

Antibiotic Stewardship

Reassessment of Guidelines for Management of Neonatal Sepsis



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KEYWORDS

• Antibiotics • Neonatal sepsis • Management • Guidelines

KEY POINTS

- The collective concerted efforts to reduce risk of early onset group B streptococcus since 1996, which have included use of antibiotics for large number of women and infants, have been successful.
- Information is emerging indicating that exposures to antibiotics may increase risk of future health problems, especially in preterm infants.
- Antibiotic stewardship is a current goal of the Centers for Disease Control and Prevention.
- Clinicians struggle with the decision to empirically treat well-appearing infants with risk-factors with antibiotics.
- Emerging large scale use of electronic health records may better inform the risk-benefit calculations that clinicians consider in deciding on use of empirical antibiotics for early onset sepsis.

DEFINING THE PROBLEM: EARLY ONSET SEPSIS

Epidemiologists define early onset sepsis (EOS) as culture positive infections occurring the first 3 postnatal days.^{1,2} The Centers for Disease Control and Prevention (CDC) defines early onset group B streptococcus (GBS) disease as blood or cerebral spinal fluid culture-proven infection occurring in the first 7 postnatal days.^{3,4} The National Institute of Child Health and Human Development's (NICHD) definition of EOS also requires that the infection be treated with antibiotics for 5 or more continuous days.² However EOS is defined, the obstetric and pediatric communities have collaborated to greatly reduce the risk of the major cause of EOS in term infants, GBS (*Streptococcus agalactiae*), since the CDC's first guidelines to reduce the risk were published in 1996.³ At the time the first guidelines emerged, the incidence of

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EOS in the United States was 3 to 4 cases per 1000 live-born infants.⁵ With guideline modifications in 2002 and 2010 strongly recommending universal screening, fine-tuning of culture methods, and intrapartum antimicrobial prophylaxis (IAP) drug choice when the mother is penicillin allergic, the incidence of EOS has decreased to 0.3 per 1000.^{2,4,6} GBS remains the leading cause of EOS in term infants, whereas *Escherichia coli* is most prevalent among premature infants.^{2,7}

At a population level, the 2- to 10-fold reduction in prevalence of EOS since 1996 is remarkable.^{2,8,9} The guidelines have saved lives. However, the guideline-based strategies that have led to this reduction have contributed to 30% of mothers in the United States receiving antibiotics during labor.^{8,10,11} On the neonatal side, single-center experiences and population estimates based on clinicians following the guidelines since the first were published indicate that 15% to 20% of term infants (more than 500,000 infants per year in the United States), most of whom are asymptomatic, are evaluated with screening blood tests for EOS and many also receive empirical antibiotics.¹¹⁻¹³

RISKS OF ANTIBIOTICS: WHY BE CAUTIOUS?

Adherence to the CDC's guidelines has resulted in significant decreases in EOS; but antibiotic exposures, in the absence of an identified infection to treat, do not seem to be totally without risk. The emerging evidence for risk provides a rationale for identifying mechanisms to limit antibiotic exposure initiation to infants at highest risk while missing extremely few if any infants with evolving infection and limiting the duration of antibiotics for those whose evolving clinical picture indicates an extremely low likelihood of infection. Aminoglycosides are among the most commonly used antimicrobials for the prevention and empirical treatment of EOS and have the potential to cause renal and ototoxicity.^{14,15} Among premature infants, the duration of the initial empirical course is associated with later-onset infection, necrotizing enterocolitis, and death.¹⁶⁻¹⁸

In a Swedish cohort, antibiotic exposure in the neonatal period was associated with almost triple the odds of later wheezing in infants 33 weeks of age and older.¹⁹ In a Dutch cohort, the use of neonatal antibiotics was associated with changes to the microbiome, which in turn were associated with atopic symptoms (eczema and wheeze).^{20,21} Although the information linking antibiotic exposure to wheezing and atopy via the microbiome is intriguing and biologically plausible, and animal studies have demonstrated the strong influence of neonatal antibiotics on later gut microbiome and respiratory outcomes,^{22,23} the investigators of meta-analyses of the cohort studies associating neonatal antibiotic exposures with later wheezing in children find that the associations are subject to bias and recommend caution before justifying the limitation of antibiotics for the purpose of avoiding asthma at the current stage of evidence accumulation.^{24,25} More immediately, clinicians and the community at large share the concern that overall use of antibiotics contributes to the development of resistant organisms, making careful and selective use of antibiotics to the highest-risk patients a universal goal. Antibiotic stewardship is the third of 4 core activities identified by the CDC to limit the development of antimicrobial-resistant organisms: (1) prevent infections, preventing spread; (2) tracking resistance patterns; (3) improving use of antibiotics; and (4) developing new antibiotics and diagnostic tests.²⁶

