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Fever

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Guest Editor

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PREFACE

Fever: A Symptom for the Ages

A fever is an expression of inner rage - Julia Roberts
[1] (*American Actress, b.1967*)

There is perhaps no more recognizable symptom of childhood illness than fever. Pediatricians are quick to ask if fever is present and parents are eager to note its presence. In fact, fever is the single vital sign that parents know, with relative certainty, what values are normal or abnormal. During the course of a febrile illness, there is great emphasis on noting the presence, height, and duration of fever. “Spiking” fevers, “high” fevers, “dangerous” fevers are frequently used terms that are often misused during exchanges between parents and practitioners. Many parents take on the difficult task of “controlling” the fever and do so with a vengeance. Frequent administration of antipyretics, sometimes even multiple types of antipyretics, sets the parent's framework for following the course of an illness. Often, parents and practitioners focus on unwarranted concerns, such as the myth that fever itself causes brain damage [2]. Parental pressure for other magic bullets—namely, the antibiotics—may force pediatricians to prescribe antibiotics for likely viral illnesses, despite repeated warnings about the dangers of unnecessary antibiotic use [3-5]. In a society where any symptom is not well tolerated and a panacea often demanded, it is not easy to embrace the presence of fever. Still, fever is one of many acute phase reactants during illness. Furthermore, unlike the white blood cell count or the C-reactive protein, fever is relatively easy to monitor. In a sense, fever is an important sign of the battle between the organism (infecting bacteria or virus) and the host. Presence of fever usually means the infection remains, whereas resolution of fever often signals the end of an illness. In that regard, we should welcome the ability of the body to mount a febrile response. So how did we as a society get to this point? When did fever become such a feared product of disease?

Many ancient civilizations believed that illness was caused by supernatural or mystical forces that were often inflicted as a punishment by a divine presence. It was not until the 400 BCE when Hippocrates rejected such beliefs in favor of a more scientific approach to disease. Hippocrates believed that normal body homeostasis was due to the

balance of 4 humors—blood, phlegm, black bile, and yellow bile—and that imbalance of these humors caused disease. Fever was one way that the excess humor would be “cooked” and brought back to normal equilibrium [6]. Thus, Hippocrates was quoted as saying, “a fever supervening is favorable” [7]. Fever was judged to be a helpful clinical sign, and its presence during a disease process was often awaited; “when persons in good health are suddenly seized with pains in the head ... and breathe with stertor, they die in 7 days, unless fever comes on” [8]. By the turn of the first millennium, Rufus of Ephesus [6], a follower of many of Hippocrates's teachings, became a strong advocate for fever therapy. Writing on the benefits of fever, he noted, “If there were a physician skillful enough to produce fever, it would be useless to seek any other remedy against disease.” Galen, one of the preeminent medical researchers of the Roman period, often noted fever as a symptom of common diseases of his time—malaria, hepatitis, and typhoid. Because patients with these diseases were often jaundiced, Galen thought that fever was the result of the accumulation of yellow bile [9]. Even as late as the 1600s, the benefits of the febrile response were still respected. Thomas Sydenham, also known as the father of English medicine, revived the Hippocratic methods of experience and reason. He was known to appreciate fever as nature's instrument and is credited with the famous quote, “Fever is a mighty engine which Nature brings into the world for the conquest of her enemies” [7,9,10].

By the 1800s, fever as a sign of underlying infectious disease was not only well appreciated but began to become a feared clinical symptom. Sir William Osler, Professor and Physician-in-Chief at Johns Hopkins Hospital (Baltimore, MD), remains one of the greatest and most admired physicians of modern medicine. During his era, severe infectious epidemics were common and, without scientific knowledge of the etiologic agents involved, the pattern of fever often served as a clue to diagnosis. During his speech in 1896 at a medical conference in Atlanta, Ga, he declared, “Humanity has but 3 great enemies: fever, famine, and war; of these, by far the greatest, by far the most terrible, is fever” [11].

Regardless of whether fever was beneficial or a feared product of disease, there was a scarce amount of scientific

evidence one way or the other. To better quantify and then study the febrile response, one needed an accurate accepted tool for measuring body temperature. To that end, Wunderlich's publication of normal body temperatures in 1868 ushered in the era of modern clinical thermometry and set the stage for the scientific study of fever [12]. Although somewhat crude by today's standards, Wunderlich reported the results of more than 1 million temperature readings in more than 25 000 patients using a foot-long axillary thermometer. Though he did report a range of normal body temperatures, as well as a diurnal variation, the mean temperature of 98.6°F eventually became etched in the society's psyche as "normal" body temperature.

In the 1900s, the refinement of thermometry, including development of the oral and rectal thermometers, made the detection of fever a process of relative ease. As such, fever became the most common reason children were brought to acute care clinics and emergency departments. Although practitioners focused on the presence or absence of fever, parents often became overly concerned about the perceived dangers. In 1980, Schmitt [2] surveyed parents about their understanding of fever and coined the term *fever phobia* to describe their overconcern about low-grade fever (<38.9°C). He also pointed out that most of the parent's concerns about fever were unjustified and that health education to counteract fever phobia should be a part of routine pediatric care [2].

Even with all the knowledge about the pathophysiology of fever, the role of fever in disease, and the different ways to treat fever, we continue to be concerned, appropriately or otherwise, about the presence of fever. Practitioners still worry about missing rare but serious causes of fever, such as meningitis. Parents continue to be "very worried" about fever and often perceive their physicians as "very worried" about fever [13]. These tensions often result in unnecessary testing and inappropriate treatment [3-5]. Furthermore, recent antibiotic use is a risk factor for infection or colonization with resistant bacterial pathogens [5]. Nevertheless, parents continue to demand antibiotics for fever, and practitioners often comply with these requests [3]. To reverse this trend, parents and practitioners need to be reeducated about the role of fever and the myriad of myths that surround its presence.

This issue of *Clinical Pediatric Emergency Medicine* reviews and updates management of several specific circumstances involving the febrile child. These areas include an update of the management for the febrile young infant with special consideration of the age of the infant, practice setting, and association of viral illness. In the past few years, the epidemiology of many childhood illnesses has changed dramatically after widespread pneumococcal vaccination. To that end, when evaluating the febrile toddler, the old concerns of occult bacteremia may be

replaced by less common, but more severe, pneumococcal serotypes. Rapid testing for viral illnesses, especially influenza and respiratory syncytial virus, has become more common in the emergency department. The ability to quickly detect these viruses has led to a reevaluation of routine testing and empirical treatment. Methodological studies of urinary tract infections in children helped drive more directed urinary testing and more precise diagnosis. In the past, a febrile child with a rash would heighten concern for meningococemia; although that concern still exists, there are other diseases that present new possibilities in the age of bioterrorism. Fever after international travel is reviewed as are empirical antibiotic choices for children with cancer and other chronic conditions. Finally, no publication on fever would be complete without a discussion of fever phobia and parental concerns.

As with any review, some opinions are based on scientific data and other opinions are based on clinical experience. The astute clinician will assimilate both types of information to provide the most appropriate care for each individual child.

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The Febrile Infant: What's New?

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Fever in young infants often accompanies bacterial disease. Approximately 10% of febrile infants younger than 2 months will have associated bacteriuria, bacteremia, or other bacterial disease. In spite of assertions to the contrary, well physical appearance does not reliably rule out the presence of bacterial disease in this population. Accordingly, the presence of fever in infants younger than 2 months demands immediate and comprehensive management. The manuscript reviews current management controversies in the evaluation and management of febrile young infants. We describe the use and applicability of various clinical predictor sets for determining which infants are at low risk for serious bacterial illness and, in particular, whether a minimum workup is required, and if so, what constitutes those necessary laboratory tests. We also discuss whether the management should vary by the age of the infant (younger than 1 month vs 1-2 months old), the practice setting (office vs the emergency department), and the presence of concurrent viral infections.

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The management of the febrile illnesses in young infants has been a topic of debate for decades. In a large part, the concerns of the practitioner lie in the knowledge that not only is the risk of serious bacterial illness higher in young infants, but also the clinical clues that are often used to detect serious illness are not reliable. During the first 2 months of life, the infant's immune system is relatively immature. Chemotactic responses such as opsonin activity, macrophage function, and neutrophil activity are decreased, making the infant more susceptible to bacterial illness. In addition, although recent vaccination for *Haemophilus influenzae* type b and *Streptococcus pneumoniae* has led to a decline in invasive illness from those organisms, the newborn is still exposed to maternally transmitted organisms. In particular, gram-negative bacilli, *Listeria*, *Enterococcus*, and group B *Streptococcus* remain frequent etiologies of disease at this age. These bacterial

diseases constitute about 10% of discharge diagnoses for infants younger than 2 months [1-5]. Although urinary tract infection is the most common serious bacterial illness identified, 1% to 3% of febrile infants have bacteremia and/or bacterial meningitis. Furthermore, clinical illness indicators such as state variation and reaction to parent stimulation are not reliable predictors of serious bacterial illness at this age [2,3,6]. As many as 65% of febrile infants with serious bacterial illness appear well on initial examination [6]. These concerns led to a conservative management strategy that was extrapolated from the experience with febrile infants in the newborn nursery. Thus, in the 1980s, the "rules" for management of febrile infants younger than 2 months generally included an evaluation for sepsis (including urine, blood and spinal fluid examination), inpatient admission, and empirical antibiotic therapy pending culture results [1,7,8].

By the 1990s, several investigators developed a combination of clinical and laboratory criteria to be used as a way of stratifying these febrile infants by their risk of serious illness [2-4]. Most of these studies showed high sensitivities and negative predictive values. Although the data sets differed somewhat in the age group studied and the specific criteria used, they were all primarily based in large urban

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hospitals. In addition, specific practice guidelines for the management of infants and children without a source of infection were published in the pediatric and emergency medicine literature [7]. By the turn of the century, these studies of risk stratification had a noticeable impact on patient management especially for the febrile infant between 1 and 2 months old. A survey of pediatricians, emergency medicine physicians, and family practitioners regarding their management of hypothetical children with fever without source was conducted in 1993 and then repeated in 1998 (Table 1) [9,10]. In particular, routine admission of the febrile 7-week old declined from 82% to 62% for pediatricians and from 96% to 70% for emergency medicine physicians. At the same time, although many practitioners embraced the possibility of managing selected low-risk febrile infants as outpatients, they often acted outside established guidelines or apart from developed low-risk criteria [11].

Although it is clear that selected febrile infants can be managed as outpatients, the specific criteria used to define this low-risk population remain in flux. Much of the debate centers on the delicate balance between minimizing testing (and accepting a very small risk of missing a serious bacterial illness) vs minimizing the risk and doing more testing. There are no hard and fast rules because these issues are dependent on the practitioner's interpretation of the existing data, the ability to apply them to their specific practice setting, and the variations associated with specific clinical epidemiology. To that end, we will review the basis for the current controversies surrounding the management of the febrile infant and whether the age of the infant, the practice setting, and concurrent viral infection should affect management.

Identification and Management of Infants at Low Risk for Serious Bacterial Illness

Of the studies that have tested screening tools to identify low-risk infants, 2 that used prospective consecutive cohort designs [2-4] have the most compelling methodology. The first published was conducted at Children's

Hospital, Boston, Mass, and tested the safety and efficacy of outpatient management with intramuscular ceftriaxone of fever in 1- to 3-month-old infants who had been judged by the investigators to be at low risk for having serious bacterial disease. In this study, 336 febrile infants aged 1 to 2 months and 167 febrile infants aged 2 to 3 months were enrolled. All of those infants were judged to be at low risk for having bacterial disease, according to screening criteria used. Even in this low-risk cohort, 27 (5%) had culture-positive bacterial diseases, including bacteremia, urinary tract infections, and gastroenteritis. All infants recovered uneventfully from their illnesses and seemed to have no complications attributable to initial outpatient management. Furthermore, all 9 infants with initial bacteremia had repeat blood cultures that were negative. When those who had bacterial disease were compared with those with nonbacterial disease, few differences in individual screening parameter results were detected. One difference that was noted was the significantly higher proportion of bands detected in those with bacterial disease, which is consistent with the findings of others [2,4,12,13].

The second large prospective consecutive cohort study was published by the investigators at Children's Hospital of Philadelphia in Pennsylvania [2]. Those investigators tested the efficacy and safety of outpatient management without antibiotics of fever in a selected group of 1- to 2-month old infants who were prospectively judged to be at low risk for bacterial disease. Of the 747 infants who presented with fever during the 5-year study period, 287 (39.4%) were, according to the screening tool used, judged to be at low risk for bacterial disease. All but one of these infants was documented to have nonbacterial diseases, yielding a negative predictive value of 99% (95% confidence interval [CI], 98-100). Using revised screening criteria, which incorporated band-to-neutrophil ratio limits, the investigators were able to prospectively identify all 1- to 2-month-old infants with fever due to serious bacterial disease. In addition, no infant classified by those criteria as low risk had bacterial disease. Thus, these authors concluded that fever in carefully selected infants could be managed safely without antibiotics on an outpatient basis, provided that a complete evaluation for bacterial disease was performed and that follow-up within 24 hours could be assured.

Table 1 Survey results on the management of a febrile 7-week-old infant [9,10].

Year of survey	Pediatricians		Family Medicine		Emergency Medicine	
	1993	1998	1993	1998	1993	1998
Admitted (%)	82	62	64	57	96	70
Treated empirically (%)	65	53	49	46	(N/A)	(N/A)
Observed (%)	17	9	15	12	(N/A)	(N/A)
Sent home (%)	19	38	37	43	14	30
Treated empirically (%)	9	28	14	18	11	23
Observed (%)	10	10	23	25	4	8

Another group of investigators (Jaskiewicz et al [4]) used the screening criteria developed in Rochester, NY, to prospectively study fever in infants younger than 60 days old. They too sought to determine the reliability of low-risk criteria in infants with fever. Of the 931 well-appearing febrile infants included in the study, 437 (47%) were classified as low risk for serious bacterial illness. Five of those low-risk infants had a serious bacterial illness. Although the negative predictive value was 98.9% (95% CI, 83.2%-97.4%), the sensitivity of their criteria was only 92.4% (95% CI, 83%-97%). In addition, there were several important limitations to their findings. Unlike the other studies from Boston and Philadelphia, there was no uniform sepsis evaluation; 97% had spinal fluid cultures and 75% had urine cultures. There were multiple observers, and the assessment of the infant's general appearance was poorly specified. Finally, empirical treatment with antibiotics was inconsistent.

The reason for the difference in predictive values of low-risk criteria for bacterial illness among the 3 studies lies in the differences in the composition of their screening evaluations (Table 2). In particular, the Philadelphia group

chose a slightly higher temperature cutoff, chose a lower peripheral white blood cell (WBC) count, included the band-to-total neutrophil ratio, and used a tested clinical appearance score. Unlike the other studies, the Rochester criteria did not include spinal fluid analysis as a routine part of their low-risk criteria, based the attainment of urine cultures upon the results of urinalyses, and included infants younger than 1 month. All the studies had high negative predictive values largely related to the overall low incidence of serious bacterial illness in febrile infants. When applied, useful criteria should also yield a very high sensitivity, thereby assuring that the risk of misclassifying an infant with serious bacterial illness as low risk is very unlikely. The Philadelphia criteria demonstrated both high negative predictive value and high sensitivity. The Boston group, which had a relatively low negative predictive value, supports the routine use of ceftriaxone in their outpatient low-risk group. The Philadelphia and Rochester groups, who used criteria that led to higher negative predictive values, do not recommend routine antibiotic use.

At the conclusion of the Philadelphia study, the febrile infant management protocol was established there as the

Table 2 Common strategies for the management of febrile infants.

	Rochester Criteria [4]	Philadelphia Criteria [2]	Boston Criteria [3]
Age	>60 d	29-60 d	28-89 d
Temperature	≥38.0°C	≥38.2°C	≥38.0°C
History	Term infant No perinatal antibiotics No underlying disease Not hospitalized longer than the mother	Not specified	No immunizations within preceding 48 h No antimicrobial within 48 h Not dehydrated
Physical examination	Well appearing Unremarkable examination	Well appearing No ear, soft tissue, or bone infection	Well appearing No ear, soft tissue, or bone infection
Laboratory parameters	WBC >5000 and <15 000/mm ³ Absolute band count <1500/mm ³ UA <10 WBC/hpf <5 WBC/hpf stool smear with diarrhea	WBC <15 000/mm ³ Band-neutrophil ratio <0.2 UA <10 WBC/hpf Urine Gram stain negative CSF <8 WBC/mm ³ CSF Gram stain negative Chest radiograph: no infiltrate Stool: no blood, few or no WBCs on smear	CSF <10/mm ³ UA <10 WBC/hpf Chest radiograph: no infiltrate WBC <20 000/mm ³
Fail low-risk criteria	Hospitalize + empirical antibacterial agent(s)	Hospitalize + empirical antibacterial agent(s)	Hospitalize + empirical antibacterial agent(s)
Meet low-risk criteria	Home No antibacterial therapy Follow-up required	Home No antibacterial therapy Follow-up required	Home Empirical antibacterial therapy Follow-up required
Reported statistics	Sensitivity 92% (83%-97%) Specificity 50% (47%-53%) Positive predictive value 12.3% (10%-16%) NPV 98.9% (97%-100%)	Sensitivity 98% (92%-100%) Specificity 42% (38%-46%) Positive predictive value 14% (11-17%) NPV 99.7% (98%-100%)	Sensitivity—not available Specificity 94.6% Positive predictive value—not available NPV—not available

Data from **Consensus in Pediatrics**. 2005;1(7):1. UA, urinalysis; hpf, high power field; NPV, negative predictive value.

standard of care. A follow-up study initiated 18 months later showed no failures of their low-risk criteria [11]. Combined data from 8 years of enrollment at that center showed a negative predictive value of 100% (95% CI, 99%-100%) for the 388 infants predicted to be at low risk for bacterial disease. Furthermore, their data indicated that each individual component of the initial evaluation for bacterial disease is important and should be performed on each infant with fever.

Thus, well-appearing febrile infants 1 to 2 months old have a variety of testing and management strategies that include options for outpatient management with or without empirical antibiotic treatment. The decision to manage fever in an infant as an outpatient should be based on not only fulfilling low-risk clinical and laboratory criteria, but also the experience of the practitioner, the ease and reliability of follow-up, and the observational skills of the parents.

The Practice Setting and the Pediatric Research in Office Settings Experience

One of the criticisms of the large prospective studies of febrile infants was that the patient samples were generally drawn from urban hospital emergency departments (EDs). To be sure, the low incidence of serious illness necessitated a large sample size, which was most likely generated from a busy academic pediatric ED. However, this led to an apparent disconnection between the practice in academic hospitals and that in a private practitioner's office. This disparity was evident since the early 1980s when surveys of practitioners in the office setting showed that they ordered fewer tests and less routine hospitalization of the febrile infant when compared with the general practice in academic hospitals [14]. Perhaps the office practitioners believed that the practice guidelines were developed from studies that could not be generalized to the patient populations they cared for. In particular, office practitioners touted better follow-up abilities and a stronger connection to ongoing care of their patients.

In 2004, a study that was specifically designed to address this patient population was published. The Pediatric Research in Office Settings (PROS) practice-based research network of the American Academy of Pediatrics, consisting of 573 members from 219 practices representing 44 States, the District of Columbia, and Puerto Rico, conducted the study [5]. A consecutive sample of 3066 febrile infants younger than 3 months was studied, 63 (2.1%) of whom had bacteremia/bacterial meningitis. Clinical appearance was judged as well/minimally ill, moderately ill, or very ill; laboratory testing was at the discretion of the practicing clinician. Thirty-six percent of the infants were hospitalized, 75% had some laboratory testing, and 57% were initially

treated with antibiotics. Of particular importance, only 125 (4%) had just single office visit and no other contact.

Of the 2249 infants who looked well/minimally ill on initial presentation, 27 (1.2%) had bacteremia/bacterial meningitis. When stratified by age, infants younger than 25 days had a bacteremia/bacterial meningitis rate of 3.4% compared with only 0.8% of those infants 25 days and older. The authors also noted that PROS practitioners' actual management practice had greater accuracy than the existing established management guidelines. Although on the surface, this study seemed to support individualized clinical judgment by office practitioners, there were important limitations. Specifically, not all practitioners in the network participated, not all febrile infants were enrolled, and standard laboratory testing was not done on all infants. The lack of standard evaluation of these infants prohibits conclusive identification of all infants with bacterial illness, and therefore, the true incidence of disease is unknown. It is possible that the sickest febrile infants bypassed the office to go to the ED, thus, leading to lower incidence rates of serious bacterial illness in the office setting [15]. However, it is also possible that the perspective of an office practitioner is limited by the number of febrile infants seen in their office compared with a busy ED. Using the PROS data, an office practitioner would evaluate a febrile infant once every 214 days, and, if the bacteremia/bacterial meningitis incidence were 1%, that practitioner would see a febrile infant in the office with bacteremia/bacterial meningitis once every 58 years. Therefore, one must exercise extreme caution in feeling secure with an individualized management strategy when the incidence of serious disease is so low.

Thus, it appears that in the absence of additional data, management of febrile infants in the office setting should be similar to that in the ED. However, the ability of an office practitioner to have reliable and consistent follow-up is an important decision modifier when deciding among different outpatient management criteria.

