

## CONCEPTS

fever, pediatric

# Practice Guideline for the Management of Infants and Children 0 to 36 Months of Age With Fever Without Source

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**Study objective:** To develop guidelines for the care of infants and children from birth to 36 months of age with fever without source.

**Participants and setting:** An expert panel of senior academic faculty with expertise in pediatrics and infectious diseases or emergency medicine.

**Design and intervention:** A comprehensive literature search was used to identify all publications pertinent to the management of the febrile child. When appropriate, meta-analysis was used to combine the results of multiple studies. One or more specific management strategies were proposed for each of the decision nodes in draft management algorithms. The draft algorithms, selected publications, and the meta-analyses were provided to the panel, which determined the final guidelines using the modified Delphi technique.

**Results:** All toxic-appearing infants and children and all febrile infants less than 28 days of age should be hospitalized for parenteral antibiotic therapy. Febrile infants 28 to 90 days of age defined at low risk by specific clinical and laboratory criteria may be managed as outpatients if close follow-up is assured. Older children with fever less than 39.0 C without source need no laboratory tests or antibiotics. Children 3 to 36 months of age with fever of 39.0 C or more and whose WBC count is 15,000/mm<sup>3</sup> or more should have a blood culture and be treated with antibiotics pending culture results. Urine cultures should be obtained from all boys 6 months of age or less and all girls 2 years of age or less who are treated with antibiotics.

**Conclusion:** These guidelines do not eliminate all risk or strictly confine antibiotic treatment to children likely to have occult bacteremia. Physicians may individualize therapy based on clinical circumstances or adopt a variation of these guidelines based on a different interpretation of the evidence.

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*This paper is not a clinical policy of the American College of Emergency Physicians. See related editorial, p 1196.*

**INTRODUCTION**

The purpose of this report is to provide specific clinical practice guidelines for the care of infants and children from birth to 36 months of age with fever without source

who are evaluated in physicians' offices and emergency departments.

Febrile children comprise a substantial proportion of ambulatory pediatric visits. The majority of children who present with fever are less than 3 years of age. Both minor and life-threatening infectious diseases, including respiratory infections, occult bacteremia, and meningitis, are common in this age group.<sup>1-7</sup> Although distinguishing a child with a viral syndrome from one with bacterial meningitis usually is not difficult, there may be considerable overlap in the clinical appearance of children with fever without source due to viral illness and of those with occult bacteremia. Occult bacteremia also may occur in children with otitis media.<sup>8</sup> When disease caused by *Haemophilus influenzae* type b was common, from 5% to 10% of bacteremic children treated as outpatients without antibiotics subsequently developed bacterial meningitis and other focal bacterial infections.<sup>5-7,9-18</sup> The management of young febrile children needs be structured to minimize the likelihood of these unfavorable outcomes.

**MATERIALS AND METHODS**

**Overview** We used a variation of the modified Delphi technique to develop the evidence-based practice guidelines that we present. One of the authors (LJB) identified the decision nodes in a draft clinical management algorithm for infants and children with fever without source. A comprehensive literature search was undertaken to identify all publications that report the results of original scientific research pertinent to each decision. Meta-analysis was used to combine the results of multiple studies when more than one report addressed a single topic area of interest. One or more specific management strategies then were proposed for each of the decision nodes in the management algorithm. The proposed management strategies and a summary of the results of the literature

**Figure 1.**

*Suggested clinical data set for febrile infants 0 to 90 days of age*

**History**

- Prematurity Y \_\_\_ N \_\_\_
- Antibiotic therapy Y \_\_\_ N \_\_\_
- Chronic illness Y \_\_\_ N \_\_\_
- Prior hospitalization Y \_\_\_ N \_\_\_

**Physical Examination**

- Vital signs: Temperature \_\_\_ Pulse \_\_\_ Respirations \_\_\_
- Blood pressure \_\_\_ Yale Observation Score \_\_\_
- Hydration abnormal Y \_\_\_ N \_\_\_
- Perfusion abnormal Y \_\_\_ N \_\_\_
- Activity abnormal Y \_\_\_ N \_\_\_
- Otitis media Y \_\_\_ N \_\_\_
- Skin infection Y \_\_\_ N \_\_\_
- Bone/Joint infection Y \_\_\_ N \_\_\_

**Laboratory Evaluation**

- WBC < 5,000 or > 15,000/mm<sup>3</sup> Y \_\_\_ N \_\_\_
- Bands > 1,500/mm<sup>3</sup> Y \_\_\_ N \_\_\_
- Urinalysis ≥ 10 WBCs/hpf Y \_\_\_ N \_\_\_
- If rales, tachypnea-chest radiograph Y \_\_\_ N \_\_\_
- If diarrhea, ≥ 5 WBCs/hpf Y \_\_\_ N \_\_\_
- Blood culture Y \_\_\_ N \_\_\_
- Urine culture Y \_\_\_ N \_\_\_
- Cerebrospinal fluid culture Y \_\_\_ N \_\_\_

**Social Situation**

- Home telephone Y \_\_\_ N \_\_\_
- Car available Y \_\_\_ N \_\_\_
- Parental maturity Y \_\_\_ N \_\_\_
- Thermometer Y \_\_\_ N \_\_\_
- ED travel less than 30 minutes Y \_\_\_ N \_\_\_

**Low-Risk Criteria for Febrile Infants**

- Clinical Criteria**
  - Previously healthy
  - Nontoxic clinical appearance
  - No focal bacterial infection (except otitis media)
  - Good social situation
- Laboratory Criteria**
  - WBC count 5,000 – 15,000/mm<sup>3</sup>, < 1,500 bands/mm<sup>3</sup>
  - Normal urinalysis (< 5 WBCs/hpf)
  - When diarrhea present, < 5 WBCs/hpf in stool

**Table 1.**

*Probability of bacterial infections in infants 90 days or younger by clinical and laboratory findings*

	Infants		
	Low Risk*	Nontoxic	Toxic
Serious bacterial infections	1.4% (0.4-2.7)†	8.6% (3.7-15.6)	17.3% (8.0-30.0)
Bacteremia	1.1% (0.2-2.6)	2.0% (0.8-3.8)	10.7% (6.7-15.7)
Meningitis	0.5% (0.0-1.0)	1.0% (0.2-2.4)	3.9% (1.7-7.1)

\*See text for definition.  
†95% confidence interval.  
From reference 25.

