Acute haematogenous prosthetic joint infection: prospective evaluation of medical and surgical management

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Abstract

The optimum treatment for prosthetic joint infections has not been clearly defined. We report our experience of the management of acute haematogenous prosthetic joint infection (AHPJI) in patients during a 3-year prospective study in nine Spanish hospitals. Fifty patients, of whom 30 (60%) were female, with a median age of 76 years, were diagnosed with AHPJI. The median infection-free period following joint replacement was 4.9 years. Symptoms were acute in all cases. A distant previous infection and/or bacteraemia were identified in 48%. The aetiology was as follows: Staphylococcus aureus, 19; Streptococcus spp., 14; Gram-negative bacilli, 12; anaerobes, two; and mixed infections, three. Thirty-four (68%) patients were treated with a conservative surgical approach (CSA) with implant retention, and 16 had prosthesis removal. At 2-year follow-up, 24 (48%) were cured, seven (14%) had relapsed, seven (14%) had died, five (10%) had persistent infection, five had re-infection, and two had an unknown evolution. Overall, the treatment failure rates were 57.8% in staphylococcal infections and 14.3% in streptococcal infections. There were no failures in patients with Gram-negative bacillary. By multivariate analysis, CSA was the only factor independently associated with treatment failure (OR 11.6; 95% CI 1.29–104.8). We were unable to identify any factors predicting treatment failure in CSA patients, although a Gram-negative bacillary aetiology was a protective factor. These data suggest that although conservative surgery was the only factor independently associated with treatment failure, it could be the first therapeutic choice for the management of Gram-negative bacillary and streptococcal AHPJI, and for some cases with acute S. aureus infections.

Keywords: Acute infection, antibiotic therapy, haematogenous infection, prosthetic joint infections, treatment.

Introduction

Prosthetic joint infection (PJI) is an uncommon complication (1–2%) of joint replacement surgery, and is associated with high morbidity and medical cost [1–7]. Successful treatment of chronic PJI often requires prosthesis removal and prolonged antimicrobial therapy. Acute PJIs are less likely to be associated with complete biofilm development or loosening of the implant; thus, there is a chance of cure without prosthesis removal. In acute infections, a conservative surgical approach (CSA) may be appropriate if it is combined with prolonged pathogen-targeted therapy [1–5,7–20]. However, the usefulness of a CSA has not been extensively evaluated, because the number of patients included in reported series is small, and acute postoperative and haematogenous PJI (AHPJI) have usually been analysed together. We review our experience in the treatment of AHPJI, focusing on patients treated with a CSA without prosthesis removal, to identify risk factors associated with treatment failure.

Patients and methods

Study population and definitions

From January 2004 to December 2006, all patients with PJI were prospectively evaluated in nine Spanish hospitals included in the REIPI (Spanish Network for Research in Infectious Disease) programme. As this was an observational study, patients were not randomized to any surgical modality or antibiotic treatment. A standardized case report form was used to abstract medical records. For the present study, we focused on patients with AHPJI.

PJI was classified as AHPJI according to the criteria of Tsukayama et al. [21], modified by Crockarell et al. [22], i.e. acute onset of symptoms more than 1 month after total joint replacement in a patient in whom the prosthesis had previously been functioning well. A prosthetic joint was classified as infected by the presence of at least one of the following clinical signs and symptoms: (i) repeated growth of the same microorganism from cultures of joint aspirate or periprosthetic tissue; (ii) positive blood cultures; and (iii) purulence surrounding the prosthesis at the time of surgery or identified by joint fluid aspiration.

Surgical treatment was classified as conservative when it involved retention of the prosthesis, and non-conservative when it involved removal of all components of the implant.

Adequate antibiotic therapy was defined as administration of appropriate antimicrobial agents according to susceptibility testing results for at least 8 weeks. In all cases, an infectious disease staff member participated in the management of these patients.

The initial assessment of improvement was based on the disappearance of clinical and biological signs at the end of medical treatment. Response to therapy was defined as follows: (i) cured—improvement with no apparent relapse at 24 months of follow-up; (ii) persistence—absence of improvement or initial improvement followed by reappearance of signs of infection during the initial planned course of antibiotic therapy and repeat isolation of the same microorganism, requiring chronic suppressive antibiotic therapy; (iii) relapse—initial improvement and then recurrence of infection with the same microorganism following discontinuation of antibiotic therapy within the 24-month follow-up period; or (iv) re-infection—initial improvement followed by recurrence of infection by a different microorganism within the follow-up period. Death was classified as related or unrelated to prosthesis infection. Treatment failure was defined as follows: (i) persistence of infection needing chronic suppressive therapy; (ii) relapse of infection during follow-up; or (iii) death due to prosthesis-related infection.

