Author’s response to reviews

Title: Topical antibiotics as a major contextual hazard toward bacteremia within selective digestive decontamination studies

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Author’s response to reviews: see over
Paradoxical bacteremia incidences among selective digestive decontamination studies versus other studies of mechanically ventilated patients. – retitled;

Topical antibiotics as a major contextual hazard toward bacteremia within selective digestive decontamination studies

J C Hurley

**Reviewer:** Ilias Siempos;

This reviewer “…suggest only a few minor essential revisions, which might enhance clarity of the Abstract.” The following changes have been made in response;

Page 2; note the abstract has been rewritten and clarified to remain within the word limit.
1. Randomized concurrent controlled trials (RCCT’s) and cluster randomized trials are contrasted here as an explanatory statement.
2. Clarification made in this sentence. The issue is whether there is a contextual hazard. Reference to VAP has been clarified.
3. “ICU pneumonia evidence base” is confusing and the term has been clarified.
4. These sentences (Page 2, line 45, Conclusion, “These paradoxical observations…” and the first sentence of the Conclusion of the main text (page 14, lines 296-298), have been transposed and relocated to begin the abstract results. The abstract conclusion is now one sentence.
5. “contextual infection” and “contextual effect” have been changed to “contextual hazard” at each appearance in the text.

**Reviewer:** Paula Ramirez

This reviewer identified as major issues whether SDD or SOD were targeted at VAP rather than bacteremia and whether bacteremia (CNS or otherwise) arises by intestinal translocation or is catheter related. As a result this reviewer found the study ‘incomprehensible’.

To clarify; the aims and objectives of this study are restated within the abstract as “….whether protocolized parenteral antibiotic prophylaxis (PPAP) is required, and whether the topical antibiotic SDD actually presents a contextual hazard to concurrent patients……The objective here is to compare the bacteremia rates and patterns of isolates in SDD-RCCT’s versus the broader evidence base”.

Toward this objective, the following note may help comprehension of the manuscript;

- this reviewer correctly states that VAP is usually the primary end point of SDD and SOD trials. However bacteremia is the secondary end point in many (but not all) studies although more recent studies of SDD and SOD have not studied VAP as an end-point at all. A clarification in the first paragraph of the methods has been made.
In this regard “Only 64 of the 206 studies in the broader evidence base [116] from which these studies were derived had evaluable bacteremia incidence data available.” – This is discussed as a limitation (last three paragraph of discussion)

With these factors in mind it is important to demonstrate that the studies selected demonstrated which did or did not have VAP and or bacteremia as end points are comparable with respect to the effects (both counterfactual and contextual) of SDD-SOD on VAP in addition to whatever effects were demonstrated against bacteremia and to determine whether this subset of SDD-SOD studies are comparable to the broader SDD evidence base.

the intention is to estimate both the potential hazard (i.e. contextual effect) over and above any apparent preventative effects (i.e. counterfactual effect) arising from the components of SDD

a counterfactual ‘effect’ (whether from a single study or in a meta-analytic summary) of any intervention is usually measured as an effect size. Commonly (as here) this is the odds ratio between the intervention and control group rates.

The estimation of a contextual effect or hazard requires a calibration of the event rates in the control groups against an external benchmark.

The importance of bacteremia as an end point is outlined in the first three paragraphs of the discussion.

there is no intention here to ascribe where the bacteremia arises from, whether by translocation or other,

the legend to figure 1 has been clarified to better outline the plan of analysis.

Note that in the time that the first version of this manuscript has been under review, a large cluster randomized study of SDD versus SOD has appeared (ref # 63) and has been included within sensitivity analysis three.

The methods part of the manuscript has been expanded with greater detail provided which adheres to the PRISMA guidelines (http://www.prisma-statement.org/). Others should be able to replicate this study from the details provided.

As an aid toward comprehension of this manuscript, the question that is asked here can be posed as follows; - what is the mean rate of bacteremia (and VAP) among the control groups of SDD and SOD studies and, moreover, what should it have been?

Reviewer: Anis Chaari

This reviewer suggested;

1. Title: We suggest to the author to modify the title of the manuscript.

In view of all three reviewers’ comments and for succinctness the study title has been changed to “Topical antibiotics as a major contextual hazard toward bacteremia within selective digestive decontamination studies.”

2. Results: The figures should be numbered.
A sentence referring to figures 2 & 3 has been added in the results. Note that figure 1, 2 & 3 are also referred to in the methods.

3. Results: More information should be given about the antibiotic used and the composition of the SDD solutions. If available, data about the prognosis impact of these bacteremia will enhance the interest of the study. The composition of the SDD solutions are each listed in the table in additional file 1. The prognosis impact of these bacteremia – see note 4 below.

4. Discussion: The authors should discuss in the limitations of the study the heterogeneity of the included study (trauma / medical /surgical).

The limitation of the study in relation to translation of the results to the patient level is considered in the last paragraph of the discussion.