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search and meta-analyses were provided to an expert panel that reviewed all materials and developed the final management strategies.

**Specific Clinical Questions** The following are the specific questions identified from the draft management algorithm that were presented to the panel with the results of literature search and preliminary analyses. 1) What is the lowest temperature that defines a fever? 2) At what age must a non-toxic-appearing infant with what degree of fever, if any, be hospitalized? 3) What are the appropriate criteria, including laboratory results, necessary to define a "low-risk" febrile infant less than 90 days of age who need not be hospitalized for possible sepsis? 4) When should outpatient antibiotics be considered for the management of these low-risk febrile infants? Which antibiotic should be used? 5) What is a reasonable plan for the evaluation of a child 3 to 36 months of age with fever without source? When should the diagnostic tests of CBC, differential count, blood culture, urinalysis, urine culture, and chest radiograph be performed? 6) When should antibiotics be considered in the outpatient management of children 3 to 36 months of age with fever without source? Which antibiotic should be used?

**Literature Search** We searched the English language literature for all publications concerning the management of febrile infants and children using the National Library of Medicine Medline bibliographic data base from 1977 through August 1991. Additional articles were identified from the bibliographies of all articles retrieved.

**Abstraction of Data** All articles were scrutinized to determine whether they presented the results of original research concerning the questions of interest. Each report was examined to see whether it reported on 1) the prevalence of bacteremia, urinary tract infection, and meningitis in febrile infants 90 or less days of age and the utility of clinical assessment and laboratory tests in identifying each of these infections; 2) the prevalence of bacteremia, urinary tract infection, and pneumonia in infants and children 3 to 36 months old with fever without source and the utility of clinical assessment and laboratory tests in identifying each of these infections; 3) the effects of alternative antibiotic therapies on the outcomes of bacteremia in infants and children. Data were abstracted from each article to a master data form that was used to construct evidence tables for each of the questions of interest.

**Meta-analysis** We used Bayesian meta-analyses to combine the data from multiple reports to estimate the posterior probability distribution and mean prevalence for each type of outcome.<sup>19</sup> From the probability distribution, we determined the upper and lower values that demarcate the region that has a 95% chance of containing the true mean. We used these values to define the Bayesian equivalent of the 95% confidence interval (CI). Meta-analyses were carried out with FAST\*PRO software (Academic Press, Boston, Massachusetts).

### Expert Panel Review and Preparation of Practice

**Guidelines** The first author selected an expert panel composed of senior full-time academic faculty with nationally

**Table 2.**  
*Bacteremia in febrile children with fever without source managed as outpatients*

Author	Year	Study Design	Age (months)	Temperature (C)	Laboratory Criteria	Blood Cultures		Fever Without Source (%)
						Positive	Total	
Teele <sup>57</sup>	1975	P <sup>‡</sup>	1-24	≥ 38.3	None	5	173	2.9
Murray <sup>7</sup>	1981	P	3-24	≥ 39.7	None	3	58	5.2
Schwartz <sup>17</sup>	1982	P	2-36	≥ 38.9	None	5	45	11.1
Carroll <sup>58</sup>	1983	RCT	6-24	≥ 40.0	WBC > 15,000/mm <sup>3</sup> or erythrocyte sedimentation rate > 30	10	96	10.4
Jaffe <sup>15</sup>	1987	RCT	3-36	≥ 39.0	None	27	995	2.7
Jaffe <sup>15</sup>	1987	P	3-36	≥ 39.0	None	15	228	6.6
Fleisher <sup>*96</sup>	1993	RCT	3-36	≥ 39.0	None	194	6,733	2.9
Bass <sup>59</sup>	1993	RCT	3-36	39.5-39.9	WBC > 15,000/mm <sup>3</sup>	21	169	12.4
Bass <sup>59</sup>	1993	RCT	3-36	≥ 40.0	None	39	343	11.4
All studies <sup>†</sup>								6.8
95% CI <sup>†</sup>								4.6 - 9.4
Studies with temperature criteria ≥ 39.0 or below and no WBC criteria <sup>†</sup>								4.3
95% CI <sup>†</sup>								2.6 - 6.5

\*96% of patients with fever without source; remainder with otitis media.

<sup>†</sup>Mean probabilities and 95% CI by Bayesian meta-analysis.

<sup>‡</sup>P, prospective; RCT, randomized, controlled trial.

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recognized expertise in pediatrics and infectious diseases or emergency medicine. There was one meeting of the panel with a goal of reaching a consensus regarding answers to the questions concerning clinical management of febrile children. Before the meeting, each panel member was provided with a copy of the complete bibliography, the draft management algorithm, each clinical question, the evidence tables and selected references, and one or more suggested management strategies pertaining to each question. Each panel member was asked to review the material as well as any other information they might have pertaining to the questions of interest and to formulate an answer to each question before the panel meeting. At the time of the panel meeting, we attempted to reach a consensus regarding appropriate management strategies. When we could not, we proposed alternative management strategies. The draft practice guidelines were circulated in the form of a manuscript to all panel members for their review. The guidelines were revised and again circulated to the panel for comments, which were incorporated into the final practice guidelines.

### RESULTS

The bibliographic search resulted in more than 300 references from 1960 to the present pertaining to the management of infants and/or children with fever; 85 met criteria for inclusion in this report.

