Author's response to reviews

Title: Clinical Manifestations and Outcome in Staphylococcus aureus Endocarditis Among Injection Drug Users and Nonaddicts - A Prospective Study of 74 Patients

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Author's response to reviews: see over
Dear Dr. Sally Simpson,

Please find enclosed the revised version of our manuscript entitled “Clinical manifestations and outcome in Staphylococcus aureus endocarditis among injection drug users and nonaddicts: A prospective study of 74 patients”.

General

First we would like to thank the four reviewers for their constructive criticism on our manuscript. We have tried to answer all the questions point by point raised by the reviewers. Majority of them has been led to changes in the manuscript highlighted on specific pages and described below. In the few cases we did not accord with the reviewer or were unable to give more information. This has been discussed below.

Response to reviewer`s report I (Stefano Bassetti):

1. The reviewer correctly notes that there is no clear data on how long an aminoglycoside treatment should be continued in native valve endocarditis caused by S. aureus. Treatment practices seem therefore to be variable. For example in “The Sandford Guide to Antimicrobial Therapy” aminoglycoside treatment for left-sided native valve endocarditis is recommended for 3-5 days but as long as 2 weeks treatment for right-sided native valve endocarditis. When this study was started longer treatment times were used more generally. We aimed at maximal effective antibiotic therapy and therefore longer aminoglycoside treatment was chosen. For the same reason rifampin was recommended to be used in cases with a deep infection although no clinical data before this study supported it. Rifampin has been of additive value in experimental studies and it was shown to reduce mortality in patients who received it in our study as well (Ruotsalainen et al. J Intern Med 2006;259:179-190; PDF version of the article is enclosed). These points have been discussed more in detail in “discussion” section on page 16 (paragraphs 2 and 3).

2. Rifampin may have drug interactions with methadone and it has been discussed on page 16 (paragraph 3). However, in Finland buprenorphine was the main substitution treatment for addicts instead of methadone at the time of our trial period.

3. We agree that compliance problems are sometimes very problematic among addicts. We have stated in Table 3 that in endocarditis transthoracic echocardiography (TTE) could be performed for all injection drug users, but transesophageal echocardiography (TEE) for only 45% of addicts partly because of compliance problems. However, this probably had no great impact for our diagnostic yield of endocarditis among addicts because they are often lean and there is generally a good view on the valves of the heart with TTE.

Unfortunately, we cannot answer accurately what is the value of the number of positive blood culture bottles for S. aureus in diagnosing endocarditis among addicts because there was a variation in the number of the blood culture sets taken from the patients on hospital admission (between 2 and 6 bottles). However, our impression is that patients with endocarditis had higher frequency of positive blood culture bottles, but unfortunately this question is not easy to study scientifically from this material.
Response to reviewer’s report II (Kate Gould):

1. The reviewer is right that much of the data presented in our manuscript confirms previous findings in smaller retrospective studies on *S. aureus* endocarditis. However, we would like to note that even the confirmatory findings are of value since our patient population was prospectively followed which is very rare in published papers on *S. aureus* endocarditis. This has been pointed out in the title. Furthermore, we think that this patient material is valuable because the data comes from a study in homogenous population with no bias due to MRSA strains. In addition, the trial included a careful clinical follow-up for 3 months with no dropouts among addicts which has been rather common in many published series.

This material is one of the largest prospective patient material comparing *S. aureus* endocarditis among addicts and nonaddicts ever published. Endocarditis among addicts has been generally thought to be milder and small studies with shorter antibiotic treatments have been published. Our data clearly shows, that complications among addicts are as common as in general population. Addicts had equally often extracardiac deep infections and tromboembolic events as nonaddicts.

We admit that the data is derived from a study originally designed for evaluation of a fluoroquinolone in addition to standard therapy in *S. aureus* bacteremia. This has been clearly stated in the text and new references to the original study has been made on pages 7 (paragraph 4) and 16 (paragraph 3).

