Author's response to reviews

Title: Two cases of cardiac device-related endocarditis due to Streptococcus dysgalactiae subsp. equisimilis (group C or G streptococci)

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Author's response to reviews: see over
Dear Miss Sheryl Ramos,

Thank you for Your letter on January 31rd, about our revised manuscript entitled ”Two cases of cardiac device-related endocarditis due to Streptococcus dysgalactiae subsp. equisimilis (group C or G streptococci)” by Sari Rantala and Suvi Tuohinen MS: 1455832500116324. We are grateful for the opportunity to resubmit the revised manuscript. We have addressed all the suggestions and recommendations of the reviewers. Please, find enclosed the corrected manuscript. The detailed descriptions of the revisions and the point-by-point answers are attached on separate sheets.

We hope that you will now consider this manuscript acceptable for publication in the BMC Infectious Diseases.

Yours Sincerely,

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Revisions and point-by-point answers

Reviewer 1. Baard Kittang:

Thank you for valuable comments.

Major Compulsory Revisions

Comment 1
This is valuable comment. We have added following microbiological methods to the text. During 2013 the BacT/ALERT 3D (bioMérieux SA, Marcy-L'Etoile, France) blood culture system with standard culture media was used. In the current cases, the Lancefield serogroups were defined by latex agglutination using the Streptex latex test system (Remel Europe Ltd, Dartford, UK). All isolates were also strain identified by a commercial test (Rapid ID 32 STREP, bioMérieux SA, Marcy-l'Etoile, France). The species identification is correct. This data has been added to text. We base this on phenotypic and biochemical tests for *S. dysgalactiae* subsp. *equisimilis*.

Comment 2
The reviewer rised an interesting point. I agree the analysis of *emm* types would be of interest. We have earlier analyzed *emm* types in collaboration with National Institute for Health and Welfare in Helsinki, but only in studies, not in clinical practise. Unfortunately, we find this request too difficult to achieve. In our earlier study, we analyzed *emm* types of recurrent *S. dysgalactiae* subsp. *equisimilis* bacteraemia and our study showed that all recurrent bacteraemia episodes were same *emm* type (Rantala, S Emerg Inf Dis 2010). Also PFGE was analyzed and it was unique and identical (Rantala, S Emerg Inf Dis 2010). It suggest that strains probably are of the same *emm* type.

Comment 3
The ability to infect both endocardium and cardiac devices and produce recurrence is an interesting point. We have clarified discussion around this topic. We have added "*S. dysgalactiae* subsp. *equisimilis* isolates can aggregate human platelets and can internalize into human endothelial cells and they may both promote persistence within the vascular system (Rohde M, Microbes and Infection 2012). Rohde, M et al have identified a fibronecting-binding protein, GfB1, from group G streptococci, which functions as an adhesin and invasin and the invasion mechanism differ from group A streptococci (Rohde, M et al Cellular Microbiology 2011)." Two new references Rohde M, Microbes and Infection 2012 and Rohde, M Cellular Microbiology 2011 are added.

Minor essential comments

General comments
a. As reviewer suggested, we have corrected the text.
b. As reviewer suggested, we have corrected the text.
c. The reviewer is right. Page and line numbers would easy the review process.

1. Abstract
a. Background
We have edited the Background part. In revised text the word *S. dysgalactiae* subsp. *equisimilis* has not repeated so many times.
b. Conclusion
We have clarified the text. *S. dysgalactiae* subsp. *equisimilis* seldom cause cardiac device endocarditis.

2. Background
a. This is a valuable comment. Pharyngitis/tonsillitis is added to the text: "The spectrum of *S. dysgalactiae* subsp. *equisimilis* diseases ranges from pharyngitis, tonsillitis and…". Also the following sentence is added "Pharyngitis and tonsillitis are the most frequent non-invasive manifestations of *S. dysgalactiae* subsp. *equisimilis* disease".

Case presentation
a. Case 1
We have corrected text as reviewer suggested.

b. Case 2
We have corrected text as reviewer suggested.

Conclusion
a. As reviewer suggested, we have corrected the sentence.
b. We have corrected "bacteremia occurs at high age".
c. We have added new references concerning the increased use of pacemakers (Voight, A et al. 2010 and Greenspon, AJ 2011)
d. As reviewer suggested, we have corrected the sentence.
e. As reviewer suggested, we have corrected the sentence.
g. We have corrected text as reviewer suggested.

Reviewer 2. Kai Hang KH Yiu:

Thank you for valuable comments.

Major comments

Comment 1
As reviewer suggested, we have edited Case presentations.

Comment 2
Microscopic pathology was available from first patient and samples from the leads extracted yielded no growth.

Comment 3
Case 1: the patient received her pacemaker 2 years prior the presented infection. She had regular controls on our pacemaker policlinic without any sings of local pacemaker infection. No entry site of infection could be identified. During the first bacteremia episode, her right glenohumeral joint was also swollen and tender, but no aspiration of joint fluid was made. Case 2: This patient received his pacemaker 14 months prior the presented infection. He, too, had regular follow-up at the
pacemaker policlinic without local signs of pacemaker infection. On his prior patient data there are several episodes of erysipelas in his legs, chronic edema. The skin was thoroughly inspected each time without any breaches of skin.

Comment 4
The reviewer is right. We have added following sentence to the Discussion "The second patient was treated with immunosuppressive treatment for his rheumatology disease and that could make him prone to rare pathogen".

Comment 5
For life-threatening infections (e.g. meningitis and endocarditis), aminoglycoside can be considered in addition to penicillin, as aminoglycoside- penicillin combination shows in vitro bactericidal synergy. Older clinical observations have been suggested to improve outcomes in patients treated with combination therapy, but no well-conducted studies exist. Several guidelines recommend the addition of aminoglycoside to penicillin therapy of streptococcal endocarditis during the first two weeks (Gould, FK, J Antimicrob Chemother 2012). Because of high nephrotoxicity risk for elderly, a narrow-spectrum monotherapy threatment with benzylpenicillin was preferred for these patients instead of combination of benzylpenicillin and gentamicin. This is added to the Discussion.

Minor comments
The dates have been corrected.