CME Article

Management of Febrile Children 3-36 Months of Age in the Post Pneumococcal Conjugated Vaccine Era: Current Trends

Mario A. Reyes, M.D., F.A.A.P.

***Editor's Note**: This is the fourth of four articles to be published in 2006 for which up to four Category 1 credit hours can be earned. Instructions on how credit hours can be earned appear inside the front cover of the journal. Exam questions follow the article.*

Address correspondence and reprint requests to: Mario A. Reyes, M.D., F.A.A.P., Director, Pediatric Hospitalists Services at MCH, Pediatric Division, Hospitalists of America, LLC, Miami Children's Hospital, 3100 SW 62nd Ave., Miami, FL 33155, U.S.A, e-mail: Mario.Reyes@mch.com. *The author received no financial support for this paper.*

Target Audience

This CME activity is intended for physicians, medical students and nurse practitioners. Emergency Department physicians and nurse practitioners will find this information especially useful.

Learning Objectives

After completion of this article, the reader should be able to:
1. state the most accepted definition of "fever" in pediatric medicine
2. discern the discrepancies between axillary and rectal temperature
3. interpret CBC and blood cultures when assessing febrile children

"Life is short, the art long, opportunity fleeting, experience treacherous, judgment difficult"

- Hippocrates

Introduction

Fever is one of the most common reasons for parents to seek medical attention for their children and accounts for millions of office visits, ER visits, and hospitalizations in the United States. The clinician evaluating a febrile child faces a significant diagnostic dilemma. The patient's age has a clear impact in the decision making process and management. Newborns and infants less than 3 months of age are particularly vulnerable. Their limited physiologic responses, the paucity of clinical signs and symptoms in the presence of serious illnesses, and their limited immunocompetency makes this age group particularly at risk for serious bacterial infections (SBIs) and subsequent negative outcomes. For this reason, it is generally accepted to be more aggressive in both testing and empiric treatment in this group.

Infants and children three (3) to thirty-six (36) months of age that have grown and evolved developmentally, have a more mature immune system and better adaptative responses to infectious diseases. Furthermore, the etiology of fever and serious bacterial infection (SBIs) in this age group is similar. For editorial purposes, we will concentrate on discussing the management of the febrile child in this age group.

Fever: Definition and Practical Consideration

The most accepted definition of "fever" is a core (rectal) temperature above 38°C, or 100.4°F (1) (2), although most of the studies in this age group have used 39°C as the threshold to include children in clinical and epidemiological trials (3) (4) (5) (6) (7) (8) (9) (10).

Measuring axillary or tympanic temperature is less invasive and more accepted by parents but the readings are affected by multiple factors. For example: The discrepancies between rectal and axillary temperature decrease with an increase of the placement time of the device at the axilla. There are bigger discrepancies with electronic thermometers than with mercury based and the differences

are more pronounced in older children (11). Measuring tympanic temperature has also shown great variability. Infrared ear thermometry measurement is not a good approximation of rectal temperature: when rectal temperature is 38° C, the reading of the ear temperature can vary between 37.4° C and 39.2° C (12). On the other hand, rectal temperature has been proven to accurately predict the temperature in the pulmonary artery, although there is certain lag in the changes of the rectal reading following changes in the core temperature (12). The wide variation of axillary and ear temperatures makes the rectal measurements more reliable for clinical decision making.

Furthermore, a commonly forgotten detail in the history of a febrile child is the effect of bundling in body temperature. A study performed in young infants suggests that "bundling" can significantly increase the skin (axillae) temperature up to 2.67 ° C per hour but does not cause significant changes in the core (rectal) temperature (13).

It has been demonstrated that subjective fever referred by parents has a good but variable sensitivity (74-89%), and lower specificity when compared with rectal measurements (2). In general, the parental perception of fever should be taken seriously and the child considered "febrile" for clinical decision purposes.

Fever: The Diagnostic Dilemma

The majority of children with fever have a clear, identifiable source that can explain the origin of the febrile response. Nevertheless, there is a group of infants and children of whom, after the detailed history and a comprehensive physical exam has been conducted, no identifiable source for the fever is found and they are "well appearing" to the clinician. The medical literature converges in calling this condition "fever without source" (FWS). These cases pose an additional diagnostic challenge.

