Author’s response to reviews

Title: Clinical and Inflammatory Response to Bloodstream Infections in Octogenarians

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Version: 4  Date: 26 December 2013

Author’s response to reviews: see over
JUSTIFICATION FOR MANUSCRIPT

Bacteraemia in the elderly is becoming increasingly prevalent, and is associated with significant morbidity and mortality. Common teachings suggest that the clinical and laboratory findings in the elderly are ‘atypical’ and non-specific compared to adult populations. It is largely held that elderly patients are less likely to mount a febrile response or elevated inflammatory markers than their adult counterparts. This study sought to examine this teaching.

The study examined every culture positive bacteraemic patient presenting to The Northern Hospital in the year 2010. The outcomes of this study did confirm that older patients are more likely to have an undifferentiated presentation. However, importantly, the study also demonstrated that there is no significant difference in the likelihood of fever or inflammatory markers in older patients compared to adults. This was a unique outcome for this study. This study also demonstrates the importance of the Charlson Index of Comorbidities as predictive factor for mortality with age and hypotension being less important but statistically significant predictive factors of mortality.

DISCLOSURE STATEMENT

The manuscript, or parts of it, have not been and will not be submitted elsewhere for publication. The authors declare there is no conflict of interest. The study was funded by Northern Health.

AUTHOR CONTRIBUTIONS

Dr Jessica Green: Primary author, data entry and literature review
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Dr Craig Aboltins: Interpretation of data and editing of manuscript
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RESPONSE TO REVIEWER COMMENTS:

Response to reviewer’s report 1

Reviewer: Irene Maeve Rea

Major Compulsory Revisions.

1. Methodology:
   a. The Methodology section has insufficient detail for clear exclusion criteria for the study and this detail is missing in the accompanying Flow Diagram 1.

      The methodology section has now been amended for clearer exclusion criteria

   b. There is no explanation for the comparator age groups to be <80 (18-80yrs) an extremely wide range and .80 years.

      Splitting the groups into 3 groups would result in significant issues in terms of power to detect differences due to the small sample size.

   c. No standard deviations are given for age.

      Older group mean 87 years SD 3.9

      Younger group mean 55 SD 16.9

   d. In addition why does the Abstract say that participants 'were taken to be all adult patients'?

      The abstract has been amended and now says participants were aged 18 and above

2. Results:
   a. How was mortality identified and at what stage was it audited in the study protocol? Mortality was identified as being death within the index admission. 30 day mortality was not calculated as this data was not available to authors.

   b. Paragraph Headings for different result sections would be useful ie patient demographics, Clinical and Laboratory Finding, Mortality etc to match the Table with this data.

      Suggested subheadings have been added to the results section

   c. P values need only be described to 2 decimal points.

      P-values have now been amended to 2 decimal points.

3. Tables:
   a. The tables need more detail and description in headings.

      The title of Table 3 has been changed to Clinical Presentation and Laboratory Measurements of Patients Presenting with Culture Positive Septicaemia

   b. Abbreviations such as LLC, HLC, numbers ( ), SD should be defined in subscript below tables.

      The tables have been amended to include definitions for abbreviations
c. Microbiology gram positive or negative finding in Table 3 would fit best in Table 4 with microbiology results.
   Thank you for this suggestion. However the authors are concerned that the graph may appear cumbersome or difficult to interpret if structured in this way.

d. In logistic regression table 3 the variables should be described more precisely i.e., what does greater age, lower Blood Pressure, Lower O2 Saturation mean in this context. It is not clear what the comparators are for each variable v Mortality in this logistic analysis.
   This table has now been amended

e. There are no legends for the Figure or any of the Tables included with manuscript.
   Legends have been added where appropriate

4. References:
   a. The Charleston Index is neither defined nor referenced in the manuscript.
      The Charlson Index of comorbidities has now been referenced in the manuscript.
   b. The references throughout do not seem to be in order or have been incorrectly indexed i.e., Background para 3 end of sentence ref 5,17. References 6-17 appear to be missing. Perhaps this should read 5-17 but this needs checking. There is no evidence of Reference 4 in the text. Similarly in the first paragraph of the Discussion references 21,29, should this be 21-29, since 22 and 23 follow etc.
      The references have now been amended to appear in correct numerical order.
Response to reviewer’s report 2

Reviewer: Jacek M. Witkowski

Major compulsory revisions:

1. These concern their study groups, and exclusion – inclusion criteria: Although their initial number of patient episodes is high, the number of those included (167 out of 1367) seems barely adequate.

   The results section has been amended to explain why the large number of screened patients did not meet the inclusion criteria.

2. These patients were divided into the older cohort (80+ years of age) and the younger one, consisting of people aged 18 – 80 (!) years. Although understandable in the light of relatively small study groups, inclusion of subjects commonly defined as young, middle-aged and old in a single “younger” cohort seems a mistake, as numerous reports show that they grossly differ in their immunological and inflammatory responses. It would be desirable if the authors split their ‘younger’ cohort into young, middle-aged and old sub-cohorts or, alternatively, removed their youngest subjects in order to define their ‘younger’ cohort as elderly.

   We have added means and standard deviations as per previous reviewer indicating a comparison between a younger group, mean age 55 years and an older group mean age 87 years. Splitting the groups into 3 groups would result in significant issues in terms of power to detect differences due to the small sample size.

   Also, the authors never mention the ethnicity of their subjects, and it is a factor that might affect the results; were their cohorts ethnically uniform, or at least balanced?

   Thank you for this interesting suggestion. Unfortunately data on ethnicity was not available to the authors in this retrospective study.

