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Antibiotic Therapy and Early Onset Sepsis

Gustave Falciglia, MD,* Joseph R. Hageman, MD,† Michael Schreiber, MD,‡ Kenneth Alexander, MD, PhD

Author Disclosure
Drs Falciglia, Hageman, Schreiber, and Alexander have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gaps
1. Evidence indicates that broadening empirical antibiotic coverage beyond ampicillin and gentamicin for early onset sepsis (EOS) is both ineffective and potentially detrimental to the growing number of antibiotic resistant organisms.
2. An attempt should be made to clarify the inconsistent data suggesting that intrapartum prophylaxis may be a contributing factor to the changing epidemiology and the antibiotic resistance of organisms implicated in EOS.

Abstract
Early onset sepsis in the newborn infant continues to be an important clinical problem for neonatologists everywhere in the world. Different routes of transmission, changes in causative agents, and potential antibiotic resistance all influence the choice of antibiotic therapy. Group B Streptococcus and *Escherichia coli* continue to be the major pathogens dictating antibiotic therapy in the United States. Ampicillin and gentamicin are the antibiotics used by most for empirical therapy; cephalosporins are used in certain clinical situations. In this review, we address the reasons for these choices while highlighting clinically relevant aspects of the antibiotics commonly used in the treatment of early onset sepsis in the newborn.

Objectives
After completing this article, readers should be able to:
1. Recall the definition of EOS; distinguish it from late onset sepsis.
2. List common causative agents in all infants in EOS, including very low birth weight (VLBW) infants.
3. Contrast the goals of empirical antibiotic therapy with definitive therapy.
4. Identify the risks associated with commonly used antibiotics in infants.

Introduction
Early onset sepsis (EOS) in the newborn infant continues to be a difficult clinical challenge for neonatologists everywhere in the world. Multiple routes of transmission, change in causative agents, and potential antibiotic resistance contribute to the difficulty of this problem. These factors influence the choice of antibiotic therapy. In this review, we address the appropriate choice of antibiotic therapy while highlighting clinically relevant aspects of the antibiotics commonly used in the treatment of EOS in the newborn.

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>EOS</td>
<td>early onset sepsis</td>
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<tr>
<td>ESBL</td>
<td>extended spectrum <em>β</em> lactamase</td>
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<tr>
<td>GBS</td>
<td>group B Streptococcus</td>
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<tr>
<td>IAP</td>
<td>intrapartum antibiotic prophylaxis</td>
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<tr>
<td>PBP</td>
<td>penicillin-binding protein</td>
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<td>VLBW</td>
<td>very low birth weight</td>
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EOS: Definitions and Causative Agents
There is no single definition of EOS in the newborn; various definitions exist, each with subtle differences. EOS refers to an infection of the blood stream or meninges proven by culture; EOS is usually acquired vertically from the mother and
manifests shortly after birth as originally characterized by McCracken. (1)(2) Philip (3) uses the terminology very early onset disease for infections presenting in the first 24 hours after birth, early onset disease for infections between 1 and 7 days after birth, and late onset disease for infections after 7 days. Scandinavian investigators have used this scheme because infection within the first 24 hours has a higher mortality rate and rarely presents with meningitis.

The Centers for Disease Control and Prevention defines EOS as a blood or cerebrospinal infection within the first 6 days after birth proven by culture. (2) In very low birth weight (VLBW) infants, EOS refers to infections occurring within the first 3 days after birth; after the third day after birth, infections tend to be nosocomial, acquired horizontally. (2)(4)

The definitions are an attempt to describe the route of transmission and, therefore, common flora associated with each route. Although there are exceptions, these distinctions serve to aid the diagnosis (what is the likelihood of meningitis) and treatment (what antibiotics to use).

