Fever in Children Less than 36 Months

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It's no longer a question of staying healthy. It's a question of finding a sickness you like.
—Jackie Mason

Learning Objectives

1. Know how to respond to common parental misconceptions about fever
2. Identify children at low- and high-risk for invasive bacterial infection
3. Know common management strategies for managing febrile young children
4. Describe the impact of pneumococcal conjugate vaccine on the management of fever in children.

Primary Reference:

1. Hamilton JL, Evans SG, Bakshi M. Management of Fever in Infants and Young Children. American Family Physician. 2020;101(12): 721-729. https://www.aafp.org/afp/2020/0615/p721.html or https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0002838X20302045

Author's note: The AAP Clinical Practice Guideline by Pantell, et al. (see Additional References) offers a deeper exploration of this important topic and is worth reviewing. Specifically, the management algorithms in Figures 1, 2, and 3 are high yield. https://doi.org/10.1542/peds.2021-052228

CASE ONE:

You are on-call for your practice and get a call in the early morning. Mr. Warm's 2-year-old daughter, Eiffel, has been "burning hot" all night. He is worried that there might be brain damage from this. "I would have gone to the ER but I'm alone with three other kids. She cried when I gave her a sponge bath so I stopped." You ask him if he has taken her temperature, and he says his thermometer is broken.

1. How accurate is a tactile temperature?

Parental palpation, usually of the forehead, is the method most often used by parents, probably because of its ease of use. This method has been shown to have a high negative predictive value (99%) but a low positive predictive value (22%). Common reasons for misinterpretation of a normal temperature as a fever include heat radiation from a well child and cold hands.

2. Can you get brain damage from a high fever?

91% of parents believe that fever can cause harmful effects, such as brain damage, coma, delirium, blindness, and death. In a survey of members of the AAP, two-thirds believed fever itself could pose a danger to children and routinely recommended treatment for temperatures higher than 38.9°C (102°F). One-fourth stated that death and brain damage were potential complications of temperatures as low as 40°C (104°F). However, without a hyperthermic insult, it is rare for a child's temperature to go over 41.1ºC (106° F), and these harmful effects are quite rare under this temperature. Parents may mistakenly believe that a child with a temperature anywhere over 37ºC (98.6ºF) has a fever, but fever is typically defined beginning at 38ºC (100.4ºF).

3. Should you treat a fever? How? Does a sponge bath help or hurt?

Positive effects of treating fever include reduction of pain and discomfort, reduction of oxygen consumption (relevant for a child with cardiovascular or pulmonary disease), and reduction of fluid demand (relevant for a child with a risk of dehydration). Multiple studies have not shown benefit for prevention of seizures in a child with febrile seizures.

On the other hand, there is a reason for fever. Elevated temperatures increase the functional ability of various immune system components, while retarding the growth of bacteria and viruses and limiting the availability of iron, which many invasive bacteria require for survival. These beneficial effects of fever should be balanced against the effects above. An appropriate reason to intervene is for the child's comfort, thus the decision to treat should be based on how the child looks and behaves, not on a particular temperature threshold.

Acetaminophen and ibuprofen are good antipyretics for use in children, lowering the hypothalamic set point effectively. Aspirin should not be used because of the potential for Reye's syndrome. Acetaminophen should not be given to a child with hepatic disease. Ibuprofen should not be given to an infant <6 months of age (due to altered pharmacokinetics in the setting of immature kidneys), a child with renal disease, or a child at risk for dehydration. Parents should not be encouraged to alternate these medications, due to the risk of overdosage and the lack of proven efficacy. However, recognizing that this practice is widespread, the AAP advocates for careful counseling about dosing and goals of therapy (i.e., emphasizing comfort over temperature reduction). The correct dosing of medications should be reviewed with caregivers since 52% of parents administer incorrect doses of antipyretics (15% overdosing, 37% underdosing). Families should be encouraged to use the dosing equipment provided with the antipyretic, whether it be a syringe or cup.

A sponge bath for a child whose temperature set point is elevated will be quite uncomfortable, as it is a forcible method of temperature, but not set point, reduction. The hypothalamus senses a wider difference between its set point and the body's temperature and tries to close the gap by stimulating the body to generate more heat with shivering and an increased metabolic rate. If, however, the child is first given an antipyretic and time for it to work, a sponge bath may be quite comfortable. Sponge baths should be given only with tepid water, not with alcohol, cool water, or a cool rag.

