Author’s response to reviews

Title: Determinants and outcomes of Access-Related Blood-Stream Infections among Irish Haemodialysis Patients; A Cohort Study

Authors:

Husham Mohamed (hsmaltawil@hotmail.com)
Alaa Ali (alminshawy84@hotmail.com)
Leonard Brown (Leonard.Browne@ul.ie)
Nuala O’Connell (nualah.oconnell@hse.ie)
Liam Casserly (liam.casserly@hse.ie)
Austin Stack (austin.stack@ul.ie)
Wael Hussein (waelhussein@icloud.com)

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Author’s response to reviews:

Please review response in included document for formatted response.

In text format:

Reviewer Comment: Reviewer #1: This is an interesting manuscript describing the determinants and outcomes of access-related bloodstream infections (AR-BSI) among a cohort of 235 Irish chronic hemodialysis (HD) patients from a regional dialysis program between Jan 2015 and Dec 2016. The findings confirm the prevailing knowledge that AR-BSI are substantially higher in central venous catheter (CVC) usage compared with arteriovenous fistula (AVF) usage. These findings persist despite advances in catheter design and anti-infective protocols and was consistent in all subgroups. Perhaps of more interest was the finding that older age (75+ vs. <75 years) was not associated with significant differences in rates of AR-BSI in unadjusted or adjusted analyses. The study also corroborated previous findings that femoral CVC access was associated with a significantly higher rate of AR-BSI (adjusted RR 4.93, 95% CI 2.69-9.01) compared with other non-femoral CVC.

Major Comments previously made:
p. 7: The authors state that "All recorded CVCs were tunneled catheters (no temporary dialysis catheters)." It seems implausible that there were no CVCs associated with temporary dialysis catheters. Was it really true that no bacteremia cases occurred in the setting of temporary dialysis catheters, or was this data just not available? If there truly were no bacteremia cases associated with temporary dialysis catheters, please speculate on why this might be.

The authors have adequately addressed this concern. They may wish to add a statement clarifying that their objective was to examine rates of bacteremia associated with access types used in the outpatient setting over prolonged durations rather than in the acute inpatient setting.

Our response: Statement added as per request

See Methodology section:

“As this study aimed to examine rates of bacteraemia associated with access types used over prolonged periods of time in outpatient settings, temporary dialysis catheters were not included in the analysis”

Reviewer Comment: -p. 10: Is there any data on the breakdown of non-femoral CVC's? That is, what were the other sites (internal jugular, subclavian, etc.) and were there differences between those?

The authors have addressed this concern by adding the statement "The internal jugular vein (IJ) was the most common access at the centre, with subclavian access only reserved for situations where IJ access was not attainable." (p. 7). They may want to add a statement that due to the very small numbers of non-IJ sites, comparisons between different non-femoral CVC's would not be reliable or informative.

Our response: Requested statement added

Reviewer Comment: -p. 10 Type of organism, p. 13 Discussion, and p. 25 Table 3: Were there any fungal infections recorded?

The authors replied that there were no fungal infections recorded. However, this should be added to the Results under "Type of organism" (p. 10-11).

Our response: Requested comment added

-p. 10 AR-BSI Outcomes: How long did it take for AR-BSI to clear for those who survived? Were there differences between femoral vs. non-femoral CVC's in terms of time to clearance of AR-BSI?
The authors replied that their policy on management of access-related bacteremia does not have a standardized protocol to check for clearance of bacteremia prior to or shortly after discontinuation of the antimicrobial agent. This precludes conducting a reliable comparison of clearance duration. This statement should be included in the Discussion as a limitation.

Our response: Requested statement added to the limitations section.

Reviewer Comment: Minor Comments previously made:

-p. 7, line 1: Eliminate a space between "were recorded..."
   This change was applied.

-p. 7, line 42: Change the spelling of "tunnelled" to "tunneled."

-p. 14, line 15: Change the spelling of "generalisability" to "generalizability."

Both of these spellings were not changed based on the authors’ preference to conform to standard spelling used outside of North America.

Reviewer Comment: Minor Comments in Revised Manuscript:

-p. 11, line 2: Eliminate "to" so it reads "contributing 23.4%."

-p. 11, line 26: Change "blood stream- infections" to "blood stream infections."

   Our response: Changes made

Reviewer Comment: Overall the manuscript was well-written and had very few grammatical/editorial errors. Some may argue that the findings are not that novel; however, if the above issues and edits are addressed, this study could be a nice addition to the literature suggesting the importance of continued vigilance for AR-BSI with CVCs even in this era of improved catheter design and infection-control programs.

   Our response: We made all the recommended changes, and would like to thank the reviewer for his/her recommendations.

Reviewer Comment: Reviewer #2: An excellent response and address of the issues that were raised.

   Our response: We would like to thank the reviewer for his/her recommendations.
Reviewer Comment:  Reviewer #3: Thanks for the consideration of my comments.

I am happy for this manuscript to be accepted as is, although I would recommend that a piece is added to the results around:

"Based on the reviewer's perceptive observation that a number of individuals prone to risk in the CVC group may be leading to an exaggeration of risk, we conducted a sensitivity analysis by excluding patients with more than 1 and more than 2 recorded CRBSI's. The following figure illustrates the frequency of infections among CVC patients in the study. No variables were found to be statistically significant when excluding patients' with more than 1 case of CBRSI (n=10). However, excluding patients with more than two cases (n=2) yielded similar results to that of the primary analysis as illustrated in the subsequent table. The median duration between CRBSI's among these patients was 117 days with a min of 50 days and a maximum of 465 days between events. We would argue that there are few hyper offenders (more than 2 cases of CBRSI's) in this study and that omission of these patients does not alter the primary findings of this study."

At present this work is only in the reply to authors, but is interesting enough that it can be added to the manuscript, either written as a directional statement qualified by "(Results not shown)", or as a formal sensitivity analysis with a supplementary online-only regression table. Honestly, this aspect of the analysis differentiates this project from others, and clarifies the certainty of evidence in the area.

All that said, congratulations and this suggestion is discretionary.

Our response: We added the following section to the Results section:

Sensitivity Analysis:

To address whether a number of individuals prone to risk in the CVC group may be leading to an exaggeration of risk, we conducted a sensitivity analysis by excluding patients with more than 1 and more than 2 recorded CRBSI's. No variables were found to be statistically significant when excluding patients with more than 1 case of CBRSI (n=10). However, excluding patients with more than two cases (n=2) yielded similar results to that of the primary analysis. The median duration between CRBSI's among these patients was 117 days with a minimum of 50 days and a maximum of 465 days between events. There were a few patients with recurrent infections (more than 2 cases of CBRSIs) in this study and omission of these patients did not alter the primary findings of this study.

All changes were made, and we would like to thank the reviewer for his/her recommendations.