

Management of Fever Without Source in Infants and Children

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Editor's Note: This article continues a series of special contributions addressing state-of-the-art techniques, topics, or concepts. State-of-the-art articles will be featured in *Annals* on a regular basis in the next several volumes.

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Twenty percent of febrile children have fever without an apparent source of infection after history and physical examination. Of these, a small proportion may have an occult bacterial infection, including bacteremia, urinary tract infection (UTI), occult pneumonia, or, rarely, early bacterial meningitis. Febrile infants and young children have, by tradition, been arbitrarily assigned to different management strategies by age group: neonates (birth to 28 days), young infants (29 to 90 days), and older infants and young children (3 to 36 months). Infants younger than 3 months are often managed by using low-risk criteria, such as the Rochester Criteria or Philadelphia Criteria. The purpose of these criteria is to reduce the number of infants hospitalized unnecessarily and to identify infants who may be managed as outpatients by using clinical and laboratory criteria. In children with fever without source (FWS), occult UTIs occur in 3% to 4% of boys younger than 1 year and 8% to 9% of girls younger than 2 years of age. Most UTIs in boys occur in those who are uncircumcised. Occult pneumococcal bacteremia occurs in approximately 3% of children younger than 3 years with FWS with a temperature of 39.0°C (102.2°F) or greater and in approximately 10% of children with FWS with a temperature of 39.5°C (103.1°F) or greater and a WBC count of 15,000/mm³ or greater. The risk of a child with occult pneumococcal bacteremia later having meningitis is approximately 3%. The new conjugate pneumococcal vaccine (7 serogroups) has an efficacy of 90% for reducing invasive infections of *Streptococcus pneumoniae*. The widespread use of this vaccine will make the use of WBC counts and blood cultures and empiric antibiotic treatment of children with FWS who have received this vaccine obsolete.

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INTRODUCTION

Febrile infants and children frequently present to primary care and emergency physicians. The majority of

these children are younger than 3 years. Most have an apparent source of infection (ie, a viral respiratory infection, acute otitis media, or enteritis).^{1,2} However, 20% of febrile children have fever without source (FWS) of infection after history and physical examination.^{3,4} Occult bacteremia occurs in approximately 3% of children younger than 3 years with FWS with a temperature of 39.0°C (102.2°F) or greater and is more frequent in children with higher fevers and WBC counts of 15,000/mm³ or greater.⁵⁻⁸ Urinary tract infections (UTIs) are almost always occult in children younger than 2 years of age. In 1993, a published practice guideline defined criteria for laboratory testing and empiric antibiotic therapy of infants and young children with FWS.⁹ Several subsequent surveys have demonstrated variable compliance with different aspects of this guideline.¹⁰⁻¹⁵ The guideline is generally followed for infants younger than 3 months but has been questioned as calling for unnecessary testing and empiric antibiotic therapy in children 3 to 36 months old.^{16,17} The introduction of the new conjugate *Streptococcus pneumoniae* vaccine should make this controversy moot within 1 or 2 years. This article reviews the significant scientific evidence on which decisionmaking for the management of infants and young children younger than 36 months with FWS should be based, including those who have received the new conjugate pneumococcal vaccine.

DEFINITION OF FEVER WITHOUT SOURCE

Clinical assessment is crucial in the evaluation of febrile infants and young children.¹⁸⁻²⁰ Evaluation and documentation of vital signs, skin color and exanthems, behavioral state, and state of hydration are essential. Measurement of blood pressure is indicated in this age group only when hypotension is suspected. Pulse oximetry may be obtained as a fifth vital sign and is a more reliable predictor of pulmonary infection than respiratory rate in patients of all ages, especially infants and young children.²¹⁻²³ Temperature should be measured by using a rectal thermometer. Axillary and tympanic membrane temperatures are unreliable in young children.²⁴⁻²⁶ Children who are afebrile but have a history of a documented fever should be considered to be febrile to the degree reported by history.²⁷⁻²⁹ Children should be completely undressed to examine for the presence of petechiae. Approximately 2% to 8% of children with fever and a petechial rash will have a serious bacterial infection (SBI), most often caused by *Neisseria meningitidis*. The absence of petechiae below the nipples makes meningococcemia less likely.^{30,31} Most children with meningococcal disease and petechiae will not be otherwise well-

appearing.³¹ The diagnosis of FWS should be considered if no source of infection is apparent after a thorough examination in a nontoxic infant or child without significant underlying illness. The degree of fever that warrants further investigation is a function of the child's age.

INFANTS YOUNGER THAN 3 MONTHS WITH FEVER WITHOUT SOURCE

Until the early 1980s, there was a tradition at most teaching hospitals that all febrile infants younger than 2 months of age should be admitted for a sepsis workup.³² Not all practitioners, including university housestaff, followed this rule.^{33,34} In 1985, the group at Rochester led by Dagan et al³⁵ questioned the necessity of this approach and developed low-risk criteria (Rochester criteria) for the selection of a group of infants who might be carefully observed as outpatients without antibiotic therapy. Investigators from Johns Hopkins had demonstrated that the hospitalization of infants to rule out sepsis is not without risk.³⁶ Baskin et al³⁷ at the Children's Hospital in Boston evaluated empiric outpatient antibiotic therapy with ceftriaxone after a complete sepsis evaluation, including a lumbar puncture. Baker et al^{38,39} at the Children's Hospital of Philadelphia have published alternative criteria (Philadelphia criteria) and data regarding the outcome of their approach.

