

Clinical Guidelines And Primary Care

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Management Of Infants And Children 0 To 36 Months Of Age With Fever Without Source

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The "Practice Guideline for the Management of Infants and Children 0 to 36 months of Age with Fever without Source" was published simultaneously in the July 1993 issues of *Pediatrics*¹ and the *Annals of Emergency Medicine*.² It was produced by an expert panel of senior academic pediatric faculty and sponsored in part by a grant from the Agency for Health Care Policy and Research and by an educational grant from Roche Laboratories, the makers of ceftriaxone.

The purpose of the guideline is to provide specific recommendations regarding care of infants and children from birth to age 36 months with fever without source whose conditions are evaluated in physicians' offices and in emergency departments. Using a literature search and review of bibliographies, data from publications regarding the management of febrile infants and children were gathered and summarized. Some of the data were analyzed with a meta-analytic technique. A management algorithm was developed, and nine specific clinical questions were defined. The data summaries, meta-analyses, draft algorithm, and the nine clinical questions were presented to the expert panel, which used a variation of the Delphi technique to develop the guidelines.

Our review of the guideline focused on the process used to develop the recommendations and on whether this set of recommendations has the attributes of a well-written guideline. The Institute of Medicine has suggested a set of desirable attributes: validity, reliability and reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, scheduled review, and documentation.³ A valid guideline is one that is evidence based and not the result of global subjective judgment. The guideline should be useful for different practitioners in different settings to be considered reliable and reproducible. Clinical applicability reflects whether the guideline is practical and avoids rigid, simplistic recommendations so as to maintain flexibility. Clarity implies the guideline avoids ambiguity. A multidisciplinary process brings perspective and balance to a guideline, and scheduled review ensures a guideline will remain up-to-date. Documentation is noting the source of each recommendation and whether it was based on scientific data or consensus. A closer look at this set of recommendations for the management of febrile infants and children shows that it has many of these attributes, but notable deficiencies are present.

Importance of the Problem

Children with fever account for a large number of ambulatory visits in pediatric and family medicine clinics and emergency departments. In 1990 for children younger than 3 years, 11 percent of visits to family physicians and 9 percent of visits to pediatricians were for the principal reason of fever, not including visits for upper respiratory tract infections and other problems often associated with fever.⁴ The guideline itself reports that 65 percent of children between birth and the age

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of 2 years visit a physician for an acute febrile illness. Evaluation of a febrile illness is usually straightforward, but at times the source of fever is not easily detected, and clinical decision making is less clear. A child with fever without source could have occult bacteremia, a diagnosis difficult to make on clinical grounds. The risk of bacteremia in children aged 3 to 36 months is quoted in the guideline to be between 3 percent and 11 percent, and the accompanying meta-analysis showed a mean probability of 4.3 percent in children with a temperature of 39.0°C or higher. Clearly, children with fever account for a substantial number of visits to physicians; a guideline that helps clinicians prevent unfavorable outcomes and that presents a cost-effective and practical approach to caring for febrile children could be a valuable decision-making tool for many physicians.

Process of Guideline Development

A panel of 6 experts chosen by the first author, Dr. LJ Baraff, to help develop this guideline were all faculty members of academic institutions. They were chosen for their expertise in pediatric infectious diseases or pediatric emergency medicine. These guidelines were written with a goal of being used in typical physicians' offices and emergency departments, yet no general pediatricians or family physicians were members of the panel.

Before the meeting of the expert panel, the first author developed a decision tree for the clinical management of febrile infants and children. Nine specific clinical questions were derived from this algorithm. A literature search was performed using the MEDLINE data base from 1977 through August 1991. The bibliographies of retrieved articles were also reviewed for additional pertinent articles. The articles obtained were examined to determine whether they contained original research data regarding the nine clinical questions, but exclusionary criteria were not specifically mentioned. Articles evaluating antibiotic therapy were also sought, but no criteria were presented stating which study designs were considered acceptable.

