Author’s response to reviews

Title: An unusual case of infective pneumocephalus: case report of pneumocephalus exacerbated by continuous positive airway pressure

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Version: 1 Date: 12 Nov 2017

Author’s response to reviews:
Dear Dr. Christian Backer Mogensen,

We would like to thank you and the reviewers for taking the time to carefully appraise our manuscript entitled “An unusual case of infective pneumocephalus: case report of pneumocephalus exacerbated by continuous positive airway pressure,” (EMMD-D-17-00071). We have made thorough revisions to the manuscript in accordance with the constructive feedback provided during the peer review process. We feel the manuscript in its revised form will be of high interest for publication in BMC Emergency Medicine. We summarize our response to the reviewers below.

Editorial Comments
Editor Comment 1: Thank you for submitting this interesting case report to BMC EM. The 3 reviewers have some suggestions to improve the report. You will notice that the reviewers have different opinion concerning the value of your flowchart in fig. 1. I suggest you to keep it.

Author Response to Editor Comment 1: We would like the thank the editor for reviewing our manuscript. We appreciate your suggestion to keep Figure 1 in this article and in accordance with your feedback we will retain Figure 1 in the manuscript.
Reviewer Comments
Reviewer 1
Reviewer 1 Comment 1: Please change in several lines, the proper form of writing Streptococcus salivarius. The scientific names of bacteria are governed by international norms stating that they are written with initial capital letters in the first word that form them, although not in the second, and entirely in italics; In addition, the scientific name should be complete the first time it is mentioned, although it is admitted that the first word is then abbreviated, taking the initial letter and retaining the italic.

Author Response to Reviewer 1 Comment 1: We would first like to thank the reviewer for their thorough evaluation of the manuscript. We have changed all instances of Streptococcus salivarius reported in the manuscript to the correct S. salivarus, adhering to internationally accepting scientific reporting standards. These changed are now noted throughout the manuscript.

Reviewer 1 Comment 2: It is necessary to better describe the case and the clinical feature of the main problem that gives relevance.

Author Response to Reviewer 1 Comment 2: We thank the reviewer and have worked to improve the quality of our case description in accordance with their constructive feedback. We have revised our manuscript to provide a thorough and clear description of the patients presenting symptoms and critical features leading to a step up in care to HDU. In accordance with feedback from the neurosurgical team, the patient was stepped up to HDU management. This decision was based on the neurological indications for HDU admission, specifically this patient presented with an acute neurological condition with impaired consciousness and GCS meeting the 9-12 cutoff for admission. We have amended our case description to ensure the pathway of care to clarified and appropriately captured. As suggested in later comments from review 1, we have now included the patients PCO2 values obtained during the initial ABG as well as a clarification as to the indications for CPAP in this patient, please refer to page 5 (paragraph 2). We apologize for any previous misunderstandings, and wish to clarify that this patient was not put on CPAP during hospital stay. This patient was using CPAP at home for the
management of sleep apnea. We have clarified this further in our case description. Please refer to page 7 (paragraph 2) and page 8 (paragraph 2).

Reviewer 1 Comment 3: It is necessary to improve the structure of abstract writing.

Author Response to Reviewer 1 Comment 3: We thank the reviewer for noting areas for improvement in our manuscript. We have revised our abstract to accurately reflect the presented case. Please refer to page 3 of the manuscript.

Reviewer 1 Comment 4: Arterial blood gases: Arterial blood gases does not mention PCO2 values, and I think this is important, taking into account the indication of the CPAP.

Author Response to Reviewer 1 Comment 4: We have revised our manuscript to include the PCO2 values, these can be found on page 7 (paragraph 2). However we again stress that the patient was not placed on CPAP during hospital stay.

Reviewer 1 Comment 5: The reason for indication of CPAP during the ICU stay was not mentioned, previous indication, apnea or hypercapnia with respiratory acidosis?

Author Response to Reviewer 1 Comment 5: We have revised our manuscript to include a clarification that the patient was not on CPAP during hospital stay. Please refer to page 8 (paragraph 2 in the manuscript).

Reviewer 1 Comment 6: The ventilatory parameters of CPAP have not been described, please include it, this is important, since this may have a direct relevance to the case ease, include it, this is important.

Author Response to Reviewer 1 Comment 6: Please refer to Author Response to Reviewer 1 Comment 5.
Reviewer 1 Comment 7: Do not use of Capital letter in a middle of a sentence. Line 7, page 7: "There was No intracranial haemorrhage".

Author Response to Reviewer 1 Comment 7: We have revised the manuscript to correct for this grammatical error on page 9 (paragraph 4).

Reviewer 1 Comment 8: Consider not including Figure 1 (Case Timeline of Acute Presentation and Management), since it is redundant and does not bring anything new to the case.

Author Response to Reviewer 1 Comment 8: We have been advised by the editor to keep this Figure, as the CARE checklist for reporting quality in case reports requires the inclusion of a figure illustrating the management pathway. Please also refer to Editor comment 1.

Reviewer 1 Comment 9: For everything else, the case seems very interesting because of the scarce literature on it, besides being apparently the first case described in relation to sinus wall osteomyelitis.

