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Managing Febrile Children Age 3-36 Months

Fever is one of the most commonly cited chief complaints for pediatric patients being brought into the emergency department (ED) for evaluation and, thereby, the most likely pediatric complaint to be encountered by the emergency physician (EP) during any given shift. The evaluation of the febrile infant who presents to the ED has changed significantly over the past few decades. The biggest challenge is to distinguish between patients who require a more robust and thorough evaluation and those who may be safely discharged home without additional invasive laboratory analysis or imaging. There is currently no universally accepted decision-making protocol for managing febrile children 3 to 36 months of age; some even advocate for reducing the age to infants 6-8 weeks. Understanding and recognizing the challenges and controversies centered on the management of fever in the patient between 3 to 36 months of age is critical for optimal management and reducing clinician risk.

— Ann M. Dietrich, MD, Editor

Introduction

Many experts have put forth clinical policies or practice guidelines for management of fever in the patient between 3 and 36 months, but the degree to which these are followed is widely variable and there is much debate as to the most effective management strategy.[1-5] The study of this problem is further complicated by the changing disease epidemiology, the advent of new vaccines and antibiotics, physician bias and experience, and parental risk tolerance.[6-8] For this reason, febrile children are traditionally risk stratified according to age, with 3-36 months encompassing the non-verbal or poorly verbal older infant and toddler.[9]

Definition of the Problem

Fever is defined by most sources as a rectal or core temperature > 38° C (100.4° F).[1,10] This definition is complicated by the various methods in which caregivers can evaluate for fever at home prior to making the decision to seek medical attention. The increasing desire of caregivers to avoid rectal thermometers and default to using less-invasive, infrared thermal detections systems can result in inaccurate readings and inappropriate classification of a febrile child. Numerous studies have evaluated the sensitivity and specificity of infrared thermometers as compared to rectal thermometers in accurately detecting a fever. Infrared thermometers are only 53% sensitive detecting rectal temperature ≥ 38° C, and only 27% sensitive detecting rectal temperature of ≥ 39° C (102.2° F).[11]

Fever in a child is a source of great concern and anxiety for many caregivers. "Fever phobia," a term coined in 1980, aptly describes the overwhelming fear that is generated when the thermometer reaches 38° C or higher.[12]

Executive Summary

- Fever is defined by most sources as a rectal or core temperature > 38° C (100.4° F).
- Characteristics of the fever itself, such as maximum temperature, duration, and response to antipyretics, should be documented but do not necessarily correlate with the presence of a serious bacterial infection.
- Febrile children presenting to the emergency department are now eight times more likely to have a false positive blood culture than a true positive.
- Antibiotics should not be delayed in critical patients; however, if antibiotics are going to be given to a well-appearing febrile child, emergency physicians should make certain that an appropriate diagnostic evaluation has been employed so as not to cloud the clinical picture.
- Evaluation for occult bacteremia is quickly approaching futility in fully vaccinated children, although unvaccinated and under-vaccinated children can still be at risk.

Misconceptions of the significance of fever plays a crucial role in prompting caregivers to seek medical attention. Over the past three decades, despite the increase in fever education and access to pediatric preventive care, fever continues to motivate the majority of pediatric ED visits in the United States.[13] In a study surveying caregivers of children seen in a pediatric ED, the median temperature that would prompt a visit to the ED was 39.4° C (103° F), with a range of 36.7° C (98° F) to 40.8° C (105.4° F).[14] Another survey of caregivers found that 25% gave antipyretics for temperatures < 37.8° C (100° F).[13] Fever illiteracy not only leads to inappropriate treatment but it also contributes to the problem of overcrowding, particularly in the winter months. There is a high level of anxiety in caregivers associated with febrile children presenting to the ED.[15] Up to 20% of children brought to clinic for a chief complaint of fever were never truly febrile.[16] Despite the benign nature of many ED visits for fever, pediatric fevers in this age group still exist that are associated with a serious bacterial infection (SBI), namely urinary tract infections (UTIs), bacteremia, meningitis, and pneumonia.

