Duration of empirical antibiotic therapy for infants suspected of early-onset sepsis

C. Michael Cotten and P. Brian Smith

Purpose of review
Clinicians' adherence to the Centers for Disease Control guidelines to prevent group B Streptococcus (GBS) early-onset sepsis (EOS) has reduced GBS EOS. Although evidence-based testing and empirical antibiotic initiation are likely saving lives, clinicians have less compelling data to guide duration of empirically initiated antibiotics when cultures remain sterile and clinical signs resolve quickly. Our purpose is to review current opinions and evidence influencing clinicians' choices for duration of empirically initiated antibiotics in newborns with sterile cultures.

Recent findings
Retrospective cohort studies indicate potential for harm with longer duration of empirical antibiotics for EOS when cultures are sterile. Cohort studies indicate timing of widely used tests used to estimate EOS risk affects their predictive value, and tests acquired 24–48 h postnatally may provide reassurance for safe discontinuation.

Summary
Every day clinicians caring for thousands of neonates in the United States stop antibiotics which were started empirically to treat EOS on the first postnatal day. Evidence is lacking to support a universal approach to decisions on duration of empirical antibiotics when cultures remain sterile. Reviewing predictive value relative to timing of laboratory testing can help clinicians develop locally appropriate antimicrobial duration decision-making guidelines.

Keywords
early-onset sepsis, empirical antibiotics, neonate, group B Streptococcus, C-reactive protein

INTRODUCTION

Early-onset sepsis (EOS) is characterized by bacteremia, pneumonia, and meningitis, and positive blood or cerebrospinal fluid (CSF) cultures obtained in the first 3 postnatal days. EOS affects an estimated 0.7% of newborns annually in the United States, resulting in 3300 cases per year [1▪▪,2▪▪]. An estimated 390 deaths per year are attributable to EOS [1▪▪,2▪▪,3]. Because of its dire consequences, the subtleties of clinical presentation, and current guidelines for empirical antimicrobial treatment based on antenatal risk factors for group B Streptococcus (GBS) EOS, the most common EOS pathogen, US clinicians empirically treat approximately 30% of mothers antenatally and approximately 10% of newborns with antibiotics in the first postnatal days [1▪▪,4]. These widespread antibiotic exposures have reduced GBS EOS by 80% since the first GBS prevention guidelines published in 1996 [1▪▪,2▪▪,5▪]. Epidemiologic evidence of increased mortality and morbidity among premature neonates with sterile cultures and long empirical antibiotic courses has recently emerged, and there are increasing concerns over rising antimicrobial resistance among common pathogens (two-thirds of isolates from *Escherichia coli* samples from infants with EOS are ampicillin resistant) [1▪▪,2▪▪,6–8]. In this brief review, we discuss the impact of guidelines on clinicians' approach to EOS and discuss use of laboratory tests that influence decisions to stop empirical antibiotics for EOS when cultures remain sterile.

Division of Neonatology, Department of Pediatrics, Duke University, Durham, North Carolina, USA

Correspondence to C. Michael Cotten, MD, MHS, Department of Pediatrics/Neonatology, 2424 Erwin Road, Suite 504, Duke University Medical Center, Box 2739, Durham, NC 27710, USA. Tel: +1 919 681 4844; fax: +1 919 681 6065; e-mail: cotte010@mc.duke.edu

Curr Opin Pediatr 2013, 25:000–000
DOI:10.1097/MOP.0b013e32835e01f6

KEY POINTS

- CDC and AAP guidelines have significantly reduced GBS EOS, but a large number of mothers and uninfected neonates receive antibiotics.
- Evidence of risk from prolonged antibiotic therapy when cultures are sterile and ongoing concerns of antibiotic resistance stimulate development of strategies to safely minimize antibiotic exposure in neonates.
- Use of currently available diagnostic tests, particularly CRP, at 24 and 48 h after initiation of empirical antibiotics for EOS can help in decisions regarding duration.

When is continuation of empirical antibiotics beyond 48 h indicated?

Neonates with positive cultures should be continued on antimicrobials, and the duration should be based on the accumulated evidence of susceptibility for the specific organism [5▪].

