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Evaluation Of The Febrile Young Infant: An Update

Abstract

The febrile young infant is commonly encountered in the emergency department, and the incidence of serious bacterial infection in these patients is as high as 15%. Undiagnosed bacterial infections such as meningitis and bacteremia can lead to overwhelming sepsis and death or neurologic sequelae. Undetected urinary tract infection can lead to pyelonephritis and renal scarring. These outcomes necessitate the evaluation for a bacterial source of fever; therefore, performance of a full sepsis workup is recommended to rule out bacteremia, urinary tract infection, and bacterial meningitis in addition to other invasive bacterial diseases including pneumonia, bacterial enteritis, cellulitis, and osteomyelitis. Parents and emergency clinicians often question the necessity of this approach in the well-appearing febrile young infant, and it is important to understand and communicate the evidence that guides the approach to these patients. Recent studies examining the risk of serious bacterial infection in young infants with bronchiolitis and the role of viral testing in the febrile young infant will also be discussed in this review.

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CME Objectives

Upon completion of this article, you should be able to:

1. Recognize and explain to parents the rationale for performance of the sepsis workup in the well-appearing febrile young infant.
2. Apply the low-risk criteria to the well-appearing febrile young infant with normal urine, serum, and cerebrospinal studies to avoid unnecessary hospitalization.
3. Consider testing for HSV infection in neonates, especially babies with skin vesicles, hypothermia, ill appearance, seizures, or hepatitis.

Prior to beginning this activity, see the back page for faculty disclosures and CME accreditation information.

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Case Presentation

On an August afternoon, a 20-day-old male presents with his mother to the ED for a rectal temperature of 38°C. The baby was born by spontaneous vaginal delivery at 39 weeks gestational age. The mother's prenatal labs were negative, including negative screening for group B streptococcus. The patient feels warm to the parents today, but otherwise, he has been asymptomatic. The baby is feeding 3 ounces every 4 hours and is making an appropriate amount of wet diapers. The physical examination is normal, including a flat anterior fontanel and good hydration. When you explain to the mother that the baby will need to undergo the full sepsis workup, including lumbar puncture, she asks if all the testing is necessary. What is the probability, since her baby looks so well, that he has a serious bacterial infection? After the testing is completed, will the baby need to be admitted to the hospital? Can other infections besides bacterial infections cause a fever, and does the baby need testing for these? Would the testing and treatment strategy change if the baby were 40 days old? What if he had bronchiolitis with a fever?

Introduction

Commonly encountered in the emergency department (ED), the febrile young infant is defined as an infant < 90 days of age with a rectal temperature $\geq 38.0^{\circ}\text{C}$. (See Table 1.)¹ Due to their immature immune systems and unique pathogens, the febrile young infant is at high risk for bacterial infections, in particular, urinary tract infection (UTI), bacteremia, and meningitis. The incidence of serious bacterial infection (SBI) in febrile young infants (< 90 days of age) is 8% to 12.5%,² and it is even higher in neonates (0 through 28 days of age), in whom the SBI rate is nearly 20%.³ In addition, bacterial meningitis is the most common missed diagnosis in pediatric medical malpractice claims.⁴ In contrast to the well-appearing febrile older infants and children who are at low risk for invasive bacterial disease,⁵ the well-appearing febrile young infant is still at risk for SBI. Baker et al reported that 8.8% of well-appearing febrile infants aged 29 through 56 days had culture-positive bacterial infections, and 11% had bacterial illness or radiographic pneumonia.⁶ Jaskiewicz et al found a similar SBI rate of 7.1% in 931 well-appearing febrile infants aged 60 days or younger,⁷ an overall incidence that is too high to forego the full sepsis evaluation in this age group.

Criteria have been developed to identify febrile young infants at low risk for SBI, and these criteria are utilized to avoid hospitalization in certain low-risk patients.⁷⁻⁹ More recently, Schnadower et al have attempted to further develop criteria to identify febrile infants with abnormal urinalysis who are at low risk for adverse events and may be discharged home from the ED.¹⁰ Nonetheless, the febrile neo-

nate is also at risk for neonatal herpes simplex virus (HSV) infection, a rare but life-threatening disease that is controversial in its workup and management.¹¹ Other current controversies include the utility of the full sepsis workup in febrile young infants with alternative sources of fever such as respiratory syncytial virus (RSV) and bronchiolitis. Understandably, parents will question why invasive testing must be performed in their well-appearing febrile baby, and the emergency clinician needs to clearly communicate the rationale behind the management of patients in this high-risk age group.

Critical Appraisal Of The Literature

An extensive literature search was performed in the PubMed database using multiple combinations of the search terms *febrile young infant*, *low-risk criteria*, *neonate*, *serious bacterial infection*, *neonatal herpes simplex virus*, and *infant less than 90 days old*. All relevant articles were selected, reviewed, and included in the bibliography. Over 80 articles were reviewed, 68 of which are cited in this article. Emphasis was placed on reviewing the most important historical evidence as well as recent reports, studies, and guidelines.

Etiology And Pathophysiology

The febrile young infant has an immature immune system¹² and a high incidence of SBI.² In this age group, SBIs include UTI/pyelonephritis, bacteremia/sepsis, meningitis, pneumonia, bacterial enteritis, cellulitis, and bone and joint infections. (See Table 1.) While investigations for pneumonia, bacterial enteritis, and bone and joint infections are performed on the basis of symptoms, blood, urine,

Table 1. Definitions¹

- Young infant: < 90 days old
- Neonate: 0 through 28 days old
- Fever: rectal temperature $\geq 38.0^{\circ}\text{C}$
- Serious bacterial infection:
 - Bacterial meningitis
 - Bacteremia/sepsis
 - Urinary tract infection/pyelonephritis
 - Pneumonia (bacterial)
 - Bacterial enteritis
 - Cellulitis
 - Abscess
 - Osteomyelitis
 - Septic arthritis
- Full sepsis evaluation
 - Complete blood count
 - Blood culture
 - Urinalysis
 - Urine culture
 - Cerebrospinal fluid cell count, glucose, protein
 - Cerebrospinal fluid culture

and cerebrospinal fluid (CSF) infections are often occult at onset, with fever as the only symptom. UTI is the most common SBI identified in this age group,^{3,10,13,14} with an incidence of up to 13.6%.¹⁴

The febrile young infant is susceptible to both perinatally acquired and community-acquired infections including group B streptococcus (GBS), *Escherichia coli* and other gram-negative infections, *Streptococcus pneumoniae*, and *Staphylococcus aureus*.^{3,15,16} *E coli* is the most common infection identified in febrile young infants.^{3,16} The neonate is also susceptible to infection with *Listeria monocytogenes*, though this infection is rare.¹⁶ Neonatal HSV is also a rare—but life-threatening—infection in this age group.¹¹

Differential Diagnosis

As described previously, the well-appearing febrile young infant should be evaluated for UTI/pyelonephritis, bacteremia/sepsis, and bacterial meningitis. Viral infections are the most common (though usually benign) cause of fever in this age group. Enterovirus is a common viral cause of fever in the young infant,¹⁷ especially in the summer and early fall months. RSV and other upper respiratory tract viral pathogens are common in the winter. While uncommon, perinatally acquired HSV is a cause of fever in neonates, especially those age 21 days old or younger.^{18,19} In addition to SBI and neonatal HSV, the emergency clinician should consider noninfectious etiologies in the septic-appearing young infant. (See Table 2.)

Prehospital Care

While emergency medical services (EMS) providers may be contacted to transport well-appearing febrile young infants to the ED, they should be prepared to provide basic and advanced life support to the sick infant with sepsis. In addition to obtaining intravenous (IV) access and providing isotonic fluids in boluses of 20 mL/kg for hemodynamic support, early identification and treatment of hypoglycemia should also be undertaken.²⁰ EMS providers should also recognize other potential etiologies of shock in the young infant (see Table 2) and be prepared to provide respiratory and cardiovascular support.

