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Antibiotic Use and Misuse in the Neonatal Intensive Care Unit

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Synopsis

Neonatal sepsis causes significant morbidity and mortality, especially in preterm infants. Consequently, clinicians are compelled to treat with empirical antibiotics at the first signs of suspected sepsis. Unfortunately, both broad-spectrum antibiotics and prolonged treatment with empirical antibiotics are associated with adverse outcomes including invasive candidiasis, increased antimicrobial resistance, necrotizing enterocolitis, late-onset sepsis, and death. Most common neonatal pathogens are susceptible to narrow-spectrum antibiotics. The choice of antibiotic and duration of empirical treatment are strongly associated with center-based rather than with individual patient risk factors, implying that these choices are modifiable across centers. Thus, clinicians should aim to treat with short courses of narrow-spectrum antibiotics whenever possible, choosing the appropriate antibiotics and treatment duration to balance the risks of potentially untreated sepsis against the adverse effects of treatment in infants with sterile cultures.

Keywords

neonatal intensive care unit; empirical; antibiotic; sepsis; infection

Background

Antibiotics are the most commonly used therapeutics in neonatal intensive care units (NICUs).[1] Neonatal sepsis often has a subtle, nonspecific presentation and results in serious consequences ranging from neurodevelopmental deficits to death.[2–5] As a result, clinicians frequently administer empirical antibiotics to symptomatic infants or infants at high risk of sepsis while awaiting culture results.[1] Antibiotic treatment in the setting of negative cultures, however, may not be benign. Broad-spectrum antibiotics (e.g., third-generation cephalosporins) are associated with an increased risk of invasive candidiasis and death,[6,7]

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and prolonged duration of antibiotic therapy is associated with increased risks of necrotizing enterocolitis (NEC), death, and late-onset sepsis (LOS).[8–10]

The cumulative incidence of early-onset sepsis (EOS)—infection within 72 hours of birth—is 0.98 per 1000 live births.[11] However, the burden of disease increases with decreasing birth weight. Very-low-birth-weight (VLBW, <1500 g birth weight) infants have a cumulative incidence of EOS of 11 per 1000 live births.[11] Of those who survive >3 days, 21% will have an episode of LOS (infection occurring after 3 days of life).[11,12]

A cohort study of VLBW infants in Israel from 1995–1998 revealed an increased risk of death with LOS (17% vs. 9%; P<0.001).[13] In a more recent cohort of 400,000 live births from 2006–2009, 389 infants were diagnosed with EOS or early-onset meningitis.[11] Overall, 16% died, and mortality was inversely related to gestational age (22–24 weeks: 54%; 25–28 weeks: 30%; 29–33 weeks: 12%; 34–36 weeks: 0%; ≥37 weeks: 3%).[11] In an NICHD Neonatal Research Network study, VLBW infants with LOS were also significantly more likely to die than unaffected infants (18% vs. 7%; P<0.001).[12] Survivors of neonatal sepsis are at a high risk of adverse outcomes. VLBW infants with a history of EOS have a significantly higher risk of severe intraventricular hemorrhage or periventricular leukomalacia (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.9, 5.5) and bronchopulmonary dysplasia (OR 2.4, 95% CI 1.2–4.7) than uninfected infants.[14] A prospective cohort study of 6093 extremely-low-birth-weight (ELBW, <1000 g birth weight) infants revealed that 65% of survivors had a history of at least 1 infection.[2] Survivors were at increased risk of impaired neurodevelopmental outcomes at 18–22 weeks corrected gestational age including cerebral palsy (OR 1.4, 95% CI 1.1–1.8), vision impairments (OR 1.7, 95% CI 1.3–2.2), and low Bayley Scales of Infant Development II scores on the mental development index (OR 1.3, 95% CI 1.1–1.6) and psychomotor development index (OR 1.5, 95% CI 1.2–1.9).[2] Additionally, they were more likely to have a head circumference <10th percentile (OR 1.5, 95% CI 1.2–1.7), a finding associated with poor cognitive function, academic achievement, and behavior at school age.[2,15]

Bacteriology

EOS is most often caused by Group B *streptococcus* (GBS, 43%) followed by *Escherichia coli* (29%).[11] Among VLBW infants, however, rates of *E. coli* infection exceed those of GBS (5.1 vs. 2.1 per 1000 live births).[11] LOS in the NICU is predominantly caused by Gram-positive organisms (70%) led by coagulase-negative *Staphylococcus* (CoNS, 48%) and *Staphylococcus aureus* (8%).[12] Gram-negative LOS is less common but is associated with greater mortality (19–36%).[4,12] Fungal infections account for roughly 12% of LOS in VLBW infants,[12] although the incidence among centers varies widely.[7]

