EDITORIAL

Short course antibiotic therapy: When is no difference the same?

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TO THE EDITOR:

In the most recent issue of *the Journal of Perinatology*, Sanchez et al. report their results of a retrospective review assessing duration of empiric antibiotic use in 414 newborns undergoing an early onset sepsis (EOS) evaluation [1]. 24-hour and 48-hour empiric antibiotic courses were compared for safety endpoints including mortality and re-initiation of antibiotics within 7 days of discontinuation. The population was comprised of term, preterm and surgical infants admitted at six Nationwide Children's Hospital network NICUs, with the majority of infants (62%) being ≥34 weeks gestational age. While the authors also included extremely low birth weight (ELBW) and very low birthweight (VLBW) infants in their cohort, they composed a much smaller percentage of the population (10 and 19% respectively). The authors found no differences in overall in-hospital mortality (sepsis-related or overall) and noted that antibiotics were more often restarted within 7 days of discontinuation in the 48-hour group. The authors concluded that a 24-hour antibiotic course for the evaluation of EOS in infants was therefore safe and preferable.

While other studies have proposed shorter antibiotic courses for EOS [2, 3], there are caveats to consider before concluding safety and adapting such practice changes. For example, the relative rarity of EOS in neonates, especially in full-term and late preterm infants (0.3–0.6 per 1000 livebirths) [4], requires a very large sample size to detect one true case of EOS. In this sample size of 414 newborns, only 3 infants (1 in the 24-hour group and 2 in the 48-hour group) had positive blood cultures, again proving the paucity of infection in this population. While the authors should be commended in their efforts to decrease antibiotic use in the NICU, given the mounting data regarding antibiotic exposure and subsequent risk of neonatal morbidity and mortality [5–9], the power analysis used to plan this study in order to detect differences between the two antibiotic groups should have been reported.

If one were to attempt to answer the question of safety for these two approaches, given the authors' focus on no difference with respect to safety, the appropriate design would be a non-inferiority trial, which requires an even larger sample size. Post-hoc analysis based on the results available to us in this publication, we can examine the potential for non-inferiority or equivalence (to allow the conclusions made by the authors) via a measure of association (in this case, odds ratio, OR) and its 95% confidence interval. If we were to have planned the study a priori with non-inferiority in mind, we would set an OR level that would conclude that the new paradigm, the 24-hour group, was "safe" with respect to sepsis-related deaths. So for instance, we may say an OR = 1.1 (24-hour vs. 48-hour) would be considered safe. If the upper bound of the 95% CI does not contain that threshold, then we could conclude that 24-hour is no worse with respect to sepsis than 48 h. In this case, post-hoc, the OR cannot be computed because of the 0 cell in sepsis-related mortality in the 48-hour group, but using the Haldane-Anscombe correction [10, 11] (adding 0.5 to each cell), the observed OR = 7.90 with a 95% CI = (0.41, 154.0). The point estimate and corresponding confidence interval do not provide evidence to support the authors' conclusion that the 24-hour regimen is no worse than the 48-hours with respect to sepsis-related deaths.

When the authors discuss the ≤28 weeks' gestation infants, which are the highest risk group for EOS (18.47 per 1000 live births) [12], they correctly state that one dose of gentamicin covers this sub-group for 48 h. Therefore, while many of these infants were characterized as being part of the 24-hour group, they were effectively receiving 48-hours of empiric gram-negative coverage. This is reassuring, as this subgroup is at the highest risk for gram-negative EOS (usually *Escherichia coli*) [12]. However, given the differences in antibiotic pharmacokinetics for the ≤28-week gestational age group, it would be appropriate to keep these infants separate from the overall analysis. While this will require an even larger sample size, focusing on a cohort of infants ≥34 weeks' gestation who meet criteria for empiric antibiotics per the Kaiser Sepsis Calculator, will allow for a more applicable comparison of safety endpoints.

Readers should be reminded that finding no statistical difference between two approaches does not mean that the approaches are, by default, similar.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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