The results of all studies that include cohorts of infants younger than 3 months who met some low-risk criteria that always include nontoxic clinical appearance and WBC criteria (usually <15,000 WBCs) are summarized in Table 1.^{35,37-45} Studies with overlapping subjects are excluded.⁴⁶ Not all studies included a microscopic urinalysis or microscopic evaluation of stool for WBCs when diarrhea was present. Examination of stool for WBCs was added by the group at Rochester, who found it to be a predictor of occult *Salmonella* infection, including bacteremia. The studies in Table 1 are subdivided by the inclusion of a lumbar puncture as part of the laboratory evaluation. The earliest studies from Rochester and the studies from the Children's Hospitals of Boston and Philadelphia include a lumbar puncture. In the 5 studies that included a lumbar puncture, there were a total of 1,051 "low-risk" infants, 30 (2.9%) of whom had an SBI. The study of Baskin et al³⁷ used unique low-risk criteria: a WBC count of less than 20,000/mm³, urine multireagent strip testing without microscopic urinalysis, and no microscopic examination of stool of infants with diarrhea. This probably explains the greater risk of SBI, including occult bacteremia, UTI, and bacterial enteritis, in this report. When this study was excluded, there were only 3 (0.5%) SBIs in 548 low-risk

infants whose evaluation included a lumbar puncture. It is unclear from these publications whether a lumbar puncture needs be included in the laboratory evaluation to determine whether a febrile infant is at low risk. Baker et al^{38,39} provide data regarding the incidence of aseptic meningitis in the 2 studies from Children's Hospital of Philadelphia. More than 10% of all infants in these 2 studies were given a diagnosis of aseptic meningitis. It is not possible to determine from review of most of these publications what proportion of these infants would otherwise have been in the low-risk group had a lumbar puncture not been performed, nor is it possible to determine from most of these 6 reports how many infants with meningitis

met all of the other low-risk criteria and had a diagnosis of bacterial meningitis only because a lumbar puncture was done. One of the infants in the 1999 report by Baker et al had pneumococcal meningitis diagnosed by means of lumbar puncture but met all the other low-risk criteria (M.D. Baker, personal communication).

Five publications report the results of low-risk laboratory criteria that do not include a lumbar puncture. There are a total of 872 low-risk infants in these studies, the majority (511) in a single study that included a total 227 low-risk infants less than or equal to 30 days of age.⁴³ Ten (1.1%) of these 872 low-risk infants evaluated without a lumbar puncture had an SBI. None had bacterial meningitis. The

Table 1.
Rates of SBIs in low-risk infants younger than 3 months.

Reference	Year	Study Design	Antibiotic Prescription	Age Group	No. Total	No. Low Risk	SBI	UTI	Occult Bacteremia	Bacterial Enteritis	Bacterial Meningitis	Comments
No lumbar puncture												
Anbar et al ⁴⁰	1986	R, IP, OP	Both	≤91 d	117	69	3	0	2	2	0	Group B streptococcus and <i>Salmonella typhimurium</i> bacteremia
Dagan et al ⁴¹	1988	P, OP	No	<2 mo	237	148	0	0	0	0	0	
Broner et al ⁴²	1990	P, IP	Yes	4–56 d	52	13	1	1	0	0	0	<i>Yersinia enterocolitica</i> + <i>Neisseria meningitidis</i> bacteremia
Jaskiewicz et al ⁴³	1994	P, OP	Both	<60 d	1,057	511	5	3	2	0	0	
Chiu et al ⁴⁴	1997	P, IP	No	4–28 d	250	131	1	1	0	0	0	
Subtotal					1,713	872	10	5	4	2	0	
Occult infection (%)							1.1	0.6	0.5	0.2	0	
Lumbar puncture												
Dagan et al ³⁵	1985	P, IP	Both	4–89 d	233	144	1	0	0	1	0	<i>Salmonella enteritidis</i> (no stool examination) No urinalysis
Crain and Gershel ⁴⁵	1988	P, IP	Yes	3–14 d	46	16	1	1	0	0	0	
Baskin et al ³⁷	1992	P, OP	Yes	28–89 d	503	503	27	9	9	10	0	WBC <20,000/mm ³ , urine dipstick, no stool examination
Baker et al ³⁸	1993	P, IP	No	29–56 d	747	287	1	0	1	0	0	101 Aseptic meningitis, including B/N ratio
Baker et al ³⁹	1999	P, OP	No	29–60 d	422	101	0	0	0	0	0	50 Aseptic meningitis, including B/N ratio
Subtotal					1,951	1,051	30	10	10	11	0	
Occult infection (%)							2.9	1.0	1.0	1.0	0	
Without Baskin et al ³⁷					1,448	548	3	1	1	1	0	
Occult infection (%)							0.5	0.2	0.2	0.2	0	
Grand total (lumbar puncture+no lumbar puncture)					3,664	1,923	40	15	14	13	0	
Occult infection (%)							2.1	0.8	0.7	0.7	0	
Without Baskin et al ³⁷					3,161	1,420	13	6	5	3	0	
Occult infection (%)							0.9	0.4	0.4	0.2	0	

R, Retrospective; P, prospective; IP, inpatient; OP, outpatient; B/N, band/neutrophil ratio.

publication by Jaskiewicz et al⁴³ presents the fully evolved Rochester criteria, which are presented as part of Figure 1.

