

Culture Negative Prosthetic Joint Infection – A Description of Current Treatment and Outcomes

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Abstract

Background: The management of prosthetic joint infections remains a clinical challenge particularly when standard aerobic and anaerobic culture techniques fail to isolate the causative pathogen, so called 'culture negative prosthetic joint infection' (CNPJI). There are few studies detailing approaches to management in this cohort of patients. This study reports the treatment and outcomes of 19 patients with CNPJI.

Results: The majority of patients (68%) with CNPJI had exposure to antibiotic therapy in the week prior to presentation with CNPJI. Patients with early (10 patients) and haematogenous (3 patients) CNPJI were treated with debridement and retention of the prosthesis. In contrast, patients with delayed and late chronic CNPJI (6 patients) were managed by two-stage exchange. In addition to the surgical management patients were commenced on broad-spectrum oral antibiotics combination therapy with rifampicin, fusidic acid +/- ciprofloxacin for a prolonged duration (median 7 months; interquartile range 3-20).

Patients were followed up for a median of 19 months (interquartile range 13-29). Two patients experienced treatment failure with a 12 month estimate of infection free survival of 95% (95% confidence interval: 68,99). Of concern, 28% patients receiving oral antibiotics experienced adverse effects necessitating change in treatment.

Conclusions: In this cohort, the outcomes for patients with CNPJI were comparable to those reported for culture positive infections, and contrary to previous recommendations, this study demonstrates that debridement and retention of a CNPJI is reasonable for patients with early infections. It also highlights the importance of exclusion of prosthetic joint infection prior to instigation of antibiotic therapy to optimise peri-prosthetic tissue culture yields to avoid this situation in which multiple broad spectrum antibiotics with potential side effects become necessary.

Keywords: Prosthetic joint infection; Culture negative; Debridement and retention; Two stage exchange; Rifampicin

General Context

Prosthetic joint infections represent a clinical challenge to orthopaedic and infectious diseases clinicians. Strategies to optimise treatment outcomes must be balanced against the potential negative impact in particular, the emergence of antibiotic resistant microorganisms.

Background

The identification of the causative pathogen of prosthetic joint infections is of paramount importance; it allows the institution of appropriate antibiotics to target the pathogen, minimising unnecessary antibiotic overuse and decreasing the incidence of drug toxicity.

One of the greatest challenges of management is culture negative prosthetic joint infection (CNPJI). In reported case series of prosthetic joint infections, the rate of culture-negative infections ranges from 5-12% [1-3]. There is little clinical research examining CNPJI and no published guidelines outlining treatment approaches. This retrospective cohort study was undertaken to examine the management and outcomes of patients with CNPJI.

Patients and Methods

Study design

A retrospective case cohort study was conducted over a 16-year period (January 1996 to December 2011).

Ethics approval

The study design was reviewed and approved by the Hospital Ethics Committee (QA022-10).

Study population

The study was conducted at St Vincent's Hospital Melbourne (SVHM), a university affiliated, tertiary hospital. The study population comprised all patients who had knee or hip arthroplasty performed over the period January 1996–December 2011. Patients were included in the study if microbiological culture performed on blood cultures, synovial fluid and multiple intra-operative tissue specimens from the affected joint failed to isolate any organisms. Cases were identified from review of the SVHM arthroplasty registry, infectious diseases database and microbiology database [4]. Data were extracted from review of the medical chart.

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At SVHM, patients with PJI are managed according to an established protocol described previously [5,6]. Patients with early and haematogenous infections with stable implants are managed by debridement and retention of the prosthesis (DAR) entailing prompt arthrotomy and aggressive debridement [7,8]. Patients typically undergo 3 arthrotomies and debridement within a 7 to 10 day period. Mobile parts and liners are not routinely exchanged. Patients receive a short course of intravenous antibiotics before commencing oral antibiotics with activity against biofilm-associated bacteria. At SVHM, the majority of patients receive antibiotic regimens including rifampicin and/or ciprofloxacin, chosen in recognition of the activity of these antibiotics against organisms residing in the biofilm [9]. Fusidic acid is often used in Australia to protect against development of rifampicin resistance in staphylococcal infections. Where these drugs are used, patients typically receive doses of 300 mg twice-daily rifampicin, 500 mg three-times daily fusidic acid and either 500 or 750 mg ciprofloxacin twice daily. Patients with delayed and late chronic prosthetic joint infections are managed by two-stage exchange of the prosthesis [8]. All surgical and antimicrobial management decisions in this patient cohort were made at the discretion of the treating clinician.