Applicability of Screening Criteria to Infants Younger Than 1 Month

Although the current screening criteria can be applied to febrile infants 1 to 2 months old, there remain insufficient data to generalize this approach to younger infants. This is largely due to reported higher rates of bacterial disease in this age group [12,16,17] and the limited abilities of young infants to portray ill appearance [6]. Rates of bacteremia and/or bacterial meningitis have been reported between 1.5% and 4% in this age group, which is more than twice that of febrile infants 1 to 2 months old [5,18]. Furthermore, clinical parameters remain unreliable; the development of a social smile, one of the most common

clinical signs of well appearance, is generally not present until after 1 month old. Justifiably, these concerns formed the basis for many investigators [2,3,18,19] to exclude febrile infants younger than 1 month from outpatient management schemes.

Others, such as the proponents of the Rochester criteria, have included infants younger than 1 month in their study sample and have provided some preliminary insight into this issue [4]. In one group of 227 infants younger than 1 month who, by Rochester criteria, were at low risk for bacterial disease, 2 had bacterial disease. Unfortunately, the group studied was not one of consecutively presenting eligible infants, which makes questionable the applicability of the results to the population as a whole.

Two studies [18,20] have shown that the published Philadelphia and Boston protocols, which were designed for use in infants older than 1 month, are not applicable to infants younger than 1 month. In a retrospective study conducted in Salt Lake City, Utah, 45 of 372 febrile 0- to 1-month-old infants were proven to have serious bacterial illnesses [20]. Of those, 13.3% by Philadelphia criteria and 17.8% by Boston criteria would have been identified as low risk for bacterial disease. In a similar prospective study of 254 febrile 0- to 1-month-old infants in Philadelphia, 5 (15.6%) of 32 who had serious bacterial illnesses would have been identified as low risk for bacterial disease according to the Philadelphia criteria [18]. Viewing that data from a different perspective, applying the screening criteria in the Philadelphia protocol to febrile neonates younger than 1 month would falsely identify them as low risk for serious bacterial illness in as many as 10 per 100 neonates with fever.

Thus, for infants younger than 1 month, risk stratification criteria are unreliable, and therefore, these infants should have a sepsis evaluation, including a lumbar puncture, hospitalization, and empirical antibiotic treatment pending culture results.

Meningitis (and the Issue of the Lumbar Puncture)

Although the prevalence of aseptic meningitis in infants with fever may be relatively high (up to 13% during seasonal outbreaks of enterovirus [2,11]), the prevalence of bacterial meningitis is quite low. The combined results of the investigations from Philadelphia reported that 1.2% of all 1- to 2-month-old infants studied had bacterial meningitis. Common experience suggests that the occurrence is less than that today, in part, because of the decline in *H influenzae* type b and *S pneumoniae* in the older infants. In a study from Boston conducted from 1992 to 1999, the prevalence of bacterial meningitis in infants younger than 2 months was approximately 0.5% [21]. Data from the PROS network corroborate these findings [5].

Though infrequent, bacterial meningitis still occurs in these infants and can be difficult to detect by means other than analysis of cerebrospinal fluid (CSF). Bonsu et al [21] studied the use of peripheral WBC counts as a screen for need for lumbar puncture in infants 3 to 89 days old. They analyzed 5353 CSF samples of consecutive infants evaluated for presence of bacterial disease in the ED at Children's Hospital, Boston, Mass. Of the 22 cases of bacterial meningitis, 41% had peripheral WBC counts between 5000 and 15 000 (low risk according to Philadelphia and Rochester criteria), and 64% had peripheral WBC counts between 5000 and 20 000 (low risk according to Boston criteria). They concluded that lumbar punctures of febrile infants should not be omitted based on the results of peripheral WBC counts. However, the study examined the use of the WBC alone and not as part of a more comprehensive set of clinical and laboratory criteria. Furthermore, they did not attempt to use other WBC count indices such as the absolute band count or the band to total neutrophil ratio that has been used as part of other predictor sets of serious bacterial illness in febrile infants. Perhaps, most importantly, there was no stratification by clinical appearance. Thus, it is possible that many febrile infants with bacterial meningitis looked clinically ill and therefore would have qualified for a lumbar puncture on that basis.

Many continue to advocate routine lumbar puncture as part of the evaluation of febrile infants younger than 2 months [2,11], regardless of clinical appearance, whereas a minority, notably those who use the Rochester low-risk criteria, does not [4,5]. To be sure, infants who are younger than 1 month have higher rates of bacteremia and bacterial meningitis and also lack many of the clinical clues necessary to make a reliable global assessment of appearance. The issue is whether a well-defined selected group of older febrile infants between 4 and 8 weeks old can have risk stratification based on clinical appearance and blood and urine studies without the routine spinal fluid analysis. To that end, one must realize that the term *febrile infants* is not a homogenous group. Infants, even at this young age, develop at different rates. Some 6-week olds are relatively immature in terms of their clinical state, ability to smile, and quality of reaction to parent stimulation, whereas others appear clinically closer to older infants. These factors should be considered when evaluating these infants and planning management strategies. There are no conclusive data to support omission of the lumbar puncture from routine evaluation of fever in infants between 4 and 8 weeks old. Nevertheless, for a selected group of older well-appearing febrile infants who meet all low-risk criteria (both clinical assessment and diagnostic testing), some experienced clinicians will elect to delay or omit the lumbar puncture, provided that reliable follow-up can be arranged and that the healthcare provider is confident that parents have appropriate observational skills. However, one must

Table 3 Suspicion for congenital HSV infection.

Full-term Infants Younger Than 4 Weeks and Premature Infants (<32 Weeks' Gestation) Younger Than 8 Weeks Who Have Any of the Following Symptoms:

1. History of HSV lesions in the mother in the third trimester
2. Skin lesions suspicious for HSV on the infant
3. Ill-appearing infant
4. Seizure associated with the current illness
5. Abnormal liver function test (s) (more than 100 for the aspartate aminotransferase/alanine aminotransferase)^{29,30}
6. CSF pleocytosis (bloody, uninterrupted CSF should be considered case by case)

keep in mind that the single most accurate and reliable indicator of bacterial meningitis remains the lumbar puncture. Therefore, any management strategy that omits the lumbar puncture carries some degree of additional risk and must be used with caution.

Infants Who Test Positive for Viruses

Because viral disease is the most common reason for fever in infants, it is not surprising that rapid testing for viruses will at times be positive. In that setting, physicians often question the need for further evaluation of fever. Although viral polymerase chain reaction testing is available for a wide variety of viral pathogens, the most common rapid viral tests used in the ED are for influenza and respiratory syncytial virus (RSV).

The issue of a positive rapid test for influenza is discussed in depth elsewhere in this journal. Although the effects of rapid influenza testing has led to a reduction of tests obtained in the evaluation of febrile infants and toddlers, the key question is whether there is an association between influenza and serious bacterial illness. Most studies show a significantly lower risk of serious bacterial illness in children older than 2 to 3 months [22-24]. However, there is, of yet, no data showing a similar result for infants younger than 2 to 3 months. Thus, in the absence of new data, febrile infants who test positive for influenza should be managed similar to those who do not.

Febrile infants who have concurrent bronchiolitis have been the subjects of several investigations. Many studies have shown that febrile infants younger than 2 to 3 months with bronchiolitis had significantly lower rates of serious bacterial illness, and when present, these illnesses were all urinary tract infections [25-27]. However, these studies were retrospective, and few had a defined control group.

In 2004, as part of the Pediatric Emergency Medicine Collaborative Practice Committee, a large prospective study involving 8 pediatric EDs enrolled 1248 infants younger than 60 days with temperatures 38°C or higher [28]. All infants had undergone blood, urine, and spinal

fluid studies as well as an RSV rapid test. The overall rates of serious bacterial infection (11.4%), bacteremia (2%), and bacterial meningitis (0.7%) were similar to prior studies. Twenty-two percent of the infants were RSV positive. Overall, RSV-positive infants were less likely to have a serious bacterial illness than RSV-negative infants (7% vs 12.5%). Urinary tract infection represented most cases of serious bacterial illness in both groups (5.4% vs 10.1%). Respiratory syncytial virus-positive infants also had lower rates of bacteremia, but the differences were not statistically significant. When the results were stratified by age, the risk of serious bacterial illness was substantial in infants younger than 28 days old and not altered by being RSV positive or RSV negative (10.1% vs 14.2%). However, for infants 29 to 60 days old, 5.5% had urinary tract infections but none had bacteremia or bacterial meningitis. Thus, for these infants, urine testing should continue to be routine. Although the rates of bacteremia and bacterial meningitis appear to be lower in RSV-positive infants, to be more data is required before the other laboratory tests for risk stratification can be modified.

Herpes Simplex Virus Infections in Young Infants

Although most of the emphasis on management of fever in infants centers on the identification of serious bacterial illness, one must not forget that certain viruses, in particular, herpes simplex virus (HSV), may cause high morbidity and mortality.

Herpes simplex virus is an uncommon cause of infection in infants younger than 2 months [29,30]. In the United States, incidence varies from 1 in 2000 to 1 in 5000 live births (approximately 1500 new cases per year). The 2 causative agents are HSV-2 (70%-75%) and HSV-1 (25%-30%). Most congenital infections are transmitted via direct contact with the infected birth canal during labor, but transplacental infection can also occur. Most (60%-80%) of the mothers of HSV-positive babies have no known history of HSV infection. The incubation period of congenital herpes infections ranges from 2 to 30 days after exposure. Signs and symptoms of these infections usually manifest between 10 and 20 days after birth.

There are 3 equally prevalent types of clinical presentations of congenital HSV infections: SEM (skin, eyes,

Table 4 Decision modifiers used in the evaluation and management of febrile infants.

1. Practice setting
2. Experience of practitioner
3. Ease and reliability of follow-up
4. Patient demographics
5. Presence of bronchiolitis
6. "Risk" assessment

mouth), central nervous system, and disseminated (increased levels of liver transaminases are seen in this group). The clinical manifestations of congenital HSV infections are diverse and vary by type [30]. In general, more than 50% of infected neonates (regardless of type) present with skin findings. The skin lesions may present as single or grouped vesicles, pustules, bullae, or denuded skin, and are often mistakenly identified as impetigo. However, between 32% and 39% of infants with congenital HSV central nervous system infection or disseminated disease do *not* have skin lesions on presentation [30]. Thus, the clinician must be acutely aware of secondary symptoms including hypothermia, poor feeding, irritability, lethargy, and vomiting.

Acyclovir (60 mg/kg per day, given in divided doses via intravenous infusion) should be empirically administered to all children with suspected congenital HSV infection. Early administration has been shown to reduce both morbidity and mortality associated with this disease [29]. One should suspect congenital HSV infection in full-term infants younger than 4 weeks and in premature infants (<32 weeks gestation) younger than 8 weeks who have any of the symptoms noted in Table 3.

Summary

Fever in young infants often accompanies bacterial disease. Approximately 10% of febrile infants younger than 2 months will have associated bacteriuria, bacteremia, or other bacterial disease. In spite of assertions to the contrary, “well” physical appearance does not reliably rule out the presence of bacterial disease in this population. Accordingly, the presence of fever in infants younger than 2 months demands immediate and comprehensive management. All such infants require complete evaluation for bacterial disease. Those younger than 1 month require empirical administration of antibiotics and careful observation, pending the results of their blood, urine, and CSF cultures.

The care of febrile infants between 1 and 2 months old can be individualized, based on the results of their physical examination and diagnostic tests. There are a variety of testing and management strategies each with defined risks and benefits. Most of these strategies include examination of the complete blood count and differential, urinalysis, chest radiograph (if respiratory symptoms), and CSF studies. The management strategy chosen should be based on a variety of decision modifiers, some of which are listed in Table 4. Once the laboratory tests are reviewed, final decisions can be made regarding administration of antibiotics and need for hospitalization. To qualify for outpatient management, the infant must appear well, must have complete results of all diagnostic tests clearly interpreted as acceptable, and must have competent caretakers at home who are confident in their ability to observe the infant and who will return with the infant for reevaluation both 24 and 48 hours later.

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Fever in the Toddler-Aged Child: Old Concerns Replaced With New Ones

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The widespread use of highly effective and safe vaccines against **Haemophilus influenzae** type b and **Streptococcus pneumoniae** has impacted the epidemiology of serious bacterial illness in the febrile child. Because of the resultant decline in the incidence of invasive pneumococcal disease, one needs to reconsider the evaluation and management of the febrile child. In particular, for well-appearing febrile children who are vaccinated, routine screening for occult bacterial infections with or without empiric treatment can no longer be recommended. At the same time, early evidence suggests that infections due to nonvaccine serotypes are increasing along with selected invasive diseases such as complicated pneumonia. Therefore, although likely to evolve, the optimal management strategy for the well-appearing, immunized, febrile child may be screening for urinary tract infections and observation with adequate follow-up. Continued surveillance of disease due to nonvaccine serotypes is essential.

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Fever is one of the most important reasons for childhood visits to the emergency department (ED) and accounts for approximately 5.4 million ED visits annually in the United States [1]. Although most febrile children have an apparent source of infection or self-limited viral infections, approximately 6% to 14% will have fever without an apparent source (FWS) [2,3]. Most children with FWS have a nonbacterial cause of fever and are clinically indistinguishable from the small proportion of those with serious bacterial infections (SBIs) (occult bacteremia [OB], meningitis, lobar pneumonia, and urinary tract infections [UTIs]) when they first present to the ED. Because there is no single reliable clinical or

laboratory (or a combination thereof) predictor of SBIs in otherwise well-appearing febrile children, practitioners frequently depend on a variety of guidelines in the evaluation of FWS [2]. This area continues to be debated, and substantial practice pattern variation has been documented in the evaluation of a child with FWS. In addition, the widespread use of highly effective and safe vaccines against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (conjugate pneumococcal vaccine PCV7) has impacted the epidemiology of SBIs, prompting experts to reconsider the evaluation and management of the febrile child [4]. However, despite effectiveness against vaccine serotypes, there is evidence that invasive disease due to nonvaccine serotypes of *S pneumoniae* is increasing since the introduction of PCV7 [5]. The disease caused by these serotypes is troubling because of its severity and resistance to antibiotics [6-8].

This article will focus on FWS in young children (3-36 months old). We will discuss the changing epidemiology, diagnosis, and management of OB, meningitis, pneumonia, and UTIs in the era of widespread Hib and PCV7 immunization.

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The Epidemiology of OB in the Pre-PCV7 Era

Occult bacteremia is defined as the presence of bacteria in the blood of a child who does not appear to be clinically septic or toxic. The epidemiology of OB has evolved substantially since the 1970s [9]. Before the introduction of Hib conjugate vaccine in 1990, the prevalence of OB was 2.4% to 11.6% in all children with FWS [10,11]. *S pneumoniae* OB was responsible for 50% to 90% of cases, 3% to 25% were due to *H influenzae*, and the rest of the cases were due to *Salmonella* species and *Neisseria meningitidis*. Since the introduction of the Hib vaccine, the incidence of invasive *H influenzae* (all types) infections among children younger than 5 years has decreased by 96%; and importantly, invasive disease due to Hib has decreased by 99% (34 cases per 100 000 in 1989 to 0.4 case in 1995) [12]. Two large studies of febrile children in the post-Hib era demonstrated a significant drop in the OB rate. In a prospective study of 9465 febrile children (3-36 months of age), Lee et al [13] found an OB prevalence of 1.57% (95% confidence interval [CI], 1.32%-1.83%). In a retrospective cohort of 5901 febrile children aged 2 to 24 months, Alpern et al [14] found an OB prevalence of 1.9% (95% CI, 1.5%-2.3%). *S pneumoniae* was responsible for 92% and 82.9% of all bacteremia pathogens, respectively.

Streptococcus pneumoniae

S pneumoniae continues to remain a serious pathogen in the developing and developed world. Its only known reservoir is the human nasopharynx, and there are 90 known immunologically distinct serotypes. This organism is responsible for 1.2 million deaths in children younger than 2 years and causes more deaths than any other vaccine-preventable organism [15]. In the United States, in the absence of vaccination, *S pneumoniae* caused approximately 17 000 cases per year of invasive disease among children younger than 5 years, 13 000 of which were OB, 700 cases of meningitis, and 200 deaths [16]. Although most cases of pneumococcal bacteremia resolve spontaneously, it was estimated that 10% to 25% of infected children develop focal complications including cellulitis, pneumonia, meningitis, and sepsis [17]. Empiric treatment with antibiotics at the time of initial evaluation has been shown to reduce the rate of focal complications (from 10% to 4%), bacteremia (from 17% to 1%), fever (from 73% to 24%), and the need for hospitalization (from 50% to 12%) [18]. The above estimates were derived on data in the pre-PCV7 era, and more recent data suggest that the risk of developing meningitis is closer to 0.04% (1 in 2500) [19,20]. In the study of Alpern et al [14], 96% of pneumococcal OB resolved spontaneously and only 0.03% developed sepsis or meningitis. Yet despite its low case fatality rate, the morbidity and mortality associated

with *S pneumoniae* meningitis are higher than those caused by *N meningitidis*, *Streptococcus* group B, *Listeria monocytogenes*, or Hib.

Prevention of Pneumococcal Invasive Disease

Prevention of invasive pneumococcal disease (IPD) by the use of vaccines is the most effective approach to reduce the burden of illness and its sequelae. The 23-valent polysaccharide pneumococcal vaccine that was licensed in 1983 is ineffective in children younger than 2 years. Covalent coupling of weakly immunogenic polysaccharides with a carrier protein, called *conjugate vaccine*, elicits strong antibody production and a booster response [15]. Based on the experience acquired with the highly effective Hib conjugate vaccine, a similar conjugate vaccine against *S pneumoniae* was developed. This vaccine, PCV7, has 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) that are responsible for 80% to 95% of invasive diseases; and these same serotypes are also the most likely to be resistant to antimicrobials. Prelicensure studies [21] showed a 94% (95% CI, 80%-99%) decline in IPD in children who received PCV7, prompting the American Academy of Pediatrics and the Advisory Committee for Immunization Practices to recommend routine immunization for all children at 2, 4, 6, and 12 to 15 months of age in 2000 [16]. Postlicensure surveillance data published in 2003 by Black et al [22] revealed no cases of vaccine serotype disease in children younger than 1 year, with similar disease reductions seen in children younger than 5 years. The most recent report by the Active Bacterial Core Surveillance Group of the Centers for Disease Control and Prevention continues to demonstrate the impact of PCV7, with the largest percentage decline (82%) and the largest absolute rate reduction in overall IPD (175.8 cases per 100 000) observed among children aged 1 year, the age group with the highest baseline disease rate [5].

The Epidemiology of OB in the Post-Pneumococcal Vaccine Era

There are few ED-based studies in the post-PCV7 era that have specifically looked at the incidence of OB. A retrospective study conducted by Stoll and Rubin [23] demonstrated that the incidence of *S pneumoniae* OB was less than 1% (0.91%; 95% CI, 0%-1.9%) in febrile children (n = 329) 2 to 36 months of age. Herz et al (2006) [24] examined 41 948 blood cultures obtained from febrile children 3 to 36 months of age over a 5-year period (1998-2003) in the EDs and outpatient clinic. They compared the epidemiology of OB before and after the implementation of PCV7 vaccination in the Kaiser Permanente Clinics of Northern California. There was an 84% reduction in *S pneumoniae* bacteremia (1.3%-0.2%) and a 67% reduction in overall bacteremia (1.6%-0.7%)

over the 5 years. In another ED-based study by Sard et al [25], the overall rate of OB was 0.7% in a community hospital ED among well-appearing febrile children 1 to 36 months of age. Sixty-one percent of the cases of OB were due to *S pneumoniae*. Finally, Carstairs et al [26] conducted a prospective observational study on febrile children (38°C, <36 months) and compared the prevalence of OB between those who had received PCV7 (n = 833) vs those who had not (n = 550). The overall rate of bacteremia was 4.2% (including contaminants), with 2.4% of nonimmunized children having OB compared with 0% of those who were immunized with any dose of PCV7 [26]. The authors were able to verify the immunization status of each enrolled child.

Although pneumococcus is the most common cause of OB, other causes of bacteremia can present with FWS. Data on other pathogens in the post-PCV7 era are lacking. The largest outpatient surveillance study in the post-PCV7 era offers some updated perspective on the relative frequency of infecting organisms [24]. This 5-year data set from Northern California revealed that bacteremia is now caused by *Escherichia coli*, nonvaccine serotypes of *S pneumoniae*, *Staphylococcus aureus*, *N meningitidis*, *Salmonella* spp., and *Streptococcus pyogenes*. *Escherichia coli* was the second most common organism grown from the blood culture reflecting bacteremia in patients with UTI, which is the most common SBI in children with FWS. Experts suggest that without the availability of effective vaccines, the incidence of invasive disease caused by *Salmonella* and *Staphylococcus aureus* is likely to remain constant [27].

In summary, the overall prevalence of *S pneumoniae* OB after PCV7 is less than 1%, much lower than the previous estimate of 1.5% to 1.9%. Nonpneumococcal organisms account for a higher proportion of OB in the post-PCV7 era.

