Females aged between 1 and 2 years presenting with fever without source should be considered at risk for having a urinary tract infection.

Level C recommendations. None specified.

V. What are the best methods for obtaining urine for urinalysis and culture?

Bag collection or clean catch. Distinguishing a true urinary tract infection from contamination of a urine sample by the collection method can be a challenge. Because of the difficulty in cleaning the perineal area, the bag-collection method poses an increased risk of contamination with periurethral flora, with false-positive results ranging from 12% to 83%.[46,78-85] Assuming a 5% prevalence rate of urinary tract infections in young children and a high false-positive rate (specificity 70%), this results in a positive urine culture from a bag specimen to be a false positive 85% of the time.[86]

A negative urine culture from a bag specimen can be helpful to rule out a urinary tract infection. Experts agree that a positive or suspicious culture, especially one with multiflora organisms, should be confirmed by urethral catheterization or suprapubic bladder aspiration.[86]

A urine sample with more than 10 WBCs and a significant number of epithelial cells must be considered contaminated, and either an improved clean-catch method or catheterization must be tried. Contamination rates for clean-catch urine samples range from 0% to 29%.[87,88]

Urethral catheterization. Suprapubic bladder aspiration or bladder catheterization are less prone to contamination and are the methods of choice for obtaining urine samples in ill or septic-appearing children.[86] Urethral catheterization requires more skill and is more time consuming than the clean-catch method, but results in specimens with higher sensitivity (95%) and specificity (99%).[89-91] The risk of introducing infection by the urethral catheterization method has not been well defined, but the consensus among experts is that the risk is low. Although believed to be very small, the risk of developing urethral strictures after catheterization has also not been well defined.

Percutaneous bladder aspiration. Percutaneous aspiration of urine through the bladder is advocated by some experts as the method to obtain the truest urine. Urine, obtained by percutaneous aspiration method and thereby free from periurethral flora, is often considered the criterion standard in research comparing the sensitivity and specificity of other methods of urine collection like bag specimens. Technical expertise is required and success rates vary from 23% to 90%.[89,92,93] In a young male infant with severe phimosis, there may be no alternative method. Because of the invasive nature of the procedure, most EDs do not use this method for obtaining urine samples.

Patient Management Recommendations: What are the best methods for obtaining urine for urinalysis and culture?

Level A recommendations. None specified.

Level B recommendations. Urethral catheterization or suprapubic aspiration are the best methods for diagnosing urinary tract infection.

Level C recommendations. None specified.

VI. What is the appropriate role of urinalysis, microscopy, and urine cultures?

Controversy exists regarding the appropriate testing required to rule in or rule out a urinary tract infection in children. In general, however, for children aged younger than 2 years, a urinalysis alone is not adequate for ruling out urinary tract infections. As many as 10% to 50% of patients with urinary tract infections, documented by positive urine culture, can have a false-negative urinalysis.[94-96] Because of the significant sequelae thought to be associated with undiagnosed and untreated urinary tract infections in children, urine cultures are recommended in children aged younger than 2 years.

Urinalysis. Rapid diagnostic tests of the urine are commonly used to help guide decisions regarding the need for urine cultures or empiric treatment pending culture results. Bacteriuria can be detected indirectly using the nitrite test. Nitrite is formed by the metabolism of urinary nitrates by certain pathogens, especially gram-negative enteric bacteria. This nitrite conversion requires extensive exposure of bacteria to the urine and

may not occur in young infants who retain urine in the bladder for shorter periods of time because of frequent voiding. The nitrite test, in general, has high specificity or true-positive results, and lower sensitivity or true-negative results. WBCs in the urine can be indirectly detected by the leukocyte esterase test. The leukocyte esterase test, in general, has higher sensitivity or true-negative results, but lower specificity or true-positive results.

