Author's response to reviews

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:

Reviewer 1 comments addressed:
Reviewer: David Isaacs

Major Compulsory Revisions

1. The definition of what constitutes true coagulase negative sepsis, as opposed to contaminated blood cultures, is given in the Discussion but not the Methods. A formal definition of CONS sepsis needs to be explicitly stated in the Methods section: e.g. clinical sepsis, one positive blood culture, pure growth (I presume it was considered a contaminant if 2 strains of CONS were isolated from the 1 bottle), and must grow within 48 hours. The authors should then state that blood cultures which grew CONS but did not meet these criteria were considered contaminants.

Response: Please see Method section, Study population subsection, paragraph 1. We believe that CONS sepsis was defined:

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, temperature instability of more than 1 degree Celsius, need for intubation or increased ventilatory support, or poor perfusion requiring fluid boluses or inotropic support. Episodes were excluded as contaminants if they did not meet these clinical criteria for CONS sepsis, or if blood culture isolated either a second non-CONS organism or if the episode was a repeat CONS sepsis.

Cultures that grew 2 strains of CONS were considered contaminants, and therefore we have added this to the last line of the paragraph. In order to be more explicit, we have changed the wording of the last line to state that the blood cultures that did not meet these criteria were considered contaminants.

This paragraph now reads:
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, temperature instability of more than 1 degree Celsius, need for intubation or increased ventilatory support, or poor perfusion requiring fluid boluses or inotropic support. Episodes were excluded as contaminants if they did not meet these clinical criteria for CONS sepsis, or if blood culture isolated either a second non-CONS organism or a second CONS strain. Repeat episodes of CONS sepsis were excluded.

2. There is also no definition of what constitutes a death from sepsis. The single death they describe sounds as if it was caused by CONS sepsis, yet the authors state in the Abstract "One death during period 2 was possibly related to CONS sepsis." Did the study protocol state in advance that death caused by sepsis would be distinguished from death possibly caused by sepsis?

Response: Unfortunately we could not be certain that the death was caused by CONS sepsis. We had defined "death due to CONS sepsis" (as opposed to "death possibly due to CONS sepsis", or "death likely
not due to CONS sepsis”) on our data collection sheets as including autopsy confirmation of CONS infection. The infant who we felt likely died of CONS sepsis did not have an autopsy. We added the words "of death due to CONS sepsis" to the end of the 4th paragraph in the results section. It now reads:

One death was considered possibly related to CONS sepsis. The patient was 25 weeks gestation, born weighing 831g, who became sick at 2 weeks of age, with apneic spells, temperature instability, poor perfusion and increased ventilator requirements. He was started on cloxacillin and gentamicin. The CONS strain in this case was resistant to both oxacillin and gentamicin. Because of clinical deterioration, vancomycin was added to therapy before the susceptibility results were available, however the infant died the same day. An autopsy was not performed to confirm the clinical impression of death due to CONS sepsis.

Minor Essential Revisions

1. The authors state in the first sentence of the Discussion that this is the largest study aimed primarily at comparing outcomes in neonates with CONS sepsis. As it was a retrospective study, like the studies they discuss from Karlowicz and Matrai-Kovalsis (references 10 and 11), I do not think the authors can validly claim the largest study. This is especially pertinent because their study was probably under-powered to detect non-inferiority.

Response: We recognize that our study is retrospective and overall is smaller than Karlowicz and Matrai-Kovalsis. However, when considering specifically CONS sepsis, we reviewed more cases of CONS than Matrai-Kovalskis and provided more detail on patients and outcomes than Karlowicz. We have, however, changed the wording of the first sentence in the discussion section to answer this point. It now reads:

This is one of the largest studies aimed primarily at comparing outcomes in neonates with CONS sepsis

2. I do not understand why the authors chose a 1% difference in mortality as being the statistical margin of non-inferiority. They mention the Wilson score method, but since one of 37 babies died from CONS sepsis when cloxacillin was used and none of 45 when vancomycin was used, there is a statistical increase in mortality. Yet a difference of one death in either arm should not reach statistical significance, unless the sample size is too small. Surely the mortality difference should be calculated on the basis of the sample size. It would help if a statistician was able to advise.

