

EDITORIAL

Moving the Field Forward to Safely Do Less With Febrile Neonates

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Newborns with suspected infections are a common source of anxiety for pediatricians.^{1,2} As the adage goes, “never trust a newborn,” and for good reason. Young infants are immunologically vulnerable and at risk for rapid progression of bacterial infections during their postnatal transition.³



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Most pediatricians can vividly describe neonates who rapidly declined despite appropriate therapy, and these experiences inform an understandable bias toward clinical conservatism that prioritizes interventions aimed at minimizing risk. At the same time, there is undeniable evidence of the iatrogenic harm from invasive testing, early antimicrobial exposure, and hospitalization for newborns.^{3,4} How best to balance the common—a young febrile infant who recovers uneventfully—with the catastrophic—the rare case of an infant with invasive bacterial infection—remains the heart of this clinical conundrum. On initial presentation, these infants are often clinically indistinguishable.¹ Emerging evidence allows pediatricians to perennially recalibrate as we strive to determine what neonates can safely receive fewer interventions.

Over the last several decades, multiple well-studied frameworks for the approach to newborns with suspected infections have been adopted into clinical practice.^{2,5} The most historically notable algorithms, each eponymously named for the city where it was developed (Rochester, Boston, Philadelphia), have offered slightly modified diagnostic approaches to identify newborns at low risk of bacterial infections.⁵⁻⁷ More recent pathways have evolved to reflect progress toward further balancing conflicting risks. The Pediatric Emergency Care Applied Research Network (PECARN) clinical prediction rule is a risk stratification calculation first described in 2019.¹ This rule aims to identify infants at low risk of bacterial infections by leveraging universally available tests including urine analysis, absolute neutrophil count, and procalcitonin. Similar to its predecessors, the PECARN clinical prediction rule was validated and directed toward identifying urinary tract infections, bacteremia, and bacterial meningitis under the umbrella of serious bacterial infections. However, as argued by the American Academy of Pediatrics (AAP) in the 2021 guideline for well-appearing febrile infants, urinary tract infections are far more common and have far lower rates of morbidity and mortality than bacteremia or meningitis.³ Therefore, instead of *serious bacterial infection*, the more apt *invasive bacterial infection* description was offered to refocus efforts toward bacteremia and bacterial meningitis as the notable bacterial infections in febrile neonates.

In this edition of *JAMA*,⁸ Burstein and colleagues present their work to pragmatically evaluate the performance of the PECARN prediction rule after an updated version was developed for invasive bacterial infections—not serious bacterial infections—among well-appearing febrile neonates. Specifically, the authors aimed to determine whether this prediction tool could accurately iden-

tify patients at low risk for invasive bacterial infections for whom invasive tests, particularly lumbar punctures, are of low diagnostic value. To answer this question, they performed a multinational prospective study analyzing pooled data from 4 international cohorts of well-appearing, full-term infants 28 days or younger presenting with fever over the past 16 years.

Among the 1537 included infants, 69 (4.5%) had invasive bacterial infections, including 58 with bacteremia and 11 with bacterial meningitis. Among the 41% of infants who were labeled by the updated PECARN rule as “low risk” only 4 were found to have an invasive bacterial infection, none of which were bacterial meningitis. In other words, if clinicians had chosen to forgo lumbar puncture on these low-risk infants, they would have prevented more than 600 lumbar punctures and not missed a single case of bacterial meningitis. A secondary analysis that included 2 additional cohorts from the US demonstrated similar performance of the PECARN rule, with 5 cases of bacteremia and no bacterial meningitis among 1079 low-risk infants.

There are several important limitations to this study. First, although not a limitation per se, the robust negative predictive values offered should be taken in the context of the very low prevalence of invasive bacterial infections among well-appearing febrile neonates in the analysis. Second, all infants were evaluated in high-income countries, and it is not known how applicable these findings are for low- and middle-income countries with different epidemiologic pressures and health care access. Similarly, only full-term infants were included, making it difficult to translate these findings to the care of preterm infants with higher rates of invasive bacterial infections. Furthermore, the study cannot comment on a devastating neonatal infection, herpes simplex virus, which requires a lumbar puncture if suspected given its propensity to cause meningoencephalitis.⁹ Last, although overall each protocol was similar, there were minor differences between study sites for exclusion criteria and for clinical adjudication of invasive bacterial infections. This limitation is reflected in the notably higher inflammatory markers seen for patients with invasive bacterial infections in Canada and the UK/Ireland, and in the higher rate of invasive bacterial infections seen among children from the cohorts in Spain and Europe, perhaps due to those cohorts' exclusion of children with clinical signs of viral infection.