The causative organisms of EOS have been changing for several decades in the United States. In the 1950s, the predominant organisms causing EOS were *Staphylococcus aureus* and group A Streptococcus (*S pyogenes*). After the introduction of antibiotics, gram-negative bacteria, especially *Escherichia coli*, became more common. (5) Since the late 1970s, group B Streptococcus (*S agalactiae*; GBS), has remained the most common cause of EOS in infants, born term and preterm. (2) With decreasing gestational ages of newborns and increasing rates of VLBW infants, there is a dichotomy in bacterial culprits. GBS is the most common cause of EOS in term newborns, whereas *E coli* is the most common cause of EOS in VLBW infants (Figs 1 and 2). (6)

The etiology of EOS in newborns in developing countries outside the United States differs from that of US-born infants. In a combined review of EOS in Latin America, the Caribbean, Asia, and Africa, the most common causes of EOS were *Klebsiella* spp, responsible for a quarter of the cases in the first week after birth. The most common gram-positive pathogen was *S aureus* (Fig 3). (7) The authors suggest that some of the organisms responsible for EOS in the first week may be acquired horizontally due to “lack of hygiene during and after delivery, poor cord care, and unhygienic newborn care practices.” (7)

**Effects of Intrapartum Antibiotic Prophylaxis**

Complicating an understanding of bacterial epidemiology in EOS is intrapartum antibiotic prophylaxis (IAP) for GBS. Does IAP against GBS increase the incidence of gram-negative bacteria, especially *E coli*? At the Yale-New Haven Hospital, Bizzarro et al. (8) sought to determine if there was an increasing incidence of *E coli* EOS in VLBW infants born during a period of no IAP (1979–1992), compared with infants born during a period of risk-factor based IAP (1993–1996), and compared with infants born during a period of GBS screening-based IAP (1997–2002). (8) Although there was a significant decrease in gestational age and birth weight across these assessment periods, the final analysis controlled for

![Figure 1. Early onset sepsis in the United States.](image1)

![Figure 2. Early onset sepsis among very low birth weight infants in the United States.](image2)
effect of these factors. The authors found that *E coli* EOS increased with the advent of maternal GBS prophylaxis. Similarly, data from the National Institute of Child Health and Human Development (NICHD) revealed that the incidence of *E coli* EOS in VLBW infants increased between the periods 1991–1993 and 1998 from 3.2 to 6.8 per 1000 VLBW births. (4)

Nevertheless, the NICHD later reported that there was no significant increase in the incidence of *E coli* EOS between 1998–2000 and 2002–2003. (6) Data from Brigham and Women’s Hospital, and the Active Bacterial Core Surveillance/Emerging Infections Program Network also revealed no significant increase in the incidence of *E coli* EOS. Instead, the authors found only that the proportion of EOS attributable to *E coli* increased, reflecting the success of GBS prophylaxis. (9) (10) In Australia, no increased incidence in *E coli* was observed in the 10-year period between 1992 and 2001. (11) Interestingly, penicillin is the prophylactic antibiotic of choice in Australia, and in the hospitals in the Boston and Active Bacterial Core Surveillance study. (9)(10)(12)

Does IAP alter the resistance pattern of maternal bacteria? The NICHD reported ampicillin resistance was not more likely among EOS infants whose mothers received IAP compared with those who did not. (13) However, Bizzarro et al. (8) noted that intrapartum ampicillin exposure was an independent risk factor for EOS due to ampicillin-resistant *E coli*, whereas there was no overall increase in ampicillin resistant *E coli*. (8) Furthermore, Towers and Briggs (14) demonstrated that mothers of infants with EOS from antibiotic resistant bacteria had received IAP with the same antibiotic. Stoll and the NICHD did not encounter ampicillin-resistant GBS. (13) Puopolo and Eichenwald (9) recently concluded that the incidence of EOS due to ampicillin-resistant bacteria and ampicillin-resistant *E coli* remain stable.