Not included in Table 1 is a recent report of the Pediatric Research in Office Settings (PROS) Network of the American Academy of Pediatrics.⁴⁷ This is a prospective observational study of a convenience sample of 3,066 febrile infants younger than 3 months with a temperature of 38.0°C (100.4°F) or greater treated over a 3-year period by 577 practitioners. The population was significantly different from that usually seen in emergency departments: 92% were white, and only 30% were seen in an urban practice setting. Specific inclusion and exclusion criteria were not stated in this non-peer-reviewed report. The study included infants who were described as “ill” (27%) and “minimally ill” (73%). Only 74.3% had a CBC count or blood culture, only 58.2% had a blood culture, only 57.8% had a urinalysis or urine culture, and 33.0% had an analysis of cerebrospinal fluid (CSF). Of the infants from birth to 1 month of age, only 47.6% of those described as minimally ill, and 80.8% of those described as ill were hospitalized. SBI was defined as bacteremia or bacterial meningitis. Sixty-three infants had either a positive blood culture result (54), a positive CSF culture result (10), or both, or culture-negative partially treated bacterial meningitis (5). Forty-two percent of the infants with SBI appeared minimally ill. The prevalence of SBI by age was as follows: birth to 1 month, 4.1%; 1 to 2 months, 1.8%; and 2 to 3 months, 0.8%. Of 1,603 infants with urine cultures, 148 (9.2%) had a UTI. The prevalence of UTI was 11.9% in girls, 2.3% in circumcised boys, and 19.5% in uncircumcised boys. Most interesting was the report that “despite lack of adherence to guidelines,” PROS clinicians “treated” 61 of 62 infants with SBI (1 of the 63 was not included) at the initial visit. Outcomes were not reported.

It has been well established that a well-appearing young infant may have an SBI.^{48,49} Therefore, laboratory evaluation is necessary. The use of a lumbar puncture is optional but should be done if empiric antibiotics are to be given. Otherwise, if the child returns and a subsequent lumbar puncture reveals pleocytosis, a negative culture result can be construed to indicate either partially treated bacterial meningitis or aseptic meningitis, and a full course of parenteral antibiotic therapy will be necessary. Given the frequency of aseptic meningitis in this age group, this is more than a theoretic possibility. It is possible that children with bacteremia who have a lumbar puncture are at increased risk of having meningitis.⁵⁰⁻⁵⁶ Therefore, parenteral antibiotics should be considered if a lumbar puncture is done. The development of automated blood culture systems has led to rapid detection of bacterial pathogens and allows for safer outpatient management of

low-risk infants.⁵⁷⁻⁵⁹ Infants with positive culture results can be called back for reevaluation, usually within 24 hours. Time to positivity and initial blood culture Gram stain results are valuable diagnostic tests in distinguishing between pathogens and contaminants.⁶⁰ Blood cultures of true pathogens are more likely to indicate positive results within 24 hours. Infants whose blood culture becomes positive after 24 hours with a Gram stain suggestive of a contaminant and who are afebrile and well-appearing may be treated as outpatients with or without antibiotics in accordance with their initial management strategy.

Treatment of infants younger than 4 weeks of age as outpatients with either strategy should be done only when the parents are reliable and close follow-up is assured. Although this practice is common in pediatrics, as demonstrated by the PROS report, prospective data validating this approach in emergency medicine are limited. It is more difficult to evaluate behavioral state in neonates, invasive infections are often caused by different bacteria (ie, group B streptococci, Enterobacteriaceae, and *Listeria monocytogenes*), and neonates are more likely to have severe life-threatening viral meningoencephalitis with herpes simplex viruses and enteroviruses.⁶¹⁻⁶⁴ In only one of the surveys referenced above were physicians specifically asked whether they would hospitalize low-risk infants younger than 4 weeks; 68% of general emergency physicians and 87% of pediatric emergency physicians reported they would.¹³

A chest radiograph is not included in the Rochester criteria but is part of the Philadelphia criteria. The inclusion of pulse oximetry as a fifth vital sign may serve to provide a diagnosis in most infants with occult bacterial pneumonia.²¹⁻²³ The absence of respiratory signs and symptoms and a normal WBC count make occult bacterial pneumonia highly unlikely.^{65,66}

INFANTS AND CHILDREN 3 TO 36 MONTHS WITH FEVER WITHOUT SOURCE

Occult UTI

All of the large prospective clinical trials of FWS exclude children with UTIs. UTI is among the most common occult bacterial infections in children, especially in young girls, occurring in 2% of febrile children younger than 5 years.⁶⁷⁻⁷⁰ A UTI is present in nearly 5% of febrile infants younger than 12 months, including 6% to 8% of girls and 2% to 3% of boys.^{67,71} The rate is higher in those with FWS and higher temperatures.⁷¹ The prevalence is greater in boys younger than 6 months than in those 6 to 12 months (2.7% versus 1.3%). The prevalence in girls 12 to 24 months is 2.1%.⁶⁷ UTIs are more frequent in white

subjects, especially white female infants with FWS, who have up to a 30% risk of UTI.⁶⁷ Most UTIs in boys occur in those who are uncircumcised.⁶⁷ Among febrile children with UTIs, approximately 60% to 65% will have evidence of pyelonephritis on 99m-Tc dimercaptosuccinic acid renal scanning.⁷²

