

Peer Review File

Article Information: <http://dx.doi.org/10.21037/ajo-21-10>

Reviewer A

Comment 1:

If the data is available and if possible could the authors add the mean or median time for the acute infective episodes to be successfully treated? Dogma in the UK states you have to treat the ear topically for about 4 weeks. Is that true? Is a longer duration of therapy linked to lower rates of later re-infection?

Reply 1:

Our institution clinical practice guideline states for topical antimicrobial treatment duration of 10 days for fungal otitis externa without tympanic membrane perforation. In the setting of tympanic membrane perforation, our clinical practice guidelines state review after 1 week of treatment for reassessment and toilet. Antimicrobial treatment duration was outside the scope of this study; however, we acknowledge the comments. A prospective study may help to draw more robust conclusions regarding treatment duration and the risk of re-infection or incomplete resolution of the initial infection.

Changes in text: (Discussion, Page 9, Line 179-183)

Duration of antimicrobial treatment was not reviewed in this study, however initial antimicrobial treatment duration in our institution is two weeks with further review, aural toilet, and reassessment for continuing treatment. Therefore, the impact of treatment time on the likelihood of persistent perforation and the rate of infection recurrence was not investigated.

Reviewer B

Comment 1:

Could the authors comment on the potential migration of otocomb/kenacomb ointment through the TMP? As I'm sure the authors are aware, there is an aminoglycoside component to this preparation.

Reply 1:

Thank you for the comment, please see the changes below.

Changes in text: (Discussion, Page 8, Line 155-161)

Indeed, the recommended RVEEH CPG treatment of Otocomb®/Kenacomb® still carries ototoxic potential due to possible migration of the ointment through the TMP and into the middle ear. Our CPG recommends painting, rather than filling, the canal with ointment in cases of large TMP to reduce the volume of ointment within the ear canal and therefore the chance of ototoxicity. It is not recommended that the ointment is placed directly in the middle ear through the perforation.

Comment 2:

In addition, the narrow ear canal present in OE makes it difficult to install the "packing"

Reply 2:

A narrow ear canal is a common feature of bacterial otitis externa, however, it is uncommon in fungal otitis externa in our experience. Our clinical practice guideline does recommend an otowick soaked with Locacorten Vioform in these instances. In our study, there were no patients with FOE who required insertion of an otowick (Page 8, Line 164-165). In addition, the use of wicks is addressed in the discussion. Please refer to page 8, Lines 161-169.

Comment 3:

Could the authors comment on the role of Clotrimazole in the middle ear and whether this is considered ototoxic?

Reply 3:

Clotrimazole is considered insoluble in water and the solvents used are irritants to middle ear mucosa and cause discomfort and burning or stinging sensation. There are no randomized control trials to confirm ototoxicity of clotrimazole in humans. One animal study suggests clotrimazole, miconazole, and tolnaftate are potentially safer antimycotic choices than nystatin.

Changes in text: (Introduction, Page 3, Lines 45-47)

The management of FOE with TMP remains a challenge due to the ototoxic potential and middle ear irritation from topical antifungal agents or solvents used in their preparation, such as clotrimazole. There are no human studies to confirm ototoxic potential of commonly used agents, however animal studies suggest clotrimazole, miconazole and tolnaftate are potentially safer choices.

Comment 4:

Line 108 - the authors state that this is the largest series - how did the authors determine this?

Reply 4:

We refer the reviewers to a literature review performed by Koltsidopoulous *et al* (cited reference #2). There were three studies found reporting number of cases with persistent tympanic membrane perforation following otomycosis. The largest cohort in this review was by Hurst *et al* (cited reference #3) which contained 22 cases. The others were Ho *et al* (cited reference #13) and Song *et al* (cited reference #7) with 18 and 11 cases respectively.