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)

Version: 1 Date: 06 Dec 2018

Author’s response to reviews:

Response included in attached word document contains supporting items that cannot be viewed in this text-only format. Please refer to the included document.

Sebustjan Bevc
BMC Nephrology

Dec 5th, 2018

Subject: Reply to Editor and Reviewers Comments

BMC Nephrology Ref: BNEP-D-18-00464

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

Authors: Husham Mohamed, Alaa Ali, Leonard D Browne, Nuala H O’Connell, Liam Casserly, Austin G Stack, Wael F Hussein

Dear Dr Sebastian Bevc,
Thank you for considering our paper for publication in BMC Nephrology. We would also like to thank the reviewers for their time and effort, and for their insightful comments.

In this letter, we include a discussion of all raised points as requested. Attached to this document, please find an edited version of the manuscript in two formats: one with tracked changes and a clean copy.

We hope that our discussion below and the changes to the manuscript satisfy all raised points, and that you accept this paper for publication.

Kind Regards,

Wael Hussein, MBBS, MSc, MRCPI

Reply to Reviewer Comments:

Point

Comment

Kelly Liang, M.D. (Reviewer 1 (R1))

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.

Our reply

Thanks for the comment

R1 -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.

Our reply We intentionally did not include temporary catheters in our analysis. Our objective was to examine rates of bacteraemia associated with access types used in the outpatient setting over prolonged durations.

R1 -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?

Our reply The reviewer raises an interesting in question regard the location of non-femoral CVC’s and whether infection is more likely to occur at one site over another. Data quality in our electronic health record system precluded us from performing this type of analysis. The internal jugular (IJ) vein is the most common access at our hospital, with subclavian access only reserved to situations where IJ access is not possible. We highlighted this in the methodology section.

R1 -p. 10 Type of organism, p. 13 Discussion, and p. 25 Table 3: Were there any fungal infections recorded?

Our reply No fungal infections were recorded in this cohort during the observation period.

R1 -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?

Our reply Our policy on management of access-related bacteraemia does not have a standardized protocol to check for clearance of bacteraemia prior to or shortly after discontinuation of the antimicrobial agent. This precludes conducting a reliable comparison of clearance duration.

R1 Minor editorial errors that should be fixed include the following:

-p. 7, line 1: Eliminate a space between "were recorded..."

Our reply Change applied. Thanks!

R1 -p. 7, line 42: Change the spelling of "tunnelled" to "tunneled."

-p. 14, line 15: Change the spelling of "generalisability" to "generalizability."
Our reply  Thanks for the observation. We prefer to maintain the current spelling, to conform with standard spelling used outside of North America. Same standard has been used for many other words across the manuscript.

R1  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 reply  Thanks!

Sandawana William Majoni, MBChB, MRCP, FRACP, MMedStats (Reviewer 2)

(R2)  This study explored factors associated with AR-BSI in a cohort of haemodialysis patients at a tertiary nephrology centre in Ireland. It is very well conducted and presented for a retrospective study. It will clearly add valuable information to the current evidence around issues of vascular access for haemodialysis patients.

Our reply  Thanks!

R2  1. Are the high rates of coagulase negative staphylococci a reflection on the unit's practice? 60% is very high. Although they have explained that the organism can be spread by poor hand hygiene and inadequate sterilisation, the authors did not explain whether this is a practice issue in their unit and what their recommendations would be.

Our reply  The overall rates of CRBSI are similar to international norms (e.g. CDC report in the US, 2.16 per 100 patient months for central venous catheter). However, we agree that our unit has a disproportionately higher proportion of coagulase negative staphylococci infection. This indeed may reflect practice patterns. Highlighting this at a local level has led to renewed care bundles to reduce rates.

Ref:


https://cjasn.asnjournals.org/content/12/7/1139
2. Why do they think diabetes was not a significant factor in their study?

Our reply

Diabetes mellitus (DM) has been cited as independent risk factor for catheter related infection among HD patients by a number of studies (Wang et al. & Fysaraki et al.) but not all (Murea et al). Studies which demonstrate and association suggest that DM leads to impaired immunologic defence and, in combination with the immunosuppression caused by uremia, may lead to increased risk for bacteraemia. In our study, DM was the highest recorded cause of primary renal disease and second highest comorbidity among chronic HD patients. In both unadjusted and adjusted analysis DM was not a significant risk factor for infection. Among studies which have identified an independent association between DM and CRBSI, it is possible that poor glycaemic control may be the predisposing factor rather than the diagnosis of DM itself.

