Published in final edited form as:
Curr Opin Pediatr. 2013 April ; 25(2): 167–171. doi:10.1097/MOP.0b013e32835e01f6.

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

C. Michael Cotten, MD MHS[1] and **P Brian Smith, MD MPH MHS**[1]
[1]Duke University Division of Neonatology, Department of Pediatrics

Abstract

Purpose of review—Clinicians' adherence to AAP and CDC Guidelines to prevent Group B Streptococcal (GBS) early onset sepsis (EOS) have reduced GBS EOS. While evidence-based testing and empirical antibiotic initiation is 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 hours postnatally may provide reassurance for safe discontinuation.

Summary—Every day clinicians caring for thousands of neonates in the US 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

empirical antibiotics; early onset sepsis

Introduction

Early onset sepsis (EOS) is characterized by bacteremia, pneumonia, and meningitis, and positive blood or CSF cultures obtained in the first three postnatal days. EOS affects an estimated 0.7% of newborns annually in the US, an estimated 3300 cases per.[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 Center for Disease Control (CDC) and American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) guidelines for empirical antimicrobial treatment based on antenatal risk factors for Group B Streptococcus (GBS) EOS, the most common EOS pathogen, clinicians empirically treat approximately 30% of mothers antenatally and approximately 10% of U.S. 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.

Corresponding Author: C. Michael Cotten MD MHS, Department of Pediatrics/Neonatology, 2424 Erwin Road, Suite 504, Duke University Medical Center Box 2739, Durham, NC 27710, Phone: 919-681-4844, Fax: 919-681-6065, cotte010@mc.duke.edu.

Dr. Cotten has no relevant conflicts of interest.
Dr. Smith has no relevant conflicts of interest.

[1**,2**,5*] Epidemiologic evidence of higher mortality and morbidity among premature neonates with sterile cultures and long empirical antibiotic courses has recently emerged, and concerns over rising antimicrobial resistance among common pathogens, including E. coli, with two thirds of isolates from EOS E. coli samples ampicillin resistant, have grown. [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.

Who gets to continue empirical antibiotics for EOS beyond 48 postnatal hours?

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 ultimately be positive.[4] Continuation even in the absence of positive cultures for continuously 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, with high likelihood of identifying bacteria in 1 mL samples 1 mL,[9] but some flexibility must be given for situations when low organisms concentrations may still cause significant problems, but may not be detectable in low volume samples.[10] Antibiotic exposure prior to obtaining cultures may reduce likelihood of identifying an organism with culture methods, although reports are reassuring that even with intrapartum antibiotics used per the CDC GBS prophylaxis guidelines, pathogens can grow in blood cultures from infected infants.[9]

Who should have antibiotics stopped at 48 hours and can the CBC help?

Neonates initiated on empirical antibiotics for EOS who have sterile cultures, with no signs of infection, and normal screening laboratory exams should have antimicrobials stopped. In a single center study of over 3000 patients admitted to the NICU who had a blood culture obtained in the first postnatal hour, and a complete blood count (CBC) obtained in the first postnatal hour and again at 8 – 12 hours, none of the 1539 neonates (49%) who had 2 normal immature to total neutrophil (I:T) ratios and a negative blood culture at 24 hours subsequently developed sepsis.[11] Therefore, if no early test was abnormal, the culture is sterile, the neonate is well, antibiotics should be stopped.

In cases where risk is perceived as higher and initial clinical signs are more numerous (tachypnea, low sugar, low temperature, but resolved in 24 hours) but resolved, and initial laboratory exams outside the normal range, clinicians may turn to the negative predictive values of additional testing to validate resolution of clinical signs by the first 24 postnatal hours. In the algorithm first proposed by COFN, antibiotics are to be continued if "lab data are abnormal", with no designation of when the laboratory tests should be obtained or how long they should be continued.[12] The timing of obtaining a laboratory test, particularly a CBC, as well as ancillary tests such as C-reactive protein (CRP), can provide reassurance, when cultures are negative, and neonates have no clinical signs of sepsis, antibiotics can be safely stopped.

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, but none had positive cultures.[13] Of the initially 1665 asymptomatic neonates, 454 (27%) had abnormal CBCs at 4 postnatal hours, including 7 of the 17 eventually diagnosed

with presumed sepsis. Nearly all (91%) with diagnosis of sepsis had more than 1 sign/symptom, and 77% had at least 3. This study reinforces the challenge in interpreting only CBCs as a basis for initiation of empirical therapy, or as a basis for decisions for subsequent management at the end of 48 hours of empirical treatment if clinical signs resolve and cultures remain sterile.

