Peer Review File

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Reviewer A

This is a large series and important for the AJO audience. I would like to see the points mentioned in the marked up work addressed.

Importantly how were the rhinogenic (central or atypical) skull base osteomyelitis cases identified in a retrospective multicentre trial?

Comment 1: I believe you are talking about Otological SBO and this should be mentioned. There is of course, a large body of research in rhinologic and other causes of SBO.
Reply: Indeed, we are discussing only otologic SBO and have made changes to make it very clear to the audience early in the manuscript that otogenic SBO is the only disease we will be discussing.
Changes made: We have re-worded the first 2 sentences of the introduction. Also Outlined "Otogenic SBO" (line 62).

Comment 2: No new paragraph here.
Changes made: agreed, and changed.

Comment 3: What do you mean acute inflammation. Is that by clinically, by blood markers, radiologically? Should be clarified
Reply: We mean blood markers of acute inflammation.
Changes made: We have adapted the description of this to "evidence of acute inflammation measured with blood markers" line 68-69.

Comment 4: Do you mean this is a hypothesis of the work to be presented. Please clarify
Reply: Absolutely, this is what we mean.
Changes made: "We hypothesize that the cause for this is premature completion of antimicrobial therapy, and that the risk relapse or failure may be mitigated by a longer course of targeted antimicrobial treatment" lines 74-76.

Comment 5: I think this discussion of surgery in the introduction would fit better in the previous paragraph.
Reply / changes made: Thankyou that's a good suggestion I have moved to prior paragraph.

Comment 6: Could you mention other possible causes of improvement here.
Reply: prior to chandlers early work the disease was not well popularized and management was even more poorly understood. Improved diagnostics leads to earlier diagnosis.
Changes made: "Owing to improvements in antimicrobial drugs, advances in diagnostic imaging techniques, and an increasing awareness of the disease itself.." lines 81-82.

Comment 7: This should be worded more accurately ie the specificity of the modality was

lower than expected, therefore, it's usefulness in determining when disease has been treated is less useful.
Reply: Thanks. I have elaborated on the data from the mentioned literature.
Changes made: “A recent meta-analysis however found the sensitivity of Gallium 67 to predict disease resolution was only 71%, and its specificity also too low to be considered useful” line 91-93.

Comment 8: Why is this methodology sentence put at the end of the introduction?
Reply: This is outlined in the instructions for Authors on the AJO website: “A statement should be included at the end of the “Introduction” to indicate which reporting checklist was followed (e.g., “We present the following article/case in accordance with the CONSORT reporting checklist.”)”
Changes made: I have moved this comment to the end of the methods section (line 151-152).

Comment 9: Is your rhinogenic SBO also included in this inclusion criteria? Consider rewording to "Inclusion criteria" and mention "exclusions" if there were any. All were definitely not rhinogenic, you had 24% biopsied from the nasopharynx, how can you be sure they are from the ear.
Reply: Thankyou I hope that by addressing the inclusion criteria wording this will be more clearly communicated as exclusively otogenic SBO to the audience.
Changes made: “All patients with clear clinical history and signs of acute otitis externa were included” (Lines 113-114)

Comment 10: This is your Primary outcome and should be worded as such.
Reply: we have simply added this to the description of the outcome
Changes made: “Our primary outcome was clinical outcome from treatment” line 125.

Comment 11: Mentioning the exact type of Ga67 scan would be good.
Reply: Thankyou I have elaborated on this
Changes made: we have added: “Gallium 67 bone scan fused with SPECT (single photon emission tomography)” line 133.

Comment 12: Why was ESR not included. There is published work suggesting it has a better predictive power in SBO than CRP
Reply: Indeed. ESR is seldom performed in our centre. In this study, ESR was recorded in only 8 patients and therefore was not used.
Changes made: Addition of text “Erythrocyte Sedimentation rate (ESR) was measure in only 8 patients and therefore was not analyzed”.

Comment 13: Good to mention lower cranial nerve palsies and it's affect on disease severity here.
Reply: though the number of patients with this was low, the outcomes were nearly universally poor for this group.
Changes made: Addition of text “Lower cranial nerve palsy was seen in 5 patients at

presentation; 2 who had clinical failure, 2 whose disease relapsed, and 1 who was clinically cured".

Comment 14: This should be in the discussion.
Reply / Changes made: the paragraph is unchanged, but moved to the end of the discussion section (lines 286-292).

