Author’s response to reviews

Title: Periprosthetic-knee infection by Mycobacterium bovis and Candida guilliermondii in the context of a zoonosis: A case report and literature review

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Author’s response to reviews:

Tibor Fülöp, M.D., Ph.D.

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Dear Mr. M.D., Ph.D. Fülöp

Thank you for the time and effort taken to review our manuscript entitled “Periprosthetic-knee infection by Mycobacterium bovis and Candida guilliermondii in the context of a zoonosis: A case report and literature review” and the positive comment from your reviewers. We have carefully reviewed the comments as well as the generalized instructions for authors and have adjusted the manuscript accordingly. Our responses are given in a point-by-point manner below and in a separate document.
We hope the revised version is suitable for publication and look forward to hearing from you in due course.

Sincerely,

The authors

Point-by-point response

1. Artikel: JMCR-D-18-00178

Periprosthetic-knee infection by Mycobacterium bovis and Candida guilliermondii in the context of a zoonosis: A case report and literature review

Emanuel Kuner; Jens Arne Jöckel; René Orler; Reto Nüesch

Reviewer 1: Dr. Nakaharai

1. Reviewer remark: This report has highly suggestive content about infection following total knee arthroplasty caused by clinically rare pathogens. To help readers understand this case, some additional information about the patient and pathogens seems to be needed.

Answer: See below

2. Reviewer remark: Line 91-92 Authors described that the patient initially presented with osteoarthritis of the knee (that was the reason for the operation). To show that the diagnosis of this case was a post-TKA infection (prosthetic-knee infection), authors should present evidence indicating that the patient did not have pyogenic arthritis before the operation.

Answer: Preoperatively, there was no suspicion of infectious arthritis. The typical symptoms of osteoarthritis of the knee were present. The routine laboratory regarding infection parameters (leukocytes, BSG, CRP) was without pathological findings.
Preoperatively, there was no suspicion of infectious arthritis. The typical symptoms of osteoarthritis of the knee were present. The routine laboratory regarding infection parameters (leukocytes, BSG, CRP) was without pathological findings.

3. Reviewer remark: Although authors mentioned the resident area of the patient and suspected source of M. bovis infection (contact with animals and drinking of raw milk), if possible, more detailed information about the patient's history of life should be presented (e.g., living environment, vaccination history including BCG, ADL, and history of travel or outdoor activity…)

Answer: The patient is a farmer. He grew up on a farm and lived there all his life. He had consumed raw milk for years. There was daily contact with animals including cattle. The history of BCG vaccinations is negative. A trip abroad during which an infection could have occurred could be excluded. We do not know what you mean with ADL.

4. Reviewer remark: As to the identification of M. bovis, authors also presented only limited information. What methods did authors use to detect M. bovis? Authors should describe the methods and process of identification.

Answer: The materials taken intraoperatively were amongst others cultured in liquid medium (BACTEC MGIT 960) and on solid media (Löwenstein-Jensen, Middlebrook 7H10 / sel / 7H11). The cultures are incubated for 8 to 16 weeks. M. bovis was detected in tissue samples. A resistance test was performed for the mycostatic drugs (isoniazid [INH], rifampicin [RMP], ethambutol [EMB] and pyrazinamide [PZA]).

5. Reviewer remark: In line 29 (Abstract), the sentence, "Fungal prosthesis infection is the exception," seems to make no sense in this context.
Answer: Periprosthetic infections with fungi are very rare. We want to express this with this sentence. Due to the limitation of the character in the abstract, we can not elaborate on this at this point.

Revised Text: Line 29-30: Fungal periprosthetic-joint infections are very rare.

6. Reviewer remark: In line 37-38 (Abstract), the sentence, "After 14 month of follow-up no further no further complication has emerged," contains duplicated terms ("no further").

Answer: Thank you we change this.

Revised Text: Line 37-38: After 14 month of follow-up no further complication has emerged.

7. Reviewer remark: I would like to recommend that authors review the abstract section again and brush it up.

Answer: Thank you for this criticism. We have now taken the detailed criticisms into account. We hope this now meets your requirements.

