The fate of acutely inflamed joints with a negative synovial fluid culture

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Abstract

Purpose The purpose of this study was to evaluate the management and fate of acutely inflamed joints with a negative synovial fluid culture.

Methods Between January and December 2009, all the patients who presented to our institution with an acutely inflamed joint and were subjected to microbiological assessment of their synovial fluid, were included in the study. Patients with a positive synovial fluid culture, a prosthetic joint replacement in situ and where an aspirate was obtained for a rheumatological diagnosis were excluded. This cohort was then divided into two groups depending on whether a diagnosis could be established through the course of their treatment. Group I included patients in whom a diagnosis could be established and group II included patients in whom a diagnosis could not be established. A thorough review of the patients' medical records and the hospital database was performed. Following this, a database consisting of the patient demographics, clinical features, investigations, treatment and outcome was created.

Results A total of 144 patients met the inclusion criteria (group I: 95, group II: 49). The most commonly affected joint in both the groups was the knee. The average time to presentation was shorter in group II. Clinical findings at presentation were comparable in both groups. However, inflammatory markers were more likely to be raised in

group II in comparison with group I. Eighty-two percent of group II required antibiotic treatment compared with 15% of group I. The mean duration of antibiotic treatment in group I was ten days and in group II was 26 days. Mean hospital stay differed significantly between the two groups, with group II being more than twice as long as compared with group I ($p=0.001$). The rate of mortality was also higher in group II (8.2%, $p=0.03$).

Conclusion Our study shows that patients presenting with an acutely inflamed joint and a negative synovial fluid culture in whom a diagnosis cannot be established during their hospital stay have a longer hospital stay and an increased rate of mortality as compared with patients in whom a diagnosis can be established.

Introduction

The task facing a clinician when presented with an acutely inflamed joint is to determine the presence or absence of infection. This task becomes more challenging when a causative organism cannot be identified. Moreover, the appropriate management of a patient with an acutely inflamed joint and a negative culture has not been established. Hitherto, the assumption has been that this cohort of patients had an infection which is not picked up by current diagnostic methods and therefore should be treated as infections because septic arthritis is associated with a significant amount of morbidity and mortality ranging from 7–15% even with effective treatment [1].

It is also not entirely clear as to what clinical criteria are utilised to separate the infected from the non-infected joints in patients with acutely inflamed joints and negative cultures. Margaretten et al., from their meta-analysis, found that history and clinical examination were of limited sensitivity

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[2]. Fever, rigors and sweating have also been found to be of limited sensitivity [2]. Other series by contrast have found that the presence of pain and swelling was predictive of septic arthritis [3, 4]. Clinical prediction algorithms have also been developed to predict the probability of infection [5]. Kocher et al. utilised four factors in their algorithm when examining patients in the paediatric age group, namely, history of fever, non-weight bearing, $\text{ESR} \geq 40$ mm/hr and $\text{WBC} > 12,000$ cells/mm³, which in their hands had a predictive value of 99.6% when all four factors were present [5]. However Luhmann et al. could not reproduce these findings when they applied the same algorithm to their own cohort of patients [6].

Furthermore, the use of gram stain and synovial fluid culture as a gold standard diagnostic test is fraught with problems because the sensitivity of the gram stain can range from 29% to 50% [7–12], and the sensitivity of the synovial fluid culture may only be as high as 76% [10]. Apart from the diagnostic challenges, the management of these patients is a far more challenging issue, with scanty literature on the subject.

The purpose of this study, therefore, was to evaluate the management and the fate of this challenging cohort of patients with acutely inflamed joints and a negative synovial fluid culture.

Methods

All the patients who presented to our institution with an acutely inflamed joint between January and December 2009 and were investigated with microbiological assessment of their synovial fluid were included in the study. The patients for the study were identified from the hospital admissions register for inpatients and the hospital emergency-room records for outpatients. A thorough review of the patient's medical record and the hospital database was carried out. A total of 148 patients were identified; four patients were excluded because of insufficient data. Patients with a positive joint aspirate, prosthetic joint replacement in situ and patients having ongoing rheumatological treatment were excluded.