REVIEW OF PAST AND CURRENT CENTERS FOR DISEASE CONTROL AND PREVENTION GUIDELINES

The third and most recent iteration of the CDC's guidelines to prevent GBS perinatal disease was published in 2010.⁴ The CDC's initial and subsequent guidelines were the

combined efforts of the CDC and numerous professional societies and experts in obstetrics, pediatrics, and microbiology.³ The first guidelines suggested obstetric caregivers choose between a solely risk factor–based approach to the use of IAP or a universal screening of mothers plus risk factors–based approach to the use of IAP. In 2002, the CDC recommended universal culture–based screening of all pregnant women at 35 to 37 weeks' gestation to optimize the identification of women who should receive IAP.²⁷

The CDC's third and most recent version of the guidelines has been endorsed by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics (AAP), the American College of Nurse-Midwives, the American Academy of Family Physicians, and the American Society for Microbiology.⁴ Most of the changes between the second and third version of the guidelines deal with the antepartum approach to the mother and the laboratory methods used for the identification of GBS and testing for antimicrobial sensitivities. Although the CDC's initial guidelines recommended penicillin as the ideal choice for IAP for GBS because penicillin has a narrower spectrum of antimicrobial activity and, therefore, might be less likely to select for resistant organism than ampicillin, one clinical trial found that penicillin and ampicillin administered intravenously intrapartum were associated equally with the presence of ampicillin-resistant gram-negative organisms on postpartum vaginal-perineal culture.^{4,28} The CDC now defines adequate IAP as greater than 4 hours of intravenous penicillin, ampicillin, or cefazolin before delivery.⁴

The CDC's 2010 guidelines also include a revised algorithm for the management of newborns with respect to the risk for early onset GBS disease that, if followed, could reduce antibiotic exposures among asymptomatic infants with risk factors compared with the earlier guidelines (Fig. 1). The 2010 guidelines state that the algorithm applies to all newborns, not just term and near-term infants. One very strong point made in the guidelines is that infants with signs of sepsis should receive a full diagnostic evaluation and receive antibiotic therapy pending the results.⁴ The full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including differential and platelet count, a chest radiograph if respiratory signs are present, and a lumbar puncture if the newborn is stable enough to tolerate the procedure and sepsis is highly suspected. Empirical therapy should include antimicrobial agents active against GBS (including intravenous ampicillin) as well as other organisms that might cause neonatal sepsis, such as *E coli*.

Well-appearing infants whose mothers had been identified as having chorioamnionitis, a difficult clinical diagnosis to make but one associated with 2- to 3-fold increase in odds of EOS,^{12,29} should have diagnostic tests including a CBC and a blood culture and be started on empirical antibiotics while awaiting culture results. In the CDC's 2010 algorithm, the asymptomatic infants whose mothers were diagnosed with chorioamnionitis are the only asymptomatic infants that are to receive empirical antibiotics. The CDC's guidelines acknowledge the poor positive predictive value of the CBC indices, particularly when the CBC is obtained at birth compared with results from samples obtained between 6 and 12 postnatal hours; but even results obtained at 6 to 12 hours are poor predictors of positive cultures.^{11,30,31} Although the CDC recommends that the CBCs and differentials and platelet counts are examined, they provide no guidance on normal ranges or advice on what clinicians should do with the results. For newborns whose mothers had chorioamnionitis and are started on empirical antibiotics, no guidance on how the results should influence the duration of antibiotics if the culture remains negative is provided.⁴

For infants with risk factors other than chorioamnionitis, the CDC's 2002 guidelines³² recommended broad use of a "limited evaluation," which included a blood