History and Physical Examination of the Febrile Young Child

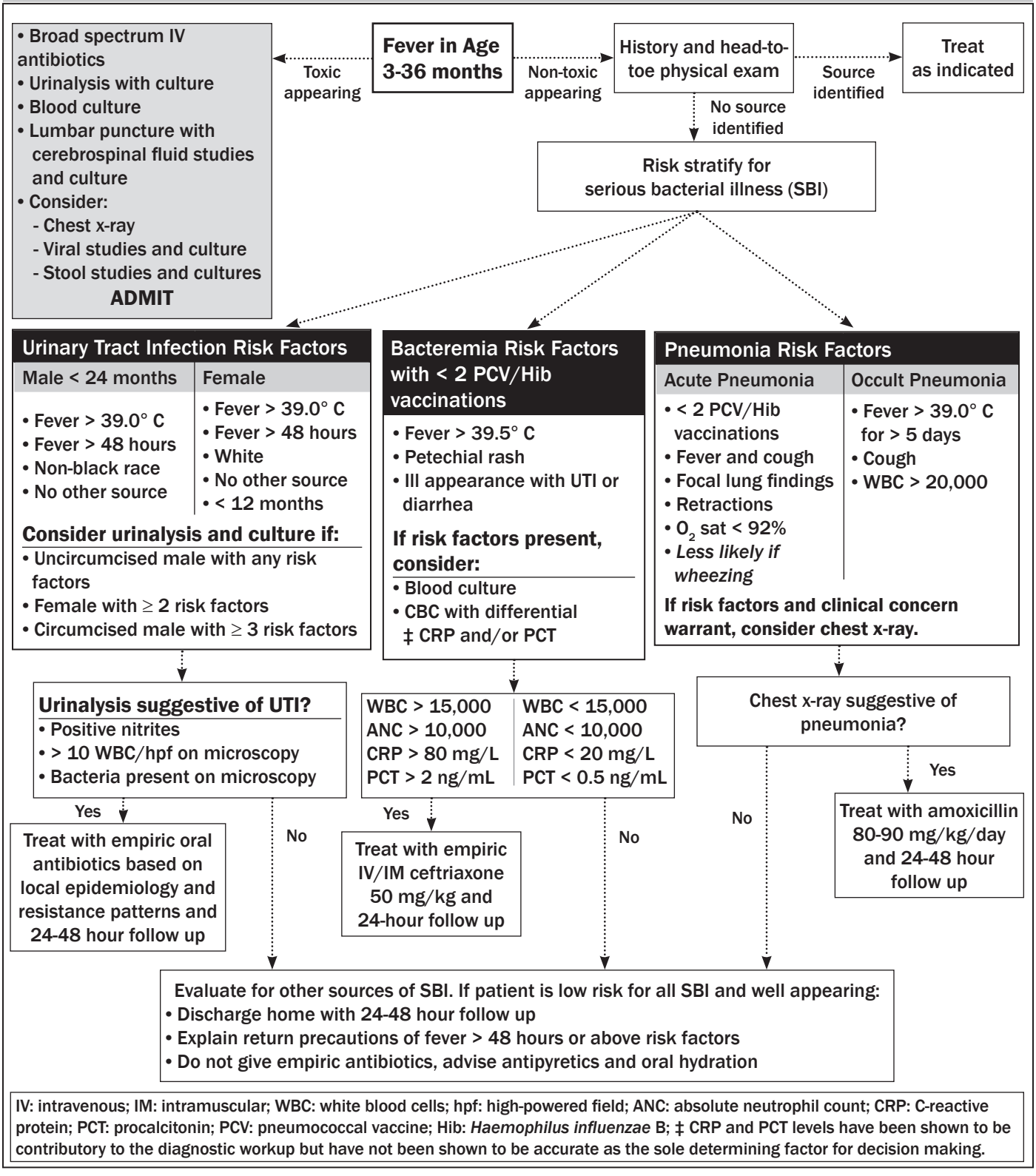
The presence or absence of fever is often a diagnostic crossroads in the evaluation of a child in the ED. Characteristics of the fever itself, such as maximum temperature, duration, and response to antipyretics, should be documented but do not necessarily correlate with the presence of an SBI.[17-22] Some studies have found that higher temperatures (> 40.0° C) are more suggestive of SBI, though others have found just the opposite, with extreme fevers more commonly associated with simple viral infections. The relationship between fever height and presence of a significant bacterial infection remains unclear.[17-19,23] A cyclic nature or prolonged duration of fever (> 5 days) may suggest an occult infection or a non-infectious etiology.[10] The initial evaluation of the febrile infant or child should be aimed at identifying the source of the fever rather than focusing on the fever itself. Concurrent symptoms, such as runny nose, cough, vomiting, diarrhea, rash, and complaints of pain in verbal children, can help identify this source. Non-verbal cues, such as refusing to bear weight or move an extremity, can help to localize a septic joint or osteomyelitis. Vaccination status and sick contact exposure also should be asked of the caregivers.

Physical examination is paramount in the evaluation of febrile young children. Toxic-appearing children should be treated aggressively for potential serious illnesses. Pay careful attention to the appearance, work of breathing, and color of the patient, as abnormalities in these three components of the physical exam can be the first clues to a serious illness.[24] Findings, such as cyanosis, rapid breathing, poor perfusion, or a petechial rash, correlate well with SBI and should prompt aggressive resuscitation, diagnostic testing, and broad-spectrum antibiotic therapy.[23,25] In a previously healthy, well-appearing child, physical exam findings can dictate the approach to the fever workup. Unlike febrile 0-3 month infants, 3-36 month children generally are thought to have a more reliable physical exam. Perform a complete head-to-toe examination on all febrile infants and young children, including removal of the diaper. If a source can be found in this age group, this decreases the likelihood of a concurrent SBI.[26] Identifiable sources that preclude further workup in the 3-36 month age groups include cellulitis or a well-known viral exanthema, such as varicella, hand-foot-mouth disease, or stomatitis. Likewise, children who test positive for influenza or who have clinical features of croup or bronchiolitis are far less likely to have a concurrent SBI.[27,28] Bear in mind that antibiotic therapy has a global effect on the patient and treatment of a "soft call" otitis media can mask or pretreat the actual cause of the illness. Review of the recent American Academy of Pediatrics (AAP) clinical practice guidelines on management of acute otitis media can help to guide antibiotic administration.[29]

If a justifiable entity for the fever cannot be found on the initial history and physical exam, a febrile child may require further evaluation

of fever without a source (FWS). Pre-vaccination estimates of SBI were 5-7% in children between 3-36 months of age.[30] Although the prevalence of SBI in this age group has not been reported in the post-vaccine era, the incidence of SBI in age 0-3 months has dropped considerably, leading most to believe that there is a similar drop in the 3-36 month age group. Although the vast majority of children with a FWS will have self-limited viral infection,[25-26] a proportion will have SBI. An algorithm for risk stratification of these entities is suggested in Figure 1.

Figure 1. Suggested Risk Stratification to the Febrile 3-36 Month Child without a Source



IV: intravenous; IM: intramuscular; WBC: white blood cells; hpf: high-powered field; ANC: absolute neutrophil count; CRP: C-reactive protein; PCT: procalcitonin; PCV: pneumococcal vaccine; Hib: *Haemophilus influenzae* B; ‡ CRP and PCT levels have been shown to be contributory to the diagnostic workup but have not been shown to be accurate as the sole determining factor for decision making.

Serious Bacterial Illnesses: Occult Bacteremia

Occult bacteremia refers to the presence of bacteria in the blood in an otherwise well-appearing febrile child without clinical evidence of sepsis. Prior to the widespread acceptance and routine use of pediatric vaccines, the prevalence of occult bacteremia was cited as between 2.4-11.6%.[30,31] The majority of cases of occult bacteremia were due to *Streptococcus pneumoniae* (50-90%), followed by *Haemophilus influenzae* (3-25%), and then *Salmonella* species and *Neisseria meningitides.*[32] Following the introduction of the *H. influenzae* type b (Hib) vaccine in 1985, the prevalence of Hib infection is nearly non-existent.[33-34] The introduction of the seven-valent pneumococcal conjugate vaccine (PCV-7) has had a dramatic effect on the prevalence of occult bacteremia in the pediatric population. The 7-valent Prevnar vaccine was first marketed by Wyeth in 2001. Although even a single dose has been shown to confer significant immunity (75%), a second dose of PCV-7 reaches upwards of 95% immunity and is usually associated with exceedingly low risk for occult bacteremia.[3,35] Studies conducted nearly a decade after the introduction of the PCV-7 have shown a dramatic decline in the prevalence of overall occult bacteremia in the pediatric population, as low as 0.16-0.7%.[36,37] Nearly a decade later, in 2010, 13-valent Prevnar (PCV-13) was approved by the FDA for distribution by Pfizer. Initial investigations into the effect of PCV-13 have shown a 42-53% decrease in invasive pneumococcal disease from the already low levels obtained by PCV-7.[38] The effect of vaccination and subsequent herd immunity completely changed the epidemiology of this SBI.[39]