A meta-analysis reviewed published studies reporting the performance of urine dipsticks. Using the urine dipstick, the presence of either nitrite or leukocyte esterase has a sensitivity or true-positive rate of 88% and false positive rate of 7% for urinary tract infection. If the results of both tests are positive, the specificity is 96% (ie, the false positive rate is less than 4%).[97] Urine clarity has often been cited as a method to identify infected urine specimens. The finding of clear urine on visual inspection had a negative predictive value of 97%.[98]

Microscopy. Pyuria is not present on the initial urinalysis in 20% of febrile infants with pyelonephritis documented by urine cultures.[96,99] Microscopy for leukocytes is variably sensitive (32% to 100%) and specific (45% to 97%). A recent study of more than 8,000 paired urinalysis and urine cultures found combined urinalysis and microscopy to have a sensitivity of 82% and a specificity of 92%.[100] Sensitivity and specificity will also vary depending on the number of leukocytes that are considered abnormal. If a high number is used, microscopy will be insensitive but specific. If a low number is used, more urinary tract infections will be identified, with more false positives. Small studies show that an enhanced urinalysis that combines cell count using a cell-counting chamber with microscopy of an uncentrifuged, Gram-stained urine specimen may be more sensitive and specific.[99] Centrifugation of urine before Gram staining can decrease specificity because cell fragments and debris concentrated in the pellet can appear to be bacteria.

Gram stain. A Gram stain of a noncentrifuged urine sample also increases the sensitivity and specificity of the urinalysis. The presence of any bacteria on Gram

stain on an uncentrifuged urine specimen had the best combination of sensitivity (93%) and false-positive rate (4%).[97]

Urine culture. Because of the significant sequelae associated with untreated pyelonephritis, most experts recommend a urine culture also be requested when evaluating a young child for a urinary tract infection. Debate exists in the literature regarding the definition of a positive urine culture. In general, isolation of a single organism from a bag urine or clean-catch urine with a colony count of more than 10×5 colony-forming-units per milliliter (cfu/mL) is thought to represent significant bacteriuria. Isolation of multiple organisms is considered a negative urine culture by most experts. Catheterized urines, thought to decrease the amount of periurethral flora that could contaminate the specimen, require lower colony-forming-units, ranging from 10×3 to 10×5 cfu/mL.[61,96] Specimens obtained by percutaneous bladder aspiration are considered positive, in general, if there are more than 10×2 cfu/mL or, in some studies, any number of colony-forming-units.

Interpretation of urine culture results must take into account the clinical presentation, any history of urinary tract infection or urinary tract abnormalities, previous antibiotic use, and the presence of pyuria and bacteriuria.

Patient Management Recommendations: What is the appropriate role of urinalysis, microscopy, and urine cultures?

Level A recommendations. None specified.

Level B recommendations. Obtain a urine culture in conjunction with other urine studies when urinary tract infection is suspected in a child aged younger than 2 years because a negative urine dipstick or urinalysis result in a febrile child does not always exclude urinary tract infection.

Level C recommendations. None specified.

VII. What is the prevalence of occult bacteremia in children aged 3 to 36 months, and how frequently does it result in significant sequelae?

Children aged 3 to 36 months account for approximately half of all pediatric ED visits, and 15% to 25% of these visits are for the evaluation of a febrile illness.[101]

After clinical evaluation, 20% of febrile children may be determined to have a fever without source of infection.[102] Well-appearing, previously healthy children aged 3 to 36 months who have fever without source comprise approximately 6% of all pediatric ED visits.[102] Although most of these febrile children will have a self-limited viral illness,[18,103] some may have occult bacteremia and be at greater risk for developing infectious complications, such as pneumonia, septic arthritis, osteomyelitis, meningitis, sepsis, or death.[104] Occult bacteremia refers to the presence of bacteria in the blood of a well-appearing child without an identifiable focus of infection. The optimal strategy in managing a well-appearing child aged 3 to 36 months, who has fever without source, depends on the prevalence of occult bacteremia and its associated incidence of significant sequelae.

Before the release of the HIB vaccine in 1987, the prevalence of occult bacteremia was likely between 2.8% and 11.6%.[18-20,105] Since the introduction of the vaccine, the incidence of invasive *Haemophilus influenzae* (all types) infections among children aged younger than 5 years has decreased 96%, and invasive disease caused by HIB has decreased 99%, from 34 cases per 100,000 in 1989 to 0.4 cases in 1995. The large variation of inclusion criteria among studies of children with occult bacteremia makes the comparing of studies of febrile children difficult. Two studies were identified that both determined the prevalence of occult bacteremia among children within the first 3 years of life and did not enroll patients before the release of the HIB vaccine[102,106] (Table 2).

