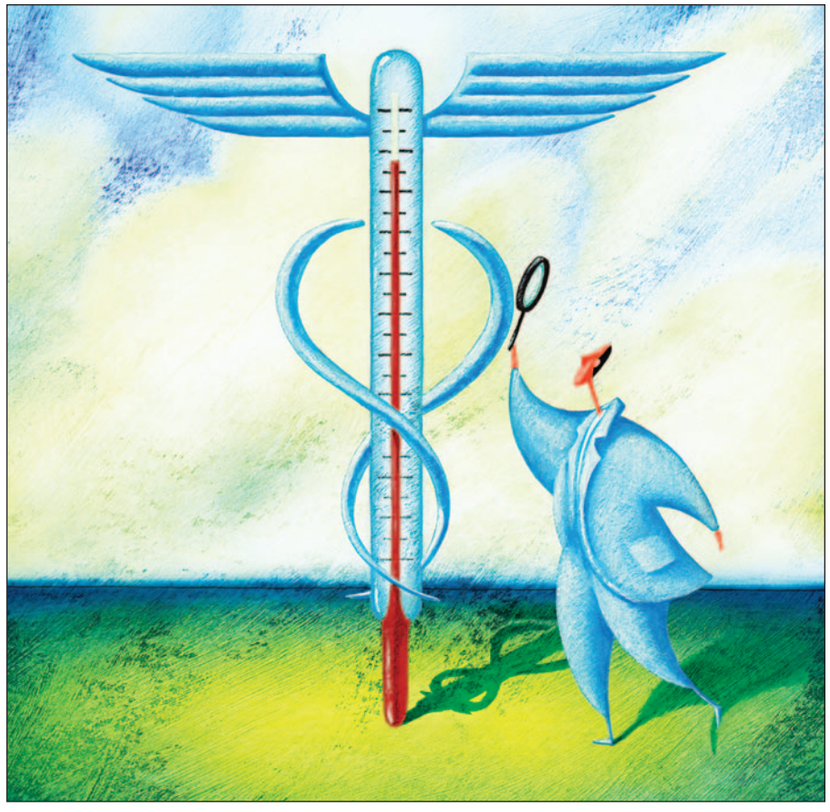
CME

Management of Infants and Young Children with Fever without Source



CME EDUCATIONAL OBJECTIVES

1. Review the current evidence upon which rational decision making for the management of infants and children with fever without source should be based.
2. Discuss an evidence-based framework for the evaluation of infants and children with fever without source.
3. Determine the most logical management scheme for infants and children with fever without source based upon their age and immunization status.

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Febrile infants and children frequently present to pediatricians and emergency room physicians. The majority of these children are less than 3 years of age. Fever is defined as a rectal temperature 38.0°C. An infant or child with a recent history of a documented fever who is afebrile in the office or emergency department should be considered a febrile child. Temperatures in infants and young children should be measured rectally. Axillary and tympanic membrane temperatures are unreliable and have a sensitivity of approximately 50% to 65%.[1,2] Although some infants with serious bacterial infections may be afebrile, most of these will appear seriously ill.

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DEFINITION OF FEVER WITHOUT SOURCE AND SERIOUS BACTERIAL INFECTIONS

Most infants and young children with fever have clinical evidence of an apparent source of infection (ie, viral respiratory infection, acute otitis media, enteritis manifested as vomiting and diarrhea, or a viral exanthema). However, approximately 20% have fever without an apparent source after a complete history and physical examination. A small portion of these infants and young children have an occult bacterial infection, including occult urinary tract infection (UTI), bacteremia, pneumonia, or even early bacterial meningitis. These are all defined as serious bacterial infections (SBIs). Occult UTIs are the most frequent SBI and are relatively common in the first 2 years of life.

AGE GROUPS AND ETIOLOGIC AGENTS

Febrile infants and young children by tradition have been assigned arbitrarily to different management strategies by age group: neonates (0 to 28 days), young infants (29 to 90 days), and older infants and young children (3 to 36 months).[3,4] This is in part explained by the difference in the bacteria commonly causing infection in neonates (ie, group B streptococcus, *Enterobacteriaceae*, and *Listeria monocytogenes*) and the difficulty in evaluating the behavior of neonates and young infants.[5,6]