This decrease in prevalence has made many question the practice of routine blood cultures in febrile 3-36 month old children. Febrile children presenting to the ED are now eight times more likely to have a false positive blood culture than a true positive.[36,37-43] Given the low rates of occult bacteremia in the pediatric population, it has been suggested that obtaining blood cultures in the otherwise well-appearing febrile child is no longer necessary in the post-vaccine era.[44-46] The majority of EPs are already practicing this way by forgoing blood cultures in fully vaccinated febrile children.[4]

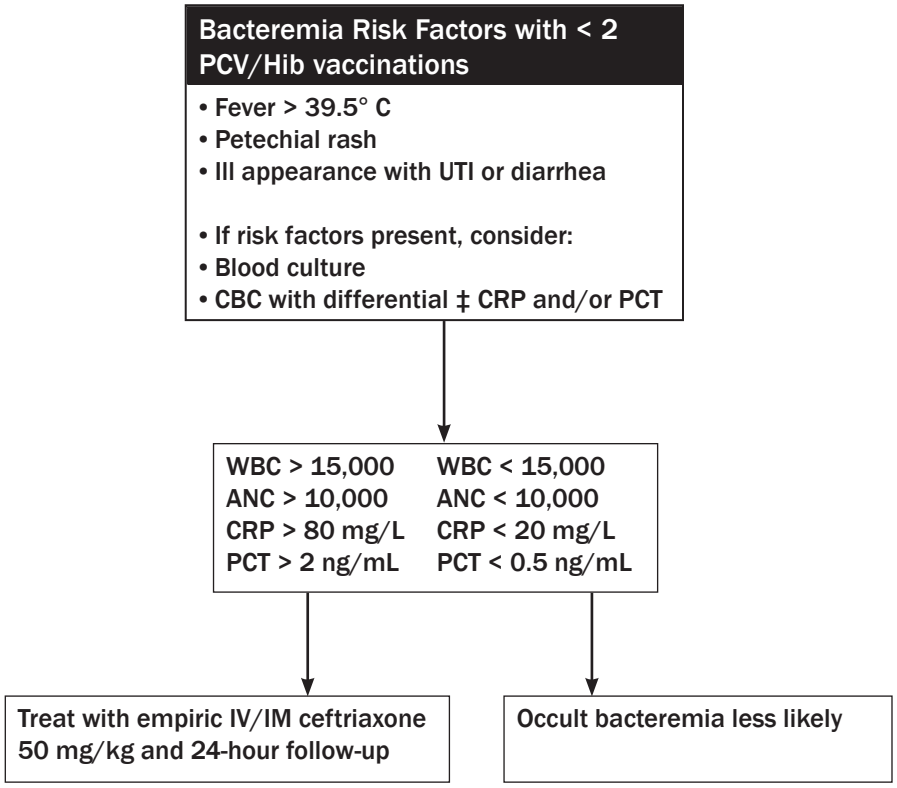
Though foregoing blood cultures is a popular trend, consider that the same study found that 20% of EPs prescribed antibiotics to children presenting with FWS during which no laboratory testing was performed. The utility of blood cultures in a well-appearing febrile child is questionable at best, but the utility of a blood culture (or any culture, for that matter) that has been pretreated with antibiotics is virtually nothing. Antibiotics should not be delayed in critical patients; however, if antibiotics are going to be given to a well-appearing febrile child, EPs should make certain that an appropriate diagnostic evaluation has been employed so as not to cloud the clinical picture.[47] Also consider that full vaccination rates at 2 years of age hit historic lows in 2011 across the country.[48] Many of these areas were clustered in neighborhoods or regions, thus making herd immunity a less reliable safety net in those areas. One study found that parents are often uncertain about their child's vaccination status with regard to Hib and pneumococcus and give false reports nearly one-third of the time.[49] For this reason, verification of vaccination status can be helpful in the management of FWS. EPs should consider asking for vaccination records or consulting state and local vaccination registries if there is any doubt, though this is not always practical or possible.[50] As a brief shorthand, EPs can inquire as to whether the child received vaccines at 2, 4, and 6 months, as these are the most common timing of pneumococcal and Hib vaccinations.

Evaluation for occult bacteremia is quickly approaching futility in fully vaccinated children, although unvaccinated and under-vaccinated children can still be at risk. This evaluation requires a blood culture as a gold standard and, traditionally, a complete blood count (CBC) as a surrogate marker. Fever > 39.5° C has been found to be the most efficient, cost-effective, and prudent cutoff to prompt a workup in children who have received one or no pneumococcal or Hib vaccination.[1,2,51,52] At these temperatures, a CBC with manual differential looking for bandemia and a confirmatory blood culture should be considered. A white blood cell count (WBC) > 15,000/mm^3 or an absolute neutrophil count (ANC) > 10,000/mm^3 should prompt more concern for occult bacteremia. Current recommendations are to consider antibiotic therapy in incompletely vaccinated patients with ceftriaxone 50 mg/kg IV or IM with 24 hours follow-up in a primary care clinic or in the ED. Ill-appearing children or children with poor follow-up and support should be considered for admission (*see Figure 2*).

Patients with *Escherichia coli* and *Salmonella bacteremia* usually have concomitant UTI and gastroenteritis, respectively. Well-appearing children with UTI or gastroenteritis are at low risk for bacteremia but ill-appearing children with evidence of UTI or diarrhea should have screening blood cultures obtained prior to antibiotic therapy. Updated epidemiologic data are needed to better understand the effect of newer vaccines and the current state of occult bacteremia.

Many decision rules have been devised in an attempt to identify those at low risk for SBI.[53-60] However, all have showed variable performance when applied to different prevalence rates and patient populations.[61,62] Many biomarkers and acute phase reactants have been studied in an attempt to discover a sensitive screening tool a specific predictor of SBI. To date, no single laboratory test has been well correlated as a marker for SBI with most showing similar diagnostic properties.[63]

Figure 2. Suggested Risk Stratification for Occult Bacteremia



IV: intravenous; IM: intramuscular; WBC: white blood cells; ANC: absolute neutrophil count; CRP: C-reactive protein; PCT: procalcitonin

‡ C-reactive protein and procalcitonin levels have been shown to be contributory to the diagnositic workup, but have not been shown to be accurate as the sole determining factor for decision making.