In the first study, Lee and Harper[102] prospectively investigated 9,465 febrile children aged 3 to 36 months who were discharged home from the ED, and found the rate of occult bacteremia among this group to be 1.57% (95% CI 1.32% to 1.83%). The rate of occult bacteremia was not significantly different among those children diagnosed with otitis media when compared with those without the diagnosis. Although this study has several important strengths, including its prospective design and large sample size, the reported rate of occult bacteremia is lower than previously published studies and not completely explained by the effects of the HIB vaccine.

In the second study, Alpern et al[106] retrospectively identified 5,901 febrile infants and children aged 2 to 24 months, who were discharged home from the ED, and found the prevalence of occult bacteremia to be 1.9% (95% CI 1.5% to 2.3%). In both studies, *Streptococcus pneumoniae* was the most frequently isolated pathogenic bacteria from blood culture, and HIB was never isolated. The distribution of blood pathogens found in each study was similar to that from previous reports (Table 3).[18-20,105] Additionally, HIB was never isolated as a pathogen in 2 other large post–HIB vaccine investigations of bacteremia (including nonoccult) among the 3- to 36-month age group.[107,108]

Before the release of the HIB vaccine, this pathogen was responsible for approximately 13% of occult bacteremia and 42% of the complications identified at follow-up.[19,20,101] Data regarding the natural history of untreated occult bacteremia are limited for several likely reasons: (1) the definition of what is considered a "significant" or "serious" sequelae varies greatly, (2) ethics prevent prospective studies from withholding treatment from patients with proven bacteremia, (3) existing retrospective studies tend to treat different percentages of patients empirically with antibiotics, and (4) undetected infectious complications from bacteremia may have already existed at the time the blood culture was taken.[18-20,102,105,106,109]

Of the 2 post–HIB vaccine investigations that studied children who had fever without source in the 3- to 36-month age group, only Alpern et al[106] reported the incidence of significant sequelae resulting from occult bacteremia. Eighteen patients were found to have a focal infection (8 pneumonia, 4 cellulitis, 2 osteomyelitis, 1 urinary tract infection, 1 septic arthritis, 1 abscess, 1 meningitis), and 1 had sepsis. If all such diagnoses are considered "significant," then these data indicate a 17% rate for significant infectious sequelae among those children ultimately diagnosed with occult bacteremia and a 0.3% rate among all previously healthy, well-appearing children aged 2 to 24 months who have fever without source.[106] When only the more serious diagnoses of meningitis and sepsis are considered, the rate of serious sequelae is 1.8% among those with occult bacteremia and 0.03% among all enrolled patients. The rate of significant sequelae among those with occult bacteremia found in Alpern et al's study is consistent with the 5% to 20% rates reported previously among similar children.[18-20,105,109] This consistency in the rate of significant sequelae compared with previous reports is surprising given the absence of HIB as a pathogen and may be explained by the variability in study definitions, treatment protocols, and sample characteristics.

Conclusions

1. The current prevalence of occult bacteremia among febrile children aged 3 to 36 months is most likely between 1.5% and 2%.

2. Preliminary studies indicate that approximately 5% to 20% of patients aged 3 to 36 months with occult

Table 2.
Studies investigating the rate of occult bacteremia after the release of the HIB vaccine in 1987.

Study	Design (Years)	Inclusion Criteria	Exclusion Criteria	No.	Occult Bacteremia Prevalence,% (95% CI)
Lee and Harper[102]	Prospective cohort (1993–1996)	3–36 mo old, temperature ≥39°C	Focal infection (except otitis media), specific viral syndrome, chronic or immunosuppressive disease, admitted to the hospital	9, 465	1.57 (1.32–1.83)
Alpern et al[106]	Retrospective cohort (1993–1996)	2–24 mo old, temperature ≥39°C	Focal infection (except osteomyelitis, gastroenteritis, bronchiolitis), lumbar puncture performed, chronic or immunosuppressive disease, admitted to the hospital	5, 901	1.9 (1.5–2.3)

bacteremia will develop significant sequelae (eg, pneumonia, cellulitis, septic arthritis, osteomyelitis, meningitis, sepsis). Approximately 0.3% of previously well children (aged 3 to 36 months) who have a fever without source will develop significant sequelae; however, only 0.03% will develop sepsis or meningitis.