Occult Pneumonia

The decision to obtain a chest radiograph in the evaluation of a child with FWS is controversial and not evidence based. Accurate diagnosis of bacterial pneumonia is difficult because (a) even if *S pneumoniae* is the most common bacterial cause of lobar pneumonia in children, most lower respiratory tract infections will be viral in nature; (b) chest radiograph results are often negative in the early stages of pneumonia; (c) it is often difficult to ascribe etiology, that is, bacterial or non-bacterial, on “positive” chest radiograph findings; and finally, (d) there is substantial variation in interpretation of chest radiographs even among trained radiologists [28]. Although the presence of pulmonary symptoms (cough) and signs (tachypnea, rales, respiratory distress, etc) increases the likelihood of a positive finding on chest radiograph, Bachur et al [29] showed that occult pneumonia was present in 26% of children younger than 5 years with fevers of more than 39°C and white

blood cell (WBC) counts of at least 20 000 cells per microliter. Most research on occult pneumonia was conducted during the pre-PCV7 era. Zhou et al [30] have shown that the routine use of PCV7 has markedly reduced the rates of all causes of pneumonia including pneumococcal pneumonia in children younger than 2 years. The only published study addressing occult pneumonia in the post-PCV7 era was done by Murphy et al [31]. They reviewed the records of all febrile children younger than 10 years who had a chest radiograph for pneumonia. Among patients categorized as having no signs of pneumonia (n = 1084), 5.3% (95% CI, 4%-6.8%) had occult pneumonia. The likelihood of occult pneumonia increased with increasing duration of fever (likelihood ratio (LR+) 1.62 for fever greater than 3 days and LR+ 2.24 for fever greater than 5 days), presence of cough (LR+ 1.24), prolonged cough (greater than 10 days, LR+ 2.25), and a WBC count greater than 20 000 cells per microliter (LR+ 2.17). The authors concluded that there is limited utility in obtaining chest radiographs in febrile children without cough [31].

In summary, given the impact of the PCV7 and the available data on occult pneumonia, it seems reasonable to obtain a chest radiograph in well-appearing children with FWS who have cough, fever longer than 3 days, and leucocytosis greater than 15 000/ μ L (if done).

Meningitis

The most recent epidemiology of bacterial meningitis in children in the post-PCV7 era is provided by Tsai et al [32] based on an extensive review of the Nationwide Inpatient Sample (1994-2004). They found a 66% decrease in the average annualized rate of pneumococcal meningitis in children younger than 2 years and a 51.1% decrease in mortality. An estimated 1822 cases of meningitis in children younger than 5 years were prevented because of PCV7. In addition, there was a 43% decrease in overall rates of meningitis in children younger than 2 years. They also documented a 17.5%, 54%, and 50% decrease in meningitis due to group B streptococcal meningitis, meningococcal meningitis, and Hib meningitis.

Thus, PCV7, along with the use of peripartum antibiotics and use of meningococcal vaccine, has substantially reduced the incidence of bacterial meningitis. In well-appearing children with FWS, routine evaluation of meningitis by a lumbar puncture cannot be recommended.

Occult UTI

Urinary tract infection is the most common cause of SBI in children with FWS, and the prevalence of UTI has not changed because of PCV7 vaccine. This topic is further discussed elsewhere in this journal, and a recent

comprehensive evidence-based review on the evaluation and management of febrile UTI was published by Shaikh et al [33].

Guidelines for the Management of FWS

The earliest version of management guidelines published simultaneously in 1993 in *Pediatrics* and *Annals of Emergency Medicine* were based on consensus opinions of an expert panel and on the available evidence [2]. These guidelines were revised by Baraff [34] in 2000. In these guidelines, screening urine analysis was recommended (based on age and sex) for all children with a fever greater than 39°C. For children who had not received PCV7 and had a temperature of 39.5°C, the recommendations were to obtain a complete blood count. Empirical treatment with ceftriaxone was recommended if the WBC count was at least 15 000 cells per microliter (absolute neutrophil count \geq 10 000). A chest radiograph was recommended in children with a WBC count greater than 20 000 cells per microliter, an oxygen saturation of less than 95%, or clinical evidence of respiratory disease. In 2003, the American College of Emergency Physicians Clinical Policy Committee revised the guidelines based on a comprehensive review of literature and graded recommendations based on the strength of evidence [28]. They recommend empiric antibiotic therapy for all febrile non-toxic-appearing children with a WBC count of at least 15 000 cells per microliter. Interestingly, the temperature cutoff in the American College of Emergency Physicians guideline is lower at 39°C; and there is no mention of the immunization status of the child, although the preceding discussion does comment on the substantial impact of PCV7 vaccine. Apart from the fact that there is variation among practitioners [35], there are several guidelines that reflect local consensus opinion and practitioner comfort in the evaluation of a child with FWS. Children's Hospital of Boston's guideline [36] recommends obtaining urine studies (analysis and cultures) if the febrile well-appearing child is older than 6 months and has received 3 doses of both Hib and PCV7 vaccine. They recommend obtaining blood (complete blood counts, blood cultures) and urine (analysis and urine cultures) only if the temperature is at least 39°C and if the infant's immunizations are incomplete or if the patient's age is younger than 6 months. Empiric antibiotics are recommended for WBC counts of at least 15 000 cells per microliter, and chest radiographs are recommended if the WBC counts are at least 20 000 cells per microliter. The algorithm suggested in the evidence-based clinical practice guidelines for FWS in children 2 to 36 months old at Children's Hospital Medical Center in Cincinnati is even less conservative [37]. The guidelines recommend screening for OB if the child has an incomplete PCV7 series for age (the child does not have to have all

3 doses of PCV7), is ill appearing, has fever of at least 40°C, or has meningococcal contacts.

In summary, there are several available management guidelines that reflect varying concerns about the prevalence and likelihood of identifying SBI in the evaluation of the well-appearing child with FWS.

FWS—Old Concerns Replaced With New

Conjugate vaccines provide serotype-specific protection. They also reduce carriage of vaccine-related serotypes that are often antibiotic resistant in the vaccinated individual, as well as in the population at large through herd immunity. However, by reducing the carriage of vaccine-related serotypes, an ecologic niche is left open that could be filled by nonvaccine serotypes [7]. The first report documenting a rise in IPD by nonvaccine serotypes was in a multicenter study of children requiring hospitalization for IPD by the United States Pediatric Multicenter Pneumococcal Surveillance Group. Kaplan et al [38] noted a rise in disease caused by nonvaccine serotypes (types 15 and 33) in children younger than 2 years (the nonvaccine serotypes accounted for 37.6% of isolates in 2002 compared with 6% of isolates in the pre-PCV7 era). In a population-based study describing the temporal trends of IPD in Utah, Byington et al [6] documented a significant increase in the proportion of severe IPD and empyema cases due to non-PCV7 serogroups. Singleton et al [39] demonstrated an 82% increase in IPD in a highly vaccinated cohort of Alaskan children younger than 2 years. Importantly, there was a 140% rise in IPD in the post-PCV7 era by nonvaccine serotypes, with serotype 19A accounting for 28.3% of all invasive disease [39]. Others have shown a rise in IPD due to serogroups 15 and 33 [40]. The Centers for Disease Control and Prevention surveillance data released in 2008 showed that the largest absolute rate increase in non-PCV7 serotype IPD was observed among children younger than 1 year (10.8 cases per 100 000). Among children younger than 5 years, the incidence of serotype 19A IPD increased from 2.6 cases in 1998-1999 to 9.3 cases per 100 000 in 2005, the largest increase for any 1 serotype. In addition, in 2005, 40% of IPD among children younger than 5 years was caused by serotype 19A. Although PCV7 serotype incidence rates continued to decline through 2005 for all children younger than 5 years, overall IPD rates plateaued during 2002-2005 [23].

The recent documented increase in antibiotic resistance among nonvaccine strains may be occurring because of "serotype switching"—an ability of the pneumococcus to incorporate parts of capsules of other serotypes [41]. Thus, the potential exists for a vaccine serotype clone that is resistant to an antibiotic to switch its capsule to a nonvaccine serotype and evade the protective effects of PCV7 [7]. In particular, 19A variants have emerged as a major driver of nonvaccine serotype multiresistant IPD.

Complicated Pneumonia

The most common complications of pneumonia in children include necrosis, empyema, parapneumonic effusion, and lung abscess. Until the introduction of the pneumococcal conjugate vaccine, *S pneumoniae* was the most frequently isolated bacteria in children with complicated pneumonia; but *S aureus* has become the most frequently isolated bacteria since 2000 [42]. A multicenter, retrospective study involving 8 children's hospitals in the United States examined 368 hospitalized children with pneumococcal pneumonia before the widespread use of the pneumococcal vaccine. Of these, 133 were complicated cases and required thoracostomy drainage. The frequency of complicated cases increased during the study period from 23% in 1994 to 53% in 1999. Ninety-eight percent of all patients recovered completely from the pneumonia [43]. A retrospective study published in 2005 looked at 230 cases of pediatric complicated community-acquired pneumonia pre- and post-universal pneumococcal vaccination in the United States (1999-2000 vs 2001-2002) and found that (1) the number of patients admitted with empyema (per 10 000 admissions) had decreased from 23 to 12.6; (2) the prevalence of *S pneumoniae* had decreased from 66% (29 of 44) to 27% (4 of 15); and (3) *S aureus* had become the most common pathogen isolated (18% vs 60%), with 78% of those being methicillin resistant [42].

Issues Surrounding the Evaluation and Management of FWS in the Post-PCV7 Era

Screening tests lack sufficient sensitivity and specificity in detecting OB. Although appearance of the child, height of fever, and young age increase the likelihood of SBI, they are by themselves insufficient for diagnosis. Screening tests such as a peripheral WBC count cutoff of 15 000/ μ L have been traditionally used as predictors of SBI, but recent literature continues to indicate that the WBC is neither sensitive nor specific (sensitivities have ranged from 45% to 80% and specificities from 67% to 79% in different studies) [44]. It is also important to recognize that traditionally accepted WBC cutoffs may no longer be relevant as the epidemiology of OB shifts away from *S pneumoniae*. Twelve percent to 16% of all children with meningococcal disease have an unsuspected infection, and Kuppermann et al [19] suggest that routine screening of febrile children for meningococcal bacteremia with complete blood counts is not useful. Zaidi et al [45] retrospectively reviewed non-typhi *Salmonella* bacteremia and showed that 54% had a median WBC count of 10 000/ μ L. The addition of biomarkers such as C-reactive protein, procalcitonin, and interleukins to routine screening tests for detecting SBIs has been unsuccessful in improving the clinician's ability to evaluate well-appearing febrile infants for SBI [44].

There is lack of agreement between published guidelines, and substantial practice pattern variation exists in the evaluation of the febrile child. A survey conducted among 7500 pediatricians and 7500 ED physicians in 2004 regarding management of 2 hypothetical cases of well-appearing febrile children (ages 7 and 20 months) with and without pneumococcal vaccine documented general reduction in the need for tests and empiric antibiotics attributed to the perceived impact of the vaccine [35]. This study also documented that there was a significant practice pattern variation in the evaluation and management of the febrile child based on the clinical setting, office vs ED.

The diagnosis of bacterial infections in young febrile children is largely dependent on culture of the microbial pathogen in the appropriate clinical specimens (cerebrospinal fluid, blood, urine, or respiratory secretions). However, many pathogens grow slowly or require complex media [46]. A significant number of clinically important microbial pathogens remain unrecognized because they are resistant to cultivation in the laboratory [47]. Furthermore, 90% of all blood cultures do not grow any organism; and of the approximately 10% that do grow organisms, only half represent true bacteremia (ie, true positives) and half represent contaminants (ie, false positives). The issue of false positives (contaminants) cannot be overemphasized because they lead to further testing, use of antibiotics, hospitalization, and iatrogenic complications [48]. All 4 studies in the post-PCV7 era had a higher false-positive blood culture rate than true positives. In fact, the analysis of Herz et al [24] revealed that more than 70% of all blood cultures were contaminants in the post-PCV7 population and the rate increased with decreasing age. The 8-year study of Sard et al [25] revealed an 80% false-positive rate; and they identified a low WBC count, lower presenting temperature, and a longer time to culture positivity as predictors for contaminants. They estimated that the cost of reevaluating a febrile child with a false-positive blood culture would be \$12 340 for every true-positive blood culture given that the rate of false-positive blood cultures has increased from 4 times to 7.2 times compared with true-positive cultures [25].

Given the declining rate of OB, it may be no longer cost effective to perform routine screening and treat young children with FWS with empiric antibiotics. Lee et al [3] conducted a cost-effectiveness analysis and concluded that if the rate of OB falls below 0.5% with widespread use of the PCV7, then strategies that use empiric testing and treatment should be eliminated. Yamamoto [49] conducted a decision analysis for febrile children at risk for OB in the post-PCV7 population and concluded that observing these children without routine blood tests or antibiotics may be the superior management strategy.

Because most children with FWS are likely to have viral etiologies for fever, advances in rapid viral detection technologies have led to increasing use of these assays for evaluation of young febrile infants; and their use is changing management strategies [50-52]. Sharma et al [50] and Bonner et al [51] in their respective studies on febrile children noted that the practitioner's awareness of influenza positivity affected ancillary testing as well as antibiotic use. Febrile children with documented viral infections had a lower prevalence of SBI, and the authors recommend that blood cultures may not be necessary in their evaluation [52].

Summary

The epidemiology of SBI (mainly OB) continues to evolve; and the impact of the 2 conjugate vaccines, Hib and PCV7, has been substantial. The overall prevalence of OB is likely well below 1%; and routine screening with blood tests should no longer be recommended because (a) they are not cost effective, (b) there is an unacceptably high rate of false-positive blood cultures, (c) screening tests lack test characteristics that would make them sufficiently discriminative, (d) there is significant practice pattern variation based on age of the child and setting of the practitioner, and (e) advances in rapid viral testing and widespread use of PCV7 are already altering physician behavior. Studies on SBI conducted in the past have used different inclusion criteria (especially age and temperature), have been retrospective in nature, have used screening tests inconsistently, and have often been conducted in single or small numbers of academic centers. It is highly unlikely in this age of effective Hib and PCV7 vaccination that a prospective multicenter study that enrolls and consistently evaluates (to eliminate selection and verification bias) febrile children with a battery of comprehensive screening tests will be undertaken. It is our opinion that, as of yet, no single published algorithm in the evaluation of FWS can be recommended. Present evidence suggests that screening for urinary tract infection must be done in well-appearing febrile children (based on age, sex, and circumcision status). Given the prior discussion, the best management strategy for well-appearing children with FWS may be observation without screening tests as long as appropriate follow-up can be ensured. Age-appropriate immunization status should be an important consideration in the decision to obtain screening blood tests. The impact of nonvaccine serotypes causing invasive disease is still unclear, but continued surveillance is important. In conclusion, we suggest that a multidisciplinary panel of experts in pediatrics, pediatric emergency medicine, and infectious diseases be formed to develop a consensus guideline that takes the impact of conjugate vaccine, physician and parent preferences, and evolving epidemiology of SBI into account and provide recommendations for the evaluation of the well-appearing child with FWS.

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Impact of the Rapid Influenza Test on Evaluation of the Febrile Child in the Emergency Setting

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The ability to diagnose viral infections has improved substantially in recent years, and rapid testing for viral infection is considered an option in the emergency setting. The most available and practical point-of-care test for viral infection is the test for influenza. Studies in febrile infants and children reveal a substantial reduction in the rates for bacteremia, urinary tract infection, and meningitis in infants with a known viral infection. This knowledge has led the clinician to develop a modified approach to evaluating the febrile infant with a viral infection. Infants who test positive for influenza may be considered at very low risk for serious bacterial infection and may not require extensive testing and empiric antibiotics. The role of vaccination policies for pneumococcal infection and influenza is further explored as it impacts on this practice.

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Evaluation of the febrile infant and child poses an ongoing challenge to the emergency clinician. As research and clinical guidelines lag behind vaccination practice and fail to keep pace with changing viral and bacterial epidemiology, much of emergency medical decision making is based on theoretical risk, historical literature, and clinical judgment. Febrile illnesses from viral and bacterial infections may have similar presentations in the pediatric population and are often difficult to differentiate from one another. Influenza often presents with nonspecific findings, and the absence of symptoms of influenza-like illness does not effectively rule out the diagnosis. Young children with influenza infection may present with high fevers and symptoms that mimic bacterial sepsis. Every winter, epidemics of influenza result in increased visits to the emergency department (ED) and hospital admission rates. Rates of serious illness and mortality are highest among the very young, usually in those younger than 2 years [1].

Clinical practice guidelines to evaluate the febrile infant and child vary widely, and most do not consider viral infection in the pathway [2,3]. This is likely attributable to the fact that routine viral culture testing is not practical in the emergency setting since confirmation may take

weeks and therefore does not effectively support clinical decision making [4]. The evaluation of the febrile infant and child often involves extensive and invasive testing including blood, urine, and sometimes cerebrospinal fluid examination. Furthermore, some patients may also require chest radiographs, antibiotic administration, and admission to the hospital. There is emerging literature exploring the impact of point-of-care rapid influenza testing in the pediatric emergency setting and whether it leads to a modified approach in the evaluation of children who have fever without an “identifiable” source [5-11]. The true question, however, lies in the prevalence of bacterial infection in the child with known viral infection [12-17]. There are several points to consider in addressing this issue.

First, the landscape of serious bacterial infection (SBI) in children has been dramatically altered over the past

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Table 1 Summary of rapid diagnostic tests for influenza available in the United States [28-30].

Name	Test	Sensitivity Median (Range)	Specificity Median (Range)	CLIA Waived
Directigen Flu A (Becton Dickinson, Franklin Lakes, NJ)	Influenza A only	90% (62%-100%)	97% (84%-100%)	No
Directigen Flu A + B (Becton Dickinson, Franklin Lakes, NJ)	Distinguishes influenza A and B	87.5% (75%-96%)	97% (93%-99.6%)	No
QuickVue (Quidel, San Diego, CA)	Influenza A and B	79% (74%-95%)	88% (76%-98%)	Yes
Flu OIA (Biostar, Iverness Medical, Princeton, NJ)	Influenza A and B	53% (37%-93%)	86% (73%-96%)	No
ZstatFLU (ZymeTx, Oklahoma City, OK)	Influenza A and B	71% (65%-96%)	83% (63%-92%)	Yes

Median positive predictive value: 80% (51%-100%). Median negative predictive value: 93% (58%-99.6%).

2 decades, initially as a result of the *Haemophilus influenzae* type B vaccine and, more recently, with the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7, Prevnar; Wyeth Pharmaceuticals, Madison, NJ) in 2000 [18]. In 2008, the Centers for Disease Control and Prevention reported a 77% reduction of invasive pneumococcal disease in children younger than 5 years in the United States [19]. There is recent literature exploring the incidence of SBI in the post-pneumococcal vaccine era [20,21]. These studies report an incidence of occult bacteremia of less than 1% in the immunized young febrile infant and recommend modifying practice based on these very low risks [22]. Despite this, there are concerns for emergence of infection caused by non-PCV7 serotypes as well as nonpneumococcal bacterial infections in this young and vulnerable population [19,23-27].

The next consideration is the risk of SBI in the child with a known viral infection. Overall, the risk of bacteremia is low; but the incidence of urinary tract infection (UTI) appears to be clinically significant among studies of febrile infants across all age groups. Febrile infants 3 to 36 months of age with an identifiable viral infection, such as uncomplicated varicella, croup, bronchiolitis, and stomatitis, appear to have a negligible risk for bacteremia and therefore may not routinely require blood cultures [12,13]. Very young febrile infants with respiratory syncytial virus (RSV) infection have a similarly reduced risk for bacteremia, although they may still have an appreciable risk for UTI (5.4%) [14]. One investigator explored the use of viral diagnostic testing in combination with the Rochester criteria to stratify infants younger than 3 months into those who are at high and low risk for SBI. A subset of high-risk infants with a known viral infection was identified as having a less than 1% incidence of bacteremia [15]. Febrile infants in the 8- to 24-week age group present a particular challenge to clinicians; but fewer than 1% of this cohort will have bacteremia in the context of a positive direct fluorescent antibody test for common respiratory viruses, whereas as many as 10% may have a UTI [16]. A recent

study examining the rate of SBI in febrile children younger than 3 years who test positive for influenza A noted a lower prevalence of bacteremia (0.6% vs 4.2%) and UTI (1.8% vs 9.9%) compared with infants who test negative. No infants with a positive influenza A test result had concurrent bacterial meningitis compared with 2.2% of patients with a negative test result [17]. In fact, none of the aforementioned studies examining the febrile infant with a viral illness reported a case of concomitant bacterial meningitis, although none were powered to detect a significant difference in meningitis incidence.

In summary, the prevalence of bacteremia is low in febrile infants with known viral infection; however, there remains a small but appreciable risk of UTI in the youngest infants. Therefore, it is suggested that, in febrile infants and children with a known viral infection, blood need not be routinely drawn for culture but urine testing should be considered on an individualized assessment.

With a comprehensive understanding of the likelihood for a bacterial infection in the febrile infant with influenza infection, one may consider how the evaluation for fever may be modified in the emergency setting. The ability to test for influenza in a time-efficient manner has enabled the practitioner to approach the workup for a febrile infant with a broader knowledge base and the capacity to discriminate between bacterial and viral infection.