Despite these limitations, this study is an important step as the field of pediatric medicine moves toward more targeted care and balanced risks for newborns with suspected infection. The authors' decision to prioritize invasive bacterial infections is what makes this article an important addition to the literature informing decision-making for practicing clinicians. The authors correctly focus on performance of lumbar punctures as a key decision point in the workup of many febrile neonates, because lumbar punctures are a source of frequent rumination in

the scenario of a well-appearing febrile infant.¹⁰ As the authors describe, parents identify the lumbar puncture as one of the most stressful aspects of the workup, and this procedure is not without risk.^{4,11,12} At the same time, neonatal bacterial meningitis is a devastating and potentially life-ending or life-altering infection that requires prompt identification and treatment to improve outcomes. This fear of missing a case of bacterial meningitis understandably sways many to err on the side of caution, having seen firsthand the damage meningitis can inflict. Indeed, most neonates in this analysis (70.3%) had cerebrospinal fluid available, although many additional neonates likely had unsuccessful lumbar punctures attempted because other studies suggest that more than 90% of newborns presenting with fever have lumbar punctures performed.¹³

This study has the potential for major clinical impact. In the US, more than 70 000 infants are evaluated for fever within the first few months of life every year.¹⁴ If the cohorts presented here are a representative sample, close to half of these febrile infants would be considered to be at low risk for bacterial infection. Implementation of the PECARN clinical prediction rule to guide care could therefore translate into tens of thousands of avoided lumbar punctures, antimicrobial courses, and hospitalizations every year in the US alone. Of course, any exuberance must be tempered by the realization that any missed invasive bacterial infection is potentially devastating, and it remains a difficult task to delineate risk tolerance that varies from one clinician and from one parent to the next. However, this study does address an important opportunity to save newborns from very real iatrogenic harm. It also highlights that additional advances in diagnostics, including efforts to better categorize transcriptomic biosignatures for bac-

terial vs viral illness in neonates, are needed to more confidently decrease low value tests and interventions.¹⁵

Although this study is another step in refining targeted diagnostic and therapeutic approach for neonatal infections, more work is needed before guidelines are changed. Similar to several studies that followed the 2021 AAP guidance, this study supports the decision to use laboratory markers to stratify risk among newborns aged 22 to 28 days to avoid low-yield studies, specifically lumbar punctures. However, the next step forward will require a similarly focused and pragmatic analysis of newborns aged 8 to 21 days as the next frontier for a tailored diagnostic approach that balances risk. Of note, all 5 of the children in the secondary analysis incorrectly labeled as being low risk by PECARN who were ultimately found to have invasive bacterial infections were aged 8 to 21 days. Roughly 35% of the included patients in the secondary analysis were aged 22 to 28 days, which may skew these findings because the percentage of newborns aged 8 to 21 days who were determined to be low risk is not known. However, a recent study on the performance of the new AAP guidelines also found a very low rate of missed infections among low-risk neonates aged 8 to 21 days, although there was a single missed case of bacterial meningitis in that similarly sized cohort.¹⁶ Further implementation of the findings presented here would benefit from a dedicated analysis for the population aged 8 to 21 days to better describe the risk for missed invasive bacterial infections in that age group specifically.

As pediatricians, efforts to find the best care for these vulnerable patients is built on decades of steady progress. The field rarely moves forward with sudden breakthroughs, but rather by iterative steps that move us closer to better and then best. This study represents an important step in that progression.

ARTICLE INFORMATION

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Published Online: December 8, 2025.
doi:10.1001/jama.2025.23133

Conflict of Interest Disclosures: None reported.

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