The first step is to obtain a detailed history of present and past illnesses. This includes pertinent details such as temperature reading, duration of the febrile illness, status of the immunization schedule, daycare attendance and household members with symptoms of viral illness, followed by a query about potential associated symptoms.

The comprehensive physical examination should begin by looking at the general condition and appearance of the child. When defining a febrile child as "non toxic" and "well-appearing", the practitioner should assess the evaluation and presence of the following clinical signs: the level of alertness including spontaneous eye opening, "eye contact" with the clinician or parents, the presence of social smile (present as a developmental milestone after 8 weeks of age), and the characteristics of the cry and degree of consolability. These findings along with a careful inspection of the skin, assessing the color, the presence of mottling or rashes, and the turgor of the mucous membranes are signs that can be obtained even before placing the hands or the stethoscope on the child's body. Further physical examination should be performed in a systematic way with an organ or system approach. The author recommends specific attention to the vital signs including blood pressure, heart rate and capillary refill: tachycardia at rest while asleep and/or afebrile, wide pulse pressure, and slow (> 3 seconds) perfusion of a digit following pressure have been found to be subtle but early indicators of serious illness.

Several studies have evaluated the correlation between examination findings and the presence of SBIs. A large, prospective, multicenter trial of children 3-36 months of age was conducted in the pre-pneumococcal immunization era in an outpatient setting. The authors used the Yale Observation Scale (YOS), a composite ordinal scoring system which includes the elements of the physical exam described above. They found that the YOS scores were significantly higher among patients with bacteremia than those without bacteremia, but there was a great overlap in the clinical appearance between the two groups. Furthermore, in the group of bacteremic patients, more than half were found to have the lower scores on the clinical observational scale (4). Another study found that children appearing "toxic" were more likely (96%) than "well appearing" (3%) to have SBIs (14). With these premises, defining a febrile child as "well appearing" is probably the most reassuring and better correlated finding with

well being and absence of serious illness, although it does not absolutely rule out the presence of bacteremia or SBIs.

No less controversial issues in the decision making process are ahead of the clinician after completing the H&P: The next immediate challenge is to identify a subset(s) of children with FWS that will need subsequent laboratory testing (or not) and will warrant empiric antibiotic treatment (or not) to prevent further complications. We will summarize some key concepts that will provide the practicing clinician with valuable tools to make a sound, evidence based decision.

Incidence of Bacteremia and SBIs

When assessing "well appearing" children 3-36 months of age with fever, we must be aware that despite how frequent this condition exists, the presence of serious illness, including SBI, is an infrequent event. Following universal immunization with Haemophilus influenzae vaccine (Hib) in the early 1990s and before the end of the last century, H. influenzae type B was no longer a culprit for SBIs. By then, the incidence of bacteremia had fallen to 1.6-3%, and Streptococcus pneumoniae accounted for 85-92% of the cases (3) (4) (6) (7) (8) (9) (10). From this small group, if untreated only 4-13% will develop localized serious infections including 2-3% or less that will develop meningitis (9) (15) (16). The other common SBIs include: sepsis, pneumonia, meningitis, urinary tract infection (UTI), bacterial enteritis and bone and soft tissue infections. The vast majority of children with the above mentioned infections, specifically with bacterial meningitis, will definitely display some clinical symptoms and signs that will automatically exclude them from the "well appearing" group.

Impact of Universal Immunization with Conjugated Pneumococcal Vaccine

In the year 2000, the Advisory Council for Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommended the universal immunization with Heptavalent Pneumococcal Conjugated Vaccine PCV-7 (Prevnar, Wyeth Lederle) at 2,4,6 and 12-16 months of age (17). The vaccine contains seven serotypes (4, 6B, 9B, 14, 18C, 19F and 23F), known to cause 82% of all invasive pneumococcal diseases before this year (18). Following universal immunization with PCV-7, the rates of pneumococcal bacteremia have decreased by 84% to a low 0.2% (19). The overall incidence of bacteremia has declined to 0.7%, and in this diminutive group, S. pneumoniae is no longer the leading cause of bacteremia. Indeed, E. coli, "non vaccine serotypes" of S. pneumoniae, and other pathogens like Salmonella species, Staphylococcus aureus and Streptococcus pyogenes account equally for 1/3 of the cases (19). Multiple studies, pre and post licensure of the vaccine, and a growing body of epidemiologic evidence suggest that for the serotypes included in the conjugated vaccine, there has been a decline of more than 90% in the incidence of bacteremia and other invasive diseases, both in immunized and non immunized ("herd" effect) individuals (19) (20) (21) (22) (23). These findings imply that bacteremia, pneumonia and meningitis due to S. pneumoniae, specifically in well appearing children, should be a very infrequent event nowadays.