**Definition of Fever** The definition of what temperature constitutes a fever was based on a survey of residency directors of pediatric and emergency medicine training programs and the opinions of panel members. The median temperatures taught by pediatric and emergency medicine residency directors as defining a fever were 38.0 C or more and 38.1 C or more, respectively.<sup>20</sup> This is in accord with studies of the measurement of normal temperatures in healthy children.<sup>21,22</sup> The panel concluded that 38.0 C (100.4 F) should be used as the lower limit of the definition of fever. This definition is based on rectal measurement of temperature. The clinician needs to recognize that serious and life-threatening infectious diseases occasionally may be present in an infant without fever to this degree and that hypothermia (rectal temperature of less than 36.0 C or 96.8 F) can be associated with serious infectious diseases in young infants.<sup>23,24</sup> Fever that has been documented at home by a reliable parent or other adult should be considered the same as a fever documented in a physician's office or ED. Fever may be a result of overbundling a small infant. When this is suspect, the child may be unbundled and the temperature retaken in

15 to 30 minutes. If this repeat temperature is normal in a healthy-appearing infant who has not received an antipyretic, the infant may be considered to be afebrile. Vaccine reactions can account for fever; therefore, parents should be questioned regarding recent immunizations.

**Definition of Fever Without Source** Fever without source is an acute febrile illness in which the etiology of the fever is not apparent after a careful history and physical examination.

**Definition of Serious Bacterial Infection** Serious bacterial infections include meningitis, sepsis, bone and joint infections, urinary tract infections, pneumonia, and enteritis.

**Toxic-Appearing Infants and Children** The panel concurred with the clinical maxim that all febrile children less than 36 months of age who are toxic appearing should be hospitalized for evaluation and treatment of possible sepsis or meningitis. Toxic is defined as a clinical picture consistent with the sepsis syndrome (ie, lethargy, signs of poor perfusion, or marked hypoventilation, hyperventilation, or cyanosis). Lethargy is defined as a level of consciousness characterized by poor or absent eye contact or as the failure of a child to recognize parents or to interact with persons or objects in the environment. Infants less than 12 weeks of age who appear toxic have a 17% probability of having a serious bacterial infection including an 11% probability of bacteremia and a 4% probability of meningitis (Table 1).<sup>25</sup> The probability of serious bacterial infections in older toxic-appearing febrile children has been reported to range from approximately 10% to 90%, depending on the criteria used to define toxic.<sup>8,17,26-30</sup>

**Definition of Low-Risk Febrile Infants** In young infants, various authors have demonstrated that clinical evaluation is inadequate to exclude reliably serious bacterial infections.<sup>31-45</sup> For example, the Infant Observation Scale is not adequate to differentiate bacteremic from nonbacteremic infants.<sup>31</sup> The mean probability of serious bacterial infection in non-toxic-appearing febrile infants less than 12 weeks of age is 8.6%, including a 2% probability of

**Table 3.**

*Outcome of occult bacteremia in febrile children 3 to 36 months of age: The effect of outpatient antibiotic therapy.*

Outcome	Antibiotics			No Antibiotics			Total		
	No.	Total	%	No.	Total	%	No.	Total	%
Persistent fever	24	154	15.6	63	113	55.8	95	275	34.5
Persistent bacteremia	3	80	3.8	14	67	20.9	37	311	11.9
Meningitis	10	222	4.5	15	163	9.2	70	957	7.3

From reference 75.

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bacteremia and a 1% probability of bacterial meningitis (Table 1).<sup>25</sup> Among the non-toxic-appearing febrile infants, clinical evaluation and laboratory studies can be used to define a population of low-risk infants who can be managed safely as outpatients.<sup>46-50</sup> These low-risk criteria are previously being healthy, having no focal bacterial infection on physical examination, and having negative laboratory screening. Negative laboratory screening is defined as WBC count of 5,000 to 15,000/mm<sup>3</sup>, less than 1,500 bands/mm<sup>3</sup>, normal urinalysis, and when diarrhea was present, less than 5 WBCs/high-power field (hpf) in stool. The mean probability of serious bacterial infection in low-risk febrile infants less than 90 days of age is 1.4% (Table 1).<sup>25</sup>

**Febrile Infants Less Than 28 Days of Age** The risk of serious bacterial infection in low-risk infants less than 28 days of age is very small. In the report by Jaskiewicz et al,<sup>50</sup> of 511 low-risk infants, 227 were in this age group. Only one had a serious bacterial infection, a urinary tract infection caused by *Escherichia coli*. Therefore, in this report, the negative predictive value of the low-risk criteria in this age group was 99.3% (95% CI, 98.0% to 99.9%). This child was treated as an outpatient without antimicrobial therapy until the result of the culture was known, and did well.

Despite the low probability of serious bacterial infections in this age group and the favorable outcome of the children managed to date with careful observation, the majority of panel members believed that under most circumstances, all febrile infants less than 28 days of age, including those in the low-risk group, should have a sepsis evaluation and be hospitalized for parenteral antimicrobial therapy pending culture results. The sepsis evaluation includes a culture of cerebrospinal fluid, blood,

and urine; a CBC and differential count; examination of cerebrospinal fluid for cells, glucose, and protein; and a urinalysis. An alternative management strategy for low-risk infants less than 28 days of age is a complete sepsis evaluation, hospitalization, and careful observation without parenteral antimicrobial therapy pending culture results.

**Low-Risk Febrile Infants 28 to 90 Days of Age** In this age group, the low-risk criteria have been used to identify children who can be treated safely as outpatients. In two studies, outpatient treatment has included initial antimicrobial therapy of all low-risk infants.<sup>47,51</sup> The study by Baskin et al<sup>51</sup> used slightly different low-risk criteria (WBC count of less than 20,000/mm<sup>3</sup> and urine screen with reagent strips for urinalysis for leukocyte esterase and nitrite). More recently, selected low-risk infants have been managed as outpatients with careful observation without antimicrobial therapy.<sup>50</sup> Eleven low-risk infants are reported to have been treated as either inpatients or outpatients without antimicrobial therapy until the results of cultures were known (six with urinary tract infections, three with occult bacteremia, and two with enteritis).<sup>42,44,45,50</sup> All did well despite the delay in antimicrobial therapy.