Adapted from: Baraff L. Management of fever without source in infants and children. *Ann Emerg Med* 2000;36:602-614.

C-reactive protein (CRP) and procalcitonin (PCT) have shown some promise in ruling out and ruling in SBI.[65-67] CRP levels of < 20 mg/L and PCT levels < 0.5 ng/mL have been correlated to a < 5% risk of SBI. CRP levels > 80 mg/L and PCT levels > 2 ng/mL have been correlated with a 72% risk of SBI.[66] A combination of CRP and PCT was even more sensitive and specific. However, the role in which any biomarkers have to play in the evaluation of FWS is still debated.[68,69] Most agree that biomarkers can play a contributory role in the evaluation but should not be the sole determining factor for decision making.[64]

Serious Bacterial Illnesses: Meningitis

The incidence of meningitis is falling along the same rate as bacteremia since the latter is usually the cause of the former. The incidence of *H. influenzae* meningitis has dropped by 97% after Hib vaccination and PCV-7 has greatly reduced the virulent strains of *S. pneumoniae* to only a few serotypes.[70-73] Many of these remaining strains have been included in the new PCV-13 series.[74,75] Patients with indwelling cranial hardware (such as ventricular shunts or cochlear implants), basilar skull fractures, recent neurosurgical intervention, and certain congenital central nervous system or genitourinary anomalies have a higher risk of meningitis and should be screened accordingly.

Meningococcemia remains a rare but important cause of bacteremia and meningitis. Children often will start with vague symptoms of fever, upper respiratory symptoms, and malaise that rapidly progress to lethargy, altered mentation, and petechiae.[76,77] Recent exposure to meningococcus should be concerning, even in patients receiving prophylaxis if they are symptomatic. Prompt recognition and aggressive antibiotic and supportive therapy is crucial for treatment as mortality is high within 24 hours of onset.[78]

Serious Bacterial Illnesses: Pneumonia

The most common culprits of pediatric pneumonia continue to be viruses and *S. pneumoniae*.[79,80] Other etiologies, such as mycoplasma, chlamydophilia, group A Streptococcus, and *Bordatella pertussis,* remain less common but notable sources in this age group. Pneumonia has long been diagnosed clinically with a history of cough, fever, and dyspnea. Clinical features do not reliably diagnose pneumonia on their own,[81] though physical exam findings of tachypnea, retractions, and focal crackles on lung auscultation have been shown to have a higher correlation.[81,82] Conversely, wheezing has been shown to make pneumonia less likely.[84] Pulse oximetry readings < 92% have been correlated with pneumonia,[85] though laboratory testing, including CBC, CRP, or procalcitonin, have had varying results in diagnosis of outpatient pneumonia.[64,86,87] (*See Figure 3.*)

There is debate over whether chest x-ray should even be considered a gold standard, as there is variation in the interpretation by radiologists[88] and chest x-ray has not been shown to reliably distinguish between bacterial and viral infections.[89,90] This has led the Infectious Diseases Society of America to suggest empiric treatment of outpatient pneumonia based on clinical findings alone as they do not appear to change the clinical

outcome.[91-93] This has sparked considerable controversy and many still feel that chest x-ray is the most reliable means of diagnosing pneumonia in this age group.[94]

Regardless of the method of diagnosis, recommendations for outpatient pneumonia therapy are high-dose amoxicillin (80-90 mg/kg/day divided q12 hours) due to high levels of resistance.[91,95-97] Young infants (ages 3-5 months), severe tachypnea, and oxygen saturations less than 90% are good predictors of outpatient failure and should be considered for admission.[98] Non-toxic admitted patients can be treated with high-dose ampicillin 400 mg/kg/day divided q6 hours in areas with low *S. pneumoniae* resistance.[91] Unimmunized children, toxic children, children with empyema, or children who live in areas with high levels of *Streptococcal* resistance should receive ceftriaxone or another third-generation cephalosporin. Blood cultures should not be obtained in patients who are well enough to be discharged, though cultures should still be obtained in admitted patients as the prevalence of true positive nears 7%.[99] Mycoplasma pneumonia is uncommon in children aged 3-36 months and combination empiric therapy with macrolide antibiotics has not been shown to change outcome in hospitalized patients.[100]

Patients with fever longer than 5 days can sometimes have an occult pneumonia, one that is present on chest x-ray but without the classic symptoms.[83] Findings predictive of an occult pneumonia include fevers > 39.0° C, fevers for longer than 5 days, cough, and WBC > 20,000/mm^3. In these patients, a chest x-ray is warranted to evaluate for an occult source for the prolonged fever (*see Figure 3*).

Figure 3. Suggested Risk Stratification for Pneumonia

Pneumonia Risk Factors	
Acute Pneumonia	**Occult Pneumonia**
• < 2 PCV/Hib vaccinations • Fever and cough • Focal lung findings • Retractions • O_2 sat < 92% • *Less likely if wheezing*	• Fever > 39.0° C for > 5 days • Cough • WBC > 20,000

If risk factors and clinical concern warrant, consider chest x-ray.

***Adapted from*: Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;128:595-610.**

Serious Bacterial Illnesses: Urinary Tract Infections

In the post-vaccine era, UTIs are the most common SBI found in febrile infants and small children.[101] However, typical symptoms of dysuria, flank pain, or abdominal pain can be difficult to ascertain in the 3- to 36-month-old child. Parental report of foul-smelling urine is suggestive of a UTI and may prompt a urinalysis.[102] The reported prevalence of UTI approaches 5% in febrile children without another obvious source on history of physical examination.[103,104] UTIs in this age group are usually ascending infections unlike the hematogenous spread in the neonatal period. For this reason, gram-negative flora from stool is usually the pathogen. The recommended method for obtaining a urine specimen in non-toilet trained children is either bladder catheterization or suprapubic aspiration.[101] A "clean catch" or bag-urine sample can be obtained by other methods; however, it is often contaminated. Any positive result on urinalysis or microscopy must be confirmed with a catheterized or aspirated specimen for culture. Once a catheterized or aspirated urine is obtained, urinalysis (either by enhanced urinalysis with microscopy or by dipstick) and culture should be performed. The gold standard remains urine culture with the growth of > 50,000 colonies/mL.[105] However, since culture results are never readily accessible in an ED setting, empiric antibiotic treatment should be started based on suggestive results from a preliminary urinalysis. Though no one portion of the urinalysis can conclusively diagnose UTI on its own,[106] evidence of nitrites or leukocyte esterase is strongly suggestive of it.[107-109] The addition of microscopy increases both the sensitivity and specificity of the examination with the addition of > 10 white blood cells per high power field and/or the presence of bacteria.[108] Antibiotic therapy should be targeted against the most common etiology, *E. coli*. However, other gram-negative bacteria and occasional gram-positive bacteria can also be culprits, so local culture prevalence and resistance patterns should guide treatment. Febrile infants and children under age 3 years of age with a UTI should be treated for 7-14 days regardless of the specific antibiotic chosen.[101]