Evidence tables were constructed with the data from each article. If a given issue was addressed by more than one study, Bayesian meta-analysis was used to combine the evidence available. Bayesian meta-analysis adjusts multiple sources of data for bias and combines them into a single probability

estimate. Advantages over classical meta-analysis include ability to combine results from studies of differing experimental design and differing measures of outcome without requiring all the studies to provide evidence for all the issues at hand and ability to adjust for bias.^{5,6} For example, the authors combined four studies examining the issue of chest radiographs and determined that the probability of a child with fever without source having a positive radiograph was 3.3 percent. This type of analysis is helpful in that it gives some predictability to a particular management strategy. A physician might choose not to order a chest film during a work-up of a febrile child with no pulmonary symptoms, and this analysis provides a probability estimate of whether that patient might actually have abnormal findings on a radiograph.

The evidence tables, the algorithm with the proposed management strategies, the nine clinical questions, and a bibliography were provided to the panel members before their single meeting. The members of the panel used a variation of the modified Delphi technique to develop the set of guidelines. The Delphi technique is a method of obtaining group consensus. It involves systematic solicitation and collection of judgments on a particular topic through a set of carefully designed sequential questionnaires interspersed with feedback of opinions derived from earlier responses. Advantages include not having to convene the experts in one place and applicability to a broad number of topics. Disadvantages include a lack of reliability and validity measurements and a lack of evidence of much difference between the responses of experts and nonexperts.^{7,8}

The members of the panel used a variation of this technique. At the one meeting they all attended, an attempt was made to reach a consensus about the management strategies, and if no consensus was reached, alternative strategies were proposed. (In the conventional Delphi technique, the experts participate individually and anonymously.) After their meeting, each member of the panel was sent a first draft of the guidelines for review. After providing their input, a second draft was circulated. The second round of input was used to develop the final set of guidelines. The use of this Delphi technique and the above-noted attempts to reach consensus show there was some element of subjectivity in the development of

these guidelines; the recommendations are not solely evidence based.

Clinical Content

The article contains definitions of concepts used throughout the guidelines, followed by recommendations regarding management of infants younger than age 28 days, infants aged 28 to 90 days, and children aged 3 months to 3 years. Figures 1 and 2 show the two algorithms used in the article to summarize the recommendations.

One of the most important definitions was what temperature constitutes a fever. The panel's decision that a fever was 38.0°C (100.4°F) or more was based on a survey of residency directors and the opinions of panel members. This definition later leads to a discrepancy in the article when 39.0°C is referred to as the cutoff for fever and treatment. The panel also attempted to define toxic, yet it remains a term that could mean different things to different evaluators. More discussion about differentiating between toxic and nontoxic would have been useful, because making this dis-

inction is a key aspect of following the guidelines, as seen in the algorithms in Figures 1 and 2.

The panel clearly defined nine clinical questions that they proposed to answer. Their conclusions are outlined below. While some recommendations are clear and well supported, others are not entirely based on evidence and sometimes seem to contradict the evidence presented.

1. *What is the lowest temperature that defines fever?* This definition was based on opinion and survey data. The panel acknowledges that seriously ill children can have normal or low temperatures.

2. *At what age must a non-toxic-appearing infant with what degree of fever, if any, be hospitalized?*

Despite citing evidence (an article submitted for publication) that the risk of serious bacterial infection in infants younger than age 28 days is very small and that children cared for with careful observation have favorable outcomes, the panel recommends that any febrile infant younger than 28 days, toxic appearing or not, should be hospitalized. In defining the age cutoff, the panel uses traditional definitions rather than exploring the evidence behind these cutoffs. The degree of fever mentioned in the question is not discussed.

3. *What are the appropriate criteria, including lab results, necessary to define a "low-risk" febrile infant less than 90 days old who need not be hospitalized for possible sepsis?*

The data used to define low-risk criteria are evidence based and include both clinical and laboratory criteria. Some confusion arises when a figure in the article shows that the laboratory criteria for low-risk infants includes a band cell count of less than 1500/mm³ when a band cell count of less than 1000/mm³ is used later in the same figure.