Emergency Department Evaluation

History

In the well-appearing febrile young infant, the emergency clinician should ask the parent the exact height of the temperature and the method by which it was measured (rectal, axillary, or ear). Tympanic and axillary temperatures may be inaccurate in infants.²¹ It is also important to inquire about associated viral symptoms such as coryza, feeding (poor or slow) and output history, and fussiness or lethargy.

The patient's birth history should be obtained in detail, including gestational age at birth, as premature infants are higher risk for bacterial infection, especially *E coli*.²² Included in the birth history are the mother's prenatal laboratory studies, most notably results of screening for HSV and GBS. If the mother is GBS-positive, the emergency clinician should inquire whether she received prenatal antibiotic therapy to reduce GBS transmission to the newborn.²³ The highest risk for perinatally acquired HSV occurs in neonates born to mothers with a first-episode primary HSV infection at the time of delivery.²⁴ While a mother with recurrent HSV may transmit the infection to her newborn, the risk is much lower due to passage of protective IgG antibodies across the placenta. The method of delivery and history of maternal fever at delivery should also be obtained, as cesarean delivery reduces the transmission rate of neonatal HSV,²⁴ and maternal chorioamnionitis is associated with neonatal bacterial infection.²⁵ The infant's postnatal history should include receipt of antibiotics while in the newborn nursery or prolonged stay in the neonatal intensive care unit.

A similar history should be obtained in the ill-appearing infant, with the addition of any family

Table 2. Differential Diagnosis Of The Febrile Young Infant

Well-Appearing Febrile Young Infants

- Serious Bacterial Infections
 - Urinary tract infection
 - Bacteremia
 - Meningitis
 - Pneumonia
 - Bacterial enteritis
 - Soft-tissue infections
 - Bone and joint infections
- Viral Infections
 - Enterovirus
 - Upper respiratory tract pathogens
 - Bronchiolitis
 - Viral gastroenteritis
 - Neonatal herpes simplex virus infection

Ill-Appearing Febrile Young Infants

- Infectious
 - Serious bacterial infections
 - Neonatal herpes simplex virus infection
 - Enterovirus
 - Respiratory syncytial virus
- Cardiac*
 - Ductal-dependent left-sided obstructive lesions
 - Ductal-dependent right-sided obstructive lesions
- Metabolic*
 - Inborn errors of metabolism
 - Congenital adrenal hyperplasia

*Patients with cardiac or metabolic disease are ill-appearing but are often not febrile.

history of early, unexplained deaths or metabolic disease that might indicate cardiac disease or inborn errors of metabolism.

Physical Examination

Important physical examination findings in the febrile young infant include whether the baby is difficult to arouse or console, as these may be signs of meningitis or sepsis. The anterior fontanel should be palpated for fullness or elevation that can be seen with meningitis. The skin should be evaluated for vesicles, though up to 40% of neonates with the severe types of HSV will not have vesicles on their skin.²⁶ Jaundice may also be noted in infants with HSV or bacterial sepsis. The emergency clinician should examine the ears for signs of acute otitis media and the lungs for crackles or wheezes that would indicate pneumonia or bronchiolitis. Tachypnea and accessory muscle use may be seen with bronchiolitis or bacterial pneumonia. In the ill-appearing infant, signs of right- or left-sided obstructive congenital heart disease may include respiratory distress, weak or absent pulses (or weak femoral compared to brachial pulses), and a murmur; however, no symptoms can easily differentiate infants with sepsis versus congenital heart disease.²⁷

Diagnostic Studies

In approaching the diagnostic workup of the febrile young infant, the critical principles to remember are that the incidence of SBI is high^{2,3} and that a well appearance does not lower the pretest probability substantially enough to defer testing for SBI.⁶ These principles provide the rationale for performance of the full sepsis evaluation (see Table 1, page 2) in this age group. The specific evaluation of the febrile young infant is dependent on the age and stability of the patient and which low-risk criteria you utilize. (The low-risk criteria are discussed in detail in the "Low-Risk Criteria And Treatment" section on page 5.)

Ill-appearing infants should receive a full evaluation for sepsis once stable after fluid resuscitation and IV broad-spectrum antibiotics.

Infants Aged 0 Through 56 Days

The well-appearing febrile neonate (aged < 29 days) has the highest prevalence of serious bacterial disease and the least reliable clinical examination. These infants should undergo a full sepsis evaluation.⁷ (See Table 3.) Consideration should be given to testing for HSV in the neonate aged ≤ 21 days,¹⁹ even in the absence of vesicles or maternal history of HSV infection.²⁶ (Testing and treatment strategies for neonatal HSV will be covered in detail in the "Controversies And Cutting Edge" section on page 11.) The well-appearing febrile young infant aged 29 through 56 days should, likewise,

undergo the full sepsis evaluation (except as delineated by the Rochester criteria and discussed in the "Low-Risk Criteria And Treatment" section beginning on page 6), as they are still at risk for SBI but at a slightly lower prevalence than their younger counterparts.^{2,3} Infants who meet high-risk criteria or who may be treated with antibiotics may still require lumbar puncture to rule out CSF infection prior to discharge.⁸

Infants Aged 57 Through 89 Days

The well-appearing febrile infant aged 57 through 89 days should undergo testing with urinalysis and urine culture.²⁸ The risk of bacteremia and meningitis is low in this age group, according to a prospective study by Hsiao et al, in which there were no patients aged 57 through 89 days with positive blood or CSF cultures.²⁸ The number of patients in this age group was relatively small, however, so the study was underpowered to find cases of bacteremia and meningitis. In addition, infants at this age should have received 1 dose of pneumococcal vaccine, which further decreases their risk of bacteremia.²⁹ The Boston criteria (see Table 3) support performing a full sepsis evaluation in all febrile infants through 89 days of age,⁸ so consideration can be given to obtaining blood and CSF studies.

The age cutoff for routinely performing the full sepsis workup depends on which low-risk criteria are utilized. In the Philadelphia criteria (see Table 3), the full sepsis workup is performed until age 57 days,⁹ while in the Rochester criteria, the upper age limit is 60 days.⁷ Subsequent studies (which are discussed later in this issue) have used cutoffs of 60 days. Because the Philadelphia criteria have the highest reported negative predictive value (NPV) and are the only criteria initially derived using a randomized controlled study to determine disposition, an age cutoff of 56 days is used in the Clinical Pathway on page 9.

Laboratory Studies

Standard microscopic urinalysis using centrifuged urine has only moderate sensitivity in infants ≤ 3 months of age.³⁰ Enhanced urinalysis that reports the number of white blood cells (WBCs) per cubic millimeter using uncentrifuged urine³¹ has been reported to have an NPV of 99.7% in febrile infants aged ≤ 60 days old¹³ and is, therefore, very sensitive in ruling out UTI in this age group. Unfortunately, this laboratory analysis is not available at many centers.

Enterovirus testing should be performed in the summer and fall months in both neonates and infants 29 through 56 days old who are being admitted to the hospital, as it is associated with a shorter length of stay and duration of antibiotic use in hospitalized febrile infants.^{17,32} The reason for the shorter length of stay and duration of antibiotic

use is that the enterovirus virus polymerase chain reaction (PCR) is resulted within 24 hours in most laboratories, which is before final bacterial culture results can be considered definitively negative (at 48 hours). Enterovirus PCR sent from both the CSF and serum increases the diagnostic yield,³³ though the cost-effectiveness of this approach has not been studied. Additionally, enterovirus CSF PCR may be positive in the absence of CSF pleocytosis.³⁴

Imaging Studies

Imaging studies should be performed based on symptoms. Bramson et al reported that none of the 361 febrile infants < 12 weeks old without respiratory signs or symptoms had an abnormal chest x-ray.³⁵ Additionally, Crain et al found that only 2 of 148 asymptomatic infants had an abnormal chest x-ray.³⁶ Therefore, routine chest radiography in the febrile young infant is not recommended unless symptoms or signs of pneumonia are present. Stool studies such as culture and fecal leukocytes for bacterial gastroenteritis should also be obtained based on symptoms (eg, blood or mucus in the stool).

