Author's response to reviews

Title: Inadequate vancomycin therapy in term and preterm neonates: a retrospective analysis of trough serum concentrations in relation to minimal inhibitory concentrations

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Author's response to reviews: see over
To:
Editor-in-chief
Dr. Peter O'Donovan
BMC Pediatrics

Amsterdam, May 15th 2014

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Dear Dr. O’Donovan,

We would like to thank you that our manuscript, entitled “Inadequate Vancomycin Therapy in Term and Preterm Neonates: A Retrospective Analysis of Trough Serum Concentrations in Relation to Minimal Inhibitory Concentrations” has been reviewed and is considered for publication in BMC Pediatrics. We thank the reviewers for their thoughtful remarks and questions.

As requested we have revised our manuscript in light of the reviewers’ comments. Changes in the text are high-lighted in the re-uploaded version. A point-by-point response to the reviewers’ concerns can be found below.

Hopefully this addition will suffice for publication of the manuscript.

With my best regards,
Sincerely yours,

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Reviewer's report

Title: Inadequate vancomycin therapy in term and preterm neonates: a retrospective analysis of trough serum concentrations in relation to minimal inhibitory concentrations

Version: 2
Date: 24 March 2014
Reviewer: Ajay J Talati

Reviewer's report:

This is a simple straightforward study with clear objectives. It is an important clinical issue with emerging MRSA in NICUs all over the world. However the study has limited data to make strong recommendations to change practice.

Areas of major concern

1. MICs of only coagulase negative staphylococci was considered, how about MRSA? The authors need to identify some cultures with MRSA and compare its MICs with the achieved concentrations.

While a common problem in various countries, MRSA is, due to stringent prevention, screening and treatment protocols in Dutch hospitals, not a common problem in the Netherlands. While we agree with the reviewer that inclusion of subjects with MRSA infection would be valuable to our study, the fact of the matter is that no subjects with MRSA were admitted to our hospital during the study period. This is in line with an incidence of MRSA of only 1.3% of all Staphylococcus Aureus infections in the Netherlands in general, as can be found in the ECDC database. Thus, inclusion of subjects with MRSA is unfortunately impossible.
However, the EUCAST database shows comparable MIC values for MRSA when compared to the coagulase-negative staphylococci in our study, as mentioned in our discussion. Thus, trough concentrations from our study could be considered therapeutic for the micro-organisms found in our study, considering the therapeutic benefit of the same concentrations in S. Aureus infections.

2. The authors do not report any problems with persistent bacteremia in spite of low levels. This would be an important clinical outcome to look at.

While we agree with the reviewer that persistent bacteremia is an important factor to look at in studies regarding the efficacy of antibiotics, unfortunately consecutive blood cultures were unavailable in most of our subjects as repeat blood cultures are not standard care. A limited amount of blood is taken in these fragile infants due to their small circulating blood volume. Only in an experimental prospective study set-up are repeat blood cultures justified. No sound conclusions can be made by sparse cases with persistent bacteremia without knowledge on all cases. However, of 14 subjects follow-up blood cultures were available, of which 13 were negative during follow-up. In 1 subjects, the initial CNS infection was not found upon follow-up blood cultures, but a different micro-organism was isolated. These numbers have been added to the Results section: page 7, line 176:

“Follow-up blood cultures were available in 14 of the 19 subjects. In 13 of the 14 subjects, follow-up blood cultures were negative, in follow-up blood cultures of 1 subject the initial CNS species was not found, but a new micro-organism was isolated.“
Hence, we were unable to draw any definitive conclusions on whether subtherapeutic vancomycin levels lead to persistent bacteremia.

3. The four groups are limited by very few patients in <26 week EGA group 1 and only 2 patients in group 2. This groups could be eliminated and only <7 days or >7days groups would have some meaningful data.

The reviewer is correct in this issue. Only sound conclusions on vancomycin treatment efficacy can be made for our largest study group. The results from the other study groups can only be used as illustration/side information. Since no results or conclusions are based on analyses in subgroups, and for the purpose of clarifying the different treatment strategies based on age, we have decided to keep the current groups in the manuscript.

4. Mortality is associated with episodes of coagulase negative staphylococci? Or other organisms?

As explained in our results section, 21 subjects died, of which 6 infants died of complicated or ongoing infections. Of these 6 subjects, 4 suffered from persistent CNS infection, while the pathogenic micro-organism was not found in 2 of these subjects. We have emphasized this in more detail in our results section.