Recently published practice guidelines by the AAP attempt to risk stratify patients into low risk and high risk.[101] These risk factors are different for males and females. Male infants < 24 months can first be categorized as circumcised or uncircumcised. Those older than 24 months have an exceedingly low-rate risk of UTI and are generally excluded from study. Uncircumcised males are more than three times more likely to have UTIs compared to those who are circumcised.[111] Independent risk factors for UTI in both groups include previous UTI, fever > 39°C, fever duration > 48 hours, non-black race, and lack of another obvious source.[112] Female infants are anatomically more likely to have UTIs and carry more than twice the relative risk of UTI when compared to males. However,

they too can be risk-stratified based on their race, age, temperature, length of fever, and exam findings. White race, age < 12 months, maximum temperature > 39°C, fever > 2 days, and absence of another obvious source for infection were all independent risk factors for UTI.[113] Ultimately, low-risk patients include females with 2 or less risk factors, uncircumcised males with no risk factors, and circumcised males with 3 or less risk factors.[101] (*See Figure 4.*)

The AAP guidelines recommend urine testing on all FWS that do not meet low-risk criteria, arguing that failure to treat UTI can lead to renal scarring, hypertension, renal failure, sepsis, and a low but not insignificant mortality rate.[113-116] However, some argue that these guidelines are too aggressive, leading to over-diagnosis, over-exposure to antibiotics, and patient discomfort.[117] Urinary catheterization also carries with it patient discomfort, parental anxiety, and a risk of false tracking. For these reasons, some authors postulate that febrile children who are otherwise well be monitored closely for 4-5 days until urinary catheterization is warranted.[117]

Figure 4. Suggested Risk Stratification for Urinary Tract Infection

Urinary Tract Infection (UTI) Risk Factors	
Male < 24 months	**Female**
• Fever > 39.0° C • Fever > 48 hours • Non-black race • No other source	• Fever > 39.0° C • Fever > 48 hours • White • No other source • < 12 months
Consider urinalysis and culture if:	
• Uncircumcised male with any risk factors • Female with ≥ 2 risk factors • Circumcised male with ≥ 3 risk factors	

Adapted from: Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011;53:e25e76.

Confounding Viral Infections: Influenza and RSV

The vast majority of fevers in children 3-36 months old are due to a viral illness that is self-limiting and often requires nothing more than supportive care. Concomitant viral and bacterial infection is not unheard of and care should be taken to fully evaluate a patient for SBI before making a clinical diagnosis of viral syndrome.[80] Laboratory-confirmed viral diagnoses, such as influenza and respiratory syncytial virus (RSV) can significantly lower the risk of SBI.[27,28,118,119] The most common co-infection continues to be UTI; however, recent studies show that rate to be as low as 1.1%.[120] Testing for RSV and influenza in the ED setting is often prudent, as clinical course and potential antiviral therapy can be predicted. On the contrary, testing for other viral etiologies does not offer change in therapy or decision-making.

Influenza can often present first with fever, and a rapid influenza screen can prove useful if obtained within the first 48 hours during influenza season.[121] Antiviral therapy with oseltamavir (6 mg/kg/day divided q12 hours) is generally recommended for children < 2 years of age.[122]

Confounding Bacterial Infections: Osteomyelitis, Cellulitis and Otitis Media

Osteomyelitis and septic joints have a very low incidence in developed countries.[123] Symptoms can include fever, refusal to bear weight or move an extremity, and warm, swollen joints.[124] CBC, CRP, and erythrocyte sedimentation rate (ESR) can aid in diagnosis. Antibiotic therapy should be directed against *S. aureus* and *S. pneumoniae* as the most common etiologies, and methicillin-resistant *S. aureus* (MRSA) should always be considered a possible pathogen.[125,126] Sickle cell patients are more prone to *Salmonella osteomyelitis* and will be discussed in more detail below. Blood cultures should be obtained on all patients suspected of bone and joint infections prior to antibiotic administration whenever possible. They are often negative but can help direct and narrow antibiotic therapy when positive.

On the other hand, the treatment of cellulitis is rarely ever changed by blood cultures. Cellulitis can usually be readily identified on physical exam as a source for fever and may even require admission for parenteral antibiotics depending on the progression and size of the affected area. Still, well-appearing patients with simple cellulitis have a low risk of bacteremia and blood cultures are not indicated, even if the child is febrile.[127] Likewise, otitis media in children aged 3-36 months is rarely complicated by bacteremia, though mastoiditis is a remote possibility.[20]

Special Situations: Febrile Seizures

Febrile seizures are common in children between the ages of 6-60 months and are frequently seen in the ED. They are of great concern to parents, as fever and seizure have traditionally been associated with meningitis.[128,129] However, recent epidemiologic studies have shown that fully vaccinated children with a first-time simple febrile seizure have a very low rate of meningitis.[130] Simple febrile seizures are defined as non-focal seizures in a previously

normal healthy child associated with a temperature of > 38.0°C lasting < 15 minutes that occur only once in 24 hours.[131] Complex seizures, in contrast, have focality to the movements, prolonged activity > 15 minutes, or two or more within a 24-hour period. While complex febrile seizures may have a higher association with epilepsy,[132] they do not seem to correlate with meningitis in the post-vaccine era.[133] Lumbar puncture is not necessarily required unless there is a high clinical suspicion or the child does not return to a normal baseline. An appropriate fever evaluation as outlined above should be employed independent of the presence of a simple febrile seizure. In contrast, complex seizures should be fully evaluated. Children with complex febrile seizures should be admitted or transferred for observation and consultation with a pediatric neurologist. Children with simple febrile seizures can be discharged home once they return to baseline.

