**Author's response to reviews**

**Title:** Tolerability and Efficacy of Long Term Treatment with Daptomycin, Ceftazidime and Colistin in a Patient with a Poly-microbial, Multi-Drug-Resistant Prosthetic Joint Re-Infection: a Case Presentation

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**Author's response to reviews:**

Reviewer: Francesco Giuseppe De Rosa

General comments:

The case is well written and plenty of data are given. Tough issues are discussed such as combination treatment, microbiology and molecular methods from samples other than blood. Perhaps at the end of the paper one may wonder about another possibility: what about a positive Septifast result from with negative cultures?

Answer: Comments on the clinical value of SeptiFast test are given in the discussion section, page 8 and 9, lines 177-195

Specific comments:

1) Query: In the abstract section, it is not immediately understandable the duration of treatment with colistin, daptomycin and ceftazidime.

Answer: This has been specified on page 2, lines 51- 52: … daptomycin, ceftazidime and colistin were administered and continued for a total of eight months without side effects.

2) Query: The choice of ceftazidime and colistin is not usual and the reader has to read the entire paper to understand.

Answer: The reason of this choice has been added in the abstract section on page 2, lines 48-50: On the basis of in vitro microbiological and antimicrobial susceptibility results, daptomycin, ceftazidime, colistin and rifampin were
administered. Four days later, rifampin was stopped due to a suspected liver toxicity. Daptomycin, ceftazidime, colistin were continued for a total of eight months without side effects.

And page 6, lines 121-125:

3) Query: The use of “reliably” at the end of abstract may not be appropriate. 
Answer: the word has been deleted.

4) Query: In the Introduction, at the end, I would not write directly “poly-microbial, multi-drug-resistant PJI re-infection”, since doing so the reader may not directly think to molecular methods and other features thoroughly presented in the report 
Answer: the sentence has been changes, as follows: A complicated case of PJ reinfection is reported (Page 4, line 78).

In the text:

5) Query: Page 4: “colositin” should be changed to “colistin” 
Answer: the correction has been made.

6) Query: Please chose between “ceftazidime” and “ceftazidim” 
Answer: “ceftazidime” has been used throughout the manuscript.

Personal comments:

7) Query: I do not like the expression “plus” (for example in the abstract and in the text).
Answer: This expression has not been used anymore.

8) Query: At the end of the abstract “Our findings regarding the reported case suggest…” may be shortened to “our findings…suggest” 
Answer: This has been changed

9) Query: I do not like numbers (1, 2, 3,) in the Introduction, although some of my mentors always did so. 
Answer: numbers have been deleted from the sentence: This is a rare event [1], but the overall burden is high, as a consequence of an increased number of implanted prosthesis in the aging population, an increased number of patients with risk factors for infection and improved methods to detect these infections (page 4, lines 70-73).

10) Query: In the text it, page 5 is not elegant to say “The pre-surgery sedimentation rate was 35 mm 1°h and C-reactive protein was not obtained” 
Answer: The sentence has been modified: Sedimentation rate (ESR) was 35 mm 1°h, white blood cell (WBC) count and differential were normal, C-reactive protein
(C-RP) was not available and a leukocyte scan resulted normal. (page 5, lines 87-89).

Reviewer: Silvano Esposito

Comments to authors:

The authors describe a polymicrobial infections of hip prosthesis due to different MDR microorganisms whose diagnosis was supported by novel diagnostic test (Septi fast) in addition to the conventional ones (bacterial cultures). The paper needs, in my opinion, some more details.

1) Query: It is unclear to me, why the patient had the hip prosthesis removed for more than one year. How was the patient managed for such a long time.