Workup For Alternative Sources Of Infection

Controversy exists as to the extent of testing that should be performed in febrile young infants with alternative sources of fever, such as viruses. For example, does the febrile infant aged ≤ 56 days with bronchiolitis require the full sepsis workup, or can the fever be attributed to a viral source? Levine et al prospectively enrolled 1248 febrile infants aged ≤ 60 days, 269 of whom were positive for RSV. RSV-negative patients had an SBI rate of 12.5%; RSV-positive patients had an SBI rate of 7.0%. This lower rate of SBI in febrile young infants with RSV was significant but still accounted for a substantial number of SBIs, especially UTI. When stratified by age, neonates aged ≤ 28 days with RSV infection had a 10.1% rate of SBI, including 3 patients with bacteremia (though no meningitis), and the SBI rate was not significantly different from RSV-negative neonates. In the 29- to 60-day age group, RSV-positive patients had a significantly lower rate of SBI than RSV-negative patients (5.5% vs 11.7%), and all infections were UTI. Rates of bacteremia and meningitis could not be compared in this age group by RSV status due to the small numbers.³⁷ Likewise, a secondary analysis of the same cohort by Krief et al found that febrile infants

Table 3. Most Common Low-Risk Criteria For Management Of Febrile Young Infants

Criterion	Rochester Criteria ⁷ (0-60 days of age)	Philadelphia Criteria ^{9,45} (29-56 days of age)	Boston Criteria ⁸ (28-89 days of age)
History and physical examination	<ul style="list-style-type: none"> • Full-term • Normal prenatal and postnatal histories • No postnatal antibiotics • Well appearing • No focal infection 	<ul style="list-style-type: none"> • Well appearing • No focal infection 	<ul style="list-style-type: none"> • No antibiotics within preceding 48 h • No immunizations within preceding 48 h • Well appearing • No focal infection
Laboratory parameters (defines low risk)	<ul style="list-style-type: none"> • WBC: 5000-15,000/mm³ • Absolute band count: < 1500/mm³ • UA: ≤ 10 WBC/ HPF • Stool: ≤ 5 WBC/ HPF on smear* 	<ul style="list-style-type: none"> • WBC: < 15,000/mm³ • Band: total neutrophil (I:T) ratio < 0.2 • UA: < 10 WBC/ HPF • Urine: Gram stain negative • CSF: < 8 WBC/mm³ • CSF: Gram stain negative • Chest x-ray: no infiltrate* • Stool: no blood, few or no WBCs on smear* 	<ul style="list-style-type: none"> • WBC: < 20,000/mm³ • UA: <10 WBC/ HPF • CSF: < 10 WBC/mm³ • Chest radiograph: no infiltrate*
Treatment for high-risk patients	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics	Hospitalize + empiric antibiotics
Treatment for low-risk patients	<ul style="list-style-type: none"> • Home • 24-h follow-up required • No empiric antibiotics 	<ul style="list-style-type: none"> • Home, if patient lives within 30 min of the hospital • 24-h follow-up required • No empiric antibiotics 	<ul style="list-style-type: none"> • Home, if caregiver available by telephone • Empiric IM ceftriaxone 50 mg/kg • Return for 24-h follow-up for second dose of IM/IV ceftriaxone
Performance of low-risk criteria	NPV: 98.9% (97.2-99.6)	NPV: 100% (99-100)	NPV: 94.6% (92.2-96.4)

*Obtained based on symptoms

Abbreviations: CSF, cerebrospinal fluid; HPF, high-power field; IM, intramuscular; IV, intravenous; NPV, negative predictive value; UA, urinalysis; WBC, white blood cell.

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aged ≤ 60 days with influenza virus had lower rates of SBI (all UTI), but the numbers were too small to compare rates of bacteremia and meningitis.³⁸

Ralston et al performed a systematic review of 11 studies that reported the rate of occult SBI in febrile infants aged < 90 days with bronchiolitis and found a 3.3% incidence of UTI (95% confidence interval [CI], 1.9%-5.7%).³⁹ Due to no cases of bacteremia in 8 of 11 studies and no cases of meningitis in any of the studies, the authors were unable to determine the rate of these infections, though the incidence appears very low.³⁹ Febrile young infants with RSV or bronchiolitis are still at risk for serious bacterial infection, especially UTI, and they should be thoroughly evaluated for sources of infection.

Given the high incidence of SBI in patients aged ≤ 28 days, the full sepsis workup should be performed in neonates with bronchiolitis or viral upper respiratory infection unless the baby's respiratory distress prohibits the performance of a lumbar puncture. There is no standard of care in febrile infants aged 29 to 60 days with bronchiolitis. Given the high incidence of UTI, a urinalysis and urine culture should be performed, and strong consideration should be given to performance of a CBC and blood culture. Should the infant be ill appearing or have a high serum WBC count on CBC, a lumbar puncture should be performed. Seven of the 11 studies included in the systematic review by Ralston et al included febrile infants aged < 90 days;³⁹ therefore, the risk of UTI should be applied to the 61- through 89-day age group with bronchiolitis as well. These patients should undergo urinalysis and urine culture, and other testing can be deferred unless the infant is ill appearing.

Less evidence is present to guide the emergency clinician in the diagnostic workup when other sources of infection are present. The guiding principle should be that the febrile young infant is a high-risk patient. Invasive infections such as cellulitis, abscess, and osteomyelitis require the full sepsis workup, including evaluation for bacteremia and meningitis.^{15,40} Two studies have evaluated the risk of SBI in young infants with acute otitis media, and they reported SBI rates of 6.2% and 8.8%, including 1 patient with bacteremia.^{41,42} While there were no cases of meningitis, the numbers were small in these studies;^{41,42} therefore, the full sepsis workup should be performed in any febrile infant aged ≤ 56 days with acute otitis media. In summary, febrile young infants with infections notable on physical examination (eg, cellulitis or otitis media) should be evaluated for disseminated infection such as bacteremia and meningitis.

Low-Risk Criteria And Treatment

Prior to the 1980s, febrile young infants would undergo the full sepsis workup, including studies for

blood, urine, and CSF, and they would be hospitalized for 48 hours pending bacterial culture results. However, 2 studies by Dagan et al demonstrated that, if the infant was full term with a normal birth history and physical examination, the serum WBC count was between 5000 and 15,000 cells/mm³, the serum band count was < 1500 cells/mm³, and the urinalysis had ≤ 10 WBC/HPF (high power field), the infant was at low risk for SBI.^{43,44} These criteria became known as the Rochester criteria. These criteria and other criteria (such as those originating in Philadelphia and Boston) became the basis for the low-risk criteria utilized today to identify febrile young infants at low risk for SBI who may be able to be discharged home without hospitalization. (See Table 3, page 5.) Different low-risk criteria are used across the country, with the Philadelphia, Rochester, and Boston criteria being the most commonly used. The Rochester criteria include neonates,⁷ while the Philadelphia and Boston criteria do not.^{8,9} Additionally, CSF studies are not automatically part of the Rochester criteria, though they may be performed at the discretion of the treating physician.⁷ The Boston criteria include infants through 89 days of age and utilize a higher WBC threshold of 20,000 WBC/mm³.⁸

After laboratory studies are performed, the low-risk criteria are applied to the febrile young infant. The Rochester criteria are applied to all infants 0 through 60 days of age, while the Philadelphia and Boston criteria are applied only to infants > 28 days of age. If the infant is not well appearing or if the laboratory studies are abnormal, the patient is hospitalized and receives empiric antibiotic therapy. If the low-risk criteria are met, the patient can be discharged home if 24-hour follow-up can be arranged. The febrile young infant can be discharged home without antibiotics, according to the Rochester and Philadelphia criteria, or with a dose of intramuscular ceftriaxone 50 mg/kg at discharge and again in 24 hours as per the Boston criteria. All 3 of the criteria were derived through prospective study.⁷⁻⁹ While the Philadelphia criteria have the highest reported NPV (at 100%), the authors of the Rochester and Boston criteria studies stated that febrile infants with SBI who were falsely classified as low risk did well at follow-up.^{7-9,45} Additionally, the Rochester and Philadelphia criteria were reevaluated in a new cohort in a 2005 prospective study by Garra et al, which reported high, but decreased, NPVs of both criteria: 97.3% (95% CI, 90.5%-99.2%) and 97.1% (95% CI, 85.1%-99.8%), respectively. However, the NPVs were likely lower due to the high rate of SBI in the cohort (25%) and the small number of low-risk patients. For example, only 34 patients were low risk per the Philadelphia criteria, and 1 patient had an SBI.⁴⁶ Overall, the low-risk criteria perform very well. In a systematic review by Huppler et al, when patients from studies in which the low-risk criteria were applied prospectively and

empiric antibiotics were withheld in low-risk infants, only 0.67% (95% CI, 0.25%-1.5%) of low-risk patients had an SBI.² Most importantly, application of the low-risk criteria would allow 30% of febrile young infants to be discharged without antibiotics.²