Commonly Used Antibiotics: Bacterial Susceptibility and Risks

Investigators examined reports of neonatal bacteremia received by the Health Protection Agency's voluntary surveillance scheme from 90% of microbiological laboratories in England and Wales between January 2006 and March 2008.[16] The majority of the 1516 EOS episodes were caused by Gram-positive organisms (82%), with GBS (31%) and CoNS (22%) being the most common. LOS was similarly dominated by Gram-positive organisms (81%), with CoNS (45%) and *S. aureus* (13%) comprising the majority of the 3482 episodes followed by Enterobacteriaceae other than *E. coli* (9%), *E. coli* (7%), and GBS (7%).

In the UK study, 94% of the EOS isolates were susceptible to penicillin or gentamicin, 100% to amoxicillin or cefotaxime, and 96% to cefotaxime alone.[16] The LOS isolates had a 96% susceptibility to amoxicillin or gentamicin, 93% to amoxicillin or cefotaxime, and 78% to cefotaxime alone. These susceptibilities were the same or higher when CoNS isolates

were excluded from the analysis. The authors concluded that, despite an overall susceptibility of ≥93% for the amoxicillin and cefotaxime combination, cefotaxime should not be included in the empirical regimen. Virulent late-onset pathogens, such as Enterobacteriaceae other than *E. coli* (75%) and *Pseudomonas* spp. (46%), are often not susceptible to cefotaxime, and cefotaxime is not considered to be effective against other common pathogens including *Enterococcus* spp., *Acinetobacter* spp., and *Listeria monocytogenes*.

Use of cefotaxime in empirical regimens may also promote bacterial resistance.[16–18] To study the effects of empirical antibiotics on the emergence of resistant bacterial strains, investigators examined 436 infants admitted to 2 NICUs within the same hospital who were assigned to either a narrow-spectrum antibiotic regimen (penicillin + tobramycin or flucloxacillin + tobramycin) or a broad-spectrum regimen (amoxicillin + cefotaxime).[18] Bacterial screening of respiratory and rectal cultures were performed on admission and then weekly for the presence of resistant bacteria. After 6 months of study, the units exchanged regimens. The rates of colonization with bacteria resistant to the empirical regimen of the unit was 18-fold higher in the cefotaxime + amoxicillin group than in the penicillin/flucoxacillin + tobramycin group.[18] Infants treated with penicillin + tobramycin were better protected against nosocomial infection because they were more likely to be infected with pathogens susceptible to empirical therapy than those in the amoxacillin + cefotaxime group.

Neonatal sepsis often presents with subtle and nonspecific signs such as lethargy, feeding intolerance, apnea, and hypotonia.[5,19,20] Because of the devastating consequences of untreated sepsis, clinicians have a low threshold for initiating empirical antibiotic therapy in high-risk or symptomatic newborns. Empirical therapy is begun once an infant exhibits signs of sepsis and continues while awaiting culture results. Ampicillin (#1), gentamicin (#2), and cefotaxime (#3) are the most commonly used therapeutics in infants.[1] Although over 95% of infants admitted to the NICU receive empirical antibiotics in the first postnatal days, only 1–5% have positive initial blood cultures.[6,8,21]

Risks Associated with Empirical Broad-Spectrum Antibiotic Treatment

In addition to the potential of promoting bacterial antibiotic resistance,[16] broad-spectrum antibiotics have been associated with altered gut colonization,[22] increased risk of *Candida* colonization and subsequent invasive candidiasis,[7,23] and increased risk of death.[6] In a cohort of 3702 preterm ELBW infants who survived ≥72 hours, previous broad-spectrum antibiotic (third-generation cephalosporin or carbapenem) use was associated with an increased risk of invasive candidiasis (OR 2.2, 95% CI 1.4–3.3).[7] The incidence of candidiasis between centers ranged from 2.4–20.2% and correlated with the average number of days of broad-spectrum antibiotic use per infant with sterile cultures throughout hospitalization. A multicenter retrospective cohort study of 128,914 infants found an increased risk of death when infants were treated with ampicillin + cefotaxime vs. ampicillin + gentamicin in the first 3 postnatal days (OR 1.5, 95% CI 1.4–1.7).[6] This risk persisted despite adjustment for potential confounding factors such as gestational age, degree of respiratory support, and perinatal or neonatal depression. There was significant site variation in the use of ampicillin + cefotaxime vs. ampicillin + gentamycin. From the wide variation in center use of ampicillin + cefotaxime vs. ampicillin + gentamycin, it appears that the empirical antibiotic choice was often made programmatically rather than from patient level of apparent illness.

