HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2016 May 23.

Published in final edited form as:

J Pediatr. 2011 August ; 159(2): 181–185. doi:10.1016/j.jpeds.2011.03.047.

Management of the Non-Toxic Appearing Acutely Febrile Child: A 21st Century Approach

Ravi Jhaveri, MD[1], **Carrie L. Byington, MD**[2], **Jerome O. Klein, MD**[3], and **Eugene D. Shapiro, MD**[4]

[1]Division of Infectious Diseases, Department of Pediatrics, Duke University Medical Center, Durham, NC

[2]Division of Infectious Diseases and General Pediatrics, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT

[3]Division of Infectious Diseases, Department of Pediatrics, Boston University School of Medicine, Boston, MA

[4]Departments of Pediatrics, Epidemiology, and Investigative Medicine, Yale University School of Medicine and Graduate School of Arts and Sciences, New Haven, CT

Keywords

fever; infant; fever without localizing signs; occult bacteremia; urinary tract infection; white blood cell count; procalcitonin; C-reactive protein

Overview of the Management of the Febrile Child Younger than 36 Months of Age

Although most febrile children <36 months of age have a self-limited viral infection that will resolve without treatment, a small proportion of them who are not obviously toxic will develop a serious bacterial infection (SBI, including bacteremia, meningitis, urinary tract infection (UTI)). There has been long-standing controversy about how best to assess and to manage such children.(1–5) Identifying which non-toxic-appearing febrile child has an SBI is a persistent challenge for pediatric practitioners. Management of febrile children is further complicated by the fact that parents and physicians value the risks and costs differently.(1) Most physicians find errors of omission (missing a child with SBI) intolerable, and parents give more consideration to procedures involving pain and discomfort for their children, such as diagnostic testing and false positive test results and their consequences.

Corresponding Author: Ravi Jhaveri M.D., Division of Pediatric Infectious Diseases, DUMC Box 3499, Duke University Medical Center, Durham, NC 27710, Phone: 919-684-6335, Fax: 919-668-4859, ; Email: ravi.jhaveri@duke.edu.

The authors declare no conflicts of interest

History

Risk of SBI is greatest in the immediate neonatal period and through the first months of life, is heightened in premature infants, and progressively decreases as the child gets older. Practice has evolved from conservatively managing febrile infants <3 months of age by conducting extensive testing, hospitalizing and treating with antibiotics to using combinations of clinical appearance, age and the results of laboratory tests to assign different degrees of risk of SBI to help determine management.(6, 7) One meta-analysis from the early 1990s found the risks of serious bacterial illness, bacteremia, and meningitis were 24.3%, 12.8%, and 3.9% vs. 2.6%, 1.3%, and 0.6%, respectively, in "high risk" vs. “low-risk” infants <3 months of age.(8). Although it is still important to perform a careful evaluation of febrile infants <3 months of age to assess the likelihood of a SBI, it is clear that many need not be subjected to rigid algorithms of testing and treatment. Infants between 61–90 days have lower risk of SBI compared with those ≤60 days.(9) An observational study of more than 3000 infants <3 months of age with fever ≥38°C treated by practitioners in 44 states found that the majority (64%) were not hospitalized.(10) Practitioners individualized management and relied on clinical judgment; “Guidelines” were followed in only 42% of episodes. Outcomes of the children were excellent. If the “guidelines” had been followed, outcomes would not have improved but the children would have undergone both substantially more laboratory tests and more hospitalizations.(3, 10)