The majority of panel members agreed that when parents are deemed reliable and close follow-up can be ensured, outpatient management of low-risk febrile infants 28 to 90 days of age with blood and urine cultures and an IM injection of ceftriaxone is an alternative to hospitalization.<sup>52</sup> Such infants should meet all the low-risk clinical and laboratory criteria except that infants in this age group with otitis media also can be treated in this manner. The use of preprinted forms will help ensure that a minimum of clinical and laboratory data are collected

**Table 4.**

Risk of bacteremia in children with fever without source managed as outpatients by WBC count

Author	Year	Study Design†	Age (months)	Temperature (C)	WBC < 15,000/mm <sup>3</sup>			WBC > 15,000/mm <sup>3</sup>			P
					Positive	Total	%	Positive	Total	%	
Teele <sup>57</sup>	1975	P	1-24	≥ 38.3	0	129	0.0	5	44	11.4	.001
Murray <sup>7</sup>	1981	P	3-24	≥ 39.7	2	40	5.0	1	18	5.6	1.000
Schwartz <sup>17</sup>	1982	P	2-36	≥ 38.9	1	31	3.2	4	14	28.6	.027
Carroll <sup>58</sup>	1983	P	6-24	≥ 40.0				10	96	10.4	
Jaffe <sup>15</sup>	1987	RCT	3-36	≥ 39.0	9	636	1.4	18	249	7.2	< .001
Bass <sup>59</sup>	1992	RCT	3-36	39.5-39.9				21	169	12.4	< .001
Bass <sup>59</sup>	1992	RCT	3-36	> 40.0	5	182	2.7	34	161	21.1	< .001
Mean probability*							2.6			13.0	< .001
95% CI*						1.2-4.5			9.0-17.8		

\*Mean probability by hierarchical Bayesian meta-analysis.

†P, prospective; RCT, randomized, controlled trial.

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and that these infants are documented to be at low risk (Figure 1). Empiric outpatient therapy with ceftriaxone of febrile infants 28 to 90 days old should be undertaken only if a lumbar puncture and blood culture are obtained to help distinguish viral from bacterial meningitis and partial treatment of occult bacteremia from a viral syndrome in the event that the clinical condition of the child deteriorates. Stool cultures are recommended only for infants and children with bloody diarrhea or when examination of the stool reveals five or more fecal leukocytes/hpf.<sup>53</sup> Ceftriaxone, a parenteral cephalosporin that has a half-life of five to six hours and is active against most of the bacteria associated with serious bacterial infections in infancy and childhood, is the antibiotic that has been used most frequently in these circumstances.<sup>47,51,54</sup> The recommended dosage is 50 mg/kg once daily.

Infants in this age group should be rechecked in 18 to 24 hours, at which time a second injection of ceftriaxone can be given.<sup>51</sup> Children with otitis media should receive oral antimicrobial therapy at this time (eg, amoxicillin 40 mg/kg/day). Infants whose blood or cerebrospinal fluid cultures are positive for known bacterial pathogens should be recalled and admitted for parenteral antimicrobial therapy. Infants with occult bacteremia caused by *Streptococcus pneumoniae* who are afebrile and appear normal at the 24-hour follow-up evaluation can be managed as outpatients with oral amoxicillin or penicillin and careful follow-up. Concern for resistant pneumococci is sufficient to recommend a second injection of ceftriaxone if the results of penicillin susceptibility tests are not available. Infants with a urinary tract infection without

bacteremia who are afebrile and nontoxic at the time of re-evaluation can be treated as outpatients with a ten-day course of an appropriate oral antibiotic as determined by susceptibility testing (eg, trimethoprim-sulfamethoxazole) and follow-up radiologic evaluation.

A recent analysis of diagnostic tests to identify infants less than 3 months old who are at low risk for serious bacterial infections concluded, based on only two of the reports of the low-risk criteria,<sup>46,48</sup> that the probability of a serious bacterial infection in an infant meeting the low-risk criteria is 0.2%.<sup>55</sup> Therefore, an alternate strategy for management of infants with fever without source and low-risk clinical and laboratory criteria is outpatient observation without antimicrobial therapy (Figure 2, option 2). Children managed in this manner should have a urine culture but do not necessarily need blood cultures or a lumbar puncture. They all should be re-evaluated within 24 hours. Those whose clinical condition deteriorates should be admitted for a complete sepsis evaluation and parenteral antimicrobial therapy. Those with positive cultures should be treated as stated above.

**Non-Low-Risk Febrile Infants 28 to 90 Days of Age** Infants who do not meet the low-risk criteria should be hospitalized and receive parenteral antimicrobial therapy pending the results of cultures of blood, cerebrospinal fluid, and urine.