Author Response to Reviewer 1 Comment 8: We thank the reviewer for their positive feedback and hope they are satisfied with the revisions made in accordance with their constructive feedback.

Reviewer 2
Reviewer 2 Comment 1: The case is very interesting and figure 1 summarizes the case very well!!!

Author Response to Reviewer 2 Comment 1: We thank the reviewer for their critical appraisal of this study. We appreciate the reviewers positive feedback of the study. In accordance with both Reviewer 2 and the Editor we will keep Figure 1 in the manuscript.
Reviewer 2 Comment 2: You describe a very atypical CNS-infection and it seems likely that use of CPAP has contributed to the pathogenesis. I think you should focus on this possible correlation.

Author Response to Reviewer 2 Comment 2: We agree with Reviewer 2 that this potential source of infection is both important and requires further discussion. We have revised our discussion section to include a more in-depth evaluation of the potential association and need for further research.

Please refer to page 11 (paragraph 2). We have also revised our introduction to include a discussion of the potential relationship between CPAP and its potential risk for infection as well as pneumocephalus. This will help ensure the audience appreciates the association between CPAP and the outcomes of our patient as a main focus of the paper.

Reviewer 2 Comment 3: The text is not easy to read. There are several linguistic inconsistencies. For instance: In the first part of the abstract, you say non-traumatic hydrocephalus "remain highly uncommon", but in the next sentence, you say there "remain many case reports". If the clinical condition is so uncommon, how come there are so many case reports? And why do you use the word "remain" twice?

Author Response to Reviewer 2 Comment 3: We apologize for any inconsistencies in our writing. We have revised both the abstract and introduction to clarify our message. There are a limited number studies to support the association between CPAP and atraumatic pneumocephalus and to our knowledge this rare presentation associated with sinus wall osteomyelitis has never been described. We originally meant to say there are more studies reporting an association between atraumatic pneumocephalus and CPAP than those reporting this rare presentation with associated osteomyelitis. Please refer to page 3 (paragraph 1) and page 6 (paragraph 3) for our revised abstract and manuscript.

Reviewer 2 Comment 4: I suggest you rewrite all parts of the case story, making it more focused and clear.
Author Response to Reviewer 2 Comment 4: We appreciate the reviewers feedback and have revised our manuscript to provide a thorough and clear description of the patients presenting symptoms and critical features leading to a step up in care to HDU. In accordance with feedback from reviewer 1 we have also included a clarified summary of the indications for step up to HDU. In agreement with feedback from the neurosurgical team, the patient was stepped up to HDU management. This decision was based on the neurological indications for HDU admission, specifically this patient presented with an acute neurological condition with impaired consciousness and GCS meeting the 9-12 cutoff for admission. We have also revised our introduction to better reflect the aims of our case report, specifically which associations we wish to highlight to the audience. Please refer to page 7 -10 for our revised case description including more details to help illustrate the patient pathway.

Reviewer 2 Comment 5: You emphasize the (possible?) sinus wall osteomyelitis, but from the case report, it is not evident how this diagnosis was confirmed. As I told you before, I find the serious CNS-infection a lot more interesting than the (possible") kranial osteomyelitis.

Author Response to Reviewer 2 Comment 5: We appreciate the reviewers interest in the CNS infection and have worked to improve the manuscript to clarify how the diagnose of sinus wall osteomyelitis was made. We refer the reviewer to page 9 (paragraph 1) where we clarify that the ENT review suggested a diagnosis of pneumocephalus with meningitis from a nasal source. The ENT assessment included a clinical examination, nasoendoscopy, and careful review of CT imaging, where they noted no defects. The ENT team suggested the growth of S. salivarius, correlated with a diagnosis of sinusitis eroding back into the cranial vault. Essentially this was a diagnosis of exclusion after the growth of S salivarius was confirmed by PCR of the CNS fluid, suggesting a sinonasal source. Thus without a defect noted on nasoendoscopy or CT imaging, it was believed the pneumocephalus was secondary to a cranial osteomyelitis - as suggested by the ENT and Microbiology team.

Reviewer 2 Comment 6: It is not adequate to describe the patients serious CNS-symptoms (dramatic decline in consciousness, GCS 10 etc.) as "non-specific systemic symptoms" as you do in the abstract.
Author Response to Reviewer 2 Comment 6: We agree with the Reviewer and have revised our abstract to include a description of the serious CNS symptoms. Please refer to page 3 (paragraph 2).

Reviewer 2 Comment 7: You write "The growth of s. salivarius, correlated with a diagnosis of sinusitis eroding back into the cranial vault". How was the sinusitis diagnosed? From what sample did S. Salivarius grow, as you say CSF- and blood cultures were negative.