2. As the reviewer states, data on patients with *S. aureus* bacteremia without endocarditis has been presented (Table 1). However, endocarditis is a subgroup of bacteremic patients and we think that differences and also similarities in these patient groups should be presented. In three of the four tables differences between IDUs and nonaddicts with endocarditis are presented. If more data on *S. aureus* bacteremia would be presented it would make the amount of information exhaustive and partly also overlap what is already published from this patient population. Therefore, we would like to keep the main focus of the manuscript on endocarditis among addicts and nonaddicts.

3. The choice of antibiotic therapy has been clarified on pages 6 (paragraph 1) and 7 (paragraph 4) as well as a more pointing reference to the original study. Furthermore, this has been discussed in the “discussion” section on page 16 (paragraphs 2 and 3) (see also our comment 1 to reviewer I above).

4. As described above the data in tables is needed to show condensed the differences between patients with *S. aureus* bacteremia only and patients with endocarditis, and differences between IDUs and nonaddicts. We think that in table form these data can be presented condensed and we think that it is useful for many clinicians. Some statistically nonsignificant findings in Table 1 might be removed into the text for “results” section if wanted. However, this would make the text more difficult to read.

5. This paper concentrates on the clinical findings in endocarditis, and the bacteriologic methods used were those in routine practice in our study hospitals. This information has been included into the “definitions” section and a reference for further information has been added on page 6 (paragraph 3). In addition, we are preparing another manuscript from this patient material concerning the microbiological and serological findings (e.g. subtyping by PFGE of the strains isolated from addicts and nonaddicts). However, to include this data into the present manuscript would make it all too exhaustive.

Response to reviewer’s report III (Itzhak Brook):

1. Fluoroquinolone treatment had no influence on the mortality of patients with *S. aureus* bacteremia only or patients with endocarditis. We are happy to inform that the data asked for is presented on page 8 (paragraph 1).

2. The doses of antibiotics have been stated on pages 7 (paragraph 4) and 8 (paragraph 1). In addition, the duration of intravenous antibiotic treatment is found on page 13 (paragraph 2).

3. We have demonstrated in “results” on page 12 (paragraph 2) and in “discussion” section on page 17 (paragraph 1) that the better prognosis among IDUs was more frequently associated with their younger age and lack of severe underlying diseases, and there was also a tendency for lower mortality among those with right-sided endocarditis.
Response to reviewer’s report IV (Michael Bronze):

1. The reviewer questions the generability of the information. In all prospective studies some patients are missed due to various reasons and only a certain proportion of patients are included. This information has been included into page 10 (paragraph 1).

Lack of MRSA strains was seen as one of the major limits for extrapolation of the results. It definitely leaves one important aspect out of our paper. However, MRSA infections are usually more difficult to treat. While concentrating only on cases caused by methicillin-sensitive strains, real differences between IDUs and nonaddicts might be better revealed without complicating effect of MRSA. This has been explained in a new chapter in the beginning of discussion on page 14 (paragraph 1).

2. Echocardiogram was done to 61% of patients with S. aureus bacteremia and it is one of highest number published in the literature. Unfortunately, there are no studies with adequate number of patients where echocardiography has been done for all patients with S. aureus bacteremia. Therefore, some patients with atypical features might have been missed in our study. However, we believe that the number of undiagnosed endocarditis must be very low because we followed patients extremely carefully for 3 months and found extracardiac deep infections in over 80% of the patients which again is the highest number in the literature. The use of echocardiography and its limitations has been clarified on page 15 (paragraph 1).

3. All three other reviewers have asked for more detailed information on antibiotics used and we have tried to meet their demands (see our comments 1-2 for reviewer I, comment 3 for reviewer II, and comments 1-2 for reviewer III above). We also think that this data should be included because adequacy of antibiotic treatment evidently affects the outcome. However, we are completely in agreement with reviewer IV that no conclusions on various antibiotic treatments can be made and this has been clarified on page 16 (paragraph 3).

4. For the value and new information presented in this study, please see our comment 1 for reviewer II above.

We hope that after these revisions you would find our manuscript suitable to be published in BMC Infectious Diseases.

Sincerely Yours

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