**Evaluation of a Child 3 to 36 Months of Age with Fever Without Source** Incidence of fever without source: Sixty-five percent of children between the ages of birth and 2 years visit a physician for an acute febrile illness.<sup>56</sup> Most of these visits (75%) are for temperatures of less

**Table 5.**

Proportion of children with fever without source with positive urine cultures by age, sex, temperature, and definition of positive culture

Author	Year	Study Design*	Age	Sex	Temperature (C)	Culture	Positive	Total	%
Craine <sup>87</sup>	1990	P	< 8 weeks	Male	≥ 38.1	> 10 <sup>4</sup>	22	177	12.4
Bauchner <sup>88</sup>	1987	P	0-3 months	Male	≥ 37.8	> 10 <sup>4</sup>	3	19	15.8
Bauchner <sup>88</sup>	1987	P	4-6 months	Male	≥ 37.8	> 10 <sup>4</sup>	2	51	3.9
Bauchner <sup>88</sup>	1987	P	7-12 months	Male	≥ 37.8	> 10 <sup>4</sup>	0	75	0.0
Roberts <sup>89</sup>	1983	P	< 2 years	Male	≥ 38.3	> 10 <sup>5</sup>	0	85	0.0
Bauchner <sup>88</sup>	1987	P	13-36 months	Male	≥ 37.8	> 10 <sup>4</sup>	0	156	0.0
Craine <sup>87</sup>	1990	P	< 8 weeks	Female	≥ 38.0	> 10 <sup>4</sup>	11	265	4.2
Bauchner <sup>88</sup>	1987	P	0-3 months	Female	≥ 37.8	> 10 <sup>4</sup>	2	10	20.0
Bauchner <sup>88</sup>	1987	P	4-6 months	Female	≥ 37.8	> 10 <sup>4</sup>	1	27	3.7
Bauchner <sup>88</sup>	1987	P	7-12 months	Female	≥ 37.8	> 10 <sup>4</sup>	1	62	1.6
Roberts <sup>89</sup>	1983	P	< 2 years	Female	≥ 38.3	> 10 <sup>5</sup>	8	108	7.4
Bauchner <sup>88</sup>	1987	P	13-36 months	Female	≥ 37.8	> 10 <sup>4</sup>	0	108	0.0
North <sup>90</sup>	1963	P	0-23 months	Both	≥ 38.0	> 10 <sup>5</sup>	0	26	0.0
Carroll <sup>98</sup>	1983	P	6-24 months	Both	≥ 40.0	NA	2	96	2.1
Murray <sup>7</sup>	1981	P	3-24 months	Both	≥ 39.7	NA	0	80	0.0
North <sup>90</sup>	1963	P	2-5 years	Both	≥ 38.0	> 10 <sup>5</sup>	2	37	5.4

\*P, prospective.

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than 39.0 C. Fever without source accounts for as many as 14% of visits.

**Risk of bacteremia:** The risk of occult bacteremia in children 3 to 36 months of age with fever without source is reported to be from 3% to 11% with a mean probability of 4.3% in children with a temperature of 39.0 C or more (95% CI, 2.6% to 6.5%) (Table 2).<sup>7,14,17,57-63</sup> A smaller proportion of children treated as outpatients with otitis media are bacteremic.<sup>8</sup> In most studies, bacteremia is most frequent in children with higher temperatures.<sup>58-60,64,65</sup> The bacteria most often isolated from the blood of children with fever without source are *S pneumoniae*, *H influenzae* type b, and *Neisseria meningitidis*, accounting for approximately 85%, 10%, and 3% of the positive blood cultures, respectively, in the reports included in Table 2. Other infectious agents that are associated with occult bacteremia in young children are *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Salmonella* sp. Since the initiation of widespread immunization of infants with *H influenzae* type b vaccine, the proportion of children with invasive disease caused by this pathogen has diminished significantly.<sup>66-72</sup>

**Clinical assessment:** The clinical evaluation of febrile children has been alluded to in this report in the definitions of lethargy and toxicity. The clinician must recognize the limitations of clinical assessment. McCarthy and colleagues reported the sensitivity and specificity of clinical assessment by private pediatricians for serious illness to be 74% and 75%, respectively.<sup>73,74</sup>

**Outcomes of bacteremia:** A review of 20 studies of the outcomes of bacteremia in febrile children treated as outpatients demonstrated that if a child with bacteremia is sent home without antimicrobial therapy, the overall risks of persistent fever, persistent bacteremia, and meningitis were 56%, 21%, and 9%, respectively (Table 3).<sup>75</sup> These

risks vary with the organism isolated from the blood and are reduced by outpatient antibiotic treatment. For example, the overall risk of meningitis as a function of the etiology of untreated occult bacteremia is 6% for *S pneumoniae* and 26% for *H influenzae*.<sup>76</sup>

**Nonspecific tests:** Nonspecific tests have been proposed as screening instruments to determine which children are bacteremic. Proposed tests include WBC count, absolute neutrophil count, absolute band count, erythrocyte sedimentation rate, and C-reactive protein.<sup>5,11,28,77-84</sup> The higher the WBC count or sedimentation rate, the greater is the absolute number of neutrophils or bands, the greater is the risk of bacteremia in a febrile child. We present by WBC count the results of a meta-analysis of the risk of bacteremia in children with fever without source treated as outpatients (Table 4).<sup>7,14,17,57-59</sup> The relative risk is fivefold higher if the WBC count is 15,000/mm<sup>3</sup> or more (13.0% versus 2.6%). Therefore, the WBC count can be used to assess which children 3 to 36 months of age with fever without source should have a blood culture and antibiotic treatment. Other nonspecific tests (erythrocyte sedimentation rate, C-reactive protein, or absolute band count) also may be used but are not recommended.

Blood cultures have a place in the outpatient management of children with fever without source as they identify children with occult bacteremia at risk for more serious sequelae. They are of value only if the child's parents can be contacted should the culture be positive. Blood cultures should be considered in children between 3 and 36 months of age with fever without source of 39.0 C or more. The WBC count can be used to determine which children with temperature of 39.0 C or more should have a blood culture. Blood cultures are not necessary when the presumptive diagnosis of a viral syndrome is supported by a benign clinical appearance and the presence of other

**Table 6.**  
Proportion of children with fever without source with positive chest radiographs

Author	Year	Study Design <sup>†</sup>	Age	Temperature (C)	Positive	Total	%
Heldrich <sup>61</sup>	1970	R	7-27 months	≥ 38.9	0	10	0.0
Leventhal <sup>92</sup>	1982	P	3 month-15 years	37.8*	0	41	0.0
Alario <sup>94</sup>	1987	P	1 month-18 years	...	6	40	15.0
Patterson <sup>93</sup>	1990	R	1 week-22 months	≥ 37.8	1	37	2.7
Patterson <sup>93</sup>	1990	P	1 week-23 months	≥ 37.8	0	121	0.0
Mean probability <sup>†</sup>							3.3
95% CI <sup>†</sup>							0.8-7.5

\*Mean temperature.  
<sup>†</sup>Bayesian meta-analysis.  
<sup>‡</sup>R, randomized; P, prospective.