Neonates with clinical signs consistent with infection that persist beyond the first postnatal day should also receive longer courses, as the more severe the signs (need for mechanical ventilation and pressors), the more likely a culture will be positive [4]. Continuation of antimicrobial therapy in the absence of positive cultures for persistently sick neonates is in part due to the potential false negative sterile blood or spinal fluid culture. Most centers use rapid bacterial growth cultures such as BACTEC systems (Becton Dickinson, Sparks, Maryland), with a high likelihood of identifying bacteria in 1 ml samples [9]. Some consideration must be given to those situations when a low bacterial inoculum, not detectable in small volume samples, is still capable of causing significant morbidity [10]. Antibiotic exposure prior to obtaining cultures may reduce likelihood of identifying an organism with traditional culture methods; however, data suggest that, even when intrapartum antibiotics are used, pathogens can grow in blood cultures from infected infants [9].

When should antibiotics be discontinued at 48 h and can the complete blood count help?

Neonates started on empirical antibiotics for EOS who have sterile cultures, with no signs of infection, and normal screening laboratory examinations should have antimicrobials stopped. In a single center study of over 3000 patients admitted to the neonatal intensive care unit (NICU) who had a blood culture and complete blood count (CBC) obtained in the first postnatal hour, and a repeat CBC again at 8–12 h, none of the 1539 neonates (49%) who had two normal immature to total neutrophil (I : T) ratios and a negative blood culture at 24 h subsequently developed sepsis [11▪].

In cases in which risk is perceived as higher and initial clinical signs are more numerous (tachypnea, hypoglycemia, hypothermia) but transient, clinicians may turn to the negative predictive values of additional testing to validate decisions to discontinue empirical antibiotics if clinical signs are resolved by the first 24 postnatal hours. In the algorithm first proposed by Committee on Fetus and Newborn (COFN), antibiotics are to be continued if 'laboratory data are abnormal', with no designation of when the laboratory tests should be obtained or how long they should be continued [12▪]. An appropriately timed laboratory test, particularly a CBC, as well as ancillary tests such as C-reactive protein (CRP), can provide reassurance that sepsis is unlikely when cultures are negative and neonates have no clinical signs of sepsis.

In a cohort of 1665 asymptomatic neonates with blood cultures and CBCs obtained at 4 postnatal hours and maternal risk factors for EOS, 17 (10%) were diagnosed with presumed sepsis in the absence of a positive culture [13]. Of the initially 1665 asymptomatic neonates, 454 (27%) had abnormal CBCs at 4 postnatal hours, including seven of the 17 eventually diagnosed with presumed sepsis. Nearly all (91%) with diagnosis of sepsis had more than one sign/symptom, and 77% had at least three. This study reinforces the challenge in interpreting a single CBC obtained in the first postnatal hours as the basis for initiation of empirical therapy, or as a basis for decisions for subsequent management at the end of 48 h of empirical treatment if clinical signs resolve and cultures remain sterile.

In another cohort study, the utility of CBC and differential was assessed in 856 term and near term neonates exposed to clinical chorioamnionitis and started on empirical antibiotics. Ninety-six percent of the 856 remained asymptomatic and had sterile cultures. All were treated with empirical antibiotics for 48 h. Asymptomatic neonates with an I : T value on either the second (12 postnatal hours) or third (24 postnatal hours) CBC were examined within 10 days of discharge by one of the investigators, and the parents were contacted by telephone within 3 weeks. Those with normal I : T ratios were followed by phone contact or in person within 3 weeks of discharge. Among asymptomatic neonates with three CBCs (first postnatal hour, 12, 24 h), 99% had at least one abnormal value on total neutrophils, I : T ratio, or total immature neutrophil count. If only CBCs from 12 and 24 postnatal hours were analyzed, 79% of asymptomatic neonates had at

least one abnormal value. Four neonates had positive blood cultures, and, although the CBCs in those four infants had abnormalities, only half of the I : T values in these four neonates were elevated. Of the asymptomatic neonates, 92% were followed in person or by telephone. Of those followed by telephone ($n = 373$), eight (2.1%) were readmitted in the month following discharge; none had culture-proven infection [14]. The authors concluded that extended antibiotic therapy should be reserved for neonates with clinical signs of infection (for example, respiratory distress, feeding disorders, apnea, temperature instability) and/or those who have a positive blood culture within 48 h [14]. We concur with this assessment and strongly consider other tests (such as CRP) before extending empirical antibiotic duration beyond 48 h.