4. *When should outpatient antibiotics be considered for the management of these low-risk febrile infants?*

The initial recommendation is for empiric outpatient antibiotics after

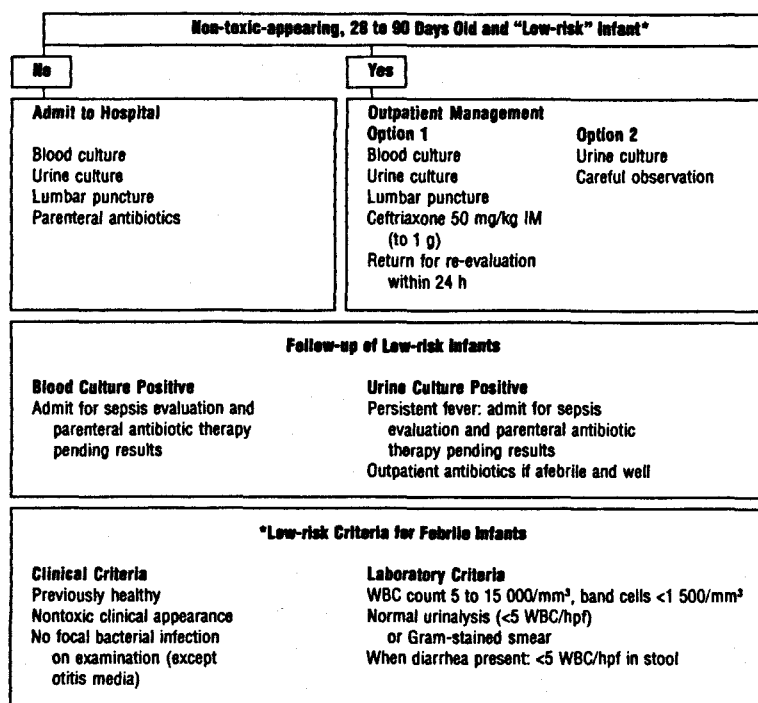


Figure 1. Algorithm for the management of a previously healthy infant 28 to 90 days of age with fever without source $\geq 38^{\circ}\text{C}$. Adapted with permission from Baraff IJ, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Pediatrics 1993; 92:5.