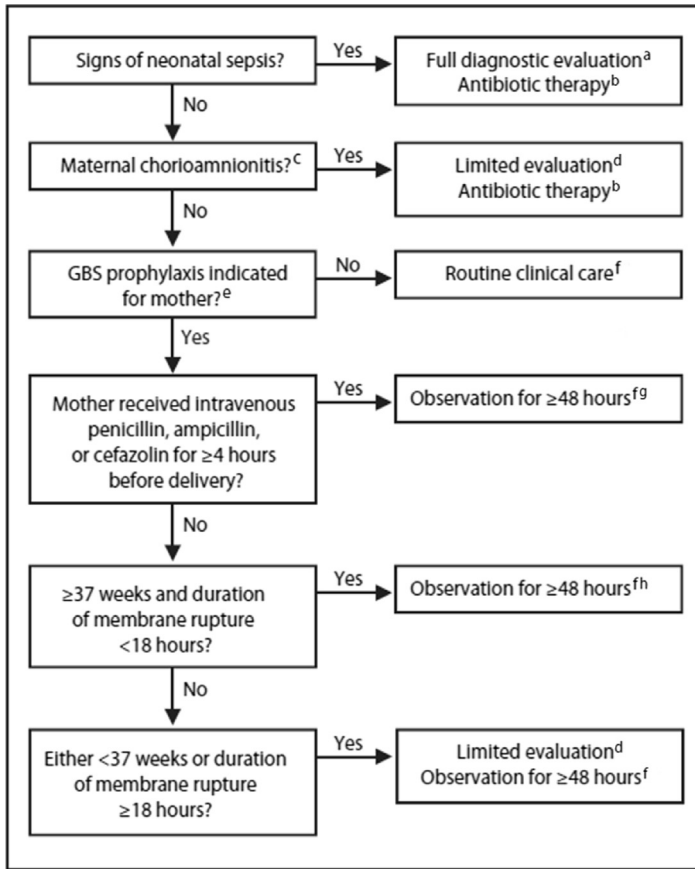


Fig. 1. The CDC's 2012 algorithm for secondary prevention of EOS GBS disease among newborns. ^a Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patients are stable enough to tolerate procedure and sepsis is suspected). ^b Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns. ^c Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific. ^d Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life). ^e Indications for intrapartum prophylaxis to prevent early onset group B streptococcal (GBS) disease. ^f If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated. ^g If 37 weeks' gestation or greater, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions are not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved. ^h Some experts recommend a CBC with differential and platelets at 6 to 12 hours of age. (From Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep* 2010;59:22.)

culture at birth and a CBC with differential and platelet count at birth and/or at 6 to 12 postnatal hours. All infants born to mothers with inadequate IAP were to have the limited evaluation. In the 2010 guideline, the CDC recommends that well-appearing infants who are 37 weeks' or more gestation whose mothers had an indication for GBS prophylaxis but received inadequate or no IAP can be managed with observation alone for 48 hours or more without diagnostic tests. For infants with inadequate IAP who are less than 37 weeks' gestational age or for infants of any gestational age whose membranes were ruptured 18 hours or more before delivery, the CDC recommends observation for 48 hours or more plus the limited evaluation but no empirical treatment unless there are clinical signs of sepsis. If signs develop, a full evaluation should be undertaken. For well-appearing late preterm infants who are 35 to 36 weeks' gestation whose mothers received adequate IAP, the CDC's 2010 guidelines do not recommend diagnostic evaluations. Evidence for these last 2 recommendations, both regarding preterm infants, arises from "opinions of respected authorities based on clinical or laboratory experience, descriptive studies, or reports of expert committees."⁴

AMERICAN ACADEMY OF PEDIATRICS COMMITTEE ON THE FETUS AND NEWBORN

In 2011, the AAP published an overall agreement with the CDC's guidelines.³³ Although the AAP's 2011 paper reviewed and summarized the CDC's guidelines, in 2012, the AAP's Committee on the Fetus and Newborn (COFN) took a step further and published a clinical report with a goal to "provide a practical and, when possible, evidence-based approach to the management of infants with suspected or proven early-onset sepsis."³⁴ The report provided a valuable and thorough review of the background behind the CDC's guidelines to reduce GBS EOS; information about the accuracy, reliability, and validity of the various diagnostic strategies for EOS; as well as a review of treatment strategies for EOS. The COFN's report included recommendations for the use of diagnostic tests and empirical treatment and also important variations from the CDC's guidelines and made a first attempt at giving guidance for the duration of empirical antibiotics in infants without signs of infection whose mothers had risk factors but whose cultures remained negative.