Hoberman et al,^{71,73,74} from the Children's Hospital of Pittsburgh, question whether a urine culture is necessary for all febrile infants. In a study of 4,253 children younger than 24 months seen in an ED, they evaluated the use of an "enhanced urinalysis" in which the presence of either pyuria, defined as 10 or more WBCs per high-power field in an unspun urine specimen examined in a hemocytometer, or bacteriuria, defined as any bacteria per high-power field on Gram staining, had a sensitivity of 95.8%, a specificity of 92.6%, a positive predictive value of 40.4%, and a negative predictive value of 99.8%.⁷¹ The presence of pyuria and bacteriuria has a much higher positive predictive value of 84.6% but a substantially lower sensitivity of 87.7%. The absence of both pyuria and bacteriuria makes a positive urine culture result unlikely. Only 9 (0.2%) of 3,750 infants without either pyuria or bacteriuria had a positive urine culture result. These investigators argue that children with fever and positive urine culture results without pyuria have fever and asymptomatic bacteriuria. Neither the use of this enhanced urinalysis nor a urine Gram stain is widespread. Most laboratories perform a microscopic urinalysis on centrifuged urine or use multireagent strips, and most studies in this age group define a positive culture result from a urine specimen obtained by catheter as 10,000 colony-forming units/mL or greater. In a recent meta-analysis, Gorelick and Shaw⁷⁵ report that a Gram stain of urine had the best combination of sensitivity (0.93) and false-positive rate (0.04) for detecting UTI in children. They report that the "urine dipstick" performed nearly as well with either a positive leukocyte esterase or nitrite test result, with a sensitivity of 88% and a false-positive rate of 4%. Other studies have demonstrated unacceptable sensitivities for routine examination of centrifuged urine for WBCs, especially in infants younger than 8 weeks.^{70,76,77} Therefore, a urine culture is recommended in high-risk populations (ie, uncircumcised boys <12 months of age, boys <6 months of age, and girls <12 months of age). Either a microscopic urinalysis or urine dipstick may be used to screen for the need for a urine culture in circumcised boys 6 to 12 months old and girls 12 to 24 months old. Specimens should be obtained by means of urethral catheterization because "bagged" urine samples are likely to be contaminated, and the false-positive rates are unacceptably high.⁷⁰

Microscopic urinalysis can be used as the basis for presumptively diagnosing a UTI and initiating antibiotic therapy. All febrile infants younger than 1 month with pyuria should be admitted for parenteral antibiotic therapy. A recent multicenter, randomized, clinical trial of oral versus initial intravenous antibiotic therapy demonstrated no difference in outcomes in children 1 to 24 months old.⁷² Therefore, children older than 1 month with suspected UTIs who appear nontoxic, are not dehydrated, and are able to take oral fluids and medications may be treated as outpatients with oral antibiotics, assuming they have a reliable caretaker and appropriate follow-up with a primary care provider is assured. A single dose of a parenteral or oral antibiotic should be given in the ED or clinic before discharge to ensure adequate blood levels of an antibiotic to which more than 95% of common uropathogens are susceptible. The choice of antibiotic should be guided by local sensitivity testing of common uropathogens (eg, *Escherichia coli*). In most areas, there is now significant resistance to amoxicillin and trimethoprim/sulfamethoxazole. In 1999, at the University of California, Los Angeles Medical Center, the sensitivities of *E coli* isolates from outpatient urine cultures were as follows: ampicillin, 60%; trimethoprim/sulfamethoxazole, 74%; cefazolin, 82%; ceftriaxone, 99%; and gentamicin, 96%. Therefore, an oral third-generation cephalosporin should probably be the drug of choice.

Occult pneumonia

The majority of pneumonias in infants and young children are nonbacterial in origin and caused by such agents as respiratory syncytial virus, parainfluenza and influenza viruses, and *Chlamydia* species.^{78,79} Bacterial infections often occur as a secondary infection after an initial respiratory viral infection. It is difficult to differentiate viral from bacterial pneumonias radiologically. When radiologic features suggest a bacterial infection, the chance of isolating a bacteria as opposed to a virus is 30%.^{80,81} Blood cultures yield positive findings in only 3% to 5% of young children with pneumonia.^{82,83}