We propose that abnormal CBCs (low absolute neutrophil count or high I : T ratios), obtained at or beyond the first 4 postnatal hours [15], reinforce the need to be on antibiotics at that time. However, we would support stopping antibiotics at 48 h, despite an abnormal initial CBC, if repeat testing at 24–48 h was reassuring, given the low likelihood of positive cultures in the absence of clinical signs.

Does a C-reactive protein at 24 and 48 h help to decide the duration of empirical antibiotic therapy?

Benitz *et al.* [16] reported on CRP levels in 1002 neonates with suspected EOS. Twenty (2%) neonates had culture-proven EOS, whereas 74 (7.4%) had probable sepsis with clinical signs but sterile cultures. CRPs drawn 24 h apart on the second and third postnatal days had negative predictive values of 99.7% for proven and proven or probable EOS. Three normal CRP levels were obtained in 694 of the 1002 neonates evaluated for EOS. Seventy-two percent of the neonates had antibiotics discontinued within 3 days; however, 13 infants required reevaluation for suspected infection within 14 days of the initial sepsis evaluation. Five of those infants were infected, none with GBS or *E. coli*. The authors concluded that two CRP levels less than 1 mg/dl obtained 24 h apart, 8–48 h after presentation, indicate that bacterial infection is unlikely, but the sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy.

Ehl *et al.* [17] determined CRP levels in 176 neonates with birth weight more than 1500 g suspected to have EOS. None of the 84 asymptomatic neonates with reassuring CRPs (<10 mg/l) at 24–48 h (in whom antibiotics were stopped) had a positive culture. Eighty-two neonates with CRP more than 10 mg/l were randomized to have daily CRPs and antibiotics stopped when the CRP was less than 10 mg/l (group 2a), or 5 days of additional antibiotics (group 2b). Group 2a averaged 3.7 additional days of antimicrobials, and group 2b averaged 5.5 days. One group 2b patient, who initially received 6 days of antibiotic treatment for blood culture-positive infection with GBS, was readmitted 14 days after discharge with positive CSF culture for GBS. These results provide a single center's reassurance regarding utilization of CRPs to guide stopping antibiotics at 48 h in neonates with sterile cultures. The results do not provide reassurance that 6 days is an adequate duration of treatment for group B streptococcal EOS, although we concur with the authors that even treatment periods longer than the 6 days used in this infant do not rule out the possibility of a second infectious episode. We agree that there is reasonable evidence to support use of serial CRP measures at 24 and 48 h to provide guidance on continuation of empirical antibiotics if clinical signs were present in the first 24 postnatal hours and resolved, or CBC parameters were abnormal but the clinical examination was normal throughout.

Why does duration matter?

Concerns about duration of antimicrobials arise from recent cohort studies showing associations of empiric treatment with antibiotics (≥5 days) with mortality, necrotizing enterocolitis (NEC), and subsequent infection. A report from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network demonstrated a positive association between longer (≥ 5 days) initial empirical antibiotic courses and increased mortality and morbidities among 4039 extremely low-birth weight neonates [6].

A study of 365 neonates (≤32 weeks, gestational age and ≤1500 g birth weight) who survived the first postnatal week without sepsis and NEC also found that duration of initial empirical antibiotics was an independent risk factor for the composite outcome: late-onset sepsis (LOS), NEC, or death. In the multivariable analysis, odds of the composite outcome were increased among neonates with at least 5 days of exposure to empirical antibiotics (odds ratio = 2.55; 95% confidence interval 1.12–6.30) [8].

INTERNAL EXPERT PANELS

Because of the potential harm from unnecessarily long courses, the potential for catastrophic relapse with inadequate treatment, and the potential for emergence of antibiotic resistance in episodes of

overuse, programs for antimicrobial stewardship are emerging [18▪]. In nurseries and NICUs, physicians' practices vary widely, which provides a rationale for audit and feedback interventions to understand and possibly limit variation and determine whether practice uniformity leads to improved outcomes [19,20]. Such programs have successfully limited vancomycin use in NICUs, but impact of antibiotic stewardship activities on duration of empirical antibiotics with sterile cultures has not been reported [21].