Unsuspected Urinary Tract Infection (UTI)

UTIs can present in young children with non specific symptoms, including FWS. The prevalence of UTIs in infants and young children is 2% to 5% (24) (25) (26). Early recognition and treatment is important to prevent long term medical problems like hypertension and renal scarring. Specifically, temperatures > 39° C without source, Caucasian females and uncircumcised males are mentioned as risk factors for higher incidence of urinary infections (24) (25). The incidence is still significant even in the presence of identifiable sources for the fever including viral infections like RSV (27). Abnormal urinalysis (more than 10 WBC/hpf or presence of bacteriae), or urine dipstick positive for leukocyte esterase or nitrites are good screening tests (28). It is recommended that whenever there is a suspicion of UTI based on any of the above mentioned risk factors or positive screening tests, a urine culture

should be obtained, preferably by bladder catheterization or suprapubic aspirate, because quantitative urine culture is the gold standard for the definite diagnosis of UTI (26). In these cases and awaiting culture results, it is recommended to treat empirically with antibiotics (26) (29).

Usefulness of CBCs and Blood Cultures

There is significant controversy on the role of blood testing when evaluating a well appearing child with fever. Bacterial cultures are the gold standard to diagnose bacterial infections in sterile sites/body fluids. Its main disadvantages are that for the final growth of real pathogens, final results are available in 95% of the samples at 48 hours and 99.7% at 72 hours. Furthermore, inappropriate collection technique can lead to the growth of bacterial contaminants in up to 2/3 of the positive specimens (30).

Based on the currently available data, ordering blood cultures in well appearing febrile children above 3 months will result in unnecessary testing of more than 99% of children with less serious illnesses i.e. viral infections. The clinical, ethical and financial implications make this practice currently not recommended.

The most commonly used test in clinical medicine is the complete blood count (CBC). Pertinent to this topic is the analysis of the white blood cell population (WBC): total and differential counts of segmented and band cells, absolute neutrophil count (ANC) and others. It has been shown that there is an increased incidence of bacteremia with increasing white blood cell counts (3) (7), but the interpretation of elevated WBCs using "leukocytosis" defined as counts above 15,000/mm3 can be deceiving: the sensitivity of this finding is 80 to 86% and the specificity is 69-77% (3) (7) (31) (32). Let us assume for didactic purposes, a sensitivity of 85% and a specificity of 75%: in a hypothetical, prospective cohort, 15 out of 100 bacteremic patients will have a normal (< 15,000/mm3). .Likewise, 25 out of 100 non bacteremic patients will have leukocytosis above this cutoff value.

Similar analyses are applicable to other calculated parameters derived from the differential counts. It has been suggested that "left shift", represented by an elevated ANC (segmented neutrophils and bands) is somehow more predictive, but only 8% of children with ANC above 10,000/mm3 will have "occult bacteremia" (3). Extensive review of the literature has shown that the clinical folklore of the bands persists, despite clear evidence that the band count shows poor and variable sensitivities and specificities as a laboratory screening test for bacterial infections (33) (34).

Finally, a well designed cost-effective analysis on management of febrile children using "cases of meningitis prevented" and "death" as negative outcomes has concluded that if the rate of pneumococcal bacteremia decreases below 0.5% (current rates achieved after PCV-7), the strategies using empiric testing like CBC and blood cultures and empiric treatment with antibiotics should be eliminated. At these very low rates of bacteremia, a high risk population may be selected at minimal additional cost and complications using solely "clinical judgment" (5).

In summary, currently available data suggests that there is no way to prospectively identify children with SBIs at the time of the initial exam based on specific test results or combination of tests from blood samples (29). The above mentioned facts suggest that the widespread use of CBCs in febrile children is a questionable practice in the attempt to identify accurately the subset of children that will undergo further testing i.e. bacterial cultures or receive empiric antibiotics.