CLINICAL ASSESSMENT

Clinical assessment is crucial in the appraisal of febrile infants and children. Evaluation of vital signs, behavioral state, and state of hydration are essential. The child should be completely undressed to permit full evaluation of skin color and turgor, and the presence of petechiae or other exanthems. Approximately 2% to 8% of children with fever and a petechial rash will have an SBI, most often caused by *Neisseria meningitidis*. The absence of petechiae below the nipples makes meningococcemia less likely.[8,9] Most children with meningococcal disease and petechiae are ill-appearing.[9] Any child old enough should be encouraged to walk from the examiner to a parent for evaluation of gait as an indicator of occult bone and joint infection and neurological impairment. Pulse oximetry may be useful as a fifth vital sign and is routine in most emergency departments. It is a more reliable predictor of pulmonary pathology than is respiratory rate.[7] Tachycardia > 180 suggests a more serious illness, either dehydration, acidosis, or a sepsis syndrome (eg, meningococcemia), and warrants careful evaluation. Infants and children whose skin is pale or ashen, who manifest lethargy or non-consolable irritability are considered "toxic appearing" and are to be hospitalized for evaluation for possible sepsis or meningitis and parenteral antibiotic therapy.

Vaccine efficacy for PCV7-associated serotypes is 97.4% in those fully vaccinated and 89.1% overall.

Neonates < 28 Days with FWS

Because of the difficulty in evaluation of the behavioral state, decreased immunologic function, and the higher frequency of SBIs in febrile infants < 2 months, it has long been the practice at most teaching hospitals that all such infants be admitted for a "sepsis evaluation."[10,11]. In 1985, the group at Rochester questioned the necessity of this approach and developed "low-risk criteria," which did not include lumbar puncture findings for the selection of a subgroup of infants < 90 days who might be carefully observed as outpatients without antibiotic therapy.[12] A subsequent study of these criteria confirmed their ability to identify most infants who could be carefully observed without antibiotics.[13] In that report, 5 of 511 infants < 60 days who met the low risk criteria had an SBI (UTI 3, bacteremia 2). Two of the subgroup of 227 infants 0 to 30 days had an SBI (UTI 1, bacteremia 1). A 29-day-old infant with *Neisseria meningitidis* bacteremia received ceftriaxone, was treated as an outpatient, and did well. A 34-day-old infant with *Yersinia enterocolitica* bacteremia was not treated initially and did well. No infant had bacterial meningitis. Subsequent studies have further demonstrated that these criteria occasionally not only fail to diagnose neonates with occult UTIs and bacteremia but also some with occult meningitis.[14-17]

Although one can presume that if discharged without antibiotic therapy, these infants would subsequently develop signs and symptoms of more serious illness and would then be diagnosed and treated, the delay in diagnosis might lead to progression of disease and higher morbidity and mortality.

Because of these risks, community practitioners are less inclined to utilize laboratory testing, especially lumbar puncture, and to hospitalize febrile neonates for parenteral antibiotic therapy. Pantell et al in 2004 described the management practices for fever in early infancy among 573 pediatricians in 219 practices.[18] The study population consisted of a convenience sample of 3,066 young infants with fever, of whom 384 were < 25 days and appeared well or "moderately ill." Thirteen of this group (3.4%) had bacteremia or bacterial meningitis. However, only 45% of pediatricians performed a complete sepsis evaluation and hospitalized infants in this age group for antibiotic therapy. The authors concluded that "relying on current clinical guidelines would not have improved care but would have resulted in more hospitalizations and laboratory testing."

The conclusions of this study were, however, significantly limited by uncertainty over enrollment and exclusion criteria. In addition, assuming that the proportion of febrile neonates with FWS was similar to the 21.4% reported for the total study population, only 82 of the 384 well-

appearing infants < 25 days had FWS, a number too few to support the position that no laboratory testing is necessary in febrile neonates. In fact, in a related publication, the authors reported that 10% of febrile infants < 30 days from whom a urine was collected (5% overall) had an occult UTI.[19] This would seem to argue for at least performing urine testing on all such infants.

Overall, febrile neonates who are not ill-appearing have a 7% risk of SBI.[13-15,17] Therefore, most training programs in emergency medicine and pediatrics advocate a "full sepsis workup" for febrile neonates, including a complete blood count, catheter-obtained urinalysis and urine culture, blood culture(s), examination and culture of cerebrospinal fluid, and hospitalization for parenteral antibiotic therapy. Neonates who are well-appearing, able to take and retain feedings, and who have negative initial laboratory studies including examination of CSF, may be discharged without antibiotics once initial results of all bacterial cultures are negative.