Because occult bacterial pneumonia does occur, the need exists for some criteria for obtaining chest radiographs in a subset of children with FWS. None of the large prospective series of the risk of occult bacteremia in children with FWS reported the incidence of occult pneumonia, bacterial or unspecified. Most publications that address this issue include only the subset of children for whom a chest radiograph was ordered.^{9,84-86} These series demonstrate that occult pneumonia is present in only 3% of infants and young children without tachypnea, respiratory distress, rales, or decreased breath sounds. None of

these studies included pulse oximetry. The inclusion of pulse oximetry as a fifth vital sign may be sufficient for diagnosis of most infants with occult pneumonia. Children with higher fever and profound leukocytosis are more likely to have an occult bacterial pneumonia. Recently, Bachur et al⁸³ reported that 26% of children with FWS with a temperature of 39.0°C (102.2°F) or greater and a WBC count 20,000/mm³ or greater had radiographic evidence of pneumonia. Because the presence of lobar consolidation or effusion probably necessitates a longer course of antibiotics than a single dose of intramuscular ceftriaxone, a chest radiograph should be considered in previously healthy infants and young children with FWS with a temperature of 39.5°C (103.1°F) or greater who have not received the conjugate *S pneumoniae* vaccine and have both a negative urinalysis result and a WBC count of 20,000/mm³ or greater. The conjugate pneumococcal vaccine reduces clinical pneumonia by 10%, radiographic pneumonia by 32%, and pneumonia with definite consolidation by 73% and probably eliminates the need for chest radiography in febrile children with no clinical signs of pneumonia.^{87,88}

Occult bacteremia

Only a small proportion of total pediatric ED visits are for children 3 to 36 months old with temperatures of 39.0°C (102.2°F) or greater (8.0%), and only 1.6% are nontoxic-appearing previously healthy children with FWS.³ The results of 3 large, prospective, randomized controlled trials (RCTs) of the effect of antibiotics on the outcomes of occult bacteremia in 8,382 children 3 to 36 months with FWS with temperatures of 39.0°C (102.2°F)

or greater are summarized in Table 2.⁵⁻⁷ The RCT of Carroll et al⁵² is not included because of its small size and the different entry criteria. The report of Jaffe et al⁵ also includes 228 children who were not randomly assigned to treatment. In addition to these 3 studies, Lee and Harper³ report on the prevalence of occult bacteremia in a cohort of 2,712 children with “fever,” 78 of whom (2.9%) had occult pneumococcal bacteremia. The conjugate *Haemophilus influenzae* vaccine has reduced the incidence of invasive *H influenzae* type b disease by 90% or more in industrialized countries.^{89,90} Thus, cases of *H influenzae* bacteremia have been excluded from Table 2. The majority of remaining cases of occult bacteremia are caused by *S pneumoniae*, with occasional cases caused by *Salmonella* species and *N meningitidis*. Overall, the risk of occult bacteremia (excluding *H influenzae*) in all nontoxic-appearing infants and young children with FWS with temperatures of 39.0°C (102.2°F) or greater in these studies ranges from 2.6% to 6.1% (mean 2.8%). The risk is substantially higher (10.4%) in the RCT of Bass et al,⁶ which included only children with temperatures of 40.0°C (104.0°F) or greater or 39.5°C (103.1°F) or greater with WBC counts of 15,000/mm³ or greater. Other risk factors for invasive pneumococcal disease include out-of-home child care, no breast-feeding, frequent otitis media, and underlying medical conditions, especially sickle cell disease and AIDS.⁹¹⁻⁹³

In the majority of children, occult pneumococcal bacteremia resolves without therapy. However, in a retrospective review from the Children’s Hospital in Boston, children with occult pneumococcal bacteremia who did not receive antibiotics were more likely to have persis-

Table 2.

Rates of occult bacteremia in infants and children 3 to 36 months enrolled in large RCTs of outpatient antibiotic therapy of FWS.

Reference	Year	Study Design	Age (mo)	Inclusion Diagnosis	Temperature	WBC Count	Total No.	Total Occult Bacteremia	Total <i>H influenzae</i> Bacteremia	Total Non- <i>H influenzae</i> Bacteremia	% Non- <i>H influenzae</i> Bacteremia
Jaffe et al ⁵	1987	RCT	3-36	FWS	≥39.0°C (102.2°F)	All	955	27	2	25	2.6
		NR	3-36	FWS	≥39.0°C (102.2°F)	All	228	15	1	14	6.1
Bass et al ⁶	1993	RCT	3-36	FWS, URI	≥40.0°C (104.0°F), ≥39.5°C (103.1°F)	All and ≥15,000/mm ³	519	60	6	54	10.4
Fleisher et al ⁷	1994	RCT	3-36	FWS, OM	≥39.0°C (102.2°F)	All	6,680	192	9	183	2.7
Total				Total: All subjects			8,382	294	18	276	3.3
				Total: No WBC criteria			7,863	234	12	222	2.8

NR, Not randomized; URI, upper respiratory tract infection; OM, otitis media.

tent fever (76.1% versus 23.9%) or persistent bacteremia (17.0% versus 1.6%) and to be admitted to the hospital (50% versus 11.7%) than those who received oral or parenteral antibiotics.³ Other complications included cellulitis, pneumonia, and meningitis. The most serious complication is meningitis. Pneumococcal meningitis has a case fatality rate of 7.7%, and of surviving children, 25% to 30% have neurologic sequelae, including 19% with mental retardation, 15% with seizure disorder, and 11% with paralysis; 17% of survivors have permanent hearing loss (multiple outcomes may occur in patients).^{94,95}