NEXT STEPS

Experts concur that antibiotics should be given promptly if there is a possibility of EOS, and stopped 36–48 h in an asymptomatic baby if laboratory results are consistently normal, there is no subsequent clinical evidence of infection, and cultures remain sterile [12▪]. The presence of abnormal clinical laboratory results in a well-appearing infant is a legitimate source of concern. There is no absolute clear consensus on well-informed approaches, mostly due to the lack of large-scale studies [12▪,22,23▪]. We believe that, if concerns over abnormal CBC parameters persist in a well-appearing child with a sterile culture, then a CRP, repeated 24 and 48 h after initiation of empirical antibiotics, may be helpful to clinicians making these decisions.

A large-scale cohort study that includes postdischarge monitoring of asymptomatic or transiently symptomatic neonates treated with 36–48 h of empirical antibiotics for EOS, with sterile cultures, and abnormal CBCs during the first 24 postnatal hours would be extremely helpful to clinicians. Such a study would provide information on the prevalence of subsequent infection or relapse of infection relative to laboratory values. Current studies are inadequate to specify appropriate testing and timing of testing in all situations in which empirical antibiotics have been started. While we await more comprehensive data and improved diagnostic testing, we offer suggestions for duration of empirical antibiotics once they are started for risk factors such as chorioamnionitis, as suggested by Centers for Disease Control (CDC) and COFN [5▪,12▪], and premature neonates born to a woman with risk factors, as recommended by COFN [12▪,23▪].

CONCLUSION

We acknowledge the limitations in the evidence to guide decisions regarding duration of empirical antibiotics for EOS for every situation. We also acknowledge that clinicians have to make these decisions daily, and we offer suggestions for approaches to term and near term neonates who were started on empirical antibiotics to treat EOS, and whose cultures are sterile at 48 postnatal hours.

Term/late preterm neonates started on empirical antibiotics for EOS with sterile cultures at 48 postnatal hours and with the following conditions:

(1) Clinical signs of infection that persisted over 24 h: recommended duration treatment 7 days.
(2) Clinical signs initially absent, but became apparent after first postnatal hour and persisted more than 24 h: recommended duration treatment 7 days.
(3) Laboratories drawn for risk factors, clinical signs absent, initial (4 postnatal hours) laboratory CBC normal: recommended duration treatment 48 h.
(4) Laboratories drawn for risk factors, clinical signs transient (resolved <24 h), initial CBC abnormal: obtain CRP at 24 and 48 h. If CRPs are low, clinical examination remains normal: stop antibiotics at 48 h.

Acknowledgements

C.M.C. received salary support for research from the National Institutes of Health and the US Department of Health and Human Services (NICHD 5U10 HD040492–10; DHHS-1R18AE000028-01; NHLBI 1R01 HL105702 01A1; NIHSBIR: 2R44HD062316–02; NICHD 5R01HL085703-04).

P.B.S. received salary support for research from the National Institutes of Health and the US Department of Health and Human Services (NICHD 1K23HD060040-01 and DHHS-1R18AE000028-01).

The authors would like to acknowledge the ongoing support, mentorship, and insights into clinical care offered by Drs Ronald Goldberg and Daniel K. Benjamin, Jr at Duke, and colleagues in the NICHD Neonatal Research Network and Pediatrix medical group. They thank them for ongoing collaborations that aim to improve outcomes for neonates.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Weston EJ, Pondo T, Lewis MM, *et al.* The burden of invasive early-onset ▪▪ neonatal sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011; 30:937–941.

This comprehensive paper is one of the first to review all EOS, and not focus only on GBS.

2. Stoll BJ, Hansen NI, Sánchez PJ, *et al.* Early onset neonatal sepsis: the burden ■■ of group B Streptococcal and *E. coli* disease continues. Pediatrics 2011; 127:817–826.

Like the study by Weston *et al.*, this report from the NICHD Neonatal Research Network reviews all EOS, and presents important trends in *E. coli* antimicrobial resistance emergence and variation in pathogen prevalence between neonates of different race and ethnicity, and between term and preterm neonates.