Definitions

The definition for prosthetic joint infection was based on current published literature and included one or more of the following criteria: (i) peri-prosthetic purulence observed at the time of operation, (ii) histopathologic features consistent with acute inflammation, (iii) elevated synovial leucocyte count ($>1.7 \times 10^3/\mu\text{L}$) or elevated synovial neutrophil (PMN) percentage ($>65\%$ PMNs) or (iv) sinus tract in direct communication with the prosthetic joint [10-12]. In addition, to meet the criteria of “culture negative” infection, the standard aerobic and anaerobic microbiological culture techniques performed on blood cultures, synovial fluid and peri-prosthetic tissue samples failed to isolate any organisms.

Definite treatment failure was defined as (i) the subsequent occurrence of prosthetic joint infection with isolation of a microorganism/s at any time after the initial presentation with CNPJI, or (ii) the presence of purulence surrounding the prosthesis at subsequent re-operation, or (iii) removal of the prosthesis due to persistence of infection, or (iv) the development of a sinus tract or death from prosthesis related infection [10]. Patients were followed from the date of diagnosis of prosthetic joint infection until date of treatment failure or discharge from outpatient clinic.

Microbiological methods

Peri-prosthetic tissue samples collected intra-operatively were cultured for 48 hours on blood agar and chocolate agar and incubated at 35°C in $5\% \text{CO}_2$ and anaerobically on anaerobic agar pre-reduced. In addition specimens were incubated in thioglycollate broth for 7 days and if the broth became turbid the specimen was Gram stained and sub-cultured aerobically and anaerobically. In addition bone samples were inoculated on saponin lysed blood agar and incubated at 35°C in $5\% \text{CO}_2$ for 48 hours. At SVHM sonication of the explanted prosthesis is not routinely performed. In addition, polymerase chain reaction (PCR) was not performed on tissue samples.

Statistical analysis

Descriptive statistics was used to summarise and report the data. Categorical data was expressed as numbers and percentages, continuous variables were reported as mean and standard deviation (SD) or median with interquartile range (IQR) if the data were skewed. The 12-month

survival rate free of treatment failure was estimated using the Kaplan-Meier survival method with 95% confidence intervals. All analyses were performed using Stata 12.1 (StataCorp College Station, TX, 2011).

Results

Nineteen patients met the diagnostic criteria for CNPJI. The basic demographic features of these patients are listed (Table 1). The majority of CNPJI involved prosthetic knee joints (79%). Patients had a median of 5 intra-operative tissue specimens obtained (IQR 3-8). Synovial aspiration was performed in 6 patients and the synovial leucocyte count was elevated in 4 of these patients. The synovial PMN percentage was elevated in all obtained aspirates. Intra-operative purulence was observed in 14 patients and histopathological specimens were obtained in 13 patients and were consistent with acute infection in 7 of these patients. Further clinical and laboratory findings at presentation are outlined in Table 2. Ten patients presented with early infections, 3 patients presented with haematogenous infections and 6 patients presented with late infections.

For the early infections, the median duration from implantation until presentation with CNPJI was 22 days (IQR 19,55) and the median duration of symptoms was 8 days (IQR 1,14). In the late presentations, the median duration from implantation was 1170 days (IQR 819,1540) and the median duration of symptoms was 548 days (IQR 365,806). For haematogenous infections, the median duration from implantation until presentation was 408 days (IQR 235,2402) and the median duration of symptoms was 4 days (IQR 1,4).

From review of the patient's medical records, 68% had received antibiotic therapy in the week prior to presentation with CNPJI. In particular, 92% of patients with early or haematogenous CNPJI had received antibiotic therapy in the week prior to presentation compared to 17% of late infections. The majority of antibiotics administered prior to obtaining of peri-prosthetic cultures had activity against staphylococcus.