Special Situations: Sickle Cell Disease and Asplenia

Several congenital and acquired pediatric conditions must be treated very differently when FWS presents. Sickle cell disease (SCD) is one such condition where aggressive management must be pursued at the first sign of fever. Patients with SCD lose the ability to fight encapsulated organisms such as *S. pneumoniae*, *E. coli*, and *Salmonella* due to autoinfarction of the spleen from sickled cells.[134] Patients with post-surgical asplenia, congenital asplenia, or functional asplenia (polysplenia) can be considered to have the same susceptibility to encapsulated organisms. Patients < 1 year of age are especially at risk for bacteremia, osteomyelitis, and acute chest syndrome (a combination pulmonary infarction and pneumonia). Vaccination with PCV-7 has dramatically decreased the risk of invasive pneumococcal disease to between 0.6-1.1%,[135,136] but rates of pneumonia remain high at > 13%.[136] Providers should inquire about vaccination with the 23-valent (PPV-23) vaccine as well as compliance with daily penicillin prophylaxis to help judge a patient's risk for SBI.[137]

Functionally asplenic patients with fever > 38.5° C should have a full fever evaluation, starting with a complete head-to-toe physical exam, focusing on the lung and musculoskeletal exam, followed by a CBC, reticulocyte count, and blood cultures. Patients with respiratory distress, hypoxia, and cough should be suspected of having acute chest syndrome regardless of the result of the chest x-ray.[138] SCD patients without an obvious source who appear toxic or have fevers > 40.0° C should receive prompt antibiotic therapy with a third-generation cephalosporin followed by broad diagnostic testing and admission to the hospital.[139] Non-toxic patients with fever < 40.0° C should also receive empiric parenteral antibiotics with a third-generation cephalosporin but may be discharged home if their workup is unremarkable and they have close follow-up, good support, and access to care. Patients who have pulmonary infiltrates on chest x-ray, WBC > 30,000/mm^3 or < 5,000/mm^3, thrombocytopenia < 100,000/mm^3, or hemoglobin < 5 mg/dL should be admitted for further monitoring and continued parenteral antibiotic therapy.

Special Situations: Neutropenic Fever

Chemotherapy-induced neutropenia is the most common immunodeficiency seen in EDs and is defined by an absolute neutrophil count < 500/mm^3.[140] Infectious causes of fever in this group can be quickly fatal if not found and treated promptly. Care of these patients should be coordinated with a pediatric oncologist whenever possible, as patients presenting through the ED have a worse outcome than those presenting through their oncologist's clinic.[141]

Patients receiving chemotherapy should have a CBC with manual differentiation to determine whether they are neutropenic. Non-neutropenic patients can be treated as previously discussed in healthy febrile children. Neutropenic patients have a much higher rate of bacteremia and fungemia. These patients should have blood cultures, both aerobic and anaerobic, urinalysis with culture, and imaging where applicable by history and physical exam.[142] Although UTIs are common in febrile neutropenic patients, it should be deferred in younger children who require catheterization as this can increase the risk of bacteremia.[143] Patients with central venous catheters should have blood cultures obtained from each port, as well as from a peripheral site to assess for line infection.

Empiric antibiotic therapy should be broad-spectrum, anti-pseudomonal ß-lactams or carbapenems but should also focus on likely etiologies. Neutropenic fever patients are at an increased risk for hospital-acquired infections and a trend toward more gram-positive bacteremia and fungemia has been seen.[144] Fungemia is usually not an ED diagnosis as it is rarely suspected until patients have continued with fever for > 6 days on appropriate broad-spectrum antibiotic therapy. Patients with indwelling catheters should have coverage for MRSA. Prompt antibiotic administration leads to better outcomes in febrile neutropenics,[141] though no evidence exists to show that starting antifungal therapy in the ED improves outcome.

Non-Infectious Sources of Fever: Kawasaki Disease and Others

Although the most common etiology of childhood fever is an infectious source, care should be taken not to ignore potentially serious non-infectious causes of fever. Reactive, rheumatologic and oncologic, pharmacologic, and genetic issues can all be sources of persistent fever that may present to the ED with multiple negative previous evaluations. Cyclical fever syndromes usually present in regular intervals over the course of years before they are diagnosed.[10] Fever along with

weight loss, bone pain, limp, and night sweats can be associated with leukemia. Rheumatologic and autoimmune disorders, such as juvenile idiopathic arthritis, systemic lupus erythematosus, and Crohn's disease, can present with fever as the most concerning of a host of symptoms. Of the non-infectious sources of fever, the most readily treatable condition is Kawasaki disease (KD).

KD is a systemic inflammatory process that primarily affects the small- and medium-sized vessels. Despite several decades of research, very little is still known about the pathophysiology of the disease. KD primarily affects young infants, with 85% of cases occurring in children younger than 5 years of age. Clinical diagnosis of "complete" KD requires the presence of fever for > 5 days and four of the five following criteria:[16,17]:

1) Conjunctivitis: bilateral conjunctivitis that is typically non-exudative and limbic sparing

2) Mucosal changes: "strawberry tongue;" diffuse erythema of the oropharyngeal mucosa without exudates; erythema, cracking, or peeling of the lips.

3) Lymphadenopathy: cervical lymphadenopathy typically a unilateral node of > 1.5 cm in diameter, or it can be manifested as several smaller firm nodes bilaterally.

4) Polymorphous rash: nonspecific diffuse maculopapular rash

5) Peripheral extremity changes: erythema or induration of the palms and/or soles in the acute phase or periungal desquamation in the subacute phase.

"Incomplete" KD can be diagnosed in children with the presence of fevers for > 5 days and only two or three of the previous criteria. The clinical manifestations of KD can be documented during any point in the acute or subacute phases of the disease. Thus, it is important to take a thorough history of clinical features when obtaining the patient's history from the parents. Other features of KD, which are often noted in patients but not included in the formal diagnostic criteria, include irritability, gastrointestinal complaints, respiratory complaints, aseptic meningitis, arthralgia, arthritis, urethritis, uveitis, and otitis. Atypical KD is a term used to describe patients who meet the definition of "complete" KD but also have concurrent features such as hydrops of the gallbladder, renal involvement, or other serious neurological sequelae.[145-146]

Although laboratory tests are not required in the diagnosis of KD, there are a few non-specific markers that could support the diagnosis, particularly in children who do not meet the criteria for "complete" KD. The acute phase of the disease is typically associated in a rise in acute phase reactants such as ESR (> 40 mm/h) and CRP (> 30 g/L). In addition, a complete blood count may reveal a high WBC (> 15,000/mm^3) with a neutrophil predominance (above normal range for age), anemia, and thrombocytosis (> 450,000/mm^3, typically after 7 days) is often noted. Finally, a basic metabolic panel may reveal hypoalbuminemia (< 3.0 g/dL) and a transaminitis (above normal range for age).[52,146]

