Risk Stratifying Febrile Infants: A Moving Target

Amir Rouhani, MD*; Ilene Claudius, MD; Solomon Behar, MD; Jessica Mason, MD; Andrew Grock, MD

*Corresponding Author. E-mail: arouhani12@yahoo.com.

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It is no surprise that the winter months bring a host of pediatric patients with fever. In fact, 1 in 5 pediatric emergency department (ED) visits is for fever, and most involve little more than parental reassurance and good return precautions.[1] With this volume, you would think that as emergency providers we would be able to simply and confidently risk stratify febrile infants younger than 90 days. Unfortunately, risk stratification continues to be a moving target. In this month's issue of *Annals of Emergency Medicine*, the article by Powell et al[2] on the epidemiology of bacteremia in febrile infants sheds some new light on the ever-changing picture of serious bacterial infections in this population.

WHY ARE FEBRILE YOUNG INFANTS SO WORRISOME?

Febrile infants are particularly susceptible to serious bacterial infections, such as meningitis, bacteremia, pneumonia, urinary tract infection or pyelonephritis, bacterial enteritis, cellulitis, and orthopedic infections (osteomyelitis, septic arthritis, etc). For infants younger than 21 day, it is also important to remember herpes simplex virus infection.[3,4] The immature immune systems of infants cannot adequately resist or contain an infection. Even worse, they often do not manifest classic signs and symptoms of their illness. Therefore, a well-appearing infant may not be well at all, and the fever may be the only harbinger of a serious bacterial infection.[5]

But how common are serious bacterial infections and invasive disease in this patient population? One 2010 review reported that 12.5% of febrile infants had a serious bacterial infection,[6] and the incidence in those younger than 28 days may be as high as 20%.[7] Newer data, however, suggest that the rate of serious bacterial infection in febrile infants is actually decreasing, especially for invasive disease such as bacteremia and meningitis. Current US figures suggest that approximately 2% of febrile infants with no source of disease have bacteremia and 0.3% to 0.4% have bacterial meningitis.[8] These declining rates are most likely due to improved peripartum screening and prophylaxis against vertically transmitted infection in combination with improved herd immunity from new vaccines and vaccination strategies.

HOW HAS RISK STRATIFICATION CHANGED OVER THE YEARS?

You may recall a time when all febrile infants younger than 6 months got a full septic evaluation! Although this age limit has decreased, efforts to identify a low-risk population in febrile infants younger than 28 days have been unsuccessful. Therefore, all infants younger than 28 days, regardless of appearance, and all febrile infants who are ill appearing are automatically considered at high risk and require a full septic evaluation, including CBC count with differential, blood cultures, urinalysis with urine culture, and cerebrospinal fluid studies if the patient is not too unstable for lumbar puncture.[9] These patients are also treated with empiric antibiotics pending culture results.

But what do we do with the well-appearing febrile infants after 28 days? In the 1990s, several criteria were developed to help risk stratify the well-appearing 29- to 90-day-old infant: the Boston, Philadelphia, and Rochester criteria (Table).[10] Although each has unique features, including the definition of fever, patient age, study population, clinical and laboratory variables, and recommended disposition, they all perform similarly well in safely identifying low-risk patients when applied to the appropriate patient. In general, to be considered low risk, febrile infants must be full term, be well appearing, be previously healthy with an uncomplicated neonatal course, have no focal source of bacterial infection, and have low-risk laboratory criteria. The Philadelphia and Rochester

Table. The Boston, Rochester, and Philadelphia Criteria.