Febrile neonates diagnosed with a UTI should be treated with parenteral antibiotics until they are afebrile, well-appearing, and eating normally, after which a 14-day course of antibiotic therapy may be completed as an outpatient. Follow-up evaluation of the urinary tract to exclude underlying anatomic abnormalities is generally advised.[20]

Most febrile neonates with CSF pleocytosis prove to have viral meningitis.[21,22] Bacterial meningitis can usually be diagnosed by characteristic CSF findings (positive Gram stain, > 500 WBCs, > 70% PMNs, CSF glucose < 30). The administration of parenteral antibiotics should not be delayed for a spinal tap in ill-appearing febrile neonates. The initial clinical and cerebrospinal fluid findings in infants with herpes encephalitis may be no different than in infants with other viral central nervous system infections. Acyclovir reduces morbidity and mortality in infants with herpes simplex encephalitis and should be considered in febrile neonates who have cerebrospinal fluid pleocytosis suggestive of viral meningoencephalitis. Treatment may be discontinued if a herpes simplex polymerase chain reaction test on the cerebrospinal fluid is negative.

Infants 29 to 90 Days with FWS who have not Received HIB and PCV7

There are four somewhat similar management strategies for infants with fever without a source < 90 days of age: the Rochester criteria discussed above (< 60 days),[13] the Boston criteria (28 to 89 days),[23] the Philadelphia criteria (29 to 60 days),[21,24] and the Pittsburgh criteria.[25] Each has its own definitions of low-risk infants based on a combination of factors including history, physical examination, and laboratory parameters. The intended goal of all of these strategies is to identify febrile young infants who may be managed as outpatients with or without antibiotics.

Lumbar Puncture

The necessity for doing a lumbar puncture as part of the evaluation for SBI is controversial. The Philadelphia and Pittsburgh criteria use the most conservative approach and include a lumbar puncture. Infants are to be considered at low risk for SBI if they appear well, have no evidence of bacterial infection on physical examination, and all laboratory values are within the defined normal ranges. Three studies using these criteria evaluated a total of 1,573 febrile infants. Of these, 515 met the low risk criteria; one of these had a SBI.[4,21,24,25]

It is not possible to determine from review of these publications the significance of the results of the lumbar puncture in assigning these infants to a low-risk group. Only one infant in the 1999 report by Baker et al[21] met all other low-risk criteria but had meningitis diagnosed because a lumbar puncture was performed per protocol. In this study, more than 10% of all infants had a diagnosis of aseptic meningitis. It is unknown how many of these infants with aseptic meningitis met all other low-risk criteria. Thus, although performing a lumbar puncture reduces the likelihood of missing occult bacterial meningitis, it increases the likelihood of what may be an unnecessary hospitalization for well-appearing febrile young infants with viral meningitis.

Two other criteria for risk stratifying this age group, the Rochester and Boston criteria, do not employ lumbar puncture to identify young infants at low risk for SBI. In five studies of the risk of SBIs in infants < 3 months of age in which examination of CSF was not performed, 872 of 1,713 febrile young infants with FWS were classified as low risk. Ten had an SBI; none had occult meningitis.[4]

Chest Radiography

A chest x-ray is not included in the Rochester or Pittsburgh criteria but is part of the Philadelphia and Boston criteria. Pulse oximetry was not included as a criterion in any of the management strategies but should serve to diagnose most infants with occult respiratory infection. The absence of respiratory signs and symptoms and a normal WBC count make occult pneumonia highly unlikely.[26-28] In a meta-analysis of a combined group of 361 febrile infants without clinical evidence of pulmonary disease on history or physical examination, all had normal chest radiographs as determined by two or more radiologists.[29] A chest radiograph is only necessary in febrile infants < 3 months who manifest one or more of the following clinical findings: tachypnea > 50 breaths/min, rales, rhonchi, retractions, wheezing, coryza, grunting, stridor, nasal flaring, or cough.

Risk Stratification

Thus, for infants in this age group with fever without source who are to be managed as outpatients, there are at least three strategies: 1) a very low risk strategy, which includes a "full sepsis workup" including lumbar puncture with or without outpatient parenteral antibiotics, 2) a low-risk strategy using a "partial sep-

sis workup" without a lumbar puncture or antibiotics, and 3) a risky strategy in which no tests are done. This last strategy will fail to identify all the occult SBIs that are present in approximately 7% of well appearing febrile infants.[13-25] Most of these infections are UTIs, which could be diagnosed by obtaining a urinalysis and urine culture. The low-risk strategy also identifies all cases of occult bacteremia but fails to identify occult bacterial meningitis. I estimate this risk to be on the order of 1 in 500 to 1 in 1,000.[4]