Rodríguez-Carmona et al., have illustrated that poor glycaemic control is a consistent predictor of subsequent risk of catheter tunnel and exit-site infection among PD patients. However, recent studies have demonstrated that demonstrated glycaemic control among HD patients with diabetes was not associated with the risk of infection-related mortality or hospitalization (Park et al. & Rhee et al.) There is a dearth of clinical data on the relationship between glycaemic control and infections in patients with DM on HD, particularly in relation to risk prediction and modification. Although a high proportion of patients in this study have DM as an underlying cause of renal disease or as comorbidity we postulate that glycaemic control may mitigate the risk of infection. However, we did not investigate this hypothesis, and further research is needed to clarify the role and mechanism of the association between DM and infection risk, hospitalisations and associated mortality.

Refs:


R2 3. Figures 2 and 3 will need reformatting as they are difficult to read. They contain very important results.

Our reply We appreciate the feedback. We enlarged the font size and image size to match journal specifications, and we clearly identified the specific subgroups. We added explanations in the footnotes to make the figures easier to read.

R2 4. On tables 1 and 2, the meaning of their p values is not clear. Can they indicate their statistical significance levels in the methods section? They have indicated in the tables values of *P<0.05 and **P<0.01. It is not clear what this means. It may be clearer if they create another column where they indicate the exact p-values. A p-value of less than 0.01 will be less than 0.05 which causes confusion in the way they have presented this.

Our reply We updated the tables to highlight items with p value <0.05.

R2 Overall, despite the above comments, this study adds significantly to the current evidence and provides additional valuable information informing safe clinical practice in vascular access management for haemodialysis patients

Our reply Thanks! We appreciate the comment.

Mark Marshall (Reviewer 3) (R3) This is a carefully-done quality improvement project that carries a simple and poignant insight. I think it is well-deserving to be in the literature, although I have a few suggestions that may add value to the study.

R3 1) I am always very concerned about comparisons between AVFs and CVCs, since the patients (or their doctors) are so fundamentally different. Irrespective of the balanced appearance of the Table 1 in this cohort, this is likely to be true for this study as well. Is it possible to do a sensitivity analysis in a restricted group
whose characteristics maybe more balanced, such as those patients who might be listed / accepted for a DDKT, or those who are on self-care or home HD?

Our reply  We agree with the comment. We also agree the suggested sensitivity analysis would reduce the imbalance between the two groups. Other studies in the literature compared outcomes in patients who had attempts at obtaining fistulas to those whom AVF was never attempted and those with catheters. We did not obtain data on transplant-listing. None of our patients were on self-care or home HD. In recognition of this limitation, we added a comment about this in the limitations section.

R3  2) Was there any effect modification by whether patients were incident or prevalent, or whether these were first or second or third catheters? Can you please split this out and do an interaction or subgroup analysis if you have the data?

Our reply  We did not obtain data on incident/prevalent status. Data quality in our currently evolving electronic system does not enable identification of a change of catheter reliably. We added a note about this in our discussion.

R3  3) Right at the start of the CVC conundrum, Maki etc showed that CABSI rates are much higher as time goes on - CABSI rates are time dependent. Firstly, what is the average duration over which patients utilize catheters in your study? How does this compare to the general landscape in the literature? Secondly, did you test for effect modification by catheter vintage? Is there a safe / honeymoon period of a few weeks for a new CVC, only after which things get hairy? I appreciate power of this analysis will be low in your study, but this is an important question. Honestly, we all know that catheters are unavoidable in many patients, particularly incident ones, and the only recourse in not really to avoid them but to minimize the duration of exposure.

Our reply  We appreciate the reviewer’s insightful feedback and astute recommendations. Our study excluded acute dialysis patients, all of the patients with CVC included in this study utilised the CVC as their primary access during the duration of the study. The mean duration of follow up was 18 months (median 20 months) for those with CVC. As the reviewer points out, previous literature suggests the risk of bacteraemia is highest in haemodialysis patients using a CVC for vascular access, and increases in a linear fashion with the duration of catheter use. The following figure illustrates the timeline of infections among CVC patients from study start. Unfortunately, we did not capture data on catheter vintage (can only detect current access type at any time point, but we do not have reliable information for when a catheter is exchanged for another catheter in the same location) and are unable to assess whether vintage modifies the relationship with infection risk or whether risk is more likely to occur after a certain time point or duration of use.
We must acknowledge that the landscape of catheter use in the Irish Health system differs to that of other regions. In a subsequent study, we have highlighted that the rate of CVC use in the Irish health system at dialysis initiation is quite high (77%) compared to other registries and that the rate of conversion form CVC to AVF is low with 59% continuing to use a CVC as their primary access 12 months after initiating RRT. This subsequent study encompasses patients from the current study as it enrolled patients initiating RRT in 2015 and 2016 nationally.