The first departure from the CDC's guidelines was the COFN's recommendation that preterm infants born to mothers with chorioamnionitis, rupture of membranes of 18 hours or more, or inadequate IAP have laboratory examinations drawn plus empirical treatment of a minimum of 72 hours. The COFN based this variation, which increased the number of infants to be treated compared with the CDC, on the higher risk of infection in premature infants compared with term infants when any of these risk factors were present.³⁵

In addition to the guidance for starting empirical antibiotics in premature infants, the COFN provided 2 algorithms to apply to asymptomatic infants whose mothers had risk factors for EOS, one for infants less than 37 weeks' gestation and one for infants aged 37 or more weeks whose mothers had chorioamnionitis. In the algorithm for premature infants, those with maternal risk factors (chorioamnionitis or prolonged rupture of membranes 18 hours or more or inadequate IAP) should have screening laboratory examinations, including blood culture at birth and a CBC and differential plus/minus a c-reactive protein (CRP) between 6 and 12 postnatal hours, and initiation of empirical antibiotics. If the culture was positive, antibiotics should continue; if the blood culture was negative and the infant remained well, antibiotics should stop. If the blood culture was negative and the infant was well, but the 6- to 12-postnatal hour laboratory examinations were abnormal, the COFN recommended continuation of empirical antibiotics

without a recommended duration. Similarly, for infants who are 37 weeks' or more gestation whose mothers were diagnosed with chorioamnionitis, cultures should be drawn at birth, screening tests should be drawn between 6 and 12 postnatal hours, and empirical antibiotics started, similar to the CDC's 2010 guidelines. Antibiotics would be continued in well-appearing infants if the culture was positive or if the culture was negative but the laboratory data were abnormal and the mother had received antibiotics during labor and delivery. As with the premature infants with abnormal screening tests, neither the duration of this continuation of empirical antibiotic treatment nor guidance on the degree of variance from normal to define abnormal screening laboratory results were provided.³⁴

IMMEDIATE RESPONSE TO THE COMMITTEE ON THE FETUS AND NEWBORN'S 2012 GUIDELINES

The pediatric community responded to the COFN's clinical report with 4 letters to the editor.^{9,36–38} The writers pointed out that the approach to the asymptomatic premature infant whose mother had chorioamnionitis, prolonged rupture of membranes, or inadequate IAP differed from the CDC's approach, which included only screening laboratories. The COFN's strategy would lead to more empirical antibiotic use than following the CDC's guideline. The writers also expressed concern that the COFN's suggestions would increase the duration of empirical antimicrobial courses in well-appearing infants based on tests with poor positive predictive value. The writers also pointed out the potential of biomarker tests other than the CBC and differential and CRP that could have value.^{9,36–38} One writer offered the suggestion of assessing maternal temperature instead of trying to define chorioamnionitis, referring to the development of an online EOS risk calculator based on the assessment of 350 cases of EOS matched 3:1 with controls taken from a population of more than 600,000 infants born at 34 weeks or more at 14 California and Massachusetts hospitals.^{9,11}

In the immediate response to these letters, the COFN's authors identified the number of days of empirical antibiotics an asymptomatic infant born to a woman treated with antibiotics for chorioamnionitis or for EOS risk factors should receive if the laboratory studies were abnormal as a major area of uncertainty in the prevention of EOS.³⁹ They modified their stance on continuing antibiotics when the results were abnormal and maintained their stance on treating premature infants with mothers with risk factors. Modifying the stance on continuation of antibiotics when laboratory results are abnormal they stated: "We would not treat a well-appearing, asymptomatic term infant with a negative blood culture longer than 48–72 hours, whose mother was treated for chorioamnionitis, even when the infant's laboratory data are abnormal."³⁹ They cited the CDC's 2010 guidelines report as providing rationale for this approach (ie, a normal physical examination at 48 to 72 hours in an otherwise well infant should exclude the possibility of EOS).⁴ For premature infants, the COFN justified the recommendation for empirical therapy initiation for asymptomatic preterm infants whose mothers had risk factors with the fact that the preterm infants are at a higher risk of EOS than term infants with maternal risk factors.³⁵ The COFN's response to the query on potential biomarkers was that more study was needed before widespread adoption and, although they liked the potential to use the risk-of-EOS calculator, which included maternal temperature during labor to quantify the risk rather than the categorical definition of chorioamnionitis, and acknowledged its use would likely decrease the number of sepsis evaluations in the late preterm and term populations,¹¹ they thought it should be validated in more studies. In summary, they said that the COFN's revised algorithms would be forthcoming.³⁹