### Empirical Versus Definitive Therapy of EOS

Antibiotic coverage should initially be directed against likely highly pathogenic bacteria (in the United States, chiefly GBS and *E coli*). Ampicillin and gentamicin are widely used empirical antibiotics because they target these highly pathogenic bacteria until the infecting organism is identified and antimicrobial susceptibilities are determined (see Table). The use of ampicillin (or amoxicillin) and gentamicin minimizes expense and causes minimal treatment-related morbidity and mortality. (15) Three recent studies from the NICHD, United Kingdom, and Israel revealed that ampicillin and gentamicin remain appropriate empirical therapy for suspected EOS. (13)(16)(17)

The temptation to broaden empirical therapy exists and is most palpable on the rare occasion that ampicillin and gentamicin were insufficient. Other antibiotics may provide broader coverage; however, broader spectrum antibiotics are associated with greater drug acquisition costs, development of resistance, higher rates of fungemia, and increased toxicity (see Figs 4 and 5). Of these complications, broad-spectrum antibiotic-induced fungemia in neonates carries a particularly high mortality.

### Ampicillin and Gentamicin, the Preferred Empirical Antibiotic Regimen

Penicillins are bactericidal β-lactams that work by binding the penicillin-binding proteins (PBPs) and disrupting bacterial cell wall synthesis. (18) Penicillin G is not effective with gram-negative bacteria; however, aminopenicillins, such as ampicillin and amoxicillin, have enhanced penetration through the outer membrane of gram-negative

### Table. Empirical Versus Definitive Therapy

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<th>Empirical</th>
<th>Definitive</th>
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<tr>
<td><strong>Directed by</strong></td>
<td>Epidemiology</td>
<td>Pathogen</td>
</tr>
<tr>
<td><strong>Usage frequency</strong></td>
<td>Common</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Termination of therapy</strong></td>
<td>A negative culture</td>
<td>Eradication of pathogen</td>
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<tr>
<td><strong>Tolerance of risk</strong></td>
<td>Low</td>
<td>Dependent on organism</td>
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bacteria and enhanced binding to PBPs. Ampicillin is a safe antibiotic with rare adverse effects that include rash, urticaria, diarrhea, and liver function test elevations. (19) Two important mechanisms contribute to ampicillin resistance. Bacteria can enzymatically inactivate the β-lactam ring, or they can alter their PBPs. (18) In the United States, 78% of E coli isolates are resistant to ampicillin. (13)

Gentamicin and other aminoglycosides work by binding ribosomal RNA and inhibiting protein synthesis. (19) Aminoglycosides also disrupt the bacterial cell membrane. Aminoglycosides are highly polar, cationic molecules that are attracted to the negatively charged lipopolysaccharide molecule of gram-negative bacteria. (19) The polar nature of aminoglycosides prevents efficient passage across the blood-brain barrier. Ototoxicity and nephrotoxicity are well known adverse effects of gentamicin therapy; however, the risk of toxicity can be mitigated with appropriate drug dosing, avoidance of other nephrotoxic drugs, frequent monitoring of renal function, and modification of therapy under renal insufficiency. (20)

High-level aminoglycoside resistance occurs through two mechanisms: ribosomal RNA mutation or modification and inactivation of the aminoglycoside molecule. (19) Bacteria can also decrease intracellular aminoglycoside concentrations by reducing aminoglycoside influx and increasing aminoglycoside efflux or by sequestering the aminoglycoside molecules resulting in decreased effective concentration. Despite these mechanisms of resistance, gentamicin resistance remains quite low. In the United States, only 4% of E coli isolates are gentamicin resistant. Abroad, the rates are slightly higher, ranging between 10% and 12%. (17)(21) Given the low rates of gentamicin resistance in the United States, gentamicin should remain part of empirical therapy for suspected EOS. (7) Outside of the United States in developing countries where Klebsiella can account for a quarter of EOS, (7) gentamicin-resistance occurs in about 60% of Klebsiella isolates. (21) As such, the role of gentamicin for presumed EOS is more debatable. The use of an additional antibiotic such as an additional aminoglycoside should be dictated by local resistance patterns as well as thoughtful antibiotic stewardship and outcomes data.