Statistical analysis

Statistical analyses were performed with the SPSS software package (version 13.0). Categorical variables are expressed as percentages, and numerical data as the mean (with standard deviation (SD)), median, and range. Categorical variables were compared with the chi-square test or Fisher's exact test (two-tailed), and continuous variables with the unpaired Student t-test. CSA patients were compared with those with prosthesis removal by comparing the time to treatment failure by use of a Kaplan–Meier analysis, and curves were then compared using the log-rank test. Stepwise multivariate logistic analysis was performed to identify predictors of treatment failure. A P-value of <0.05 was considered to be statistically significant in the multivariate model.

Results

Study population and clinical presentation

Among 500 PJIs occurring over the 3-year study period, 50 (10%) episodes in 50 patients were considered to be AHPJIs. The median age of patients with this condition was 76 years (range, 31–92 years). Treatment was for infection of total knee replacement in 30 (60%), total hip replacement in 19 (38%), and a prosthetic shoulder joint in one (2%). Following total joint replacement, patients had a median infection-free period of 4.9 years (range, 0.3–18.7 years). All patients presented with an acute onset of symptoms. Sinus tract was present in only one case, and prosthesis loosening in seven. Demographic data, comorbid conditions, risk factors predisposing to PJI and symptoms at presentation are shown in Table 1.

Microbiological findings

The microbiological findings of 50 episodes of AHPJI are outlined in Table 2. Staphylococcus aureus (38%) and Streptococcus spp. (28%) were the most commonly isolated microorganisms.

TABLE 1. Demographic data, comorbid conditions, risk factors and symptoms at presentation in 50 episodes of acute haematogenous prosthetic joint infection

Variable	Value
Age (years), median (range)	76 (31–92)
Sex, female/male	30 (60)/20 (40)
Comorbid conditions	
Cardiac failure	12 (24)
Rheumatoid arthritis	8 (16)
Diabetes mellitus	7 (14)
Chronic renal failure	7 (14)
Malignancy	6 (12)
Immunosuppressive drugs	4 (8)
Risk factors	
Documented bacteraemia due to the same microorganism	10 (20)
Distant previous infection due to the same microorganism[a]	16 (32)
Procedures predisposing to bacteraemia[b]	3 (6)
Symptoms at presentation	
Pain	50 (100)
Inflammatory signs	38 (76)
Fever (temperature ≥38°C)	35 (70)
Purulence drainage	15 (30)
Biological signs at presentation	
Leukocyte count before debridement, median (range)	12 300 × 10^9 (1000–27 650)
CRP before debridement, mean (SD), mg/dL	106 (102.4)
ESR before debridement, mean (SD), mm/h	83.5 (28.9)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation.
Data are number (%), unless otherwise indicate.
[a]Distant previous infections due to the same microorganism that caused prosthetic joint infection: four urinary tract infections (two due to *Streptococcus agalactiae* and two to *Escherichia coli*), three cases of infectious enteritis (two due to *Salmonella enteritidis* and one to *E. coli*), two cases of infectious endocarditis due to *Staphylococcus aureus* (in both cases, bacteraemia was also documented), two cases of pneumonia (one due to *Streptococcus pneumoniae* and 1 to *S. aureus*), two cases of cellulitis (one due to *S. aureus* and one to *Pasteurella multocida* in a patient who had been scratched by a cat), one case of cholecystitis, one case of suppurative adenitis due to methicillin-resistant *S. aureus*, and one case of dacryocystitis due to *S. aureus*.
[b]Procedures predisposing to bacteraemia include prior dental procedures in two patients and intravenous drug use in one.

