COMMENTARY

Management of Late-Preterm and Term Neonates at Risk for Early-Onset Sepsis

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The management of patients at risk for a low-frequency but serious illness poses many challenges for health professionals. Neonatal early-onset sepsis (EOS) in late-preterm and term neonates is a classic example of such a low-frequency serious condition. Faced with the possibility that such an infant, even if well appearing, can develop EOS, clinicians have traditionally erred on the side of treating with antibiotics until the EOS is ruled out by some combination of a continued normal clinical examination, negative blood cultures, and negative rapid diagnostic test results. A liberal antibiotic treatment strategy resulted in a large number (as high as several hundreds) of infants being needlessly treated with antibiotics for every neonate with true EOS. This strategy has been relatively easy for clinicians to follow because the burden of administering a short course of antibiotics is relatively low, and the adverse effects of antibiotics (eg, emergence of antibiotic resistance, altered microbiome) are not immediately apparent or dramatic. In contrast, most clinicians have experienced in their careers or heard about newborn infants with catastrophic consequences or even death from EOS, especially during an era when group B streptococcal infection was more common than today. Thus, there was significant overtreatment of infants as well as much interinstitutional and interclinician variation in the frequency of antibiotic use for neonates at risk for EOS. In recent years, this calculus of weighing of a possible catastrophic event that occurs at low frequency against the invisible and delayed hazards of antibiotics has changed. Nationally and internationally, alarms are being raised about the hazards of antibiotics, the widespread emergence of bacterial resistance to antibiotics, and the drying up of the pipeline of new antibiotics. This has led to the emergence of approaches designed to better identify and target infants at risk for EOS to avoid needless antibiotic therapy. Two such broad approaches (which can be complementary and are not mutually exclusive) have emerged for the management of well-appearing late-preterm or term newborns at risk for EOS.

The first approach is prospective risk categorization by using a combination of maternal and infant clinical and laboratory variables soon after birth, followed by actions directed by the level of risk (diagnostic testing for sepsis and treating if the probability of sepsis exceeds the test threshold and treatment threshold, respectively). Risk categorization can be performed with multivariate statistical models, an example of which is a Web-based EOS risk calculator,[1] or by using criteria and algorithms based on a combination of published evidence and expert judgment.[2] In theory, the advantages of prospective risk stratification are that antibiotic therapy can be initiated before the

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level of bacteremia becomes high enough to cause symptoms, and for infants categorized as low risk, staff time beyond that required for routine care of the neonates is not required. The disadvantages are that the method used for risk quantification may misclassify infants and therefore still expose some infants (the false-negatives[3]) to the risk of delayed treatment of sepsis and some (the false-positives) to unnecessary treatment with antibiotics. If a multivariate statistical model, such as the sepsis risk calculator is used, clinicians should critically appraise the evidence supporting this method, ensure that the model is applicable to the population of newborns that is being managed, and remember that the accuracy of the prediction model may change over time with changes in patient demographics, disease patterns, clinical practices, and other input variables. The sepsis risk calculator also requires, as an important input variable, the institution-specific incidence of EOS, data that might not be available at all institutions.

The second approach is clinical monitoring of at-risk infants in the hospital for a period (usually 48 hours) after birth with intervention (diagnostic testing for sepsis and treating) if clinical signs of sepsis become apparent.[4,5] With clinical monitoring, the theoretical advantages are that every at-risk infant is closely evaluated (thereby eliminating the risk of false-negatives) and the cost and pain of blood sampling, insertion of intravenous catheters, and antibiotic administration are avoided in a certain number of patients (ie, in the false-positives). However, clinical monitoring requires more time and effort on the part of the nurses and clinicians performing the monitoring (a particular challenge in resource-poor settings), requires skilled personnel, may cause separation of the infant and mother if the monitoring occurs in the NICU, and only leads to treatment of infants after they demonstrate clinical signs (and not preemptive treatment before clinical presentation). Clinical monitoring may result in false-positives, too, with resultant unnecessary antibiotic therapy. Treatment initiated later in the course of illness evolution may theoretically lead to worse outcomes than preemptive treatment.

