Author's response to reviews

Title: Incidence, prevalence, and occurrence rate of infection among adults hospitalized after traumatic brain injury: study protocol for a systematic review and meta-analysis

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Version: 2 Date: 1 August 2013

Author's response to reviews: see over
July 31, 2013

Drs. David Moher, Paul Shekelle, and Lesley Stewart
Editors-in-Chief, Systematic Reviews

Dear Drs. Moher, Shekelle, and Stewart and the Systematic Reviews Editorial Team:

Thank you for your thoughtful review of our manuscript entitled “Incidence, prevalence, and occurrence rate of infection among adults hospitalized after traumatic brain injury: study protocol for a systematic review and meta-analysis” (MS: 9794915321009913). We have revised the manuscript as suggested, and feel that the appended document is an improved report, which addresses the comments and suggestions afforded by the Reviewer, Associate Editor Dr. Susanne Hempel. Please find below an itemized list of detailed responses to each of the Reviewer’s comments, including a description of the changes made to the manuscript (which are highlighted in yellow within the manuscript). Within this itemized list, we first cited each comment verbatim in bold type before providing our response for ease of review.

1. “The PROSPERO registration number should be added to the abstract.”

Thank you for the reminder. The PROSPERO registration number (ID: CRD42013005146) has now been added to the abstract (Page 5) and the methods (Page 9) of the manuscript, which read:

“This protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42013005146).”

2. “Generally, the use of abbreviations should be minimized throughout the manuscript to improve readability.”

Thank you for this suggestion. We have reduced the number of abbreviated words used from eight down to three of the most commonly recurring abbreviations, which include intensive care unit (ICU), traumatic brain injury (TBI), and randomized controlled trial (RCT).
3. “I would suggest searching CINAHL for pertinent studies.”

We thank you for this suggestion and agree. We will search CINAHL for relevant studies, and have now included our intent to query this database into the search strategy listed in the abstract (Page 4) and the methods (Page 10) of the manuscript.

4. “A test run of the search strategy would be very helpful to decide whether the search strategy is too restricted - studies may report the number of infections but may not use incidence or prevalence terms in the title, abstract, and keywords of the publication.”

We thank you for this excellent suggestion. We developed and refined our search strategies with the assistance of an information scientist/medical librarian (H.L. Robertson). Although we agree that our search strategy is more restrictive with the addition of the incidence and prevalence terms contained in the incidence/prevalence search theme, these were only added in response to concerns from Ms. Robertson that the study may not be feasible given the number of citations found using more sensitive search strategies. Originally we had planned to conduct a more sensitive search that included only two search themes: traumatic brain injury and infection. However, with this strategy we obtained a large number of articles from each of the queried databases outlined in the search strategy (as an example, 12,918 hits were located in MEDLINE alone) during search piloting testing. Thus, the incidence/prevalence search theme was piloted and then subsequently added in order to conduct a somewhat more specific yet feasible search without being too restrictive.

With the addition of the incidence/prevalence search theme, we reduced the number of articles to a workable amount (e.g., 5,521 in MEDLINE). However, as we are somewhat concerned that some articles may not report incidence or prevalence terms in their titles or abstracts (as outlined by the Reviewer), we will utilize several additional methods to locate any citations that could have potentially been missed. We will screen the reference lists of all included articles and identified relevant review articles (including systematic reviews of randomized trials, which we believe would likely be those that would have the highest risk of using alternate terms for incidence), use the PubMed “related articles” function, and search personal files and conference proceedings (The American Association of Neurological Surgeons, Neurocritical Care Society, Society of Critical Care Medicine, The American Association for the Surgery of Trauma, The Trauma Association of Canada, The Eastern Association for the Surgery of Trauma, and The Western Trauma Association). Finally, we will search the personal files of two co-investigators (A.H.K., D.A.Z.), who are academic neurointensivists, one of which previously conducted a graduate thesis on non-neurological complications of traumatic brain injury (D.A.Z.).

5. “The intervention criterion should be added to the inclusion criteria to specify which interventions patients may receive in studies that are eligible for inclusion in the review.”

We apologize for the lack of clarity and thank you for this suggestion. We have revised the Study Selection section to include a description of which interventions will and will not be eligible. This section now reads:
“Among RCTs that meet the inclusion criteria, we will include only the placebo group (and not the treatment group) for studies examining the interventions listed above (prophylactic antibiotics, glucocorticoids, immunosuppressants, barbiturates, and hypothermia) as these treatments are known to influence the risk of infection. In contrast, we will include both the placebo and treatment groups for RCTs that meet the inclusion criteria in which the intervention is not one listed above (e.g., trials examining use of calcium channel blockers or anti-epileptic drugs).” (Pages 11-12)

6. “The comparator criterion seems out of place (if it is optional it is not a criterion determining the eligibility of studies).”