TABLE 2. **Microbiological findings in 50 patients with acute haematogenous prosthetic joint infection, according to surgical approach**

Microorganism	Conservative surgical approach	Non-conservative surgical approach	Total episodes
Staphylococcus aureus[a]	16 (32)	3 (6)	19 (38)
Streptococcus spp.[b]	6 (12)	8 (16)	14 (28)
Gram-negative bacilli[c]	8 (16)	4 (8)	12 (24)
Polymicrobial infections[d]	3 (6)	0	3 (6)
Anaerobic infections[e]	1 (2)	1 (2)	2 (4)
Total	34 (68)	16 (32)	50 (100)

Data are number (%).
[a]Two episodes due to methicillin-resistant strains.
[b]Eight episodes due to *Streptococcus agalactiae*, two to viridans group streptococci, one to *Enterococcus faecalis*, one to *Streptococcus pneumoniae*, one to *Streptococcus bovis*, and one to group G streptococci.
[c]Eight episodes due to *Escherichia coli*, three to *Salmonella* spp., and one to *Pasteurella multocida*.
[d]One episode due to methicillin-resistant *Staphylococcus aureus* and *Enterobacter* spp., one to *Staphylococcus simulans* and *Alcaligenes* spp., and one to *Enterococcus faecalis* and *Escherichia coli*.
[e]One episode due to *Bacteroides* spp. and one to *Peptostreptococcus* spp.

TABLE 3. **Univariate and multivariate predictors of treatment failure in 50 patients with haematogenous prosthetic joint infection[a]**

Characteristics	Relative risk (95% CI)	p
Conservative surgical approach	10.3 (1.2–87.9)	0.018
Surgical approach 7 days after symptom onset	1.5 (0.4–5.7)	0.74
Staphylococcus aureus infection	5.3 (1.4–19.9)	0.013
Gram-negative bacillary infection	0.6 (0.5–0.8)	0.01
Streptococcus spp. infection	0.5 (0.1–2.1)	0.49
Antimicrobial treatment for more than 8 weeks	1.03 (0.2–4.08)	1.0
Antimicrobial treatment for more than 12 weeks	1.7 (0.5–6.02)	0.53

[a]Conservative surgical management with retention of the prosthesis was the only factor independently associated with treatment failure in the multivariate analysis (OR 11.6, 95% CI 1.29–104.8, p 0.028).

TABLE 4. Univariate predictors of treatment failure among 34 cases of haematogenous prosthetic joint infection treated with a conservative surgical approach

Characteristics	Relative risk (95% CI)	p
ASA score ≥3	4.15 (0.4–36.7)	NS
Male sex	2.2 (0.5–9.3)	NS
Female sex	0.4 (0.1–1.7)	NS
Diabetes mellitus	1.4 (0.2–8.5)	NS
Rheumatoid arthritis	4.9 (0.4–53.2)	NS
Immunosuppression[a]	0.2 (0.02–2.9)	NS
Staphylococcus aureus infection	3.08 (0.7–12.9)	NS
Streptococcus spp. infection	1.45 (0.2–8.5)	NS
Gram-negative bacillary infection	0.46 (0.3–6.9)	0.013
Primary prosthesis	0.8 (0.14–4.1)	NS
Surgical approach within 7 days of symptom onset	0.35 (0.06–1.8)	NS
Antimicrobial treatment for more than 8 weeks	0.26 (0.05–1.2)	NS

ASA, American Society of Anesthesiologists score; NS, not significant.
[a]Immunosuppression includes cirrhosis, malignant disease, and treatment with immunosuppressive drugs.

Medical therapy

Patients were treated with specific antibiotics according to the susceptibility pattern of the isolated microorganism for a mean of 15.9 weeks (SD: 11.4) in CSA patients and 10.5 weeks (SD: 7.4) in non-CSA patients (p 0.54). Among 45 patients who survived and completed antibiotic therapy, 36 (78%) received more than 8 weeks of adequate antimicrobial treatment.

S. aureus infections were treated for a mean of 18.1 weeks (SD: 11.4). In all but one patient, methicillin-susceptible S. aureus infections were treated initially with intravenous cloxacillin combined with rifampicin (600–900 mg/day), followed by an oral quinolone (levofloxacin at 500–750 mg/day) plus rifampicin (600–900 mg/day) (74%) or co-trimoxazole (trimethoprim/sulfamethoxazole, 160/800 mg three times daily) plus rifampicin (600–900 mg/day). Two patients with methicillin-resistant S. aureus (MRSA) infection received a glycopeptide followed by co-trimoxazole (trimethoprim/sulfamethoxazole, 160/800 mg three times daily) plus rifampicin (600–900 mg/day). Infections due to Streptococcus spp. were treated for a mean of 10.1 weeks (SD: 6.6) with an intravenous β-lactam, followed by oral amoxycillin in six cases. Infections due to Gram-negative bacilli were treated for a mean of 14.7 weeks (SD: 6.1), mainly with fluoroquinolones (ciprofloxacin 750 mg twice daily) preceded by intravenous cephalosporins.

