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%.12 Although some infants with serious bacterial infections may be afebrile, most of these will appear seriously ill.
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). 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.5,9 Most children with meningococcal disease and petechiae are ill-appearing.5 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. 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-consumable irritability are considered “toxic appearing” and are to be hospitalized for evaluation for possible sepsis or meningitis and parenteral antibiotic therapy.6

Neonates < 28 Days with FWS
Because of the difficulty in evaluation of the behavioral state, decreased immunologic function, and the difficulty of evaluating 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.” 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. 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. 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.

Most febrile neonates with CSF pleocytosis prove to have viral meningitis. 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), the Boston criteria (28 to 89 days), the Philadelphia criteria (29 to 60 days), and the Pittsburgh criteria. 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. 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. 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. 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, corzya, 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 1,000.5

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 ≥ 39.0°C.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/mm3.3 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 non-specific 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 ≥ 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 ≥ 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%. Among febrile children with a UTI, approximately 60% will have evidence of pyelonephritis on 99m-Tc dimercaptosuccinic acid (DMSA) renal scan. 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. 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. These specimens should be obtained by urethral catheterization because “bagged” urines are likely to be contaminated by urethral catheterization because “bagged” urines are likely to be contaminated and the false positive rates are unacceptable high. 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. 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 bacteruria 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%. 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.

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. 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 Chlamyphila trachomatis. Bacterial pneumonia is less com-

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**SIDEBAR 1. Guidelines for Diagnostic Testing of Infants and Children with Fever without Source (FWS)**

<table>
<thead>
<tr>
<th>Neonates &lt;28 days with FWS &gt; 38.0°C</th>
<th>Complete sepsis workup</th>
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<tbody>
<tr>
<td></td>
<td>Complete blood count, differential, and blood culture</td>
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<tr>
<td></td>
<td>Urinalysis and urine culture</td>
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<td></td>
<td>Cerebrospinal fluid studies:</td>
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<tr>
<td></td>
<td>Tube 1: Culture and sensitivity</td>
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<tr>
<td></td>
<td>Tube 2: Protein and sugar</td>
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<tr>
<td></td>
<td>Tube 3: Cell count and differential</td>
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<tr>
<td></td>
<td>Tube 4: HSV PCR if CSF compatible with viral meningoencephalitis</td>
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<td></td>
<td>± Chest x-ray</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Infants 28-90 Days with FWS &gt; 38.0°C</th>
<th>Low-risk clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previouslly healthy, term infant with uncomplicated nursery stay</td>
<td></td>
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<tr>
<td>Non-toxic clinical appearance</td>
<td></td>
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<tr>
<td>No focal bacterial infection on examination (except otitis media)</td>
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<th>Low-risk laboratory criteria</th>
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<tr>
<td>Negative urine leukocyte esterase and nitrite, or &lt;10 WBCs/hpf</td>
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<tr>
<td>WBC count 5-15,000 and &lt;1,500 bands or band/neutrophil ratio &lt; 0.2</td>
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<tr>
<td>When diarrhea present: No blood and &lt; 5 WBCs/hpf in stool</td>
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<tr>
<th>Optional Very Low Risk Laboratory Criteria Per Parent and Physician Preference</th>
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<tbody>
<tr>
<td>CSF: &lt;8 WBCs/mm3 and negative Gram stain</td>
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<tr>
<td>Chest x-ray: no infiltrate</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Infants &gt;90 Days of Age with FWS &gt; 39.0°C who have received Hib and PCV-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis or urine “dip” and urine culture for:</td>
</tr>
<tr>
<td>All females and uncircumcised males &lt; 24 months</td>
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<tr>
<td>Circumcised males &lt; 6 months</td>
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<tr>
<td>All infants with history of prior UTI</td>
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</tbody>
</table>
in infants and young children. 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 pneumonia radiologically. When radiological features suggest a bacterial infection, the chance of isolating a bacterial agent as opposed to a virus is 30%.

No laboratory criteria allow differentiation of bacterial from viral pneumonia other than a positive blood culture. There are no laboratory tests necessary in this age group for obtaining chest radiographs in a subset of infants and young children who have received Hib and PCV-7 vaccines at low risk for occult bacteremia and meningitis. Therefore, the only laboratory tests necessary in this age group with FWS >39.0°C are a urinalysis and urine culture for circumcised males <6 months of age and uncircumcised males and females <24 months of age.

**REFERENCES**

15. Kadish HA, Loveridge B, Tobey J, Bolte RG, Cor...


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