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family members or frequent contacts with obvious viral syndrome, such as an upper respiratory infection. When blood cultures are used, there needs to be a mechanism that allows the laboratory personnel to communicate results to the clinician as soon as cultures are presumptively positive.

**Lumbar puncture:** A lumbar puncture is indicated in any child in whom the clinician considers the diagnosis of sepsis or meningitis based on history, observational assessment, or physical examination. No other test can be used to exclude the diagnosis of meningitis. Approximately 1% of children with a normal cerebrospinal fluid cell count, normal chemistries, and a negative Gram-stained smear of cerebrospinal fluid will have a positive cerebrospinal fluid culture. This usually is associated with meningitis caused by *N meningitidis*.<sup>85,86</sup> Therefore, it is not possible to exclude completely the diagnosis of meningitis at the time of lumbar puncture. However, if the lumbar puncture was done to exclude the diagnosis of meningitis in a child with a low prior probability, these children need not necessarily be admitted if the parents are reliable and follow-up is ensured. Because we presume that children with signs or symptoms suggestive of meningitis who have normal cerebrospinal fluid are at increased risk of bacteremia, a blood culture should be obtained from all children who are to be managed as outpatients, and treatment with ceftriaxone should be considered.

**Urinalysis and urine culture:** Urinary tract infections occur in approximately 7% of male infants 6 months old or younger and 8% of female infants 1 year or younger

who have fever without source (Table 5).<sup>7,58,87-90</sup> Approximately 20% of young children with urinary tract infections will have a normal urinalysis or a negative urine reagent strip test for leukocyte esterase, nitrite, or both.<sup>91</sup> A Gram-stained smear of urine sediment is the most sensitive (99%) screening test for a urinary tract infection; however, only a urine culture can establish or exclude the diagnosis of a urinary tract infection. A Gram-stained smear of urine in conjunction with examination of the urine sediment for WBCs or a urine dipstick test for leukocyte esterase and nitrite may be used as a screening test to determine which children to culture. Positive cultures of urine collected by plastic receptacles attached to the perineum can result from contamination with fecal flora; therefore, the use of these receptacles is discouraged. It is more expedient and reliable to obtain urine with a catheter or by suprapubic aspiration for Gram-stain and culture.

**Chest radiographs:** Chest radiographs usually are negative in children with fever without source who have no signs or symptoms of lower respiratory infection (eg, tachypnea, cough, rales, or rhonchi).<sup>6,61,92-94</sup> Table 6 presents the results of four reports of chest radiographs in children with fever without source. The mean probability of an infiltrate on chest radiograph is 3.3% (95% CI, 0.8% to 7.5%). The majority of non-toxic-appearing children with pulmonary infiltrates are presumed to have a viral infection. Therefore, chest radiographs need not be obtained in most of these children. Children with higher temperatures (40 C or more) or WBC counts of

**Table 7.** Probabilities of outcomes in children 3 to 36 months of age with fever without source and WBC count of 15,000/mm<sup>3</sup> or more

	Risk in Subgroup	Risk per Child		No. of Complications per 100,000 Children	
		No Antibiotics	IM Antibiotics	No Antibiotics	Antibiotics
<b>Outcome of Bacteremia</b>					
Persistent bacteremia	0.10	0.01100	0.00275	1,100	275
Meningitis	0.06	0.00660	0.00165	660	165
Death	0.15	0.00099	0.00025	99	25
Serious sequelae	0.17	0.00112	0.00028	112	28
Moderate sequelae	0.10	0.00066	0.00017	66	17
No sequelae	0.58	0.00383	0.00096	383	96
<b>Antibiotic Adverse Reactions</b>					
Anaphylaxis		0.00000	0.00006	0	6
Death	0.100	0.00000	0.00001	0	1
Serious sequelae	0.100	0.00000	0.00001	0	1
Recovery	0.800	0.00000	0.00005	0	5
Minor adverse reactions		0.00000	0.05000	0	5,000

Assumes elimination of *H influenzae* disease by *H influenzae* type b vaccine and based on risks and outcomes of *S pneumoniae* bacteremia only. Probability of bacteremia is 0.11. In children with bacteremia, probability of persistent bacteremia for untreated is 0.1 and for antibiotic treatment is 0.025; probability of meningitis for untreated is 0.06 and for antibiotic treatment is 0.015.



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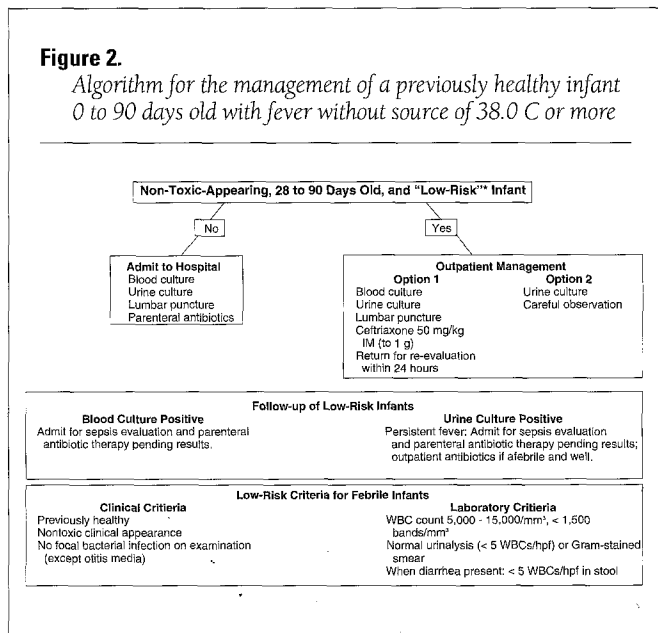
15,000/mm<sup>3</sup> or more may be more likely to have an infiltrate on chest radiograph. Treatment with ceftriaxone should be adequate for those with pneumococcal pneumonia. Children with *H influenzae* type b pneumonia probably will have a positive blood culture. Follow-up evaluation of children with a positive blood culture should include a chest radiograph if another focus of infection is not apparent and the child is not afebrile and well.

