RE: Management of Neonates Born at ≤34 6/7 Weeks’ Gestation With Suspected or Proven Early-Onset Bacterial Sepsis

The Clinical Report is important and timely in attempting to limit antibiotic use to those patients most likely to benefit from them, but I am concerned that the implications of the statement may leave some patients undertreated.

I am most concerned with discontinuing antibiotics in high-risk, ill patients who may have received antibiotics trans-placentally and whose blood cultures show no growth. The authors attempt to justify this by showing time to positive blood cultures are no different in infants whose mothers did versus did not receive antibiotics. This negates the concept of bacterial killing time after exposure to antibiotics, which for Group B Streptococcus, is ~4–6 hours. I am concerned about possible partial treatment of true bacterial infections with early termination of antibiotics.

Neonatal clinicians frequently manage patients exposed to maternal antibiotics for hours, and this conceivably will inhibit bacterial growth. According to the report, with a positive blood culture, clinicians should use Red Book guidelines to determine length of therapy (for instance with Group B Streptococcus, 10–14 days depending on the CSF result). In circumstances where antibiotics MAY HAVE inhibited bacterial growth in the blood culture, surely stopping antibiotics at 36–48 hours is not advised. It would be as if a positive blood culture was followed after 24 hours of antibiotic therapy with a repeat culture that is negative, and antibiotics are stopped after a 2–3 day treatment. That negative culture should give the clinician confidence that they chose the correct antibiotic, but not that a sufficient antibiotic course has been delivered.

In addition, clinicians need to remember that blood is only 1 organ, and other organs may be infected without the blood being inoculated. In the autopsy review of neonatal deaths by Barton et al., infection was not diagnosed clinically 61% of the time with deaths in these cases attributed to RDS or immaturity, many of whom were not treated with antibiotics.

Finding no growth in the blood culture at 36–48 hours after multiple hours of in utero antibiotic exposure may be reassuring when no other markers of infection are present, and this is where the use of inflammatory markers such as CRP can be helpful. Although the clinical report mentions other conditions that may be associated with elevations of the CRP, such as asphyxia and pneumothorax (not referenced), certainly an inflammatory response from infection remains the overwhelming etiology of an elevation. In the face of significant risk for neonatal infection, like PPROM and chorioamnionitis, in a mother who received antibiotics prior to delivery AND the infant has elevation of the non-specific inflammatory markers, it not only seems reasonable but also prudent to consider that the CRP or procalcitonin is elevated due to infection. In addition, as shown by Benitz, serial normal CRP values have a 99% negative predictive value of serious infection at 48 hrs and should give confidence to discontinue antibiotics. This approach should meet the goal of limiting antibiotics to those most likely infected while minimizing exposure to those not infected.

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REFERENCES
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Authors’ Response

We appreciate the thoughtful commentary by Dr. Burchfield. His concerns are commonly encountered by neonatal clinicians and were considered carefully in the preparation of the revised Clinical Report.

His first concern addresses the decision to continue or stop antibiotics among infants receiving empirical treatment when blood cultures are sterile after maternal intrapartum antibiotic treatment. Culture media with antibiotic neutralization material are widely used in clinical microbiology laboratories to mitigate the impact of circulating antibiotics. If appropriate blood volumes and cultures methods are used, a sterile blood culture provides strong evidence that the infant is not bacteremic. Dr. Burchfield also raises concern that an infant who is not bacteremic still may have a focal bacterial infection that will recrudesce if antibiotics are stopped prematurely. This theoretical concern cannot be definitively resolved without a controlled trial of antibiotic administration in the absence of bacteremia. Nonetheless, available observational data (cited in the Clinical Report) suggest that extended antibiotic administration in the absence of a positive blood culture does not result in better outcomes among preterm infants, whether measured by the incidence of death or significant morbidities.

We do not agree that the data of Barton et al support his concern. In that autopsy case series of 111 infants with birth weight 300–1000 g who died in...
1990–1993, the authors identified infection as the primary cause of death if white blood cell infiltrates were observed histologically in autopsied organs. “Congenital infection” was diagnosed in 30 cases, among which only 11 infants had blood cultures obtained before death. Pathogenic bacteria were isolated from 9 of 11 (no data are provided for 2 cultures), demonstrating that neonatal blood cultures confirmed the authors’ histologic diagnosis in at least 82% of the cases.

Finally, Dr Burchfield suggests that clinical decision-making will be enhanced by obtaining serial CRP values from infants born in the setting of intrapartum antibiotic administration. While it is true that consistently low CRP levels over the first 48 hours imply an approximately sixfold reduction in the probability of culture-proven sepsis, the positive predictive value of CRP levels up to 6 mg/dL was <5% in the cited study and even levels >6 mg/dL had poor positive predictive values for culture-proven sepsis. Nonetheless, the threefold increase in the posterior probability of infection implied by an elevated CRP level may convince some clinicians to extend antibiotic treatments in specific culture-negative cases. The Report states, “Consistently normal values of CRP and procalcitonin over the first 48 hours of age are associated with the absence of EOS, but serial abnormal values alone should not be used to extend antibiotic therapy in the absence of culture-confirmed infection.” The key word is alone; context is important.

Dr Burchfield’s commentary highlights the difficulty of uncertainty. The revised Clinical Report discusses the relative merits of different approaches to risk assessment among term and preterm infants. In the end, no predictive model, clinical algorithm, or laboratory test result will perform perfectly, and we agree with Dr Burchfield that individual cases will always require some degree of clinical judgment.

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