	Boston	Rochester	Philadelphia
Publication year	1992	1994	1999
Age, days	28–89	0–60	29–56
Rectal temperature, °C (°F)	38.0 (100.4)	38.0 (100.4)	38.2 (100.8)
Evaluation	CBC with diff Urinalysis Urine culture Blood cultures Lumbar puncture with cytology and culture CXR (if respiratory symptoms) Stool WBC counts if diarrhea	CBC with diff Urinalysis Urine culture Blood cultures If starting antibiotics, lumbar puncture with cytology and culture Stool WBC counts if diarrhea	CBC with diff Urinalysis Urine culture Blood cultures Lumbar puncture with cytology and culture CXR
High risk (admit and administer empiric antibiotics)	WBC count >15,000 Band-neutrophil ratio >0.2 UA >10 WBCs/hpf Urine Gram's stain positive CSF >8 WBCs CSF Gram's stain positive CXR with infiltrate Stool with blood or moderate WBC counts	WBC count <5,000 or >15,000 Absolute bands >1,500 UA >10 WBC/hpf Stool >5 WBCs	WBC count >20,000 UA >10 WBCs CSF >10 WBCs CXR with infiltrate

CBC, Complete blood count; *CXR*, chest x-ray; *WBC*, white blood cell; *UA*, urinalysis; *CSF*, cerebrospinal fluid.

criteria allow discharge of low-risk febrile infants with close outpatient follow-up without antibiotics. The Boston criteria recommend full sepsis evaluation, including lumbar puncture, followed by empiric treatment with parenteral ceftriaxone, and reevaluation within 24 hours if stratification indicates low risk. Because all of these guidelines perform well, consistent use of an evidence-based guideline is likely much more important than which specific criterion is used.[11]

Since the classic Rochester, Philadelphia, and Boston criteria were published, the management of febrile infants has continued to evolve. New biomarkers that help identify patients with serious bacterial infections have led to newer strategies such as the Lab Score. Combining procalcitonin, c-reactive protein, and urine dipstick, this score has been validated as a more accurate tool for identifying serious bacterial infection in febrile children aged 7 days to 36 months. Unfortunately, the sensitivity in febrile infants may not be high enough, and it appears to be more useful in ruling in rather than ruling out serious bacterial infection—a big problem when the goal is to accurately identify a low-risk group.[12]

Wouldn't it be great to combine the best components of classic approaches with the newer biomarker-driven strategies? Yes! It's called the step-by-step approach.[13] This new algorithm for evaluating febrile infants aged 0 to 90 days incorporates all of the risk-stratification strategies discussed above. The first step is to classify sick versus not sick, using the Pediatric Assessment Triangle. Well-appearing febrile infants older than 21 days who meet certain laboratory criteria (negative urine dipstick result, procalcitonin level <0.5 ng/mL, c-reactive protein level <20 mg/L, and absolute neutrophil count level <10,000 cells/mm^3) are deemed to be at low risk. If the patients fail any of these criteria, they are considered to be at intermediate or high risk and should receive a full diagnostic evaluation. Keep in mind that the serious bacterial infections in low-risk febrile infants according to the step-by-step approach were predominantly in 22- and 28-day-old infants and in patients with fever onset less than 1 hour before ED arrival.

WHAT DOES THE ARTICLE BY POWELL ET AL ADD TO THIS?

The article by Powell et al is a prospective observational study that describes the current epidemiology of bacteremia in well-appearing, healthy, near-term (>36 weeks' gestational age), febrile infants younger than 60 days who presented to the 26 participating Pediatric Emergency Care Applied Research Network (PECARN) EDs between 2008 and 2013 and had blood drawn for culture. The study found that the overall prevalence of bacteremia in infants younger than 28 days was 3.1% compared with 1.1% in 29- to 60-day-old infants. In addition, prevalence differed by week of age for infants younger than 28 days, peaking in the second week (5.3% at 8 to 14 days) and then decreasing steadily to 1.6% in the fourth week. The incidence of bacterial meningitis was 1.3% in febrile infants younger than 28 days. There were no cases of bacterial meningitis after the sixth week of life or in infants older than 42 days. *Escherichia coli* and group B streptococcus were the most common bacterial pathogens identified across all groups, followed by *Staphylococcus aureus*.