The Philadelphia and Boston criteria are not applied to neonates, as 2 studies have demonstrated that low-risk criteria do not perform as well in infants < 29 days of age. In a study published in 1999, Baker et al retrospectively applied the Philadelphia criteria to 254 febrile infants aged 3 to 28 days. Per the criteria, 109 infants were low risk, and 5 patients had an SBI, including 2 with bacteremia. The NPV of the Philadelphia criteria in neonates was 95%, although the 95% CI ranged from 90% to 99% (meaning that up to 1 out of 10 low-risk neonates could have an SBI).⁴⁷ A 2009 study by Schwartz et al reported that 14 of 226 (6.2%) low-risk neonates aged 3 to 28 days had an SBI, including 1 patient with *S pneumoniae* bacteremia and meningitis. The NPV of the low-risk criteria, when applied to neonates in this study, was 93.8% (95% CI, 90.1%-96.4%).³ The bottom line from these studies is that the low-risk criteria do not perform as well in neonates, and this is the rationale for not applying the criteria to this age group. Therefore, neonates are automatically admitted on empiric antibiotics pending bacterial culture results at 48 hours.

Antibiotic Therapy

Empiric antibiotic therapy for neonates and high-risk febrile infants aged 29 through 60 days (through 89 days in the Boston criteria) should be tailored to the most likely pathogens. As discussed in the "Etiology and Pathophysiology" section on page 2, the febrile young infant is susceptible to both perinatally acquired and community-acquired infections, including GBS, *E coli* and other gram-negative infections, *S pneumoniae*, *S aureus*,^{3,15,16} and *L monocytogenes* in the neonate. In the well-appearing febrile neonate, routine empiric antibiotic therapy is IV ampicillin 200 mg/kg/day divided every 6 hours and cefotaxime 150 mg/kg/day divided every 8 hours. Gentamicin has been previously used in this age group, but it does not penetrate the CSF and has renal toxicity, so it has largely been replaced by cefotaxime. In the well-appearing febrile infant older than 28 days, *L monocytogenes* is not a pathogen so ampicillin is no longer needed. Therefore, a broad-spectrum cephalosporin such as cefotaxime or ceftriaxone monotherapy is sufficient. Ampicillin therapy alone in both age groups is not adequate therapy due to a high percentage of ampicillin-resistant pathogens causing SBI in the febrile young infant.⁴⁸

In the ill-appearing febrile infant, or in the infant with CSF pleocytosis, purulence, or positive Gram stain (indicating potential bacterial meningitis), coverage should be broadened to treat highly resistant

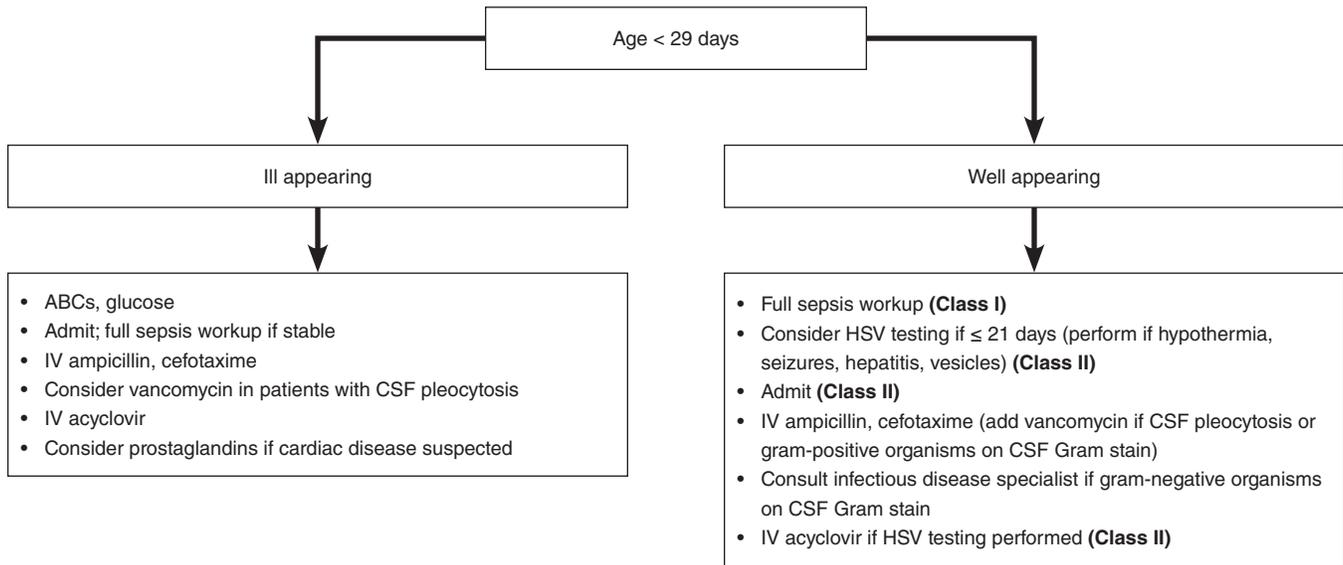
S pneumoniae as well as the less common *S aureus*. Coverage includes the addition of vancomycin to the aforementioned antibiotics at a dose of 15 mg/kg/dose in the febrile young infant aged 0 through 89 days.⁴⁹ In the rare but potentially devastating scenario of a positive CSF Gram stain of gram-negative rods (indicating gram-negative meningitis), immediate consultation with the local infectious diseases specialist should be undertaken, and coverage with broad-spectrum antibiotics (such as imipenem and amikacin) should be considered.

Two questions that arise are in regard to the definition of CSF pleocytosis in the febrile young infant and whether to adjust the CSF WBC count for CSF red blood cell (RBC) count. A 2010 cross-sectional study by Kestenbaum et al provided the best evidence for CSF norms in the febrile young infant. In seemingly normal patients without bacterial or viral meningitis, the authors reported a median CSF WBC count of 3 WBC/mm³ in the neonate aged 0 through 28 days (with a 95th percentile value of 19 WBC/mm³) and a median CSF count of 2 WBC/mm³ in the young infant aged 29 through 56 days (with a 95th percentile value of 9 WBC/mm³).⁵⁰ The low-risk criteria used < 8 WBC/mm³ to define normal CSF, which is consistent with the study results. For the neonate, using a cutoff of < 19 WBC/mm³ to define CSF pleocytosis is reasonable, although lowering that number to the 90th percentile in the study (12 WBC/mm³) would improve sensitivity.⁵⁰ While there are multiple formulas to adjust the CSF WBC count for CSF RBCs, a neonatal intensive care unit study of neonates (aged 0-30 days) reported that adjustment of CSF WBCs for CSF RBCs only improved specificity slightly while decreasing sensitivity.⁵¹ Therefore, since the evidence is not robust, adjustment for RBCs should not be performed in the high-risk febrile young infant.