We have added the following to our limitations in our discussion.

“The study reflects a single centre experience, which may limit generalisability. In addition, we did not differentiate between incident or prevalent Haemodialysis patients in our study. Therefore, we must acknowledge we were unable to assess whether dialysis/ catheter vintage modifies the relationship with infection risk in those with CVC’s.”

R3 4) I might have missed it, but I think some description of AVF site is important (BC / RC/ BB / thigh etc).

Our reply We did not obtain this information. We only obtained information about whether the access was in the upper extremities or femoral. We added a note about this in the methods section.

R3 5) I think the definition of CRBSI in the study is fine, but it should be acknowledged that it does not include sampling from a peripheral vein (as recommended by the Centres of Disease Control and Prevention). As I say, this is fine and not a deal-breaker, and your definition is certainly more pragmatic than that of the CDC. However, this difference should be stated. You might want to quote Pelletier et al from 2016 who showed the peripheral culture adds little to sensitivity and specificity of the CVC drawn culture.

Our reply Note added in the methods section

Refs:


R3 6) I don't understand what the Fem is in table 1 and 2. Is this a percent?

Our reply Consistent with all figures in these two tables, these are percentages. This is indicated in the footnote.
7) Is IV drug abuse a big thing in Ireland?

Our reply

The Ireland Drug report 2018 provides an estimate of high-risk opioid and indicates that there were 18,988 opioid users (6.18 per 1 000 population aged 15-64 years) in Ireland.

While we are not aware of data on absolute rates of IV drug use in Ireland, data from the European Monitoring Centre for Drugs and Drug Addiction show that rates of heroin use among new entrants to treatment centers can vary widely from 6% to 62%, with Ireland coming in at 42%. This would suggest that the rates of IV drug use are relatively high in the general population of opiate users.

However, IV drug use is very infrequent at our HD centre, and we do not believe that this is an important factor in our rates of infection or CVC use. A recent study by our group suggests that there are other facility related factors that account for variation and high use of CVC’s in the Irish health system (Hussein et al.).

Refs:


8) Finally, I am always concerned in studies that use rates in a small number of patients with frequent occurrences may be driving the comparison. Could you please do some sort of frequency table or graphic to determine whether there were some hyper-offenders in the CVC group that might be leading to an exaggeration of risk? If you do identify any of these folks, could you please do a sensitivity analysis and leave them out, and see if the conclusion as it stands is still robust?

Our reply

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 CRBSI (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 CRBSI’s) in this study.
and that omission of these patients does not alter the primary findings of this study.

Figure 2. Histogram illustrating frequency of occurrence of CBRSI’s among HD patients with CVC’s.

Table 1. Rate ratios of access-related bloodstream infection events among patients receiving dialysis by tunnelled central venous catheter excluding patients’ with more than 1 and more than 2 cases of CRBSI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Excluded patients &gt; 1 CBRSI</th>
<th>Exclude patients &gt; 2 CRBSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Femoral vs. non femoral)</td>
<td>2.14 (0.56-8.25)</td>
<td>3.99 (1.97-8.10)</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;75 yrs. vs. &lt; 75 yrs.)</td>
<td>1.22 (0.52-2.87)</td>
<td>0.88 (0.43-1.79)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Female vs. Male)</td>
<td>0.74 (0.31-1.73)</td>
<td>0.82 (0.43-1.55)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes vs. No)</td>
<td>0.85(0.36-1.98)</td>
<td>0.85(0.46-1.56)</td>
</tr>
</tbody>
</table>

Multivariable model was adjusted for site of insertion, sex, diabetes and age group.

Multivariate Poisson Regression (IRR) Results excluding patients with more than 2 infections

Rate ratios of AR-BSI in patients receiving dialysis by tunnelled catheter by access site adjusted by age group, gender and diabetes