There is a wide variety of rapid tests available (Table 1). Only two are Clinical Laboratory Improvement Amendments of 1988 (CLIA) waived so that emergency personnel may perform the test onsite. The unique test characteristics for the rapid influenza test reflect a median sensitivity of 70% to 75% and a median specificity of 90% to 95% when compared with standard viral cultures [4]. Testing for influenza is greatly impacted by the prevalence of disease and is therefore most reliable during the highest peak incidence in a community. Accordingly, a high positive predictive value is desirable to ensure true positive tests for influenza. Testing reliability is also affected by the modality of testing, with the nasal/nasopharyngeal aspirate being

Table 2 Impact of rapid testing for influenza on evaluating the febrile infant and child in the emergency setting [5-11].

Authors	Patient Age	Inclusion	IP/Total Enrollees	Findings
Noyola and Demmler [5]	0-22 y	IP RT Control 1: IN, RT Control 2: IP, RU T >39°C	56/168	IP RT vs IP RU: fewer antibiotics, shorter hospital LOS
Sharma et al [6]	2-24 mo	T >39°C	72/144	IP RT vs IP RU: fewer CBCs, urinalyses, antibiotics
Bonner et al [7]	2 mo-21 y	T >100.4°F; and malaise, cough, headache, coryza, myalgia; and <72 h	202/391	IP RT vs IP RU: fewer CBCs, blood cultures, urinalyses, urine cultures, chest radiographs, cost, antibiotics, ED LOS; no difference urine dip and CSF testing
Abanses et al [8]	Subgroup: 2-36 mo		126/241	same findings
	3-36 mo	T >39°C or home T >102°F	156/1007	RT vs RU: fewer RSV tests
Poehling et al [9]	<5 y	Fever, respiratory symptoms	88/468	IP RT vs IP RU: fewer CBCs, blood cultures, RSV tests, urinalyses, chest radiographs, ED LOS, cost RT vs RU: fewer tests, chest radiographs, blood cultures IP RT vs IP RU: no difference for tests or treatment
Benito-Fernandez et al [10]	0-36 mo	3-36 mo: T >39°C; <3 mo: T >38°C; ED physician discretion to test for influenza	84/206; <3 mo: 37/95	IP RT vs IN RT: fewer urine, blood tests, chest radiographs, lumbar punctures, ED LOS, antibiotics, hospital admission Infants <3 mo, IP RT vs IN RT: fewer blood tests, lumbar punctures, ED LOS, antibiotics, hospital admission
Iyer et al [11]	2-24 mo	2-3 mo: T >38°C	205/700	No difference for urine testing and chest radiographs RT vs RU: no difference for laboratory tests, chest radiographs, antibiotics, ED LOS, hospital admission, costs
		3-24 mo: T >39°C		IP vs IN: fewer urine tests, blood tests, antibiotics, ED LOS, hospital admission; no difference for chest radiographs, lumbar punctures, or cost IP RT vs IP RU: fewer urine tests; no difference for blood tests or antibiotics

IP indicates influenza positive; IN, influenza negative; RT, rapid influenza testing in the ED; RU, results of influenza test unknown to ED physician; T, temperature; CBC, complete blood count; LOS, length of stay; RSV, respiratory syncytial virus; CSF, cerebrospinal fluid.

more reliable than the nasal swab [4,30]. Interestingly, most studies examining the utility of the rapid test used the nasal swab, most probably because of better tolerability of this method compared with nasal aspirate.

A summary of the most recent studies examining the effect of the rapid influenza test on the clinical evaluation of the febrile infant and child is depicted in Table 2. These studies sought to identify whether knowledge of confirmed influenza infection by the ED physician impacts the subsequent diagnostic evaluation and management of the febrile child. Of these, 6 studies compared practice patterns in the evaluation of febrile infants testing positive for influenza when the ED physician had knowledge of confirmed influenza infection (ie, by point-of-care testing in the ED) compared with when the ED physician was unaware of these results during the visit [5-9,11]. Four studies noted a reduction in blood and urine testing, chest

radiographs, antibiotics, ED length of stay (LOS), and hospital admission rate when the influenza test was positive and known to the clinician [5-8]. In one recent study, the extent of testing for SBI was no different for all infants who had the rapid test performed in the ED compared with those who did not; however, infants testing positive for influenza on the rapid test had fewer urinalyses and urine cultures. This is of particular interest because prior studies reported low rates of bacteremia, but appreciable rates of UTIs [12,14,16,17]. Urine testing is probably the single study that should endure as the evaluation of the febrile infant with influenza is modified.

Two studies examining the impact of the rapid test on the evaluation for an SBI reveal outcomes that support a minimal role for the rapid test. In one study, there was no difference between testing or treatment of SBI in patients who tested positive for influenza on the rapid test

compared with patients for whom the test result was unknown to the clinician at the time of care [9]. Another study illustrated that infants testing positive for influenza had fewer tests to evaluate for SBI compared with infants who tested negative for influenza, regardless of whether the clinician was aware of the test result at the time of evaluation [11]. These findings suggest that decision making may be based on clinical symptoms suggestive of influenza infection or that influenza test confirmation did not influence the evaluation for SBI. In fact, there are many respiratory viruses that may similarly impact the need to test for SBI in febrile infants and children; however, they cannot be identified in a practical manner. It may be possible for clinical pathways and medical decision making to consider symptoms suggestive of a viral infection rather than to rely on ED test results that may be cumbersome to obtain. Large, multicenter studies examining the prevalence of SBI in infants with signs and symptoms of respiratory virus infection may help guide this practice.

There are some notable limitations in these studies. In most, data were collected in a retrospective manner, thereby increasing the risk for subjectivity and missed information [5,6,8-10]. Study periods were variable and not always based on community surveillance for influenza activity, thereby reducing the reliability of the rapid influenza test [5,6,8]. Most interestingly, no study found SBI (blood, urine, or CSF) in patients testing positive for influenza [5-11]. However, some studies may have missed cases of SBI, as they lacked follow-up of influenza-positive patients who did not undergo complete testing [5,6,8,9,11].

Worth mentioning is a barrier to performing the rapid test. Although it is considered "rapid," meaning the test is performed in the ED and the result is available to the clinician immediately, in reality, the procedure requires sequential closely monitored and timed steps and takes approximately 10 to 15 minutes. In the setting of a busy ED, with most clinical staff required to "multitask," this dedicated "single-task" activity may be difficult to achieve reliably [30]. As was illustrated in the study by Abanses et al [8], expecting the triage nurse to perform the rapid test before the physician encounter proved unsuccessful, with more than 25% of eligible patients not having the rapid test performed at triage. Most other studies had a dedicated research nurse or assistant perform the rapid test; however, this may not be feasible in most ED settings [7,9,11]. Identifying a practical solution to the technical performance of the rapid test is required to incorporate it into practice.

In 2007, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practice recommended expanding the use of nasal influenza vaccine to include healthy children aged 2 to 4 years. The intramuscular vaccine is now recommended beginning at 6 months of age to reduce the risk of becoming ill with influenza and transmitting infection to others. As the immunized population grows and the prevalence of influenza decreases, the utility of the rapid test may be reduced [1].

Summary

Rapid testing for influenza in the emergency setting may enable a practical reduction in the performance of invasive studies when evaluating a febrile infant or child for potential bacterial infection. Incorporating the technical process of the rapid test into the ED requires planning. Consideration must be made for the risk of SBI given the age of the child, the clinical examination, the patient's immunologic status, and the regional prevalence for influenza at the time of presentation. Testing of urine may still be advised because there remains a small but appreciable risk for UTI in the young febrile infant with a known viral infection.

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Pediatric Urinary Tract Infection

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Urinary tract infection is a common source of fever in pediatric patients, especially infants who are not yet toilet-trained. Clinical findings are frequently nonspecific, making recognition and diagnosis challenging. This article presents an overview of the epidemiology and clinical features of pediatric urinary tract infection, the available diagnostic tests for screening and definitive diagnosis, and an approach to management including antibiotic treatment and follow-up.

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KEYWORDS fever, child, urinary tract infection, urinalysis, emergency

Urinary tract infection is a common diagnosis made in pediatric patients presenting to the emergency department (ED), accounting for 5% to 14% of annual visits made by children [1]. Presentation of urinary tract infection (UTI) is varied and in younger children rarely involves traditional symptoms, that is, dysuria, frequency, urgency. Untreated urinary tract infections may cause immediate and long-term morbidity including: hypertension, renal scarring, pre-eclampsia, and end-stage renal disease. Prompt recognition and treatment of pediatric UTI in the ED is therefore essential.

Definition and Causes

Urinary tract infections are commonly categorized into either lower tract, located in the bladder and/or urethra (cystitis and urethritis), and upper tract, located in the ureter, collecting system, and renal parenchyma (pyelonephritis). Most commonly, bacteria ascend through the urinary tract from the urethra. During early infancy, UTI may also be caused through a hematogenous route. Although UTI can be caused by a multitude of organisms, gram-negative bacteria are most frequently identified. The

Enterobacteriaceae family is most often isolated with *Escherichia coli* represented most frequently (70%-80%) in otherwise healthy children. Please see Table 1 for a list of other common pathogens.

Pathogenesis

As stated above, most UTIs are caused by bacteria ascending from the perineum. The higher rates of UTI in females is primarily due to their shorter urethra. The pathogenicity of bacteria in UTI is due to many host and bacterial factors including adhesion, motility, host immune response, and genetic factors [2]. Other factors that influence the occurrence of UTI include anatomical factors such as posterior urethral valves or bladder diverticula, voiding dysfunction, and chronic constipation. Sexual activity in teen girls also increases the risk of UTI.

Epidemiology

The epidemiology of UTI in children varies by age, race, and sex. The incidence is bimodal; highest during the first year of life and peaking again during adolescence. In the United States, prevalence of UTI among febrile infants younger than 1 year is approximately 7% [3]. Boys and girls have equal incidence during early infancy, after which boys experience a sharp drop-off [4]. This may in part be due to circumcision, with rates of UTI being up to 10 times higher in uncircumcised males [3]. After 1 year of age, circumcision status becomes unimportant as UTI rates in

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Table 1 Common UTI pathogens isolated

Gram-Negative	Gram-Positive
<i>Escherichia coli</i>	<i>Enterococcus</i>
<i>Klebsiella</i>	Group β streptococcus
<i>Proteus</i>	<i>Staphylococcus aureus</i>
<i>Serratia</i>	<i>Staphylococcus saprophyticus</i> (adolescent girls)
<i>Enterobacter</i>	
<i>Pseudomonas</i> (indwelling catheters)	

males decline significantly. In girls, rates decline over the first 6 years of life. Incidence does not peak again until adolescence and significantly increases in sexually active females [5].

Race appears to be an important factor in infancy with white infants at higher risk for UTI than all other races [6,7]. Race does not seem to be an independent risk factor for UTI during adolescence.

Children with a history of UTI do also appear to have a higher risk for infection than children with no previous history, with older studies estimating 6- to 12-month reinfection rates ranging from 20% to 48%. A recent study looked at specific characteristics within the subgroup of previously infected children that increase risk for recurrent UTI; these included white race and higher grade of vesicoureteral reflux (VUR) (grades 4, 5). Sex and milder grades of reflux (grades 1, 2, and 3) do not seem to affect reinfection rates [8].

Clinical Presentation

The traditionally described clinical signs of UTI (ie, dysuria, frequency, urgency) are typically not present in the non-toilet-trained child. Symptoms of UTI in young children are often nonspecific and fever is frequently the only presenting complaint [7]. Although nonspecific symptoms including vomiting, poor feeding, and diarrhea have been postulated as signs of UTI in young children, this association has not been verified [7]. Malodorous and/or cloudy urine, although suggestive of UTI, is rarely reported. Certain characteristics that do appear to be associated with UTI in addition to fever include female sex, white race, no other source for fever, and in males, being uncircumcised [9].

A clinical decision rule based on history and physical has been created and validated to determine risk for UTI in girls younger than 2 years [9]. The decision rule factors included fever of 39°C or greater, fever for more than 2 days, white race, age younger than 12 months, and absence of another source for fever. With 2 or more of the 5 factors present, UTI was predicted with a sensitivity of 95% and a specificity of 31%. Using this decision rule, a strategy to obtain urine cultures only from those females with 2 or

more factors would serve to identify 95% of those with a UTI and eliminate 30% of unnecessary cultures [9].

In older children and adolescents, the traditional symptoms of UTI commonly reflect bladder and urethral irritation. They include: increased urinary frequency, voiding hesitancy or urgency, dysuria, suprapubic tenderness, and enuresis. Hematuria more frequently occurs with viral cystitis. Systemic symptoms including flank pain, fevers and chills, nausea, and vomiting may occur in the setting of pyelonephritis.

Physical Findings

The physical examination in a child with a UTI may not be particularly helpful. In one large prospective study enrolling more than 2000 febrile young children, half of the infants with UTI were described as “well-appearing” [7]. The examination of the febrile child is mainly helpful when another source for fever is found (ie, pneumonia, viral exanthem) as presence of another source significantly reduces the likelihood of UTI. However, it should be said that finding another potential source for fever does not entirely rule out the possibility of UTI. Studies on children with reported infections such as otitis media or viral upper respiratory tract infection have reported concurrent UTI rates as high as 3.5%. Findings such as abdominal pain, flank pain, and even costovertebral angle tenderness have not been found to be specific or sensitive in the diagnosis of UTI or pyelonephritis.

Laboratory Findings

A positive urine culture a normally sterile body fluid, is the gold standard for diagnosis. However, interpreting results from a urine culture can be challenging. First, it is imperative to know how the culture was obtained, as not all collection methods are equally effective. Commonly used collection methods include urine bag, clean-catch, urethral catheterization, and suprapubic aspiration.

Urine bags have been shown to have very high contamination and false-positive rates, leading to over-treatment and overuse of resources [10,11]. However, screening for those children who will require a catheterized sample by using a urine bag seems to be a reasonable option if adequate time exists to capture the 2 samples required in a child with suspicious results from a urine bag [11]. Catheterization, with false positive rates of less than 2%, appears to be the most precise and frequently used method in non-toilet-trained children in the ED [12]. Suprapubic aspiration does offer the advantage of avoiding perineal contamination; however, this approach is felt to be more painful and requires knowledge of proper technique (and occasionally ultrasound guidance).

In older children, a midstream clean-catch is the preferred method for sample collection. The method is most successful with older children, circumcised males, and in younger girls seated rear-facing on the toilet to spread the labia. Cleaning before sample collection lowers contamination rates from 24% to 8% [13].

Rapid Screening

To facilitate rapid assessment and treatment of patients within the ED setting, analysis of urine samples can occur in several ways, including urine dipstick, traditional urinalysis, and enhanced urinalysis.

The dipstick looks at many aspects of the urine sample, but most relevant for UTI are the presence of nitrites (a metabolic product of gram negative enteric bacteria) and leukocyte esterase (an indicator of the presence of white blood cells in the urine). A meta-analysis of 70 pediatric studies assessed the accuracy of the urine dipstick in children younger than 5 years [14]. A dipstick negative for both leukocyte esterase and nitrite had an likelihood ratio (LR) of 0.20 (95% confidence interval [CI], 0.16-0.26). Likelihood ratio tells us how much to increase or decrease suspicion of disease related to the results of a particular test. An LR of 1 is equivocal. The further an LR is from 1, the more likely it will change your post-test probability of disease. A dipstick positive for both leukocyte esterase and nitrite had an LR of 28 (95% CI, 17-46). A dipstick positive for either leukocyte esterase or nitrite had an LR of 6.1 (95% CI, 4.3-8.6) [14].

Traditional urinalysis involves the microscopic examination of a centrifuged sample for white blood cells and bacteria. The same meta-analysis showed that a urinalysis negative for both white blood cells (cutoff not detailed in this article) and bacteria had an LR of 0.11 (95% CI, 0.05-0.23). A urinalysis positive for both white blood cells and bacteria had an LR of 37 (95% CI, 11-126). Testing positive for either white blood cells or bacteria had an LR of 4.2 (95% CI, 2.3-7.6) [14].

Enhanced urinalysis involves examination of an uncentrifuged sample for the same parameters, and although reported to be more sensitive and specific, is not available in most laboratories [15].

Overall, it appears that urine dipstick and microscopy both perform well and similarly as diagnostic tools. One must take into account departmental resources as well as time constraints when choosing a screening test. Certainly one must also take into account how the specimen was collected and processing time when evaluating results. Frequent voiding (as may occur in younger infants) leads to low nitrite values (decreased time for production), whereas long specimen handling times lead to white blood cell lysis and bacterial overgrowth. Either method has its weaknesses if specimens are not handled promptly and efficiently.

Other testing done may include serum inflammatory markers (including erythrocyte sedimentation rate, C-reactive Protein) and complete blood count. Although potentially helpful in tracking inflammation and the presence of an inflammatory response, these tests are not specific for or diagnostic of UTI.

Finally, when considering ED screening tests, it must be noted that although both commonly used methods (urinalysis and dipstick) are good at "screening," they should never be used as the "gold standard" as neither are sufficiently sensitive to exclude with certainty the presence of a UTI. Similarly, whereas both tests have low false-positive rates, with a relatively low prevalence of UTI in children, empiric therapy based only on screening test results would lead to large numbers of children unnecessarily treated.

Treatment and Outcomes

Prompt treatment is essential in UTI as delayed diagnosis and therapy leads to immediate and long-term morbidity. Therefore, in a clinical situation suggestive of UTI (eg, strongly positive screening test, very high clinical suspicion based on risk factors), empiric therapy should be initiated. Therapy, however, should not be started without a confirmatory culture being sent. Culture results will not only dictate future interventions required but will also tailor antibiotic therapy if necessary. In a clinical situation less suggestive of UTI, it is appropriate to delay treatment until final culture results are back.

Treatment is based not only on patient age and severity of infection but also on the rates of antimicrobial resistance within a community. Simple cystitis is typically treated with a 5- to 7-day course of oral antibiotics. The shorter courses (1-3 days) usually prescribed for adults are effective in female adolescents but have not been shown to be equally efficacious in younger children [16]. First-line therapy of amoxicillin has been in question with high prevalence of resistant *E coli* seen in many communities, making cephalosporins, trimethoprim-sulfamethoxazole, and amoxicillin-clavulanate more acceptable choices. Quinolones, traditionally not used in pediatric patients because of concerns for joint development, have been shown to be effective in multidrug-resistant infections in patients with complex medical problems. Data on their safety in children are promising but limited at this point [17].

Febrile UTIs in children generally require 10 to 14 days of antibiotic therapy. Traditionally, younger infants with suspected pyelonephritis were admitted for parenteral antibiotics, but recent studies indicate that in an otherwise well-appearing infant, oral therapy is equivalent when following the markers of subsequent renal scarring, defervescence, and time to sterile urine [18]. Any child not able to tolerate oral antibiotics or those who appear to be dehydrated or septic require hospital admission and parenteral antibiotic therapy.

If dysuria is a complaint associated with the infection, oral analgesics (ibuprofen, acetaminophen) are certainly appropriate. In more severe cases, pyridium (a urinary analgesic) may be used but for no more than 48 hours.

Follow-Up

Follow-up is key when a UTI diagnosis made in the ED. Simply completing the antibiotic course is not sufficient, especially in the younger child. Most clinicians will perform a follow-up culture if symptoms persist despite treatment. There is also substantial debate about radiologic imaging after a first childhood UTI. Imaging has been the standard of care since a link between VUR and renal scarring was noted in the late 1950s. Currently, there is much research and debate on the need for imaging and the best modality. In 1999, the American Academy of Pediatrics published a practice parameter recommending that a voiding cystoureterogram and renal ultrasound be performed on all children younger than 2 years presenting with febrile UTIs [19]. However, a study published in 2003 by Hoberman et al found that renal ultrasound done after a first UTI in children who have undergone a prenatal ultrasound after 30 weeks of gestation is not of added benefit diagnostically [20].

Antibiotic prophylaxis for children with VUR is also a subject of much debate and research. Typically, children noted to have moderate to severe reflux are placed on antibiotic prophylaxis, but duration and type of treatment have been variable and clinical benefit has not been well demonstrated. A recently published study by Pennesi et al [21] showed that antibiotic prophylaxis in children younger than 30 months with VUR and diagnosed pyelonephritis was ineffective at reducing the rates of subsequent pyelonephritis and renal damage.

Currently, there is a multicenter, double-blinded, randomized controlled study, entitled the RIVUR (randomized intervention for children with vesicoureteral reflux), that hopes to shed some further light on this hot topic. The study will measure the clinically important measures of time to reinfection, antibiotic resistance, and renal scarring [22].

Summary

Pediatric UTI is a common diagnosis seen in the emergency department. Enterobacteriaceae account for most infections seen in otherwise healthy children. The incidence of UTI is highest in children younger than 1 year and peaks again during adolescence. Symptoms and physical findings for UTI in young children are often nonspecific and fever is often the only presenting complaint. A positive urine culture is the gold standard, but the method of obtaining the urine sample should be known when interpreting the results. Screening tests such as microscopy and labstick are

useful but must be done properly to be useful in making a diagnosis. Early treatment, based on age, severity of symptoms, and local antimicrobial resistance profiles, improves immediate and long-term morbidity. Follow-up with the child's primary care physician is necessary for all patients with an ED UTI diagnosis. Antibiotic prophylaxis and imaging studies are subjects of much debate, and studies are on-going in these areas to help elucidate the proper procedure after a UTI diagnosis.