Special Circumstances

An issue that arises is the risk of bacterial meningitis in the well-appearing febrile young infant older than 28 days with an abnormal urinalysis but normal CBC. Do CSF studies need to be obtained? Tebruegge et al reviewed the available literature and reported that the earlier studies reporting higher rates of coexisting meningitis in young infants with UTI had methodological flaws and likely overestimated the risk of meningitis. The authors concluded that the current data have limitations but suggested that the risk of meningitis is < 1% in febrile infants aged 1 to 3 months with UTI.⁵² However, since the current incidence of bacterial meningitis is < 1% in this age group, the studies included in this review are not adequate to determine whether CSF can be excluded in febrile young infants with UTI. A subsequent retrospective study by Paquette et al included

Clinical Pathway For Evaluation Of Febrile Young Infants (< 29 Days Old)



Abbreviations: ABCs, airway, breathing, circulation; CSF, cerebrospinal fluid; HSV, herpes simplex virus; IV, intravenous.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II

- Safe, acceptable
- Probably useful

Level of Evidence:

- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:

- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate

- Continuing area of research
- No recommendations until further research

Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

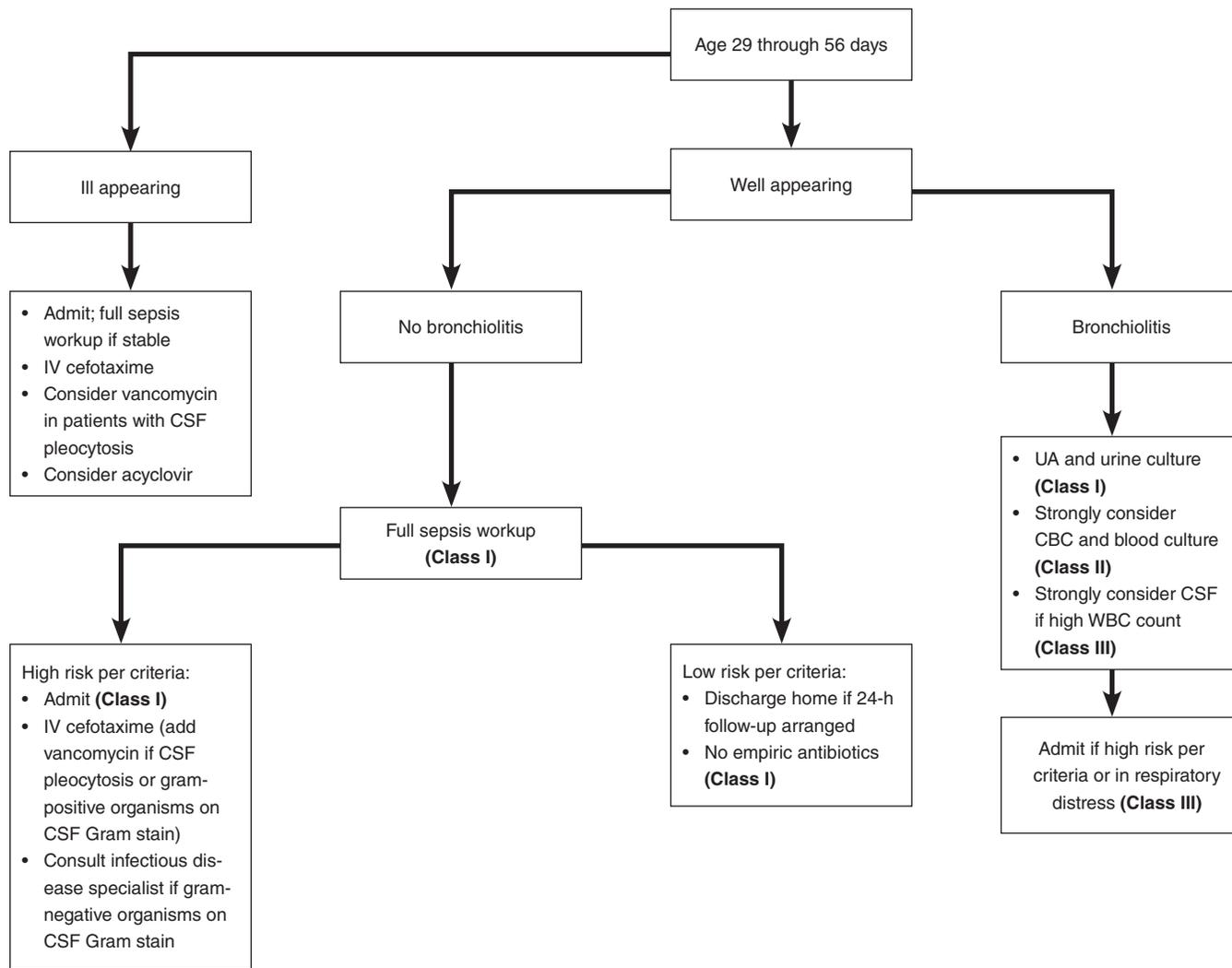
Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and represen-

tatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Clinical Pathway For Evaluation Of Febrile Young Infants (29 Through 56 Days Old)



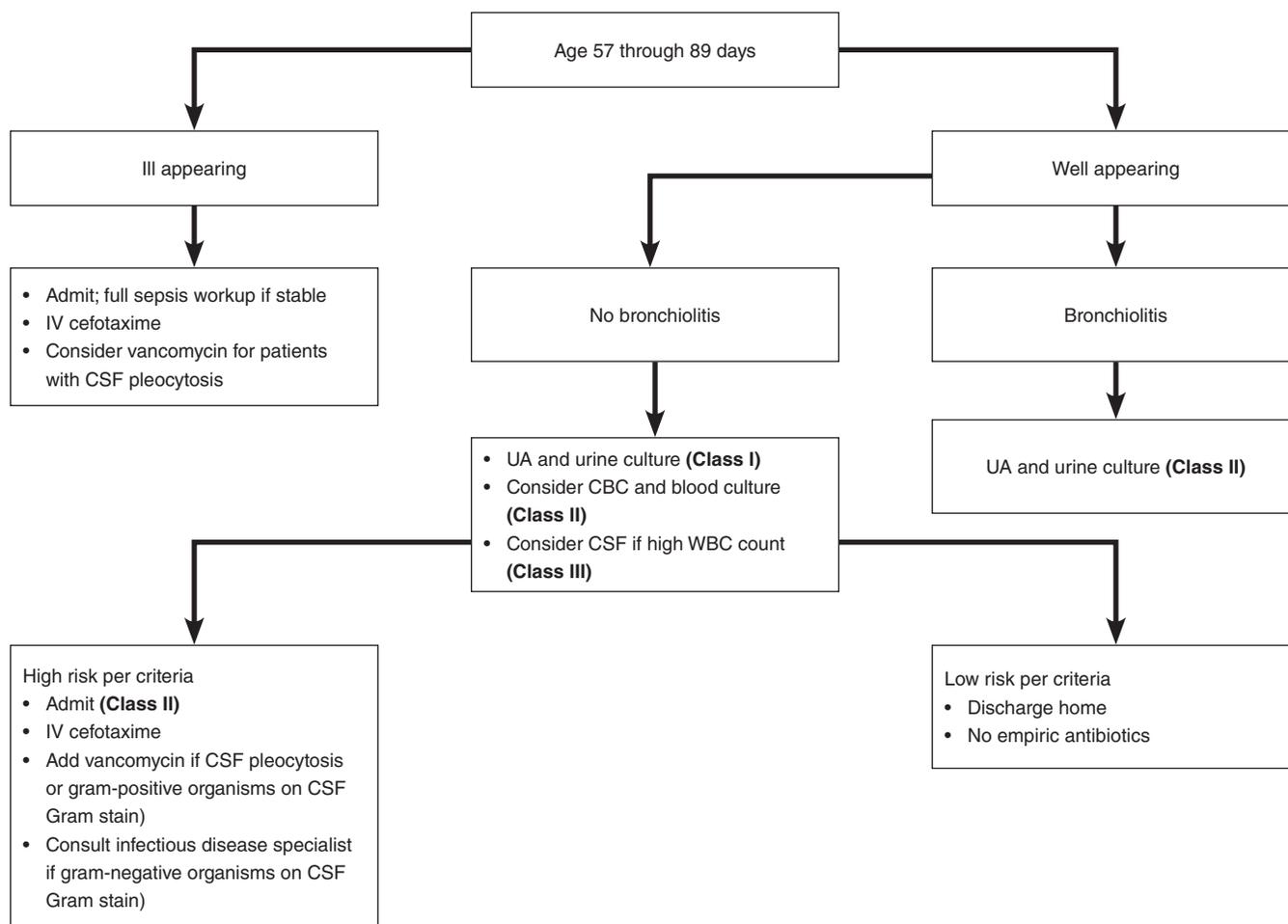
Abbreviations: CBC, complete blood count; CSF, cerebrospinal fluid; HSV, herpes simplex virus; IV, intravenous; UA, urinalysis; WBC, white blood cell. For class of evidence definitions, see page 8.

