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Choosing the right empirical antibiotics for neonates

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Muller-Pebody *et al* provide a description of antibiotic sensitivities from a large number of bacterial isolates from neonatal blood cultures.[1] The Health Protection Agency's voluntary surveillance scheme captures the microbiology results from 90% of the laboratories in England and Wales; a strength of this study. The study defined early-onset sepsis as a positive blood culture in the first 48 hours of life and late-onset sepsis as a positive blood culture obtained between day of life 2 and 28. From January 2006 to March 2008, 1516 bacteria were isolated from neonates in the first 48 hours of life and 3482 bacteria were isolated from neonates 2–28 days of age.

Gram-positive organisms composed 82.2% of early-onset sepsis isolates and 80.7% of late-onset sepsis isolates. Nearly all (94%) of the early-onset isolates were sensitive to an antibiotic regimen of penicillin + gentamicin and 100% were sensitive to the combination of amoxicillin + cefotaxime. For late-onset isolates, 93% were sensitive to amoxicillin + cefotaxime, and 96% were sensitive to a regimen of amoxicillin + gentamicin. Excluding coagulase negative staphylococci (CoNS) from the analysis, the authors continued to observed high rates of sensitivity (95–97%) of the remaining isolates to relatively narrow spectrum antibiotic regimens including penicillin + gentamicin and flucloxacillin + gentamicin. The authors concluded that regimens including cefotaxime should be avoided due to lower sensitivity rates and potential for promoting resistant isolates.

Neonatal sepsis is associated with increased mortality and morbidities including neurodevelopmental impairment and prolonged hospital stay.[2–4] Because of the subtle and nonspecific initial signs of neonatal sepsis (e.g., lethargy, temperature instability, irritability, feeding intolerance), the immaturity of the neonate's immune system, and the high associated mortality;[5–7] neonatologists commonly administer empirical antibiotics.[8] Given the difficulty of diagnosis and the potential consequences of missed diagnosis, antibiotics are the most commonly used therapeutics in the NICU. The most frequently prescribed therapeutics in neonates [9] are ampicillin (given most frequently in North American NICUs), gentamicin (#2), and cefotaxime (#3). Over 95% of neonates admitted to the NICU receive empirical antibiotics in the first postnatal days, despite the fact that the fraction of positive blood cultures for bacteria in this population is 1–5%.[8,10,11]

As observed by Muller-Pebody *et al*, group B *Streptococcus* is the most commonly isolated pathogen in early-onset sepsis among US newborns. However, Gram-negative pathogens (*Escherichia coli*) predominate among very-low birth weight (<1500 g birth weight) neonates with early-onset sepsis.[10] Similarly, in US neonatal intensive care units, Gram-positive organisms, CoNS and *Staphylococcus aureus*, are the most commonly isolated pathogens during episodes of late-onset sepsis.[12–14]

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No well-powered randomized trials exist to guide empirical antibiotic therapy, and the use of broad-spectrum antibiotics (e.g. 3rd third-generation cephalosporins and carbapenems) vs. more narrow-spectrum antibiotics (ampicillin and gentamicin) as empirical therapy varies substantially by nursery.[8,15] The use of broad-spectrum antibiotics substantially alters the colonization patterns of the neonatal intestinal flora,[16] increases the risk of subsequent invasive fungal infections,[15] promotes multi-drug resistant bacteria, and increases the risk of subsequent necrotizing enterocolitis (NEC) and death.

In a cohort of 128,914 term and preterm neonates treated with ampicillin/cefotaxime or ampicillin/gentamicin as empirical therapy at birth for early-onset sepsis, cefotaxime use was associated with an increased risk of mortality (odds ratio = 1.5 [1.4, 1.7]).[8] Among neonates <1000 g birth weight in the NICHD-sponsored Neonatal Research Network, prolonged empirical antibiotic therapy (≥5 days) at birth was associated with increased risk of NEC and death (odds ratio = 1.5 [1.2, 1.8]).[11]

For premature neonates, choice of empirical therapy may also increase the risk of other nosocomial infections including candidiasis. In a cohort of 3702 neonates <1000 g birth weight, the incidence of invasive candidiasis ranged from 2.4% to 20.2% between similar academic NICUs. This variance was directly related to the average number of days of broad-spectrum antibiotics received by each neonate and the average number of days of broad-spectrum antibiotics received with negative cultures per neonate.[15] We speculate that the widespread use of narrow spectrum empirical therapy is a plausible reason that the incidence of invasive *Candida* infections, a nosocomial pathogen associated with substantial mortality in neonates, in the UK is relatively low compared to US centers and other centers in European Union.[15,17–19]

The argument for narrow spectrum empirical antibiotic coverage made by Muller-Pebody *et al* and others is also supported by the lack of increased attributable mortality associated with Gram-positive organisms including CoNS and *Staphylococcus aureus*. Although these organisms are universally resistant to ampicillin/amoxicillin and often resistant to beta-lactamase resistant penicillins [3,8,15] and they can cause substantial morbidity,[4] these organisms have been associated with minimal attributable mortality in large cohort studies. [3,13]

Sepsis in the newborn can have catastrophic consequences. However, empirical antibiotic therapy exposes 10–100 neonates to drug side effects and alterations in intestinal flora for each neonate with a positive blood culture. The bedside clinician is often faced with a difficult risk-benefit analysis in which they must weigh the potential short-term (24-hour mortality), intermediate (school-age neurodevelopment), and long-term (resistance and NICU public health) consequences. These often difficult decisions require a multi-disciplinary approach to collection and interpretation of data.

This contemporary surveillance of bacterial isolates from neonatal blood cultures provides important reassurance to clinicians choosing to administer relatively narrow-spectrum empirical antibiotic regimens to neonates with suspected sepsis.

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