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Fever: Parental Concerns

Arezoo Zomorodi, MD, Magdy William Attia, MD

Although fever is a common pediatric complaint, temperatures less than 41.7°C rarely cause neurologic sequelae such as obtundation and death. Most cases of fever in children cause no more than transient discomfort. Fever phobia is an exaggerated misconception about causes and consequences of fever and is very common among parents. Unsubstantiated parental concerns often push health care providers to overtreat fevers and further reinforce the phobia. To decrease this response, it is important to educate health care workers about thermometry, the pathophysiology of fever, the distinction between hyperthermia and fever, and safe evidence-based treatment strategies. Informed practitioners will in turn be better equipped to educate parents.

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Fever is not in and of itself a disease but rather a symptom of an underlying illness. The most common problems associated with fever include reversible discomfort and mild dehydration. In fact, only hyperpyrexia, with temperatures greater than 41.7°C, can cause grave complications such as obtundation, cerebral edema, or even death. Fortunately, a well-designed homeostatic balance prevents temperatures from reaching these alarming levels in healthy individuals. Yet overabundant parental angst regarding fever taxes vital health care resources. Fever accounts for more than 20% of emergency department (ED) visits, one third of office visits, and more than 50% of after-hour phone calls to private physicians [1-3].

Fever Phobia

Fever phobia is an exaggerated, unrealistic misconception about fever. Parental surveys regarding perceptions about fevers in 2001 [4] confirmed that the magnitude of the problem has not significantly improved since a prior survey in 1980 [5] despite attempts to increase parental education by physicians in this period. Forty-four percent of caregivers considered a temperature of 38.9°C to be a “high” fever, and 7% thought that a temperature could rise to more than 43.4°C if left untreated. Fifty-six percent of caregivers were very worried about the potential harm of

fever in their children. Seizure, brain damage, and death were listed by 32%, 21%, and 14%, respectively, of caregivers as harmful effects of fever. Eighty-nine percent of caregivers gave antipyretics before the temperature reached 38.9°C, 27% alternated the use of acetaminophen and ibuprofen, and a startling 44% gave ibuprofen at intervals of less than 5 hours [4].

According to survey responses by health care providers, they may be reinforcing fever phobia. Sixty-five percent of pediatricians believed that fever could be dangerous to a child and 60% concluded that temperatures more than 40°C could lead to complications such as seizures, brain damage, or death [6]. Twenty-nine percent of pediatric ED registered nurses believed that permanent brain injury or death could occur from fever and 18% thought it was dangerous for a child to leave the ED if still febrile [7]. Although these surveys were restricted to specific geographies and might not be generalizable, they do raise concern. Proper parental education can only

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occur after appropriate physician and nursing education is accomplished.

Thermometry and Definition of Fever

Normal temperature is tightly controlled by the thermoregulatory center in the anterior hypothalamus and varies throughout the day, reaching its peak in the evening and nadir in the morning [8]. The daily variation is linked to sleep-wake cycles and generally fluctuates by a mean of 0.5°C in adults. Infants and young children have higher body temperatures than older children and adults due to both increased metabolic rates and greater surface areas. Children also have more pronounced diurnal variability in temperature than do adults [9].

In addition to numerous physiologic factors, mechanism and location of temperature attainment also impact thermometry. Oral readings vary by up to 0.95°C from the rear sublingual pocket to the anterior floor of the mouth [10]. In addition, oral temperatures are impacted by mastication, ingestion of cold foods [11], and by whether the mouth is opened or closed [12]. Therefore, patient cooperation is extremely important for obtaining meaningful measurements. Tympanic membrane [13,14], forehead [15,16], and axillary [17,18] temperatures are highly variable and imprecise. One study by Mayfield et al [19] showed axillary temperatures taken with mercury thermometers to be as reliable as rectal temperatures in newborns. However, concerns about mercury exposure when broken and difficulty reading these thermometers have decreased their popularity. Rectal temperatures are considered standard of care for infants younger than 3 months.

Often parents do not measure temperatures and only report subjective fevers. Palpation by parents has a sensitivity of 74% to 84% and specificity of 76% to 86% in children older than 2 months [20-22]. Parental palpation is not as sensitive in children younger than 2 months. Therefore, reports of tactile temperatures by parents for children older than 2 months should not be overlooked.

Fever is defined as a temperature above the reference range and is classified as a rectal temperature above 38°C, an oral temperature above 37.8°C, and an axillary temperature above 37.2°C [23]. The relationship between rectal, oral, axillary, and tympanic membrane temperatures is highly variable. There are no reliable formulas for converting readings from one site to another [11,24], and any such attempts should be done cautiously.

Pathophysiology of Fever

The febrile response is a complex reaction to disease that is characterized by activation of numerous physiologic, endocrinologic, immunologic [25], and behavioral systems. The preoptic area of the anterior hypothalamus functions as the body's thermostat by controlling thermoregulatory mechanisms that balance heat loss with heat production. The body's normal metabolic rate produces more heat than necessary to keep the set-point euthermic. Therefore, at baseline, the hypothalamic temperature control is regulating the amount of heat loss via vasodilation. When the set point rises above the body temperature, the hypothalamus activates the sympathetic system to induce vasoconstriction, increase skeletal muscle activity to induce vasoconstriction, increase skeletal muscle activity either as an insensible increase in muscle tone or as frank shivering, and to increase cell metabolism. This cascade of

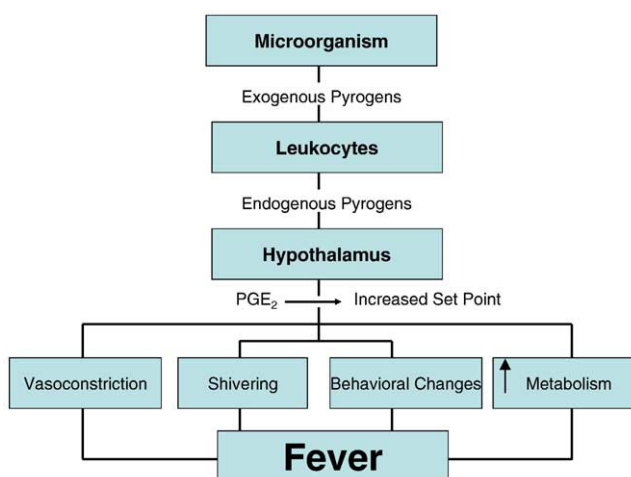


Figure 1 Pathophysiology of fever. Invading microorganisms release exogenous pyrogens that activate leukocytes to release endogenous pyrogens. These pyrogens act on receptors in the vascular organs of the hypothalamus to liberate PGE₂. Prostaglandin E₂ then raises the thermoregulatory set point that initiates the cold response. Vasoconstriction, shivering, behavioral changes, and increased metabolism ultimately raise the body temperature to the new febrile set point.

responses in turn increases core body temperature to reach the set point. Conversely, if the set point is lowered below the body temperature, hypothalamic signals cause vasodilation, sweat formation, decreased metabolism, and behavioral responses such as taking off clothing or moving to cooler environments to decrease body temperature back to its set point.

Infection by microorganisms triggers a series of events that ultimately increase the body's set point to produce fever. The invading organism releases exogenous pyrogens including lipopolysaccharide (LPS), superantigens, peptidoglycans, and muramyl dipeptides that in turn activate leukocytes to release endogenous pyrogens including interleukin 1, interleukin 6, interferon- α , and tumor necrosis factor (TNF). These endogenous pyrogens, which are produced both centrally and peripherally, signal receptors in endothelial cells of the hypothalamic vascular organs to activate phospholipase A₂, which subsequently liberates prostaglandin E₂ (PGE₂) from the cyclooxygenase pathway. Prostaglandin E₂ then raises the thermoregulatory set point in the anterior hypothalamus, and the sympathetic response that ensues raises the core temperature to the febrile set-point (Figure 1).

Clinically, fever is characterized by 3 distinct phases: chill, fever, and flush [26]. During the chill phase, vasoconstriction and shivering increase the core temperature to the new thermal set point. Balance is struck between the production and loss of heat during the fever phase. Once the set point drops back down, vasodilation and diaphoresis ensue, with a flushed appearance marking the peak of the fever.

A system of checks and balances prevents temperatures from commonly exceeding 41.1°C [27]. Arginine vasopressin, α -melanocyte stimulating hormone, and TNF are endogenous cryogens that function to counterbalance the effect of pyrogens and thus prevent temperatures from rising to dangerous levels [28]. There is evidence to suggest that TNF acts both as a pyrogen and a cryogen [29]. Cryogens are produced in greater quantities during fever to curtail the magnitude and duration of fever.

To Treat or Not To Treat

It appears that fever offers the host both advantages and disadvantages. Numerous members of the animal kingdom including mammals, reptiles, amphibians, fish, and invertebrates generate a febrile response after injections of endotoxin or other pyrogenic substances [30]. Fever is an energy-expensive process; for every increase of 1°C over 37°C, there is a 13% increase in oxygen consumption [31]. If fever has such a cost to the host, then its immunologic benefit must outweigh this burden, thus withstanding evolution.

Both animal and human studies have suggested host advantages from the febrile response. Reptiles *Dipsosaurus dorsalis* infected with *Aeromonas hydrophila* showed a direct

correlation between body temperature and survival [32]. These findings were later confirmed in a study involving goldfish [33]. In a retrospective study of 218 human patients with gram-negative bacteremia, there was a positive correlation between maximal temperature and survival [34]. Children with chickenpox treated with acetaminophen as compared to placebo had longer time to scabbing and higher symptom scores [35]. Patients with measles had longer prodrome and delayed Koplik spot eruption when treated with aspirin as compared to placebo [36].

Disadvantages of fever include increased metabolic rate, oxygen consumption, and carbon dioxide production. Patients with underlying cardiovascular pathology or who are in shock have more difficulty tolerating the increased oxygen consumption that fever causes. Lowering these patients' temperatures may prevent deterioration of their condition. In addition, Mayoral et al showed that fever can worsen cerebral injury [37]. After intracerebral injury was induced on monkeys, half were maintained in a euthermic state, whereas the other half were maintained at a temperature of 40°C or more for 4 hours after the injury and were then euthanized. The hyperthermic monkey brains had a 40% increase in edema and worsening hemorrhage in the traumatized area of the brain [37]. It would therefore be prudent to maintain victims of brain-injury euthermic.

In most healthy hosts, fever has little harmful effects. There is no evidence that fever itself causes brain damage unless it reaches at least 41.7°C [27]. Fortunately, as has already been discussed, most fevers seen in children that are caused from infections rarely reach this alarming temperature. The most common side effects of fever are benign and include minimal dehydration, increased sleepiness, and discomfort. Febrile seizures only occur in 4% of febrile patients and most are self-limited without any long-term sequelae.

Pharmacologic Treatment

There is great variability in antipyretic preferences among practitioners. In general, acetaminophen and ibuprofen are the most common antipyretics used for children older than 6 months. Ibuprofen is contraindicated in children younger than 6 months, and acetylsalicylic acid is not used in infants and children due to its association with Reye syndrome. A survey of 160 pediatricians reported antipyretic preferences for acetaminophen 10 mg/kg every 4 hours, acetaminophen 15 mg/kg every 4 hours, ibuprofen 10 mg/kg every 6 hours, and ibuprofen 7.5 mg/kg every 6 hours, as 33%, 33%, 22%, and 8% respectively [38].

A meta-analysis comparing single dose ibuprofen 5 to 10 mg/kg vs acetaminophen 10 to 15 mg/kg concluded that 15% more children were likely to have a febrile temperature reduction at 4 to 6 hours after therapy with ibuprofen compared to acetaminophen. Restricting their

analysis to 10 mg/kg ibuprofen vs 10 to 15 mg/kg acetaminophen increased the antipyretic advantage of ibuprofen to 38% [39]. They did not, however, compare acetaminophen 15 mg/kg with ibuprofen 10 mg/kg dosing. The safety profiles of the medications were analogous. Another meta-analysis confirmed that ibuprofen was significantly more effective than acetaminophen in reducing fever after a single dose; however, both medications were equally efficacious when multiple doses were administered [40]. It appears that ibuprofen is somewhat more effective than acetaminophen at reducing fever and has a longer duration of action than acetaminophen after one dose. However, the drugs are similarly effective antipyretics when multiple doses are administered. Because crossover studies have not been performed, it is not known if patients who fail to respond to one medication will respond better to the other.

Fifty percent of pediatricians recommended alternating acetaminophen and ibuprofen [38]. Their method of dosing varied from acetaminophen every 4 hours alternating with ibuprofen every 6 hours to alternating the 2 products every 2 to 4 hours. Twenty-nine percent of respondents cited the American Academy of Pediatrics as the source for their regimen, although no such guidelines exist. The efficacy of alternating acetaminophen and ibuprofen has not been clearly proven. Although a few studies have analyzed single administration of alternating acetaminophen with ibuprofen by health care providers [41,42], only one study has addressed the parental administration of alternating antipyretics beyond a single dose [43].

Sarrell et al [43] randomized patients to receive either 12.5 mg/kg acetaminophen every 6 hours, ibuprofen 5 mg/kg every 8 hours, or alternating doses of acetaminophen and ibuprofen every 4 hours for 3 days. Half of the patients in each of the treatment groups were initially loaded with acetaminophen 25 mg/kg, whereas the other half were loaded with ibuprofen 10 mg/kg. The patients in the group that alternated acetaminophen with ibuprofen had significantly lower mean temperatures, received less total antipyretic medication, and reported less stress levels than either of the 2 monotherapy groups, regardless of initial loading medication. Critics of this article argue that it is not standard of care to give loading doses of antipyretic in the United States and that the antipyretic dosing was subtherapeutic. Furthermore, the alternating group used fewer doses as early as the first 24 hours, which could be due to a more self-limited cause for fever in that group [44]. The study ensured numerous safeguards including written directions, pharmacist reiteration of directions, and follow-up, which would not occur in practical clinical or telephone-care settings [45]. Concern regarding untoward consequences of medication alternation warrant validation of this study's results. In the meantime, pediatricians should be cautious and concrete about their recommendations to families.

Nonpharmacologic Treatment

Sponging reduces fever by the 3 modalities of conduction, convection, and evaporation. Through conduction, heat is exchanged from the warm body of the patient to the water. Heat moves from warm to cool air by convection. Finally, heat is lost as water evaporates from the patient's body. Several small studies have evaluated the clinical utility of sponging for fever reduction in pediatric patients with infection related fevers. Unfortunately, most of the studies have methodological limitations, making it difficult to draw definitive conclusions.

Steele et al found that sponging with ice water (4.4°C-10°C) or tepid water (29.4°C-32.2°C) after administration of acetaminophen significantly reduced fever faster than acetaminophen alone [46]. However, patients sponged with ice water had high levels of shivering and discomfort. Patients in this study were sponged until temperatures dropped below 38.3°C, which took up to 2 hours. It is impractical for families or physicians to sponge patients for this length of time. Also, temperatures were not measured after sponging was ceased to determine if there was a rebound increase in temperature. Newman compared tepid sponging after administration of antipyretic with administration of antipyretic alone [47]. He found no difference in temperature reduction between the 2 groups. However, some of the patients had received unknown dosages of antipyretics at home and patients who experienced shivering were withdrawn from the study. Sharber [48] found no significant decrease in fever among 10 febrile patients who received acetaminophen compared with 10 febrile patients who received 15 minutes of tepid sponging after receiving acetaminophen. The sample size in this study was very small.

In summary, sponging with ice water causes significant patient discomfort and should not be used. Also, sponging with alcohol in children is dangerous because the alcohol can be absorbed through the skin and cause toxicity. Antipyretic medication alone is superior to sponging alone for fever reduction. Sponging with tepid water after administration of antipyretic medication might initially drop temperature faster than medication alone, but the end result over time of this combination has not been proven to be definitively superior to medication alone.

Hyperthermia

Hyperthermia occurs when temperatures rise to alarmingly dangerous levels and is caused by mechanisms that do not involve the thermoregulatory set point. Hyperthermia supervenes when either heat production exceeds heat loss, as is the case with malignant hyperthermia, hyperthyroidism, and elevated environmental temperatures, or when heat loss is defective, as with dehydration, ectodermal dysplasia, heat stroke, or anticholinergic poisoning. During hyperthermia peripheral mechanisms

such as sweating and vasodilation fail to dissipate enough heat to decrease body temperature back to the untouched set point. Unlike fever, hyperthermia can cause confusion, delirium, stupor, or coma via an interplay of hypoxia, metabolic derangements, hypotension, and dehydration [49]. Not many patients have survived more than a few days or weeks with temperatures greater than 41.7°C [27].

Because hyperthermia does not involve the thermoregulatory center, treatment with centrally acting antipyretic medications is futile. Instead, appropriate management begins by identifying and addressing the inciting cause. Vigorous cooling techniques including removing clothing, bedside fans, cooling blankets, and sponging should be instituted. True hyperthermic emergencies should be treated with more drastic measures including immersion in ice water, intravenous administration of cool fluids, intraperitoneal and gastric lavage with cool fluids, and even extracorporeal circulation [49].

Summary

Fever phobia causes both health care providers and parents to overtreat fevers. This places children at risk of medication toxicity, needless repeat temperature readings, and parental panic. Fortunately, the homeostatic balance of the body's temperature control mechanism prevents fevers from reaching alarming levels of hyperthermia for most healthy individuals. It is the physician's role to educate parents regarding the facts and myths about fevers to decrease unsubstantiated parental fears.

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Fever and Rash: A Changing Landscape in the 21st Century

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Although fever and rash is a common complaint in the pediatric emergency department, most causes are benign. Of the more severe causes, several have been greatly reduced by vaccination programs. In addition, new vaccines such as those for invasive meningococcal disease hold promise for an even brighter future. Although meningococemia remains an important concern when evaluating a child with fever and a rash, the resurgence of measles, the emergence of invasive group A streptococcal disease and antibiotic-resistant *Staphylococcus aureus*, as well as the fear of agents of bioterrorism (anthrax, smallpox) have changed the landscape of fever and rash in the 21st century. The purpose of this article is not to offer a comprehensive differential of febrile exanthema, but rather to highlight some new concerns related to the evaluation of fever and rash in today's emergency department.

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KEYWORDS fever, rash, emergency, measles, anthrax, smallpox, meningococemia, streptococcus, staphylococcus

Although an isolated rash in a previously healthy child may present an interesting differential diagnosis, in the presence of a fever, the rash often gives a cause for more urgent concern. When accompanied by fever, the cause of the rash is likely to be infectious; however, rheumatologic diseases and medications may also be responsible. The purpose of this article is not to offer a comprehensive differential of febrile exanthema, but rather to highlight some new and resurgent causes of "fever and rash" that deserve consideration in today's emergency department (ED).

Measles

Once a mainstay of pediatric infectious disease, measles has become a rare entity in the United States because of a very successful immunization program; children receive 2 doses of measles vaccines before entering the school system. Recently, the Centers for Disease Control and Prevention (CDC) reported a rise in the cases of measles in United States in the first 4 months of 2008 [1]. This outbreak is believed to have originated in parts of Europe and Israel where immunization rates have declined because

of parental concerns regarding vaccine safety. Furthermore, 63 of the 64 patients with confirmed cases in the United States were not immunized against measles. Despite the seemingly small number of patients involved, this outbreak and the recent severe acute respiratory syndrome outbreak serve as reminders of the global nature of modern epidemics in an age where international air travel is commonplace. It also highlights the potential dangers of vaccine noncompliance on herd immunity, a central factor in a community's defenses against a real measles epidemic [2,3]. Therefore, patients presenting with fever and rash should be asked about recent travel, exposure to visitors from other countries, and immunization status.

The measles virus is highly contagious and is spread either via direct contact or by contact with an infected person's aerosolized respiratory secretions. Because of the

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nature of this illness, patients with measles will usually be brought to medical attention. Inasmuch as physicians training today are not likely to have encountered measles, raising awareness of this resurgent disease may prove to be of great importance in combating the next outbreak. After an incubation period of 4 to 12 days, clinical symptoms usually begin with high fever and the classic triad of cough, coryza, and conjunctivitis (“the three C’s”). Koplik spots, tiny white spots surrounded by a red ring present on the buccal mucosa, are pathognomonic for measles, but should not be relied on because they may be present for less than a day. The classic measles rash is an erythematous, maculopapular exanthem that appears after a child has been ill for several days. It starts from the forehead or posterior occipital area and spreads to the trunk and extremities within 3 days. The rash fades from red to copper brown and disappears in the same cephalocaudal direction [4]. Although such a quick review of signs and symptoms of measles can be helpful, clinicians encountering a possible case of measles should draw on the experience of older physicians and those from countries where measles may have been a common part of their clinical experience.

Early identification, respiratory isolation, and supportive care are the mainstay of therapy. In certain situations, vitamin A supplementation should be considered in addition to routine supportive care [4]. Children who are exposed to measles and have not received vaccine, but have no contraindications to receiving measles vaccine, should be vaccinated within 72 hours of exposure. For children who are younger than 1 year or have other contraindications (eg, immunocompromised) to vaccination, immunoglobulin can be used.