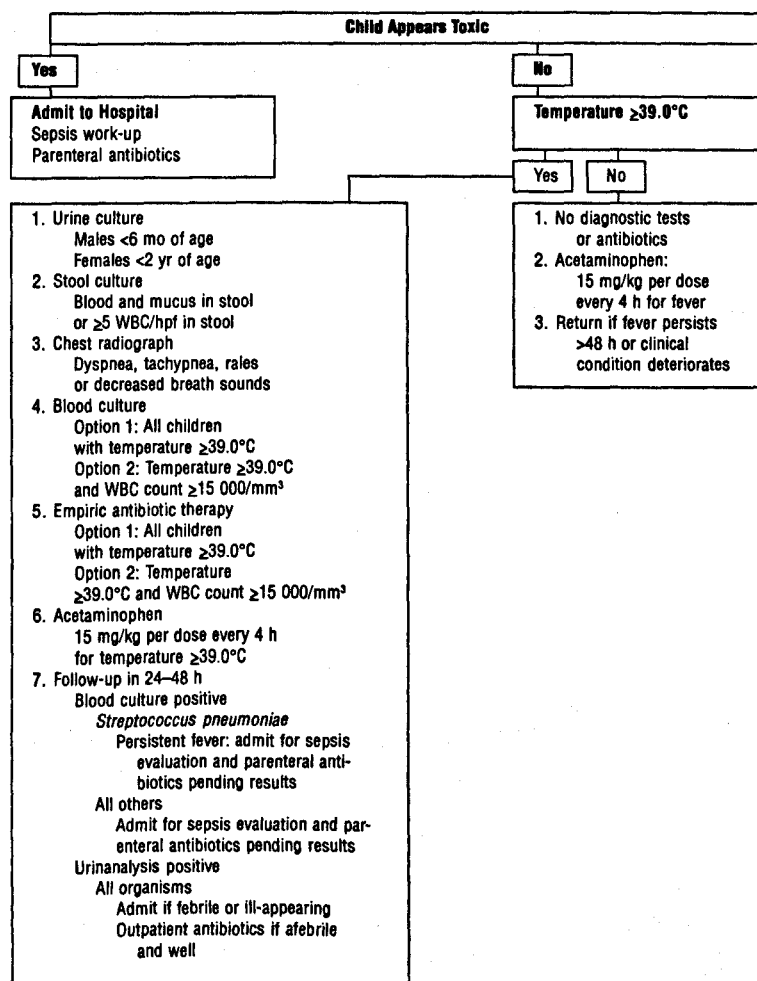


Figure 2. Algorithm for the management of a previously healthy child 91 days to 36 months of age with fever without source. Adapted with permission from Baraff LJ, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. *Pediatrics* 1993; 92:9.

obtaining cerebrospinal fluid, urine, and blood cultures. The panel also presents an alternate outpatient management scheme of obtaining a urine culture only, followed by careful observation with no antibiotics. The text explains that this strategy is based on an analysis of two reports that showed the probability of a serious bacterial infection in an infant meeting the low-risk criteria is 0.2 percent, yet this number conflicts with a 1.4 percent probability listed for the same category infant in an associated table.

5. Which antibiotic should be used?

Intramuscular ceftriaxone is recommended for empiric treatment of fever in infants in this low-risk category. Ceftriaxone has been the antibiotic traditionally used, and the advantage of its broad spectrum is cited. No evidence is cited showing

that ceftriaxone is the most effective antibiotic for empiric treatment.

6. What is a reasonable plan for the evaluation of a child 3 to 36 months of age with fever without source?

This portion of the guideline is, in general, better supported by evidence. The panel addresses the limitations of subjective clinical assessment. Nonspecific laboratory tests are discussed, and the authors provide data showing that the white cell count is the most helpful nonspecific test. The flow chart used to summarize the evaluation of fever in children 3 to 36 months of age is not easily comparable with the flow chart for infants 0 to 90 days of age.

7. When should the diagnostic tests of complete blood cell differential count, blood culture, urinalysis, urine culture, and chest radiograph be performed?

The guidelines do not clarify when a complete blood count should be done; it is discussed as a screening test to help determine which children should receive culture and treatment. Two options are presented in the flow chart of Figure 2 as to when to do a blood culture (all

children with temperature $\geq 39.0^{\circ}\text{C}$ or temperature $\geq 39.0^{\circ}\text{C}$ and a white cell count $\geq 15,000/\text{mm}^3$), but in the text, the first option is described as unacceptable. Also, to accomplish the second option practically, a blood culture should be drawn at the same time the complete blood count is obtained. Regarding urinalysis and urine culture, the panel discourages collection of the specimen with a plastic receptacle attached to the perineum, but the practicality of the suggestion to obtain a urine specimen with a catheter or by suprapubic aspiration to determine who needs a culture is questionable.

The panel's recommendation to obtain a chest radiograph only in children with abnormalities on lung examination is well supported by data. The panel suggests a stool culture only if the child has diarrhea, but the recommendation for empiric

treatment with antibiotics for signs of invasive bacterial diarrhea (before culture results) is not referenced.

8. *When should antibiotics be considered in the outpatient management of children 3 to 36 months with fever without source?*

While the panel acknowledges that the decision to treat with empiric antibiotics is based on a consideration of risks, benefits, and costs, panel members conclude that "treatment with parenteral antibiotics is a cost-effective and reasonable approach in the management of children at risk of occult bacteremia" based on a single reference of a "formal decision analysis." This decision analysis is not outlined for the reader to decide about its validity.

When discussing empiric outpatient parenteral antibiotic therapy, the panel offers analysis of a theoretical cohort showing that the risk of persistent bacteremia or meningitis as an outcome of bacteremia is greater than the risk of an antibiotic adverse reaction. The panel uses data to show why the white cell count is the best non-specific test and discusses why this test should be used to determine from which children to obtain a blood culture and to determine which will receive empiric antibiotic therapy.