Response: Margins of non-inferiority are a priori chosen, and are therefore independent of the results. These cut-off points are generally determined by clinical experts (and/or based on previous literature) to demonstrate to what acceptable extent one intervention is judged substantially not worse than another. In this case, 1% was chosen given the severity of the outcome. We feel that if mortality in the cloxacillin and gentamicin group were to differ from mortality in the vancomycin and gentamicin group by more than 1%, then cloxacillin could not be considered clinically non-inferior than vancomycin. Of note, the confidence interval around the difference in mortality rates (-13.8%, 5.5%) do fail to show statistical increase in mortality rate. However, we recognize that this conclusion might be attributable to a lack of power.

Reviewer 2 report
Reviewer: Anne Matlow

Major Compulsory Revisions

1. In using time to the first negative blood culture as one of the key outcome measures, it should be explicitly stated whether there was a protocol in place to repeat blood cultures a particular interval after starting treatment. The authors recognize in the discussion that they did not have follow up cultures on all patients, but without the above it is difficult to have confidence in this outcome measure.

Response: Unfortunately, due to the small blood volume of our tiny premature babies, there was no standard protocol for repeat of blood cultures. If antibiotics were switched due to culture insensitivity, cultures were routinely repeated prior to the switch. As such, duration of sepsis could only be defined with a negative culture if it was available.

We have added this to the first paragraph of the laboratory methods section to be more explicit. The paragraph now reads:
There was no standard protocol for repeat of blood cultures. If the baby remained clinically unwell, or if antibiotics were switched due to culture insensitivity, cultures were routinely repeated prior to changing or adding antibiotics. Cultures of catheter tips, if removed, were not routinely obtained.

As mentioned, we do recognize this as a limitation to the study. (discussion, paragraph 4):

Second, even with a clear definition of recovery from sepsis, it is difficult to be certain that sepsis had resolved. Not all infants had a documented repeat blood culture to confirm clearance of the organism, therefore duration of sepsis was recorded in days, rather than hours, which would have allowed for more precise comparison. We attempted to minimize this bias by having a single investigator responsible for assigning duration of sepsis based on a pre-specified definition for all infants.

2. Was there a protocol in place for duration of treatment of CONS bacteremia?

Response: Although no protocol for length of treatment of CONS sepsis existed in the NICU during the study time period and treatment length was left to the discretion of the attending neonatologist, babies were generally treated for 7-10 days from the onset of sepsis if no central line was in place or if the line was removed. If a line was not removed, treatment tended to be 7-10 days from a negative culture. We did not change the manuscript to reflect this as no standard length of treatment was used.

3. It would be helpful if we knew that patients who received vancomycin had therapeutic levels. If not, this adds further question as to whether the isolates were contaminants or true pathogens. If data are not available, this should at least be included as another limitation.

Response: Our patients routinely had pre- and post-vancomycin levels drawn with the 3rd dose of the drug. Vancomycin dose was adjusted based on these results to ensure levels were therapeutic.

We have added a comment to address this in the methods section, study design subsection. It now reads:

Patients routinely had pre- and post-drug levels drawn with the 3rd dose of vancomycin and gentamicin. Drug dose was adjusted based on these results to ensure levels remained therapeutic.

4. The authors should address the significance of the data "mean time between sepsis and prior antibiotics"

Response: We feel that prior antibiotic use is a risk factor for resistant organisms. The mean time between sepsis and prior antibiotic use was used in the table to demonstrate that there was not a statistically significant difference between the groups with respect to the time between the CONS sepsis episode and prior antibiotic use. We feel that in addition to lack of statistical significance, the difference is not clinically significant. We have not changed the manuscript to address this. The first paragraph of the result section reads:

Baseline characteristics of the excluded infants/episodes were comparable to those of the included ones.

Minor Essential Revisions

1. Staphylococcus aureus should be underlined or italicized wherever it appears.
   Thank you, we have italicized the organism where it appears.

2. HICPAC is the Hospital Infection Control Practices Advisory Committee. The word Practices is omitted on the first page of the background, and in reference 9
   Thank you, we have changed the manuscript accordingly