Author's response to reviews

Title: Two-stage revision surgery with preformed spacers and cementless implants for septic hip arthritis: a prospective, non-randomized cohort study.

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Author's response to reviews: see over
We wish to thank the reviewers for their valuable comments that improved our work. Answers to the specific points are given below (reviewer’s comments in bold, our answers in plain text, and newly added text in red).

Reviewer #1: Thomas Bauer

**METHOD:**

**Surgical management:** It is quite unclear whether all the patients had a preoperative hip aspiration and if a medical treatment was attempted for all of them or not (because the delay between onset of the symptoms and surgery is quite long)

We have inserted the following in the Results section:
“In 11 patients, joint aspiration was performed prior to surgery at our institution; none presented with draining fistulas; previous cultures were either not available or negative.”

We also added in the Methods section:
“All the referred patients had received one or more unsuccessful systemic antibiotic treatments prior to coming our observation.”

**Why do you choose between long and short stems for the spacers.**

We added in the Methods section:
“The InterSpace® Hip comes in three different head sizes and two stem sizes, short (260 mm) and long (360 mm), which may be intraoperatively chosen on the basis of the femoral bone loss and the need for distal fixation of the implant.”

**Why not full weight bearing after arthroplasty?**

Immediate full weight bearing after cementless primary hip prosthesis is, to our knowledge, still a matter of discussion, with only recent evidence that it could be safely performed in patients with optimal bone stock and bone quality (cf. [http://www.ncbi.nlm.nih.gov/pubmed/15995431](http://www.ncbi.nlm.nih.gov/pubmed/15995431), [http://www.ncbi.nlm.nih.gov/pubmed/20012073](http://www.ncbi.nlm.nih.gov/pubmed/20012073)). In our cohort of patients, the bone quality was considered suboptimal because of the septic process, previous spacer implant and partial weight bearing and because most of our patients were not young and active, but aged and with co-morbidities. For these reasons, we preferred a rehabilitation protocol that included protected weight bearing after surgery, as described.

**RESULTS:**

**What can we consider with the 5 cases of negative intraoperative cultures (there are only 4 in the table 1)?**

The following has been amended in the Results section:
“Cultures were positive in 16 of 20 hips (80%).”

**Was the preoperative aspiration positive, what are the reasons for negative intraoperative samples?**

Pre-operative aspiration was positive in 7 out of the 11 patients in whom it had been performed. Intraoperative negative cultures are not unusual and may be due to previous antibiotic treatments and difficulty in growing positive cultures in joint infections.
How explain a so long delay before prosthesis implantation (22 months) although the antibiotic therapy duration was 4 months?

Average time to reimplantation after spacer implantation was 22 weeks and not 22 months, as indicated in Results section:
“All 20 hips were successfully converted to THA an 22.3 ± 5.1 weeks after spacer implantation.”

Did you perform a hip aspiration systematically before the second stage?

This point is mentioned in the Methods section:
“In cases of clinical suspicion of persistent infection, the hip joint was aspirated before reimplantation and samples were obtained for culture and white blood cell count.”

We now added the following in the Results section:
“Joint aspiration was also performed in 2 patients with clinical suspicion of persistent infection prior to spacer removal; the culture tested negative in both cases and the leukocyte count was 600/uL and 480/uL, respectively.”

How did you manage the 2 cases with intraoperative positive cultures at time of arthroplasty (longer antibiotic time?)

We added the following in the Results section:
“No alteration in the routine postoperative protocol as regards antibiotic treatment duration (4 weeks) was made in either case; the choice of antibiotics (vancomycin and levofloxacin in both cases) was decided according to the results of antibiogram testing of the bacteria isolated from intraoperative cultures ..”

DISCUSSION:
It is not sure that the antibiotic mixed in the commercially available cement could have a therapeutic benefit as the levels are to low and only have a prophylactic effect. The most important effect of the spacer is mechanical with maintaining of the joint space and avoiding large shortening.

We added the following in the Discussion section:
“The most relevant clinical advantage of using an antibiotic-loaded spacer is that it helps to maintain joint space and minimizes the risk of large limb shortening, while local antibiotic delivery prevents bacterial recolonization of the implant [4 – 10].”

REFERENCES:

The reference has been added, with the following comment and relative changes in Table 2:
“The relevant data from the four other more detailed papers are reported in Table 2 and compared with those of the present study. The infection recurrence rate after prosthesis implantation ranges from 0 to 15%. This latter result was reported by Bauer et al. [19], who recently described a retrospective mixed series of patients treated with either one- or two-stage procedures after hip or knee septic arthritis. In this paper, “evolutive septic arthritis” (17 knees and 13 hips) was treated with a two-stage procedure. The short time interval between stages (mean, 6 weeks) and the
absence of antibiotic in the cement spacer may explain the relatively high incidence of infection recurrence.”

TABLES:
only 4 cases of negative intraoperative cultures but 5 in the text.

The following has been amended in the Results section: “Cultures were positive in 16 of 20 hips (80%).”

orthograph for staphylococcus

Amended.
Reviewer #2: Reviewer: Suresh Antony

Quality of written English: Needs some language corrections before being published

1. Please review the English grammar, spelling punctuations etc in the paper

The English has been checked by a native English speaker.

2. In the methods section there is 19 patients and then 20 hips-please clarify

One patient had bilateral hip involvement two years apart. To better clarify this point, the following sentence has been included in the Methods section:
“The cohort consisted of 19 consecutive patients (total of 20 hips as both hips in 1 patient [FF in Table 1] were treated 2 years apart)”

3. do these patients actually have osteomyelitis or severe septic arthritis that have failed conservative therapy-need to elaborate as this is important in selection of the patients and outcomes

The following has been added in the Methods section:
“All the patients had received one or more unsuccessful courses of systemic antibiotic therapy prior to coming to our observation.”