Adverse Effects with Prolonged Duration of Antibiotic Therapy

Culture-proven neonatal sepsis is treated with a full course of antibiotics informed by antimicrobial susceptibility results. A more difficult consideration is determining the

appropriate length of antibiotic treatment in the setting of suspected sepsis in an infant with negative cultures. Modern automated blood culture systems are able to detect bacteremia due to common neonatal pathogens within 48 hours.[24] However, obtaining blood cultures from preterm infants is technically difficult, with small total blood volumes (often <1 mL) measuring less than the 2 mL needed for reliable culture results.[25] Low blood volume decreases the sensitivity of the blood culture, leading to frequent prolonged antibiotic treatment in infants with sterile cultures that may have simply missed collecting the offending organism.

A multicenter retrospective cohort study examined the duration of empirical antibiotic therapy in 790 ELBW infants with suspected or confirmed EOS.[9] Investigators compared infants who received ≤3 days of empirical therapy with those who received ≥7 days. Six hundred ninety-five infants had negative cultures, and, of these, 40% received ≤3 days of therapy while 34% received ≥7 days. The duration of therapy was unrelated to perinatal risk factors for EOS or measures of illness severity including birth weight, gestational age, sex, preeclampsia, chorioamnionitis, prolonged premature rupture of membranes, premature labor, Cesarean section, Clinical Risk Index for Babies scores, ventilator use, or survival.[9] Half of the 30 centers administered antibiotics beyond 3 days in ≥50% of the infants with sterile cultures, suggesting that the duration of empirical antibiotic therapy in infants with sterile cultures is an institutional decision and not dictated by clinical indicators of illness. Infants ≤26 weeks' gestational age at the time of initial empirical therapy who received ≥7 days of antibiotics had a longer average length of hospitalization (75 days vs. 59 days, P=0.01) and more ventilator days (31 days vs. 26 days, P=0.05) compared with infants who received ≤3 days.

A 19-center study of 5693 ELBW infants with sterile cultures who began initial empirical antibiotic treatment within the first 3 postnatal days found that the initial median duration of empirical antibiotic treatment was 5 days.[8] However, there was a large degree of center variability in antibiotic prescribing practice, and the median duration by center ranged from 3–9.5 days. The proportion of infants receiving prolonged treatment (defined as ≥5 days) ranged from 27–85% by center. In risk-adjusted multivariable analyses, prolonged duration of antibiotic therapy was associated with NEC or death (OR 1.30, 95% CI 1.10–1.54) or death alone (OR 1.46, 95% CI 1.19–1.78).[8] Each additional day of antibiotic therapy was associated with a 4% increase in the odds of NEC or death, a 7% increase in the odds of NEC alone, and a 16% increase in the odds of death alone. This analysis was repeated in infants who were intubated for the first 7 postnatal days as an indicator of illness severity. The association between prolonged antibiotic therapy and NEC or death, NEC alone, and death alone remained.

A case-control study examined the association between antibiotic use and the risk of NEC in a single center.[26] One hundred twenty four cases of NEC were matched with 248 controls on the basis of gestational age, birth weight, and year of admission. Potential risk factors for NEC were collected, including antenatal corticosteroid exposure, 5-minute Apgar score, small for gestational age, respiratory distress syndrome, the presence of a patent ductus arteriosus, laboratory-confirmed bloodstream infection, feeding practices (day of first enteral feeding, type of feeding, maximum enteral volume achieved, and day of full enteral feedings), antibiotic exposure, and umbilical catheter use. The duration of antibiotics was calculated as the cumulative number of days of antibiotic therapy prior to the day of an NEC diagnosis in case subjects. In subjects without a history of bloodstream infection, each day of antibiotic exposure was associated with a 20% increase in the risk of NEC. After 1–2 days of antibiotic therapy, the OR for the development of NEC was 1.19 and continued to increase to 1.43 at 3–4 days, 1.71 at 5–6 days, 2.05 at 7–8 days, 2.45 at 9–10 days, and 2.94 at >10 days of exposure.