Although the risk of SBI is substantially lower in children 3–36 months of age, the entity of "occult bacteremia" (OB)--bacteremia in febrile children who on evaluation were thought not to have an SBI and were sent home but a culture of blood obtained at the time grew a potential pathogen, was described in the 1970s.(11) Two large studies from the pre-conjugate-vaccine era showed that the overall risk of OB in children 3–36 months of age with fever ≥39°C was slightly less than 3%.(12, 13) Most children with OB had a benign clinical course but some progressed to severe focal infections. Children at risk of OB included those who were young (6 months to 36 months of age), had elevated temperature (> 39.4°C or 103°F), and had increased white blood cell (WBC) count (>15,000).(11, 14) The majority of OB was caused by *Streptococcus pneumoniae* (Sp), a smaller number by *Haemophilus influenza*-type b (Hib) and occasional cases by *Neisseria meningitidis* (Nm), *Staphylococcus aureus*, group A streptococcus, *Escherichia coli and Salmonella* species.(12, 14, 15) Because of concern that children with OB might go on to develop a more serious focal infection, particularly bacterial meningitis, many investigators tried to develop strategies that would identify which febrile child was at risk of OB.(16) Although there were statistically significant associations between test results, particularly of an elevated WBC count and OB, because of the low prevalence of OB, positive predictive value of test results were poor (10–15%).(2, 17) Moreover, most cases of OB were due to Sp, which often resolved spontaneously.(18) Compared with the risk of meningitis among children with occult pneumococcal bacteremia (about 1%), the risks of developing meningitis among children with OB due to Hib and Nm were about 12 times and 86 times greater, respectively. (19) In a single trial, Fleisher et al reported that intramuscular ceftriaxone was effective for prevention of meningitis and other bacterial sequelae in young, febrile children at risk for OB.(12) In an attempt to offer a consensus viewpoint, Baraff et al published “guidelines” for diagnosis and management of febrile children at risk of SBI which included routine use of

WBC to identify children at risk, cultures of blood to document the presence of bacteremia and use of ceftriaxone for children deemed to be at risk of SBI.(15) These “guidelines” were controversial given the relatively low risk of meningitis (about 1/1,400), the lack of evidence that either testing for markers of risk or expectant treatment provided substantial benefit to these children and perceived flaws in design and analyses that created bias towards finding efficacy of ceftriaxone in preventing SBI.(2, 12, 20)

What has changed since the 1970s about management of the febrile infant without a focus of infection?

After introduction of conjugate Hib vaccine in 1988, the incidence of Hib disease in children aged <5 yrs declined by 99% from 1987 to 2007. After introduction of the seven-valent conjugate pneumococcal vaccine (PCV7) in 2000, the incidence of pneumococcal meningitis among children aged < 2 yrs fell by 64% with further decreases anticipated following the introduction of PCV13 in 2010. (20–22) Chemoprophylaxis during labor to prevent early onset infection of infants of pregnant women colonized with group B streptococcus (GBS) also has been effective, with an 80% decrease in early onset disease since publication of the first guidelines in 1996. (23) There has been no decline in late onset disease.

In febrile infants ≤90 days of age, the group at highest risk of SBI, availability of new diagnostic tests also has improved the ability to estimate risk more accurately in these febrile infants. Abnormalities in total WBC count, absolute neutrophil count (ANC), and absolute band count all have been associated with SBI. Total WBC counts < 5,000/mm^3 and >15,000/mm^3 have been associated with SBI.(8) Although abnormalities of the WBC count are not specific for SBI and have a positive predictive value ranging from 26–80% depending on what population is being studied, the chosen WBC cutoff value and how SBI is defined (6, 24), recent studies continue to document the utility of the WBC in evaluating febrile infants. In one study of 408 infants 7–90 days of age, those with WBC counts >15,000/mm^3 were more likely to have SBI with a likelihood ratio of 2.11 and an area under the receiver operating curve of 0.71.(25) Another study of 1257 infants had similar findings and including the CBC as part of the evaluation for febrile infants reduced the frequency of missed SBI.(26)

Both elevated C-reactive protein (CRP) and procalcitonin (PCT) have been associated with SBI in febrile infants.(25) The sensitivity and specificity of both are superior to those of the WBC count.(24, 25) However, CRP rises more slowly than PCT, so in infants who have been febrile for <12 hours, PCT is a more sensitive test for SBI.(24, 25) Furthermore, CRP also is less specific than PCT because it is elevated in nearly 25% of infants with viral infections.(24) In contrast, PCT is usually normal in infants with viral infections, including respiratory syncytial virus (RSV) and enteroviral infections,(24, 27) two of the most common causes of fever in infants ≤90 days old.(28) Although PCT performs better than WBC or CRP, there are disadvantages of this test that include longer time until results are available and higher cost. More research is needed to determine whether PCT can be used to identify febrile infants identified as being at high-risk of SBI based on traditional criteria,

but who actually have a viral illness and could be managed as outpatients and/or without antibiotics.