THE NEXT ROUND

In 2013, before the publication of the COFN's revised algorithms published in June 2014, Brady and Polin⁴⁰ wrote independently with the purpose "to clarify AAP policy" on EOS, acknowledging the differences between the CDC's 2010 guidelines and the COFN's 2012 clinical report.^{34,40} They reinforced the revised guidance on antibiotic duration provided in the response to the letters that followed the COFN's 2012 clinical report's guidance, which emphasized continuing empirical antibiotics based on persistently abnormal physical examination findings rather than laboratory values.⁴⁰ They pointed out that the COFN's 2012 clinical report noted that in some situations, approaches that differed from the 2010 CDC Guidelines could be altered, and may depend on local practice and resources. The 2013 commentary by Brady and Polin⁴⁰ states that the guidelines from the COFN and CDC concur in 2 situations: (1) symptomatic infants should be treated with broad-spectrum antibiotics and (2) healthy-appearing term and preterm infants whose mothers had chorioamnionitis should have a blood culture at birth, have empirical treatment started, and have laboratory examinations drawn between 6 and 12 postnatal hours (a CBC with differential plus/minus CRP); but the CDC did not offer guidance on what to do with the laboratory results.⁴⁰

The COFN and CDC still differed in the approach to 2 situations. First, for well-appearing term infants whose mothers did not have chorioamnionitis but who had an indication for IAP and were inadequately treated, the CDC and COFN agree that these infants can be observed without additional testing if rupture of membranes (ROM) is less than 18 hours. The COFN thinks infants who are 35 and 36 weeks' gestation can be treated similarly. Differences between the CDC and COFN arise if ROM is 18 hours or more and IAP is inadequate. The CDC's guidelines recommend a limited evaluation, which would include a CBC with differential at birth or 6 to 12 postnatal hours and hospital observation for 48 hours.⁴ The COFN recommends observation for 48 hours, without the laboratory tests, unless close observation is not possible.⁴⁰ The second area of discrepancy is for well-appearing infants less than 37 weeks' gestation whose mothers did not have suspected chorioamnionitis but had another indication and did not receive adequate IAP. The CDC recommended a limited evaluation (blood culture and CBC) and observation in the hospital for 48 hours, whereas the COFN recommended a CBC plus/minus CRP obtained between 6 and 12 postnatal hours and only obtaining a blood culture if antibiotics were to be started because of abnormal laboratory values. This statement seems to differ from the algorithm in the COFN's 2012 clinical report, which provides guidance for infants less than 37 weeks' gestation with inadequate IAP, including obtaining laboratory tests, a blood culture, starting empirical antibiotics (while obtaining the culture and awaiting laboratory results), and continuing antibiotics if the laboratory results were abnormal.^{35,40}

The final recommendation in the 2013 commentary by Brady and Polin⁴⁰ points out that the CDC did not address the duration of empirical antibiotic treatment. The COFN made their initial recommendations based on laboratory testing results and then reiterated their written response to the community comments on their clinical report: "healthy-appearing infants without evidence of bacterial infection should receive broad-spectrum antimicrobial agents for no more than 48 hours. In small premature infants some may continue antibiotics for up to 72 hours while awaiting bacterial culture results."⁴⁰ There was no further discussion or a definition of the levels of laboratory values to consider abnormal or whether the abnormal laboratory values should be considered evidence of infection that could drive clinicians to continue empirical treatment and how many more days of empirical antibiotics should be continued.

