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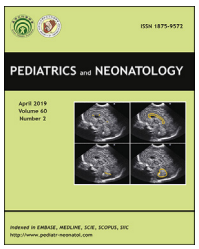

Editorial

How to predict serious bacterial infections in young febrile infants in the emergency department?

Fever is the most common reason for young infants (age <90 days) being brought to the emergency department (ED). Discriminating young febrile infants from those with severe bacterial infections (SBIs) still remains a challenge because of a lack of diagnostically reliable signs and symptoms during the initial clinical evaluation. In general, patients in this age group are presumed to be more susceptible to bacterial infections due to risks of perinatal bacterial exposure, vaccine nativity, and relatively immature immunity. SBIs include urinary tract infection, bacterial gastroenteritis, and more invasive bacterial infections (IBIs) such as bacteremia and meningitis. The incidence rate of all SBIs in young infants in the United States has been estimated at 3.75/1000 full-term infants. Moreover, the prevalence rates of SBIs and IBIs among young febrile infants are 5%—15% and 2%—5%, respectively.[1,2]

Since the past few decades, several clinical experts have made numerous attempts to identify young febrile infants at risk for SBIs, which have resulted in several clinical criteria that are now widely used, including the Rochester criteria, the modified Philadelphia criteria, the Boston criteria, and the Yale Observation Scale (YOS). The sensitivity of these criteria for the risk stratification of febrile infants with SBIs has been reported to be >90% more than 20 years ago. Nevertheless, due to today's changing epidemiology, the performance of these criteria requires reevaluation. In 2018, Aronson et al. conducted a retrospective case-control study to evaluate the Rochester criteria and the modified Philadelphia criteria for the risk stratification of febrile infants with IBIs aged ≤60 days. They reported that the sensitivity of the modified Philadelphia criteria was higher than that of the Rochester criteria, but the specificity was lower. In addition, two infants with meningitis were misclassified to the Rochester low-risk group without CSF testing when discharged from the ED.[3] In 2017, Nigrovic et al. demonstrated that neither the YOS score nor the unstructured clinician suspicion reliably identified infants with IBIs aged ≤60 days in a large prospective cohort study.[4] Although these criteria have earlier shown acceptable negative predictive value, there is a need for more accurate clinical and laboratory predictors to risk-stratify febrile infants.

When young febrile infants are brought to the ED, the complete blood cell count (CBC) is the most commonly obtained test. However, several studies have demonstrated suboptimal performance characteristics of CBC parameters, including the peripheral white blood cell count, the absolute neutrophil count, and the neutrophil-to-lymphocyte ratio, for IBIs. Nonetheless, these results require further validation. In 2017, Cruz et al. conducted a large prospective observational cohort study and found that CBC parameters had poor accuracy in distinguishing febrile infants with IBIs.[5] The possible explanation for the poor performance of CBC may be the changing epidemiology of IBIs in young infants due to the effect of immunity resulting from the use of conjugate vaccines of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* and the development of screening and antibiotic prophylaxis of Group B *Streptococcus*. The most common pathogens of SBIs identified in the modern era is *E. coli*; it may produce less of an inflammatory response and less leukocytosis by the host and thus decrease the sensitivity of CBC. Therefore, better diagnostic tools other than the CBC are required in the post-conjugate vaccine era.

C-reactive protein (CRP) is the most investigated and a commonly used biomarker. In this issue of Pediatrics and Neonatology, Chiu et al. have reported the findings of their retrospective study conducted at a tertiary medical center in southern Taiwan to evaluate the clinical characteristics and routine blood tests in young febrile infants. They have demonstrated that CRP levels >25 mg/L can predict IBIs with greater accuracy in febrile infants.[6] Furthermore, a similar result was reported by Hamiel et al., in 2017, showing that CRP was the best single discriminatory marker

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of SBIs in young febrile infants compared with CBC. When the CRP level is high (>46.1 mg/L), there is a high risk of developing an SBI.[7] However, we must pay attention to some factors that may decline the sensitivity of CRP, such as low birth weight or extremely preterm infants and those with an earlier onset of sepsis.[8] To summarize the above mentioned findings, plasma CRP level could be a good marker for predicting SBIs but not to rule out the early onset of sepsis or guide the empirical choice of antibiotics.