Viral diagnostic testing has also improved greatly during the last two decades. There are many types of diagnostic tests, including rapid chromatographic immunoassays, direct fluorescent antibody (DFA), and the polymerase chain reaction (PCR) assay that are accurate and for which clinical laboratories can often report results in <24 hours. SBIs are less common in febrile infants with laboratory-confirmed influenza, RSV and enteroviral infections.(28–32) The ability to rapidly identify infants with viral infections has resulted in changes in the management of febrile infants ≤90 days (and in older febrile infants and children), including decreased ancillary testing, decreased use of antibiotics, and shorter hospital stays.(33, 34)

What has not changed about management of the febrile child without a focus of infection?

The modes of pathogenesis that need to be considered include *in utero* infections: infections acquired at delivery; infections acquired in the nursery; infections acquired in the household; and infections acquired due to underlying anatomic or physiologic abnormalities. Many of these problems persist for infants 29–90 days of age and also include late onset GBS and *E. coli* sepsis. Invasive meningococcal disease has attack rates in the first year of life greater than that in any other age group; no vaccine is approved for infants yet.

UTI and urosepsis need be considered in the febrile child without a clinical focus of infection. Selection of children for lumbar puncture remains a challenge for physicians even though the incidence of bacterial meningitis has diminished. Children with immunosuppressive conditions (e.g., sickle cell disease, asplenia, HIV infection, malignancy) remain at higher risk of invasive bacterial infections and require aggressive management for febrile episodes.

What are the issues with existing practice guidelines in the current era?

The practice “guidelines” by Baraff *et al* represented an attempt to provide guidance for practitioners faced with the dilemma of managing a febrile child.(15) These “guidelines” were never officially endorsed by a professional body at the time of initial publication, but there is a clinical policy currently endorsed by the American College of Emergency Physicians that is virtually identical to the initial Baraff et al recommendations.(35) The “guidelines” favored the potential benefits of treating with antibiotics and hopefully preventing the development of severe sequelae over the risks of isolating organisms that are contaminants and of performing unnecessary testing. There are several reasons why these “guidelines” should be modified

The “guidelines” reflect the epidemiology from 25 years ago and not from today

Even before introduction of the Hib conjugate vaccine, Hib was the causative organism in only a minority of children with OB who presented with fever without localizing signs, though it was the most common organism to lead to serious focal infections.(19) With the

universal administration of Hib vaccine to infants that began in the late 1980's, Hib disease has virtually disappeared, and with this disappearance so has much of the serious sequelae of OB that the original guidelines were designed to prevent.(20)

The "guidelines" treat all agents that cause bacteremia equally in terms of subsequent risks when this is not accurate

After elimination of Hib, complications of OB due to Sp was the major justification for continued testing and empiric treatment of these febrile children. Although Sp was the most common cause of OB, it was not associated with the same risk of severe complications.(19) The vast majority of OB due to Sp resolved either without treatment or with oral antibiotics.(18)

In 2000, with the approval PCV7 pending, investigators calculated that routine use of PCV7 would eliminate 97% of OB due to Sp.(36) Several studies have now demonstrated this prediction was correct, with Sp OB rates of less than 0.5% (Table).(37–41) Studies also show that contaminants are isolated from blood cultures 10–20 times more often than are pathogens and WBC counts are no longer a useful way to assess risk of OB in children >90 days of age.(37, 40) Although surveillance data have demonstrated that non-vaccine serotypes are the major cause of invasive pneumococcal disease today, overall rates of invasive pneumococcal disease remain stable at levels ~50% lower than that prior to introduction of PCV7. Non-vaccine serotypes cause predominantly sinopulmonary infections including empyema and sepsis associated with "obvious" rather than occult bacteremia.(42)

Nm can cause OB that leads to serious complications. However, Nm is far less common than Sp and current rates of invasive disease are more than 60% lower than those observed in the 1990's,(43) so it is a rare cause of SBI in children with OB. Universal immunization of adolescents may further decrease the reservoir and protect young children who are not currently targeted for immunization.