Author Response to Reviewer 2 Comment 7: S. salivarius was identified from the CNS sample using PCR analysis, which was subsequently carried out after the initial gram stain, and culture were negative. PCR results normally come in last as they take the longest to complete. This clarified on page 9 (paragraph 1) of the manuscript. A suggested diagnosis of sinusitis came from the ENT review where they suggested the growth of S. salivarius, correlated with a diagnosis of sinusitis eroding back into the cranial vault. This was a diagnosis of exclusion after the growth of S salivarius was confirmed by PCR of the CNS fluid, suggesting a sinonasal source, please refer to page 9 (paragraph 1 of the manuscript).

Reviewer 2 Comment 8: This very a interesting case story deserves a much better "package". I hope you will work on it!

Author Response to Reviewer 2 Comment 8: We thank the reviewer for their positive feedback and hope they are satisfied with the revisions made in accordance with their constructive feedback.

Reviewer 3

Reviewer 3 Comment 1: This is an interesting case of pneumocephalus, S. salvarius meningitis, sinusitis and possible osteomyelitis. The authors identify that the novelty of this case lies in the association with sinusitis and osteomyelitis. In the introduction, the authors make a connection of CPAP and pneumocephalus with a rare case of previously undescribed sinus wall osteomyelitis. The rest of the manuscript however seems to tell the story of this rare case of S. salivarius
sinusitis, likely osteomyelitis and finding of pneumocephalus that may have resulted from nocturnal CPAP use. The authors should clearly identify the association they are trying to highlight with this manuscript in the introduction. The way it is currently written presents an association that seems a little disconnected from the rest of the manuscript.

Author Response to Reviewer 3 Comment 1: We would like to thank Reviewer 3 for both their interest in this study as well as their constructive feedback. We have revised our introduction to more adequately reflect the findings of our study. We appreciate the main focus of this work has been to carefully describe an unusual presentation of S. salivarius infection with associated osteomyelitis and finding of pneumocephalus. However, the potential source of infectious transmission through the use of CPAP in this patient seemed a both interesting and important finding for this clinical discourse. However, we acknowledge this conversation may be better reserved for the discussion of our case-report. Thus, we have revised the introduction to better reflect the case-report.

Reviewer 3 Comment 2: The diagnosis of osteomyelitis in this patient seems to have been made on imaging and not based on biopsy as the patient was not deemed to be a surgical candidate. It is not till much later in the discussion that the CT evidence of osteomyelitis becomes clear to the reader (page 9 lines 4-6). However on page 8 lines 47 - 57 the manuscript suggests that the ENT surgeon's diagnosis was in fact sinusitis with meningitis. The authors should make the link to osteomyelitis more clear as this seems to be a pivotal point for the novelty of this report.

Author Response to Reviewer 3 Comment 2: We agree with Reviewer 3 that there is need for earlier clarification and discussion of the diagnostic evidence for osteomyelitis. We have revised the manuscript to address this concern. Please refer to page 9 (paragraph 2) where we have now outlined our evidence for osteomyelitis within the case presentation section of this study.

Reviewer 3 Comment 3: The authors never address why CPAP was permanently stopped in this patient despite the recommendation in the literature that CPAP be stopped for a period of 6 - 8 weeks followed by re-evaluation for possible re-introduction. It is unclear if the authors in fact mean that CPAP was stopped in this patient for the duration of therapy for sinusitis,
osteomyelitis and meningitis or whether in fact CPAP was stopped 'permanently' as the patient's OSA was evaluated and felt to not require CPAP therapy.

Author Response to Reviewer 3 Comment 3: The patient’s CPAP was stopped for the duration of therapy for sinusitis and osteomyelitis. In addition a formal discussion was had with the patient about abstaining from CPAP during periods of sinusitis due to their previous susceptibility to infective pneumocephalus, which was likely exacerbated by the use of CPAP. During periods of sinus infection and rhinorrhea it was advised the patient not use their CPAP machine. Symptoms of sinusitis and rhinorrhea were explaining in detail, such that the patient understood when to abstain from CPAP. We have clarified this on page 9 (paragraph 3) of the manuscript.

Reviewer 3 Comment 4: Further, there are several minor grammatical concerns the authors should address and revise:
Page 5 line 44: 'Patient GCS...' should be 'Patient's GCS'
Page 5 line 49: take out 'exhibited' so sentences reads as '...clonus and hyper reflexia throughout.'
Page 7 lines 6-11: The CT report findings seem to be taken directly from a radiology report and the authors should consider summarizing the findings in grammatically correct sentences rather than short phrases that are questionably copied and pasted from the radiology report. Alternatively the radiology report should be cited as such.
Page 10 line 2: '...a recent studies...' or '...recent studies...'?

Author Response to Reviewer 3 Comment 4: We have revised these grammatical concerns within the manuscript.

Reviewer 3 Comment 5: The conclusion is strong and the reason why this case is interesting to report in the literature. The introduction of this manuscript however is slightly disconnected from this conclusion and could easily be revised.

Author Response to Reviewer 3 Comment 5: We again thank the reviewer for the time and effort they have put into critically appraising this work. We appreciate their positive feedback and suggestions for improvement. We hope the revisions made satisfy the reviewer.
We thank the reviewers and editor for their constructive evaluation of this work. We hope we have clarified any of the issues brought forward. We thank you for considering this work.

Yours Sincerely,

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