Author's response to reviews

Title: Limitations of caspofungin in the treatment of obstructive pyonephrosis due to Candida glabrata infection

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Author's response to reviews: see over
Re: Revised manuscript (6178926351019096): Limitations of caspofungin in the treatment of obstructive pyonephrosis due to Candida glabrata infection

Dear Editor and reviewers,

We would like to thank both reviewers for the interest in our case report and their valuable comments which we have tried to incorporate in the revised manuscript. We hope our improved manuscript will now be suitable for publication.

Our point-by-point response to the comments is as follows:

Reviewer: Maria do Rosario Silva

1) *The name of the azole resistant* drugs have been added. This information is also apparent from the MIC data.

2) *Why have we not used voriconazole?* We very much agree with the reviewer that voriconazole has been used to treat *C. glabrata* infections. However, there are two issues why we have not used this drug as a second line treatment option in our patient. Firstly, this patient was severely ill and suffered from severe renal failure. Under these clinical circumstances voriconazole is known to precipitate acute kidney failure, nephritis and renal tubular necrosis (VFEND summary of product characteristics, section 4.4 adverse events and table on adverse drug reactions, Pfizer Ltd. UK). Secondly, voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine (VFEND summary of product characteristics, 5.2 Pharmacokinetic properties, Pfizer Ltd. UK).

We have chosen not to discuss this aspect in our case to keep the manuscript at reasonable length as well as the fact that the main focus was on the pharmacokinetic of caspofungin. Nevertheless, we have added a final sentence to the discussion regarding the need for further clinical data on other antifungal agents such as voriconazole.

Reviewer: Annette Fothergill

1) *Abstract:* strains has been changed to singular.

2) *When was caspofungin introduced and for how long?* We recognize that the management of this patient is quite complex. To summarize: the patient presented originally with acute renal obstruction and she developed severe sepsis due to *C. glabrata* during the insertion of bilateral renal nephrostomy tubes. This septic episode was treated with AMB for 4
weeks. During this time she had also the left tubes replaced by a stent. She then had a 4 months ‘anti-fungal break’ and came back to the hospital for a routine stent insertion of the right nephrostomy tube which failed. Unfortunately AMB was only started shortly after this procedure and the patient developed again a severe Candida sepsis (positive urine and blood cultures) with acute renal failure. At this time AMB was given for three days and then changed to caspofungin which was given for 12 days (see original text) by which time the blood and urine became sterile.

3) We did measure the MIC’s for various anti-fungal drugs from the C. glabrata isolates obtained after the ‘failed’ stenting (and before AMB) and there was no difference. In order to keep the manuscript at a reasonable length, we have not included this data.

4) Testing caspofungin levels. Unfortunately, we didn’t obtain caspofungin levels from the urine or serum as the patient seemed to have responded to the treatment and there was no ‘clinical’ need at the time. However, retrospectively, this data would have been interesting. Animal studies have demonstrated that the majority of unchanged caspofungin is secreted during the first days, at later time (eg 16 d) the cumulative excretion of the unchanged drug seems to be low (9%) [Balani et al. 2000]. It seems that at a later time point the metabolites of the drug are mainly excreted but not the unchanged original compound [Sandhu et al. 2004]. Unfortunately we could not find much information on the clinical efficacy of these various excreted metabolites otherwise we would have included it in the discussion.

5) We agree that a single case report is not sufficient to dismiss the use of this drug in the treatment of uti’s. We appreciate the fact that there is very little clinical data on the use of caspofungin in the treatment of complicated urinary tract infection and there is a need for more clinical data. We have therefore included a sentenced in the discussion to make this clearer. However, this case report is also to emphasise the fact that in cases of ‘obstruction’ drainage of the pus is probably more important than a systemically used antifungal drug.

Yours sincerely,

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