Surgical treatment

Surgery was performed in 50% of patients within 7 days of the onset of symptoms. Thirty-four patients were treated with a CSA (early debridement in 25, and joint aspiration of purulent drainage in nine), and 16 had prosthesis removal (two-stage exchange arthroplasty in nine, and definitive resection arthroplasty in seven). Outcomes according to the type of surgical management are shown in Fig. 1.

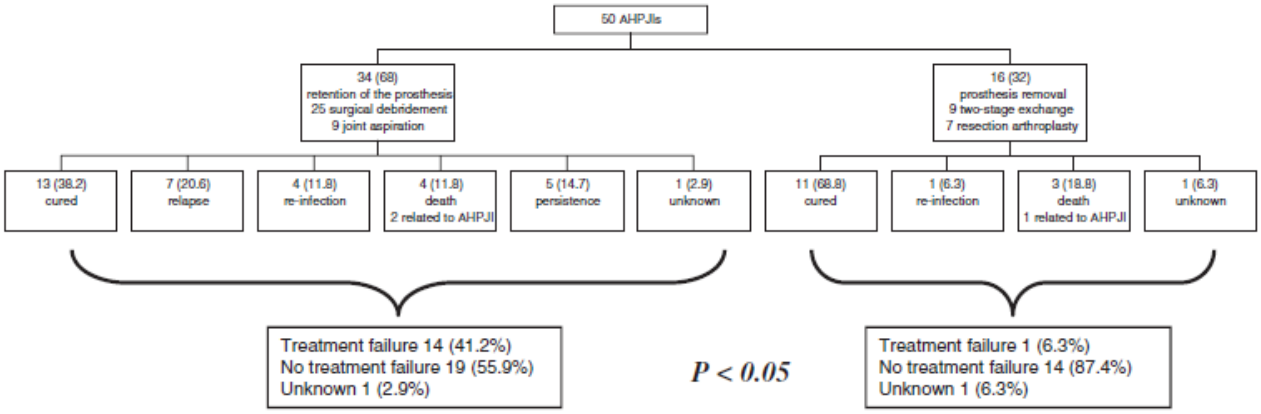

FIG. 1. Clinical outcome of 50 patients with acute haematogenous prosthetic joint infection (AHPJI) (24-month follow-up) according to surgical approach. Data are presented as number (%) of episodes. Treatment failure includes: seven relapses, five persistent infections, and two infection-related deaths.

Outcome analysis

At 2 years of follow-up, 24 (48%) patients were cured, seven (14%) had relapsed (one ultimately died), seven (14%) had died (three from PJI, and four from unrelated causes), five (10%) had persistent infection requiring chronic suppressive antimicrobial therapy, five (10%) were re-infected with a different microorganism, and two (4%) had an unknown evolution.

Overall, the treatment failure rates were 11 of 19 (57.8%) for staphylococcal infection, two of 14 (14.3%) for streptococcal infection, and zero of 12 (0%) for Gram-negative bacillary infection. On Kaplan–Meier survival analysis, the cumulative probability of treatment failure in patients treated with prosthesis retention was significantly worse (p 0.023) than in those with prosthesis removal (Fig. 2).