Procalcitonin (PCT) has been frequently reported to have higher sensitivity than CRP for the identification of IBIs, although some studies have shown that the accuracy of PCT and CRP was similar for SBIs.[9] However, a meta-analysis of studies assessing the correlation of PCT cutoff value for the identification of low- and high risk groups among young febrile infants concluded that measuring serum PCT concentrations alone was inferior to the Rochester criteria, although it could distinguish some SBIs.[10] In addition, PCT might not currently be a routine laboratory investigation in some clinical settings, and it requires a relatively higher cost than that for other biomarkers. Therefore, these limitations restrict the routine usage of PCT for the discrimination of SBIs in young febrile infants in the ED.

Other biomarkers for identifying SBIs are currently under investigation, e.g., presepsin, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), interleukin-27 (IL-27), soluble urokinase plasminogen activator receptor (suPAR), neutrophil CD64, cell-free DNA, and microRNA. These are considered to be potential markers for sepsis among pediatric patients in the future; however, none of these have yet been applied to clinical use.

In conclusion, discriminating infants with SBIs from young febrile infants still remains a disturbing problem for clinicians. None of the clinical criteria or diagnostic markers could be used alone to reduce the risk of making significant errors. PCT and CRP appear to be superior in predicting SBIs compared with CBC, and the clinical criteria have an acceptable negative predictive value for SBIs. However, there is no obvious increasing effect even when these approaches are combined. Therefore, we should still be cautious in case of young febrile infants, and there remains a need to develop better diagnostic methods.

Conflict of interest

The author has no conflicts of interest relevant to this article.

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References

1. Woll C, Neuman MI, Pruitt CM, Wang ME, Shapiro ED, Shah SS, et al. Epidemiology and etiology of invasive bacterial infection in infants ≤60 Days old treated in emergency departments. *J Pediatr* 2018;**200**:210—7. e1.
2. Esposito S, Rinaldi VE, Argentiero A, Farinelli E, Cofini M, D'Alonzo R, et al. Approach to neonates and young infants with fever without a source who are at risk for severe bacterial infection. *Mediators Inflamm* 2018;**2018**:4869329.
3. Aronson PL, Wang ME, Shapiro ED, Shah SS, DePorre AG, McCulloh RJ, et al. Risk stratification of febrile infants ≤60 Days old without routine lumbar puncture. *Pediatrics* 2018; **142**. pii: e20181879.
4. Nigrovic LE, Mahajan PV, Blumberg SM, Browne LR, Linakis JG, Ruddy RM, et al. The Yale observation Scale score and the risk of serious bacterial infections in febrile infants. *Pediatrics* 2017;**140**. pii: e20170695.
5. Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, et al. Accuracy of complete blood cell counts to identify febrile infants 60 Days or younger with invasive bacterial infections. *JAMA Pediatr* 2017;**171**:e172927.
6. Chiu IM, Huang LC, Chen IL, Tang KS, Huang YH. Diagnostic values of C-reactive protein and complete blood cell to identify invasive bacterial infection in young febrile infants. *Pediatr Neonatol* 2019;**60**:197—200.
7. Hamiel U, Bahat H, Kozer E, Hamiel Y, Ziv-Baran T, Goldman M. Diagnostic markers of acute infections in infants aged 1 week to 3 months: a retrospective cohort study. *BMJ Open* 2018;**8**: e018092.
8. Lai MY, Tsai MH, Lee CW, Chiang MC, Lien R, Fu RH, et al. Characteristics of neonates with culture-proven bloodstream infection who have low levels of C-reactive protein (≦10 mg/L). *BMC Infect Dis* 2015;**15**:320.
9. Milcent K, Faesch S, Gras-Le Guen C, Dubos F, Poulalhon C, Badier I, et al. Use of procalcitonin assays to predict serious bacterial infection in young febrile infants. *JAMA Pediatr* 2016; **170**:62—9.
10. England JT, Del Vecchio MT, Aronoff SC. Use of serum procalcitonin in evaluation of febrile infants: a meta-analysis of 2317 patients. *J Emerg Med* 2014;**47**:682—8.