4. What kind of thermometer do you recommend?

Taking into account efficacy, ease of use, and cost, the ideal thermometer is a digital readout thermometer that can be used in the rectum, the axilla, or the mouth and can be easily cleaned between uses. Rectal measurement gives the best approximation of core temperature in the first 3-4 years of life, but accuracy is affected by incorrect technique, stool in the rectum, and poor perfusion. In older children, oral temperature is generally preferred. Pacifier thermometers, though relatively cheap, must be retained in the mouth for at least 4 minutes to get an accurate readout. Tympanic thermometers are easy to use, but efficacy is limited by the age of the child (only for use in children over 1) and by the user's ability; they are also much more expensive than digital readout thermometers. Temporal artery scanners are the most expensive option, and while accuracy continues to improve, their performance relative to oral or rectal standard is still suboptimal.

CASE TWO:

After this morning call, Mrs. Nole brings her 8-week-old son, Tyler, to see you. Tyler developed a fever of 101.4 rectally this afternoon. Other than some fussiness yesterday, he has previously been well. He is still breastfeeding normally. An extensive history reveals no localizing symptoms. On exam he is initially crying, but is easily consolable. He appears well overall with normal color and hydration status. His temperature is 101.2°F, HR 124, RR 28, BP 88/42, O2 saturation 99%. The exam is otherwise unremarkable with no localizing findings.

5. What is the likelihood that this child has an invasive bacterial illness?

In febrile children under 3 months of age, the overall rate of urinary tract infection (UTI) and/or invasive bacterial infection (IBI), defined as bacteremia and/or bacterial meningitis, has ranged from 4-12% in several studies. Although some studies use a temperature of 38.2ºC or 38.4ºC as the cut-off for a fever, most studies and criteria use a threshold of 38.0ºC, especially in young infants. A retrospective cohort study, which included 35,070 visits to pediatric emergency departments (ED) at 37 hospitals, reported that 8.4% of febrile infants <90 days old had a UTI or IBI, highest among infants ≤28 days old (11.1%) with a peak in the third week of life. The prevalence of IBI, specifically, is 3% in febrile infants

in the first month of life and 2% in the second month. In studies of infants who are classified as low risk (defined below), the rate of UTI or IBI is much lower, 0.7% in one meta-analysis. A study of over 3000 febrile infants under 3 months of age showed that those who were well-appearing, aged 25 days or older, and whose fever was less than 38.6°C had a 0.4% rate of IBI.

Several risk stratification algorithms are used in clinical practice to identify infants who are well-appearing and at low-risk for UTI or IBI. The newest risk stratification algorithms do not include routine CSF and focus on identification of infants at low- and high-risk for IBI. The 2021 AAP clinical practice guideline on evaluation of febrile infants recommends the use of procalcitonin (PCT)-based algorithms, such as the Pediatric Emergency Care Applied Research Network (PECARN) prediction rule and the Step-by-Step approach (Table). The PECARN prediction rule was derived and validated in a cohort of 1,821 infants and includes 3 variables to define low-risk infants: urinalysis, ANC, and PCT. The rule demonstrated high sensitivity and negative predictive value for UTI and IBI. No infant with bacterial meningitis was misclassified. The Step-by-Step approach was developed to identify low-risk infants ≤90 days and incorporates age, clinical appearance, PCT, CRP, and ANC for risk stratification. The Step-by-Step approach also demonstrates high sensitivity and negative predictive value for IBI.

For settings in which PCT is not available, the AAP recommends using the following criteria to define low-risk: temperature ≤38.5°C, ANC ≤4,000-5,200/mm^3, and CRP ≤20 mg/L, with use of white blood cell (WBC) count not recommended. The temperature and upper limit ANC threshold of 5,200/mm^3 are partly based on the four-part "IBI score" derived for febrile infants ≤60 days old, and for which a score of ≥2 has a sensitivity of 98.8% and specificity of 31.3% for IBI. The AAP guideline also recommends stratifying young infants into three age groups: 8-21 days, 22-28 days, and 29-60 days old.

Discuss the differences (as well as the relative merits and drawbacks) of the criteria. Moderators can refer to the following Table. As a general principle, clinicians balance the trade-off between extent of testing with sensitivity.