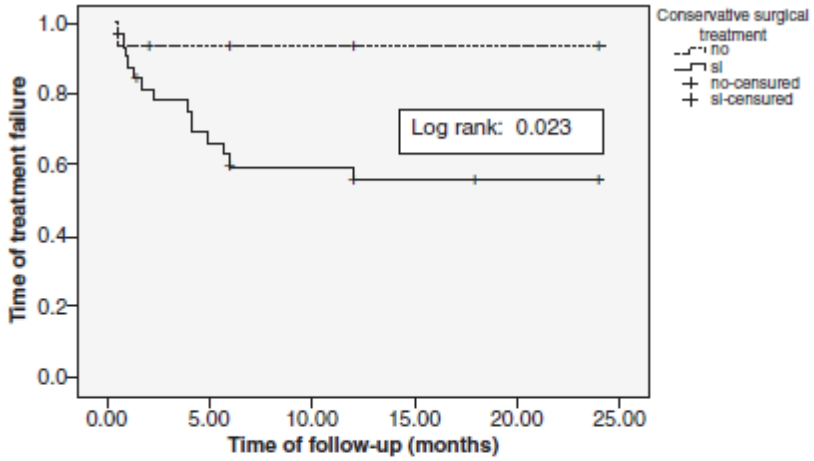

FIG. 2. Kaplan–Meier estimates of cumulative risk of failure according to surgical treatment group. The dashed line represents patients treated with prosthesis removal (n = 15), and the solid line represents patients treated with prosthesis retention (n = 33).

On univariate analysis, factors significantly associated with treatment failure were CSA and S. aureus infection, whereas a Gram-negative aetiology was a protective factor (Table 3). On multivariate analysis, CSA was the only factor independently associated with treatment failure (OR 11.6; 95% CI 1.29–104.8).

Among the seven cases with signs of prosthesis loosening, three died early, so the outcome could not be evaluated, and four were treated with prosthesis removal and were cured.

As better outcome with prosthesis removal was predictable, we performed an independent analysis of the 34 CSA patients, who included 14 (41%) with treatment failure. All failures were diagnosed within 6 months of follow-up, except for one diagnosed within 1 year. Failures were due to S. aureus infection in ten patients, including five relapses (one patient died of S. aureus sepsis), two initial infection-related deaths, and three cases of persistent infection. There was Streptococcus agalactiae infection in two patients. The remaining two episodes were due to persistent infection with Streptococcus pneumoniae and a polymicrobial cause. Thus, the failure rate for S. aureus infections treated with a CSA was 62.5% (10/16). The failure rate was five of 11 (45.4%) for cases debrided within 7 days of onset of clinical symptoms. All five cases drained after 7 days of clinical symptoms had treatment failure ($p < 0.093$). No treatment failures occurred among infections due to Gram-negative bacilli. On univariate analysis, no predictive factors significantly associated with treatment failure were identified, but Gram-negative bacillary infection was found to be a protective factor (relative risk (RR) 0.462; 95% CI 0.305–0.699, p 0.013) (Table 4). The failure rate in patients with hip prostheses was 41.7% (5/12), which was similar to that observed in patients with infected knee prostheses (40%, 8/20). The outcomes of the nine patients treated only with joint aspiration was as follows: six cases cured, two failed (one persistence and one relapse), and one lost to follow-up.

Discussion

To our knowledge, this is the largest reported case series of patients with AHPJI, which, in our experience, is responsible for 10% of all PJIs. Although the incidence of this complication is unknown, it is estimated to be low; only 8% of 188 cases of prospectively reported bacterial arthritis were haematogenous infections associated with prosthetic joints or osteosynthetic material [23].

It is of note that almost half of the patients had a previous infection at a distant site. The risk of acquiring AHPJI in patients with orthopaedic prostheses following different distant infection is unknown, except that in a report on S. aureus bacteraemia, it was as high as 34% (15/44) [6]. In that study, 19% of patients had previous catheter-related bacteraemia and 31% a skin and soft tissue infection, conditions that are usually treated with a short course of antibiotics. Because of the high risk of AHPJI in patients with S. aureus bacteraemia, prolongation of antibiotic therapy should be considered to prevent this complication. Prophylaxis prior to dental procedures in patients with prosthetic joints is controversial. Our data and those of previous studies [24–26] suggest that dental work is not a risk factor for subsequent prosthesis infection [26].