Unfortunately, only the smallest of the RCTs of the outpatient management of FWS in Table 2 included a placebo group. This group had only 7 children with *S pneumoniae* bacteremia. Another 9 children who were not randomly assigned were also not treated. This sample size is too small to determine the risk of bacterial meningitis in

children with FWS and *S pneumoniae* bacteremia. Therefore, other studies should be examined to estimate the risk of meningitis in children with FWS and occult pneumococcal bacteremia who do not receive antibiotics. These studies are less reliable because they were not designed to determine the risk of occult bacteremia in a similarly defined population of children, and most are retrospective in nature or include only a small number of patients. Most of these studies have been previously reviewed,⁹⁶ and this has been repeated with more diligence by Rothrock et al.^{97,98} They excluded children who had lumbar punctures, although a negative lumbar puncture result does not exclude the diagnosis of FWS. They concluded that the risk of meningitis in untreated children is 2.7% and that antibiotics reduce the risk of bacterial meningitis in 1,010 infants and children with FWS, otitis media, or upper respiratory tract infection, and

Table 3. Outcomes of occult bacteremia in infants and children with FWS, otitis media, or upper respiratory tract infection.

Author	Year	Design	No Antibiotic		Oral Antibiotics		Intramuscular Antibiotics		Total	
			Meningitis	Bacteremia	Meningitis	Bacteremia	Meningitis	Bacteremia	Meningitis	Bacteremia
<i>S pneumoniae</i>										
Baron et al ⁹⁹	1989	R	0	7	0	11			0	18
Bass et al ⁶	1993	RCT			0	18	0	33	0	51
Bratton et al ¹⁰⁰	1977	R	1	48					1	48
Carroll et al ⁵²	1983	RCT	2	5	0	5	0	4	2	14
Dershowitz et al ¹⁰¹	1983	P	0	2	0	18			0	20
Fleisher et al ⁷	1994	RCT			1*	80	0	84	1	164
Harper et al ¹⁰²	1995	R	1	48	2	205	1*	129	4	382
Jaffe et al ⁵	1987	RCT	0	16	0	20			0	36
McCarthy et al ¹⁰³	1976	R	1	12	0	14	0	1	1	27
Rosenberg and Cohen ⁵⁴	1982	R	3	30	1	8			4	38
Woods et al ⁵⁵	1990	R	2	84	0	117			2	201
Yamamoto et al ¹⁰⁴	1987	P	0	1	0	2	0	8	0	11
Total			10	253	4	498	1	259	15	1010
Mean (95% CI)				4.0% (1.9%–7.1%)		0.8% (0.2%–2.0%)		0.4% (0.1%–2.1%)		
<i>N meningitidis</i>										
Bass et al ⁶	1993	RCT			0	1	0	1	0	2
Dashefsky et al ¹⁰⁵	1983	R	2†	4	2	6			4	10
Fleisher et al ⁷	1994	RCT					0	2	0	2
Hamrick and Murphy ⁵³	1978	R	1	1					1	1
Jaskiewicz et al ⁴³	1994	P					0	1	0	1
Sullivan and LaScolea ¹⁰⁶	1987	R	3	7					3	7
Total			6	12	2	7	0	4	8	23
Mean (95% CI)				50% (21.1%–78.9%)		29% (3.6%–71.0%)		0% (0.0%–60.2%)		

R, Retrospective; P, prospective.

*Culture result negative.

†Sepsis, died.

occult bacteremia caused by *S pneumoniae* are presented in Table 3.^{5-7,43,52,53,55,99-106} Duplicate studies and case reports are excluded from this table. Unlike the reports by Rothrock et al, I did not exclude children who had a negative lumbar puncture result as part of their initial evaluation. The risk of bacterial meningitis in these combined studies was 4.0% in the no antibiotic group, 0.8% in the oral antibiotic group, and 0.4% in the parenteral antibiotic group. The 95% confidence intervals (CIs) of the different treatment groups all overlap; however, for *S pneumoniae*, when the oral and parenteral antibiotic groups are combined, the 95% CI is 0.2% to 1.5%, which does not overlap the 95% CI of the no-therapy group. The only child with meningitis in the parenteral antibiotic group had a negative CSF culture result. Because of the bias inherent in the retrospective studies included in this table and the inclusion of children who had a lumbar puncture as part of their initial evaluation, one can safely consider 4% to be the upper limit of the risk of pneumococcal meningitis in children with FWS and occult bacteremia treated as outpatients without antibiotics.

In the 2 largest multicenter studies of FWS in children with temperatures of 39.0°C (102.2°F) or greater, occult meningococcal bacteremia was observed in only 4 (0.06%) of 7,199 children.^{5,6} Although occult meningococcal bacteremia is infrequent, the risk of serious sequelae is greater and includes meningococemia, purpura fulminans, and meningococcal meningitis. I identified only 23 cases of occult meningococcal bacteremia in children with FWS managed as outpatients in this age group for which the effect of antibiotic therapy on outcome was known. Six (50%) of 12 children who did not receive antibiotics later had meningitis. Kuppermann et al¹⁰⁷ describe an additional 44 children with unsuspected meningococcal disease treated as outpatients, 2 of whom died. However, details regarding outpatient antibiotic therapy were not included in this report. The effect of antibiotic therapy on the outcome of occult meningococemia is also presented in Table 3.

