Author's response to reviews

Title: Use of daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections: a short case series

Authors:

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Version: 2 Date: 21 March 2013

Author's response to reviews:

Hayley Henderson
BioMed Central
Floor 6
236 Gray's Inn Road
London, WC1X 8HL
United Kingdom
March 21, 2013

Re: Manuscript # 1011755051848813 entitled “Use of daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections: a short case series”

Dear Dr Henderson:

On behalf of my co-authors, I would like to thank you for your email of February 13, 2013. I would also like to thank the two reviewers for their valuable and insightful comments. As requested, we have addressed the reviewers’ comments below and also in the text of the manuscript as appropriate.

We look forward to hearing from you.

Kind regards,

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Reviewer's report

Title: Use of daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections: a short case series

Version: 1 Date: 10 January 2013

Reviewer: George Alangaden

Reviewer's report:

Manuscript review
Use of daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections (UTI): a short case series

General Comments:
The authors describe their experience in using daptomycin for the treatment of symptomatic UTIs caused by vancomycin-resistant enterococcus (VRE) in 10 hospitalized patients. The patients were identified over a 3 year period. Daptomycin was administered in doses ranging from 5mg/kg q 24hr to 8mg/kg q 24hr for the treatment of VREUTI. Duration of therapy was generally 3 days. All patients had resolution of symptoms and eradication of VRE noted at completion of therapy. The study adds to the limited literature on the use of daptomycin for VREUTIs. However there are certain questions that the authors need to respond to before a decision can be made on publication. These are noted below.

Specific Comments:
1. Background:

In the interest of antibiotic stewardship the therapeutic options listed for the treatment of VREUTIs mention should include nitrofurantoin and fosfomycin (for cystitis), doxycycline for (cystitis and pyelonephritis) and strains of VRE may be remain susceptible to ampicillin.

Author response: We have added nitrofurantoin, fosfomycin, and doxycycline to the list of therapeutic options based on their in vitro activity against VRE, in keeping with the original list compiled that was also based on in vitro activity against VRE (daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline). We have not included ampicillin because its activity against VRE UTIs is poor, especially among resistant E. faecium strains (Zhanel GG et al. J Antimicrob Chemother 2003; 52:382-388) and because susceptibility to ampicillin is not based on whether isolates are vancomycin resistant or vancomycin sensitive.

The MIC90 of VRE (E faecalis and E. faecium) and the CLSI resistance
breakpoint when discussing susceptibility of daptomycin.

Author response: We have added MIC90s for vancomycin-resistant E. faecalis and E. faecium found in the literature to the Background section, as requested. CLSI resistance breakpoints related to vancomycin-resistant enterococcus have not yet been determined for daptomycin.

(The state our objective is to offer .....infection control challenge is unclear and should be deleted).

Author response: In order to clarify, we have modified the statement to focus on the fact that there is an important therapeutic challenge in the treatment of VRE UTIs that we are attempting to address with our report.

2. Methods:

Why was informed consent obtained from subjects for a retrospective study?

Author response: As standard practice, St Mary’s requires that informed consent be obtained from all subjects when publication of details of their cases is being considered.

The inclusion criteria should be all VRE-symptomatic UTI treated with daptomycin, as the 20 patients with VRE-UTI not included because ID was not consulted did not receive daptomycin.

Author response: We agree with the reviewer about the inclusion criteria and have included an inclusion criteria statement. Since the 20 patients who did not receive daptomycin were not part of this report, we have deleted the statements referring to them to eliminate confusion.

Definition: Pyuria is generally defined as >10 WBC/HPF

Author response: It is our experience that pyuria is commonly defined as >5 WBC/HPF (see Gorelick MH and Shaw K. Screening tests for urinary tract infection in children: A meta-analysis. Pediatrics. 1999;104(5):e54; and Dieter RS. Sterile pyuria: a differential diagnosis. Compr Ther. 2000;26 (3):150–2). It is also the definition of pyuria used in St Mary’s.

The urinary symptoms should be listed and it would be essential to classify symptomatic UTIs as a) either cystitis or pyelonephritis (upper tract disease) or b) else as complicated versus uncomplicated. This is important due to the potential overuse of agents such as daptomycin and linezolid for cystitis/uncomplicated UTIs. The duration of therapy of 3 days suggests most patients had cystitis. This should be clearly stated.