Prolonged antibiotic therapy has also been associated with LOS. In the study of 5693 subjects discussed above, both 4 and 5 days of initial empirical antibiotic treatment were associated with increased risk of the combined outcome of LOS caused by organisms other than coagulase-negative *Staphylococcus* or death (4 days: OR: 1.32 [95% CI:1.11–1.58]; 5 days: OR: 1.24 [95% CI: 1.06–1.44]).[8] A study of 365 infants ≤32 weeks gestation and ≤1500 g birth weight found that prolonged antibiotic therapy (≥5 days) initiated on the day of birth was associated with LOS alone (OR 2.45, 95% 1.28, 4.67) and the composite outcome of LOS, NEC, or death (OR 2.66, 95% 1.12, 6.30) after 7 days of life.[10] The regression models controlled for birth weight, gestational age, race, prolonged premature rupture of membranes, number of days on high-frequency ventilation in the first week of life, and the amount of breast milk received in the first 14 days of life. Each additional day of antibiotics was associated with increased risk of these outcomes (LOS: OR 1.27, 95% CI 1.09–1.49; LOS, NEC, or death: OR 1.24, 95% 1.07–1.44).

Perinatal GBS Prevention: Opportunities Missed

In 1996, the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists released guidelines for intrapartum antibiotic prophylaxis (IAP) to prevent perinatal GBS infections, the leading cause of early neonatal infectious morbidity and mortality in the United States. Candidates for IAP were identified by either a risk-based or screening-based approach under the initial guidelines, but the revised 2002 guidelines recommended a universal screening-based approach to better identify appropriate IAP candidates.[27] Since the initiation of IAP, the cumulative incidence of early-onset GBS disease has fallen appreciably from 1.7 cases per 1000 live births in the early 1990s to 0.41 cases per 1000 live births from 2006–2009.[11,14] However, the potential for improvement in the implementation of guidelines still exists.

In 2002, the IAP guidelines recommended culture-based screening at 35–37 weeks for all pregnant women.[27] The guidelines stipulated that women who presented with threatened preterm labor and no culture results within 4 weeks should undergo recto-vaginal cultures and receive IAP if delivery seemed imminent.[27] However, only 50% of the mothers who delivered preterm were screened before delivery, and only 18% were screened at admission.[28] Women were more likely to be screened with longer intervals between admission and delivery. Among those for whom the interval between admission and delivery was ≥48 hours, 59% were screened at admission.

Proper implementation of IAP was also lacking during preterm births.[28] Mothers who delivered preterm were less likely to receive IAP when indicated than mothers who delivered at term (relative risk 0.81, 95% CI 0.75–0.87). Of the women who delivered preterm and had positive cultures, 84% received IAP; however, only 63% of women who delivered preterm with unknown GBS colonization status were given IAP. Those with unknown status were less likely to receive IAP when the interval between admission and delivery was <4 hours as compared with ≥4 hours.

Guidelines regarding proper antibiotic choice in the setting of a penicillin allergy also were rarely followed.[28] The 2002 guidelines recommended the use of cefazolin in women with penicillin allergies at low risk for anaphylaxis, a recommendation that was reiterated in the 2010 guidelines.[27] However, 70% of allergic women at low risk for anaphylaxis received clindamycin for prophylaxis, and only 14% received cefazolin.[28] There is limited evidence that clindamycin crosses the placenta and concentrates in fetal tissues and amniotic fluid at bacteriocidal concentrations, and the available data suggest that it does not do so adequately.[29,30] Furthermore, GBS resistance to clindamycin has increased over the last 20 years to 13–20%.[31–33] Only 1% of GBS-positive women who were allergic to penicillin had

documented susceptibilities to clindamycin.[28] Because the effectiveness of clindamycin, erythromycin, or vancomycin (their alternative in the case of resistance) has not been studied, no duration of these therapies is considered adequate prophylaxis.[27]

The result of these failures of screening and treatment is that well-appearing preterm newborns undergo a limited evaluation for sepsis including a complete blood count with differential and blood culture under both the 2002 and 2010 CDC guidelines.[27] Lack of screening or proper administration of IAP leads to increased sepsis evaluations of infants and subsequent increased administration of empirical antibiotic therapy to these infants.

Summary

Neonatal sepsis causes significant morbidity and mortality, especially in preterm infants. Consequently, clinicians are compelled to empirically administer antibiotics to infants with risk factors and infants with signs of suspected sepsis. Unfortunately, both broad-spectrum antibiotics and prolonged treatment with empirical antibiotics are associated with adverse outcomes including invasive candidiasis, increased antimicrobial resistance, NEC, LOS, and death. Most common neonatal pathogens are susceptible to narrow-spectrum antibiotics. As a result, clinicians should aim to treat with short courses of narrow-spectrum antibiotics whenever possible. The choice of antibiotic or duration of empirical treatment is often not associated with risk factors for sepsis or indicators of illness severity but rather with center. Antibiotic exposure in infants could be minimized through conscientious monitoring of culture results, antibiotic choice, and duration. Improving adherence to guidelines for GBS IAP provides another opportunity to potentially reduce unnecessary antibiotic exposure in hospitalized infants.

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