Although in decline, the prevalence of bacteremia and meningitis among febrile infants remains significant. In the article by Powell et al, the prevalence of bacteremia and meningitis remained significantly higher in infants younger than 28 days versus those older than 29 to 60 days. Although the step-by-step protocol applies to febrile infants older than 21 days, caution should be exercised in the population aged 21 to 28 days. Because no cases of bacterial meningitis were identified in patients after the sixth week of life, a lower threshold may be indicated for lumbar puncture in febrile infants younger than 42 days versus older patients. Last, the article by Powell et al identified the most common bacterial pathogens, *E coli* and group B streptococcus, as well as *S aureus* as a prevalent resistant pathogen, which may influence future guidelines on recommended antibiotic regimens for febrile infants.

SO HOW DO WE APPROACH THESE PATIENTS AGAIN?

The initial approach to febrile infants is the same as for every patient: think ABCs. Next, all febrile infants younger than 28 days and ill-appearing infants aged 29 to 90 days should be classified as high risk and receive appropriate resuscitation, a full septic evaluation, empiric antibiotic therapy, and hospitalization. For the well-appearing 29- to 90-day-old infants, decision tools can help identify low-risk febrile infants. The classic Rochester, Philadelphia, and Boston criteria have high sensitivities to identify febrile infants at increased risk of serious bacterial infection if applied to the appropriate patient. The step-by-step approach incorporates components of the classic approaches with the newer biomarker-driven strategies, and works best in infants older than 28 days with fever onset greater than 1 hour before arrival.

Author affiliations: From the Departments of Emergency Medicine and Internal Medicine, Olive View–UCLA Medical Center, Sylmar, CA (Rouhani); the LAC + USC Department of Emergency Medicine, Los Angeles, CA (Claudius); the Long Beach Memorial/Miller Children's Hospital and Children's Hospital Los Angeles, and the Department of Pediatrics, University of California, Irvine (Behar); the Department of Emergency Medicine, University of California, San Francisco–Fresno, Fresno, CA (Mason); and the David Geffen School of Medicine, Department of Emergency Medicine, University of California, Los Angeles, Los Angeles, CA (Grock).

REFERENCES

1. Ipern ER, Henretig FM. Fever. In: Fleisher GR, Ludwig S, Henretig FM, eds. *Textbook of Pediatric Emergency Medicine*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2006;295-306.
2. Powell EC, Mahajan PV, Roosevelt G, et al. Epidemiology of bacteremia in febrile infants aged 60 days and younger. *Ann Emerg Med*. 2017;71:211-216.
3. Levine DA, Platt SL, Dayan PS, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics*. 2004;113:1728-1734.
4. Kimberlin DW, Whitley RJ. Neonatal herpes: what have we learned? *Semin Pediatr Infect Dis*. 2005;16:7-16.
5. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85:1040-1043.
6. Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: review of the literature. *Pediatrics*. 2010;125:228-233.
7. Schwartz S, Raveh D, Toker O, et al. A week-by-week analysis of the low-risk criteria for serious bacterial infection in febrile neonates. *Arch Dis Child*. 2009;94:287-292.
8. Greenhow T, Hung YY, Herz AM, et al. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33:595-599.
9. Jaskiewicz JA, McCarthy CA, Richardson AC, et al. Febrile infants at low risk for serious bacterial infection—an appraisal of the Rochester criteria and implications for management. Febrile Infant Collaborative Study Group. *Pediatrics*. 1994;94:390-396.
10. Mason J, Wyatt C. 8-Week-old girl with cough and "fever.". In: Weinstock M, Klauer K, Joseph M, eds. *Bouncebacks! Pediatrics*. Columbus, OH: Anadem Publishing; 2015:343-358.
11. Byington CL, Reynolds CC, Korgenski K, et al. Costs and infant outcomes after implementation of a care process model for febrile infants. *Pediatrics*. 2012;130:e16-e24.
12. Bressan S, Gomez B, Mintegi S, et al. Diagnostic performance of the lab-score in predicting severe and invasive bacterial infections in well-appearing young febrile infants. *Pediatr Infect Dis J*. 2012;31:1239-1244.
13. Gomez B, Mintegi S, Bressan S, et al. Validation of the "step-by-step" approach in the management of young febrile infants. *Pediatrics*. 2016; http:doi.org/10.1542/peds.2015-4381.