Clinicians caring for young febrile infants have struggled with risk stratification algorithms for invasive bacterial infections (IBIs) (bacteremia and/or bacterial meningitis) for decades because of the tension between not wanting to miss infants with IBIs yet not wanting to over-test and over-treat these vulnerable infants. Risk stratification algorithms using complete blood counts (CBCs) with or without cerebrospinal fluid (CSF) data, developed in the 1980s and 1990s, have several limitations: (1) laboratory thresholds were not derived by statistical methods, resulting in suboptimal test accuracies; (2) algorithm precision was limited by the relatively few infants with IBIs; (3) the epidemiology of IBIs has changed in the past decades with an increase in Escherichia coli and a decrease in group B Streptococcus infections due to perinatal screening; (4) algorithm specificity has been insufficient to limit the use of lumbar punctures, empirical antibiotics, and hospitalizations; and (5) newer biomarkers, including C-reactive protein (CRP) and particularly procalcitonin (PCT), are substantially more sensitive than the CBC for detecting infants with these infections.

In a well-conducted retrospective case-control analysis from 11 emergency departments (EDs) between 2011 and 2016, Aronson et al derived and internally validated a prediction model without using CSF data for identifying febrile infants ≤60 days with IBIs. They documented 4 factors associated with low risk of IBI: age 21 to 60 days, history of fever only (or a fever documented in the ED <38.5°C), normal urinalysis, and absolute neutrophil count (ANC) <5185 cells per mm³. Using multivariable modeling, they used statistically derived thresholds for the ANC and temperature to help identify infants at “low risk” and “not low risk” and created a scoring system for IBI using the adjusted odds ratio of each significant predictor. The scoring system based on low risk versus not low risk had a high sensitivity for detecting infants with IBIs (98.8%).

The study has several other strengths, including (1) the inclusion of a large number (181) of infants with IBIs, allowing for high-precision risk estimates; (2) recent data (2011–2016) that reflect current epidemiology of IBIs; and (3) the use of statistical modeling to identify evidence-based rather than consensus-based thresholds. Notably, the ANC threshold is similar to that identified in a large prospective study conducted in the Pediatric Emergency Care Applied Research Network to identify risk factors for IBIs in similarly aged febrile infants. The Aronson et al study, however, has certain limitations that deserve further comment. The specificity (31.3%) was similar to older rules and lower than that of current algorithms that employ newer biomarkers. The risk of herpes simplex virus infections is not evaluated by this rule, so the use of this rule without obtaining CSF in the youngest infants could miss herpes simplex virus infections. Given the
study's retrospective nature, it is unclear whether documentation of well appearance was done before results of laboratory tests, including lumbar punctures, were known. ED documentation typically occurs after patient evaluation, leading to a potential reporting bias in documenting the appearance of the infant. Subjective variables including "duration of fever," "household sick contacts," and "upper respiratory infection symptoms or signs" used in this study are subject both to variable accuracy of parental reporting and clinician's history-taking practices. Furthermore, as the authors mentioned in the discussion, the algorithm lacks newer biomarkers such as CRP or PCT, which are significantly more accurate than the CBC for identifying infants with IBIs,7,11,12 and result in prediction algorithms with greater specificities.15,16 CRP and PCT are routinely used for the evaluation of febrile infants in Europe, and the capability of PCT analysis is increasingly available in the United States.

Finally, it is unclear how to apply the proposed prediction rule. A temperature <38.5°C in the ED or a fever documented only at home are criteria indicating lower risk. According to the prediction algorithm, multiple fever assessments during an ED stay can be used; therefore, the IBI risk assessment might change over time, making the algorithm less practical. It is also unclear whether the recommendation for all infants not at low risk is to receive full evaluations for sepsis and hospital admission for parenteral antibiotics. This study does, however, add to the growing literature identifying low-risk febrile infants for whom lumbar punctures, antibiotics, and hospitalizations can be obviated.

Fortunately, a unified field theory in the evaluation and management of young febrile infants is on the horizon. Gene expression analysis using RNA biosignatures holds promise for replacing cultures as the gold standard for diagnosing IBIs and specific viral infections.18–20 With progress toward short turnaround times, this technology may potentially replace prediction algorithms, achieving the unified field theory by making the prediction algorithm and the gold standard definitive test one and the same (and available at the point of care). We anticipate that the use of gene expression analysis in the evaluation of young febrile infants will ultimately bring decades of efforts to develop the optimal algorithm to a satisfying conclusion.  

ABBREVIATIONS

- ANC: absolute neutrophil count
- CBC: compete blood count
- CRP: C-reactive protein
- CSF: cerebrospinal fluid
- ED: emergency department
- IBI: invasive bacterial infection
- PCT: procalcitonin

REFERENCES

14. Cruz AT, Mahajan P, Bonsu BK, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with


Prediction Models for Febrile Infants: Time for a Unified Field Theory
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