Effect of Empiric Antibiotic Treatment in Outcomes

When assessing febrile children, the ultimate goal of the practitioner is to prevent undesirable negative outcomes like the development of "focal" infections i.e. pneumonia, bone and soft tissue infections, persistent bacteremia, and less frequently, but more concerning, the occurrence of meningitis or death. Few large, retrospective studies on this topic were conducted before the PCV-7 era. In one study, febrile children discharged from the ER without

antibiotic treatment who were found to have positive blood cultures, were followed at 24 hours. The authors reported that 19% of them had persistent bacteremia, 13% had new focal infections and 2.2% had meningitis (15). Another study showed that if untreated, occult bacteremia can lead to 9.7% of serious infections and 2.7% of cases with meningitis (35).

The effect of oral or parenteral antibiotics in febrile children without source on the above mentioned outcomes have been extensively researched. In a large, prospective, multicenter study in 10 tertiary Children's Hospitals completed in the early 1990s, febrile children were randomized to receive either Ceftriaxone IM or PO Amoxicillin and followed at 24 hours. The incidence of "definite" of "probable" infections was 3% in the Ceftriaxone group and 6.5% in the "Amoxil" group. The incidence of meningitis was 2% in the Ceftriaxone group and 3.2% in the Amoxil group; in either case the differences were not statistically significant. The authors concluded that when compared to oral Amoxicillin, Ceftriaxone did not significantly reduce the likelihood of developing neither focal infections nor meningitis in this subset of children (9). In addition, multiple studies conducted in the pre PCV-7 era, strongly suggest that the use of empiric antibiotics, either oral or parenteral, may reduce the development of new focal infections, but have failed to show significant advantage of Ceftriaxone versus oral antibiotics in preventing new SBIs, specifically meningitis (8), (9) (10) (15) (16) (35).

Conclusion

In the era following universal immunization with PCV-7, it seems reasonable to have a more liberal approach to the well appearing child 3-36 months of age with fever above 39°C and the decision making process should be based predominantly on the use of "clinical judgment".

The Use of Clinical Judgment

If the fully immunized child looks well and "non toxic" at the time of the visit, then the patient should be considered at low risk of having bacteremia and other SBIs and should receive only antipyretics and parental education on "fever". Neither testing nor empiric antibiotics are recommended. Follow up in the next 24 hours either by phone, e-mail or preferably direct physician observation is mandated.

The routine request of CBC seems ingrained in clinical practice but interpretation of the results are frequently overestimated as a screening test for the diagnosis of bacterial infections. Additionally, there should be no role for the empiric use of Ceftriaxone in well appearing children with fever, taking into consideration that neither oral antibiotics nor Ceftriaxone seems to prevent bacterial meningitis in this subset of children. If a hesitant clinician is concerned with the development of new focal infections, the empiric use of oral Amoxicillin at 80-90 mg/kg/day in two divided doses seems an excellent choice.

Due to the higher prevalence of UTI in this age group, a variant to this recommendation will be to obtain an enhanced UA and/or urine dipstick in Caucasian females less than 2 years or uncircumcised males with fever above 39°C for more than 24 hours. If any of those rapid tests are suspicious of UTI, then a urine culture should be obtained and outpatient management with oral antibiotics started i.e. third generation Cephalosporins. The use of parenteral Cephalosporins is reserved for children who look ill, have vomiting, or do not tolerate the oral route.

The above approach can be characterized as the practice of "evidence based medicine", modified for the individual patient, the clinician's expertise, and the conscientious, explicit, and judicious use of the current and changing "best evidence" found in the medical literature. Like all recommendations, these need to be carefully validated with prospective studies before final conclusions may be drawn as to its safety and cost effectiveness.

Future Developments

The practicing clinician should be aware that nasopharyngeal colonization and further development of invasive diseases by non-vaccine serotypes of Streptococcus pneumoniae (11, 15, 19A and 29)

seem to be on the rise (23) (36). Local and national surveillance systems should carefully monitor the epidemiologic changes of invasive pneumococcal disease to identify potential serotypes to be included in future multi-valent conjugated vaccines.

Future development in the field of laboratory medicine should lead to more rapid and reliable tests than the CBC. For example, using currently available flow-cytometry techniques, it is possible without extra cost, to quantify morphologic changes in the white blood cell population including mean white blood cell volume, conductivity to radio frequency current and the reflection of the ultraviolet light (37).