Of great significance is the predilection for vasculitis of the coronary arteries. Having an appropriately high index of suspicion and prompt recognition and treatment of KD is vital to the prevention of long-term cardiac injury, most notably, coronary artery aneurysm. The incidence of coronary artery aneurysms is as high as 20% in untreated children diagnosed with KD. Management, therefore, requires hospital admission and rapid administration of IV immunoglobulin (IVIG). The American Heart Association recommends a single dose of 2 g/kg IVIG infused over 12 hours. In addition, it recommends giving high-dose aspirin (80-100 mg/kg/day divided q6 hours) while the child is febrile and then switching to low-dose aspirin (3-5 mg/kg/day) after the child has been afebrile for 48-72 hours.[145]

Summary

Pediatric fever is a common ED complaint that provokes anxiety in both caregivers and medical providers. The effect of widespread vaccination has had a profound effect on decreasing the rate of SBI. Though most febrile children aged 3-36 months now have benign viral illness, the risk of SBI remains, albeit much smaller. Risk stratification should be used to guide the emergency physician's clinical judgment as to which patients warrant diagnostic testing. Ongoing studies and new biomarkers have shown some promise in assisting with sensitive rule-out criteria and specific diagnostics. Patients with special health care needs, assistive indwelling devices, or medical conditions such as sickle cell disease or immunosuppression should be screened much more closely for SBI, although these patients are also showing lower rates than in previous years. Non-infectious sources should still be considered in ED presentations of fever, but infectious sources remain the most pressing cause. Further study into the post-vaccine epidemiology of SBI should focus on identifying the next generation of SBI and the appropriate screening criteria for these new common illnesses.

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CME Questions

1. What is currently the most common serious bacterial illness in children 3-36 months of age?
   a. Pneumonia
   b. UTI
   c. Bacteremia
   d. Meningitis
2. Which of the following febrile infants is most likely to have a serious bacterial illness?
   a. 3-month-old male with runny nose, cough and fever of 38.0° C for 4 days
   b. 2-year-old female receiving chemotherapy for acute lymphoblastic leukemia who has fever to 38.3° C and an absolute neutrophil count of 1,500/mm^3
   c. 3-year-old uncircumcised African-American male with fever to 39.5° C, vomiting, and diarrhea
   d. 2½-year-old female with fever to 40.2° C who has never been immunized
3. Which of the following routine tests should be avoided in neutropenic patients with fever without clinical symptoms?
   a. Complete blood count with differential
   b. Catheterized urinalysis with culture
   c. Blood culture
   d. Chest x-ray
4. Which of the following is a mandatory finding for diagnosis of Kawasaki disease?
   a. Fever > 5 days
   b. Bilateral conjunctivitis
   c. Strawberry tongue
   d. Erythrocyte sedimentation rate > 40 mm/h
5. Which of the following is the most important step in the management of an 18-month-old male with sickle cell disease and a fever of 39.6° C and no apparent source?
   a. Urinalysis with culture
   b. Antipyretics
   c. Chest x-ray
   d. Blood cultures and empiric parenteral antibiotics
6. A previously healthy 2-year-old male with fever to 39.0° C for 6 days and a completely normal physical exam is most likely to have:
   a. an occult pneumonia; a chest x-ray should be ordered.
   b. Kawasaki disease; intravenous immunoglobulin should be given.
   c. osteomyelitis; a magnetic resonance imaging study should be ordered.
   d. fungemia; empiric antifungal therapy should be given.

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Pediatric Emergency Medicine Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in pediatric patients presenting to the emergency department;
- describe the epidemiology, etiology, pathophysiology, historical and examination findings associated with conditions in pediatric patients presenting to the emergency department;
- formulate a differential diagnosis and perform necessary diagnostic tests;
- apply up-to-date therapeutic techniques to address conditions discussed in the publication;
- discuss any discharge or follow-up instructions with patients.

7. A toxic-appearing 20-month-old female is brought into the emergency department. She is intubated and intraosseous line is placed. Blood cannot be aspirated from the intraosseous line but a bolus of fluids is easily infused. Which of the following is the next most appropriate step in management?
   a. Bladder catheterization to obtain urine for culture
   b. Administration of empiric broad-spectrum antibiotics through the intraosseous line
   c. Lumbar puncture to obtain cerebrospinal fluid for culture
   d. Central venous catheter placement to obtain blood for culture

8. Which of the following patients is most likely to have a urinary tract infection?
   a 2-year-old white female with fever to 38.5° C, runny nose, and cough for 24 hours
   b. 7-month-old circumcised white male with diarrhea and fever to 39.8° C for 6 hours
   c. 10-month-old uncircumcised African-American male without a prior UTI history now with vomiting and fever to 39.1° C for the past 24 hours
   d. 3-year-old white male with fever to 39.5° C for the past 3 days and no prior history of UTI and no obvious source on exam.

9. Which of the following well-appearing patients should have further evaluation for SBI with a fever to 39.5° C?
   a. 12-month-old female with cough and clear nasal discharge
   b. 18-month-old male with oral vesicles
   c. 8-month-old female with diffuse wheezing
   d. 2-year-old male with bilateral bulging tympanic membranes with effusion
   e. None of the above

10. A 2-year-old Hispanic female has a generalized seizure lasting 2 minutes associated with a fever of 38.3° C in the emergency department. Patient was otherwise well this morning and developed a fever prior to onset of the seizure. Patient has been fully immunized. On exam, the patient is well-appearing, playful, and back to baseline per her parents. No obvious source for her fever can be found. Which is the next most appropriate step in management?
    a. Catheterized urinalysis with culture, complete blood count (CBC), blood culture, lumbar puncture, empiric antibiotics, and admission
    b. Catheterized urinalysis with culture, CBC, blood culture, lumbar puncture, empiric antibiotics, and discharge if results are normal
    c. No testing needed but patient should be admitted for monitoring and neurology consultation
    d. No testing needed, patient can be discharged home with primary care follow up