VIII. What is the appropriate role of empiric antibiotics among previously healthy, well-appearing children aged 3 to 36 months with fever without a source?

Of children aged 3 to 36 months with fever without a source, 1.5% to 2% will have occult bacteremia, and only a small percentage of those will go on to develop significant sequelae.[18-20,105,106,109] Meningitis is among the most serious of infectious complications. Childhood pneumococcal meningitis may result in mental retardation (19%), permanent hearing loss (17%), seizure disorders (15%), paralysis (11%), and death (7.7%).[110] Young children with occult bacteremia are, by definition, well-appearing and indistinguishable by observation alone from their nonbacteremic counterparts.[111-113]

Table 3.

Distribution of pathogenic bacteria cultured from the blood of patients with occult bacteremia.[*]

Pathogenic Bacteria	Lee and Harper[102] 1998 (N=149)		Alpern et al[106] 2000 (N=111)	
	Frequency	Percentage	Frequency	Percentage
Streptococcus pneumonia	137	91.9	92	82.9
Salmonella species	7	4.7	6	5.4
Neisseria meningitides	2	1.3	0	0
Streptococcus pyogenes (Group A)	2	1.3	5	4.5
Streptococcus agalactiae (Group B)	1	0.7	0	0
Streptococcus fecalis (Group D)	0	0	2	1.8
Moraxella catarrhalis	0	0	2	1.8
Staphylococcus aureus (Coagulase positive)	0	0	2	1.8
Escherichia coli	0	0	1	0.9
Campylobacter species	0	0	1	0.9

[*]No *Haemophilus influenzae* was isolated in either study.

Two meta-analyses published in the late 1990s failed to show a benefit of empiric oral or parenteral antibiotics in the prevention of meningitis among children with occult pneumococcal bacteremia.[114,115] In another meta-analysis, Bulloch et al[116] reviewed only randomized clinical trials and similarly found that antibiotics did not reduce the incidence of significant sequelae in general among febrile children who had fever without source. However, when just the subset of children with proven occult bacteremia were analyzed, antibiotics did significantly reduce the incidence of infectious sequelae, and parenteral antibiotics were significantly more effective than oral antibiotics. After pooling data from 18 studies, Baraff[110] also found that, among children with proven pneumococcal occult bacteremia, the rate of meningitis was significantly lower among those children treated with empiric antibiotics.

In 1993, a consensus panel published practice guidelines that recommended the obtaining of blood cultures and the initial empiric administration of parenteral antibiotics to all children aged 3 to 36 months with fever greater than 39°C (>102.2°F) and a WBC count greater than 15×10^9/L.[117] The development of these guidelines took into account the results of a complex, well-conceived pre–HIB vaccine decision analysis paper published by Lieu et al[118] in 1991. Two randomized controlled trials were identified that evaluated the role of empiric antibiotic administration among children aged younger than 3 years with fever without a source.[19,20] Although the enrollment period for both of these studies began in 1987 (the same year as the HIB vaccine release), their samples of patients represent the most recent of the randomized, controlled trials, and therefore consist of the largest percentage of children studied after the HIB vaccine was released. In the first study, Bass et al[19] randomized 519 patients with either a temperature of 40°C or greater (≥104°F), or a temperature of 39.5°C or greater (≥103.1°F) combined with a WBC count of 15,000/mm³ or greater to receive a single dose of intramuscular Ceftriaxone (Rocephin) or 3 doses of oral amoxicillin and clavulanic acid (Augmentin). In the second study, Fleisher et al[20] randomized 6,733 patients with a temperature of 39°C or greater (≥102.2°F)

to receive either a single, intramuscular dose of Ceftri-axone or oral amoxicillin for 6 days. Studies using different enrollment criteria are usually difficult to compare. However, in a recent review paper, Baraff[110] contacted Fleisher's group, gathered unreported data, combined the data with Bass et al's study, and reported the results (Table 4).

