



ORIGINAL ARTICLE

The use and misuse of antibiotics in the neonatal intensive care unit



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Abstract Antibiotic use in the neonatal intensive care unit (NICU) is very common practice. It is crucial that providers remain judicious in their prescribing habits in order to treat presumed infections effectively while also avoiding the possible complications of unnecessary and inappropriate use. Antibiotic resistance, deadly infections, and lifelong complications can all stem from the misuse of antibiotics in the NICU. While research continues to identify tools to improve diagnosis and clinical decision making, providers must continue to remain cognizant of the possible negative outcomes of antibiotic use and tailor their interventions accordingly.

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Antibiotics are one of the most commonly used classes of drugs in the neonatal intensive care unit (NICU). Infants in the NICU comprise a vulnerable population that is at risk for morbidity and mortality due to a wide range of infections. The timely administration of antibiotics is crucial, however, the inappropriate use and overuse of antibiotics in this setting has also been linked to several negative outcomes including antibiotic resistance and necrotizing enterocolitis (NEC), which can be even more life threatening than the original infections for which the antibiotics were developed. The

act of prescribing broad spectrum antibiotics for unnecessarily lengthy periods of time has been associated with several outbreaks of resistant infections including methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum β -lactamase-producing Gram-negative bacilli (ESBLs), vancomycin-resistant Enterococci (VRE), and *Serratia marcescens*, all of which can prove deadly for premature and sick infants in the NICU with compromised immune systems (Russell et al., 2010). Healthcare providers who work in the NICU setting must be judicious not only in their antibiotic choices and prescribing habits, but also in their infection prevention strategies in order to reduce the burden of neonatal infection.

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Antibiotic use in the NICU

Infants admitted to the NICU rarely make it through their hospital stay without some form of antibiotic treatment. Infection in the neonate can present silently or with unspecific signs and symptoms, yet rapid deterioration in clinical status can occur if treatment is not started as soon as possible. Because of this, providers tend to air on the side of caution and treat with broad-spectrum empiric antibiotics while awaiting lab results or further information (Johnson, 2012). Even when lab results are obtained, some of the most commonly used markers, including total leukocyte count, immature-to-total neutrophil ratio, and C-reactive protein (CRP), can be misleading, as these lab values lack sensitivity and specificity in many instances and can be indicative of many other conditions (Yang et al., 2012). In addition, some antibiotics, such as fluconazole, an antifungal agent, are used prophylactically in the NICU in order to prevent infection in this high-risk population (Schulman et al., 2015). It remains difficult to distinguish cases where antibiotics are truly needed versus those where they are not, and only a fraction of those infants who are started on an antibiotic course actually end up developing a true bacterial infection (Yang et al., 2012).

Presumed or suspected early onset sepsis (EOS) is one of the initial reasons for starting empiric antibiotic therapy in infants admitted to the NICU. EOS is defined as sepsis that either occurs within the first 48–72 h, or within the first week of life. Tachypnea, respiratory distress, temperature instability, and feeding difficulties have all been described as possible presenting features, however, often these signs and symptoms are not caused by sepsis. Group B streptococcus (GBS) is the most commonly identified bacterium in EOS (Russell et al., 2010).

Late onset sepsis (LOS), which occurs after the first 48–72 h of life, is much more common in infants less than 32 weeks gestation and in extremely low birth weight (ELBW) infants (Russell et al., 2010). Coagulase negative staphylococci (CoNS) are implicated in 54% of all LOS cases (Russell et al., 2010).

One of the most frequently chosen empiric combinations for infants with suspected sepsis is gentamicin and ampicillin. Ampicillin serves as a broad-spectrum antibiotic, while gentamicin provides narrower coverage. This combination of antibiotic therapy is associated with a lower risk of mortality than two broad-spectrum antibiotics, such as ampicillin and cefotaxime, quite possibly

due to the fact that antibiotic resistance can be reduced with judicious choices in antibiotic therapy (Johnson, 2012). Just as important as the decision as to what specific antibiotics to use is the decision of when to stop antibiotic therapy. Most experts in the field tend to agree that antibiotics should be discontinued as soon as possible in order to prevent the negative consequences associated with prolonged antibiotic use, and 48–72 h of empiric antibiotic use is a generally agreed upon treatment length for suspected sepsis without any positive blood cultures. Some push for even shorter periods of treatment, such as 36–48 h (Russell et al., 2010; Soll and Edwards, 2015).

Highlighting just how difficult it can be to decide on when and how to start antibiotic therapy in this population is the fact that among NICUs there is a remarkable amount of variation in antibiotic use. Schulman et al. (2015) reported that among 127 NICUs in the state of California, a 40-fold variation in antibiotic use exists that is independent of NICU level of care, proven infection, occurrence of NEC, surgical volume, or mortality. This wide variation in antibiotic use appears to be related to individual provider preference and interpretation, even though a large percentage of these decisions may be unwarranted based on infection rates in NICUs (Schulman et al., 2015).

The negative effects of antibiotic overuse and misuse

The possible short and long-term effects of inappropriate antibiotic use have been thoroughly explored and documented over the years. Research has shown that antibiotic use, particularly prolonged and inappropriate use of antibiotics can alter a human's healthy bacterial colonization, which can increase the risk of NEC and nosocomial infection in neonates in the NICU (Soll and Edwards, 2015). Antibiotic therapy that is continued for greater than five days in infants weighing less than 1000 g at birth has been associated with an increased risk of death and NEC (Russell et al., 2012). Gentamicin, a frequently used antibiotic in the NICU setting, has been associated with gentamicin-induced ototoxicity and sensorineural hearing loss, and there must be careful dosing and monitoring of levels when this antibiotic is used (Russell et al., 2010).

Antibiotic resistance is a very real problem in the NICU with various organisms developing resistance mechanisms, such as enzymatic inactivation, which can be used to render a wide variety of

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