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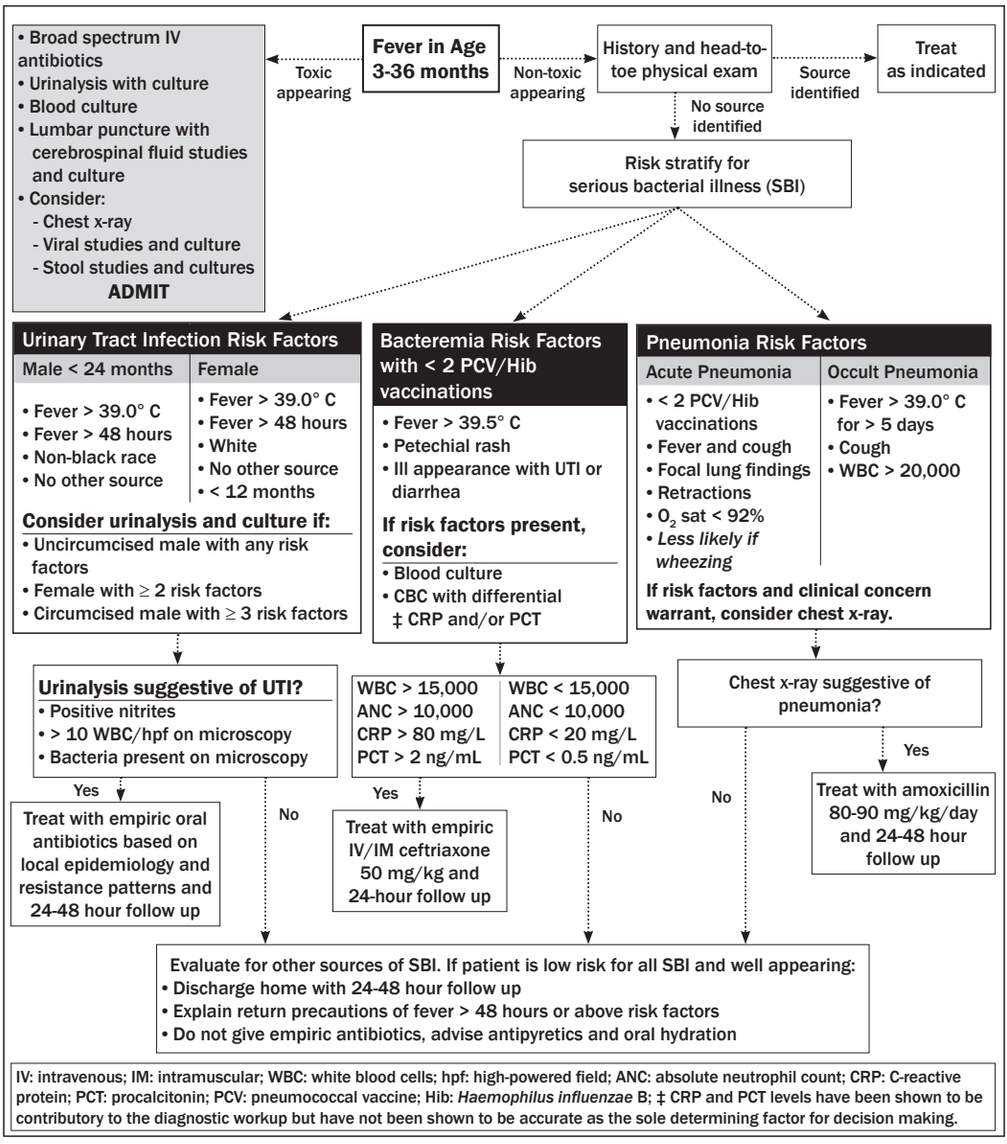
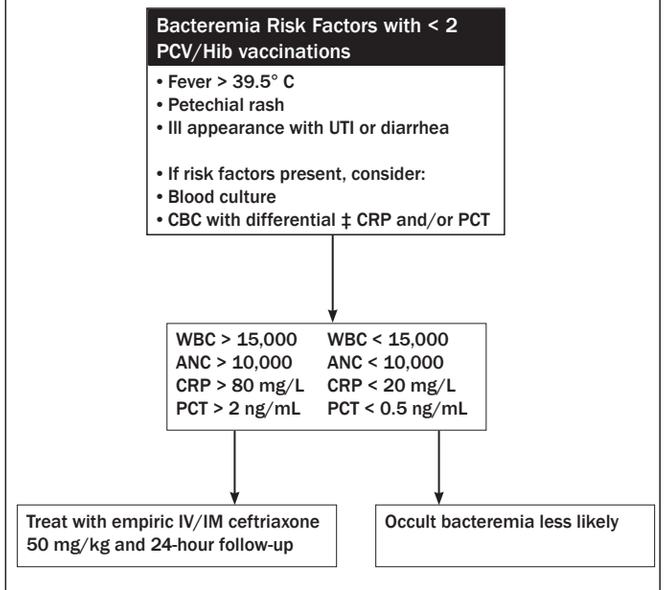
Managing Febrile Children Age 3-36 Months

Suggested Risk Stratification to the Febrile 3-36 Month Child without a Source



IV: intravenous; IM: intramuscular; WBC: white blood cells; hpf: high-powered field; ANC: absolute neutrophil count; CRP: C-reactive protein; PCT: procalcitonin; PCV: pneumococcal vaccine; Hib: *Haemophilus influenzae* B; ‡ CRP and PCT levels have been shown to be contributory to the diagnostic workup but have not been shown to be accurate as the sole determining factor for decision making.

Suggested Risk Stratification for Occult Bacteremia



IV: intravenous; IM: intramuscular; WBC: white blood cells; ANC: absolute neutrophil count; CRP: C-reactive protein; PCT: procalcitonin

‡ C-reactive protein and procalcitonin levels have been shown to be contributory to the diagnositic workup, but have not been shown to be accurate as the sole determining factor for decision making.

Adapted from: Baraff L. Management of fever without source in infants and children. *Ann Emerg Med* 2000;36:602-614.

Suggested Risk Stratification for Pneumonia

Pneumonia Risk Factors	
Acute Pneumonia	**Occult Pneumonia**
• < 2 PCV/Hib vaccinations • Fever and cough • Focal lung findings • Retractions • O_2 sat < 92% • *Less likely if wheezing*	• Fever > 39.0° C for > 5 days • Cough • WBC > 20,000

If risk factors and clinical concern warrant, consider chest x-ray.

Adapted from: Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;128:595-610.

Suggested Risk Stratification for Urinary Tract Infection

Urinary Tract Infection (UTI) Risk Factors	
Male < 24 months	**Female**
• Fever > 39.0° C • Fever > 48 hours • Non-black race • No other source	• Fever > 39.0° C • Fever > 48 hours • White • No other source • < 12 months

Consider urinalysis and culture if:

- Uncircumcised male with any risk factors
- Female with ≥ 2 risk factors
- Circumcised male with ≥ 3 risk factors

Adapted from: Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011;53:e25e76.

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