Reviewer’s report

Title: CD64 as a biomarker in septic arthritis

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Reviewer: Vasileios Fotopoulos

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MAJOR COMPULSORY REVISIONS

1. In group 4 (acute arthritis) 8 patients were excluded due to uncertain final diagnosis. 4 patients presented with acute arthritis had spontaneous recovery without the administration of antibiotics. These last 4 were considered to be of non-bacterial etiology and were analyzed with group 3. This is probably wrong. If you can somehow rule out septic arthritis in one patient, this does not mean the patient suffers from rheumatic arthritis. There are numerous conditions other than rheumatic arthritis that mimic septic arthritis.

2. In group 4 (acute arthritis), 26 patients had septic arthritis whereof 9 were related to prosthetic joints. There are a lot of researchers that would reject this study because the authors did not separate these two subgroups – native joint infections vs. prosthetic ones. According to literature, prosthetic joint infections behave in an entirely different way leading to more indolent clinical presentations or even normal laboratory findings [see Diagnosis and Management of Prosthetic Joint Infection Curr Opin Infect Dis 2012;25(6):670-676]. If there is a more indolent inflammatory response in prosthetic joint infections, this could jeopardize the credibility of the whole study against the use of CD64 as a biomarker in septic arthritis. However, the authors state that the values for CD64 and PCT did not differ significantly between patients with native vs. prosthetic joints. I would like to see these data in the script in order to overcome this lack of segregation.

3. In Septic arthritis group there is one case of Mycobacterium abscessus infection and one case of Lyme disease. We know that mycobacterial infections cause chronic, slow progressive monoarthritis rather than acute septic arthritis (duration of symptoms 30 days > 2 weeks). On the other hand, the diagnosis of Borrelia-arthritis was based on history (recent tick exposure) and a high serum IgG-titer (IgM-titer just above cut-off). These do not necessary prove actual Borrelia arthritis. Borrelia can cause a type of reactive arthritis. Thus, it would be better if the authors excluded these two cases.

4. Again in table 2, there is one case of prosthetic joint infection by S.epidermidis with duration of symptoms greater than 2 weeks (30 days). This is not an acute arthritis. This case should be excluded too.

5. A short clinical relevance should be discussed (Part of the conclusions should be included).

6. Except for the last sentence, the whole paragraph of the conclusions includes data that should have been part of the discussion. The conclusion should be
based on data found in the manuscript itself.

7. Limitations of the study must be mentioned. Except for the subgroup analysis in group 2 (UTI) there is no other limitation of the current study mentioned. In view to the above remarks, the authors should clearly state the limitations of their study. There is no perfect study and certainly this one has a lot of controversial issues for a prospective study. Of course it is always difficult to deal with septic arthritis and its heterogeneity of the cases.

MINOR ESSENTIAL REVISIONS

1. Group 3 (chronic rheumatic arthritis): This group consisted of patients with an acute disease flare. Perhaps it is better to erase chronic from the title of the group in order for the reader to understand what the authors want to pose – differentiation between acute septic and aseptic arthritis.

2. The authors should give more details in table 2 regarding CNS (CNS: S.epidermidis, S.capitis, and S.lugdunensis) and the affected joint.

3. It would be better if the authors started the discussion with the most significant findings of the study.

4. A few minor corrections:
   • Last paragraph, last sentence of the results: with native or prosthetic joints.
   • Second page, middle paragraph, second sentence of the discussion: and provided CD64 with the greatest AUC.
   • Table 2, microbes in 15-17: S.lugdunensis.

DISCRETIONAL REVISIONS

1. Subgroup analysis was conducted to evaluate the influence of the causative agent being CNS on the discriminatory power of the inflammatory markers. Although this kind of subgroup analysis is very interesting, I feel that the authors should have split the Septic arthritis group to Gram-positive vs. Gram-negative infections [This is not applicable due to small size of the Gram-negative infections] or high virulence bacterial infections vs. low virulence ones. This discrimination has a lot more value for the clinician rather than CNS vs. all other bacterial infections (some by low virulence bacteria too).

2. One proposition to improve the overall impact of the study would be to investigate the effect of previous administration of antibiotics. I understand the size is rather small (only 6 out of 26), but it may reveal a tendency.

3. The title though is a little too sharp. Since serum CD64 did not prove its sensitivity in septic arthritis I would change the title to: CD64 as a possible biomarker in septic arthritis.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.