Concerns of Empirical Therapy
Additional antibiotics have been used for empirical therapy of EOS. It is tempting to broaden initial coverage and increase the spectrum of gram-negative coverage. However, such an attempt is not without risk.

Cephalosporins are β-lactam antibiotics that are mechanistically similar to penicillin but are not inactivated by β-lactamases. (18) Although first generation cephalosporins are used for methicillin-sensitive S aureus, the majority of cephalosporins used in newborns are third generation. (20) In addition to having enhanced gram-negative coverage, third generation cephalosporins have excellent central nervous system penetration. (18)(20)
Nevertheless, third generation cephalosporins should be used judiciously. Common adverse effects of third generation cephalosporins include intravenous site pain, phlebitis, fever, emesis, diarrhea, increased liver enzymes, and cholelithiasis. Serious adverse effects include seizure, hemolytic anemia, thrombocytopenia, and leukopenia. (20) Ceftriaxone is not recommended for use in the first week after birth, as ceftriaxone can displace bilirubin from albumin. (22) Furthermore, several cases of sudden calcium-ceftriaxone precipitate in newborn lungs and kidneys prompted the Food and Drug Administration to warn against administration of ceftriaxone and calcium-containing products within 48 hours of each other. (16)(23)

Cefotaxime and ampicillin are commonly used as a substitute for ampicillin and gentamicin for the presumptive treatment of EOS. However, there appears to be an increased risk of death with the use of ampicillin and cefotaxime. (24) This retrospective study looked at physician rationale for the use of cefotaxime in lieu of gentamicin. The authors found that clinicians frequently cited asphyxia and suspected gram-negative sepsis as the most common reasons for using cefotaxime. However, logistic regression analysis could not exclude the use of ampicillin and cefotaxime as an important factor in the death of the newborns in the study. Although Benjamin et al. (25) were careful not to infer causation, third generation cephalosporin use is probably a risk factor for invasive candidiasis.

Finally, rates of cephalosporin resistance are increasing. (26) Cephalosporinases are susceptible to degradation by cephalosporinases (commonly seen in Enterobacter spp.) and by extended spectrum β-lactamases (ESBLs, commonly seen in Klebsiella spp.). The former are located on inducible chromosomal DNA, whereas the latter are located on plasmid DNA. (27) Unfortunately, inducible resistance may not be detected by routine tests for cephalosporin sensitivity.

Carbapenems are a newer class of antibiotics that also target the PBPs. Carbapenems are not inactivated by cephalosporinases or ESBLs. As such, carbapenems are an ideal choice for definitive therapy of bacteria with cephalosporinase- or ESBL-mediated resistance. Carbapenems are also ideal for polymicrobial infections. (27) Adverse effects of carbapenems include thrombophlebitis and seizures. The risk of seizure is lower with meropenem. This lower risk of seizures is one of the reasons that meropenem is preferred to imipenem in newborns. (20)(27)

Carbapenems are potent inductors of cephalosporinases and select for ESBLs on plasmids. This would potentially render later treatment with cephalosporins ineffective. Much like cephalosporins, carbapenems destroy colonizing flora, resulting in an increased risk of fungemia. (27)

Criteria for Change

A regimen such as ampicillin and gentamicin should remain the empirical therapy of choice for presumed EOS until a correlation between antibiotic resistance and treatment failure has been observed. At regular meetings, neonatologists and microbiologists should continuously evaluate their antibiotic choices for empirical EOS therapy. The central question should be is there a correlation between antibiotic resistance and treatment failure? Decisions to modify antimicrobial regimens for EOS should be driven by outcomes data, not solely resistance patterns.