Physician and Parent Preference

The use of the low-risk criteria for antibiotic treatment or hospitalization assures that almost all young infants with SBIs are treated in a timely manner. However, it results in diagnostic testing for all young infants with FWS and the treatment of those with abnormal test results, most of whom do not have an SBI. We have previously studied the incorporation of patient preferences into practice guidelines for management of infants and children with FWS and found that parents could correctly identify the management strategy with the higher probability of an adverse outcome.[30] The majority of parents chose the option with less testing and treatment despite the greater risk of an adverse outcome. Parents' reasons for this choice were the following: fewer painful tests and procedures, less time waiting, smaller chance of unnecessary antibiotics, and ability to return if their child's condition deteriorated. Apparently many community physicians are also willing to take some risk to avoid diagnostic testing. In the aforementioned study by Pantell et al, only 42% of community pediatricians obtained a white blood cell count or urinalysis in "minimally ill" infants 31 to 90 days.[18] Only 36% did a complete sepsis evaluation with hospitalization and antibiotics for moderately ill appearing infants of this age. When urine testing was done in this age group, the rate of UTI was approximately 8%.[19]

INFANTS AND CHILDREN > 90 DAYS WITH FWS WHO HAVE RECEIVED HIB AND PCV7 VACCINE

Occult Bacteremia

Prior to the widespread use of the conjugate pneumococcal vaccine, the risk of occult pneumococcal bacteremia was estimated to be 3% in children 3 to 36 months with FWS $\geqslant$ 39.0ºC.[3] In 1993, an expert panel advocated the use of a white-blood cell count for risk stratification and a blood culture and empiric antibiotic therapy with ceftriaxone for those with a WBC > 15,000/mm^3.[3] Although this approach may still be appropriate in unvaccinated children, the reduced risk of occult bacteremia in infants who have received the conjugate Hib and PCV7 vaccines makes screening with WBC count or other nonspecific tests impractical.

The Hib and PCV7 vaccines are usually given at 2, 4, and 6 months. Once an infant has had 2 doses of either, the risk of occult bacteremia and meningitis due to these organisms is dramatically reduced. Hib vaccine has reduced the incidence of invasive *H. influenzae* type b disease by more than 95% in the United States.[31] Vaccine efficacy for PCV7 associated serotypes is 97.4% in those fully vaccinated and 89.1% overall.[32] Even a single dose affords considerable protection. In a study of the immunogenicity of a nonavalent pneumococcal conjugate vaccine (PCV9) in Soweto, South Africa, after one dose, > 90% of infants had protective antibody to seven vaccine serotypes and 75% to the remaining two serotypes. After two doses, > 95% of infants had protective antibody for all nine vaccine serotypes.[33] In the United Kingdom, it has been demonstrated that a 2-dose infant priming schedule of PCV9 is comparable with the 3-dose schedule and may thus be equally protective.[34] In that study, toddlers had protective levels of serotype specific pneumococcal antibodies for eight of nine vaccine serotypes after their first dose. Although PCV7 has markedly reduced invasive pneumococcal disease, there has been the emergence of pathogenic pneumococcal serotypes not included in the vaccine, particularly 19A.[35] The expected use of newer multivalent vaccines should provide even better protection for infants at risk.[36,37] Currently, clinicians can presume that infants who have received two doses of the Hib and PCV7 vaccines are at very low risk of occult bacteremia.

Because no vaccine is 100% effective and because PCV7 contains only seven serotypes, even vaccinated infants and young children are at some risk of invasive disease caused by *S. pneumoniae*, as well as *N. meningitidis* and *Salmonella* species,[38] particularly those who are ill-appearing and who have a fever $\geqslant$ 40.0° C Therefore, WBC count, chest x-ray, blood cultures and empiric antibiotic therapy may be appropriate when initial urine test results are non-diagnostic in this population. Occult bacteremia due to *Salmonella* occurs in approximately 0.1% to 0.2% of U.S. pediatric outpatients 3 to 36 months with temperatures > 39.0° C. Most children with "occult" *Salmonella* bacteremia have diarrhea.[39] Approximately 0.02% of children 3 to 36 months with temperatures of > 39.0° C have occult bacteremia due to *N. meningitidis.*[40] Although SBI due to *N. meningitidis* is uncommon, 25% to 50% of children with this illness are discharged to home after outpatient evaluation.[41,42] As opposed to occult pneumococcal bacteremia, WBC counts are frequently normal in children with occult meningococcal and *Salmonella* bacteremia.[43]

