Author's response to reviews

Title: High-dose daptomycin and fosfomycin treatment of a patient with endocarditis caused by daptomycin-nonsusceptible Staphylococcus aureus: Case report

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Author's response to reviews: see over
Dear Editor,

Thank you very much for your critical suggestion on reviewing this article. The answers to the questions were provided points by points. We adjusted the paragraphs orders in the discussion part as suggested by the English editing department, and also replaced the term “daptomycin-nonsusceptible” to the abbreviation “DNS” according to recent published reports. The article had been modified according to your suggestion. We had marked all these corrections in yellow color. We hope the article is now acceptable to be published in your esteemed Journal.

To Associated Editor:

Q1: The author must provide more clinical details as requested by both reviewers. Most importantly, the specifics of the prior therapies need to be included.

A1: We had added more clinical details including the treatment duration in the text as the two reviewers’ suggestion in the manuscript.

Q2: The authors must also consider the possibility that daptomycin alone may have been successful if the pacer lead were removed as pointed out by one reviewer. In other words, focus removal is just as important as antibiotic therapy

A2: We had added this reference and several sentences on p. 11. “…As reported by del Rio A et al. the prevalence of treatment failure is greater among patients receiving only antibiotics therapy compared to those treated with surgical removal of implanted device and antibiotics therapy. …It is possible that with daptomycin alone the patient could have been cured in the first attempt if the
ICD lead had been surgical removed.” We also added sentences in the discussion part on p. 11-12 discussing about the use of daptomycin alone might be effective after ICD-device removal.

Q3: The authors must also provide baseline rationale for trying this combination by citing prior literature.

A3: We had added the baseline rationale for trying this combination and cited prior literature in the introduction part on p. 4-5 as the suggestion of the two reviewers.

To Reviewer #1:

Q1: Authors should explain what was the rational to use the combination of daptomycin plus fosfomycin to treat a case of ICD device-related MRSA endocarditis after daptomycin failure with a non-susceptible daptomycin strain. It would be interesting to perform time-killing curves in order to check if there was synergy. They should also provide appropriate references.

A1: We had added the baseline rationale for trying this combination and cited prior literature in the introduction part on p. 4-5 as your suggestion. It is still possible to treat this patient successfully with only high dose daptomycin after surgical removal of the ICD device, but before the decision of surgical intervention by the cardiovascular surgeon, the combination therapy was chosen for more effective biofilm management.

The time-killing curve method was not performed for lack of golden standard interpretation method, and also for limited time available to complete that. The fractional inhibitory concentration index method was used only to interpret the results of combination and was shown
value between 0.5-1. Additive effect might be more suitable for this condition and we also added the term in the text on 10.

Q2: Pacemaker and ICD device-related staphylococcal endocarditis must be always treated with the combination of antibiotics plus surgery (generator plus lead removal). Authors should include the following reference: Del Rio A et al. Chest. 2003 Oct; 124(4):1451-9. It is possible that with daptomycin alone the patient could have been cured in the first attempt if the removal of the ICD lead had been performed.

A2: We had added this reference and several sentences on p. 11. “…As reported by del Rio A et al. the prevalence of treatment failure is greater among patients receiving only antibiotics therapy compared to those treated with surgical removal of implanted device and antibiotics therapy…It is possible that with daptomycin alone the patient could have been cured in the first attempt if the ICD lead had been surgical removed” We also added sentences in the discussion part on p. 11-12 discussing about the use of daptomycin alone might be effective after ICD-device removal.

Q3: The term “prosthesis-related” endocarditis is confusing. Please, replace it by ICD device-related endocarditis in all the manuscript.

A3: Thank you for critical suggestion. We had replaced the term “prosthesis-related” by “ICD device-related” endocarditis in all the manuscript.

Q4: The daptomycin dose approved by the FDA and the EMEA for treating SAB and endocarditis is 6 mg/kg/day.
A4: Thank you for your critical suggestion. We had corrected the sentences on p.4 in the introduction to “The once daily dosing of daptomycin 6 mg/kg approved by the USA Food and Drug administration showed non-inferiority to the standard therapy for treating *S. aureus* bacteremia and endocarditis” Citation of the reference “Fowler VG et al. NEJM 2006: 355(7): 653-665” was added.

Q5: What was the rational to combine vancomycin and linezolid. This is a well known antagonistic combination.

A5: We did not use this combination of vancomycin and linezolid. The treatment course was intravenous vancomycin for 14 days first followed by oral oral linezolid for another 14 days. We had corrected the sentences to “Intravenous antibiotics with vancomycin 1 g every 12 hours for 14 days followed by oral linezolid 600 mg every 12 hours for another 14 days were prescribed for her endocarditis,” on p. 5-6

Q6: Please, explain in detail the doses and duration of all antibiotics given and the duration of bacteremia (number of positive blood cultures/number of blood cultures performed).

