Author’s response to reviews

Title: Paediatric Focal Intracranial Suppurative Infection: a UK single-centre retrospective cohort study

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Author’s response to reviews:

Dear Professor Zalm,

We are pleased to submit the attached revised original major article entitled ‘Paediatric Focal Intracranial Suppurative Infection: a UK single-centre retrospective cohort study’ for consideration for publication in BMC Pediatrics

Our study, which is among the largest case series available, and the largest single-centre case series, reviewed 95 paediatric cases of focal intracranial suppurative infection, a disease still known to cause significant mortality and morbidity. Currently there are no uniform guidelines regarding treatment and our study provides considerations regarding antibiotic treatment. We found a bimodal age distribution, and observed Streptococci were most commonly isolated. Only 12.7% of patients cultured anaerobe microorganisms. Furthermore, mortality was relatively low at 3.2% and there was significant short-term and long-term neurological morbidity, 38.5% and 24.2% respectively.

In this manuscript, we show there is a wide variability of empirical antibiotics used to treat these children effectively, but we also show that 90.5% of children would have been sufficiently covered with a standard empirical regimen of a third-generation cephalosporin plus metronidazole. This manuscript is relevant to BMC Pediatrics as it provides microbiological and treatment data for focal intracranial suppuration combined with descriptions of clinical predisposing factors, symptomatology, and outcome data. Therefore, it provides a broad, comprehensive overview which can help other centres to optimise their guidelines and practice regarding paediatric focal intracranial suppuration, and
We confirm that this manuscript is original and has not been published elsewhere and is not considered for publication by any other journal. All of the authors have seen and approved this manuscript for submission to BMC Pediatrics and fulfil the authorship criteria. There has not been any writing assistance. We prefer to have our figures published in black and white.

Thank you for your consideration of our manuscript. Please, find our response to the reviewers comments which have contributed to improving this manuscript attached. We look forward to hearing from you.

Yours sincerely

On behalf of the authors,

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Technical Comments

We thank the reviewers’ and editor’s comments for their kind comments in aid to improve our manuscript.

- Title Page: Please include e-mail addresses of all authors in the title page
  - E-mail addresses were added

- Tables: Please place your tables in the main manuscript file after the figure legends and references
  - Tables were moved to the requested location in the manuscript.

Editor Comments (from both reviewers)
• The glycopeptid teicoplanin is used instead of vancomycin; As known the penetration of teicoplanin to CSF is limited. Why did the authors used teicoplanin and lineozolid? What is the reason for less using of vancomycin?
  o Indeed, we used teicoplanin in 18 patients. However, these patients received additional teicoplanin for suspected central line infections (as per protocol) and not for the treatment of their intracranial infection (as stated in lines 155-157), since they already received adequate antibiotics for their intracranial bacteria.
  o Linezolid was used because it’s known to have a good penetration to CSF even when the meninges are not inflamed, whereas vancomycin tends to have a lesser penetration once the meninges are not inflamed anymore. This makes linezolid a more effective option in high-risk patients, and in the final stages of treatment of brain abscess. Furthermore, linezolid is available as an effective oral option, whereas vancomycin doesn’t get absorbed well in its oral form. Therefore, linezolid can be used effectively without having to change to other antibiotics. Lastly, we tend to see less adverse effects from linezolid and save vancomycin for occasional intrathecal use. (lines 184-187)

• I wonder if the patients with focal intracranial suppurative infection who has unexpected course were searched for underlying undiagnosed primary immune deficiency?
  o Patients with an unexpected clinical course were screened for underlying primary immune deficiency, yet only 1 patient was diagnosed with an immunodeficiency later in childhood. (added lines 223-224)

• What is the screening panel of PCR?
  o Streptococcus spp, Neisseria meningitides, Fusobacterium spp, Aspergillus spp. Staphylococcus spp. This information was added. Although we need to mention that PCR availability increased over time and not all patients had material sent for PCR diagnostics (lines 68-69).

• The antibiotics resistance of the grown microorganism were not addressed; ie penicillin resistance for the isolated pneumococci strains.
  o We used antibiotic resistance patterns in our analysis of antibiotic coverage (lines 171-183), in order to assess how adequate empirical antibiotics covered the microorganisms cultured in our patients. We did not observe penicillin resistance for isolated pneumococcal strains and we described all relevant resistant organisms in the manuscript (lines 174-180). An extensive analysis of all antibiotic resistance patterns in order to identify if certain resistant strains were present, was outside the scope of this study. If the editor however feels it is important to add a specific comment we are happy to do so.

  o This study has been discussed and was used as a reference for this manuscript (see reference no. 18)

• Finally I propose also to investigate the relationship of the mortality and morbidity with consciousness level (Glasgow Coma Scale) at the admission to the hospital.
  o In our raw data we collected data on the patient’s Glasgow Coma Scale (GCS) on admission. Unfortunately this was not always well documented in the paper patient dossiers, although
often terms varying from alert to drowsy were often written up. Therefore, we were unable to conduct a statistical analysis to investigate the relation of consciousness level and mortality/morbidity. Still, we did have children in this cohort who had a low GCS and they tended to have worse outcomes. Similarly we had alert, GCS 15 children who also had worse outcomes due to fast deterioration after admission. (lines 215-219, and 262)