Page 7, line 176: “Of these 21 subjects, 6 neonates died due to respiratory and circulatory compromise during an episode of severe clinical sepsis. In 4 of these 6 subjects, CNS was isolated, while in 2 subjects the causative micro-organism was not found.”

5. Some discussion of potential toxicity is warranted if authors are suggesting a change in recommendations for
therapeutic range.

We agree with the reviewer that toxicity should be addressed. We have addressed this issue in the discussion session at page 11, line 280: ‘While increasing the therapeutic range will be most certainly increase the efficacy of vancomycin for the treatment of Gram positive bacteremia, this may also give rise to a potential increase in toxicity and adverse effects of vancomycin.”

6. Neofax, widely used in US NICUs, as a drug reference for neonates, do suggest a higher trough target, but only in deep tissue infections with MRSA. The discussion should also focus on need for higher troughs with deep tissue infections.

While Neofax suggests higher trough levels for deep tissue infections, the body of literature on this topic is scarce, and no literature conclusively shows that deep tissue infections should be treated with higher trough targets. Hence, our study is one of the first to try and provide an evidence-based method for dosing of vancomycin.

7. Figure 1, indicate a significant number of infants <33 weeks had a high trough (>20 mg/L). The potential of toxicity in this population is also high because of poor renal clearance of the drug, the authors do not provide any data or discussion regarding this issues.

Unfortunately, data on serum creatinine following vancomycin treatment were unavailable. Indeed high trough levels may have caused nephrotoxicity. We have addressed the discussion to discuss this in more detail at page 9, line 214: “Conversely, 8 subjects had supratherapeutic levels
above 20 mg/L of vancomycin. All these subjects were under 29 weeks of gestational age. In these very young subjects there is a potential for nephrotoxicity. Unfortunately, our study could not provide any evidence of nephrotoxicity as follow-up of serum creatinine was not available in most subjects. However, the rapid increase in renal function shortly after birth, may significantly help overcome any supra-therapeutic levels of vancomycin and hence reduce the risk of toxicity."

8. Discuss limitations in detail

Minor concern;

Some typos need to be corrected eg. Line 242 should have “trough” instead of “through”

Discretionary:

A discussion of optimal way of dosing Vancomycin (e.g. first dose kinetics) may be helpful for readers to achieve desired trough concentrations

The optimal way of dosing Vancomycin has been extensively covered in previous literature, and we would like to refrain from providing a dosing scheme, since this was beyond the scope of this article.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interest
Reviewer's report

Title: Inadequate vancomycin therapy in term and preterm neonates: a retrospective analysis of trough serum concentrations in relation to minimal inhibitory concentrations

Version: 2
Date: 10 April 2014
Reviewer: Deanne Wilson-Costello

Reviewer's report:

This is an outstanding article which is extremely important to clinical practice. This manuscript is well written and of great interest to many types of pediatricians. It has a large number of patients and a very low lost to follow up rate.

Major compulsory revisions: none

Minor Essential Revisions: The discussion should include a statement that vancomycin use prior to 7 days of life is not typical. This is important to point out, especially since there are very few treated patients prior to 7 days.

'We thank the reviewer for her kind words regarding our article. We agree that vancomycin use in subjects prior to 7 days of life is atypical, which is indeed illustrated by the low number of subjects younger than 7 days of age treated. We have addressed this in our Discussion session:

Page 11, line 276: “Almost all our patients were included in the fourth age category, as treatment of infections with vancomycin in subjects under 7 days of age is not considered a standard treatment. Thus, considering […]”

Minor Discretionary Revisions: If the authors have data on length of hospital stay or rates of neonatal morbidities, it would be nice to determine whether infants with
subtherapeutic levels actually had worsened outcomes.

Unfortunately, due to the retrospective nature of our studies, neonatal comorbidities were not adequately registered, and hence comorbidities and length of stay were not routinely available. However, in a subset of subjects, follow-up blood cultures were available, to determine persistent bacteremia, which is an important outcome parameter considering the goal of our study.

These numbers have now been outlined in the Results section of our paper, page 7, line 176:

“Follow-up blood cultures were available in 14 of the 19 subjects. In 13 of the 14 subjects, follow-up blood cultures were negative, in follow-up blood cultures of 1 subject the initial CNS species was not found, but a new micro-organism was isolated. “

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.