IMPACT ON PRACTICE AND THE LATEST WORD FROM THE COMMITTEE ON THE FETUS AND NEWBORN

Clinicians may feel the need to use the CBC and differential and other biomarker tests, such as CRP, because of the potential for false-negative results from blood cultures, especially in cases when the blood sample volume is low or when intrapartum antibiotics have been administered.^{35,41} When laboratory values, particularly the CBC, differential, and CRP, are measured in cases of asymptomatic infants born to mothers with risk factors, the prevalence of abnormal results can be quite high. Jackson and colleagues⁴² reported on 2427 neutrophil counts and ratios of immature to total neutrophil (I:T) obtained during the first 24 postnatal hours from 856 infants born to mothers diagnosed with chorioamnionitis. Ninety-seven percent of symptomatic infants had abnormal neutrophil counts; 99% of the asymptomatic infants had an abnormal neutrophil count, immature neutrophil count, or I:T ratio.⁴²

More recently, Kiser and colleagues⁴³ reported their center's experience managing infants whose mothers had chorioamnionitis. Their local guideline resembled the algorithm for the management of infants born to mothers with chorioamnionitis provided by the COFN in 2012, with the inclusion of continuing antibiotics to 7 days in asymptomatic infants who had abnormal CBC or CRP results. Of the 554 infants studied, 4 (0.7%) had positive cultures and 22 (4%) were treated for sepsis based on clinical signs without a positive culture. One hundred twelve (20.2%) asymptomatic infants were treated with prolonged antibiotics based on abnormal laboratory data. Most of the infants also had spinal taps, and none had a positive cerebrospinal fluid culture.

Following up on the pledge to provide revised algorithms and concurrent in the issue of *Pediatrics* that included Kiser and colleagues'⁴³ report, Drs Polin, Watterburg, Benitz, and Eichenwald⁴⁴ wrote a commentary on the "Conundrum of Early-Onset Sepsis." The researchers acknowledge that deciding how best to evaluate and treat an infant at risk for EOS is exemplary of every clinician's never-ending dilemma of dealing with the real world where decisions for individual patients are made absent informative results from high-quality randomized trials. To that point, they summarize Kiser and colleagues'⁴³ finding that, based on an algorithm similar to the COFN's 2012 algorithm and consistent with Jackson and colleagues'⁴² earlier report, many asymptomatic term infants born to women with chorioamnionitis would receive prolonged antibiotic courses, counter to the COFN's revised statement that healthy-appearing infants with negative cultures should receive no more than 48 to 72 hours.^{40,43,44} They further clarified that healthy-appearing infants with negative cultures should have antibiotics stopped "even when the infant's laboratory results are abnormal."^{39,44} For Kiser and colleagues'⁴³ cohort, this could have decreased the percentage of infants treated for greater than 48 hours from 24% to 4%.⁴⁴ Polin and colleagues⁴⁴ go on to make several conclusions from the accumulating evidence and experience, including that the physical examination is as good or better than most laboratory tests in "ruling in or ruling out sepsis," and that "commonly used laboratory tests have a limited positive predictive accuracy and should never be used as a rationale to continue treatment in an otherwise healthy term infant at 48–72 hours of life."⁴⁴ They cite the 2012 clinical report³⁴ for the conclusion that "laboratory tests should never be used," although that report included the algorithm that guided clinicians to continue treatment if the laboratory values collected between 6 and 12 postnatal hours were abnormal.

The authors of this most recent commentary then makes 3 suggestions for the management of newborns suspected of EOS: (1) antibiotics may be discontinued by 48 hours in well-appearing term newborns born to women with chorioamnionitis; (2) longer (to 72 hours) empirical treatment might be considered for premature infants or

infants with abnormal screening studies; and (3) lumbar punctures are recommended in cases whereby the blood culture is positive, the infant does not improve on appropriate antimicrobial coverage, or the clinician views the infant as having a high probability of sepsis because of clinical signs or abnormal laboratory data.⁴⁴ So with this latest update, the author allows (without recommending) the laboratory values to influence the decision to treat longer than 48 hours and whether a spinal tap is done or not.

WHERE DO WE GO NEXT?