Comment 15: Why do you think it has increased? No discussion is presented.
Reply: Demographic changes, and an increase in the population of survivors of severe chronic disease, especially diabetes mellitus.
Changes made: We have added text to the discussion and referenced this in the bibliography. "The Pacifika population continues to grow in New Zealand, particularly in the Auckland region, and is approximately twice as likely to have diabetes mellitus than other ethnic groups in New Zealand (including Māori). These factors likely contribute in part to an increasing rate of disease observed". (Lines 250-253)

Comment 16: Can you discuss this more. Why do you think ear disease is more accessible transnasally? Could you be biopsing rhinogenic SBO?
Reply: prior literature has illustrated the various routes of spread of otogenic SBO, which include medially into the central skull base. Our study illustrates a propensity for this in our cohort.
Changes made: We have adapted the text between lines 259 and 264 and use a case of penetration to the contralateral lateral skull base.

Comment 17: A little more discussion on what may be done in tissue/ swab negative disease would be beneficial for the audience.
Reply: We have added text to guide the reader.
Changes made: We have added lines (269-273) which outline what to do in the culture negative scenario when the patient is not improving on empiric treatment.

Comment 18: Discussion of the mortality with a median of 49 days of treatment would be good for the audience. Any suggestions from the authors about how to improve outcomes? Did the patients who died have tissue/ swab negative disease? Did they have abscesses or necrotic tissue that could have been removed to improve the bioavailability ratio of the treating antibiotics?
Reply: We have discussed mostly the reduction in relapse of disease by prolonging the treatment in a hope for curing these cases. The median days to failure has been added.
Changes made: Addition of text lines 281-285.

Comment 19: Detail of the FDG PET and possible PET/ MRI to have a higher specificity in

identifying disease cure would be good here. FDG PET is quicker to do with a 60-70% reduction in radiation exposure. Nice to mention some detail for the audience.
Reply: With respect to disease monitoring through imaging, the ideal modality is still very much undecided. We feel that in in this patient group, reduction in radiation exposure is a secondary and less important consideration; but has been included.
Changes made: Added text 293-297 which extends the discussion about different imaging modalities and their benefits / deficiencies.

Comment 20: Can you really say this? Probably not. I understand the positive predictive value in your study (94%) but do you think the tissue biopsies under GA were patients that were going to be negative or were negative in an OPD setting before being referred in to a tertiary centre.
Reply: The reason we mentioned opportunistic biopsy in an awake patient was to forego the anaesthetic risk in this group of highly comorbid patients. EAC granulations are also easily accessed, and were fruitful. Certainly, if there wasn't any visible tissue to biopsy, patients would likely require anaesthesia for deeper biopsy. Many of these happened to be through mastoidectomy, which was fairly low yield.
Changes made: lines 314-318 have been added. This outlines a practical approach to the patient with respect to biopsies

Comment 21: In early disease the technetium is often negative. What about Gallium (which is not as defined) or even FDG PET or T1 weighted MRI +/- diffusion restriction?
Reply: similar response to comment # 20, lines 314-318 address, with references, the approach to diagnostic imaging assisting in planning culture.
Changes made: Lines 214-318 addition.

Comment 22: Can you even say this? I am not sure you have convinced me that the transnasal cases were not rhinogenic.
Reply: we have further mentioned our preference to biopsy via the nose in cases with central BOS extension and we believe medial extension is common. All patients had symptoms and signs of severe otitis externa, which we apologies for omitting initially. Refer also to the case mentioned of observed contralateral spread of disease via the central skull base.

Reviewer B

The study's stated aims are to identify the epidemiology, microbiology, prognostic indicators, and diagnostic accuracy of investigations in the management of skull base osteomyelitis patients in the Auckland region.

The study was a retrospective, multi-institution, cohort study of adult patients with skull base osteomyelitis. The cohort size is substantial when compared to the published seminal literature. It is worth noting that the patient population from the authors prior study (20 patients from 2004-2011)

has likely been included in this current study (63 patients from 2004-2019) but this is not discussed.

There are issues with how the results data is analysed and presented that requires correction. The authors should also include their local ethics approval for the study. The conclusions, as currently stated by the authors, are not directly supported by their study results.

Overall, this study would be a useful contribution to the scientific literature with appropriate revisions.

Changes made: line 113-114: this discloses this inclusion of these patients, who have been researched and reported on previously. All raw data was sourced independently by the primary investigator.

Specific Comments:
Comment 1: Page 3: "The diagnostic criteria vary and there exist at least 27 versions…". I do not know where the number 27 has been obtained – it is not mentioned in the quoted article.
Reply: this meta-analysis referred to, illustrated 27 variations in diagnostic criterion which are listed in table 3 of that article.
Changes made: I have elaborated on the meta-analysis findings and made it clearer by adding: .."with a meta-analysis in 2018 identifying 27 publications that used varying combinations of 22 variables; as criteria to make the diagnosis"

Comment 2: Page 4: "therapy are debated (10-12)" First sentence is missing a period.
Reply / Changes made: period added.