Group A β -Hemolytic Streptococcus

Group A β -hemolytic streptococcus (GAS) is held responsible for a wide array of diseases, the most common being acute pharyngotonsillitis and impetigo, and their nonsuppurative sequelae. There are numerous accounts of devastating streptococcal outbreaks in the preantibiotic era. Scarlet fever outbreaks killed thousands in Europe in the 1600s and in the New World in 1736, with mortality rates of 25% to 35%. Outbreaks of rheumatic fever and acute glomerulonephritis have also been documented through history. Each of these outbreaks reached its resolution without the availability of antibiotics, but not without taking a heavy toll. With the advent of penicillin and readily available testing, the mortality associated with scarlet fever and other GAS diseases dropped dramatically [5].

In the early 1980s, GAS received significant attention in the lay media under the moniker *flesh-eating bacteria*. In recent years, invasive, deadly diseases such as necrotizing fasciitis, myositis, and toxic shock syndrome (TSS)

continue to occur sporadically with occasional clusters [6-9]. In addition, these severe forms of disease appear to affect previously healthy children and young adults, and not just vulnerable populations [10-12]. A combination of change in virulence factors in the organism (many of the implicated strains are M protein type 1 or 3) as well as host factors may play a role in the resurgence of severe invasive GAS diseases [5].

Invasive GAS disease can be classified into 4 syndromes that sometimes overlap: necrotizing fasciitis, myositis, streptococcal TSS, and invasive GAS without TSS (eg, pneumonia, osteomyelitis). For these forms of disease, the mortality remains high, despite antibiotic and supportive therapy. This likely reflects the primary role of toxin in these diseases and in particular the streptococcal pyrogenic exotoxins, which act as superantigens that overactivate the immune system. Criteria for the diagnosis of streptococcal TSS were established in the 1990s and include isolation of GAS from the host, shock, and evidence of multiorgan dysfunction (eg, renal or hepatic dysfunction, coagulopathy, adult respiratory distress).

The rash of invasive GAS infections varies and depends on the type and stage of disease. A generalized erythematous macular rash that desquamates may accompany streptococcal TSS. For patients with necrotizing fasciitis and myositis, fever, chills, and severe pain are *often out of proportion* to the early cutaneous findings, which include minimal amounts of localized swelling and erythema. In necrotizing fasciitis, infection spreads in the subcutaneous tissues, rapidly destroying fascia and fat. Late skin manifestations include swelling, purplish discoloration, hemorrhagic bullae, and necrosis.

Given the subtle dermatologic manifestations that belie the severe nature of invasive GAS disease, the diagnosis is often missed in its early stages. This is especially true when the portal of entry of the organism is not clear. Hematomas due to minor nonpenetrating trauma, deep bruises to calf muscle, vaccinations, burns, or even muscle strains have been implicated as a nidus for infection. A strong association between varicella and GAS necrotizing fasciitis has become apparent in children. Typically, necrotizing fasciitis occurs on the third to fourth day of the varicella exanthem and should be considered in the differential diagnosis of a child with varicella who develops a new fever. Several case reports have described an association between nonsteroidal anti-inflammatory drug use and necrotizing fasciitis, especially in children with varicella; and many experts advise against nonsteroidal anti-inflammatory drug use in patients with varicella.

A high level of suspicion is essential for the early diagnosis of invasive GAS disease. Elevated serum creatinine phosphokinase or rising level of creatinine phosphokinase may help with the diagnosis of myositis. Magnetic resonance imaging is helpful in diagnosing and defining the extent of fasciitis and myositis. Evidence of multisystem involvement typical of TSS should be ascertained,

including hypotension, renal or liver failure, and coagulopathy. Early aggressive surgical debridement and parenteral antibiotics are necessary for an improved outcome.

Mortality is generally much higher in cases of invasive GAS if the patient develops streptococcal TSS [9,11-13]. Streptococcal TSS may be clinically indistinguishable from staphylococcal TSS in patients who present with fever, erythroderma, and rapid-onset hypotension with multi-organ involvement. Although evidence of focal skin or deeper soft tissue infection may be present, a significant number of cases do not have an obvious source of infection. Interestingly, GAS pharyngitis has rarely been associated with TSS and invasive diseases in general. Intensive supportive therapy, along with aggressive local debridement, when indicated, is most important in managing patients with TSS.

Based on the clinical presentation, it may be necessary to provide empiric staphylococcal (see below) and streptococcal antimicrobial coverage for patients with invasive GAS disease. Once a diagnosis has been confirmed, therapy can be tailored appropriately. Group A β -hemolytic streptococcus remains susceptible to penicillin and β -lactam antibiotics in general; but resistance to macrolides, trimethoprim-sulfamethoxazole, and clindamycin has been described. For patients with TSS, clindamycin should be included in the initial antibiotic regimen (ie, not alone, but in addition to standard antimicrobial therapy). The rationale for clindamycin therapy relates in part to its ability to inhibit protein synthesis (including toxin production). Intravenous immunoglobulin therapy may provide neutralizing antibodies against streptococcal toxins and should be considered as adjunctive therapy for patients with TSS.

Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

Staphylococcus aureus has long been known as a major cause of infections of skin and wounds as well as the respiratory tract, lymphatic system, and bone. It is also known to cause a variety of toxin-mediated syndromes (ie, TSS and staphylococcal scalded skin syndrome) [14]. The epidemiology and treatment of *S aureus* disease have undergone major changes since the introduction of antibiotics in the 1940s and the subsequent emergence of antibiotic resistance. Beginning in the 1990s, community-acquired methicillin-resistant *S aureus* (CA-MRSA) emerged as a significant cause of health problems. In the lay press, the term *superbug* has been used to imply that CA-MRSA has outsmarted all available antibiotics and to bring attention to this “epidemic.”

Community-acquired methicillin-resistant *S aureus* infections were first recognized in Australian Aborigines who had never had any contact with Western medical care [15]. Over the last 15 years, CA-MRSA has emerged to affect a much broader group of populations globally. Many

outbreaks have been reported in groups where close contact facilitates transmission, such as among young healthy athletes, most notably in the United States among the members of the St Louis Rams football team [16]. High person-to-person transmission rates also account for the very high intrafamilial spread of this disease. Once colonized intranasally, carriers may have upward of 4 times higher rates of infection. The spread of CA-MRSA has culminated in what many are calling an epidemic [17]. The CDC estimates that between 1998 and 2005, the cases of MRSA doubled. A recent multicenter study found that CA-MRSA is the most common pathogen identified in patients with skin and soft tissue infections presenting to EDs in the United States [18].

Community-acquired methicillin-resistant *S aureus* infection is mostly limited to skin and soft tissue ranging from furuncles to cellulitis and abscesses, abscesses being by far the most common. Paradoxically, the most prevalent strain (USA 300 ST-8) of CA-MRSA is now being found in the inpatient setting causing soft tissue infections. Pyomyositis, myositis, and necrotizing fasciitis are some of the more serious invasive diseases caused by CA-MRSA with significant morbidity and mortality. Skin manifestation may be a late finding in these patients. Fever and pain that are out of proportion to physical findings may be a clue to more deep-seated infection [19].

Although it is uncommon to see systemic signs of inflammation such as fever and leukocytosis with furuncles and abscesses, cellulitis may be associated with systemic signs. Incision and drainage should be used for all infectious collections likely to be due to CA-MRSA. In fact, some data suggest that smaller isolated abscesses (<5 cm) that are not associated with any signs and symptoms of systemic diseases may be managed with simple incision and drainage alone [20]. Systemic antibiotics are warranted for larger abscesses and cellulitis. For CA-MRSA, methicillin resistance is encoded by the *mec-IV* plasmid. This plasmid is smaller than the plasmid found in hospital-acquired MRSA and does not encode antibiotic resistance to non- β -lactam antibiotics. As a result, agents such as trimethoprim-sulfamethoxazole, clindamycin, and doxycycline, which have been around for many years, may be effective in treating CA-MRSA in the outpatient setting. Nonetheless, resistance patterns are community specific; and antimicrobiograms should be reviewed regularly to determine current susceptibilities. Vancomycin has been the mainstay of intravenous therapy for MRSA, and reports of vancomycin-resistant MRSA are rare. Alternative agents that may be useful in the treatment of serious CA-MRSA infections include linezolid, daptomycin quinupristin/dalfopristin, and tigecycline [21]. An unusual property of CA-MRSA is its tendency to cause recurrent skin infections. Affected individuals may benefit from strategies designed to eradicate carriage of this organism. The optimal strategy for decontamination remains to be



Figure 1 Four-month-old female infant with gangrene of the hands due to meningococemia (image 1334 of public health image library courtesy of the CDC/Mr Gust).

determined; but recommendations have included the following approaches, both separately and in combination: nasal application of mupirocin, chlorhexidine baths, and even systemic antimicrobial therapy [14].

Meningococemia

Neisseria meningitidis is a gram-negative diplococcus that causes rapidly progressive sepsis that may or may not involve meningitis. Meningococcal septicemia, which can begin as a nonspecific febrile illness, can rapidly (within hours) progress to multisystem organ failure and death. Initial nonspecific symptoms of fever, headache, myalgia, and abdominal pain may be quickly followed by signs and symptoms of shock [22]. The rash may also progress rapidly from macular, maculopapular, or urticarial to petechiae and purpura, or ecchymosis. Ultimately, these lesions may evolve into large areas of necrosis involving the skin, digits, and limbs (Figure 1). These dermatologic manifestations reflect underlying vasculitis and disseminated intravascular coagulation induced by the organism. Most deaths occur within the first 48 hours of illness. Case fatality has been reported to be as high as 50%. Predictors of poor outcomes include young age, absence of meningitis, presence of coma, temperature less than 38°C, hypotension (mean arterial pressure <2 SD below mean for age), leukopenia (white blood cell count <10 000/mm³), and thrombocytopenia (platelet count <100 000/mm³).

By contrast, in meningococcal meningitis, which is the most common form of invasive meningococcal disease, only about 80% of cases have a visible rash at the time of presentation [23]. In the absence of a rash, the clinical features of meningococcal meningitis (fever, headache, photophobia, lethargy, irritability, and neck stiffness) are indistinguishable from meningitis caused by any other bacteria.

Because of the rapidly fulminant nature of meningococemia, this diagnosis should be considered in the differential diagnosis of all patients who present with fever and petechiae. All ill-appearing patients or patients with unstable vital signs, petechiae/purpura, and fever should be presumed to have invasive meningococcal disease. Blood cultures (and polymerase chain reaction if available) should be collected, but empiric therapy (antibiotics and hemodynamic support) must be initiated quickly. Pulmonary edema may necessitate mechanical ventilation, and renal insult may lead to hemodialysis. Close contacts of patients with meningococcal disease should receive chemoprophylaxis [22].

All children 11 years and older should receive the quadrivalent polysaccharide conjugate meningococcal vaccine (MCV 4) [22]. Younger children (2 years and older) with specific risk factors (eg, asplenia, complement deficiency, and travel to an endemic area) should also receive the conjugate vaccine. This vaccine contains polysaccharide from serogroups A, C, Y, and W-135. Current vaccine research is targeting the B serogroup, which is the most common cause of meningococcal disease in the United States [24]. *Neisseria meningitidis* invasive disease may be significantly reduced in decades to come [25], much as pneumococcal and *Haemophilus influenzae* type B disease has with the widespread use of vaccines for those pathogens.

The development of the new meningococcal conjugate vaccine (MCV4) has provided a number of advantages over the old meningococcal polysaccharide vaccine (MPSV4), including induction of immunologic memory and booster effect with no hyporesponsiveness upon subsequent dosing. MCV4 also provides a longer immune response, and it can reduce nasopharyngeal carriage with possible herd immunity. However, MCV4 vaccine has its own limitations. The immune response in infants and very young children is less than ideal and is relatively short-lived. An association of Guillain-Barre syndrome and MCV4 vaccine (17 cases) is still being monitored, and patients with history of Guillain-Barre syndrome are advised to take the old nonconjugated polysaccharide vaccine.

Anthrax

In the fall of 2001, bioterrorism became a real threat to the American public when 22 people in the United States became infected with *Bacillus anthracis* (the causative agent of anthrax) through mail sent to media outlets and political offices. Overnight, a fear of anthrax entered the consciousness of a very threat-sensitive public after the terrorist attack on the World Trade Center and Pentagon a month earlier. As a result of the anthrax attacks, 5 people were killed and 30 000 more people received prophylactic antibiotics for possible exposure to the spores [26].



Figure 2 A cutaneous anthrax lesion on the arm (image 2332 of public health image library courtesy of the CDC/Dr Philip S Brachman).

Bacillus anthracis makes a good biologic agent for terrorism because its spores are highly stable and the inhalational form of anthrax has a high mortality. Anthrax can present in 3 forms: cutaneous, inhalational, and gastrointestinal tract disease. Mortality rate for cutaneous cases are usually less than 1%, whereas inhalational and gastrointestinal forms can exceed 50%. The disease, in its most common cutaneous form, causes vesicles or papules at the site of exposed, broken skin. Over several days, the vesicles may rupture, leaving a necrotic ulcer, with subsequent development of a painless black eschar (Figure 2). There is usually surrounding edema and erythema with regional lymphadenopathy. All forms of anthrax have an incubation period of less than 2 weeks. With the inhalational form, an initial prodrome of nonspecific, flu-like symptoms (fatigue, fever, sweats, cough, and vomiting) is followed in 2 to 5 days with dyspnea, hypoxia, and fulminant shock. Early chest x-ray findings of hilar fullness, mediastinal widening and effusions, or hemorrhagic infiltrates can be helpful in distinguishing early anthrax from viral infections. The gastrointestinal form can initially present with either oropharyngeal ulcers or symptoms of nausea, anorexia, or vomiting followed by signs and symptoms of gastrointestinal bleed and shock. In all suspected cases of anthrax, patients should be initially treated with either ciprofloxacin or doxycycline regardless of the patient's age until susceptibility testing indicates otherwise [5,27,28].

Smallpox

Schoolchildren are taught of the 19th century success of Edward Jenner in using cowpox exposure to immunize against smallpox. Since then, smallpox eradication by vaccination (the last reported case was in 1977) is one of the triumphs of modern preventive medicine. The disease, if reintroduced, would likely cause havoc because routine

vaccination has been discontinued throughout the world. To prevent a devastating outbreak, there have been recommendations for reintroduction of the vaccine in select groups, such as at-risk laboratory workers, some health care providers, military personnel, and first responders [29]. With a mortality rate of about 30%, potential for rapid spread, and no known cure, smallpox was propelled, along with anthrax, into our collective awareness of potential bioterrorism threats [30].

The disease is characterized by severe prodromal symptoms (including high fever, severe headache, backache, and malaise) that are debilitating. These symptoms are followed initially by lesions on the mucosa of the mouth and pharynx with progression to the skin. The skin lesions progress from macules to papules to vesicles to deep-seated hard pustules over 1 week, spreading cephalocaudally. In contrast to varicella, these lesions are more deep seated, often involve the palms and soles, and tend to be of the same stage on each affected part of the body. Death often occurs in the second week of illness because of severe viremia [27,29].

Smallpox vaccine is a live virus vaccine that contains a related, but relatively attenuated, vaccinia virus. In contrast to the most common vaccines, this vaccine is administered by 2-pronged needle that is dipped in vaccine solution. The vaccine, when given before exposure, is highly effective in preventing smallpox. In addition, vaccination of exposed individuals (within 7 days of exposure) may significantly shorten and lessen the severity of the disease. The vaccine has adverse effects and associated mortality in people with atopic dermatitis, those who are immunocompromised, or those who have heart conditions [31]. A hyperimmune globulin is being studied for the treatment of adverse effects associated with smallpox vaccination. The vaccine produces a local vesiculopustular lesion that itself is contagious and must be covered to prevent autoinoculation and exposure to others.

At the present time, although the US government has enough vaccine to immunize everyone in the United States, the risks far outweigh the benefits for routine immunization [32]. Isolation of sick patients, surveillance, and reporting are the mainstays of a public health response to a smallpox scare.

Summary

Although “fever and rash” is a common complaint in the pediatric ED, most causes are benign. Of the more severe causes, several have been greatly reduced by vaccination programs. Indeed, new vaccines such as those for invasive meningococcal disease hold promise for an even brighter future. However, the resurgence of forgotten oldies such as measles, the emergence of invasive group A streptococcal disease, the superbug status of antibiotic-resistant *S. aureus*, and the fear of a bioterrorism attack have changed the landscape of fever and rash in the 21st century.

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Fever After International Travel

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Fever in a child after international travel may represent a benign self-limited illness or may be a manifestation of a more severe life-threatening disease. Knowledge of these illnesses is extremely important for a clinician managing a febrile child after travel. This article presents an approach to history taking and evaluation of the febrile child after travel, stressing knowledge of diseases endemic to geographic regions, timing of symptoms, travel exposures, and specific presenting signs and symptoms. The article also discusses in detail some of the more commonly encountered systemic febrile illnesses, including malaria, dengue fever, typhoid fever, rickettsial infections, and leptospirosis. Clin Ped Emerg Med 9:250-257 © 2008 Elsevier Inc. All rights reserved.

KEYWORDS fever after travel, malaria, dengue, typhoid, rickettsiae, leptospirosis

Each year, more than 300 million episodes of travel occur between the United States and foreign countries [1], and approximately 6% of these travelers are children [2]. Reflecting the large immigrant population to the United States, a significant portion of these children are visiting with family and friends in developing countries and may be exposed to endemic infectious diseases that are rare within the United States. Up to 8% of individuals visiting developing countries are ill enough to seek health care while abroad or after returning home [3,4]. Fever is reported as a chief reason for seeking medical care in 28% of these returned travelers [5]. Although many of these fevers represent benign self-limited infections, they may also be manifestations of progressive life-threatening diseases, and it may be difficult to initially distinguish between the two. This is especially true if physicians are unfamiliar with the types of infections that a child may have been exposed to while traveling. Thus, it is important to have a systematic approach to the diagnosis and management of children presenting with fever after international travel.

Approach to Fever After Travel

Inquiring about recent travel should be routine any time a child presents with fever. This is especially true when working in a setting in which families frequently travel to their countries of origin where certain infectious diseases are endemic. Nevertheless, the first consideration, in terms

of epidemiology, remains illnesses the child is at risk for had there been no travel history. Routine causes of fever will still present more commonly, even after international travel.

The differential diagnosis should then be expanded based upon specific details from a thorough travel history. Important points to consider would include the geographic regions visited (including layovers), the dates of travel, onset of specific symptoms, and exposures such as the environment of activities, foods consumed, any insect bites, sexual activity, and ill contacts. It is also important to inquire about any vaccines received before travel and the use of chemoprophylaxis.

Knowledge of the geographic regions visited will help narrow the differential diagnosis. The largest current database regarding febrile illness after international travel comes from GeoSentinel sites, which are more than 30 specialized travel or tropical medicine clinics on 6 continents that collect surveillance data on travel-related diseases [5,6]. GeoSentinel data on 17 353 patients who presented between June 1996 and August 2004 demonstrated that systemic febrile illness without localizing findings occurred disproportionately among those return-

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ing from sub-Saharan Africa or Southeast Asia [6]. Overall, malaria was the most common cause of systemic febrile illness and was one of the 3 most frequent causes among each of the developing geographic regions studied, most predominant in sub-Saharan Africa. Dengue fever was the most common presentation in the Caribbean, South America, South Central Asia, and Southeast Asia. Typhoid fever was a significant contributor to febrile illness among travelers returning from South Central Asia, and rickettsial infections appeared primarily after travel to sub-Saharan Africa. Other good resources for geographic-specific illnesses are the Centers for Disease Control and Prevention (CDC) Web site, [7] www.cdc.gov, or the World Health Organization (WHO) Web site, www.who.int/en/. Under “Travelers' Health” on the CDC Web site, searches can be performed for current information on the epidemiology of infectious diseases within specific countries [8].

The timing of symptoms as a reflection of incubation periods of different infections is also helpful in refining a differential diagnosis (Table 1) [9-11]. Although most infections in travelers have incubation periods of less than 30 days, several may present weeks to months after a return from travel, such as vivax malaria, hepatitis, and tuberculosis [5]. It is therefore important to inquire about travel within the past year for any child who presents with a febrile illness without a localizing source. A high index of suspicion for potentially fatal illnesses should be maintained for fever occurring shortly after a return from travel, because illnesses such as falciparum malaria and viral hemorrhagic fevers are likely to manifest at this time. Conversely, if fever occurs more than 3 weeks after return, dengue fever, rickettsial infections, and viral hemorrhagic fevers are very unlikely [10]. Antimicrobial chemoprophylaxis may delay the onset of symptoms of falciparum malaria [5].

Specific symptoms or findings may help to narrow the differential. Relapsing fevers may represent malaria, leishmaniasis, Lyme disease, or filariasis [9]. Jaundice is

often seen in hepatitis, malaria, and leptospirosis. Hepatomegaly may suggest typhoid, hepatitis, malaria, or leptospirosis, whereas splenomegaly may manifest in malaria, brucellosis, typhoid, or dengue. Fever associated with hemorrhage may be seen with meningococemia, malaria, leptospirosis, rickettsial infections, and viral hemorrhagic fevers [10]. Respiratory symptoms in a febrile traveler may be secondary to common pathogens such as *Streptococcus* or influenza, but other infections such as mycoplasma, legionellosis, tuberculosis, histoplasmosis, coccidioidomycosis, and Q fever should be considered.