Patient demographics, joint involvement, time between first manifestation of symptoms and presentation to the hospital, history of recent antibiotic use, history and physical findings including the presence of fever, joint warmth, pain at rest, painful joint movement, sweating and joint swelling, laboratory investigations including WBC, ESR, CRP, blood and joint aspirate cultures, treatment, complications, supportive therapy including the need for central venous catheterisation, artificial feeding, dialysis and intensive therapy unit admission, period of admission, outcome and mortality were recorded for each patient and a database created.

Fever was defined as a temperature of $\geq 38.0^\circ\text{C}$ using tympanic thermometers at initial presentation. A raised white cell count was defined as $\geq 11 \times 10^9$ cells/L, a raised ESR as ≥ 15 mm/hr and a raised CRP as ≥ 20 mg/L.

Synovial fluid cultures were performed on all aspirates. Culture methods conformed to the industrial standards for synovial fluid. Specimens were cultured by inoculating in four different agar plates: Colombia agar with chocolate horse blood (37°C in a 5% carbon dioxide atmosphere for ≥ 48 h), Colombia agar with horse blood (37°C in a 5% carbon dioxide atmosphere for ≥ 48 h), CLED cystine lactose electrolyte deficient agar plates (37°C in air for 48 h) and fastidious anaerobic agar (in anaerobic conditions at 37°C for five days). Plates were examined daily for growth. The diagnosis of true septic arthritis (criteria for exclusion) was explicitly assigned when a patient had a positive finding on culture of the joint fluid. The final diagnoses were made depending on the diagnosis established through the course of the treatment or at review/discharge information.

Patients were divided into two groups depending on whether a diagnosis could be established through the course of the treatment. In group I, a diagnosis was established. In group II, a diagnosis could not be established. Treatment was divided into (1) surgical debridement and washout of the joint, (2) intravenous or oral antibiotics and (3) close observation. All patients were followed-up until resolution of their symptoms.

Statistical analysis

Specific features of interest were analysed within groups and compared across groups using the *t* test, chi square test, Wilcoxon's test and the Pearson's test where appropriate. All analyses were performed using Stata 10.

Results

Demographics

A total of 144 patients were included in this study; there were 86 males and 58 females (60% male, 40% female). Ninety-five patients had their diagnoses established through the course of treatment (group I), and in 49 patients a diagnosis could not be established or a suspicion of septic arthritis could not be excluded (group II). Both the groups were matched for sex and age ($p=0.25$).

Presentation and diagnosis

A single joint was involved in 91% (131) of the individuals in the sample and multiple joints were involved in 9% of the individuals (13). The most common joint involved in both

Fig. 1 Joint involvement

the groups was the knee joint ($n=99$). There was no association between the groups and the number of joints involved ($p=0.32$). Figure 1 shows the distribution of joints involved in each of the two groups.

In group I, the mean time to presentation was 8.05 days (SD 14.07, range 4.78–11.22) and in group II it was 4.70 days (SD 9.85, range 4.55–9.13) (Table 1). These means were not found to be significantly different ($p=0.22$).

Antibiotic intake prior to aspiration of the joint was found to be associated with group II as more than half the patients in group II received antibiotics prior to admission compared with less than 20% in group I ($p<0.001$).

The clinical findings at presentation were comparable in both the groups with joint warmth and fever being the only statistically significant parameters differentiating the two groups (Table 2). Whilst the mean values of WBC were found to be significantly different across groups ($p=0.04$), mean values of ESR and CRP were not ($p=0.46$ and $p=0.15$ respectively), although there is some evidence to suggest that mean values in group II were higher than in group I (Table 2).

Table 1 Patients demographics

Demographics	Group I	Group II
Number of patients	95	49
Mean age and range (years)	60 (7–94)	65 (1–96)
Sex	59 male; 36 female	27 male; 22 female
Average time to presentation (SD)	4.70 days (± 9.85)	8.05 days (± 14.07)
Antibiotics before aspiration	13 (14%)	25 (51%)

SD standard deviation

In group I the final diagnoses were: crystal arthropathy (40), haemarthrosis (25), inflammatory arthritis (10), osteoarthritis (8), reactive arthritis (7), bursitis (3), and skin infection (2).