Strategies for Managing Well-appearing Infants with Temperature ≥38.0°C without routine CSF

	Step-by-Step	PECARN	AAP Guideline (if PCT not available)
Age	22-90 d	≤60 d	22-60 d
History	Previously healthy No prior antibiotics	Previously healthy Term infant No prior antibiotics	Previously healthy Term infant
Physical examination	Well-appearing No clear source	Not critically ill No skin or soft tissue infection	Well-appearing No bronchiolitis or focal bacterial infection Highest temperature ≤38.5°C
Laboratory parameters (define lower risk patients)	No leukocyturia PCT <0.5 ng/mL CRP ≤20 mg/L ANC ≤10 000/mm^3	Negative urinalysis PCT ≤0.5 ng/mL ANC ≤4000/mm^3	CRP ≤20 mg/L ANC ≤4000-5200/mm^3
Higher risk patients	At discretion of hospital	At discretion of hospital	At discretion of hospital
Lower risk patients	Discharge home with 24-hour follow-up	Discharge home with 24-hour follow-up	Discharge home with 24-hour follow-up
Performance characteristics for IBI	Sensitivity 92% (84–96%) Specificity 47% (45-49%) PPV 7% (5-8%) NPV 99% (99-100%)	Sensitivity 97% (83–99%) Specificity 62% (59-64%) PPV 4% (3-6%) NPV 99.9 (99-100%)	Sensitivity 100% (87–100%) Specificity 46% (43-50%) PPV N/A NPV 100% (99-100%)

6. Are any tests indicated? If so, how will these help in your management of this patient?

In general, the use of laboratory tests is well studied in children under 3 months of age (see criteria listed above). The Step-by-Step approach applies to infants between 61–89 days of age, while the other commonly used algorithms apply only to infants ≤60 of age. **Review management of this child based on the table above.** However, one must consider that many fever experts believe the evaluation of well-appearing febrile children between 2-3 months of age need not be as aggressive as that of younger infants. Management specific to this age group has not been adequately studied.

Emergency medicine physicians and community pediatricians demonstrate substantial variation in adherence to guidelines (i.e., testing and treatment strategies). This variation has not been shown to lead to significant differences in outcomes.

However, given the grave implications of untreated bacterial illness in young infants, it is prudent to use a strategy that incorporates one of more of the established criteria. Because of a high-risk of IBI in infants younger than 3 weeks old, it is the standard of care to perform a full sepsis workup (urine, blood, and CSF cultures) and admit to the hospital for empiric antibiotics in this age group. If there is increased risk for HSV then further studies should be sent (CSF and serum PCR, surface swabs for PCR and culture) and acyclovir would be included in the regimen.

Urinalysis and culture: Most studies on the utility of urinalysis as a diagnostic test have focused on urine WBC count, leukocyte esterase, and nitrites. Tzimenatos and colleagues demonstrated that if all three of these tests are performed and any one of them is abnormal (using >5/high power field as the abnormal value for WBCs), the aggregate sensitivity is 94% and aggregate specificity is 91%, with an even higher sensitivity in febrile infants with bacteremic UTIs (100%). With a positive urinalysis, a urine culture is still required for diagnosis. With a negative urinalysis, the AAP recommends against sending a urine culture because of the risk of a false positive result or asymptomatic bacteriuria.

CBC: Although the WBC count has historically been used to help predict which children are at higher risk for UTI or IBI, its utility has diminished since introduction of pneumococcal conjugate vaccine (PCV) and it is no longer recommended to guide decision-making per the 2021 AAP guideline. The majority of the information about the performance characteristics of the CBC are based on studies in children older than 3 months before PCV was available. While WBC is not a component of the newest risk stratification algorithms, ANC is, though at different levels in the IBI score, Step-by-Step approach, and PECARN prediction rule.

Inflammatory markers: CRP is produced by hepatocytes within 4-8 hours of the onset of inflammation and levels generally peak around 36 hours. A 2011 meta-analysis found a 72% probability of serious bacterial infection in febrile young children found to have CRP levels ≥80 in emergency departments. The probability was 5% when CRP was <20. PCT, a prohormone of calcitonin that is released by hepatocytes and mononuclear cells, is an acute phase reactant that rises more rapidly than CRP in bacterial infection. It is incorporated into the Step-by-Step approach and PECARN prediction rules at a level of 0.5 ng/mL. The PCT is typically normal in infants with viral infections. Studies suggest that PCT is more sensitive and specific for IBI compared to the WBC and CRP. However, PCT is not yet available in some hospitals.

