

Should We Evaluate Febrile Young Infants Step-by-Step in the Emergency Department?

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In this issue of *Pediatrics*, Gomez et al¹ present a new “Step-by-Step” algorithm for management of febrile young infants. Although bacteremia and bacterial meningitis, termed invasive bacterial infection (IBI),² occur in only 1% to 2% of febrile young infants,^{3,4} clinicians fear “missing” these infections due to potential for mortality and morbidity.^{5,6} It is longstanding practice that young febrile infants undergo a “sepsis workup,” often including lumbar puncture, and many are hospitalized to expectantly treat for bacterial infection.⁷ More than 2 decades ago, various criteria (Rochester,⁸ Philadelphia,⁹ and Boston¹⁰) were developed to identify febrile infants at low-risk of bacterial infection, the so-called “low-risk” criteria. Application of these criteria allows for a subset of infants >28 days of age to be safely discharged from the emergency department (ED), with or without antibiotics. However, previous studies evaluating the performance characteristics of these criteria included low numbers of infants with IBI, and varied approaches to define the subjective features of well appearance.¹¹

In the current study, Gomez et al¹ prospectively validated a “Step-by-Step” approach among >2000 febrile infants ≤90 days of age across 11 European pediatric EDs, of whom 4% had an IBI. This approach uses well appearance, age >21 days, leukocyturia, procalcitonin <0.5 ng/mL, C-reactive protein ≤20 mg/L, and absolute neutrophil count ≤10 000/mm³

in a stepwise fashion to identify febrile infants at high, intermediate, and low-risk of IBI. Unlike the Philadelphia and Boston criteria, the algorithm does not incorporate routine cerebrospinal fluid testing. This algorithm demonstrated a high sensitivity (92%) and negative predictive value (99.3%) for IBI in young febrile infants, although 7 infants (0.7%) classified as low-risk had an IBI, none with bacterial meningitis.

In practice, the Step-by-Step approach is similar to the Rochester criteria, in which reassuring urine and blood testing may preclude performance of a lumbar puncture in the well-appearing infant. Although the reported sensitivity for IBI is higher with the Step-by-Step approach, the algorithm proposed primarily differs from the Rochester criteria in the identification of an intermediate-risk group. However, we suspect that most clinicians would treat the intermediate-risk group similarly to high-risk infants, as the 3.4% risk of IBI likely warrants performance of cerebrospinal fluid testing and expectant antimicrobial treatment.

Although this stepwise approach has high sensitivity to identify febrile infants with IBI, the real question is what risk is low enough to consider not performing lumbar puncture, withholding antibiotics, and discharging the infant from the ED? With a 0.7% risk of bacteremia among low-risk infants with the Step-by-Step approach, would most clinicians feel comfortable correctly classifying

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143 febrile infants as low-risk at the expense of missing 1 infant with IBI?

To fully understand the context of how these findings should be incorporated into practice, we need to understand the implications of discharging a low-risk infant without antibiotics. Unfortunately, the data are lacking in this area, and in the Gomez et al¹ study, 5 of the 7 low-risk infants with IBI received parenteral antibiotics and were hospitalized. A large study of office-based pediatricians observed that among 63 febrile infants with IBI, 2 experienced a delayed diagnosis, 1 with bacteremia and 1 with bacterial meningitis. Both infants were ≤ 4 weeks of age and did well with close follow-up.¹² In the Rochester, Philadelphia, and Boston criteria studies, all of the low-risk infants diagnosed with IBI were either initially hospitalized and observed without antibiotics,^{8,9} or administered parenteral ceftriaxone and discharged from the ED.^{8,10} The risk of “missing” a low-risk infant with IBI using the Step-by-Step approach, without inpatient observation or expectant antibiotics, is largely unknown. Thus, clinicians need to consider the paucity of outcome data when deciding how best to apply this algorithm to febrile infants.

In this Step-by-Step study, among the 7 low-risk infants with IBI, 4 were 22 to 28 days old, an age group routinely hospitalized on expectant antibiotic therapy in the United States^{7,13} due to diminished performance of the low-risk criteria among infants <1 month of age.^{14,15} Among previously healthy, well-appearing febrile infants >28 days of age, this stepwise approach failed to identify 2 patients (0.2%) with IBI. In this older age range, approximately 500 low-risk febrile infants could potentially avoid lumbar puncture, antibiotics or hospitalization to identify 1 case of IBI. This may be a more tolerable

risk threshold for clinicians when determining whether to withhold antimicrobial therapy and discharge the infant from the ED.

The specificity of the Step-by-Step approach was low (47.0%), and only 6.7% of children classified as non-low-risk had an IBI, reflecting the low prevalence of IBI among febrile infants, and a management approach that maximizes sensitivity at the expense of specificity. The low specificity may result in lumbar puncture, hospitalization, and expectant antibiotic therapy for a substantial number of infants, along with potential for iatrogenic risks and parental stress and anxiety.^{16,17} Continuing to reassess the components of the Step-by-Step approach and a better understanding of the parents’ perspective are warranted to balance the risk and benefit of testing, treatment, and hospitalization in this patient population.

The Step-by-Step approach is a highly sensitive, prospectively validated management algorithm to identify IBI in febrile infants. Future studies demonstrating the safety of implementing this stepwise approach are warranted.

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ABBREVIATIONS

ED: emergency department
IBI: invasive bacterial infection

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