New Antibiotic Dosing in Infants

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KEYWORDS

• Neonates • Infants • Antibiotics • Dosing • Pharmacokinetics • Prematurity

KEY POINTS

- Infection is common and devastating in premature infants, and antibiotics are the most commonly used medications in the neonatal intensive care unit.
- Antibiotic dosing regimens in premature infants are often extrapolated from data in adults and older children and may be incorrect because they do not account for developmental changes in infant physiology.
- Pharmacokinetic (PK) studies in infants are scarce because of low study consent rates; limited blood volume available to conduct PK studies; difficulty in obtaining blood from infants; limited use of sensitive, low-volume drug concentration assays; and a lack of expertise in pediatric modeling and simulation.
- New studies using innovative techniques and requiring smaller sample volumes are providing PK data in premature infants.
- PK data in infants provide appropriate dosing regimens for commonly used antibiotics including ampicillin, clindamycin, meropenem, metronidazole, and piperacillin/tazobactam.

INTRODUCTION

Blood culture–proven infection affects approximately 20% of very-low-birth-weight (VLBW; <1500 g birth weight) infants and causes death in up to 18% of infected infants; those with sepsis are three times more likely to die than those without sepsis (35% vs 11%).[1,2] Survivors often suffer from significant morbidities, including periventricular leukomalacia and neurodevelopmental impairment.[3] VLBW infants with sepsis are also exposed to longer periods of mechanical ventilation and are significantly more likely to develop bronchopulmonary dysplasia; they are also more likely to have longer hospital stays, resulting in higher costs of care.[1]

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Because infection is such a common and significant complication in this population, most infants admitted to the neonatal intensive care unit (NICU) are exposed to antibiotics, with ampicillin and gentamicin being the most commonly prescribed medications in the NICU.[4] Despite the widespread use of antibiotics in premature (<37 weeks gestation) infants, dosing regimens are often extrapolated from data in adults or older children, increasing the risk of drug toxicity and lack of clinical efficacy. Furthermore, these dosing regimens may be incorrect because they do not account for infants' developmental changes in renal function, metabolic capacity, body composition and surface area, gastrointestinal absorption, and immunocompetence.[5]

MECHANISMS FOR THE STUDY OF DRUGS IN CHILDREN

In 2002 and 2003, the Food and Drug Administration (FDA) implemented the Best Pharmaceuticals for Children Act (BPCA), which provides incentives for pediatric drug studies, and the Pediatric Research Equity Act, which requires pediatric studies of safety and effectiveness for drugs that may be of meaningful therapeutic benefit to children. The FDA reauthorized the BPCA and Pediatric Research Equity Act under the FDA Amendments Act in 2007 and made them permanent in 2012 under the FDA Administration Safety and Innovation Act.

Despite these legislative initiatives, infants, especially those born prematurely, continue to be therapeutic orphans because of the inherent difficulties of conducting clinical trials in this unique and vulnerable population. Pharmacokinetic (PK) studies in premature infants have been scarce because of low study consent rates; limited blood volume available to conduct PK studies; difficulty in obtaining blood from infants; limited use of sensitive, low-volume drug concentration assays; and a lack of expertise in pediatric modeling and simulation. However, newer techniques are emerging with minimal-risk study designs, including ultra-low-volume assays, PK modeling and simulation, and opportunistic drug protocols.[6] These new techniques provide more efficient ways to conduct PK studies in infants with smaller blood volumes and less frequent blood sampling.

However, implementation of these techniques has been slow and most drugs used in infants lack FDA labeling. Thus, clinicians often prescribe these drugs "off-label" to infants without evidence-based dosing regimens from clinical trials. In response to this, the Eunice Kennedy Shriver National Institute of Child Health and Human Development sponsored the Pediatric Trials Network (PTN) to conduct pediatric clinical trials to generate or revise pediatric drug labeling in infants and children. With new data emerging from trials conducted by the PTN and other groups, safer, more accurate, antibiotic dosing regimens are becoming available for premature infants.

AMPICILLIN

Ampicillin is a β-lactam antibiotic and is the most commonly prescribed drug in hospitalized infants.[4] In the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, 96% of extremely low-birth-weight (<1000 g birth weight) infants received empiric treatment with a combination of two antibiotics, with ampicillin and gentamicin being the most common combination.[7] Despite the frequency of use, the FDA label has no specific dosing of ampicillin for infants.

The PK of ampicillin in infants was recently evaluated by the PTN in the National Institutes of Health (NIH)–sponsored Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care Study (POPS Trial, clinicaltrials.gov