Answer: This has been discussed in detail, page 9, lines 196-215: Regarding the most effective surgical strategy for PJIs and the best time of prosthesis reimplant, the decision depends on the operating orthopedic surgeon, medical specialists, and the patient [16]. Concerning the use of spacers, some researchers recommend avoiding cement spacers when infections are due to multi-drug resistant or difficult to treat microorganisms such as quinolone and rifampin resistant staphylococci, quinolone resistant gram negative microorganisms, small colony variants, or fungi [5-8,16,17]. Yet, other researchers suggest avoiding external fixations in the presence of bone infection, but instead perform debridement repeatedly and change spacers as necessary. Furthermore, antimicrobial impregnated spacers, either pre-mixed or prepared by the surgeons, can cause systemic toxicity [16]. The optimal timing for prosthesis reimplant is another issue lacking controlled, randomized studies to support a specific recommendations [16]. In our patient, initially, a cement spacer was positioned, then, after recurrent wound dehiscences, it was removed. For a three month interval our patient was left without a spacer, continuing intravenous antimicrobial therapy, therefore, after a further interval without antimicrobials and clinical signs of infection, the patient was readmitted to be reimplanted. Overall, in our patient there was a delay of one year between prosthesis explant and reimplant, due to the fact that he infection did not seem to be fully controlled until the spacer was left in place. Moreover, the patient had two previous PJIs and was at high risk for further infective complications.

2) Query: Please specify what do you mean for "all the investigation were done to exclude residual infections". What is the role of ERS an PCR in your protocol?

Answer: This has been specified in page 5, lines 86-89: Sedimentation rate (ESR) was 35 mm 1°h, white blood cell (WBC) count and differential were normal, C-reactive protein (C-RP) was not available and a leukocyte scan resulted normal.

ESR and P-CR are used on admission and to follow the patient during treatment. See page 7, lines 138-141: During the entire period antimicrobial therapy was administered, the patient was monitored clinically and, every 10 days, ESR,
C-RP, blood count, creatine phosphokinase (CPK), liver and kidney function tests and electrolytes were also obtained.

3) Query: Was ciprofloxacin administered orally?
Answer: Yes, it is and it was specified in page 5, line 96-97: Oral ciprofloxacin 500 mg twice per day was started.

4) Query: Please specify how were adverse events monitored during therapy (CPK, liver and kidney function...)
Answer: This has been specified in the revised manuscript. Page 7, lines 138-141: During the entire period antimicrobial therapy was administered, the patient was monitored clinically and, every 10 days, ESR, C-RP, blood count, creatine phosphokinase (CPK), liver and kidney function tests and electrolytes were also obtained. No side effects were observed during treatment.

5) Query: Please specify the weight of the patient in order to better understand the appropriateness of antibiotic dosages (for example teicoplanin).
Answer: Patient weight was 68 kg. This has been added in page 5, line 104.

Appropriateness of medical treatment was discussed at page 10, lines 216-221: In our case, recovery from infection was obtained by surgical therapy and a combination antimicrobial treatment with daptomycin, ceftazidime, and colistin, that were finally effective and well tolerated. Indeed, it is possible that initial antibiotic treatments were not completely effective against the multiple causative pathogens due to biofilm infection, suboptimal dosing of teicoplanin, and CoNS ciprofloxacin resistance.

6) Query: Please specify how colistin was administered (route and number of administration).
Answer: Colistin was administered intravenously 3 times a day. Different dosages were used during the eight months treatment (page 6 lines 123; page 6, lines 128-129; page 6 lines 136-137; page 7 line 151).

7) Query: Was Acinetobacter susceptible to tigecycline?
Answer: Breakpoints to define susceptibility of Acinetobacter to tigecyclin are not available either according to CLSI or EUCAST guidelines. EUCAST was not used by the laboratory at the time of our case. Tigecyclin minimal inhibitory concentration (1.5 mg/l) has been reported. Page 6, lines 110-112: Tigecyclin minimal inhibitory concentration (MIC) was 1.5 mg/l, but no breakpoints were available for this antimicrobial agent against A. baumannii, according to CLSI [11].

Discussion

8) Query: The management of this case should be discussed much more extensively as one of the major issue of the case itself is the complexity of the
therapeutic approach.

Answer: Discussion has been extended. In particular, the complex medical and surgical management has been focused. See page 9-10, lines 196-221.

9) Query: The reader would be very much interested to better understand how was the patient managed in an outpatient setting.

Answer: After hospital discharge, intravenous antimicrobial therapy was administered in a protected residence. The patient was seen and monitored with laboratory tests every 10 days. See page 6, lines 126-129: After almost 12 weeks of antimicrobial treatment the patient was accepted in a protected residence where intravenous antimicrobial therapy with daptomycin 500 mg day, ceftazidime 2 g three time a day, and colistin 3 million three times a day were continued.