

VIEWPOINT

Reassessing Lumbar Punctures for Very Young Febrile Infants—How Much Evidence Is Enough?

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Approximately 2% to 3% of healthy, term-born infants will be evaluated in emergency departments for fever during the first 60 days of life.^{1,2} For more than 30 years, the evaluation of these febrile young infants has been driven by the concern for missing bacterial meningitis.³ Because a delayed or missed diagnosis of bacterial meningitis can be devastating, most international guidelines continue to recommend routine lumbar puncture (LP) for cerebrospinal fluid testing, hospitalization, and empirical antibiotics for febrile infants in the first month of life. In more recent practice, bacterial meningitis occurs in fewer than 1% of febrile infants aged 28 days and younger, yet LPs are undertaken in 45% to 75% of their emergency department encounters.^{1,2,4} This results in tens of thousands of LPs in this infant population annually in the US alone. Because bacterial meningitis is uncommon, missed cases will be rare and may never be encountered at a single institution. Yet preventing these rare events comes at a measurable cost to infants, their families, and health systems. LPs can cause pain, respiratory compromise, uninterpretable or false-positive results, prolonged hospitalization, and increased system-wide resource utilization.³ Furthermore, parents identify LPs as the single most stressful aspect in the evaluation of their febrile infants.⁵ The question is not whether LPs have a role, but which infants are most likely to benefit from these procedures.

The trade-off between routine LPs and the very small probability of missed bacterial meningitis among infants who satisfy validated low-risk criteria has changed with the ongoing study of blood biomarkers, particularly serum procalcitonin.

Recommendations for cerebrospinal fluid testing for all febrile infants in the first months of life were developed when laboratory risk stratification tools were limited, procalcitonin was unavailable, and risk estimates of invasive bacterial infections (bacteremia and bacterial meningitis) were imprecise. These also predated widespread vaccination and intrapartum group B streptococcus prophylaxis, and methods to risk stratify for herpes simplex virus infection were immature. Modern prediction models have substantially changed this landscape. The Pediatric Emergency Care Applied Research Network (PECARN) rule, based on urinalysis, absolute neutrophil count, and procalcitonin, was derived statistically,⁶ externally validated, then updated to simplify predictive thresholds and subsequently evaluated in large international prospective cohorts.^{7,8} Among 2531 prospectively enrolled infants aged 0 to 28 days, including 22 with bacterial meningitis, the updated PECARN rule had a sensitivity of 94.8%, specificity of 43.3%, positive predictive value of 6.1%, and negative predictive value of 99.6% for bacteremia or bacterial meningitis. Importantly, no infant meeting the updated PECARN low-risk criteria had bacterial meningitis, and given no missed cases, the estimated negative predictive value for ruling out bacterial meningitis specifically was greater than 99.96% (95% CI,

99.82%-100%).⁷ These findings were broadly generalizable across multiple countries, health care systems, and disease prevalences, and diagnostic accuracy of the rule was even higher among 5497 infants aged 29 to 60 days.⁸

The current evidence base is remarkably consistent. Across the largest studies evaluating febrile young infants using the updated PECARN criteria, both prospectively and retrospectively, only a single case of bacterial meningitis has been reported among infants classified as low risk. That case, from a retrospective multicenter cohort of 10 293 infants aged 8 to 60 days, was an infant aged 14 days with few clinical details available.⁹ Taken together, these data from more than 18 000 infants aged 60 days and younger and meeting PECARN low-risk criteria, the relevant question is now whether routine LPs can be justified despite their extraordinarily low diagnostic yield, even among those in the first month of life.

Many febrile young infants are initially evaluated in emergency departments and outpatient clinics where procalcitonin and other laboratory testing may not be available with timely turnaround. Ideally, these infants should be referred to settings where such testing is available for risk stratification. When procalcitonin is unavailable, we suggest following the American Academy of Pediatrics febrile infant management recommendations, with risk stratification using the combination of C-reactive protein, absolute neutrophil count, and maximum fever temperature.³ However, there is much less robust data on this approach than with the use of procalcitonin in the first month of life. How to optimize risk stratification in these youngest febrile infants when procalcitonin is unavailable is an ongoing area of research,¹⁰ with larger analyses of international prospectively collected data actively underway.

In the pooled international prospective studies, the updated PECARN rule missed no infant 0 to 60 days of age with bacterial meningitis; however, 9 who were classified as low risk had bacteremia.^{7,8} Three of these 9 had clinical characteristics consistent with blood culture contamination, leaving 6 probable true bacteremias misclassified among 8028 infants.^{7,8} Importantly, bacterial meningitis carries far worse clinical outcomes than isolated bacteremia, with an approximately 16-fold higher risk of death or major neurologic complications. Current guidelines for treatment of febrile infants already acknowledge the possibility of a delayed diagnosis of bacteremia. Many well-appearing febrile infants with bacteremia present after more than 24 hours of fever, demonstrating that infants with occult bacteremia may remain clinically stable for some time. Likewise, it is not uncommon for well-appearing febrile infants to be discharged home pending culture results and be recalled 12 to 24 hours later when a blood culture result becomes positive. Although these infants should be treated promptly, delayed recognition of isolated bacteremia is not regarded as a diagnostic failure, unlike a delayed

diagnosis of bacterial meningitis. As a further safeguard, existing pathways [recommend](#) that decisions about LPs for infants in the first month of life incorporate shared decision-making, and those infants treated without LPs should still be hospitalized for observation without antibiotic treatment. Shared decision-making should communicate the risks and benefits of performing LPs in terms understandable to families, leveraging the precise risk estimates of bacterial meningitis now available.

An argument for maintaining current practice is that larger studies may provide more precise risk estimates for bacterial meningitis, especially for infants in the first month of life. However, it is unlikely that any larger prospective study of febrile young infants will ever be undertaken. The recent pooled international analyses required decades of recruitment across multiple countries and pediatric research networks to achieve meaningful estimates.^{7,8} The resulting evidence base is larger than for many other accepted pediatric practice recommendations. Requests for substantially larger prospective studies risk becoming less a scientific imperative than an unattainable standard. Additionally, fewer LPs may reduce procedural

experience, thus increasing reliance on simulation for skill maintenance. However, this is not a justification for unnecessary procedures.

The history of medicine is filled with interventions that persisted long after evidence supporting them had eroded. The relevant question is therefore not whether selective testing eliminates all risk, but whether continuing routine LPs produces more benefit than harm. After decades of research, large international validation studies, and substantial recent cumulative data, the evidence suggests that among well-appearing febrile young infants, including those in the first month of life, who meet modern low-risk criteria, routine LP is more likely to cause harm than prevent it.

Future investigations should focus not only on improving specificity through optimized combinations of biomarkers and novel host-response transcriptomic and proteomic biosignatures, but also on expanding timely access to validated biomarker testing across varied practice settings. The next frontier is no longer determining whether low-risk febrile infants can safely be treated without routine LPs but rather expanding the settings in which low-risk infants can benefit from this approach.

ARTICLE INFORMATION

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