3. Xu J, Kochanek KD, Murphy SL, *et al.* Deaths: final data for 2007. National Vital Statistics Reports Web Release. Vol. 58. Hyattsville, MD, USA: National Center for Health Statistics; 2010.
4. Escobar GJ, Li DK, Armstrong MA, *et al.* Neonatal sepsis workups in infants >/=2000 grams at birth: a population-based study. Pediatrics 2000; 106:256–263.
5. Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National ■ Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, 2010. MMWR Recomm Rep 2010; 59 (RR–10):1–36.

This report summarizes the updated CDC recommendations on GBS prophylaxis, and reviews the reduction in GBS since initiating prophylaxis guidelines in 1996.

6. Cotten CM, Taylor S, Stoll B. NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009; 123:58–66.
7. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics 2008; 121:689–696.
8. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr 2011; 159:720–725.
9. Garcia-Prats JA, Cooper TR, Schneider VF, *et al.* Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics 2000; 105:523–527.
10. Schelonka RL, Chai MK, Yoder BA, *et al.* Volume of blood required to detect common neonatal pathogens. J Pediatr 1996; 129:275–278.
11. Murphy K, Weiner J. Use of leukocyte counts in evaluation of early-onset ■ neonatal sepsis. Pediatr Infect Dis J 2012; 31:16–19.

This paper emphasizes the importance of serial laboratory testing to provide reassurance for stopping antimicrobials in less than 48 h and to identify neonates at higher risk of culture-positive infection.

12. Polin RA, the Committee on Fetus and Newborn. Management of neonates ■ with suspected or proven early-onset bacterial sepsis. Pediatrics 2012; 129:1006–1015.

This clinical management review from COFN discusses dilemmas faced by clinicians trying to decide to initiate and then whether or not to continue empirical antibiotics for EOS. The included algorithms for duration of empirical antibiotics when cultures were sterile generated discussion about the lack of strong supportive evidence to guide decisions to stop antimicrobials at 48 h in certain cases.

13. Ottolini MC, Lundgren K, Mirkinson LJ, *et al.* Utility of complete blood count and blood culture screening to diagnose neonatal sepsis in the asymptomatic at risk newborn. Pediatr Infect Dis J 2003; 22:430–434.
14. Jackson GL, Engle WD, Sendelbach DM, *et al.* Are complete blood cell counts useful in the evaluation of asymptomatic neonates exposed to suspected chorioamnionitis? Pediatrics 2004; 113:1173–1180.
15. Newman TB, Puopolo KM, Wi S, *et al.* Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics 2010; 126:903–909.
16. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics 1998; 102:E41.
17. Ehl S, Gering B, Bartmann P, *et al.* C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics 1997; 99:216–221.
18. Centers for Disease Control and Prevention. 12-Step Program to Prevent ■ Antimicrobial Resistance in Healthcare Settings. http://www.cdc.gov/drugresistance/healthcare/default.html. [Accessed 4 November 2012]

This publicly accessible website provides extremely useful background information on rationale and tools for implementation of antimicrobial stewardship.

19. Spitzer AR, Kirkby S, Kornhauser M. Practice variation in suspected neonatal sepsis: a costly problem in neonatal intensive care. J Perinatol 2005; 25:265–269.
20. Patel SJ, Saiman L, Duchon JM, *et al.* Development of an antimicrobial stewardship intervention using a model of actionable feedback. Interdiscip Perspect Infect Dis 2012; 2012:150367.
21. Chiu CH, Michelow IC, Cronin J, *et al.* Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J 2011; 30:273–278.
22. Russell AB, Sharland M, Heath PT. Improving antibiotic prescribing in neonatal units: time to act. Arch Dis Child Fetal Neonatal Ed 2012; 97:F141–F146.
23. Polin R. Re:Empirical Antibiotic Therapy for Suspected Early-Onset Bacterial ■ Sepsis. Pediatrics 2012; 130:e1055–e1057.

In this thorough response to Letters to the Editor regarding ref [12▪], COFN provides rationale for empirical treatment of preterm infants with risk factors for EOS (versus observation as recommended by CDC) and discusses upcoming clarifications to algorithms, including in reference [12▪].