The initial laboratory workup for a febrile child without a localizing source after international travel will vary based on the individual history, but will likely include a complete blood count, liver function tests, urinalysis, blood culture, and peripheral blood smears for malaria. Additional testing may include cultures of stool and urine, chest radiography, and specific serologic assays such as those for dengue, rickettsiae, schistosomes, *Leptospira*, and human immunodeficiency virus [10].

Specific Etiologies

Malaria is by far the most common specific etiology diagnosed in patients with systemic febrile illness after travel [5]. After malaria, the most common etiologies include dengue fever, typhoid fever, rickettsioses, and leptospirosis. According to the GeoSentinel data, fever is a chief reason for seeking care in 90% of those with malaria, 82% with dengue, 87% with typhoid, 72% with rickettsial infections, and 96% with leptospirosis [5].

Malaria

Malaria is a major worldwide health concern, affecting approximately 270 million people and causing 1 million deaths each year [12]. Endemic malaria was eradicated in the United States more than 50 years ago, such that most US health care providers are unfamiliar with the disease and its clinical signs. Because travel between countries and continents has become easier and less expensive, the number of imported cases of malaria to the United States is increasing. Approximately 1200 to 1500 cases of malaria are reported in the United States every year [13]. Oftentimes, the diagnosis is delayed because of the inexperience of US health care providers with this illness [9,12].

Malaria is caused by a protozoa transmitted by female mosquitoes. There are 4 distinct species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*. *P. falciparum* causes more than 50% of malaria cases in the United States and has the greatest potential to cause death. *P. vivax* causes approximately 25% of reported US cases, and interestingly, in almost one quarter of the cases, the species is undetermined [13]. *P. falciparum* is found in sub-Saharan Africa, Hispaniola,

Table 1 Incubation periods for infections causing fever in travelers.

Incubation Period	Possible Infections
<10 d	Malaria, dengue fever, viral hemorrhagic fevers (yellow, Lassa), enteric bacterial infections, Rocky Mountain spotted fever, arboviral encephalitis, influenza, legionellosis
11-30 d	Malaria, typhoid fever, rickettsial infections, leptospirosis, human immunodeficiency virus, African trypanosomiasis, brucellosis, <i>Strongyloides</i> , polio, histoplasmosis, coccidioidomycosis, Q fever
>30 d	Malaria, hepatitis, tuberculosis, schistosomiasis, amebic liver abscesses, human immunodeficiency virus, leishmaniasis

and Papua New Guinea. *P. vivax* is seen in South Asia, eastern Europe, northern Asia, and Central and South America. *P. ovale* occurs mostly in West Africa [12]. There are 3 stages to the *Plasmodium* life cycle involving the mosquito, the human liver, and the human red blood cells. The greatest human morbidity and mortality occurs during the asexual stage of the life cycle occurring in the red blood cells. *P. vivax* and *P. ovale* also have a dormant liver stage, which can reactivate weeks to months later, causing recurrence of disease [12].

When assessing a patient with fever, travel history is very important. Malaria should be considered in any patient who presents with fever after travel to an endemic area within the last year. In studies evaluating diagnoses in pediatric and adult patients presenting with fever after travel, malaria is the most common specific etiology, noted in 21% of presentations to GeoSentinel sites [5,6] and in as high as 27% of hospitalized patients [14]. In most cases, symptoms of malaria will develop within 1 to 2 months of return from an endemic area [6,9,12,14]. Patients infected with *P. vivax*, *P. ovale*, or *P. malariae* may have a longer incubation period. However, infection with all 4 species can take longer to present in the face of inadequate prophylaxis or treatment, an individual's immune response, or relapse [12]. Fever occurs in 78% to 100% of patients with malaria; however, they are not always febrile at the time of presentation [15,16]. The classic description of the malaria fever consists of a periodicity associated with the rupture of red blood cells, releasing the merozoite stage of the parasite into the blood stream. Infection with *P. vivax* or *P. ovale* is associated with fever spikes every 48 hours, whereas *P. malariae* has a fever periodicity of every 48 to 72 hours. Oftentimes, a fever pattern cannot be determined in *P. falciparum* infections [9,17]. Other symptoms include chills, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, and myalgias, often presenting in the same periodic fashion. Physical examination findings can include hepatosplenomegaly, pallor, and jaundice [12,15,17].

The criterion standard for diagnosis of malaria is the presence of parasites on Giemsa-stained thick and thin blood smears. If the diagnosis is suspected, but the initial blood smears are negative, repeat samples should be obtained every 12 to 24 hours for a 48- to 72-hour period [9,12,17,18]. The parasite density, or percentage of infected erythrocytes, is a measure of severity of disease and should be followed to measure response to treatment. Other laboratory findings may include anemia, thrombocytopenia, a low white blood cell count, elevated liver transaminase levels, evidence of renal failure, or evidence of hemolysis (elevated bilirubin levels) [12,15].

There is no prophylactic treatment available today that can prevent malaria 100% of the time, even if taken exactly as directed. For the last several decades, most *P. falciparum* has developed resistance to chloroquine, whereas sporadic resistance to other medications has been seen more

recently [12,13,15,17]. This has made both prophylaxis and treatment of malaria more difficult. The treatment of malaria can be complicated and is best undertaken with the assistance of an infectious disease specialist. The type and duration of treatment depends on several factors, including the infecting species, the percentage of parasitemia as seen on thin blood smear, patterns of drug resistance, clinical signs of severe malaria, and the ability to tolerate medications by mouth [9,12]. Signs of severe disease that would require intravenous treatment and intensive care monitoring would include coma, seizures, acute renal failure, respiratory distress, disseminated intravascular coagulation, or parasitemia more than 5% [12]. In brief, chloroquine-sensitive *P. falciparum* is best treated with chloroquine. For chloroquine-resistant *P. falciparum*, there are 3 options: (1) quinine plus tetracycline, doxycycline, or clindamycin (depending on the age of the patient); (2) atovaquone-proguanil; or (3) mefloquine. Chloroquine is still the treatment of choice for *P. ovale* and *P. malariae* infections. It can also be used to treat most *P. vivax* infections, except those acquired in Papua New Guinea and Indonesia. Because of resistance, these infections are best treated with quinine plus either tetracycline or doxycycline, or with mefloquine alone. Primaquine should also be administered to patients with *P. vivax* or *P. ovale* infections to prevent relapse due to hepatic hypnozoites. However, primaquine cannot be given to patients with glucose-6-phosphate dehydrogenase deficiency because it can precipitate a hemolytic crisis [12]. For those patients in whom malaria is suspected but not confirmed, or if the infecting species cannot be identified, treatment of chloroquine-resistant *P. falciparum* should be initiated immediately [13]. A more detailed and current discussion of malaria treatment including geographic resistance patterns can be found at the CDC Web site.

Dengue Fever

The first reports of major epidemics of a disease believed to be dengue fever date back more than 200 years [19,20]. The viral etiology has been understood since the 1940s, at a time when the ecologic disruption of Southeast Asia and the Pacific Islands during World War II created ideal conditions for increased transmission and a global pandemic [19]. Recurrent epidemics and continued endemics have persisted since. Each year, an estimated 100 million cases of dengue fever, 250 000 cases of dengue hemorrhagic fever (DHF), and 25 000 deaths occur [21]. In certain regions, especially Southeast Asia, dengue is a leading cause of hospitalization and death among children [22].

The dengue viruses are single-stranded RNA viruses of the family Flaviviridae [23,24]. There are 4 serologically distinct serotypes. Infection induces long-term immunity to only the infecting serotype so individuals may be infected up to 4 times [23,25]. Humans are the main reservoir for the virus, though nonhuman primates may

also become infected. Dengue virus is transmitted by mosquitoes of the genus *Aedes*, primarily *Aedes aegypti*, found worldwide in tropical and subtropical regions [23,24]. *A. aegypti* is an extremely efficient vector because it is very susceptible to the dengue virus, it feeds primarily on human blood, it is a daytime feeder, the bite is often unnoticeable, it typically bites several people in a single meal, and it breeds in clean stagnant water containers often found near homes in developing urban settings [21]. Humans become infected after being bitten by an infected female *Aedes* mosquito. The incubation period is typically about 4 to 6 days, and individuals remain viremic until their fever breaks [26,27].

The incidence and geographic distribution of dengue have been increasing, largely because of human population growth, increasing urbanization with overcrowding and poor water and waste management, lack of mosquito control, increased *A. aegypti* breeding grounds such as water-filled plastic containers and tires, and increased human travel [19,26]. Although rising, the true incidence of dengue in returned travelers is probably underestimated. In many countries, it is not necessarily reported, and because of the short incubation period, it may present while an individual is still traveling [21]. The diagnosis may also be missed because of nonspecific symptoms. It is important to inquire where returned travelers with fever have been because the most commonly diagnosed systemic illness will be dengue fever when returning from Southeast Asia, the Caribbean, South Central Asia, and South America [6].

After a child is bitten by an infected mosquito, the virus replicates in regional lymph nodes and disseminates throughout the lymphatic system and blood [23]. Clinical manifestations range from an asymptomatic infection, to a self-limited systemic illness, to DHF and shock. Young children are more likely to have asymptomatic disease, whereas severe disease is more common with secondary infections.

Classic dengue fever presents with a sudden onset of fever, severe headache, retroorbital pain, and fatigue [9-11,23]. Myalgias and arthralgias are often present, which evoked the term *breakbone fever*. A macular or maculopapular rash, often confluent with spared patches, is present in more than half of cases, usually appearing near defervescence and occasionally accompanied by scaling and pruritus [23,28]. Other findings may include gastrointestinal symptoms, diffuse lymphadenopathy, hepatomegaly, injected conjunctival and oropharyngeal surfaces, and mild upper respiratory symptoms. Occasionally, hemorrhagic findings such as petechiae and purpura or gastrointestinal bleeding may occur, and very rarely will patients have myocarditis, hepatitis, or neurologic abnormalities [23]. Common laboratory findings in dengue fever include leukopenia, thrombocytopenia, and moderate elevations of hepatic aspartate transaminase.

Dengue hemorrhagic fever is defined by a triad of hemorrhagic manifestations, a platelet count of less than

100 000 mm⁻³, and evidence of capillary leakage including pleural effusion, ascites, or hypoproteinemia [23,29]. Dengue hemorrhagic fever typically presents 4 to 7 days after the onset of dengue fever at the time of defervescence. Mortality rates may be as high as 10% to 20% but are much lower with inpatient hospital management [21]. The term *dengue shock syndrome* is used when symptoms of shock (tachycardia, hypotension) accompany DHF. Mortality from shock syndrome may be as high as 40% [21].

The diagnosis of dengue fever is made primarily on the clinical symptoms. Clinicians should consider the diagnosis in patients presenting with a systemic febrile illness less than 14 days after returned travel from an endemic location, associated with leukopenia and thrombocytopenia. A confirmed diagnosis may be established by serum culture of the virus, polymerase chain reaction, or serologic assays, but each of these tests has limitations, and results may not be timely to assist in management [23]. A probable diagnosis may be established from a positive immunoglobulin (Ig) M antibody test result, but this is often negative for the first 4 to 5 days of symptoms. Management should be based upon clinical suspicion.

No specific treatments exist for the dengue virus, so treatment should be supportive based upon symptoms. Platelet counts and hematocrit determinations should be checked daily. Platelets counts of less than 100 000 mm⁻³ are usually a criterion for hospital admission because of the increased risk of DHF. Early initiation of fluid management may reduce the mortality from DHF and shock syndrome [23]. In addition to crystalloid fluids, pressors, fresh blood, or fresh frozen plasma may be necessary in severely ill patients. The WHO has published guidelines for the rates and timing of fluid infusions [30].

Typhoid Fever

Enteric (typhoid or paratyphoid) fever is a systemic febrile illness caused by *Salmonella typhi* and *Salmonella paratyphi*. Their only reservoir is humans, and acquisition is by consumption of fecally contaminated food and water. The CDC estimates that there were 21.6 million new cases of typhoid and 5 million new cases of paratyphoid in 2000, causing 200 000 deaths worldwide [31]. Prevalence is highest in South Central Asia and Southeast Asia followed by the rest of Asia, Africa, Latin America, and the Caribbean Basin. The estimated incidence of typhoid among travelers to these areas of the world is 3 to 30 cases per 100 000 travelers [3]. A recent study showed that 40% of the cases of typhoid fever occurred in travelers visiting friends and relatives in their native countries, whereas only 4% of cases occurred in traditional tourists [32]. While staying with friends and family members, travelers likely have less control over what they eat and drink. In that study, 42% of all travel-associated cases occurred in patients younger than 18 years.

Table 2 World Health Organization antibiotic recommendations for uncomplicated typhoid fever [40].

Susceptibility	Optimal Therapy	Alternative Therapy
Fully sensitive	Fluoroquinolone, eg, ofloxacin, ciprofloxacin	Chloramphenicol, amoxicillin, TMP-SMX
Multidrug resistance	Fluoroquinolone or cefixime	Azithromycin, cefixime
Quinolone resistance	Azithromycin or ceftriaxone	Cefixime

TMP-SMX, trimethoprim/sulfamethoxazole.

After ingestion of the bacteria, the usual asymptomatic incubation period is 7 to 14 days, with a range of 3 to 60 days. Clinical illness typically begins with fever and flu-like symptoms, including anorexia, nausea and vomiting, abdominal pain, myalgia, headache, and cough. Diarrhea is more common in young children, whereas constipation is more often seen in adolescents and adults [33,34]. Physical examination can be notable for toxic appearance, abdominal tenderness, and hepatosplenomegaly. Rose spots, erythematous maculopapular blanching lesions 2 to 4 mm in diameter occurring primarily on the abdomen and chest as well as the back, arms, and legs, are seen in 5% to 30% of patients. A relative bradycardia is also not unusual. The peripheral white blood cell count may be normal or decreased. Liver enzyme elevations are usually 2 to 3 times normal. Complications occur in 10% to 15% of patients and are more likely in young patients and in those who have been ill more than 2 weeks. Gastrointestinal bleeding can occur in up to 10% of patients and usually results from erosion of a necrotic Peyer's patch through an enteric vessel [33]. Intestinal perforation occurs in about 3% of patients with an overall mortality of about 40% [35]. The presentation of perforation can vary from an acute abdomen to simply a worsening of abdominal pain with accompanying signs of shock. The third most concerning complication is typhoid encephalopathy. These patients are commonly apathetic but arousable; however, presentations can include agitation, delirium, obtundation, and coma. Corticosteroids may be lifesaving in these patients [36]. A generally milder relapse of encephalopathy occurs in up to 10% of properly treated patients, usually within 3 weeks of resolution of the initial illness [33]. Case fatality rates in children are less than 2% with younger age, hypotensive shock, hypothermia, obtundation, seizures, anemia, and leukocytosis being associated with higher mortality [34].

Definitive diagnosis of enteric fever requires the isolation of *S. typhi* or *S. paratyphi*. Blood cultures are positive in 60% to 80% of adult patients providing that a large volume (15 ml) of blood is cultured. Children generally have higher levels of bacteremia than adults [37]. The sensitivity of blood cultures is higher during the first week of illness. In individual patients, the bacterial content of the bone marrow is generally 10 times that of the peripheral blood. Culture of marrow is therefore more sensitive. Positive results are obtained in 80% to 95% of patients with enteric fever and may remain positive up to 5 days or longer after initiation of appropriate antibiotic therapy [38].

Antibiotic choices for the treatment of the child with presumed or confirmed enteric fever should be tailored to the region of the world from which the disease was obtained and the severity of the illness. Most patients with typhoid fever can be managed in the outpatient setting with oral antibiotics, but those with severe illness, persistent vomiting, severe diarrhea, or abdominal distension should be hospitalized and given parenteral treatment [39]. Patients returning from Latin America and the Caribbean Basin can be assumed to have fully sensitive strains; however, for travelers returning from South Asia, it should be assumed that they have a multidrug-resistant strain, and for travelers returning from Southeast Asia, quinolone resistance should be assumed. The WHO recommendations for antibiotic treatment of typhoid fever are presented in Table 2 [40].

Rickettsial Infections

Rickettsial infections are generally underreported because there is a wide variation in presentation. Early signs and symptoms are fairly nonspecific and may mimic benign viral infections, though as a group, rickettsial infections are responsible for severe illness and death in many otherwise healthy travelers [41]. Rickettsial disease can be found worldwide, but most of the rickettsial infections in travelers occur after visits to sub-Saharan Africa, mostly reflecting the emergence of the species *Rickettsia africae* in southern Africa in recent years [6]. Numerous cases have also been reported in South Central Asia and Southeast Asia.

The term *rickettsiae* conventionally includes a large seemingly ever-growing group of microorganisms in the class Proteobacteria, which, in addition to the group *Rickettsia*, also includes *Orientia*, *Ehrlichia*, *Anaplasma*, *Neorickettsia*, *Coxiella*, and *Bartonella* [42]. The infections considered "rickettsioses," however, traditionally include scrub typhus due to *Orientia tsutsugamushi*; the rickettsial typhus group consisting of *Rickettsia prowazekii* and *Rickettsia typhi*; and the spotted fever group, which consists of more than 15 species causing human disease including Rocky Mountain spotted fever (*Rickettsia rickettsii*), African tick bite fever (*R. africae*), Mediterranean spotted fever (*Rickettsia conorii*), and rickettsialpox (*Rickettsia akari*) [42,43]. The rickettsiae bacteria are gram-negative obligate intracellular rods [11,43]. They are transmitted by arthropod vectors including ticks, mites, fleas, and lice, and their natural life cycle involves

mammalian reservoirs [11,42,43]. Travelers are at risk of exposure to rickettsial infections if they engage in recreational or occupational activities which bring them in contact with the habitats supporting the vectors or animal reservoirs, such as camping, hiking, or traveling on a safari in grassy or scrubby areas [10].

Most of the rickettsial infections have an incubation period of 1 to 2 weeks [9,11]. Epidemic typhus (*R. prowazekii*) is transmitted by the body louse. Most outbreaks occur in impoverished communities in cold mountainous regions of Africa and South America [43]. Murine typhus (*R. typhi*) is primarily transmitted by fleas from rodent reservoirs. The typhus group illness is characterized by an abrupt onset of high fever, chills, myalgias, and headache. A rash appears 4 to 7 days after onset of illness, and changes in mental status are common. Cardiac and renal failure may occur with severe illness, and mortality is as high as 30% if untreated. Murine typhus is typically a more mild disease than epidemic typhus, and children tend to display a more mild illness.

Most spotted fever group rickettsiae are transmitted by ticks, except for rickettsialpox (*R. akari*), transmitted by mites, and *Rickettsia felis*, transmitted by cat fleas [42]. All spotted fever group rickettsioses cause a triad of fever, headache, and intense myalgias. Other symptoms vary from region to region and host to host [10,11,42,43]. Most will also cause a generalized rash a few days after the onset of fever and/or a localized painless eschar at the site of the arthropod bite. The most characteristic rashes are macular, maculopapular, and petechial, though a few species will cause vesicular eruptions. Conjunctivitis, pharyngitis, and regional lymphadenopathy are common; some patients may also have vomiting, diarrhea, and arthralgias. A smaller percentage of patients with severe disease will develop pulmonary, central nervous system, cardiac, or renal complications. Leukopenia, thrombocytopenia, and elevated liver enzymes are common laboratory abnormalities [43].

The diagnosis of most rickettsial infections is usually based upon clinical features and epidemiologic clues. Serologic assays may confirm the diagnosis. Most patients will demonstrate increased IgM titers by the end of the first week and IgG titers by 7 to 10 days [9]. Other diagnostic techniques include polymerase chain reaction amplification, immunohistologic detection, and isolation of rickettsiae [42]. The treatment for rickettsial infections is doxycycline for both adults and children, though chloramphenicol may also be used [9,42]. Most patients can be treated as outpatients, but inpatient supportive care may be necessary for those with severe disease.

Leptospirosis

Leptospirosis is a zoonotic disease caused by numerous species of the *Leptospira* genus of spirochetes. They can be found throughout the world but tend to cause more human infection in tropical regions. Humans acquire the infection

through contact with infected urine from carrier animals, most often through contaminated soil or water. Outbreaks tend to occur during times of heavy rainfall [44,45]. Many individuals with leptospirosis will have a subclinical infection or only mild symptoms such as fevers and myalgias, and therefore, often do not present to medical attention [44,46-48]. Those with more severe symptoms often report high fevers, chills, headache, nausea, and vomiting. Conjunctival suffusion and severe myalgias of the calves and lumbar area have been described as characteristic features of infection [9,44,48]. The disease may be biphasic with symptoms returning after 3 to 4 days of apparent recovery [44,48]. The most severe forms of the disease include Weil's disease and severe pulmonary hemorrhage syndrome. The symptoms of Weil's disease include jaundice, nonoliguric renal failure, and hemorrhage secondary to thrombocytopenia. Mortality for this form may reach 15% [44,49]. Patients with severe pulmonary hemorrhage syndrome often have hemoptysis and show signs of acute respiratory distress syndrome. Mortality is greater than 50% [50].