9. *Which antibiotic should be used?*

The panel recommends ceftriaxone for empiric therapy, again without providing supporting evidence. The panel discusses the increasing incidence of invasive infections caused by strains of penicillin-resistant *Streptococcus pneumoniae* and recommends inpatient parenteral antibiotics for these particular infections.

Commentary

Considering the Institute of Medicine attributes of a well-written set of clinical practice guidelines, does this report have these characteristics?

Validity

This attribute reflects whether the recommendations are based on scientific evidence or on a collection of expert opinions. When too much weight is given to consensus opinion, the result can be biased recommendations. Even formal methods of consensus development ultimately have the limitation of using opinion to decide appropriateness with no specific link between

quality of evidence and recommendations.⁹ This limitation is seen in this guideline in which a formalized method of obtaining expert opinion was used (the modified Delphi technique), and at times subjectivity seems to take the place of evidence-based recommendations. Most of the recommendations are accountable, but a few are not supported by data or contradict the data offered. Though the formal method of obtaining consensus was described, it was not clear how disagreements regarding certain management and therapy issues were resolved.

Reliability and Reproducibility

Whether this set of recommendations is applicable in different practice settings and whether consistent outcomes can be expected for the management strategies offered in the guideline are unknown. No trial of using the guideline in an office or emergency department is cited. Though it would be difficult to carry out a controlled trial, these guidelines should be evaluated in some manner within the practice settings for which they were designed.

Clinical Applicability

In general, the guideline is clinically applicable because it makes recommendations for a common problem that is often seen in family practice and pediatric offices. The panel offers strategies to manage febrile children as outpatients at a time when cost-saving measures in health care are paramount. The issue of feasibility is acknowledged when the panel makes recommendations about laboratory work. The panel recommends using a white cell count to determine from which children to obtain a blood culture and subsequently for which to prescribe antibiotic therapy. This test is more easily done than a blood culture in physicians' offices and is less expensive than recommending a blood culture and empiric antibiotic therapy for all patients, a strategy the panel notes that would be more acceptable in emergency departments.

Clinical Flexibility

This set of recommendations is a guideline and is by definition flexible: guidelines are to be followed in most, not all, cases depending on the patient and other factors. Such guidelines are in contrast to standards, intended to be followed rigidly,

and options, leaving providers free to make any choice.¹⁰ The panel maintains flexibility within the guideline by offering two possibilities for some of the management strategies, but guidance in how to choose between the two is not offered. The authors are careful to recommend caring for each patient in an individualized manner.

Clarity

In general, the recommendations are clearly stated, but in some areas clarity is lacking because the text and figures do not always agree. Although clinical toxicity is an ambiguous area because of the subjectivity involved, a more complete definition would have been helpful.

Multidisciplinary Approach

Clearly a multidisciplinary approach is lacking when there are no specialties other than pediatrics represented, though the guideline addresses a common problem seen in family physicians' offices. The recommendations were not subjected to peer review by experts outside the panel before publication.

Scheduled Review

No mention is made of any scheduled review of the guideline, and suggestions for further research are not specifically offered.

Documentation

Documentation for the recommendations is usually presented. When specific data are not referenced, the panel invokes consensus opinion, as when recommending that all febrile infants younger than age 28 days be hospitalized for a sepsis evaluation and antibiotics. The reasoning behind the recommendations is thoroughly explained in some cases (as in the discussion about the laboratory tests) but is absent in other instances (as in the two outpatient management options for infants aged 28 to 90 days).

Overall Assessment

In summary, the recommendations contained in this guideline provide a step-by-step approach to the management of the febrile child and are generally, but not always, evidence based. Specific and practical strategies are offered with only a few ambiguities. If a physician recognizes the limitations of the guidelines, the recommendations can be considered a useful aid in the care of febrile children. As with any set of clinical guidelines, knowing the strengths and weaknesses helps a clinician use the guidelines more wisely.

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