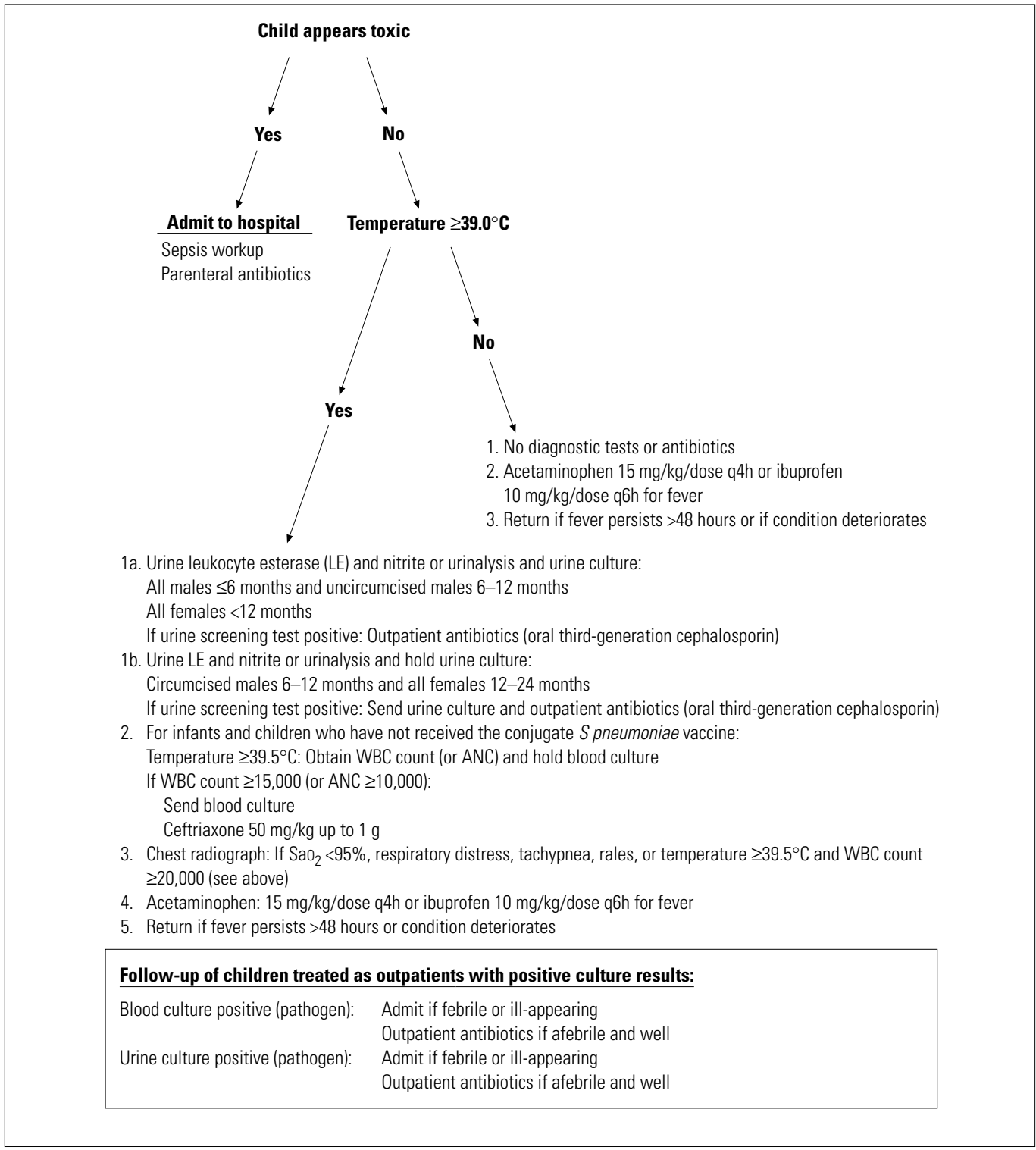
In the absence of widespread vaccination, *S pneumoniae* is responsible for an estimated 7 million cases of otitis media, 500,000 cases of pneumonia, 50,000 cases of bacteremia, and 3,000 cases of meningitis each year in the United States.¹⁰⁸ The results from a phase III US trial in the Northern California Kaiser Permanente Group of a conjugate pneumococcal vaccine are similar to those for the conjugate *H influenzae* type B vaccine.⁸⁷ In this trial, of 37,868 infants randomly assigned to receive conjugate pneumococcal vaccine or the control vaccine (conjugate meningococcus C vaccine), vaccine efficacy for vaccine-associated strains was 97.4% in those fully vaccinated

and 89.1% overall. There were 6 cases of invasive disease in 18,927 conjugate pneumococcal vaccine recipients and 55 in 18,941 control vaccine recipients (intention to treat, including all serotypes).

There are 90 recognized serotypes of *S pneumoniae*; many of these serotypes are capable of causing invasive disease. The conjugate pneumococcal vaccine (Prevnar, Wyeth Laboratories) was licensed in the United States in February 2000. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends primary immunization at 2, 4, 6, and 12 to 15 months.¹⁰⁹ Catch-up immunization schedules have been developed for children up to 5 years. Children older than 24 months with underlying illness (eg, sickle cell disease, HIV infection, or asplenia) will be given higher priority. It is possible that reducing nasopharyngeal carriage of the vaccine serotypes may leave an ecologic niche that will be filled by invasive serotypes not included in the vaccine.¹¹⁰ There is evidence of serotype replacement, as measured by nasopharyngeal carriage of nonvaccine serotypes in 3 pneumococcal conjugate clinical trials.¹¹¹⁻¹¹³ However, there is not yet evidence of increasing rates of invasive disease caused by nonvaccine strains in vaccinated children. The vaccine used in the above-referenced trial incorporates only 7 serotypes. Conjugate vaccines with serotypes 9 and 11 are in clinical trials. Until the vaccine is in widespread use, unvaccinated children remain at risk for invasive disease caused by *S pneumoniae*. The following discussion is directed toward this diminishing population of children.