The diagnosis of leptospirosis is usually made by the microagglutination test that detects agglutinating antibodies. It is a difficult test to perform and may lose sensitivity and specificity in instances in which many subspecies could be the infecting agent [44]. The decision to treat is controversial because rapid diagnosis of leptospirosis is impossible, and most mild cases resolve spontaneously [46]. However, most experts would advocate treatment because it can shorten the duration of symptoms in milder forms of the disease and decrease mortality in those with more severe infection [51]. The WHO recommends that mild disease be treated with ampicillin, amoxicillin, or doxycycline, whereas severe infection is best treated with intravenous penicillin G or ceftriaxone [52]. Some experts would recommend ceftriaxone over penicillin for its simpler administration schedule and its greater efficacy against leptospirosis in in vitro studies [46,53,54].

Summary

Primary care clinicians should help to educate patients about diseases endemic to specific geographic regions before international travel and assist in prophylaxis. Vaccine-preventable infections occur in 3% of returned travelers who present with fever, most commonly typhoid fever, hepatitis A, and influenza A [5]. Malaria chemoprophylaxis may also significantly reduce morbidity and mortality in travelers.

For the returned pediatric traveler who presents to the emergency department with fever, it is extremely important to have a systematic approach to the travel history. Knowledge about the diseases endemic to regions the child traveled to, the timing of the onset of symptoms, and any exposures during travel in addition to presenting symptoms will help to narrow a differential diagnosis and direct

appropriate laboratory evaluation. Emergency physicians should also familiarize themselves with helpful online resources [8], involve infectious disease or travel medicine specialists, and consider appropriate empiric therapy for ill-appearing febrile children after international travel.

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Empiric Antibiotics for the Complex Febrile Child: When, Why, and What to Use

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There are multiple patient care scenarios where empiric antibiotics are indicated in the practice of pediatric emergency medicine. Patients with fever and neutropenia, ventriculoperitoneal shunt(s), cystic fibrosis, and short bowel syndrome are unique patient populations that are often instructed to seek further evaluation for any concerns of possible infection. When seen in the emergency department, fever is usually the presenting complaint; however, they may also present with more subtle signs and symptoms of infection that require prompt evaluation. This article briefly reviews these 4 unique patient populations as well as when, why, and what empiric antibiotics are often used to treat them.

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KEYWORDS fever, neutropenia, emergency, chronic disease, cystic fibrosis, short bowel syndrome, ventriculoperitoneal shunt

Although the cause of fever in the otherwise healthy child is usually of benign etiology, fever in a child with a chronic medical condition or indwelling hardware (ventriculoperitoneal [VP] shunt, central venous catheter) is often a sign of a serious underlying infection. Because of repeated infections, these children tend to develop more complicated infections, often with drug-resistant organisms. It is important for the emergency department (ED) physician to understand not only the likely etiologies of these infections but which antibiotic therapies are appropriate for empiric treatment on presentation.

Empiric Antibiotics in Patients with Fever and Neutropenia

Neutropenia can be congenital, idiopathic, and/or acquired in etiology. The causes of acquired neutropenia include infections, immune disorders, nutritional deficiencies, chemicals, and medications. Patients with fever and neutropenia are at risk for serious infection. Empiric antibiotics included in this section are based on guidelines for patients with cancer receiving chemotherapy but are applicable to most patients with fever and neutropenia regardless of etiology.

Patients with cancer are at greater risk of infection if they have central venous catheters and when their absolute neutrophil count (ANC) decreases during chemotherapy.

The ANC is calculated by multiplying the total white blood cell (WBC) count by the combined percentage of segmented neutrophils and bands ($ANC = WBC \text{ count} \times \text{percentage [neutrophils + bands]}$). It is thought that at least one half of neutropenic patients who become febrile have an established or occult infection and at least one fifth of febrile patients with neutrophil counts of less than of 100 cells per cubic millimeter have bacteremia [1].

The Infectious Diseases Society of America issued guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever in 1990 that were revised in 1997 [2]. The Infectious Diseases Society of America Fever and Neutropenia Guidelines Panel issued guidelines in 2002 for the use of antimicrobial agents in neutropenic patients with cancer. *Neutropenia* is defined as an ANC less than 500 cells per cubic millimeter or less than 1000 cells per cubic millimeter with a predicted decrease to less than 500 cells per cubic millimeter. *Fever* has been defined as a single oral temperature of at least 38.3°C

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(101°F) or a temperature of at least 38.0°C (100.4°F) for at least 1 hour [1-3]. Rectal temperature measurement may precipitate bacteremia and is therefore not recommended. Neutropenic patients may be afebrile or hypothermic at presentation [3]. Although fever in this patient population may be associated with transfusions, medications, or the underlying cancer itself, patients should be evaluated and treated for infection until proven otherwise [1].

Broad-spectrum antibiotics are initiated to cover gram-negative and gram-positive bacteria after completion of a thorough history and evaluation. The initial evaluation should include a physical examination, complete blood cell count, and blood cultures obtained from a peripheral vein and/or all central line lumens. Additional laboratory and radiological testing should be performed as indicated by the history and physical examination. The choice of a particular empiric antibiotic regimen may vary depending on the individual patient, cause of neutropenia, type of infection, treatment setting, local antimicrobial susceptibility pattern, cost, toxicity, and expected time to recovery from neutropenia. Although national guidelines are available for the management of febrile children with neutropenia, local microbiologic epidemiology is more important when deciding the empiric antibiotic regimen for the individual patient. Therefore, consultation with local hematology/oncology and infectious disease specialists is recommended [1-3].

Most bacterial infections in neutropenic patients are caused by endogenous skin, oral, or intestinal flora. Historically, most of the bacterial septicemia in this patient population was due to gram-negative organisms. Gram-negative bacilli, specifically *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* species, remain prominent causes of infection. However, gram-positive bacteria currently account for approximately 60% to 70% of microbiologically documented infections. Fungal infections are usually superinfections, although *Candida* species or other fungi can cause primary infections [1-5].

There are 3 general intravenous antibiotic regimens: single-drug therapy (monotherapy), 2-drug therapy without a glycopeptide (vancomycin), and single-drug or 2-drug therapy with vancomycin. Multiple studies have shown no difference between monotherapy and multidrug therapy for empirical treatment of uncomplicated episodes of fever and neutropenia [1]. Because fungal, viral, and/or protozoal organisms rarely cause primary infections in patients with fever and neutropenia, initial antibiotic therapy is directed against bacterial pathogens [3].

Choices for single-drug therapy include a third-generation cephalosporin (ceftazidime), fourth-generation cephalosporin (cefepime), or a carbapenem (imipenem-cilastatin or meropenem). The advantages of single-drug therapy are convenience, decreased cost, and lower toxicity. These antibiotic choices do not cover coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, some strains of penicillin-resistant *Streptococcus pneumoniae*, and viridans streptococci [1].

Choices for 2-drug therapy without vancomycin include an antipseudomonal cephalosporin (ceftazidime or cefepime) with an aminoglycoside (gentamicin, tobramycin, or amikacin), a carbapenem (imipenem-cilastatin or meropenem) with an aminoglycoside, or an antipseudomonal penicillin (ticarcillin-clavulanic acid or piperacillin-tazobactam) with an aminoglycoside. The advantages of multidrug therapy are expanded bacterial coverage, enhanced potential synergistic interaction, and prevention of drug resistance emergence. The disadvantages are lack of activity against some gram-positive bacteria and the nephrotoxicity, ototoxicity, and hypokalemia associated with aminoglycosides and carboxypenicillins (ticarcillin-clavulanic acid) [1].

If the patient does not require vancomycin, single-drug therapy is indicated in uncomplicated cases; and 2-drug therapy is indicated in complicated cases or for suspected antimicrobial resistance. Single-drug therapy choices are ceftazidime, cefepime, imipenem-cilastatin, or meropenem. Two-drug therapy choices are ceftazidime or cefepime with an aminoglycoside, a carbapenem with an aminoglycoside, or an antipseudomonal penicillin with an aminoglycoside [1].

The addition of vancomycin to single-drug or 2-drug therapy should be considered in patients with the following: clinically suspected serious catheter-related infections, known colonization with penicillin- and cephalosporin-resistant pneumococci or MRSA, confirmed isolation of a gram-positive organism from a blood culture before final identification and susceptibility testing, or hypotension or other evidence of cardiovascular impairment [1].

If the patient requires vancomycin, begin treatment with a 2- or 3-drug regimen with ceftazidime or cefepime plus vancomycin with or without an aminoglycoside, a carbapenem plus vancomycin with or without an aminoglycoside, or an antipseudomonal penicillin plus vancomycin with an aminoglycoside [1].

Modification and duration of antibiotic therapy during the first week of treatment are guided by the resolution or persistence of fever and neutropenia as well as clinical status, identification of a source of infection, and culture results. Antibiotic regimen choices include no change, change to oral ciprofloxacin plus amoxicillin-clavulanic acid, discontinuation of vancomycin, addition of an antifungal drug, or discontinuation of therapy. Changes should be made in consultation with local hematology/oncology and infectious disease specialists [1,3].

Empiric Antibiotics for Patients with VP Shunt(s)

Cerebrospinal fluid (CSF) shunt placement is the most common pediatric neurosurgical procedure performed. As a result of very high complication rates, patients with VP

shunts are frequently brought to the ED for evaluation of suspected malfunction. Although obstruction is the most common complication, infection is responsible for 20% to 25% of all shunt complaints [6]. Seizures, ventriculitis, meningitis, and subdural empyema are secondary problems that can develop as a result of shunt infections.

Half of all VP shunt infections are observed during the initial 2 weeks after placement, and 75% occur within the first 2 months. Among patients beyond 6 months from surgery, shunt infection is very unlikely [7].

Most shunt infections occur because of colonization of the shunt at the time of surgery or, less frequently, secondary to skin breakdown of the postoperative wound. These proximal shunt infections are predominantly caused by low-virulence organisms found in skin flora. The typical presentation involves nonspecific complaints of fever without a source, poor feeding, or not acting right. The classic symptoms of shunt infection such as headache, lethargy, fever, and meningismus are less likely. Meningismus is present in only 25% of cases, with headache occurring in 5% to 10% and lethargy in 10% to 15% of patients with shunt infections [8,9]. Fever is present in 80% to 90% of cases, but the absence of fever does not exclude the possibility of infection [10]. In reality, clinical signs of increased intracranial pressure may develop only when infection has caused shunt obstruction and subsequent malfunction.

The most commonly cultured organisms are *Staphylococcus epidermidis* (40-50%), *S aureus* (25%), and *Propionibacterium acnes* [11]. Patients with VP shunts also have an increased risk of meningitis caused by the traditional pathogens *S pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Reports of fungal central nervous system infections have increased in recent years especially because of *Candida* species.

Ventriculoperitoneal shunt infections may also develop via direct contamination of the distal end of the shunt by hematogenous seeding. These infections manifest as abdominal pain due to bowel perforation and peritonitis or pseudocyst formation with distal obstruction. In addition to *Staphylococcus* species, gram-negative organisms or mixed flora may be isolated. Patients with gram-negative VP shunt infections are usually more ill appearing. Particularly at risk for gram-negative shunt infections are infants younger than 6 months. The rate of infection is twice that of children at least 1 year of age at the time of the shunt insertion [10].

In patients with VP shunts, wound infections are usually located over the site of the reservoir or in the abdominal wall. Infection generally occurs at the time of shunt placement and appears as warmth, redness, and possible purulent drainage at the affected surgical site. *Staphylococcus* species are the most frequently cultured organism.

Any patient presenting with complaints that are suspicious for a shunt problem should be evaluated with a thorough history and physical examination. If the possibility of infection remains, a diagnostic evaluation

Table 1 Recommended parenteral therapy for known organisms in VP shunt infections.

Organism	Antibiotics
S epidermidis or MRSA	Vancomycin ± rifampin
Methicillin-sensitive	Oxacillin or nafcillin
S aureus	
Gram-negative	Cefotaxime, cefepime,
bacteria	or meropenem
P acnes or Streptococcus	Penicillin G ± gentamicin
species	
Fungi	Amphotericin B

should be initiated; and prompt neurosurgical consultation should be obtained. Laboratory tests are of limited value in determining the probability of VP shunt infection. It has been demonstrated that even with a documented shunt infection, 25% of patients will have a normal WBC count [12]. Analysis of CSF is necessary, and a shunt tap is preferred to lumbar puncture because it can identify obstruction and is more sensitive in detecting infection. This is important because one third of patients with shunt obstruction are found to have a concurrent shunt infection. The CSF should be sent for cell count, glucose, protein, gram stain, and culture. Cerebrospinal fluid cultures are critical for organism identification and directing further antibiotic therapy. The other component necessary when evaluating a shunt is radiographic imaging. Plain radiographs of the shunt valve and tubing are needed to assess the continuity of the system and to rule out kinking of the tube. Cranial computed tomography is used to demonstrate evidence of ventriculitis or CSF obstruction. Comparison with a previous computed tomography is essential, as children with VP shunts often do not have normal baseline ventricular size even with a normally functioning shunt [11].

Treatment of an infected shunt involves removal of the shunt, sterilization of CSF with antibiotics, and placement of a new shunt. It is essential to give the first dose of intravenous antibiotics in the ED. Empiric parenteral antibiotic coverage includes vancomycin and a third-generation cephalosporin (cefotaxime) for endogenous gram-positive and gram-negative pathogens in children. Vancomycin combined with ceftazidime, cefepime, or meropenem is indicated to cover nosocomial gram-positive and gram-negative pathogens in adults [13]. Linezolid may have utility in treating infections caused by resistant *S aureus* [14]. If an organism is known or sensitivities are available, more specific antibiotic coverage can be selected (Table 1).

Empiric Antibiotics in Patients with Cystic Fibrosis

Patients with cystic fibrosis (CF) often present to the ED for evaluation and treatment of pulmonary exacerbations.

It is extremely important to diagnose and treat new or worsening infections to limit progression of chronic lung disease. Furthermore, a variety of factors make the eradication of respiratory pathogens in children with CF especially difficult (Table 2).

In early disease, infections are associated with acute respiratory complaints and new physical findings. Over time, a repeating cycle of infection, inflammation, and structural injury leads to end-stage lung disease and bronchiectasis. Once chronic lung disease has developed, acute exacerbations can be difficult to diagnose. The following clinical features have been found to concur with the criterion standard of physician diagnosis of a pulmonary exacerbation in CF: increased cough, increased sputum production or chest congestion, increased fatigue, decreased appetite, increased respiratory rate or dyspnea at rest, change in sputum appearance, fever, increased nasal congestion or drainage, and decreased exercise tolerance or increased dyspnea with exertion [15].

Treatment of any pulmonary exacerbation in patients with CF is highly individualized. Antibiotic selection is dictated by the severity of the exacerbation, the extent of existing underlying lung disease, and the patient's respiratory tract flora. Mild to moderate exacerbations can be successfully treated with oral antibiotics. Intravenous antibiotics are indicated for severe exacerbations, treatment failure associated with previously administered oral antibiotics, or infections caused by resistant organisms. Antibiotics should be directed against any new pathogen detected in the respiratory secretions. If no such organism is identified, the most recent respiratory culture and sensitivity results for each patient should guide the initial antibiotic choice.

Staphylococcus aureus is the most common pathogen isolated in infants and young children with pulmonary exacerbations. *Haemophilus influenzae* and *P aeruginosa* are more prevalent in older children and adults. Mild exacerbations due to *S aureus* and *H influenzae* may be effectively treated with trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, or oral cephalosporins. Intravenous cephalosporins are recommended for more serious *S aureus* and *H influenzae* infections. The emergence of antimicrobial resistance has greatly impacted on the treatment of patients with CF. The prevalence of MRSA among patients with CF reported to the CF Foundation Patient Registry increased from 7% in 2001 to 19% in 2006

[16]. A combination of nebulized vancomycin, oral rifampin, and sodium fusidate has been used to effectively treat less serious MRSA infections. A tetracycline (doxycycline) and linezolid are other oral choices for mild to moderate MRSA exacerbations. Vancomycin or teicoplanin is recommended for severe infections requiring intravenous therapy.

Isolation of *P aeruginosa* in the sputum represents an important transition in the pulmonary status of patients with CF. Pseudomonal infection leads to a more rapid decline in lung function and an increase in mortality. The initial isolation and presumed infection may respond well to oral fluoroquinolones used in combination with aerosolized tobramycin. Patients with chronic infection, however, may be colonized with several strains of *Pseudomonas* species in their sputum; and identifying the strain responsible for acute infection can be a challenge. The most commonly chosen intravenous regimens for *P aeruginosa* infections combine aerosolized tobramycin treatments with a semisynthetic penicillin (ticarcillin-clavulanic acid or piperacillin-tazobactam), a third-generation cephalosporin (ceftazidime), a fourth-generation cephalosporin (cefepime), or a carbapenem (imipenem-cilastatin or meropenem). A recent comparative trial of intravenous tobramycin and meropenem or ceftazidime found the 2 options to be equally effective in the treatment of CF patients with pseudomonal lung infections [17]. Regardless of the combination chosen, guidelines recommend the addition of vancomycin or linezolid for those patients found to be coinfecting with *P aeruginosa* and MRSA.

When patients fail to respond to conventional therapy, other diagnoses should be considered. *Burkholderia cepacia* is a plant pathogen that can cause severe pulmonary disease in patients with CF. Both ceftazidime and meropenem have shown activity against some strains of *B cepacia*. Tobramycin should be added for resistant strains. Allergic bronchopulmonary aspergillosis is a reaction to a type of fungus that can occur in association with CF. The fungus does not invade and destroy the lung tissue, but instead colonizes the airways and causes recurrent inflammation. Recommended treatment consists of oral prednisone and itraconazole. Finally, infection with atypical mycobacteria is not common, but can occur in young children with CF. Treatment is generally prolonged and requires the selection of a multiple drug combination based on the specific organism involved.

Table 2 Factors that contribute to the difficulty in eradicating respiratory pathogens in children with CF.

Development of antibiotic resistance
Poor penetration of antibiotics through respiratory secretions
Defects in host mucosal defenses
Very slow growing bacteria often involved
Bacterial produced "biofilms" that interfere with phagocytic killing

Empiric Antibiotics in Patients with Short Bowel Syndrome

Short bowel syndrome can result from congenital or acquired reasons. Congenital etiologies include gastroschisis, intestinal atresia, and midgut volvulus; and acquired etiologies include necrotizing enterocolitis or Crohn's disease. Long-term parenteral nutrition has resulted in improved long-term survival and quality of

life in this patient population; for that reason, patients with short bowel syndrome require prolonged use of central venous catheters. Consequently, parenteral nutrition-associated liver failure and catheter-related bacteremia are the leading causes of morbidity and mortality in patients with short bowel syndrome [18,19].

Initial evaluation of patients with short bowel syndrome should include a physical examination, comprehensive metabolic panel, complete blood cell count, and blood cultures from a peripheral vein and/or all central line lumens. Additional laboratory and radiological testing should be performed as indicated by the history and physical examination. Consultation with local gastroenterology and infectious disease specialists is recommended.

Patients with short bowel syndrome are at increased risk of infection from both endogenous and nosocomial pathogens. Gram-negative bacteria, specifically *E coli*, *Enterobacter* species, *Klebsiella* species, *Proteus* species, and *Pseudomonas* species, are prominent causes of infection. Infection with gram-negative bacteria may be secondary to external contamination or bacterial translocation. Gram-positive organisms, specifically, *S epidermidis* and *S aureus*, and *Candida* species are also associated with external contamination [20,21].

Empiric broad-spectrum parenteral antibiotics are initiated to cover gram-negative and gram-positive bacteria. Antibiotic therapy choices include a third-generation cephalosporin (cefotaxime or ceftazidime), a carbapenem (imipenem-cilastatin or meropenem), or a semisynthetic penicillin (ticarcillin-clavulanic acid or piperacillin-tazobactam). Vancomycin is added for coverage of gram-positive bacteria including MRSA. An aminoglycoside (gentamicin, tobramycin, or amikacin) may be used for gram-negative coverage in patients with no renal insufficiency.

The choice of antibiotic therapy should be guided by the patient's previous culture results and sensitivities as well as local antibiotic resistance patterns whenever possible. Lastly, if fungal infection is suspected, empiric antifungal therapy should also be initiated with an amphotericin formulation.

Relevant Antibiotic Alerts

The US Food and Drug Administration (FDA) initiated a safety review of cefepime in November 2007 after concerns of increased mortality in patients treated with cefepime were raised in a published meta-analysis. In May 2008, the FDA announced it was continuing to review safety data concerning cefepime [22,23]. Additionally, the FDA initiated a safety review of linezolid in March 2007 after concerns of increased mortality in patients with catheter-related bacteremia and catheter site infections treated with linezolid were raised in an open-label randomized trial. The chance of death was related to the type of organism causing infection, with no difference in mortality in patients with gram-positive infections and higher mortality in patients with gram-negative-only, mixed, or no organ-

ism infections. Linezolid is not approved for the treatment of catheter-related bloodstream, catheter site, or gram-negative infections [24].

Summary

Children with fever and neutropenia, VP shunt(s), CF, and short bowel syndrome frequently present in the ED with a complaint of fever with or without additional signs and symptoms. In addition to a thorough evaluation and stabilization of the patient, the ED physician is often responsible for initiating empiric antibiotics to treat suspected bacterial infections in these complex febrile children. The choice of a particular empiric antibiotic regimen may vary depending on the individual patient and suspected infection as well as local antimicrobial susceptibility patterns. This article summarizes several available antibiotic treatments. Consultation with subspecialty services, if available, is recommended.

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