

Authors' reply: methodological considerations in evaluating outcomes of neonatal bacterial meningitis

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Dear Editor,

We thank the authors of the Letter to the Editor for their careful reading of our article, "Factors for poor outcomes of neonatal bacterial meningitis: a retrospective multicenter study,"¹ and for their valuable insights.² We appreciate the opportunity to clarify the methodological aspects of our research.

Regarding the exclusion of neonates with gestational age <34 weeks and birth weight <1500 g: We deliberately set the inclusion criteria to neonates with a gestational age greater than 34 weeks and birth weight above 1500 grams. Extremely preterm and very-low-birth-weight infants possess a significantly high baseline risk for neurodevelopmental delays and severe intracranial complications (such as intraventricular hemorrhage) that are independent of meningitis.³ Including this highly vulnerable population would have introduced substantial confounding factors, making it difficult to definitively attribute poor outcomes to bacterial meningitis. Consequently, our findings cannot be directly extrapolated to extremely preterm infants, and we agree that this specific population warrants separate, dedicated investigations.

Regarding the reliance on microbiologically confirmed infections: The diagnosis in our cohort required confirmation by cerebrospinal

fluid (CSF) Gram-stained smear or bacteriological culture. We acknowledge the concern that prior antibiotic use can yield sterile cultures, potentially introducing selection bias by excluding partially treated cases.⁴ However, relying solely on clinical evidence and CSF pleocytosis in a retrospective multicenter study would inevitably introduce confounding conditions that mimic bacterial meningitis. For instance, without microbiological gold standards, it is notoriously difficult to differentiate partially treated bacterial meningitis from viral meningoencephalitis (such as enterovirus or herpes simplex virus infections). Furthermore, aseptic meningitis associated with systemic inflammatory conditions, such as Kawasaki disease, presents a significant diagnostic challenge when cultures are negative.⁵ Therefore, applying these strict microbiological criteria was essential to ensure absolute diagnostic certainty and cohort homogeneity, avoiding the inclusion of these non-bacterial or sterile neuroinflammatory mimics.

Regarding neuroimaging: In our routine clinical practice, cranial magnetic resonance imaging (MRI) is systematically scheduled as a standard evaluation for every neonate suspected of having bacterial meningitis, rather than being restricted only to severe cases. Virtually all patients in our cohort underwent neuroimaging, with the only exceptions being the exceedingly

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rare instances where parents explicitly refused the examination. Thus, the detection of acute neurological complications in our study was both comprehensive and robust.

Regarding developmental assessments: As we noted in our limitations section, evaluating neurodevelopmental outcomes using the Gesell Developmental Diagnosis Scale (GDDS) rather than more comprehensive neuropsychological tools may have resulted in the underestimation of subtle cognitive or behavioral impairments. Furthermore, because follow-up data were retrospectively extracted from outpatient electronic medical records, the evaluating clinicians conducting routine follow-ups typically had access to the infants' medical histories, precluding strict blinding.

Regarding the hearing evaluation: In our clinical centers, brainstem auditory evoked potential (BAEP, equivalent to BERA as mentioned in your query) is a mandatory and routine examination for all neonates and infants diagnosed with bacterial meningitis. This standardized assessment is systematically performed both during the acute disease course and throughout the long-term follow-up. The unilateral hearing loss documented among the neurological sequelae in our study was exclusively based on these rigorous and comprehensive BAEP evaluations.

We thank the readers again for highlighting these important clinical considerations. We believe this discussion further contextualizes our findings and underscores the necessity of early neurological assessment and structured long-term follow-up in affected neonates.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: FL; data collection: FL; analysis and interpretation of results: FL; draft manuscript preparation: FL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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