Comment 3: Page 4: "We present the following article in accordance with the STOBE guidelines" missing a period after this sentence. This statement should be moved to footnotes.
Reply / Changes made. Period added. statement moved to footnotes.

Comment 4: Results: The results are presented inconsistently in style and when citing relevant Figures/Tables. This hinders the reader's understanding of the results, for example:
- Page 7, Paragraph 1: "30 of the 37" and later "31/63 (49%)"
- Page 8, Paragraph 2: "in 59 patients" and "in four patients"
- Inconsistent citing of tables/figures "(figure 1)" and "Microbial data is presented in table 2"

Reply / Changes made: A consistent use of recording has been adopted in the above examples.

Comment 5: Page 7, Paragraph 3: "17 patients (26%) had swabs but no tissue submitted." The percentage figure is incorrectly rounded and should be 27%.
Reply / Changes made: corrected.

Comment 6: Page 9, Paragraph 1: "patients suffered a relapse of disease at a median of 51 days (range = 14-471 days)". A relapse should not be able to occur at 471 days - as per the authors' definition of "cure" at 12 months (or 365 days).

Reply / Changes made: thankyou, this was incorrectly stated, 471 days had included admission date - relapse for this patient. The duration was in fact 292 days and has been changed.

Comment 7: Page 9, Paragraph 1: “severe disease (2)” the reference is quoted in superscript.
Reply / Changes made: corrected

Comment 8: Page 9, Paragraph 2 “Radiological outcomes”: this paragraph is unclear as to the numbers of patients with appropriate imaging that had “radiological cure” or “radiological failure” at the end of treatment. It is unclear if the authors are presenting results for “clinical failure” or “radiological failure” at times.
Reply / Changes made: This paragraph has been changed and re-worded to more clearly dissect the specificity and sensitivity calculation of the gallium scan. We have opted to group failure and relapse as adverse outcomes together in this calculation.

Comment 9: Page 10, entire Paragraph 1 “This review is limited by…”: this paragraph should be moved to the discussion as it does not present any data/results.
Reply / Changes made: this was moved to discussion.

Comment 10: Page 10, Paragraph 2 “in other literature (19), (2) (table 1).”: references should appear consecutively in the same parentheses as per the Vancouver reference style.
Reply / Changes made: corrected.

Comment 11: Page 11, Paragraph 2 “reached statistical significance (table 3).”: incorrect table cited.
Reply / Changes made: Thank you. Indeed, changed to table 5.

Comment 12: Pages 11 & 12, Conclusion: Most of the statements in the conclusion are not supported by the results of this study but these paragraphs could be moved to the discussion to accompany the authors justifications for their updated protocol.
Reply / Changes made: The conclusion has been completely re-written and contents of it have either been deleted or incorporated into the discussion.

Comment 13: Figure 3 “If C. not met at 8 weeks”: How can 8 weeks of IV therapy being delivered not be met at 8 weeks? This part of the protocol is unclear.
Reply / Changes made: Absolutely. I have deleted this condition in the protocol.

Comment 14: Figure 3 “I C. not met…” & “If D. not met…”: inconsistent period after protocol options.
Reply / Changes made: "if C not met..." has been removed from the figure.

Comment 15: Table 1 “NS = difference did not reach statistical significance”: there is no statistical analysis on the table, data not reported by other studies could be left blank.
Reply / Changes made: NS has been deleted from the cell, and the caption of the table.

Comment 16: Table 4: Some 95% confidence intervals do not include the cited odds ratio e.g. Diabetes has an odds ratio for relapse of 3.4 with a 95% CI of 0.001 to 0.899.
Reply / Changes made: This table has been re-drawn as the confidence intervals were incorrectly stated in the original submission.

Comment 17: Table 4 & 5: "SUCCESS" in the tables should be changed to clinically CURED as previously defined by the authors.
Changes made as suggested.

Comment 18: Table 5: This table is unclear as there are multiple variables in one cell. Also, all data points should be rounded to the same decimal place.
Reply / Changes made: This table had been re drawn to make it easier to view and interpret.

Comment 19: Ethics approval: the study does not list any ethics board approval or the required Ethical Statement Footnote as per the Author Guidelines.
Reply / Changes made: Ethical approval granted and attached to this submission. Ethical statements added in footnote.