A third possible approach, that of performing universal rapid diagnostic laboratory testing for sepsis in well-appearing neonates at risk for sepsis, has generally not been adopted because of the poor sensitivity and specificity of current laboratory tests for sepsis[6] but might become a viable option in the future if rapid-molecular-assay–based tests for sepsis are proven to be highly sensitive and specific.[7]

Of the first 2 approaches described above, is 1 superior to the other? To answer this question with confidence would require a randomized controlled trial comparing these 2 approaches head to head. Such a trial has not been conducted. Therefore, in the absence of high-quality evidence, clinicians and policy makers have to make decisions on the basis of lower-quality evidence derived from observational studies. Such observational studies have typically been based on single or multiple institutions that introduced a practice change and reported their results before and after the introduction of the change. A key question in such studies in which researchers aim for more precise antibiotic targeting and a reduction in antibiotic use is whether any of the patients not receiving antibiotics under the newer restrictive approach, who would have previously received antibiotics under a more liberal approach, developed clinical manifestations of sepsis or an adverse outcome because of a missed diagnosis of sepsis. Such a missed diagnosis could be catastrophic, especially if the newborn has already been discharged from the hospital. In most published observational studies, authors rely on a lack of documented episodes of sepsis in untreated infants to claim that their approach of restrictive antibiotic use was safe. This claim can only be reliable if every single untreated infant was clinically managed to verify the occurrence or nonoccurrence of sepsis. In the absence of such universal follow-up, claims that no untreated infant had a sepsis episode should be accepted with caution.

In this issue of *Hospital Pediatrics*, Joshi et al[8] describe the results of a practice change in a single institution where an approach of liberal treatment with antibiotics for chorioamnionitis-exposed infants was replaced by clinical monitoring, with antibiotic therapy being provided only to symptomatic neonates. In this study, ~95% of neonates undergoing clinical monitoring avoided antibiotic therapy, there was a large reduction in the use of antibiotics and laboratory testing, and clinical monitoring detected multiple causes of clinical deterioration (only 1 of 15 infants with clinical deterioration had sepsis). Had the 596 chorioamnionitis-exposed neonates in this study hypothetically been managed by using risk categorization with the sepsis risk calculator, a net of 20 more infants would have been treated with antibiotics without any benefit. Another important feature of this study is that clinical monitoring in the postpartum nursery under a model of couplet care had similar results to monitoring in the level 2 NICU, findings that minimize some of the disadvantages of clinical monitoring.

This study adds to the body of literature (cited in the article by Joshi et al[8]) describing close clinical monitoring in the first 48 hours of life as 1 reasonable approach and an alternative to use of the sepsis risk calculator to ensure patient safety while avoiding needless antibiotic exposure and its accompanying burdens. The likely equivalency of these approaches (which admittedly is based on low-quality evidence) is described in the recent American Academy of Pediatrics guideline on EOS as well.[9] The study by Joshi et al[8] also provides some reassurance that the approach of clinical monitoring of late-preterm and term infants at risk for EOS can potentially be safe (subject to the limitation of follow-up mentioned above) even if performed under the couplet care model and need not occur in the NICU.

Ultimately, clinicians should review the evidence to support each approach, incorporate local contextual and practice conditions, and develop a local guideline with a strong implementation strategy to ensure consistent practice in their institutions. They should also closely monitor the results of any practice change to identify unintended consequences and

ultimately ensure that they are achieving a balance between treating EOS early while avoiding needless antibiotics.

REFERENCES

1. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. *JAMA Pediatr*. 2017;171(4):365–371
2. Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease–revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10):1–36
3. Carola D, Vasconcellos M, Sloane A, et al. Utility of early-onset sepsis risk calculator for neonates born to mothers with chorioamnionitis. *J Pediatr*. 2018;195:48–52.e1
4. Berardi A, Tzialla C, Travan L, et al; GBS Prevention Working Group of Emilia-Romagna. Secondary prevention of early-onset sepsis: a less invasive Italian approach for managing neonates at risk. *Ital J Pediatr*. 2018;44(1):73
5. Higgins RD, Saade G, Polin RA, et al; Chorioamnionitis Workshop Participants. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. *Obstet Gynecol*. 2016;127(3):426–436
6. Hedegaard SS, Wisborg K, Hvas AM. Diagnostic utility of biomarkers for neonatal sepsis–a systematic review. *Infect Dis (Lond)*. 2015;47(3):117–124
7. Pammi M, Flores A, Versalovic J, Leeflang MM. Molecular assays for the diagnosis of sepsis in neonates. *Cochrane Database Syst Rev*. 2017;2:CD011926
8. Joshi N, Gupta A, Allan J, et al. Management of chorioamnionitis exposed infants in the newborn nursery using a clinical examination-based approach. *Hosp Pediatr*. 2019;9(4)
9. Puopolo KM, Benitz WE, Zaoutis TE; Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018;142(6):e20182894

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