In another cohort study, utility of CBC and differential was assessed in 856 term and near term neonates exposed to clinical chorioamnionitis and started on empirical antibiotics. 96% of the 856 remained asymptomatic and had sterile cultures. All were treated with empirical antibiotics for 48 hours. Asymptomatic neonates with an abnormal immature to total neutrophil (I:T) value on either the second (12 postnatal hours) or third (24 postnatal hours) CBC were examined within 10 days of discharge by 1 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 3 CBC's (first postnatal hour, 12 hours, 24 hours) 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 CBCs had abnormalities, only half of the I:T values in these 4 neonates were abnormal. Of the asymptomatic neonates, 92% were followed in person or by telephone. Of those followed by telephone (n = 373), 8 (2.1%) were readmitted in the month following discharge, all with normal I:T's on serial CBCs, and none had culture-proven infection.[14]

The authors of the study of neonates empirically treated after chorioamnionitis concluded that extended antibiotic therapy should be reserved for neonates with clinical signs of infection (e.g., respiratory distress, feeding disorders, apnea, temperature instability) and/or those who have a positive blood culture within 48 hours.[14] We concur with this assessment, and strongly consider other tests (such as C-Reactive Protein) before extending empirical antibiotic duration beyond 48 hours if CBCs had persistent abnormal values at 24 and/or 48 hours leading to clinical uncertainty despite absence of clinical signs of infection or positive cultures.

We propose that abnormal CBC's, with low ANC, high I:T ratios, obtained in an optimal time period (at or beyond the first 4 postnatal hours [15]) reinforce need to be on antibiotics at that time. However, we believe that, with the low likelihood of positive cultures in the absence of clinical signs even in this group with an abnormal CBC, that repeat testing at 24 and possibly 48 hours to monitor values that if normal, would be consistent with an absence of infection, and would support stopping antibiotics at 48 hours.

Does CRP at 24 and 48 hours aid duration of empirical antibiotic for EOS decision-making?

Benitz et al reported on CRP levels in 1002 neonates with suspected EOS. Twenty (2%) neonates had culture proven EOS, while 74 (7.4%) had probable sepsis with clinical signs but sterile cultures. CRPs drawn 24 hours apart on the 2nd and 3rd 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. 499 of 694 (72%) neonates had antibiotics discontinued within 3 days, 13 required reevaluation for suspected infection within 14 days of the initial evaluation. Five of these were infected, none with GBS or E. coli. The authors felt that two CRP levels <1 mg/dL obtained 24 hours apart, 8 to 48 hours 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.[16]

Ehl et al studied 176 neonates with birthweight > 1500 g, suspected to have EOS. None of the 84 neonates with low CRP (< 10 mg/L) at 24 and 48 hours and antibiotics stopped at 48 hours based on CRP results (Group 1) had a sepsis workup with positive cultures within 4 weeks of stopping initial antibiotics. Four Group 1 neonates had later sepsis workups, all with sterile cultures. Three had low CRPs, and one had facial lacerations and CRPs > 10 mg/L, and was treated for 4 days. Eighty-two neonates with CRP > 10 mg/L were randomized to have daily CRPs and antibiotics stopped when CRP was < 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. A 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 cerebrospinal fluid culture for GBS. These results provide a single center's reassurance regarding utilization of persistent low CRPs to guide stopping antibiotics at 48 hours in neonates with sterile cultures. The results do not provide reassurance that 6 days is adequate duration for Group B strep EOS, although we agree with the authors, that even longer treatment periods than the 6 days used in this infant do not rule out the possibility of second infectious episodes in all neonates.[17] We agree that there is reasonable evidence to support use of serial CRP measures at 24 and 48 hours 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 exam was normal throughout.

Why does duration matter?

Concerns about duration of antimicrobials arise from recent cohort studies showing associations with mortality, necrotizing enterocolitis (NEC), and subsequent infection. In a report from the Eunice Kennedy Shriver NICHD Neonatal Research Network, multivariable analysis showed associations between longer initial empirical antibiotic courses and mortality and morbidities among 4039 extremely low birthweight neonates who survived >5 days, received initial empirical antibiotic treatment, and had sterile cultures through the first 3 postnatal days. The median therapy duration was 5 days (range: 1–36 days), and approximately one half of neonates received prolonged (≥ 5 days) empirical therapy (center range: 27%-85%).[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 ≥ 5 days 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 unnecessary 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 practice variation and possibly limit variation and track whether less variation 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 have 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 hours in an asymptomatic baby if laboratory results are consistently normal, there is no subsequent clinical evidence of infection, and cultures are all sterile.[12] The asymptomatic neonate with clinical laboratory results that vary from low levels found in most normal, asymptomatic, culture negative neonates cause clinicians legitimate concern. There is no absolute clear consensus on well-informed approaches, mostly due to lack of the large scale studies needed. [12, 22, 23] We believe that if concerns over abnormal CBC results persist in a well appearing child with sterile culture, that the CRP, repeated 24 and 48 hours after initiation of empirical antibiotics can be helpful to clinicians in the U.S. making these decision for thousands of neonates each year.