The "guidelines" do not sufficiently focus on UTI, the most common SBI in febrile children

Many studies have shown that the most common SBI in children with fever without localizing signs is UTI, which occurs in 4–6% of febrile children,(40, 44) and in up to 8.2% of febrile infants classified as high-risk (3.4% in viral positive vs. 10.4% in viral negative).(28) Studies have shown that girls are at greater risk than boys, with the sex differential increasing significantly with age.(44, 45) Although current recommendations include evaluation of the urine, studies have shown that evaluation of the urine is not always done, despite being recommended by the AAP practice parameter.(40, 45) New guidelines should emphasize evaluation for UTI in all infants and young children with fever without localizing signs, with the possible exception of circumcised boys.(45)

In an era of increasingly limited resources, "guidelines" should be demonstrated to be cost-effective

In the current health care environment, the cost-benefit of every evaluation and intervention must be assessed. In 2001, an assessment of various strategies for evaluation of infants with

fever without localizing signs found that for rates of OB at or below our current rate of 0.5%, no screening and/or pre-emptive treatment strategies were cost-effective compared with clinical assessment.(4) A cost-benefit has been demonstrated for diagnosis of UTI in children, taking into account the long-term risk of renal scarring and overall quality of life.(46)

A discussion of the febrile infant would not be complete without some mention of herpes simplex virus (HSV) infection in early infancy. Many cases of HSV will present with focal signs (skin lesions, seizures) that provide an obvious direction for evaluation and management. However, Approximately 1/3 of infants with HSV infection present with fever, lethargy, or poor feeding.(47, 48) The possibility of infection with HSV should be considered in neonates with unexplained fever, particularly those in the first month. Infants with disseminated HSV are the most likely to have non-specific signs of illness, the least likely to be evaluated and treated for HSV, and have the highest mortality. The diagnosis should be pursued if there are signs that suggest HSV such as skin lesions or seizures and should be considered in infants with non-specific laboratory findings including elevated hepatic enzymes or mononuclear CSF pleocytosis with either negative test results for bacteria and enteroviruses or during a season when enteroviruses are not prevalent (winter, spring).(47)

What should the new guidelines include?

It is important to emphasize that regardless of age, an infant or child who is judged to be seriously ill- or toxic-appearing mandates full evaluation and, in most cases, antimicrobial therapy. For infants ≤30 days of age, a full evaluation of blood, urine and cerebrospinal fluid for those considered high-risk by Rochester or similar criteria is still favored in most circumstances, with infants from 31–90 days having an “intermediate risk” for SBI where acceptable management can range from a full evaluation listed above to just observation and follow up. Infants with laboratory-documented viral illnesses may not require as extensive evaluation. For infants and children aged 3–36 months, an evaluation of the urine is warranted. For those with at least 2 doses of both Hib and pneumococcal conjugate vaccines, additional testing beyond evaluation of the urine is no longer necessary. Children who are unimmunized or underimmunized still may be protected if they are surrounded by children who are fully immunized. This more limited approach has long been advocated by many experts.(49, 50) Although the United States has not had any new content guidelines/policies since 1993, the United Kingdom (UK), which started using PCV7 in 2006, developed new policies for evaluation of infants and children with fever.(51) The UK guidelines recommend clinical assessment for toxicity, routine evaluation of the urine and elimination of routine use of blood counts, blood cultures and antibiotics in non-toxic-appearing children aged 3 months to 3 years. In the United States, these policy and practice changes are long overdue.

Summary

Although it is clear that controversy remains about how best to manage the acutely febrile child, there are several areas about which most can agree. Infants ≤60 days of age continue to have the highest rates of SBI and pose a challenge to practitioners when determining how

extensive an evaluation to perform in a non-toxic-appearing child. Urinary tract infections are the most common SBIs in all age groups. It is our opinion that assessment for UTI should be part of any evaluation for all but the lowest risk patients (circumcised boys). Technologies that can more rapidly diagnose common viral and bacterial infections and recommendations that simplify the management of these febrile infants and children are needed.