A few studies in the adult population with sepsis have shown promising results when using those parameters as a tool to identify serious infections in adults (38). Furthermore, rapid analysis of inflammatory substances like C-reactive protein (CRP), procalcitonin, inflammatory cytokine levels (IL-1, IL-6, and IL-10) (39) (40), as well as rapid analysis of WBCs expression of surface antigens like CD 14 and CD16 (33) (41) could provide additional tools for early identification of sepsis and bacteremia. Finally, rapid detection of specific bacterial DNA sequences by using PCR amplification and microarrays technologies could become commercially available in the future.

Nevertheless, regardless of the future developments of laboratory medicine, there is no substitute for the continuous improvement and refinement of our clinical skills and judgment. These are the primary and most important diagnostic tools when evaluating children with fever in practicing clinical pediatrics.

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Management of Febrile Children 3-36 Months of Age in the Post Pneumococcal Conjugated Vaccine Era: Current Trends
By Mario A. Reyes, M.D., F.A.A.P.
Director, Pediatric Hospitalists Services
Miami Children's Hospital
3100 SW 62nd Avenue
Miami, FL

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Management of Febrile Children 3-36 Months of Age in the Post Pneumococcal Conjugated Vaccine Era: Current Trends
Reyes M. *Int Pediatr* 2006; 21(4) 218-227.

1. The most accepted definition of "fever" in pediatric medicine is:
- a. 101° F obtained in the axilla
- b. 100.4° F measured by rectal thermometry
- c. 99.4° F measured in the axilla
- d. 100° F measured in the rectum

2. Regarding body temperature reading, select the incorrect answer:
- a. Discrepancies between axillary and rectal temperature are more pronounced if measured with electronic thermometers.
- b. The rectal measurements can accurately predict the temperature in the pulmonary artery (core temperature).
- c. Bundling infants increase both rectal and axillary temperature reading.
- d. "Subjective fever", referred by parents has good sensitivity and should be taken seriously when consider ing a child "febrile".
- e. Discrepancies between rectal and axillary temperatures are less pronounced in infants and young children.

3. The following are proven results after universal immunization with Conjugated Pneumococcal Vaccine (PCV-7) in the USA.
- a. Overall decrease of the incidence of bacteremia below 1% in immunized infants.
- b. Decrease of the incidence of Pneumococcal bacteremia below 0.5% in immunized infants.
- c. Decrease of the incidence of invasive Pneumococcal diseases both in immunized and non immunized individuals ("Herd immunity") caused by serotypes included in the vaccine.
- d. Increase in the incidence of nasopharyngeal colonization and invasive diseases due to some serotypes not included in the vaccines.
- e. All of the above.

4. Regarding the interpretation of CBC and blood cultures when assessing febrile children:
- a. They are indicated in the majority of infants and young children with fever without source.
- b. Leukocytosis above 15,000WBC/mm3 can accurately predict the presence of serious bacterial infections due to its very high specificity.
- c. The presence of "bandemia" and "left shift" have excellent sensitivities, specificity and positive predictive value for the diagnosis of serious bacterial infections.
- d. Blood and sterile sites cultures are currently the gold standard for the diagnosis of serious bacterial infec tions but they are not routinely indicated in well appearing infants and children.
- e. The growth of bacterial contaminants in the blood culture is a rare event reported in less than 10% of all "positive" cultures.

5. Regarding the use of empiric antibiotics in well-appearing infants/children without source.
- a. Both oral Amoxicillin and parenteral Ceftriaxone seem to decrease the further development of seeded bacterial infections but not the development of bacterial meningitis.
- b. Parenteral Ceftriaxone seems to reduce the likelihood of further development of bacterial meningitis.
- c. They are routinely indicated when the fever is above 39° C after CBC and blood cultures were obtained.
- d. All of the above.

Management of Febrile Children 3-36 Months of Age

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A. Yes (please indicate the behavioral change that you anticipate)
B. No

Please fax the completed forms to (305) 663-8446 or mail to International Pediatrics Quarterly CME Program, Miami Children's Hospital, 3100 SW 62nd Avenue, Miami, FL 33155 (USA). All responses must be prepaid.