Median age in years (IQR)	70 (63,76)
Gender	
Male	11 (58%)
Female	8 (42%)
Index surgery indication	
Primary arthroplasty	14 (74%)
Revision arthroplasty	1 (5%)
Tumour endoprosthesis	3 (16%)
Trauma	1 (5%)
Median body mass index in kg/m^2 (IQR)	32.4 (25.6,35.7)
Underlying diabetes mellitus	4 (21%)
ASA	
1	1 (6%)
2	7 (44%)
3	8 (50%)

Table 1: Demographic features of patients with CNPJI.

	Early (n=10)	Haematogenous (n=3)	Delayed/Late (n=6)
Sinus Tract	1 (14%)	0	0
Pain	5 (50%)	2 (67%)	6 (100%)
Wound erythema	5 (50%)	2 (67%)	1 (17%)
Fever ($>37.5^\circ\text{C}$)	4 (40%)	2 (67%)	0
Elevated peripheral leucocyte count ($>11.0 \times 10^9/\text{L}$)	4 (40%)	1 (33%)	0 (0%)
Elevated C-reactive protein ($>5 \text{ mg}/\text{ml}$)	9 (90%)	3 (100%)	2 (50%)

Table 2: Presenting clinical and laboratory features of patients with CNPJI.

Patient	Implant age (days)	Days of symptoms	Abx in prior week	IV Abx	Days IV Abx	Oral Abx	Complication and therapy change	Days oral Abx	Outcome	Follow up (months)
Early Prosthetic Joint Infection										
1	13	1	CFZ	V, CTX	7	R, FA, Ci	Achilles tendonitis: Ci changed to co-trimoxazole	737	Cured	19
2	19	11	FI	V, CTX	8	R, FA	Nausea and vomiting: all ABx ceased	69	Cured	7
3	19	14	FI	CFZ	9	R, FA, Ci	Rash: no change to therapy	169	Cured	10
4	22	2	FI	V, CTX	12	R, FA	-	601	Cured	24
5	22	9	CLX	V, M	12	R, FA, Ci	-	365	Cured	6
6	55	38	-	E	48	R, FA, Ci	-	667	Cured	28
7	66	35	FI	V, CTX	12	R, FA	-	368	Failure	26
8	64	7	FI	V, CTX	8	R, FA, Ci	Severe nausea and vomiting: Ci ceased	726	Cured	29
9	28	1	V, T	V, T	11	Nil	-	0	Failure	<1
10	16	1	CLX	V, CFZ	14	R, FA, Ci	-	177	Cured	26
Haematogenous Prosthetic Joint Infection										
11	2402	1	CTX	V, CTX	12	R, FA, Ci	-	538	Cured	18
12	408	4	V, T	V, CTX	13	R, FA, Ci	-	747	Cured	56
13	235	4	FI	V, T	12	R, FA, Ci	-	357	Cured	15
Late Prosthetic Joint Infection										
14	818	365	-	V, E	93	R, FA, Ci	Acute interstitial nephritis: oral Abx ceased	35	Cured	56
15	819	806	-	V, T	11	R, FA, Ci	Nausea no change to therapy	188	Cured	15
16	880	150	-	T	12	AmC	-	57	Cured	73
17	1924	730	Tr	V, M	48	R, FA, Ci	Nausea and vomiting: Abx changed to pristinamycin	226	Cured	38
18	1459	1364	-	V, M	34	R, FA, AmC	-	195	Cured	9
19	1450	365	-	V, CTX	4	R, FA, Ci	-	102	Cured	19

Abx: Antibiotic; V: Vancomycin; CFZ : Cephazolin; M: Meropenem; T: Ticarcillin-clavulanate; CLX: Cephalexin; FA: Fusidic acid; AmC: Amoxicillin/clavulanate; IV: Intravenous; CTX: Ceftriaxone; FI: Flucloxacillin; E: Ertapenem; Tr: Trimethoprim; R: Rifampicin; Ci: Ciprofloxacin

Table 3: Management of CNPJIs according to patient and presentation.

The management of the individual patients is outlined in Table 3. Patients presenting with early or haematogenous CNPJI underwent DAR whereas delayed and late chronic CNPJI were managed by two-stage exchange. All patients undergoing two-stage exchange had a spacer impregnated with gentamicin inserted at resection and the median duration until re-implantation was 82.5 days (IQR 43,119).