Acknowledgments

E.S. is supported by CTSA (grants KL2 RR024138 and UL1 RR024139), National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) (grant # K24 RR022477), and NIH Roadmap for Medical Research. C.B. is supported by the Robert Wood Johnson Foundation, NIH/NCRR (grant UL1RR025764), and NIH/NICHD (grant K24 HD047249 and AHRQ R18HS018034). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Robert Wood Johnson Foundation, AHRQ, NCRR, NICHD, or the NIH.

References

1. Kramer MS, Etezadi-Amoli J, Ciampi A, Tange SM, Drummond KN, Mills EL, et al. Parents' versus physicians' values for clinical outcomes in young febrile children. Pediatrics. 1994; 93(5):697–702. [PubMed: 8165064]
2. Kramer MS, Shapiro ED. Management of the young febrile child: a commentary on recent practice guidelines. Pediatrics. 1997; 100(1):128–134. [PubMed: 9200370]
3. Roberts KB. Young, febrile infants: a 30-year odyssey ends where it started. JAMA. 2004; 291(10): 1261–1262. [PubMed: 15010450]
4. Lee GM, Fleisher GR, Harper MB. Management of febrile children in the age of the conjugate pneumococcal vaccine: a cost-effectiveness analysis. Pediatrics. 2001; 108(4):835–844. [PubMed: 11581433]
5. Wald ER, Dashefsky B. Cautionary note on the use of empiric ceftriaxone for suspected bacteremia. Am J Dis Child. 1991; 145(12):1359–1361. [PubMed: 1669659]
6. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. J Pediatr. 1985; 107(6):855–860. [PubMed: 4067741]
7. Dagan R, Sofer S, Phillip M, Shachak E. Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. J Pediatr. 1988; 112(3): 355–360. [PubMed: 3346773]
8. Baraff LJ, Oslund SA, Schriger DL, Stephen ML. Probability of bacterial infections in febrile infants less than three months of age: a meta-analysis. Pediatr Infect Dis J. 1992; 11(4):257–264. [PubMed: 1533030]
9. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. PLoS One. 2010; 5(8):e12448. [PubMed: 20805983]
10. Pantell RH, Newman TB, Bernzweig J, Bergman DA, Takayama JI, Segal M, et al. Management and outcomes of care of fever in early infancy. Jama. 2004; 291(10):1203–1212. [PubMed: 15010441]
11. McGowan JE Jr, Bratton L, Klein JO, Finland M. Bacteremia in febrile children seen in a "walk-in" pediatric clinic. N Engl J Med. 1973; 288(25):1309–1312. [PubMed: 4145198]
12. Fleisher GR, Rosenberg N, Vinci R, Steinberg J, Powell K, Christy C, et al. Intramuscular versus oral antibiotic therapy for the prevention of meningitis and other bacterial sequelae in young, febrile children at risk for occult bacteremia. J Pediatr. 1994; 124(4):504–512. [PubMed: 8151462]
13. Jaffe DM, Tanz RR, Davis AT, Henretig F, Fleisher G. Antibiotic administration to treat possible occult bacteremia in febrile children. N Engl J Med. 1987; 317(19):1175–1180. [PubMed: 3309658]