Occult Urinary Tract Infection

A UTI is present in nearly 5% of febrile infants younger than 12 months, including 6.5% of girls and 3.3% of boys.[44-46] The rate is higher in those younger than 12 months with FWS and in infants with higher fevers. The prevalence of UTIs in the second year of life is 8.1% in girls and 1.9% in boys.[20,44,47] Most UTIs in older boys occur in those that are uncircumcised. In boys less than 1 year, the rate of UTIs is reduced by circumcision from

8.0% to 1.2%.[47] Among febrile children with a UTI, approximately 60% will have evidence of pyelonephritis on 99m-Tc dimercaptosuccinic acid (DMSA) renal scan.[48] For girls 2 to 24 months, the presence of two or more of the following risk factors has a sensitivity of 95% and specificity of 31% for detecting UTI: FWS, fever > 39° C, fever for > 2 days, white race, and age younger than 1 year.[49] For male infants the following risk factors are associated with UTI: FWS, age younger than 6 months, and being uncircumcised.

UTI should be considered in any child with prolonged, unexplained fever or with a known urinary tract anatomic abnormality. Therefore, urinalysis and urine culture should be obtained on all boys < 6 months of age, and all uncircumcised males and all females younger than 24 months with FWS.[20] These specimens should be obtained by urethral catheterization because "bagged" urines are likely to be contaminated and the false positive rates are unacceptably high.[20] The degree of fever that necessitates this diagnostic testing is variable. I generally use a temperature of > 39.0° C as a criteria for urine testing in infants younger than 3 months.

Pyuria may not be present on the initial urinalysis in 20% of febrile infants with pyelonephritis documented by urine culture.[50,51] The absence of both pyuria and bacteruria on a catheter-obtained urine makes a positive urine culture unlikely. A UTI is best defined by a urine WBC count of > 10/hpf and a colony count of a single organism > 50,000/mL. Observation of a single organism per high-power field on a Gram-stained unspun urine has been shown to reflect bacteriuria with a colony count of ⩾ 100,000 organisms/mL. Most facilities perform a microscopic urinalysis on centrifuged urine or use multi-reagent strips. Using multi-reagent strips, the presence of either nitrites or leukocyte esterase has a true-positive rate of 88% and false positive rate of 7% for UTI. If the results of both tests are positive, the specificity is 96%.[52] Although microscopic urinalysis or leukocyte esterase and nitrite tests cannot be used without urine culture to diagnose a UTI in a child with FWS, they can be used as the basis for initiating antibiotic therapy.

SIDEBAR 1.

Guidelines for Diagnostic Testing of Infants and Children with Fever without Source (FWS)

Neonates <28 days with FWS > 38.0°C
Complete sepsis workup
Complete blood count, differential, and blood culture
Urinalysis and urine culture
Cerebrospinal fluid studies: Tube 1: Culture and sensitivity Tube 2: Protein and sugar Tube 3: Cell count and differential Tube 4: HSV PCR if CSF compatible with viral meningoencephalitis
± Chest x-ray
Infants 28-90 Days with FWS > 38.0°C
Low-risk clinical criteria
Previously healthy, term infant with uncomplicated nursery stay
Non-toxic clinical appearance
No focal bacterial infection on examination (except otitis media)
Low-risk laboratory criteria
Negative urine leukocyte esterase and nitrite, or <10 WBCs/hpf
WBC count 5-15,000 and <1,500 bands or band/neutrophil ratio < 0.2
When diarrhea present: No blood and < 5 WBCs/hpf in stool
Optional Very Low Risk Laboratory Criteria Per Parent and Physician Preference
CSF: <8 WBCs/mm3 and negative Gram stain
Chest x-ray: no infiltrate
Infants >90 Days of Age with FWS >39.0°C who have received HIB and PCV-7
Urinalysis or urine "dip" and urine culture for:
All females and uncircumcised males < 24 months
Circumcised males < 6 months
All infants with history of prior UTI

Children with UTI who appear toxic, dehydrated, and/or unable to take oral fluids or antibiotics should be admitted for parenteral antibiotic therapy. A multicenter randomized clinical trial of oral versus initial intravenous antibiotic therapy demonstrated no difference in outcomes in children 1 to 24 months.[48] Therefore, children older than 1 month with suspect UTI who are non-toxic appearing and are able to take oral fluids and medications may be treated as outpatients with oral antibiotics. A single dose of ceftriaxone may be given to assure adequate initial therapy. The choice of oral antibiotic should be guided by local susceptibility testing of common uropathogens. In most areas, there is now significant resistance of most organisms causing a UTI to amoxicillin and TMP/SMX. Therefore, a first or third generation cephalosporin should probably be the drug of choice. Cefixime 8mg/kg/d as a single daily dose for 14 days is a convenient regimen.