Peri-operatively patients were treated with broad-spectrum antibiotics, typically vancomycin and ceftriaxone or cephazolin. There were no complications associated with the intravenous antibiotic therapy. The duration of antibiotic therapy differed between early/haematogenous and delayed/late chronic CNPJI. Patients with the early and haematogenous infections received a median of 12 days of intravenous antibiotic therapy (IQR 9,12) whereas patients with delayed/late chronic infections had a median 23 days of intravenous antibiotic therapy (IQR 4,48). In delayed/late chronic infections, patients were treated with vancomycin combined with broad-spectrum beta-lactam antibiotics (predominantly carbapenem or ticarcillin-clavulanate).

In patients with early and haematogenous infections, the median duration oral antibiotic therapy was 368 days (IQR 177,667) compared to 145 days (IQR57,195) in delayed/late chronic infections. The majority of patients received rifampicin combination therapy (89%). Rifampicin was combined with fusidic acid in 17%, with fusidic acid plus ciprofloxacin in 68%, and fusidic acid plus amoxicillin/clavulanate

in 5%. Two patients did not receive rifampicin based therapy: 1 patient died from prosthetic joint related sepsis while receiving intravenous antibiotic therapy and the second patient was treated with amoxicillin/clavulanate, the clinical reason for this decision was not apparent in the medical record.

Eight patients (44%) reported complications from the oral antibiotic regimen and this was severe enough to warrant change to treatment in 5 patients (28%). Three patients had severe nausea and vomiting, 1 patient developed acute interstitial nephritis and acute renal failure and 1 patient developed an Achilles tendonitis secondary to ciprofloxacin. There were no episodes of hepatotoxicity. No patients experiencing complications from the oral antibiotic regimens subsequently had treatment failure.

Patients were followed for a median of 19 months (IQR 13,29). Two patients had definite treatment failure according to the *a priori* definition (11%). As previously discussed, 1 patient died from prosthetic joint related sepsis in the setting of a recent fractured neck of femur and significant co-morbidities. The second treatment failure occurred in a patient with an early infection managed with DAR. The patient underwent three open debridements and lavage of the joint and was treated with vancomycin and ceftriaxone for a total of 12 days and then commenced on oral rifampicin and fusidic acid. The patient reported good compliance with the antibiotic regimen without any adverse

reactions. The antibiotics were ceased after 12 months, at that time the joint was pain free. Fourteen months after completing oral antibiotics, the patient represented with erythema and pain involving the same prosthetic joint following a recent upper respiratory tract illness. Group C *Streptococcus* (which was sensitive to rifampicin) was isolated from the joint aspirate and the patient subsequently underwent successful two-stage revision. No patients undergoing two-stage exchange experienced treatment failure. The 12-month estimate of infection free survival was 95% (95% CI: 68,99). For DAR, the 12-month estimate of infection free survival was 92% (95% CI: 57,99).

Discussion

The results of this study suggest outcomes with the treatment protocol used at this institution for CNPJI are similar to culture positive infections. The overall success of 2-stage exchange for management of delayed and late chronic infections mirrors other studies [10,13]. This study however, reports on improved outcomes for DAR. In a study of CNPJI by Berbari et al., the outcome of DAR was worse than for patients undergoing two-stage exchange (71% v 94% 5-year estimate of survival free of treatment failure) although this difference was not statistically significant [10]. Agents with activity against bacteria residing in biofilms such as rifampicin and ciprofloxacin were not administered in the study by Berbari et al. and this may account for the improved results in this current study [8,10].

However, the benefit and potential adverse impact of agents such as ciprofloxacin and rifampicin must be carefully balanced. Patients in this study received prolonged durations of broad-spectrum antibiotic therapy; a median of 12 months following DAR and 5 months for 2-stage exchange. The optimal duration of antibiotic therapy, particularly following DAR, remains an issue of contention. Current observational studies suggest outcomes are similar with 3-6 months of therapy compared to ≥ 6 months of antibiotic therapy [14]. Indeed Byren et al. suggested in patients managed by DAR, cure of infection occurred early during treatment courses and prolongation of therapy was not of additional benefit [15]. This study however did not focus on CNPJI which are inherently different to the culture positive situation.