Blood cultures: A blood culture should be obtained in all febrile infants ≤60 days of age, and in many infants age 61 to 90 days. Some authors question the need for obtaining a blood culture in the management of previously healthy, well-appearing infants age 61 to 90 days with high fevers who have been immunized with at least one dose of PCV, but this approach has not been fully substantiated.

Chest x-ray: Multiple studies have shown that a CXR is not a necessary test unless there were specific respiratory findings such as tachypnea.

Molecular detection: It is now possible to detect the presence of infection using highly sensitive and oftentimes more rapid molecular assays, such as multiplex DNA PCR assays (e.g., BioFire Meningitis/Encephalitis Panel). Current FDA-approved multiplex panels targeting multiple organisms simultaneously are available for a large number of respiratory viral, gastrointestinal, and CNS infections. Recent studies have demonstrated promise with identifying the source of infection more rapidly, differentiating between bacterial and viral infections, and identifying bacterial and viral co-

infections. However, these are still not a replacement for routine cultures, which can allow for antibiotic susceptibility testing.

CSF analysis: See next question.

CASE continued:

Mrs. Nole is very concerned about a spinal tap. Her niece had presented to the ED with a fever several months ago and had a lumbar puncture that was fairly traumatic for the entire family. She asks if this will be necessary for her son.

7. Which febrile children need lumbar punctures? What are the risks associated with performing and not performing the procedure?

As per the AAP guideline, obtaining CSF for analysis and culture is the standard of care in febrile infants ≤21 days of age. For infants 22-28 days old who are well-appearing with no evident source of infection, the AAP recommends starting with a urinalysis, blood culture, and inflammatory markers (PCT, ANC, +/- CRP). If inflammatory markers are elevated, then lumbar puncture is recommended. However, if inflammatory markers are not elevated, the AAP recommends performing shared decision-making with parents about lumbar puncture.

The risk of bacterial meningitis is extraordinarily low in well-appearing infants 29 to 60 days of age who fall into the low-risk category using other established (i.e., non-CSF) predictors, and therefore lumbar puncture is not recommended. For infants 29-60 days old with elevated inflammatory markers, the AAP recommends consideration of lumbar puncture, dependent on clinician and parent values and preferences. Importantly, even though urinalysis is a criteria of all risk stratification algorithms, febrile infants with positive urinalyses are not at higher risk of bacterial meningitis and a positive urinalysis alone should not be used to decide on lumbar puncture.

As noted by Aronson, et al. in a study of algorithms that avoid routine CSF testing, "ultimately, clinicians must balance the rarity of bacterial meningitis in febrile infants >28 days of age who do not appear ill and the risks of a lumbar puncture with the potential for serious neurologic sequelae or death if treatment is delayed." When CSF testing is not done, it is important to disclose potential risks of deferring testing, and to ensure close follow up.

Febrile children over 60 days of age generally do not need a lumbar puncture if they are well appearing and have no red flags on clinical assessment.

In any age group, lumbar puncture should be performed if there is clinical suspicion for bacterial meningitis. The risks of a serious complication after a lumbar puncture are very low in children. A study by Howard, et al. of lumbar punctures in children with acute lymphoblastic leukemia found that in the 5223 lumbar punctures evaluated, no serious complications were encountered. If antibiotics are to be started empirically in a child under 3 months of age to treat IBI, a lumbar puncture should be performed first. Diagnosing meningitis becomes more challenging if a lumbar puncture must be performed in the days after antibiotics have already been started. The exception is for infants age 29 to 60 days of age with a positive urinalysis but who otherwise meet low-risk criteria. The risk of bacterial meningitis is very low in these infants, and two recent studies reported that none of over 1,000 febrile infants with positive urinalyses treated with empiric antibiotics without CSF testing had a delayed diagnosis of meningitis. Infants with positive urinalyses but normal inflammatory markers should be closely monitored for signs of bacterial meningitis while receiving treatment as outpatients for presumptive UTI.

CASE continued:

You send a CBC, procalcitonin, and urinalysis. WBC is 12,000, with 5% bands and 30% neutrophils, and the procalcitonin is 0.1 ng/mL. Urinalysis shows 0-5 WBCs and is negative for nitrites or leukocyte esterase.