In the pre-conjugate *S pneumoniae* vaccine era, age, temperature, and WBC count were used to identify infants and children at greater risk of occult bacteremia as candidates for empiric antibiotic therapy. Children younger than 24 to 36 months are at greatest risk. In the report by Jaffe et al,⁵ the risk of occult bacteremia was 2.5% in the 3- to 24-month age group and 4.0% in the 25- to 36-month age group. In the RCT of Fleisher et al,⁷ the prevalence of occult bacteremia in children with temperatures of 39.5°C (103.1°F) or greater with a WBC count of less than 15,000/mm³ versus 15,000/mm³ or greater was 1.5% versus 7.5% (N. Kuppermann, personal communication). In the RCT of Bass et al,⁶ the prevalence of occult bacteremia in children with temperatures of 39.5°C (103.1°F) or greater and WBC counts of 15,000/mm³ or greater was 16.7%. When the RCT results of Fleisher et al and Bass et al are combined, the prevalence of occult pneumococcal bacteremia in children with FWS with temperatures of 39.5°C (103.1°F) or greater is 1% in those with a WBC count of less than 15,000/mm³ and 10% in those with a WBC count of 15,000/mm³ or

Figure 2.
Algorithm for the management of a previously healthy child (3 to 36 months) with FWS.



Permission to reprint this algorithm granted with acknowledgment.

greater. If it is assumed that without therapy 3% of children with occult pneumococcal bacteremia will develop meningitis, then the risk of meningitis in untreated children in the group at higher risk is approximately 0.3% (1/333). The risk of pneumococcal meningitis in the total population of all children with FWS with temperatures of 39.0°C (102.2°F) or greater (no WBC criteria) in this age group who are not treated with antibiotics is much smaller (3% of 2.8% = 0.1%).

Those unwilling to take this risk in children who have not received the conjugate *S pneumoniae* vaccine should use a laboratory screening strategy to determine which children should receive antibiotic therapy. In view of the low risk of occult bacteremia in children with temperatures of less than 39.5°C (103.1°F) and in children with temperatures of 39.5°C (103.1°F) or greater and a WBC count of less than 15,000/mm³, I recommend a modification of the practice guideline published in 1993: raising the temperature threshold for obtaining a screening WBC count to 39.5°C (103.1°F) or greater (Figure 2). In a recent review, Kuppermann¹¹⁴ presents an acceptable alternative management strategy that uses a different combination of age, temperature, and absolute neutrophil count to determine which children should receive empiric antibiotic therapy. There are those who believe that the overall risk in unselected children with FWS who have not received the conjugate *S pneumoniae* vaccine, approximately 1 in 1,000, does not warrant testing and selective treatment and who advocate a no test—no treatment strategy with careful watchful waiting.^{16,17,115}

Although the randomized trials comparing oral therapy with ceftriaxone demonstrated only slightly fewer SBIs in the ceftriaxone group, ceftriaxone has the advantage of ease of use, assurance that the child has received antibiotic therapy, and less resistance among invasive strains of *S pneumoniae*.¹¹⁶⁻¹¹⁹ There have been cases of meningitis caused by resistant pneumococcal strains that were refractory to therapy with ceftriaxone.^{120,121} Therefore, children who are febrile, ill-appearing, or both when a blood culture result is presumptively positive for a pathogen, should be admitted for a complete sepsis evaluation and parenteral antimicrobial therapy pending results of bacterial identification and susceptibility testing.

Children who have received the conjugate *S pneumoniae* vaccine can be assumed to be at low risk of occult bacteremia because the vaccine is 90% effective in preventing invasive disease. However, because no vaccine is 100% effective and because the licensed vaccine contains only 7 serotypes, even vaccinated children are at some risk of invasive disease caused by *S pneumoniae*, as well as that caused by *N meningitidis* and *Salmonella* species.

Assuming vaccine efficacy remains at 90%, the 1993 practice guideline for empiric antibiotic therapy of occult bacteremia in children 3 to 36 months old will be obsolete.⁹ The overall prevalence of occult pneumococcal bacteremia should decrease by 90%, making screening with WBC count or absolute neutrophil count impractical.

The revised management strategies presented herein are meant to assist clinicians in deciding how to evaluate and treat infants and children with FWS. They are not intended to be rigidly applied to every child with FWS. Physicians may choose to individualize therapy on the basis of unique clinical circumstances or may adopt a variation of these guidelines on the basis of their own interpretation of the evidence in the medical literature. It is impossible to eliminate all risk in life and in medical practice. These management strategies are primarily meant to identify children at greater risk of occult bacterial infections and guide the judicious use of antibiotic therapy to prevent both minor and more serious sequelae.

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