An extra-articular source of infection was identified in 33 patients in group II: lower urinary tract infection (18), respiratory tract infection (8), positive blood culture (7), and skin infection (2); whilst eight patients were identified with an extra-articular source in group I: lower urinary tract

Table 2 Baseline physical and haematological examination

Parameter	Group I	Group II
Baseline physical examination		
Pain	82 (86%)	43 (88%)
Swelling	77 (81%)	42 (86%)
Painful joint movement	58 (61%)	31 (63%)
Joint warmth	35 (37%)	29 (59%)
Fever	16 (17%)	15 (31%)
Sweating	1 (1%)	1 (2%)
Insufficient information	8 (8%)	0 (0%)
Number of joints involved		
Single joint	85 (89%)	46 (94%)
Multiple joints	10 (11%)	3 (7%)
Baseline haematological examination		
WBC	10.29 (SD ± 3.51)	10.03 (SD ± 6.24)
NA	11	1
ESR	46 (SD ± 37)	60 (SD ± 31)
NA	57	29
CRP	86 (SD ± 79)	136 (SD ± 88)
NA	20	9

infection (1), colitis (2), skin infection (4), and respiratory tract infection (1).

Treatment

Patients in group II were more likely to have received active treatment (Table 3). Eighty-two percent of patients in group II required antibiotic treatment (34% had one antibiotic, 18% had two antibiotics, while in 29% three or more antibiotics were administered) compared with 15% of group I, and the duration of antibiotic treatment was more than twice as long as in group II. The most common antibiotics used were Flucloxacillin, Benzyl penicillin and Co-amoxiclav.

Fate and complications

The hospital stay was almost three times as long in group II compared with group I, which was statistically significant ($p=0.004$). A third of the patients in group II had complications related to acute joint inflammation, allergic reaction to antibiotics (2), confusion (6), diarrhoea (5), liver impairment (1), renal impairment (5), lower respiratory tract infection (5), pressure sore (1) and urinary tract infection (2) (Table 3). There were four (8.2%) mortalities identified and these were related to group II.

Patients without diagnosis

We further examined the patients in group II with respect to the presence or absence of accompanying extra-articular infection. Sixteen patients (33%) did not have an accompanying extra-articular infection whilst 33 patients (67%) had an accompanying infection. Patients who had an accompanying infection were older than those without. There were no significant differences in WBC ($p=0.52$), ESR ($p=0.59$)

Table 4 Comparison between absence and presence of extra articular infection in group II

Group II characteristics	Present extra articular infection, $n=33$	Absent extra articular infection, $n=16$
Age (SD)	72.27 (22.68)	51.31 (27.19)
WBC (SD)	12.42 (7.11)	11.18 (3.77)
ESR (SD)	63.23 (33.63)	55.14 (28.72)
CRP (SD)	142.24 (92.48)	124.56 (79.60)
Hospital stay (SD)	23 (± 22)	11 (± 11)
Complication	$N=12$ (36%)	$N=3$ (19%)
Mortality	$N=4$ (12%)	$N=0$ (0%)
Support therapy	$N=15$ (45%)	$N=3$ (19%)
Treatment		
Observation	$N=9$ (27%)	$N=0$ (0%)
Antibiotics	$N=24$ (73%)	$N=16$ (100%)
Antibiotics and washout	$N=9$ (27%)	$N=9$ (56%)
Washout	$N=9$ (27%)	$N=9$ (56%)

SD standard deviation

and CRP ($p=0.51$) between patients with accompanying infections and patients without accompanying infection (Table 4).

Four of the patients with an accompanying infection died, whilst no patients in the group of patients without infections died. No evidence was found of the proportion of mortalities being different across both subgroups (test of equality of proportions, $p=0.14$). Similarly, no significant association was found between the location of affected joint and the presence or absence of accompanying infection ($p=0.57$).

Discussion

Many conditions including crystal arthropathy and systematic diseases such as rheumatoid arthritis can present with an acutely inflamed joint [1, 12–17]. These conditions can have a clinical picture that may be indistinguishable from the clinical presentation of septic arthritis. The absence of a single highly sensitive and specific test for making the diagnosis in an acutely inflamed joint makes the management of these patients fairly challenging.