In the consideration of meningitis only, Baraff[110] concludes that health care providers who are uncomfortable with a 1 in 1,000 risk among children with a temperature of 39°C or greater (≥102.2°F) and fever without a source should obtain a WBC count and empirically treat with antibiotics only those patients with a WBC count of 15,000/mm³ or greater. Similarly, among patients with a temperature of 39.5°C or greater (≥103.1°F), he concludes that, if a risk for meningitis of 3 in 1,000 is considered too great, then a WBC count should be obtained and the empiric administration of antibiotics reserved for those with a WBC count of 15,000/mm³ or greater.

In a recently published cost-effectiveness analysis, Lee et al[103] studied the management of children aged 3 to 36 months with fever greater than 39°C (>102.2°F) without source of infection. Given the current rate of occult bacteremia assumed by the analysis of 1.45%,

Table 4.
Baraff's[110] data among well-appearing children with fever without a source.

Measured Outcome	Children With Temperature ≥39.5°C (≥103.1°F) and WBC Count ≥15,000/ mm³, %	Children With Temperature ≥39.5°C (≥103.1°F) and WBC Count <15,000/ mm³, %	All Children With Temperature ≥39°C (≥103.1°F), %
Prevalence of occult pneumococcal bacteremia	10	1	2.8
Risk of meningitis among those with occult pneumococcal bacteremia*	0.3	0.03	0.1

*Assuming 3% of untreated children with occult pneumococcal bacteremia may develop meningitis.

"CBC alone plus selective treatment" using a WBC count cutoff of 15,000/mm³ was the preferred strategy.[103] However, if the future rate of occult bacteremia decreased to below 1%, then strategies using empiric testing and treatment would no longer be cost-effective.[103] Other decision analyses have had similar findings.[119]

Among children younger than 5 years, pneumococcal infections in the United States are believed to cause 1,400 cases of meningitis, 17,000 cases of bacteremia, 71,000 cases of pneumonia, and 5 to 7 million cases of otitis media annually.[120] In February of 2000, a conjugate pneumococcal vaccine active against 7 of the 90 serotypes of *Streptococcus pneumoniae* (Prevnar, Wyeth Laboratories, Philadelphia, PA) was approved by the US Food and Drug Administration for use in the United States.[120] In an efficacy trial completed by the Northern Kaiser Permanente Vaccine Study Center, 37,868 children were randomized to receive the conjugate pneumococcal vaccine or an experimental vaccine of meningococcal C that served as a control. Among those fully vaccinated, the efficacy was 97.4% against vaccine-associated strains of pneumococcus and 89.1% overall. Six cases of invasive pneumococcal disease occurred among the 18,927 vaccine recipients compared with 55 cases among the 18,941 control recipients.[120] These results are similar to those found with the conjugated HIB vaccine.[110] Once the pneumococcal vaccine becomes broadly included within pediatric practice, future studies will be necessary to determine whether empiric antibiotic treatment of children suspected of harboring occult bacteremia is warranted.

Patient Management Recommendations: What is the appropriate role of empiric antibiotics among previously healthy, well-appearing children aged 3 to 36 months with fever without a source?

Level A recommendations. None specified.

Level B recommendations. Consider empiric antibiotic therapy for previously healthy, well-appearing children, aged 3 to 36 months, with fever without a source with a temperature of 39.0°C or greater (≥102.2°F) when in association with a WBC count of 15,000/mm³ or greater if obtained.

Level C recommendations. In those cases when empiric antibiotics are not prescribed for children who have fever without a source, close follow-up must be ensured.

This clinical policy was developed by the American College of Emergency Physicians Clinical Policies Committee and the Clinical Policies Subcommittee on Pediatric Fever.

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APPENDIX A.

Literature classification schema.[*]

Design/ Class	Therapy[†]	Diagnosis[‡]	Prognosis[§]
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

[*]Some designs (eg, surveys) will not fit this schema and should be assessed individually.
[†]Objective is to measure therapeutic efficacy comparing $\geq$ 2 interventions.
[‡]Objective is to determine the sensitivity and specificity of diagnostic tests.
[§]Objective is to predict outcome including mortality and morbidity.

APPENDIX B.

Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	1	2	3
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X