392 febrile infants aged 30 to 90 days, 57 of whom had an abnormal urinalysis. Only 1 patient (an ill-appearing 71-day-old infant with a WBC count of 2900/mm³) had bacterial meningitis; therefore, the authors concluded that routine lumbar puncture is not required in well-appearing febrile infants aged 30 to 90 days with a normal CBC. However, only 57 patients in this study had an abnormal urinalysis, so the study was underpowered to determine the true rate of coexisting bacterial meningitis in febrile young infants with UTI.⁵³

Schnadower et al performed a large multi-center retrospective study of 1895 febrile infants aged 29 through 60 days with UTI to derive a prediction model to identify patients at low risk for adverse events (defined as death, shock, bacterial meningitis, intensive care unit admission, need for ventilatory support, need for surgical intervention, or other substantial clinical events). Febrile young infants with UTI were at low risk

for an adverse event if they were clinically well in the ED and did not have a high-risk past medical history (such as a history of genitourinary abnormalities, previous SBI, prematurity, or severe systemic disease such as congenital heart disease, chronic lung disease, or neurologic diseases). This prediction model had an NPV of 99.9% (95% CI, 99.5%-100%), so it seems to perform well. However, this study was retrospective, and 90.7% of the cohort were hospitalized and 95.5% were treated with parenteral antibiotics for a median duration of 4 days, possibly confounding the results, as the risk of adverse events decreases due to antibiotic therapy.¹⁰ Therefore, while this multicenter retrospective study is a good first step to identify febrile young infants with UTI who are at low risk for adverse events and meningitis, at this current time, these infants should still have CSF testing and be hospitalized on IV antibiotics pending further prospective study.

Clinical Pathway For Evaluation Of Febrile Young Infants (57 Through 89 Days Old)



Abbreviations: CBC, complete blood count; CSF, cerebrospinal fluid; IV, intravenous; UA, urinalysis; WBC, white blood cell.
For class of evidence definitions, see page 8.

In summary, while the overall risk of meningitis is probably low in febrile young infants with UTI, patients with an abnormal urinalysis should undergo lumbar puncture, pending further prospective or larger studies.

Controversies And Cutting Edge

Neonatal Herpes Simplex Virus Infection

While the evidence for identifying febrile young infants at low risk for SBI is expansive, controversy exists as to which infants should be tested and empirically treated for HSV infection. Neonatal HSV is rare, with an incidence of 9.6 per 100,000 births¹⁸ or approximately 1500 cases per year.¹¹ The vast majority of HSV infections are acquired in the peripartum period.¹¹ Brown et al performed the landmark study that identified that the highest risk for HSV transmission to the neonate is a primary, first-episode maternal infection at the time of delivery as there is no time for development of protective IgG antibodies. The rate of neonatal HSV was 30.8% in babies born to these mothers.²⁴ Other risk factors for transmission of neonatal HSV included premature delivery (< 38 wk gestational age) and vaginal versus cesarean delivery.²⁴ These risk factors are important, as the highest-risk babies are likely those that have been born to a mother who had no prior history of HSV and may not know she had HSV infection at the time of delivery (due to subclinical disease).

According to a retrospective cohort study using the Healthcare Cost and Utilization Project Kids' Inpatient Database, the mean age at admission of infants with neonatal HSV was 14 days.¹⁸ There are 3 types of neonatal HSV, discussed in order of increasing severity. (See Table 4.) The first type is skin,

eye, mouth (SEM) HSV disease. The most benign type, SEM HSV is limited to the skin and mucous membranes and accounts for approximately 45% of disease. The second type is central nervous system (CNS) HSV disease. It is HSV in the CNS plus/minus the skin and mucous membranes and accounts for 30% of patients. The third type is disseminated HSV disease, which is essentially HSV sepsis, with diffuse organ injury including liver dysfunction, pulmonary involvement, disseminated intravascular coagulopathy, and (in 60% to 75% of patients) CNS involvement. Disseminated disease accounts for approximately 25% of patients.¹¹ Importantly, if the 30% of patients with CNS HSV is added to the 60% to 75% of patients with disseminated disease who have CNS involvement, only approximately 50% of babies with neonatal HSV will have HSV in the CNS. This has implications for testing.

While the presence of vesicles (the hallmark of HSV) is helpful in the diagnosis, in the landmark study by Kimberlin et al, only 63% of patients with CNS disease and 58% with disseminated disease had vesicles at presentation.²⁶ No other single symptom identifies the majority of patients, and symptoms and signs include lethargy, fever, seizure, and coagulopathy.²⁶ In a retrospective study by Caviness et al, of the 10 neonates with HSV, 6 had vesicles, 2 had hypothermia, 1 had lethargy and CSF pleocytosis of 836 WBC/mm³, and 1 had fever with severe transaminitis.⁵⁵ Infants who are ill at presentation with altered mental status, pneumonia, or disseminated intravascular coagulopathy have higher mortality rates, as do premature babies with neonatal HSV.^{26,56} Therefore, early identification of neonates with HSV prior to the development of severe illness may improve mortality and neurologic morbidity. Indeed,

Table 4. Clinical Presentation Of Neonatal Herpes Simplex Virus^{11,26}

Features	Type		
	Skin, Eyes, Mouth	Central Nervous System	Disseminated
Age (mean) at presentation	12 days	19.7 days	11.4 days
Areas involved	Skin +/- mucous membranes	CNS +/- skin and mucous membranes	Liver, pulmonary, coagulopathy +/- CNS, +/- skin and mucous membranes
Symptoms and signs	Vesicles, conjunctivitis	Seizures, lethargy, coma, +/- SEM symptoms	Respiratory distress, hypotension, hypothermia, bleeding, +/- SEM and CNS symptoms
Laboratory and imaging abnormalities	None	CSF pleocytosis	Transaminitis, DIC, pulmonary infiltrates, acidosis, +/- CSF pleocytosis
Method of diagnosis ¹¹	HSV PCR from vesicles and HSV culture from eye, oropharynx, rectum	HSV PCR from CNS	HSV PCR from serum and CNS
Therapy ⁵⁴	High-dose acyclovir (20 mg/kg/dose q8h) x 14 days	High-dose acyclovir x 21 days	High-dose acyclovir x 21 days

Abbreviations: CSF, cerebrospinal fluid; CNS, central nervous system; DIC, disseminated intravascular coagulation; HSV, herpes simplex virus; PCR, polymerase chain reaction; q, every; SEM, skin, eye, mouth.

in a retrospective multicenter cohort study by Shah et al, each day's delay in acyclovir initiation was associated with increased mortality,⁵⁷ likely due to progression of disease.

Which neonates should be tested and empirically treated for neonatal HSV? Certainly, if the neonate has a maternal history of HSV, is lethargic, and has cardiovascular instability, seizures, or vesicles, HSV testing and empiric acyclovir therapy should be undertaken. But what about the well-appearing neonate presenting to the ED for fever or other non-specific symptoms? First, it is important to recognize that neonatal HSV is uncommon after 21 days of age, with Long et al reporting in their retrospective study that 90% of patients with neonatal HSV had symptoms at or earlier than 21 days of age.¹⁹ In the previously described retrospective study by Caviness et al, hypothermic neonates had a 1.1% rate of HSV, and among febrile infants, only 0.3% had HSV. In febrile neonates with CSF pleocytosis, the risk of enterovirus was 20 times higher during enterovirus season (March to September) and 6 times higher during the other months. Additionally, bacterial meningitis was 5 times higher than the rate of HSV in febrile neonates with CSF pleocytosis.⁵⁵ In an economic analysis by Caviness et al, testing (with CSF HSV PCR) and empirically treating febrile neonates with CSF pleocytosis was the most cost-effective strategy.⁵⁸ However, as discussed previously, up to 50% of neonates with HSV will have negative CSF testing, and this testing and treatment strategy would miss some neonates with this HSV. Importantly, RBCs in the CSF were not associated with HSV infection in a case-control study by Caviness et al,⁵⁹ and the absence of bloody CSF should not dissuade the emergency clinician from testing for HSV.