A large scale cohort study that includes post-discharge monitoring of neonates started on empirical antibiotics for EOS, with sterile cultures, abnormal CBCs during the first 24 postnatal hours, and were asymptomatic within the first postnatal hours, or never had signs of infection and had antibiotics stopped would be extremely helpful to clinicians. Such a study would provide information on prevalence of subsequent infection and likelihood of relapse or infection emergence relative to laboratory values. The current studies are not adequate to dictate specific tests at specific times in all situations where empirical antibiotics have been started, but clinicians have to decide what to do today with available resources. While we await more comprehensive data and better diagnostic tests we offer suggestions for duration of empirical antibiotics once they are started for risk factors such as chorioamnionitis, as suggested by 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 neonate on empirical antibiotics for EOS plus sterile cultures at 48 postnatal hours and:

1. Clinical signs of infection that persisted over 24 hours: 7 days
2. Clinical signs initially absent, but became apparent after first postnatal hour and persisted more than 24 hours: 7 days
3. Labs drawn for risk factors, clinical signs absent, initial (4 postnatal hours) laboratory CBC normal: 48 hours
4. Labs drawn for risk factors, clinical signs transient (resolved by 8 hours), initial CBC abnormal: obtain CRP at 24 and 48 hours. If CRPs are low, clinical exam stays normal, stop antibiotics at 48 hours.

Acknowledgments

Dr. Cotten received funding for work related to this manuscript from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network 5U10 HD040492-10

Dr. Smith received funding for work related to this manuscript from the AHRQ funded R-18 AE000028-01 Accelerating Adoption of Comparative Effectiveness Research in Premature Infants.

We 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. We thank them for ongoing collaborations that aim to improve outcomes for neonates.

Dr. Cotten receives salary support for research from the National Institutes of Health and the U.S. Department of Health and Human Services [NICHD 5U10 HD040492-10; DHHS-1R18AE000028-01; NHLBI 1R01 HL105702 01A1; NIHSBIR: 2R44HD062316-02; NICHD 5R01HL085703-04.

Dr. Smith received receives salary support for research from the National Institutes of Health and the U.S. Department of Health and Human Services [NICHD 1K23HD060040-01 and DHHS-1R18AE000028-01].

Abbreviations

AAP	American Academy of Pediatrics
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CSF	Cerebrospinal fluid
COFN	Committee on Fetus and Newborn
dL	deciliter
EOS	Early onset sepsis
GBS	Group B Streptococcus
I:T ratio	Immature:Total neutrophil ratio
L	Liter
mg	milligrams
mL	Milliliter
NEC	necrotizing enterocolitis
NICU	Neonatal intensive care unit

References

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. [PubMed: 21654548] . 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. [PubMed: 21518717] . Like the Weston paper, 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. National Vital Statistics Reports Web Release. Vol. Vol. 58. Hyattsville, MD: National Center for Health Statistics; 2010. Deaths: Final Data for 2007.
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. [PubMed: 10920148]
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(RR10):1–36. [PubMed: 21088663] . 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, et al. 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. [PubMed: 19117861]
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. [PubMed: 18381532]
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. [PubMed: 21784435]
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. [PubMed: 10699103]
10. Schelonka RL, Chai MK, Yoder BA, et al. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996; 129:275–278. [PubMed: 8765627]
11. Murphy K, Weiner J. Use of Leukocyte Counts in Evaluation of Early-onset Neonatal Sepsis. Pediatric Infectious Disease Journal. 2012; 31:16–19. [PubMed: 21860335] . This paper emphasizes the importance of serial laboratory testing to provide reassurance for stopping antimicrobials in ≤ 48 hours, 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. [PubMed: 22547779] . 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 hours 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. [PubMed: 12792384]
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. [PubMed: 15121926]
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. [PubMed: 20974782]
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. [PubMed: 9755278]
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. [PubMed: 9024449]
18. Centers for Disease Control and Prevention. 12-Step Program to Prevent Antimicrobial Resistance in Health Care Settings. Accessed November 4, 2012Available at: http://www.cdc.gov/drugresistance/healthcare/default.html.. This publicly accessible website provides extremely useful background information on onale 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. Journal of Perinatology. 2005; 25:265–269. [PubMed: 15616610]
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; 150367:6 pages.
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. [PubMed: 21085051]
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. [PubMed: 21037285]
23. Polin R. on behalf of the AAP Committee on Fetus and Newborn. In Reply. Pediatrics. 2012; 130:e1055–e1057. [PubMed: 23035242] . 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.

Key Points

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