Title: Cloxacillin versus Vancomycin for Presumed Late-Onset Sepsis in the Neonatal Intensive Care Unit and the Impact upon Outcome of Coagulase Negative Staphylococcal Bacteremia: A Retrospective Cohort Study

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Author's response to reviews: see over
Minor Essential Revisions

1. The wording "a test failed to show non-inferiority." is misleading because it sounds as if one would yet know that one treatment is non-inferior to the other (in this case this study would not be necessary).

Response: We have changed the wording of the abstract in response to this comment. It now reads:

Although we failed to show non-inferiority of duration of sepsis in the cloxacillin and gentamicin group compared to the vancomycin and gentamicin group, duration of sepsis was clinically similar.

2. Since it appears that the treatment was allowed to be adjusted over time this study evaluates rather the effectiveness rather than the efficacy of two treatments (first page of methods section). Because adjustment was done according to measurements that could be related to the outcome it's difficult to see what the results mean for efficacy. This needs to be discussed.

Response: We are unclear as to what the reviewer is referring to. This study was undertaken to ensure the change in empiric antibiotics did not lead to increased morbidity or mortality. Treatment could be changed based on sensitivity results of the organism isolated in blood cultures, similarly in both periods. We were not evaluating efficacy per se of the empiric antibiotic regimens, rather whether or not avoiding a broad-spectrum antibiotic initially was as safe as giving the broad-spectrum antibiotic initially. The word effective was therefore used in the abstract to reflect effectiveness and we couldn't find reference to efficacy in the methods section. I refer to the conclusion in the abstract section:

Restricting vancomycin for confirmed cases of CONS sepsis resistant to oxacillin appears effective and safe, and significantly reduces vancomycin use in the NICU.

3. More information is required on the definition of CONS sepsis. How was lethargy assessed? What is an "increased frequency of apneic spell"? What time period does temperature instability refer to?

Response: The assessment of CONS sepsis is arguably quite subjective. We looked at many clinical signs as well as blood cultures to try to exclude false positives. "Lethargy" is a subjective evaluation done by the nursing staff on their flow sheets. The infant's activity is rated as: active, active with stimulus, hyperactive, irritable, lethargic, sleepy, sedated, paralyzed, or seizure activity. As this was a retrospective chart review nurses should not be biased to interpret lethargy differently between the time periods. "Increased number of apneic spells" was evaluated by looking at the “spell sheet” and assessing whether the baby had an increased number of spells over the ‘usual’ daily number for that child. We were unwilling to assign a number of spells to signify
“increased”, because in some infants even one spell was considered unusual if it was not a baby who had spells in recent days; in other infants, 2 or 3 above the baseline was considered abnormal if the baby was typically having 5 or 6 spells a day. We are aware that this is not precise, however it is only one of many clinical signs that an infant may be septic. Temperature instability was assessed over a 24 hour period when the infant was cultured for suspected sepsis. The wording of the manuscript has been changed to reflect these comments:

**CONS sepsis was defined as one positive blood culture for CONS (within 48 hours of incubation) plus one or more of the following signs of infection:** lethargy, increased frequency of apneic spells over baseline, temperature instability of more than 1 degree Celsius over 24h, need for intubation or increased ventilatory support, or poor perfusion requiring fluid boluses or inotropic support.

4. Baseline characteristics should rather be evaluated descriptively than with statistical tests. For instance, the degree of confounding introduced by birth weight solely depends on the mean difference between the groups (and the effect of birth weight on the outcome), p-values are functions also of the group sizes. See the textbook D Altman: Practical statistics for medical research. Some of the differences found might require adjustment (lethargy, increased frequency of apneic, need for increased ventilatory support, both cloxacillin and gentamicin resistance).

Response: We agree with the reviewer that the use of statistical tests for detecting baseline differences is inappropriate for randomized controlled trials. However, for observational studies, statistical comparisons of the baseline characteristics are essential to rule out the possibility that study groups are not incomparable to begin with. By running these tests, one can then assess with more confidence that differences detected at the end of the observation period are more likely to be related to the treatment effect, not to differences that were already present at the beginning. The only baseline characteristic that was found to be significantly different was lethargy. As previously mentioned, this is a very subjective evaluation and was meant to be only one of many signs that an infant is clinically septic. In addition, the significant difference observed between groups is downsized by the number of tests performed on baseline characteristics (17 items). In fact, when a Bonferroni correction is applied, the level of significance becomes 0.003, leaving the lethargy item not significantly different between the two study groups.

5. Comparisons between groups should be quantified with the confidence intervals rather than reported just in terms of statistical tests.

Response: Confidence intervals have been added to the baseline characteristics table.

Discretionary Revisions (which the author can choose to ignore)
1. In the abstract the number of individuals in the treatment group should be mentioned.

Response: There is no “treatment group” as this is not a controlled study. The numbers of patients in each of the time periods is mentioned in the abstract:

There were 45 episodes of CONS sepsis during period 1 and 37 during period 2.

2. “Presence of a central line” (just above “Results”) requires explanation.

Response: We have addressed this comment by clarifying the presence of the central line was at the time of sepsis:

A Cox regression model was fit to explore the relationship between the duration of sepsis in the two treatment periods and presence of a central line at the onset of sepsis.

3. The aggregated comparison presence of a line vs. no presence of a line over both groups hardly makes sense when the effect of that factor is different in both treatment groups (adjustment for treatment does not solve this problem)

Response: As demonstrated in table 1, the presence of a central venous line at the onset of sepsis was not significantly different between the groups. We have therefore chosen not to address this question.