14. Teele DW, Marshall R, Klein JO. Unsuspected bacteremia in young children: a common and important problem. Pediatr Clin North Am. 1979; 26(4):773–784. [PubMed: 43959]
15. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH Jr, Powell KR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. Ann Emerg Med. 1993; 22(7):1198–1210. [PubMed: 8517575]
16. Bass JW, Steele RW, Wittler RR, Weisse ME, Bell V, Heisser AH, et al. Antimicrobial treatment of occult bacteremia: a multicenter cooperative study. Pediatr Infect Dis J. 1993; 12(6):466–473. [PubMed: 8345978]
17. Kramer MS, Tange SM, Mills EL, Ciampi A, Bernstein ML, Drummond KN. Role of the complete blood count in detecting occult focal bacterial infection in the young febrile child. J Clin Epidemiol. 1993; 46(4):349–357. [PubMed: 8482999]
18. Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a pediatric emergency department: current prevalence, time to detection, and outcome. Pediatrics. 2000; 106(3):505–511. [PubMed: 10969095]
19. Shapiro ED, Aaron NH, Wald ER, Chiponis D. Risk factors for development of bacterial meningitis among children with occult bacteremia. J Pediatr. 1986; 109(1):15–19. [PubMed: 3088242]
20. Progress toward elimination of Haemophilus influenzae type b disease among infants and children--United States, 1987–1995. MMWR Morb Mortal Wkly Rep. 1996; 45(42):901–906. [PubMed: 8927012]
21. Invasive pneumococcal disease in children 5 years after conjugate vaccine introduction--eight states, 1998–2005. MMWR Morb Mortal Wkly Rep. 2008; 57(6):144–148. [PubMed: 18272956]
22. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children - Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. 59(9):258–261. [PubMed: 20224542]
23. Control CfD. Prevention of Perinatal Group B Streptococcal Disease -- Revised Guidelines from CDC, 2010. MMWR Recomm Rep. 2010; 59(RR-10):1–36.
24. Fernandez Lopez A, Luaces Cubells C, Garcia Garcia JJ, Fernandez Pou J. Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker. Pediatr Infect Dis J. 2003; 22(10):895–903. [PubMed: 14551491]
25. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J. 2007; 26(8):672–677. [PubMed: 17848876]
26. Bilavsky E, Yarden-Bilavsky H, Amir J, Ashkenazi S. Should complete blood count be part of the evaluation of febrile infants aged</=2 months? Acta Paediatr. 2010
27. Gendrel D, Bohuon C. Procalcitonin in pediatrics for differentiation of bacterial and viral infections. Intensive Care Med. 2000; 26(Suppl 2):S178–S181. [PubMed: 18470716]
28. Byington CL, Enriquez FR, Hoff C, Tuohy R, Taggart EW, Hillyard DR, et al. Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. Pediatrics. 2004; 113(6):1662–1666. [PubMed: 15173488]
29. Bender JM, Ampofo K, Gesteland P, Sheng X, Korgenski K, Raines B, et al. Influenza virus infection in infants less than three months of age. Pediatr Infect Dis J. 2010; 29(1):6–9. [PubMed: 19915513]
30. Krief WI, Levine DA, Platt SL, Macias CG, Dayan PS, Zorc JJ, et al. Influenza virus infection and the risk of serious bacterial infections in young febrile infants. Pediatrics. 2009; 124(1):30–39. [PubMed: 19564280]
31. Rittichier KR, Bryan PA, Bassett KE, Taggart EW, Enriquez FR, Hillyard DR, et al. Diagnosis and outcomes of enterovirus infections in young infants. Pediatr Infect Dis J. 2005; 24(6):546–550. [PubMed: 15933567]
32. Levine DA, Platt SL, Dayan PS, Macias CG, Zorc JJ, Krief W, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics. 2004; 113(6):1728–1734. [PubMed: 15173498]