Further prospective studies to assess optimal duration of antibiotic therapy are of paramount importance to minimise the adverse impact on the patient, medical costs and the ecological impact on microorganisms and emergence of bacterial resistance [16-18]. The impact of antibiotic therapy on the patients is evidenced by the high proportion (28%) experiencing severe adverse reactions. In previously published studies from SVHM, 30% of patients receiving rifampicin and fusidic acid experienced adverse effects and 10% ceased therapy due to severe adverse reactions [6,19]. The addition of ciprofloxacin may account for the increased rate of adverse reactions and it warrants caution and close supervision of patients receiving these antibiotic combinations.

The ecological impact of prolonged exposure on the selection of antibiotic-resistant microorganisms was not measured in this current study [18]. However, there is strong epidemiological data linking increased use of antibiotics such as fluoroquinolone with the emergence of resistant microorganisms and complications such as *Clostridium difficile* diarrhea [20,21].

The impact of prior antibiotic exposure on the likelihood of obtaining positive culture results has been previously described [10,22,23]. In this current study 92% of patients with early or haematogenous CNPJI had received antibiotic therapy in the week prior to presentation, in particular antibiotics with activity against staphylococcus, the most common aetiological agent of prosthetic joint

infection [8]. Previous studies have reported a four-fold increased risk of CNPJI in patients receiving antimicrobial therapy in the three months prior to presentation with infection [24]. This study reiterates the need for education of medical professionals about recognition of prosthetic joint infections and the importance of excluding deep infections prior to commencement of antibiotic therapy (except in patients with clinical features of acute sepsis where timely administration of antibiotic therapy is critical) [25]. Some expert recommendations suggest ceasing antibiotic therapy for a minimum of two weeks prior to obtaining microbiological samples, however, this is in variance with other clinical studies, which advocate prompt surgical debridement and instigation of appropriate antimicrobial therapy for management of infections, particularly when retention of the prosthesis is attempted [8,26]. While delay in antibiotic therapy may be quite reasonable for late or chronic infections, in contrast, for early infections delay in appropriate antibiotics has been associated with worse outcomes [27]. This highlights the need for clinicians to have a high level of suspicion for deep infection and expedite appropriate microbiologic sampling where possible, rather than pursue empiric antibiotic therapy which can hinder later pathogen identification. As this study demonstrates, in the absence of a known pathogen, the patient is often committed to long term broad spectrum antibiotic combinations that can carry considerable side effects.

In this study population, the majority of CNPJI occurred in prosthetic knee joints. This increased propensity for culture negative infections in knee arthroplasty is similarly reported by Bejon et al., but not by Berbari et al. [10,13]. We speculate the association between knee arthroplasty and culture negative infections relates to the vulnerability of prosthetic knee joints to superficial wound complications and a subsequent prescription of empiric antibiotic therapy which can impede later pathogen identification [28].

The limitations of this study include the lack of gold standard for diagnosing prosthetic joint infections. We have attempted to limit this through the use of careful definition of prosthetic joint infections, which has been consistently used in other published literature. At SVHM, tissue specimens are routinely cultured for 7 days; it is arguable that prolongation of cultures to 14 days may have increased the diagnostic yield of organisms such as *Propionibacterium acnes* [29]. Likewise, sonication on explanted prosthesis and PCR testing on tissue samples was not routinely performed [22]. These strategies may be important to help identify pathogen in these difficult clinical situations, and their role clearly deserves further exploration. Finally this study involves a small patient cohort however there is little literature reporting treatment approaches for CNPJIs and therefore this study contributes to current knowledge regarding treatment.

Conclusion

This study affirms the importance of education of clinicians to recognize prosthetic joint infections and highlights the need to be cautious about using antibiotics in patients with suspected wound complication before appropriate cultures are taken, as this may impede the later identification of pathogens.

This study provides an example of a successful regimen to help guide clinicians facing this difficult clinical challenge, and as demonstrated that the outcomes and overall treatment success rate of culture negative infections in this cohort were comparable to culture positive infections. A significant proportion of patients experience adverse reactions to the broad-spectrum antibiotic therapy so investigations into better strategies for the identification of the causative pathogen are still very important.

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