3. The paper describes a single hospital study – could it affect the result (by preferential types of nosocomial infections in a single hospital)? Would not a multi-hospital approach be better, as averaging the types of infections present in the study cohorts as well as increasing the numbers of those finally included in the study?

   Thank you for this suggestion. The authors agree that a multi-hospital study would be an excellent way in which to expand upon the current study in the future.

4. Finally, the authors mention that “Patients were excluded from the study if their blood culture specimen contained likely contaminants, or if they were undergoing chemotherapy.”

   However, they give no explanation of these ‘likely contaminants’ and their meaning other than saying “contaminants were determined on a case by case basis by file review by an infectious diseases physician”. It is unclear what the authors mean by the statement “Chemotherapy patients were excluded as they are immunosuppressed and often do not grow organisms despite high fevers.” What kind of chemotherapy they have in mind? Anti-microorganism? Anti-tumor? Once again the text is imprecise and thus hard to perceive.

   The chemotherapy referred to by authors was anti-tumour chemotherapy. Contaminants were defined as organisms grown such as Staph coagulase negative where there were no clinical features of an infection and the growth of the organism was likely to be a result of a
contaminated collection process. The Methods section of the manuscript has been amended to reflect this detail.

5. In the Discussion, the authors use the term “bacteremic patients”. DO they consider it synonymous to “patients developing sepsis”? Bacteremia may not lead to septic complications!
   Thank you for identifying this issue. The underlying assumption made by the authors in this study is that the complications which arose during the episode of bacteraemia are secondary to sepsis.

6. Later on the same p.11, the authors summarize that “… older patients do not mount a poorer immune response than younger patients. In fact, on average these patients had higher C-reactive protein, white cell count and neutrophil count.” Apparently, the authors are not familiar with the concept of inflamm-aging, describing increased pro-inflammatory factors in a subgroup of an elderly cohort as putting them at high mortality risk.
   Thank you for this suggestion. The authors believe that inflammaging refers to a chronic inflammatory process from chronic exposure to antigens. This is distinct from an acute systemic response to an infection where the general doctrine is that older patients have a less rigorous acute response such as absence of pyrexia.

7. The abstract concludes that their “older patients are more likely to have an undifferentiated presentation”; however, the term is not explained and vague, especially in the light of next sentence “However, importantly, there is no significant difference in the likelihood of fever or inflammatory markers.”. What do authors have in mind? In the Introduction (p.5) they mention that older patients are more likely to react to infections in a nonspecific way, but never use the term ‘undifferentiated’. It would be desirable if they were more precise.
   The abstract has been amended and the word “undifferentiated” has been removed.

8. In the Data Analysis section of M&M, the authors mention the reference model, but under that name they list the name and version of the SPSS statistical package. Only from the legend of Table 2 the reader can understand that they applied one of the SPSS Regression Models, but it remains a mystery which one.
   Thank you for this suggestion. The logistic regression model used is also referenced in the data analysis sub-section of the Methodology section.

9. Also, they never reference any source for the major tool they applied in their study, i.e. the Charlson Index of Comorbidities. Did they apply the original, or any of its variants and if the latter, which one?
   Thank you for identifying this gap. The Charlson Index of Comorbidities is now referenced.

10. Especially, that on p. 12 they mention factors that were not examined in their study, including possibly kidney and liver ailments, which clearly are included in the original Charlton Index!
    Thank you for this comment. In the discussion section, the authors do refer to other literature which suggests poor prognostic value of underlying cognitive status, functional ability, chronic urinary incontinence, elevated lactate dehydrogenase and hypoalbuminaemia. The authors are not aware of a reference to kidney and liver ailments in this section of the study.

11. There are inconsistencies in their numbers. For instance, they mention 167 subjects included (in the Abstract), but then only 155 (117 ‘younger’ and 38 ‘older’) in the text, which agrees with the data in tables. Where this inconsistency comes from?
Thank you for identifying this discrepancy. These figures have now been amended and should appear consistent in the study.

12. However, data presentation in the tables also leaves plenty to wish for. The tables’ row descriptions do not include any units, so they are hard to read. Also, the listed totals in the table 4 never (!) equal the sum of the columns.
   Thank you for reviewing the tables. The authors have re-evaluated the totals of the rows and columns which appear accurate.

13. Description of the results is also imprecise and doubtful. For instance, on p. 11 the authors say “The difference in neutrophil count was on average three x10^9/L higher in older patients…” which is hard to understand. Was the difference in neutrophil count higher? Or, more likely, the neutrophil count itself?
   Thank you for identifying the confusion in wording. Yes, the authors are referring to the size of the difference between the two groups which is on average $3 \times 10^9$/L higher in the older group.

14. The most important results of the study are illustrated in the Table 2. However, the factors included in the analyses are imprecise again. What is “lower systolic blood pressure”? “Lower oxygen saturation”? “Greater respiratory rate”? What are the numerical delimiters for “lower” and “greater” in each case? In fact, table 3 should precede table 2, as it lists the vital parameters of the subjects, while table 2 is the result of their analysis.
   Thank you for identifying the confusion in Table 2. This table has now been amended and the classifiers greater and lower have been removed. The authors hope the table should read more clearly now.

15. On p. 11, they mention “This study also demonstrated a similar total number of gram positive and gram negative organisms…”; certainly, they did not mean the actual numbers of bacteria per person, as might be interpreted from that statement.
   Thank you for identifying this area of uncertainty. Here the authors are referring to whether or not a gram negative or a gram positive organism was cultured in a given blood culture specimen.

Minor revisions:

The authors refer to Tables and Appendices, yet there are no Appendices included in the file nor available online. Please explain and/or correct.

This error has now been amended, and references to appendices have been removed.