We agree, and thank the Reviewer for this comment. While we aim to estimate infection occurrence among patients with TBI, we will also extract data regarding patients without TBI when possible (if included in the same study) to examine differential infection estimates among patients with and without TBI. However, as we agree that that the identification of patients without TBI should not be listed as a separate comparator criterion (given that it is optional and not a criterion determining the eligibility of studies), we have removed the comparator criterion as suggested from the list of selection criteria (Page 9). We have also added a description of our statistical methods for determining pooled estimates of the differences in odds of infection between patients with versus without TBI into the Statistical Analyses section of the manuscript:

“Calculation of the pooled differential odds of infection among patients with TBI versus without TBI:

Where available, estimates of the most-adjusted prevalence or incidence odds ratio relating the odds of infection among patients with TBI versus without TBI will be pooled using random effects models and the methods previously outlined by Ronksley and colleagues for handling variably adjusted individual study estimates [37]. Individual odds ratio estimates will only be entered into the model when the odds ratio was estimated from similar study designs and patient populations (e.g., cohort studies relating the odds of infection among poly-trauma patients with TBI versus without TBI). If only relative risks are available from any of the identified studies, these measures will be converted into odds ratios using the method proposed by Deeks and Altman [38].” (Page 17)

7. “I would suggest to limit the outcome criteria section to a description of what studies have to report in order to be included in the review. This includes deciding how you are going to proceed with studies reporting only composite outcomes of adverse events. The data extraction and analysis, e.g., how a cumulative incidence will be calculated, should be explained in the analysis section.”

Thank you for these suggestions. We agree and have therefore moved the calculations for cumulative incidence, incidence rate, prevalence, and occurrence rate to the analysis section
(Pages 15-16). We have also revised the Study Selection section to address studies reporting composite outcomes:

“Two investigators (B.N.V.S. and D.J.R.) will independently screen titles and abstracts to identify studies concerning infection among adult civilian patients hospitalized after TBI. Articles will be included if they meet the following criteria: 1) original research; 2) cohort, cross-sectional, or RCT study design; and 3) reported a cumulative incidence, incidence rate, prevalence, or occurrence rate of infection (or sufficient information is available to calculate an estimate). We will exclude: 1) animal studies; 2) pediatric studies; 3) case reports, case-series, case-control studies, and non-original articles; 4) studies that included less than 10 patients; 5) treatment groups in studies investigating the effect of prophylactic antibiotics, glucocorticoids, immunosuppressants, barbiturates, or hypothermia; and 6) studies focused on military/combat-related TBI, as the results would not be generalizable to the source population of civilian patients with TBI. Studies that report composite outcomes (for example, rate of infection and mortality), without sufficient information to obtain an individual estimate of infection will be excluded. Among RCTs that meet the inclusion criteria, we will include only the placebo group (and not the treatment group) for studies examining the interventions listed above (prophylactic antibiotics, glucocorticoids, immunosuppressants, barbiturates, and hypothermia) as these treatments are known to influence the risk of infection. In contrast, we will include both the placebo and treatment groups for RCTs that meet the inclusion criteria in which the intervention is not one listed above (e.g., trials examining use of calcium channel blockers or anti-epileptic drugs).” (Pages 11-12)

8. “It may be useful to have a separate synthesis section in the protocol to outline how the body of evidence will be evaluated and which criteria will be applied, e.g., number of studies, consistency of estimates across studies etc.”

We agree and have added a Data Synthesis section to the manuscript. This now reads:

“**Data synthesis:**

Both a narrative synthesis and, where possible, a quantitative meta-analysis of the data will be presented. Studies will be clustered according to design (randomized versus non-randomized), setting (ICU versus non-ICU), severity of TBI, and, where available, timing of determination of occurrence rate estimates. After the studies have been grouped into common clusters, their characteristics (including their specific design and study details and a description of the number and characteristics of the study participants included) will be presented in summary tables [33]. These study groupings will also be utilized to identify those studies for which occurrence rate estimates have been derived from similar enough patient populations and study designs such that a quantitative meta-analysis may be possible.” (Page 14)
9. “The funding source and the role of the funder in the review process should be explicitly stated.”

We thank you for this request. This research is supported by an Alberta Innovates - Health Solutions (AIHS) Graduate Studentship Awarded (to B.N.V. Scott) and the Alberta Sepsis Network. These funders have had no role in the design of this study, nor will they have a role in its conduct.

The Acknowledgements section has been revised to read:

“BNVS is supported by an Alberta Innovates - Health Solutions (AIHS) Graduate Studentship Award and the Alberta Sepsis Network. DJR is supported by an AIHS Clinician Fellowship Award, a Knowledge Translation Canada Strategic Funding in Health Research Fellowship, and funding from the Canadian Institutes of Health Research (CIHR) and Clinician Investigator and Surgeon Scientist Programs at the University of Calgary. SSO is funded by the CIHR, the AIHS, Canada Foundation for Innovation, and the Multiple Sclerosis Society of Canada. These funding sources will have no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.” (Page 20)

Thank you once again for the thoughtful review of our manuscript. We hope that you will find this revised version suitable for publication in Systematic Reviews. We look forward to your response.

Sincerely,

David A. Zygun for the authors.