Author response: All cases were cystitis (ie, lower tract disease), which we now point out in the Results section. Patient 3 received a longer course of daptomycin treatment due to a concurrent bacteremia. The distinction between “complicated” and “uncomplicated” infection was not made at the time of treatment in our study.
Duration of follow-up should be stated, especially since on page 7 the statement is made that “no relapse was noted for 2 years.” How was this monitored? It would be better to utilize end-of-therapy resolution of symptoms and microbiological eradication as the objective endpoints.

Author response: There was 1 patient who was followed for 2 years with no subsequent UTI; however, because the statement identified by the reviewer may be misleading, we have removed it from the text.

Most patients had follow-up urine cultures for microbiologic assessment by the 3rd day of treatment and were followed clinically up to 7 days posttreatment. This information has been added to the legend of Table 2. Indeed, resolution of symptoms (clinical cure) and VRE eradication (microbiologic cure) were our endpoints, as indicated in the manuscript.

3. Results:

Table 1: State the criteria used to stage kidney disease (1-5).

Author response: Serum creatinine levels and creatinine clearance were determined using the Cockcroft-Gault equation to stage the level of kidney disease in each patient. Clarification has been added to the legend of Table 2.

It would be important to include daptomycin MICs if done in the table. This may clarify why high doses of daptomycin were selected.

Author response: Daptomycin MICs were not performed. As indicated in the Methods and Results sections, daptomycin doses were chosen to promote adequate concentrations for VRE treatment in the urinary tract, based on our empiric experience and in the absence of specific recommendations in the literature.

Table 2: State when were the urine cultures done post treatment?

Author response: As indicated in the Methods section, urine cultures were performed at the end of daptomycin treatment or as close as feasible (eg, if the exact date fell on the weekend, no follow-up occurred that day) as a confirmation of microbiologic cure. We have added approximate urine culture timing in the legend of Table 2.

In the 3 patients with indwelling urinary catheter were the catheters discontinued or exchanged?

Author response: Although it is the usual practice at St. Mary’s to exchange catheters, this information is not always captured in nurses’ notes, so we are unable to give a definitive answer on this for the 3 patients in this study.

The statement on relapse should be deleted or justified see above comment on follow up.

Author response: The statement on relapse has been removed as indicated in
response to an earlier comment.

4. Discussion:

Should be more focused on the results. First 2 paragraphs could be omitted.

Author response: We believe that the first 2 paragraphs help set the stage to discuss the importance of the results presented in this manuscript, and as such, we have retained them.

The MICs of daptomycin to E faecalis and E. faecium and the breakpoints should be stated.

Author response: As stated in response to an earlier comment, we have added MIC90s to the Background section; breakpoints have not yet been established.

The discussion should focus on and include a more detailed comparison of the study with the other 2 studies of daptomycin use in VRE-UTI (references 12, 13). This is important to understand the population studied, endpoints, doses of daptomycin, etc. For instance reference 12 included 22 patients with complicated VRE-UTIs and used does of 4mg/kg whereas reference 13 used even lower doses.

Author response: As requested by the reviewer, we have expanded the comparison of our study with previous work. Upon review of our original submission, we realized that we had mistakenly included the case study series of Naber KG et al (Daptomycin versus ciprofloxacin in the treatment of complicated urinary tract infection due to gram-positive bacteria. Infect Dis Clin Pract 2004, 12:322-327) as a report on daptomycin use for VRE UTIs. The enterococcus-related UTIs in the Naber report were not identified as vancomycin-resistant; hence, we have removed reference to this publication from our manuscript.

Limitations of the study should be stated

Author response: As requested, we have added a Limitations section to the Discussion.

5. Abstract:

Methods: Inclusion criteria should include symptomatic VRE_UTIs and treatment with daptomycin.

Author response: We modified the abstract as requested.

End point of clinical resolution of symptoms is missing

Author response: We modified the abstract as requested.

Results: should be specific such as number of patients with CKD, Foleys, etc rather than general statements.
Author response: We have added more specifics as requested.

Reviewer's report:

Title: Use of daptomycin in the treatment of vancomycin-resistant enterococcal urinary tract infections: a short case series

Version: 1 Date: 27 January 2013

Reviewer: James Malone Lee

Reviewer's report:

I like this case report and believe it to be important. Enterococcus is a real swine and reports on its treatment are invaluable. Whilst this may not be an RCT, their expense and the time that its takes to complete them, mean that this sort of report is essential for development.

It is very well written and a most interesting read and I should be very keen for it to be published. The authors give all of the information that interested parties would wish to know and they present a balanced and reflective case

Author response: Thank you for this review. No actions taken.