Revised Text: Line 27-48: Introduction: Periprosthetic-joint infections are a major challenge for the treating physicians. Musculoskeletal infections with Mycobacterium bovis are extremely rare, with an assumed incidence of 0.08–0.1%. Consequently, periprosthetic-joint infections with M. bovis are even less frequent. Fungal periprosthetic-joint infections pros thesis infection is the exception are very rare. No cases of Candida guilliermondii infection of implanted prostheses are described in the literature.

Case presentation: We present the first described case of periprosthetic-joint infection after total knee arthroplasty (TKA) by both M. bovis and C. guilliermondii in the context of a zo-onosis with 14 month of follow-up. The infection was presumed to originate over 55 years earlier, when these infectious agents were still present in cattle in Switzerland. After diagnosis of the pathogens, the patient was successfully treated with tuberculostatic and mycocide medication, and a two-stage revision knee arthroplasty was performed. The medication was given for one year.
The postoperative course was normal and the patient achieved ambulant musculoskeletal rehabilitation. After 14 month of follow-up no further complication has emerged. At all routine consultations, there were no indications for joint inflammation, wound healing was normal, and the range of motion was flexion/extension 110/0/0°.

Conclusions: We found no comparable cases in our literature search. Only a few joint infections by M. bovis after intravesical instillation of bacillus Calmette-Guerin (BCG) are described. Primary infections without previous BCG injection appear to be even less frequent. In cases where mycobacterial infection cannot be ruled out, we recommend cultivating mycobacteria cultures for weeks. In addition, a histological examination of the tissue should be carried out. After diagnosis, the concept of the two-stage reimplantation of TKA with long mycostatic for one year and antimycotic therapy appears to be effective.

Reviewer 2: Namaha Raman

1. Reviewer remark: The study reports a first case of the co-occurrence of Mycobacterium bovis and Candida guilliermondii infection in Periprosthetic-knee, each of which, based on literature, is individually extremely rare/nonexistent when associated with Periprosthetic-knee. So this is a unique case. The authors do a good job of laying out the sequence of events and corresponding action taken.

Answer: Thank you!

2. Reviewer remark: In line 38, the authors may want to edit "no further" that is written twice in the abstract

Answer: Thank you we change this.

Revised Text: Line 37-38: After 14 month of follow-up no further complication has emerged.
3. Reviewer remark: Can the authors elaborate on what were the culture methods used for detecting the presence of M. bovis and C. guilliermondi. Were these methods also done in the earlier one-stage knee replacement?

Answer: In the one-stage knee replacement only standard bacterial cultures were carried out. Mycobacteria were not searched. The materials taken intraoperatively during the sec-ond knee replacement were cultured in liquid medium (BACTEC MGIT 960) and on solid media (Löwenstein-Jensen, Middlebrook 7H10 / sel / 7H11). The cultures are incubated for 8 to 16 weeks. A resistance test was performed for the primary antituberculosis drugs (isonia-zid [INH], rifampicin [RMP], ethambutol [EMB] and pyrazinamide [PZA]).

Revised Text: Line 92-96: The materials taken intraoperatively were amongst others cultured in liquid medium (BACTEC MGIT 960) and on solid media (Löwenstein-Jensen, Middlebrook 7H10 / sel / 7H11). The cultures are incubated for 8 to 16 weeks. M. bovis was detected in tissue samples. A resistance test was performed for the mycostatic drugs (isonia-zid [INH], rifampicin [RMP], ethambutol [EMB] and pyrazinamide [PZA]).

4. Reviewer remark: The authors conclusions are very terse and does not do justice to the rest of their study. Authors should give a better and more detailed conclusion (For example, their "conclusion" section of the abstract gives a better explanation and conclusion than their final conclusion)

Answer: Thank you for the justified hint.

Revised Text: Line 145-151: In summary, a zoonosis with M. bovis is extremely rare, making it difficult to find treatment guidelines with high evidence. We found no comparable cases in our literature search. Only a few joint infections by M. bovis after intravesical instillation of bacillus Calmette-Guerin (BCG) are described. Primary infections without previous BCG injection appear to be even less frequent. In cases where mycobacterial infection cannot be ruled out, we strongly recommend cultivating mycobacteria cultures for weeks. In addition, a histological examination of the tissue should be carried out. After diagnosis, the concept of the two-stage reimplantation of TKA with long mycostatic and antimycotic therapy appears to be effective, as we could show with this case.