Occult Pneumonias

The majority of pneumonias in infants and young children are non-bacterial in origin caused by such agents as respiratory syncytial, parainfluenza, and influenza viruses, and *Chlamydophila trachomatis*.[53,54] Bacterial pneumonia is less com-

SIDEBAR 2.

Guidelines for Treatment of Infants and Children with Fever without Source (FWS)

Neonates <28 days with FWS

- Admit for IV antibiotics pending culture results
- Cefotaxime 150 mg/kg/d IV q8h and ampicillin 200 mg/kg/d IV q6h, or vancomycin 30 mg/kg/d IV q12h (if CSF gram positive cocci)

If CSF pleocytosis suggestive of viral meningoencephalitis CSF for herpes PCR; acyclovir 60 mg/kg/d q 8h

Infants 29-90 Days with FWS

- Outpatient management without antibiotics if all low-risk criteria met
- Outpatient management with antibiotics if UTI and able to take oral medications
- Admit for lumbar puncture and antibiotics pending culture results if not UTI and other low risk criteria not met. Antibiotics same as above.

Outpatient Management of UTI in Non-toxic Febrile Infants >28 days

- Ceftriaxone 50 mg/kg IM x1 if concerned about compliance; then cefixime 8 mg/kg/d PO qd for 14 days; or cephalexin 50 mg/kg/d PO q6h for 14 days

mon in infants and young children and is predominantly caused by *Streptococcus pneumoniae*, *Staphylococcus aureus,* and group A streptococci. Bacterial infections often occur as a secondary infection following an initial respiratory viral infection. It is not possible in most cases to differentiate viral from bacterial pneumonias radiologically. When radiological features suggest a bacterial infection, the chance of isolating a bacterial agent as opposed to a virus is 30%.[55,56] No laboratory criteria allow differentiation of bacterial from viral pneumonia other than a positive blood culture, bronchoscopy, or lung puncture. Endoscopy and lung puncture are inappropriate in the routine diagnosis of pneumonia, and blood cultures are positive in only 3% to 5% of young children with pneumonia.[57,58]

Chest Radiograph

Because occult bacterial pneumonia does occur, there need to be some criteria for obtaining chest radiographs in a subset of children with FWS. Most publications that address this issue include only those children for whom a chest radiograph was ordered.[59-61] 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 together with clinical findings should serve to identify most infants with occult respiratory infection.[7] Children with fever ⩾ 40.0° C or WBC count > 20,000 are more likely to have an occult bacterial pneumonia. Thus, a chest x-ray may be considered in these infants and children with FWS.

SUMMARY

There is considerable variation in the clinical management of infants and children with FWS. Community pediatricians generally do not follow clinical practice guidelines that are taught and used at academic training institutions. These guidelines are presented in Sidebar 1 (see page 677) and Sidebar 2. In general, the guidelines provided that all febrile neonates (>38.0ºC) should have a "full sepsis evaluation", including lumbar puncture, and be admitted for parenteral antibiotic therapy. Non-toxic appearing infants 29-90 days of age with FWS >38.0ºC can be managed using low risk laboratory and clinical criteria. Non-toxic appearing infants >90 days of age who have received Hib and PCV-7 vaccines are at low risk for occult bacteremia and meningitis. Therefore, the only laboratory tests necessary in this age group with FWS >39.0oC are a urinalysis and urine culture for circumcised males <6 months of age and uncircumcised males and females <24 months of age.

