Procalcitonin a promising biomarker to identify invasive bacterial infections in febrile infants
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Infants younger than 90 days of age with fever often are evaluated in the emergency department due to their risk of serious bacterial infections (SBI) such as urinary tract infections (UTI) and invasive bacterial infections (IBI), including bacteremia and bacterial meningitis.

IBI are reported to affect 0.5% to 2% of febrile young infants. Because of poor discrimination of the clinical exam to identify SBI coupled with the risk of dire outcome if missed, physicians rely on intensive and invasive evaluations that often include urine, blood and cerebral spinal fluid studies. In addition, many of these infants are expectantly admitted to the hospital and receive intravenous antibiotics until cultures are negative.

Although UTIs may be identified early with urinalysis results, there has long been a quest for a test that could provide adequate early discrimination between febrile young infants with and without IBI.

Two recent European studies have evaluated procalcitonin (PCT) as a diagnostic tool to identify IBI in young febrile infants and potentially decrease the need for invasive testing and hospitalization.

In a prospective study done in France, PCT was found to have diagnostic accuracy superior to that of C-reactive protein (CRP) in identifying IBI (Milcent K, et al. JAMA Pediatr. 2016;170:62-69).

The study enrolled febrile infants ages 7 to 91 days. Although 100% of patients had a PCT measurement and 99.5% had a CRP, a limitation of the study was that only 61.5% of patients had a blood culture and 65% underwent lumbar puncture.

Among the 2,047 infants enrolled, 6.8% were diagnosed with SBI and 1% with IBI. Compared to CRP, PCT had better diagnostic accuracy to identify febrile infants with IBI despite similar accuracy for SBI.

In an associated editorial, Kuppermann and Mahajan concurred that although PCT alone was shown to be superior to other biomarkers in identifying IBI, clinical prediction rules that incorporate PCT are likely to be even more discriminating in identification of low-risk infants. In addition, future development of genomic methods to identify the infection itself will be imperative for full resolution of this diagnostic quandary, they said (JAMA Pediatr. 2016;170:17-18).

In another recent study, Gomez and colleagues validated a step-by-step approach, including PCT, to identify febrile infants 90 days of age or younger who are at low risk of IBI and could be managed as outpatients without lumbar puncture or empirical antibiotic therapy (Pediatrics. 2016;138:e20154381). The components of the step-by-step approach, applied sequentially to identify risk assessment, included ill appearance, age (21 days), leukocyturia, PCT (0.5 ng/mL), and CRP (>20 mg/L) or absolute neutrophil count (>10,000/mm3).

In this multicenter study that included 11 emergency departments in Europe, the step-by-step approach was validated and compared with the Rochester criteria and the lab score. Results showed the prevalence of IBI in the 2,185 enrolled patients was 4%. General appearance, age and urine dipstick identified 80% of the IBI patients. A fully implemented step-by-step approach had a sensitivity of 92%, specificity of 46.9% and negative predictive value of 99.3% for identifying IBI.

The step-by-step approach misclassified seven (0.7%) infants with IBI as low risk, whereas the Rochester criteria and the lab score missed 16 and 35, respectively. Four of the seven patients misclassified by the step-by-step approach were between 21-28 days and six of the seven missed patients had fever duration of less than
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two hours. This short fever duration group may indicate a biological limitation of the biomarker itself.

Aronson and Neuman commented in their editorial response that the risk of missing IBI with step-by-step is one in 143. They pointed out that as the study was a retrospective application of the data instead of a prospective testing of the full process, five of the seven patients who would have been "missed" by the step-by-step process were actually admitted to the hospital and treated with parenteral antibiotics (Pediatrics. 2016;138:e20161579). A further assessment of the threshold of "how low is low enough" from the provider, parent and patient perspective is necessary prior to full implementation.

These articles highlight procalcitonin as a potentially important biomarker in the evaluation of young febrile infants to identify IBI. More studies are needed to understand the true impact of procalcitonin in improving the outcome of this patient population.

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