Based on current data, ampicillin and gentamicin should remain the empirical antibiotic therapy of choice for EOS. The combination of ampicillin and gentamicin is effective against all strains for GBS and most strains of E. coli. Presumptive EOS therapy with ampicillin and gentamicin is safe, inexpensive, and effective.

Finally, the best way to ensure that ampicillin and gentamicin remain effective is responsible antibiotic stewardship. Cultures should be drawn before initiating empirical therapy. Physicians should treat sepsis, not bacterial colonization. (28) Finally, antibiotics should be discontinued with negative cultures after 2 to 3 days of negative cultures unless there is compelling clinical evidence against stopping them.

American Board of Pediatrics Neonatal–Perinatal Medicine Content Specifications

- Understand the treatment and complications of sepsis.
- Know the infectious agents that cause neonatal sepsis.
- For antibiotics used commonly in the neonate, know indications for their use, clinical effects, pharmacokinetics, side effects, and toxicity.

References


9. Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years. *Pediatrics*. 2010;125(5). Available at: www.pediatrics.org/cgi/content/full/125/5/e1031


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1. Early onset sepsis in the newborn refers to an infection of the bloodstream or the cerebrospinal fluid that is proven by culture. Early onset sepsis typically manifests shortly after birth, is acquired vertically by spread from mother to fetus, and carries a high risk of death. Of the following, according to the Centers for Disease Control and Prevention, early onset sepsis is defined as infection that typically manifests after birth within the first
   A. 0–24 hours
   B. 0–72 hours
   C. 0–6 days
   D. 7–13 days
   E. 14–20 days

2. A 12-hour-old term newborn has respiratory distress from suspected pneumonia. Maternal history is significant for chorioamnionitis characterized by purulent amniotic fluid. You start antibiotic treatment based on your knowledge about the microorganisms most likely to cause early onset sepsis in term neonates in your nursery. Of the following, the most common microorganism responsible for early onset sepsis among term neonates in the United States is
   A. Enterococcus faecalis
   B. Escherichia coli
   C. Klebsiella pneumoniae
   D. Staphylococcus aureus
   E. Streptococcus agalactiae

3. A preterm neonate, who weighs 980g at birth at an estimated gestational age of 28 weeks, is suspected to have early onset sepsis. Maternal history is significant for preterm prolonged rupture of membranes, which occurred approximately 60 hours before birth of the infant by cesarean delivery. In choosing the antibiotics for treatment, you review the profile of microorganisms likely to cause early onset sepsis in preterm neonates in your nursery. Of the following, the most common microorganism responsible for early onset sepsis among very-low-birthweight neonates in the United States is
   A. Escherichia coli
   B. Klebsiella pneumoniae
   C. Pseudomonas aeruginosa
   D. Staphylococcus aureus
   E. Streptococcus agalactiae

4. The use of ampicillin and gentamicin as the initial empirical antibiotic combination is the current recommendation for the treatment of early onset sepsis in neonates. Although other antibiotics may provide broader antibacterial coverage, such treatment is of concern because of its side effects. Of the following, the most significant adverse effect of broad spectrum antibiotics used as the initial empirical combination in the treatment of suspected early onset sepsis in neonates is
   A. Anaphylactic reactions
   B. Development of bacterial resistance
   C. Greater cost
   D. High rate of fungemia
   E. Increased toxicity
5. Cephalosporins are beta-lactam antibiotics that are mechanistically similar to penicillin but are not inactivated by beta-lactamases. In addition to providing broader coverage, especially of gram-negative microorganisms, cephalosporins have greater central nervous system penetration and therefore are more effective in the treatment of meningitis. However, caution is warranted in the empirical use of cephalosporins for the treatment of early onset sepsis in neonates because of their adverse effects. Of the following, the most serious adverse effect of ceftriaxone, a third-generation cephalosporin, when used in the treatment of suspected early onset sepsis in neonates is:

A. Bilirubin toxicity  
B. Cholelithiasis  
C. Diarrhea  
D. Hepatic dysfunction  
E. Phlebitis
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