REFERENCES

1. Reliability of infrared tympanic thermometry in the detection of rectal fever in children. *Ann Emerg Med*. 1995;25(1):21-30.
2. Muma BK, Treloar DJ, Wurmlinger K, Peterson E, Vitae A. Comparison of rectal, axillary, and tympanic membrane temperatures in infants and young children. *Ann Emerg Med*. 1991;20(1):41-44.
3. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH Jr, Powell KR, Schriger DL. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. *Ann Emerg Med*. 1993;22(7):1198-1210.
4. Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Me*d. 2000;36(6):602-614.
5. Byington CL, Rittichier KK, Bassett KE, Castillo H, Glasgow TS, Daly J, Pavia AT. Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin-resistant pathogens. *Pediatrics*. 2003;111(5 Pt 1):964-968.
6. Synnott MB, Morse DL, Hall SM. Neonatal meningitis in England and Wales: a review of routine national data. *Arch Dis Child*. 1994;71(2):F75-F80.
7. Mower WR, Sachs C, Nicklin EL, Baraff LJ. Pulse oximetry as a fifth pediatric vital sign. *Pediatrics*. 1997;99(5):681-686.
8. Baker RC, Seguin JH, Leslie N, Gilchrist MJ, Myers MG. Fever and petechiae in children. *Pediatrics*. 1989;84(6):1051-1055.
9. Mandl KD, Stack AM, Fleisher GR. Incidence of bacteremia in infants and children with fever and petechiae. *J Pediatr*. 1997;131(3):398-404.
10. Baker MD. Evaluation and management of infants with fever. *Pediatr Clin North Am*. 1999;46(6):1061-1072.
11. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85(6):1040-1043.
12. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr*. 1985;107(6):855-860.
13. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection — an appraisal of the Rochester criteria and implications for management. Febrile Infant Collaborative Study Group. *Pediatrics*. 1994;94(3):390-396.
14. Ferrera PC, Bartfield JM, Snyder HS.Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections. *Am J Emerg Med*. 1997;15(3):299-302.
15. Kadish HA, Loveridge B, Tobey J, Bolte RG, Cor-