8. What is your approach to treatment? Will you use antibiotics?

The lab values (normal PCT, ANC <4,000/mm^3) and other clinical parameters put this patient in a low-risk category. If 24-hour primary care clinic follow-up can be arranged, one can send the patient home without antibiotics and follow-up on culture results over the next 24-48 hours.

CASE continued:

After talking with Mrs. Nole and examining Tyler, you realize that there has been a typo on the demographics sheet and that Tyler is actually 4 months old.

9. How will this affect your management?

The approach to febrile children above three months is more controversial than in younger children. Given the greater degree of heterogeneity of children aged three to 36 months, the approach is more individualized than in younger children. History and physical are usually more accurate and the prevalence of UTI and IBI is less than 3% and 0.5%, respectively, in well-appearing young febrile children. Many experts suggest using a higher fever threshold to initiate diagnostic studies, often 39 degrees, sometimes even 39.5. With a lack of updated evidence-based guidelines and given the relatively low risk of IBI in immunized, well-appearing children ages >3 months of age, Madsen, et al. suggest incorporating parental preferences into evaluation and treatment decisions for older febrile children.

Immunization status helps determine the extent of further workup. In general, a completely immunized child has received the primary booster series of three immunizations with PCV13, and at least two or three doses of Hib as recommended for the first 6 months of life. Based on these criteria, any child under 6 months is not completely immunized. In children who are not completely immunized, the threshold for diagnostic testing might be lower, especially in regards to blood cultures, though the prevalence of IBI in these infants is still low.

The following would be a possible approach to a child older than 3 months old without a source of fever.

- Urinalysis and urine culture for young children with ≥1% probability of UTI as defined in the 2011 AAP Clinical Practice Guideline for UTI. In children ≤24 months of age, the probability threshold is crossed in all uncircumcised boys, circumcised boys with at least 3 of 4 clinical predictors (non-Black race, temperature ≥39°C, fever >24 hours, absence of another fever source), and girls with at least 2 or 3 of 4 clinical predictors (age <12 months, temperature ≥39°C, fever ≥2 days, absence of another fever source). Importantly, the previous inclusion of white race as a predictor has been questioned, as race is a social but not a biological construct, and race will likely be removed from future guidelines. If urinalysis is positive, initiate empiric outpatient antibiotics while awaiting culture results.
- For infants and children who are not immunized, if temperature ≥39°C and there is no identifiable source (e.g., upper respiratory symptoms): consider obtaining WBC count (or ANC) and hold blood culture – if WBC count ≥15,000 (or ANC ≥10,000), send blood culture. Some would consider giving a dose of IM antibiotic (e.g., ceftriaxone) if WBC ≥15,000. The use of PCT in this setting needs further exploration
- Chest radiograph is based on findings concerning for bacterial pneumonia, though viral pneumonia is substantially more likely. Most febrile infants and young children do not require a chest radiograph, though imaging may be considered with findings of focal rales, temperature ≥39.5°C with SaO2 <90%, tachypnea, and/or respiratory distress. However, chest radiographs should be interpreted with caution given the likelihood of a viral etiology.
- Acetaminophen 15 mg/kg/dose every 4 hours or ibuprofen 10 mg/kg/dose every 6 hours (only if >6 months old) as needed for fever
- Follow up on culture results at 24 and 48 hours
- Return if fever persists >48 hours or condition deteriorates

The epidemiology of pediatric fever has changed in the past decade with the addition of PCV-13 in 2010, and improved use of prophylactic antibiotics before delivery. A recent review of the etiology of bacteremia among a sample of previously healthy febrile infants <90 days old found that *Escherichia coli* was the most common cause, followed by group B *Streptococcus*, *Streptococcus viridans*, and

Staphylococcus aureus. Pneumoccocus was more common in infants >60 days of age, and there were no cases of *Listeria monocytogenes* infections. However, because of changes in serotypes causing disease noted in several studies, a cautious approach continues to be warranted in the young febrile child.

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Resources:

1. Fever information for parents from AAP. http://www.healthychildren.org/English/health-issues/conditions/fever/pages/Fever-Without-Fear.aspx
2. Mayo Clinic fever handout for parents. http://www.mayoclinic.com/health/fever/ID00052

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