What is the bottom line for testing and empirically treating neonates for HSV? There is no consensus, as evidenced by the previously discussed studies and by well-written editorials from David Kimberlin, MD and Sarah Long, MD, who are experts on neonatal HSV.^{60,61} Neonates with lethargy, respiratory distress, seizures, elevated transaminases, skin or mucosal vesicles, hypothermia, and/or fever with CSF pleocytosis outside of enteroviral season should be tested and empirically treated with acyclovir.⁶⁰ A clinical strategy to also test and empirically treat all febrile neonates \leq 21 days of age is also an acceptable practice,⁶¹ especially since these neonates should undergo the full sepsis workup and be hospitalized on empiric antibiotics for 48 hours. Hepatic function panel testing is not part of the routine sepsis workup, but it could be considered as a screen for disseminated disease in the well-appearing febrile infant.⁵⁵ Importantly, given that delay in acyclovir therapy is associated with worse outcomes, HSV testing should be accompanied by empiric acyclovir therapy.⁵⁷ Testing should include both serum and CNS HSV PCR as well as HSV cultures from the skin

and mucous membranes when the disease is highly likely. Empiric therapy is high-dose acyclovir at 20 mg/kg/dose, which has been shown to significantly reduce 24-month mortality with few side effects.⁵⁴

Biomarkers

Recent research has also focused on serum biomarkers for identification of febrile young infants with SBI. The goal of these studies is to refine diagnostic accuracy for SBI in the febrile young infant, possibly with a serum test that can differentiate SBI from viral infections or other causes of fever. Procalcitonin is a biomarker that is very low in normal, healthy patients but has been shown to markedly increase with bacterial disease. A 2008 prospective study by Maniaci et al reported significantly higher procalcitonin levels in the febrile infant aged \leq 90 days with an SBI versus a nonbacterial cause of the fever.⁶² A 2012 study by Woelker et al likewise reported favorable diagnostic accuracy of procalcitonin when compared to the Rochester criteria in febrile infants aged 2 to 60 days.⁶³ A 2012 multicenter retrospective cohort study by Gomez et al also reported favorable test characteristics of procalcitonin in the well-appearing febrile young infant.⁶⁴ However, while procalcitonin is commonly used in Europe, most laboratories in the United States do not currently test for procalcitonin. Pending further study and refinement of appropriate cutoff values, procalcitonin should not be routinely utilized in the diagnosis and risk stratification of the febrile young infant. An ongoing multicenter prospective study by the Pediatric Emergency Care Applied Research Network is currently evaluating procalcitonin and other biomarkers in the febrile young infant.

For more information on the role of biomarkers on the evaluation and treatment of pediatric patients, see the October 2012 issue of *Pediatric Emergency Medicine Practice*, "The Role Of Biomarkers In Common Pediatric Emergency Department Complaints: An Evidence-Based Approach."

Disposition

As discussed previously, the neonate aged 0 to 28 days should be hospitalized on empiric antibiotic therapy, and consideration should be given to empiric acyclovir therapy. The ill-appearing febrile infant aged 29 through 56 days (at high risk for SBI per the low-risk criteria) should likewise be hospitalized on empiric antibiotic therapy. The well-appearing low-risk febrile infant aged 29 through 56 days can be discharged home if the family lives within 30 minutes of the hospital and 24-hour follow-up can be arranged. Similarly, the well-appearing febrile infant aged 57 to 89 days with normal laboratory studies can be discharged home with 24-hour primary care follow-up. The Boston criteria recommend treatment for all low-risk infants aged 28 through

89 days at discharge with intramuscular ceftriaxone and again at a return visit at 24 hours for a second dose of ceftriaxone, but this practice is not established elsewhere in the country.

A common question is whether otherwise well-appearing, low-risk febrile infants aged 29 through 89 days with only a positive urinalysis can be discharged home on oral antibiotics, as UTI is the most benign of the SBIs. As discussed in the "Low-Risk Criteria And Treatment" section beginning on page 6. Schnadower et al performed a multicenter retrospective study of 1895 febrile infants aged 29 through 60 days with UTI to derive a prediction model to identify patients at low risk for adverse events. Febrile young infants with UTI were at low risk for an adverse event if they were clinically well in the ED and did not have a high-risk past medical history; however, the study was retrospective, and the vast majority of the study sample received parenteral antibiotics.¹⁰ Therefore, at the current time, febrile young infants with UTI should still be hospitalized on IV antibiotics.

Summary

The febrile young infant is at high risk for SBI, and even the well-appearing baby is at risk for occult bacterial illness such as UTI, bacteremia, and meningitis. Therefore, all febrile young infants aged ≤ 56 days should undergo the full sepsis workup with urine, serum, and CSF testing. Even with normal laboratory testing, the febrile neonate is still at risk for SBI and should be hospitalized on empiric antibiotic therapy, and consideration should be given to testing

Cost- And Time-Effective Strategies

- Application of the low-risk criteria would allow approximately 30% of febrile young infants to be observed without the need for hospitalization or empiric antibiotic therapy, thereby reducing cost in addition to lowering the risk of nosocomial infection and adverse medication effects.⁴
Risk Management Caveat: The low-risk criteria only apply to well-appearing febrile young infants. In addition, 24-hour follow-up with the baby's primary care physician should be arranged prior to ED discharge to ensure that culture results are followed and a repeat physical examination is performed to identify any changes in clinical status.
- Development of evidence-based institutional clinical practice guidelines and pathways can standardize the workup of the febrile young infant and lead to more efficient and cost-effective care.⁶⁸

and treatment for HSV. If the febrile infant aged 29 through 56 days meets the low-risk criteria discussed, he can be discharged home if an outpatient care plan is established. The febrile infant aged 57 through 89 days is still at risk for UTI and should undergo testing for UTI, at a minimum, and may undergo the full sepsis workup depending on the standard practice of the treating emergency clinician.

Case Conclusion

Due to a nearly 20% incidence of SBI in febrile infants, the febrile 20-day old boy underwent a full sepsis workup with urine, serum, and CSF studies, including testing for enterovirus and HSV. The baby's enhanced urinalysis had 0 WBC, the CBC had a WBC count of 12,000/ mm³ with no bandemia, and the CSF had 2 WBCs. Recognizing that the low-risk criteria do not perform as well in neonates, he was hospitalized on empiric ampicillin, cefotaxime, and acyclovir therapy. Though the baby had a normal respiratory exam, you discussed with his mother that a full sepsis workup would have been performed even if the baby had bronchiolitis, as the risk of SBI is still high in the neonatal age group.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study will be included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, will be noted by an asterisk (*) next to the number of the reference.

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Risk Management Pitfalls For Febrile Infants (continued on page 15)

1. **“The neonate had a fever, but he was so well-appearing, I couldn’t justify doing the full sepsis workup. There was little chance he had a serious infection.”**

The febrile neonate is at high risk for an SBI; nearly 1 in 5 febrile neonates will have an SBI.³ This rate of infection is too high to defer testing in this age group. The well-appearing febrile young infant aged 29 to 56 days is also at risk for an SBI, with 8.8% of these patients testing positive for an SBI in a study by Baker et al.⁶

2. **“The baby was bundled, so we thought the rectal temperature of 38°C was probably environmental and that we didn’t need to perform the sepsis workup.”**

While temperatures can be falsely elevated from excessive external heat, the febrile young infant is a high-risk population, and a rectal temperature of 38°C should be assumed to be true and the full sepsis workup performed. It is unclear how to manage infants with fever by axillary or ear thermometers, which are less accurate than rectal thermometers. The guiding principle is that, due to the high incidence of SBI in this age group, strong consideration to performance of the full sepsis workup should be given.