The COFN panel acknowledges that they are breaking new ground with their evolving recommendations on the duration of empirical therapy and the lack of strong data to support their decisions.⁴⁴ We await either cohort study data or randomized trials of the COFN's 2012 clinical report approaches, like Kiser and colleagues'⁴³ cohort study, versus the COFN's 2012 in-reply approaches, which, for the most part, disregard the ancillary tests. Choosing an outcome of greatest importance that is feasibly measured (more likely hospital readmissions rather than wheezing at school age) but has a low incidence (4 of 404 readmitted for fever or suspected sepsis in Jackson and colleagues'⁴² cohort study) will make such a study challenging. For a study to have 90% power to detect a difference between a 1% rehospitalization rate for suspected infection in infants managed with a strategy of giving empirical antibiotics for longer than 2 to 3 days versus 3% among infants managed with an approach that stopped empirical antibiotics after 48 hours regardless of laboratory values like the more recent modified recommendation^{39,44} with an alpha of 0.05, 1028 infants would be needed for each study arm. Not insurmountable, but this type of study may be hard to do given the strength of entrenched local opinion on a specific clinical approach and the challenges of achieving equipoise among clinicians and families agreeing to enroll their newborn into the study and not entrusting their own doctor with the decision.

In addition to the duration of antibiotics questions, alternatives to the CDC and COFN's algorithms to obtain diagnostic tests based on the risk factors inclusive of chorioamnionitis and start treatment warrant some discussion. Chorioamnionitis can be a subjective definition, and obstetricians wishing to maximize the likelihood that mothers and infants stay together and get discharged to home in the first postnatal day may avoid classification of a mother as having chorioamnionitis.^{9,12} Escobar and colleagues¹² and Puopolo⁹ acknowledge this clinical reality and propose that we adopt a multifactor assessment approach that includes the objective measure of maximum maternal temperature in labor in calculating the odds ratios for sepsis in infants. Clinicians could use the calculated odds ratio based on the Web-available tool that is the product of their cohort study to develop an individualized approach for each infant, incorporating known, objective maternal risk factors. This clinical tool is available as an online tool: <http://www.dor.kaiser.org/external/DORExternal/research/InfectionProbabilityCalculator.aspx>.^{6,9,12}

Finally, all the investigators of the commentaries, guidelines, and clinical reports agree that infants with signs of infection deserve treatment, even when intrapartum antibiotics were used. Escobar and colleagues¹² reported much higher odds of EOS among symptomatic versus asymptomatic infants evaluated for EOS, but the asymptomatic infants with risk factors still had higher odds of EOS than the overall population rate.¹² That said, most clinicians would agree that for term and later preterm infants, there is some tolerable duration of signs to resolve that would allow for not treating, especially in the absence of risk factors. In the last report by Polin and colleagues,⁴⁴ they say, "Symptomatic neonates without risk factors for infection (who improve over the first 6 hours of life)

may not require treatment, but must be monitored closely.”⁴⁴ The severity of the clinical signs must also be considered and a shorter duration tolerated before empirical antibiotics are started when a variation from the expected norms are extreme.

SUMMARY

Since their inception in 1996, the guidelines aimed at preventing perinatally acquired GBS, and indirectly EOS, have led to a significant reduction in EOS and EOS-related mortality. In their 2010 iteration, the CDC’s guidelines have narrowed the categories of infants who receive empirical antibiotics from prior versions and continue to recommend laboratory tests in the evaluation of infants at risk for EOS. The COFN has taken steps into the less-charted waters of the duration of empirical antimicrobial therapy for suspected EOS but, more recently, have reconsidered the reliance of abnormal laboratory test results to drive the duration of empirical antibiotics beyond 48 to 72 post-natal hours. Undoubtedly, the guidelines from the CDC and the COFN will continue to adapt to emerging evidence on the contributions of novel biomarkers as we learn more about the intricacies of the newborn’s response to infection.^{45–47} While we await the future guidelines and better predictive value from novel biomarker tests and combinations of risk factors and biomarker levels, following the COFN’s most recent compilation of recommendations, basing the initiation of treatment on the presence and persistence of signs of infection and basing the duration of treatment primarily on the presence of signs in the absence of positive cultures seem reasonable. The ancillary tests may inform clinicians and provide rationales for closer observation and even longer empirical treatment when clinical signs are equivocal or complete resolution is delayed.

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