Exchange arthroplasty continues to be the standard of treatment, particularly in chronic PJI [3–5,9,19]. However, patients with acute infections and stable implants are considered to be appropriate candidates for a CSA, with early debridement, replacement of the polyethylene component, and retention of the implant, as well as active antibiotics for at least 3 months [1,3–5,7,13,18]. In our study, the failure rate in CSA patients was 41%, similar to the 50% reported by Betsch et al. [27]. The cure rates of acute infections treated with a CSA show considerable variation, with success rates ranging from as low as 23% [18,22,28–30] to higher than 70% [15,16,18,21,31,32]. Several factors can explain these differing results, including the definition of failure, degree of debridement, presence of a sinus tract or prosthesis loosening, and long duration of symptoms before debridement, all of which are associated with higher failure rates [3,4,14,18,27,28]. Overall, we found no differences between patients undergoing debridement within 7 days after symptom onset and those undergoing it later, but we did observe a tendency for there to be a worse prognosis in cases of late surgical debridement and S. aureus infection. Some authors suggest that combined antibiotic therapy with rifampicin results in better

outcomes [13,17,31,32]; we could not evaluate this, as almost all of our patients with staphylococcal infections were treated with this combination.

The microorganism responsible for the infection can be also a crucial factor related to outcome. In our study, the overall failure rate in streptococcal infections was 14.3%, but only 33.3% of them were managed with a CSA. In the literature, success rates for a CSA in streptococcal infections are as high as 93% and 89% [12,15]. We observed no treatment failures in Gram-negative infections, which is in accordance with recent studies carried out with fluoroquinolones, in which these infections were successfully treated in four of four (100%), four of six (66.6%) and 13/13 (100%) patients, respectively [10,14,21].

In the present study, the overall failure rate in S. aureus infections was 57.8%. Some authors [17,32,33] have reported higher cure rates (>90%) with a CSA in cases of acute infection. However, the sample sizes were small, and in one of the studies [17] patients who died were classified as non-evaluable. Other authors have reported failure rates of 92% [29] and 69% [28]. The failure rate seems to be particularly high in MRSA infections: Bradbury et al. [34] recently reported an 86% failure rate in acute MRSA PJI. A better outcome in Gram-negative infections than in S. aureus infections could be related to the increased capacity for biofilm formation in staphylococcal infection, which can make eradication of the microorganism difficult, especially if rifampicin is not used. The results of this study and the literature review suggest that for acute Gram-negative and streptococcal PJI, CSA is a safe option with high cure rates. For staphylococcal infections, the decision to apply a CSA is more difficult, as failure rates are higher. However, patients with infections of particularly short duration may be candidates for a CSA as a first therapeutic option. Only three of our patients with staphylococcal infections were initially treated with prosthesis removal, so it was impossible to compare outcome results with those of cases treated with a CSA. Thus, the decision should be individualized and based on the age of the patient, surgical risk, type of infection, difficulty of removing the prosthesis, and methicillin resistance. In any case, if a CSA is used, the patient should be closely followed up to exclude persistence or relapse of the infection, particularly after completion of antibiotic therapy.

Together with surgery, antimicrobial therapy is a cornerstone of treatment for PJI. Initially, the intravenous route is preferred; nevertheless, rifampicin, quinolones, co-trimoxazole, clindamycin and linezolid have good bioavailability and can be used orally in bone infections [1,4,16,17]. Our poor outcome in CSA patients cannot be attributed to the duration of the antibiotic course, as it was longer than in patients treated with prosthesis removal.

The present study had certain limitations. First, because of its observational nature, patients were not randomized to any surgical modality or antibiotic treatment; hence, we were unable to control for confounding variables such as the tendency to use a non-CSA in younger patients with better baseline conditions and a CSA with joint salvage in elderly patients. Second, we defined treatment failure as persistence of infection, occurrence of a relapse due to the same microorganism at any time during follow-up, or occurrence of a related death. In patients with acute infection, it is difficult not to attribute death to this condition, although all four cases classified as unrelated death were re-evaluated. On the other hand, the strengths of this study are the prospective data collection and patient management by a specialized team in all of the participating centres.

In conclusion, AHPJI is caused by Gram-positive cocci in 66% of cases. No factors other than a CSA were found to be independently associated with treatment failure. However, a CSA could be the first tentative therapeutic approach for acute, Gram-negative, streptococcal infections, and in some cases with acute S. aureus infections.

Author Contributions

D. Rodriguez, C. Pigrau and X. Ariza were responsible for the conception and design of the manuscript, the acquisition, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. G. Euba, J. Cobo, J. García-Lechuz, J. Palomino, M. Riera, M. D. del Toro and A. Granados made substantial contributions to the acquisition and interpretation of data, revising the manuscript critically for important intellectual content, and final approval of the version to be published.

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Transparency Declaration

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Appendix

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