**Stool cultures:** Stool cultures are of value only in infants and children with diarrhea. The common causes of bacterial diarrhea in children are *Salmonella*, *Campylobacter*, *Shigella*, *Yersinia*, and enteroinvasive or toxigenic strains of *E coli*.<sup>95</sup> In most cases of bacterial enteritis, symptoms will have resolved before the results of bacterial cultures are known. When signs of invasive bacterial diarrhea are present (ie, bloody or mucoid diarrhea or 5 or more WBCs/hpf on microscopic examination), empiric antibiotic therapy should be initiated, and the stool should be cultured for bacterial pathogens.

**Empiric antibiotic therapy of fever without source in children 3 to 36 months of age:** The decision to undertake empiric antibiotic therapy is based on consideration of the risks, benefits, and costs of both antibiotic treatment and no such treatment. A formal decision analysis provided the conclusion that the use of parenteral antibiotic therapy is a cost-effective and reasonable approach in the management of children at risk of occult bacteremia.<sup>96</sup> Table 3 presents the beneficial effects of outpatient antibiotic therapy on the outcomes of occult bacteremia. The majority of

**Figure 2.**

Algorithm for the management of a previously healthy infant 0 to 90 days old with fever without source of 38.0 C or more



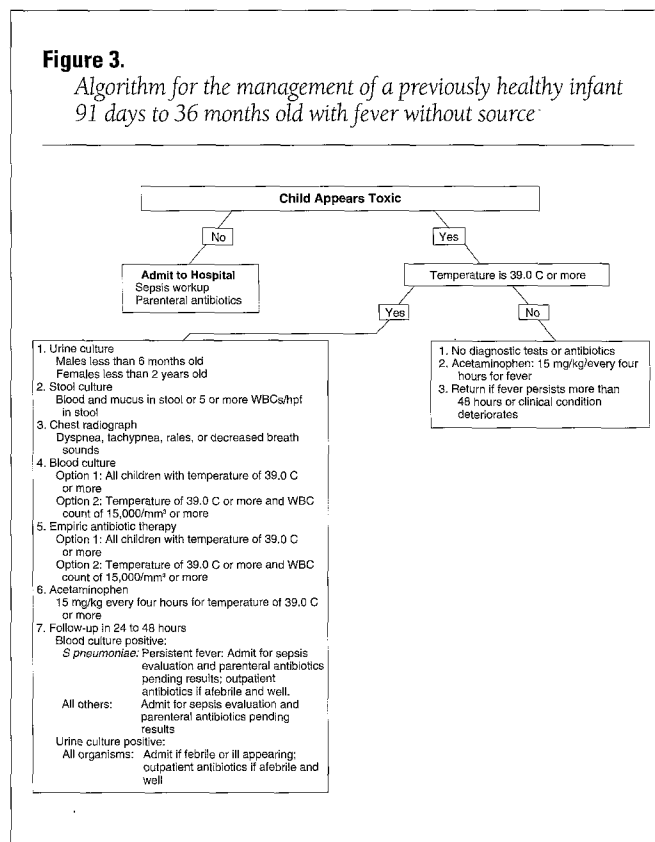
the treated patients reported in this table were administered oral antibiotics.

Recently, there have been two multicenter, randomized, controlled trials comparing oral antibiotic therapy with IM ceftriaxone for the outpatient therapy of occult bacteremia.<sup>59,97</sup> These studies demonstrated parenteral antibiotics to be associated with either fewer sequelae of occult bacteremia or a reduction in the duration of fever. A meta-analysis that included these two recent studies demonstrated parenteral antibiotics to be significantly more effective than either no or oral antibiotic therapy in reducing the risk of subsequent bacterial meningitis.<sup>75</sup> The mean probabilities of subsequent bacterial meningitis in a child with occult bacteremia were for no antibiotics, 9.8%; oral antibiotics, 8.2%; and parenteral antibiotics, 0.3%.

Oral antibiotics are effective in children with bacteremia caused by *S pneumoniae*. The risks associated with antibiotic therapy are low. Lieu et al estimated the risk of anaphylaxis with IV ampicillin to be 0.0004.<sup>96</sup> The risk of anaphylaxis is not known for ceftriaxone, but anaphylactic reactions to cephalosporins generally are considered to occur in 10% to 15% of patients with a penicillin allergy.<sup>98,99</sup> Of 3,333 ceftriaxone-treated children, in the

**Figure 3.**

Algorithm for the management of a previously healthy infant 91 days to 36 months old with fever without source



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multicenter study by Fleisher et al,<sup>97</sup> 1.5% had dermatologic and 4.2% had gastrointestinal adverse reactions that were characterized as probably attributable to therapy.