neli HM.Applying outpatient protocols in febrile infants 1-28 days of age: can the threshold be lowered? *Clin Pediatr (Phila)*. 2000;39(2):81-88.
16. Baker MD, Bell LM.Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Arch Pediatr Adolesc Med*. 1999;153(5):508-511.
17. Chiu CH, Lin TY, Bullard MJ. Application of criteria identifying febrile outpatient neonates at low risk for bacterial infections. *Pediatr Infect Dis J*. 1994;13(11):946-949.
18. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004;291(10):1203-1212.
19. Newman TB, Bernzweig JA, Takayama JI, Finch SA, Wasserman RC, Pantell RH, Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study. *Arch Pediatr Adolesc Med*. 2002;156(1):44-54.
20. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics*. 1999;103(4 Pt 1):843-852.
21. Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics*. 1999;103(3):627-631.
22. Kimberlin DW, Lin CY, Jacobs RF, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics*. 2001;108(2):230-238.
23. Baskin MN, O'Rourke EJ, Fleisher GR. Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr*. 1992;120(1):22-27.
24. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329(20):1437-1441.
25. Herr SM, Wald ER, Pitetti RD, Choi SS. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. *Pediatrics*. 2001;108(4):866-871.
26. Losek JD, Kishaba RG, Berens RJ, Bonadio WA, Wells RG. Indications for chest roentgenogram in the febrile young infant. *Pediatr Emerg Care*. 1989;5(3):149-152.
27. Crain EF, Bulas D, Bijur PE, Goldman HS. Is a chest radiograph necessary in the evaluation of every febrile infant less than 8 weeks of age? *Pediatrics*. 1991;88(4):821-824.
28. Heulitt MJ, Ablow RC, Santos CC, O'Shea TM, Hilfer CL. Febrile infants less than 3 months old: value of chest radiography. *Radiology*. 1988;167(1):135-137.
29. Bramson RT, Meyer TL, Silbiger ML, Blickman JG, Halpern E. The futility of the chest radiograph in the febrile infant without respiratory symptoms. *Pediatrics*. 1993;92(4):524-526.
30. Oppenheim PI, Sotiropoulos G, Baraff LJ. Incorporating patient preferences into practice guidelines: management of children with fever without source. *Ann Emerg Med*. 1994;24(5):836-841.
31. Adams WG, Deaver KA, Cochi SL, et al. Decline of childhood Haemophilus influenzae type b (Hib) disease in the Hib vaccine era. *JAMA*. 1993;269(2):221-226.
32. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J*. 2000;19(3):187-195.
33. Huebner RE, Mbelle N, Forrest B, Madore DV, Klugman KP. Immunogenicity after one, two or three doses and impact on the antibody response to coadministered antigens of a nonavalent pneumococcal conjugate vaccine in infants of Soweto, South Africa. *Pediatr Infect Dis J*. 2002;21(11):1004-1007.
34. Goldblatt D, Southern J, Ashton L, et al. Immunogenicity and boosting after a reduced number of doses of a pneumococcal conjugate vaccine in infants and toddlers. *Pediatr Infect Dis J*. 2006;25(4):312-319.
35. Moore MR, Gertz RE Jr, Woodbury RL, et al. Population snapshot of emergent Streptococcus pneumoniae serotype 19A in the United States, 2005. *J Infect Dis*. 2008;197(7):1016-1027.
36. Scott D, Ruckle J, Dar M, Baker S, Kondoh H, Lockhart S. Phase 1 trial of 13-valent pneumococcal conjugate vaccine in Japanese adults. *Pediatr Int*. 2008;50(3):295-299.
37. Prymula R, Chlibek R, Splino M, et al. Safety of the 11-valent pneumococcal vaccine conjugated to non-typeable Haemophilus influenzae-derived protein D in the first 2 years of life and immunogenicity of the co-administered hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, Haemophilus influenzae type b and control hepatitis A vaccines. *Vaccine*. 2008;26(35):4563-4570.
38. Hsiao AL, Chen L, Baker MD. Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. *Pediatrics*. 2006;117(5):1695-1701.
39. Jaffe DM, Tanz RR, Davis AT, Henretig F, Fleisher G. Antibiotic administration to treat possible occult bacteremia in febrile children. *N Engl J Med*. 1987;317(19):1175-1180.
40. Lee GM, Harper MB. Risk of bacteremia for febrile young children in the post-Haemophilus influenzae type b era. *Arch Pediatr Adolesc Med*. 1998;152(7):624-628.
41. Friedman AD, Fleischer GR. Unsuspected meningococcemia treated with orally administered amoxicillin. *Pediatr Infect Dis*. 1982;1(1):38-39.
42. Dashefsky B, Teele DW, Klein JO. Unsuspected meningococcemia. *J Pediatr.* 1983;102(1):69-72.
43. Kuppermann N, Malley R, Inkelis SH, Fleisher GR. Clinical and hematologic features do not reliably identify children with unsuspected meningococcal disease. *Pediatrics*. 1999;103(2):E20.
44. Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D.Prevalence of urinary tract infection in febrile infants. *J Pediatr.* 1993;123(1):17-23.
45. Roberts KB, Charney E, Sweren RJ, et al. Urinary tract infection in infants with unexplained fever: a collaborative study. *J Pediatr*. 1983;103(6):864-867.
46. Bauchner H, Philipp B, Dashefsky B, Klein JO. Prevalence of bacteriuria in febrile children. *Pediatr Infect Dis J*. 1987;6(3):239-242.
47. Shaw KN, Gorelick M, McGowan KL, Yakscoe NM, Schwartz JS. Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics*. 1998;102(2):e16.
48. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104(1 Pt 1):79-86.
49. Gorelick MH, Shaw KN. Clinical decision rule to identify febrile young girls at risk for urinary tract infection. *Arch Pediatr Adolesc Med*. 2000;154(4):386-390.
50. Shaw KN, McGowan KL, Gorelick MH, Schwartz JS. Screening for urinary tract infection in infants in the emergency department: which test is best? *Pediatrics*. 1998;101(6):E1.
51. Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M. Is urine culture necessary to rule out urinary tract infection in young febrile children? *Pediatr Infect Dis J*. 1996;15(4):304-309.
52. Gorelick MH, Shaw KN.Screening tests for urinary tract infection in children: A meta-analysis. *Pediatrics*. 1999;104(5):e54.
53. Boyer KM, Cherry JD. Nonbacterial pneumonia. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Disease*. 3rd ed. Philadelphia, PA: WB Saunders; 1992.
54. Turner RB, Lande AE, Chase P, Hilton N, Weinberg D. Pneumonia in pediatric outpatients: cause and clinical manifestations. *J Pediatr*. 1987;111(2):194-200.
55. Bettenay FA, de Campo JF, McCrossin DB. Differentiating bacterial from viral pneumonias in children. *Pediatr Radiol*. 1988;18(6):453-454.
56. McCarthy PL, Spiesel SZ, Stashwick CA, Ablow RC, Masters SJ, Dolan TF Jr. Radiographic findings and etiologic diagnosis in ambulatory childhood pneumonias. *Clin Pediatr (Phila).* 1981;20(11):686-691.
57. Hickey RW, Bowman MJ, Smith GA. Utility of blood cultures in pediatric patients found to have pneumonia in the emergency department. *Ann Emerg Med*. 1996;27(6):721-725.
58. Bachur R, Perry H, Harper MB. Occult pneumonias: empiric chest radiographs in febrile children with leukocytosis. *Ann Emerg Med*. 1999;33(2):166-173.
59. Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. *Clin Pediatr (Phila)*. 1982;21(12):730-734.
60. Zukin DD, Hoffman JR, Cleveland RH, et al. Correlation of pulmonary signs and symptoms with chest radiographs in the pediatric age group. *Ann Emerg Med*. 1986;15(7):792-796.
61. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. *Ann Emerg Med*. 1989;18(1):13-20.