3. **“The febrile baby was 61 days old, which was beyond the upper age limit of both the Philadelphia and Rochester criteria. We didn’t have to do any testing.”**

The Boston criteria extend the upper age limit for performance of the full sepsis workup through 89 days. While the Philadelphia and Rochester criteria have upper age limits of 56

and 60 days, respectively, the febrile young infant does not become low risk for SBI when he becomes 61 days old. The incidence of UTI is still high,²⁸ and, at minimum, a urinalysis and urine culture should be performed. Consideration should be given to performance of a CBC and blood culture, and, if the infant is ill-appearing or has a high serum WBC, CSF studies should be ordered.

4. **“The CBC was normal in the ill-appearing febrile young infant, so the risk of meningitis was very low, and I didn’t perform the lumbar puncture.”**

In a retrospective study of 5353 febrile infants aged 3 through 89 days, 22 of whom had bacterial meningitis, the WBC was normal (between 5000 and 15,000 WBC/mm³) in 41% of patients with meningitis.⁶⁵ The CBC alone is not an adequate screen for meningitis in this age group; therefore, a lumbar puncture should be performed.

5. **“The urinalysis, CBC, and CSF cell count were all normal in my febrile 10-day-old patient, so he met the low-risk criteria. I felt comfortable sending him home for his pediatrician to follow up the cultures.”**

The low-risk criteria do not perform as well in neonates, as demonstrated by 2 retrospective studies that showed a lower NPV of the criteria in neonates, with potential to falsely classify up to 1 in 10 febrile neonates as low risk.^{3,47} Therefore, neonates should be admitted on empiric antibiotic therapy pending culture results.

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Risk Management Pitfalls For Febrile Infants (continued from page 14)

6. **“While the 40-day-old febrile baby was very fussy on my examination, the laboratory tests were normal, so he met the low-risk criteria, and I discharged him home.”**
All the low-risk criteria require the baby to be well appearing on physical examination. (See **Table 3, page 5**.) Even with normal laboratory studies, if the infant is ill appearing or has a focal infection, the baby should be hospitalized on empiric antibiotic therapy.
7. **“The mother denied any history of HSV, so her 12-day-old baby who looked ill likely had a bacterial infection and did not have neonatal HSV.”**
The highest risk for transmission of neonatal HSV is to babies born to mothers who have a primary infection at the time of delivery.²⁴ The infection may be subclinical, so the mother may not know she had HSV when the baby presents to the ED. While the incidence of neonatal HSV is low,^{18,19} HSV testing and empiric acyclovir therapy should be performed in the ill-appearing, hypothermic, or seizing neonate or in the presence of vesicles.^{26,55}
8. **“Acyclovir is a toxic drug, so we waited for HSV testing to result in 24 or 48 hours before starting acyclovir therapy.”**
In the landmark neonatal HSV therapy study by Kimberlin et al, the only adverse effect directly attributed to acyclovir was transient neutropenia. Elevated creatinine and low hemoglobin occurred in the sickest babies with disseminated HSV infection, so the abnormalities were possibly related to the HSV and not to the acyclovir.⁵⁴ Additionally, in a retrospective study by Shah et al, each day’s delay in acyclovir initiation was associated with increased mortality in neonates with HSV.⁵⁷ Therefore, empiric acyclovir therapy should accompany HSV testing in the neonate.
9. **“I checked a bag urine sample in my febrile 70-day-old patient. The urinalysis was negative, so I didn’t perform a catheterization for urine culture.”**
In infants aged ≤ 90 days, the urinalysis is not as sensitive as in older infants and children, with a cross-sectional study by McGillivray et al reporting a sensitivity of 77% (95% CI, 54% to 100%) for urinalysis from bagged specimens in this age group.⁶⁶ The American Academy of Pediatrics’ 2011 UTI clinical practice guideline recommends that catheterized or suprapubic aspiration be utilized to obtain both urinalysis and urine culture in febrile children age 2 to 24 months in whom UTI is being evaluated.⁶⁷
10. **“The neonate was in shock. I gave antibiotics, which should have treated the sepsis.”**
While bacterial sepsis is a likely diagnosis in the neonate in shock, other etiologies include neonatal HSV, ductal-dependent congenital heart disease, and inborn errors of metabolism. (See **Table 2, page 3**.) In addition to antibiotic therapy and hemodynamic support, consideration should be given to initiation of acyclovir therapy, prostaglandin infusion, and testing with an ammonia level.

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1. The incidence of culture-positive bacterial illness in the well-appearing febrile infant aged 29 through 56 days is approximately:
 - a. < 1%
 - b. 8%
 - c. 20%
 - d. 30%
2. Which pathogen is the most common cause of SBIs in the febrile young infant?
 - a. *S aureus*
 - b. *L monocytogenes*
 - c. Group A streptococcus
 - d. *E coli*
3. A diagnosis to consider in the ill neonate is:
 - a. Sepsis
 - b. Ductal-dependent congenital heart disease
 - c. Inborn errors of metabolism
 - d. All of the above
4. The Philadelphia criteria are used to identify febrile neonates aged 0 through 28 days at low risk of serious bacterial infection.
 - a. True
 - b. False
5. In addition to urine, serum, and CSF studies, other routine testing to consider (regardless of symptoms) in the febrile young infant includes:
 - a. Chest x-ray
 - b. Stool cultures
 - c. Computed tomography of the brain
 - d. Enterovirus PCR
6. The incidence of SBI in febrile infants aged ≤ 60 days with RSV infection is approximately:
 - a. < 1%
 - b. 7%
 - c. 20%
 - d. 30%
7. Febrile infants aged 29 through 56 days who meet the Philadelphia low-risk criteria can be:
 - a. Hospitalized on vancomycin and gentamicin
 - b. Discharged home if 24-hour follow-up can be arranged
 - c. Hospitalized on IV ampicillin
 - d. Discharged home on oral amoxicillin
8. The mean age at presentation of neonatal HSV infection is approximately:
 - a. 1 day
 - b. 3 days
 - c. 14 days
 - d. 27 days
9. Which of the following is a type of neonatal HSV infection?
 - a. Central nervous system disease
 - b. Skin, eye, mouth disease
 - c. Disseminated disease
 - d. All of the above
10. What approximate percentage of neonates with disseminated and CNS types of neonatal HSV will have skin vesicles at presentation?
 - a. 5%
 - b. 20%
 - c. 60%
 - d. 95%

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Pediatric Diabetic Ketoacidosis: An Outpatient Perspective On Evaluation And Management

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Diabetic ketoacidosis is a common, potentially-serious complication in children with diabetes mellitus. Diabetic ketoacidosis can accompany new-onset insulin-dependent diabetes mellitus, or it can occur with established insulin-dependent diabetes mellitus during the increased demands of an acute illness or with decreased insulin delivery due to omitted doses or insulin pump failure. Additionally, diabetic ketoacidosis episodes in children with type II diabetes mellitus are becoming more frequent. The initial management of children with diabetic ketoacidosis is frequently done in an emergency department. Although the diagnosis is usually straightforward in a known diabetic patient with expected findings, a fair proportion of new-onset diabetics present in diabetic ketoacidosis. Physicians must be cognizant that diabetic ketoacidosis is an important consideration in the differential diagnosis of pediatric metabolic acidosis. The purpose of this issue of *Pediatric Emergency Medicine Practice* is to acquaint emergency physicians with the pathophysiology, treatment, and potential complications of this disorder.

Acute Otitis Media: An Evidence-Based Update

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Acute otitis media is one of the most common pediatric illnesses. However, there has been considerable controversy in its management. While most cases are treated with antibiotics, there is a growing concern regarding antibiotic overuse and subsequent drug resistance. Researchers in the Netherlands have developed a “wait and see” approach that has been successful in treating acute otitis media, although it has not gained much popularity in the United States. This issue of *Pediatric Emergency Medicine Practice* will summarize the latest research on the diagnosis of acute otitis media and on the different treatment regimens, including the efficacy of a “wait and see” approach.



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