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Ampicillin-Induced Seizures in Neonates - A Review of Current Literature and Future Directions

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"Neonatal seizures encompass critical clinical syndromes that require a comprehensive evaluation and assessment to protect infants from long-term neurological damage."

Neonatal seizures encompass critical clinical syndromes that require a comprehensive evaluation and assessment to protect infants from long-term neurological damage. The incidence of neonatal seizures is approximately 80-120 per 100,000 and is inversely correlated to birth weight (1). Common etiologies include ischemic encephalopathy secondary to hypoxia during labor and delivery and/or neonatal respiratory distress syndrome, infection, and intracranial hemorrhage. Infectious etiologies require a complex approach to assessing seizure risk due to multiple associated risk factors such as fever, cortex irritation secondary to meningitis, and alteration of seizure threshold due to antibiotic usage.

Regarding neonatal infectious etiology, it is essential to discuss Group B Streptococcus due to its effect on neurological development. Infants with GBS have a 69% likelihood of sepsis and an 11% likelihood of developing meningitis (2). The treatment of choice for GBS in many clinical settings is ampicillin. Due to the primary role of ampicillin in Neonatal Intensive Care Unit settings, we discuss the complex interplay of ampicillin-induced seizures within the context of risk factors associated with neonatal infections.

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Though limited literature, sizeable retrospective cohort studies have been performed to investigate correlations of ampicillin-induced seizures against other parameters. In particular, ampicillin has increased seizure likelihood in neonates with higher birthweight and gestational age (3). Though this seemingly deviates from the inverse correlation of birth weight and seizure risk, it aligns with the seizure risk, specifically from Group B Streptococcal meningitis (4). Importantly, ampicillin seems to adversely affect the seizure threshold consistent with the total drug exposure and concentration in the steady state, with a reported cutoff of 140 micrograms per milliliter.

Assessing seizure risk in the context of ampicillin use would require coverage of ampicillin pharmacokinetics, which presents a challenge due to various unknown variables. Importantly, its unknown protein binding properties create variability regarding its steady-state concentration, with calculated simulations showing a 50% increase in the proportion of patients crossing the 140 micrograms per milliliter threshold when the dose is doubled from 50 to 100 mg/kg when assuming a 20% protein binding fraction (5). Dosages of 50 to 100 mg/kg, respectively, are recommended by the American Academy of Pediatrics for the treatment of GBS for infants ≤34 weeks gestational age and infants older than 34 weeks, respectively (6).

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This practice guideline may play a role in the higher incidence of ampicillin-induced seizures in neonates with higher gestational birth weight.

Further, robust clinical trials are necessary to allow for a risk assessment tool for ampicillin-induced seizure in neonates. Furthermore, research need not be limited to correlation analysis of patient parameters. Research into streamlining ampicillin treatment protocols due to variability in treatment amongst different NICU settings may be helpful, as the current literature suggests a relatively high frequency of overtreatment (6). Additional considerations, such as the potentially protective role of gentamicin (7), may allow for more efficient streamlining of antibiotic protocols.

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