4. As far as the spacer goes-do they have gentamicin and vancomycin or both? In which cases were a single antibiotic used and which cases were both used

At the time of treatment of this cohort of patients, preformed spacers were only available with pre-loaded gentamicin, while only in the last year of the study did gentamicin and vancomycin pre-loaded spacers become available. So, in all the reported cases we only used gentamicin-loaded cement spacers. However, our technique also included fixation of the spacer in the proximal part of the femur with gentamicin and vancomycin cement, as described in the Methods section:

“The cement is pre-loaded by the manufacturer with gentamicin (1.9%). The InterSpace® Hip comes in three different head sizes and two stem sizes, short (260 mm) and long (360 mm), which may be intraoperatively chosen on the basis of femoral bone loss and the need for distal fixation of the implant. To prevent implant rotation, the spacer was fixed only in the proximal part with one pack of antibiotic-loaded cement (Cemex Genta, Tecres) containing gentamicin (1.9%) and vancomycin (5%). The vancomycin powder was thoroughly mixed with the cement powder to obtain a fine consistency before adding the liquid monomer.”

5. did the patient with pseudomonas infection get vancomycin as well

In the cement spacer yes, since bacterial isolation only came after surgery in this case.

6. what were the antibiotics given prior to implantation and what was the dosage and duration in each case-maybe it can be added to the table

The following has been added in the Results section:
“The duration of postoperative antibiotic treatment after spacer implantation was from 4 to 6 weeks (mean 5.2±1.1); methicillin-sensitive gram-positive bacteria were treated with a combination of amoxicillin/clavulanic acid or cephalosporins and levofloxacin, or trimethoprim/sulfamethoxazole or rifampicin; methicillin-resistant bacteria were treated with a combination of a glycopeptide (vancomycin or teicoplanin) with either levofloxacin or trimethoprim/sulfamethoxazole or rifampicin. Patients with negative culture results were treated empirically with a combination of vancomycin or teicoplanin and levofloxacin; the 1 patient with *Pseudomonas aeruginosa* infection was treated with meropenem and levofloxacin according to the antibiogram.”

7. Justify the use of IV antibiotics post implant-why not sulphur based or clindamycin or Linezolid?

Both sulfur-based antibiotics and clindamycin were used. Linezolid is not approved for bone and joint infections in Italy and other European countries and there is still scarce literature as regards its use in joint infections.

8. Define Type B host in the paper

The following has been added in the Results section:

“i.e., patients with one or more risk factors for infection (Table 1),”

9. In the 2 pts with recurrent infection-why do you think this happened, what were the antibiotics used and did they have any unusual risk factors?

We observed only one infection recurrence after hip prosthesis implant (“One patient (AP) developed recurrence of infection associated with sinking of the femoral stem which required re-revision two years after the intervention.”).

He had, in fact local and general risk factors. We added the following in the Results:

“This patient was a heavy smoker with a history of diabetes, post-traumatic hip infection, associated with osteomyelitis of the proximal third of the femur, and had presented with draining fistulas and enterococcus infection.”

We had two more patients in which

“At the time of spacer removal, a single intraoperative specimen gave a positive culture result in 2 patients (coagulase-negative bacteria in both cases), without pre-operative signs of infection.”

We added the following sentence:

“No alteration in the routine postoperative protocol as regards antibiotic treatment duration (4 weeks) was made in either case; the choice of antibiotics (vancomycin and levofloxacin in both cases) was decided according to the results of antibiogram testing of the bacteria isolated from intraoperative cultures .”

10. define which cases of septic hip arthritis merit a 2 stage procedure i.e failed conservative therapy, osteomyelitis like septic arthritis, pts with underlying immunocompromised states etc
The following has been added in the Methods section:
“All patients had received one or more unsuccessful courses of systemic antibiotic therapy prior to coming to our observation. The indications for two-stage revision were: failure of conservative treatments; clinical and laboratory signs of persistent inflammation; functional impairment of the affected joint; and radiographic signs of joint damage (joint-line narrowing, subchondral osteolysis, bone loss and/or femoral head necrosis).”

11. Mention if this procedure would be useful in patients with high level resistant vancomycin staph. Infections-should other drugs like daptomycin, Linezolid be considered in the spacer and IV therapy-mention this in the discussion

The following has been added in the Discussion section:
“The choice of antibiotics loaded to the cement spacer and administered systemically in this series was clearly effective, with proper surgical technique, in eradicating infection in patients with septic hip arthritis due to different bacteria, including methicillin-resistant strains. However, with the growing occurrence of multi-drug and vancomycin-resistant strains, the use of more recently available antibacterial agents may be necessary in selected cases. The efficacy of daptomycin or linezolid in treating septic arthritis is currently under study [26, 27].”

12. mention the limitations of the study such as sample size, long term outcomes etc

The following has been added in the Discussion section:
“The main limitations of the present study are the limited sample size, the lack of a comparator group, and the relatively short duration of follow-up. Due to the relatively low prevalence of septic arthritis of the hip, coordinated multicenter randomized trials are needed to evaluate long-term outcomes after two-stage revision with this technique.”
Editorial Requests:

1. In your manuscript please provide more information on the consent procedure used in your study. Specifically, please indicate whether the consent was written and whether you obtained consent to publish the clinical images.

2. Please indicate in your manuscript the name of the ethical review board that approved your study.

The following has been added in the Methods section:
“All patients provided written consent to participate in the study and permission to publish clinical images. The ethics committee of Local Health Authority 1, Milan, Italy approved the study protocol.”

3. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

The files have been re-formatted according to http://www.biomedcentral.com/info/ifora/medicine_journals