A6: The duration of treatment was presented in days for each course and was added in the manuscript including vancomycin, linezolid, daptomycin, tigecycline, teicoplanin, and final combination therapy of daptomycin plus fosfomycin. We are sorry for offering insufficient medical history of this patient due to the limitation of word count in a case report form, and the clinical condition of this patient in real life was much more complicated than that presented in
this case report form. The number of positive/total blood cultures was also added in the text on p5-6.

Q7: Authors should discuss a recent publication done by Steed ME, et al. Antimicrob Agents Chemother. 2010 Dec; 54(12):5187-92 because they studied novel daptomycin combinations against daptomycin-nonsusceptible MRSA in an in vitro model of simulated endocardial vegetations. They found that the combination of daptomycin plus cotrimoxazol was bactericidal.

A7: We added several sentences on p.10 as your kindly suggestion. “…Steed et al. also reported that the combination of daptomycin plus clotrimoxazole was bactericidal against DNS MRSA in an in vitro model of simulated endocardial vegetations…”

To Reviewer #2:

Major Compulsory Revisions:

Q1: No balance is given to the activity and use of fosfomycin against staphylococci, including MRSA. Although high dose daptomycin use in treating non-susceptible strains is interesting, this has been reported previously. The most interesting aspect is the use of fosfomycin, for which the authors failed to give proper introduction to the reader. Review of this could be done in just a few sentences in the introduction.

A1: We had added the review of fosfomycin in the introduction part on p. 4-5 as well as the discussion part on p10-11.
Q2: Some of the references in the introduction and conclusion do not seem to properly support the statement given. There are many examples throughout, but one introduction example is referencing the 6-8 mg/dl dose for S. aureus bacteremia and endocarditis with a reference from 2004, two years before dosing in this disease state was established in clinical trials. A careful review all references is needed, and the authors should adjust accordingly.

A2: We had reviewed all the references and adjusted those errors carefully. We apologized for those mistakes and also thank you for the critical suggestion on this manuscript. And We also corrected the sentences on p.4 in the introduction to “The once daily dosing of daptomycin 6 mg/kg approved by the USA Food and Drug administration showed non-inferiority to the standard therapy for treating S. aureus bacteremia and endocarditis” Citation of the reference “Fowler VG et al. NEJM 2006: 355(7): 653-665” was added.

Q3: The timeline of the disease-treatment course is unclear. Can the authors provide specifics to the duration of treatment for each course (Ex: how many days was the patient on vanco and linezolid therapy, daptomycin therapy?)

A3: The duration of treatment was presented in days for each course and was added in the manuscript including vancomycin, linezolid, daptomycin, tigecycline, teicoplanin, and final combination therapy of daptomycin plus fosfomycin. We are sorry for offering insufficient medical history of this patient due to the limitation of word count in a case report form, and the clinical condition of this patient in real life was much more complicated than that presented in this case report form.
Q4: Using broth dilution is not an approved standard for fosfomycin susceptibility testing. Did the authors also perform agar dilution testing (recommended standard) of control strain for verification.

A4: Thank you very much for the critical suggestion. We had performed both the broth and agar dilution for fosfomycin on the isolates and QC strain, but mislabeled broth dilution method results in the table. This error was corrected, and the MICs by the broth dilution all showed less than 8 mg/L.

Minor Essential Revisions:

Q1: There is no sufficient evidence for daptomycin as an option for hVISA and VRSA. This statement should be revised to state daptomycin as a treatment option for staphylococcus aureus endocarditis, including MRSA.

A1: We had corrected this sentence as your critical suggestion on p.4 to that “Daptomycin is a 13-aminoacid compound derived from fermentation of Streptomyces roseosporus and is a new treatment option for S. aureus endocarditis, including vancomycin-resistant S. aureus”

Q2: For susceptibility testing of fosfomycin, was 25 mg/L of glucose-6-phosphate added to the media as indicated by CLSI?

A2: Thank you for the kindly suggestion. We did add 25 mg/L glucose-6-phosphate in the agar media as the agar dilution media indicated by the CLSI. On performing broth dilution, the same concentration of G6P was also added. We had added a sentence of glucose-6-phosphate in p. 8.
Q3: In the second paragraph of the conclusion, authors state that isolate st06 was susceptible to daptomycin in combination with fosfomycin. This indicates that synergy testing was performed. If so, no results are given.

A3: The time-killing curve method was not performed for lack of golden standard interpretation method, and also for limited time available to complete that. The fractional inhibitory concentration index method was used only to interpret the results of combination and was shown value between 0.5-1. Additive effect might be more suitable for this condition and we also added the term in the text on 10.

Discretionary Revisions:

Q1: Authors could mention the effects of the mutational genes identified in dapto-NS. Ex: membrane fluidity changes and others (Jones T. Antimicrob Agents Chemother 2008)

A1: We added several sentences discussing about the mutational genes both in the introduction and discussion part, and the references were properly cited.

Q2: Although no CLSI interpretive standards are given for fosfomycin MICs in S. aureus, EUCAST breakpoints exist for staphylococci (susceptible <=32 mg/L) and would help add some relevance to the MICs reported in the paper.

A2: Thank you for your kindly suggestion and we had added the interpretation susceptibility for fosfomycin in EUCAST on p. 8.