Table 7 presents the effect of outpatient parenteral antibiotic therapy on outcome in a theoretical cohort of 100,000 children with fever without source with temperatures of 39.0 C or more and WBC count of 15,000/mm<sup>3</sup> or more. The outcomes are based on the data presented above and the assumptions that *H influenzae* type b will eliminate all disease resulting from *H influenzae* and that parenteral antibiotic therapy will reduce the probability of all outcomes by 75%. The probabilities of *S pneumoniae* bacteremia in fever without source, subsequent meningitis in bacteremic children, and the outcomes of bacterial meningitis are derived from meta-analyses of the outcomes of bacteremia and bacterial meningitis in children.<sup>76,100</sup> We presumed a 5% rate of minor adverse reactions with a single injection of ceftriaxone. These data favor expectant antibiotic therapy as the number of serious adverse outcomes is substantially less in the treated group. If *H influenzae* type b vaccine is less than 100% effective, the benefits of empiric antibiotic therapy are greater.

We have chosen to recommend that a WBC count be used to determine which children to culture and treat. This will result in some children with bacteremia (approximately 25%) being undetected and untreated.<sup>15,17,57,84</sup> We have made this recommendation because WBC counts are more easily obtained in many physicians' offices and are less expensive than a blood culture and because such a strategy reduces the number of children treated empirically. We believe that the proportion of children with occult bacteremia with WBC count of 15,000/mm<sup>3</sup> or less will decrease as systemic infections caused by *H influenzae* type b diminish as a result of the effect of routine immunization with *H influenzae* type b vaccine. We recognize that a strategy that combines blood culture and empiric antibiotic therapy for all patients prevents the highest number of complications and consider this strategy acceptable in settings where it is practical (eg, EDs and outpatient departments of teaching institutions). Empiric parenteral antibiotic therapy of all children with fever without source without blood cultures was considered unacceptable as blood cultures are necessary to help differentiate viral from bacterial meningitis and partial treatment of occult bacteremia from a viral syndrome in the event that the clinical condition of the child deteriorates.

One needs to consider whether it is safe to use empiric antibiotic therapy in young infants with fever without source without performing a lumbar puncture. Children with early bacterial meningitis may have no signs or

symptoms of this infection.<sup>6</sup> Therapy with ceftriaxone can result in partial treatment and delayed diagnosis with an unknown effect on eventual morbidity or mortality. Alternatively, such therapy may result in sterilization of the cerebrospinal fluid.<sup>59,97</sup> We have concluded that such therapy can be used without performing a lumbar puncture in nontoxic children with fever without source, especially in children who have been immunized with *H influenzae* type b vaccine.

When the results of the blood or urine culture are reported as presumptively positive, the child should be recalled for re-evaluation. Children who are still febrile or who appear ill and children whose blood cultures are positive for *H influenzae* or *N meningitidis* should have a repeat blood culture and a lumbar puncture and be admitted for parenteral antibiotic therapy pending the results of these cultures. Children whose blood culture is positive for *S pneumoniae* and who are afebrile and well appearing can be treated on an ambulatory basis with a second injection of ceftriaxone and a ten-day course of oral penicillin. If only the urine culture is positive and the child is afebrile and well appearing, treatment with a ten-day course of an oral antibiotic to which the causative agent is sensitive is appropriate.

The incidence of invasive infections caused by strains of *S pneumoniae* resistant or relatively resistant to penicillin has been increasing.<sup>101-107</sup> Recently, 5.3% of *S pneumoniae* isolated from blood at Texas Children's Hospital in Houston were reported as relatively resistant to penicillin.<sup>106,107</sup> Although the optimal therapeutic regimen for serious infections due to relatively resistant strains of *S pneumoniae* has not been established, cefotaxime and ceftriaxone are the most active of the third-generation cephalosporins against these organisms.<sup>109,110</sup> However, there have been cases of meningitis caused by resistant pneumococcal strains that were refractory to therapy with these agents.<sup>111-113</sup> Therefore, children with occult bacteremia caused by *S pneumoniae* who are not afebrile and well appearing when the results of cultures are known need to be admitted for a complete sepsis evaluation and parenteral antimicrobial therapy pending results of susceptibility testing.

**Management Guidelines for the Febrile Children** Figures 1 and 2 are algorithms for the management of previously healthy infants and children 0 to 90 days and 3 to 36 months of age, respectively, with fever without source based on the above discussion. All toxic-appearing infants and children are to be hospitalized for parenteral antibiotic therapy after an expeditious evaluation that includes cultures of blood, urine, and cerebrospinal fluid. All

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febrile infants 28 or less days of age should be hospitalized after a complete evaluation for sepsis and meningitis. Infants not meeting low-risk criteria should receive parenteral antimicrobial therapy. Febrile infants 28 to 90 days of age should be evaluated to determine whether they are in a low-risk group. Those who are considered low-risk can be managed as outpatients as described above if close follow-up is ensured. The remainder should be admitted for a complete sepsis evaluation and parenteral antibiotic therapy.

Older children with fever without source of less than 39 C need no laboratory tests or antibiotics, but parents should be instructed to return if the child's fever persists for more than two or three days or if their condition deteriorates. Older children with fever of 39.0 C or more should have a WBC count. Those whose WBC count is 15,000/mm<sup>3</sup> or more should have a blood culture and be treated with a single injection of a parenteral antibiotic (ceftriaxone 50 mg/kg) pending culture results. Urine cultures should be obtained by catheter or suprapubic aspiration from all boys less than 6 months of age and all girls less than 2 years of age who are treated with antibiotics.

These practice guidelines are meant to assist physicians in managing infants and children with fever without source. They are not intended to be applied rigidly to every child with fever without source. Physicians may choose to individualize therapy based on unique clinical circumstances, or they may adopt a variation of these guidelines based on a different interpretation of the literature concerning the issues we have addressed. These guidelines do not completely eliminate all risk (negative predictive value of WBC count of less than 15,000/mm<sup>3</sup>, 97.6%), nor do they strictly confine antibiotic treatment to children likely to have occult bacteremia (positive predictive value of WBC count of 15,000/mm<sup>3</sup> or more, 13.0%). It was our goal to reduce risk to a minimum at a reasonable cost with guidelines that are practical in physicians' offices and EDs.

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