33. Ramers C, Billman G, Hartin M, Ho S, Sawyer MH. Impact of a diagnostic cerebrospinal fluid enterovirus polymerase chain reaction test on patient management. JAMA. 2000; 283(20):2680–2685. [PubMed: 10819951]
34. Benito-Fernandez J, Vazquez-Ronco MA, Morteruel-Aizkuren E, Mintegui-Raso S, Sanchez-Etxaniz J, Fernandez-Landaluce A. Impact of rapid viral testing for influenza A and B viruses on management of febrile infants without signs of focal infection. Pediatr Infect Dis J. 2006; 25(12): 1153–1157. [PubMed: 17133161]
35. Clinical policy for children younger than three years presenting to the emergency department with fever. Ann Emerg Med. 2003; 42(4):530–545. [PubMed: 14520324]
36. Alpern ER, Alessandrini EA, McGowan KL, Bell LM, Shaw KN. Serotype prevalence of occult pneumococcal bacteremia. Pediatrics. 2001; 108(2):E23. [PubMed: 11483833]
37. Stoll ML, Rubin LG. Incidence of occult bacteremia among highly febrile young children in the era of the pneumococcal conjugate vaccine: a study from a Children's Hospital Emergency Department and Urgent Care Center. Arch Pediatr Adolesc Med. 2004; 158(7):671–675. [PubMed: 15237067]
38. Carstairs KL, Tanen DA, Johnson AS, Kailes SB, Riffenburgh RH. Pneumococcal bacteremia in febrile infants presenting to the emergency department before and after the introduction of the heptavalent pneumococcal vaccine. Ann Emerg Med. 2007; 49(6):772–777. [PubMed: 17337092]
39. Sard B, Bailey MC, Vinci R. An analysis of pediatric blood cultures in the postpneumococcal conjugate vaccine era in a community hospital emergency department. Pediatr Emerg Care. 2006; 22(5):295–300. [PubMed: 16714955]
40. Waddle E, Jhaveri R. Outcomes of febrile children without localising signs after pneumococcal conjugate vaccine. Arch Dis Child. 2009; 94(2):144–147. [PubMed: 18539684]
41. Wilkinson M, Bulloch B, Smith M. Prevalence of occult bacteremia in children aged 3 to 36 months presenting to the emergency department with fever in the postpneumococcal conjugate vaccine era. Acad Emerg Med. 2009; 16(3):220–225. [PubMed: 19133844]
42. Kaplan SL, Barson WJ, Lin PL, Stovall SH, Bradley JS, Tan TQ, et al. Serotype 19A Is the most common serotype causing invasive pneumococcal infections in children. Pediatrics. 125(3):429–436. [PubMed: 20176669]
43. Cohn AC, MacNeil JR, Harrison LH, Hatcher C, Theodore J, Schmidt M, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998–2007: implications for prevention of meningococcal disease. Clin Infect Dis. 50(2):184–191. [PubMed: 20001736]
44. Roberts KB, Charney E, Sweren RJ, Ahonkhai VI, Bergman DA, Coulter MP, et al. Urinary tract infection in infants with unexplained fever: a collaborative study. J Pediatr. 1983; 103(6):864–867. [PubMed: 6644419]
45. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics. 1999; 103(4 Pt 1):843–852. [PubMed: 10103321]
46. Harmsen M, Adang EM, Wolters RJ, van der Wouden JC, Grol RP, Wensing M. Management of childhood urinary tract infections: an economic modeling study. Value Health. 2009; 12(4):466–472. [PubMed: 19171007]
47. Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. Pediatr Infect Dis J. 2008; 27(5):425–430. [PubMed: 18360301]
48. Caviness AC, Demmler GJ, Almendarez Y, Selwyn BJ. The prevalence of neonatal herpes simplex virus infection compared with serious bacterial illness in hospitalized neonates. J Pediatr. 2008; 153(2):164–169. [PubMed: 18534225]
49. Baraff LJ. Management of infants and young children with fever without source. Pediatr Ann. 2008; 37(10):673–679. [PubMed: 18972849]
50. Ishimine P. Fever without source in children 0 to 36 months of age. Pediatr Clin North Am. 2006; 53(2):167–194. [PubMed: 16574521]

51. Excellence NIfHaC. Feverish illness in children: assessment and initial management in children younger than 5 years. In: Service NH. , editor. CG47. London: National Institute for Health and Clinical Excellence; 2007. p. 1-18.

Table 1

Rates of OB post-PCV7

Reference	Site, years, # children	Pathogens	Contaminants
Stoll and Rubin[36]	Long Island, 2001–2003 329 children	**0.9% Sp** (3 episodes in 2 patients, one with no vaccine)	**1.2%**
Carstairs et al[37]	San Diego, 2000–2002 1383 children	**0% after PCV7**, 2.4% w/ no PCV7 (1% of overall)	**3%**
Sard and Vinci[38]	Boston, 1997–2005 2971 children	**0.7% overall** **(0.45% Sp)**	**2.8%**
Waddle and Jhaveri[39]	Durham, 1997–1999; 2001–2004, 423 children	**6.7% pre-PCV7,** **0.4% post-PCV7,** **4% vs. 0% Sp**	**4.7%**
Wilkinson et al[40]	Phoenix, 2004–2007 8408 children	**0.25% Sp**	**1.89%**

Abbreviations: OB-occult bacteremia, Sp-Streptococcus pneumoniae, PCV7-7-valent conjugate pneumococcal vaccine, N/A-not applicable