Margaretten et al., in their meta-analysis on septic arthritis in adults, showed that history and physical examination alone are of limited help in making the diagnosis of septic arthritis [2].

Kaandorp et al. found that joint pain and swelling are reasonably sensitive and should raise the suspicion of septic arthritis [3, 4] while the sensitivity of fever is only 57%, indicating that the absence of fever cannot rule out septic

Table 3 Treatment, inpatient stay, morbidity and mortality

Parameter	Group I	Group II
Conservative treatment	76 (80%)	9 (18%)
Antibiotics	14 (15%)	40 (82%)
Antibiotics alone	9 (9%)	22 (45%)
Antibiotics + washout	5 (5%)	18 (37%)
Washout alone	4 (4%)	0 (0%)
Period of antibiotics (SD)	10 (± 10)	26 (± 17)
Hospital stay in days (SD)	7.48 (± 10.09)	18.09 (± 19.89)
Supportive therapy	0 (0%)	18 (37%)
Morbidities	3 (3%)	15 (31%)
Mortality	0 (0%)	4 (8%)

SD standard deviation

arthritis as almost half the patients may be afebrile [3, 4]. Rigors and sweating have an even lower sensitivity, while WBC, ESR and CRP had high sensitivity but poor specificity [2]. Past studies have reported variable sensitivities of the laboratory tests for septic arthritis. Li et al. found that the sensitivity of an elevated WBC ranges from 19% to 77% while an elevated ESR ranges from 71% to 94%, and the sensitivity of the joint WBC greater than 50,000 cells/mm³ ranges from 0% to 92% [18]. Even diagnostic algorithms such as the one proposed by Kocher et al. have not been found to be reliable in confirming a diagnosis [5].

Gupta et al. compared a group of patients with culture negative septic arthritis with culture proven septic arthritis and found that the demographics, clinical examination, laboratory parameters, complications rates, and the use of supportive measures were similar in both the groups. Consequently he suggested that the complex treatment regime necessary for septic arthritis could be justified even in the absence of proof of the organism on culture [1]. This highlights the need for further specific laboratory tests to confirm alternative diagnoses such as crystal arthropathy or osteoarthritis [19, 20].

The acutely swollen joint with a negative synovial fluid culture has therefore been presumed to be septic in the majority of patients where the diagnosis is unclear. It could however mean a partially treated joint with septic arthritis, septic arthritis with organisms that are difficult to grow on the specific culture medium, atypical organisms or viral arthritis. Alternatively, these patients might not have septic arthritis, but current thinking based on the clinical presentation and after efforts to eliminate other clinical diagnosis means that we feel that this is less likely.

The choice and duration of antibiotic therapy is still a matter of controversy in the treatment of septic arthritis. However, the advice of the British Society for Rheumatology (BSR) Standards, Guidelines and Audit Working Group is to give two weeks of intravenous antibiotics followed by a further four weeks of oral antibiotics [21]. Krogstad et al. recommended a minimum duration of three weeks in culture positive septic arthritis [22], although shorter courses have been suggested as well [23, 24]. Chang et al., in their comparison of the characteristics of culture negative versus culture positive septic arthritis, found that antibiotic therapy was shorter in the culture-negative than in the culture-positive group, but they still had a better outcome [25].

A majority of patients that presented with an acutely inflamed joint in our series had a diagnosis. However, in a significant number of patients, septic arthritis could not be excluded and a diagnosis could not be reached during their inpatient stay. This group had a mortality rate of 8.2%, similar to the mortality rate of culture positive septic arthritis even when treated as septic arthritis [1, 3, 26, 27]. As no other diagnoses were demonstrated, we assume that these patients were likely to have an infection.

Another important finding from our study was that an infection might not be the cause of the inflammation in up to two-thirds of patients presenting with an acutely inflamed joint with negative synovial fluid cultures. Data from this study suggests that a joint pathology other than infection is more likely to be responsible. The data also confirms the common clinical experience that many conditions including crystal arthropathy and systemic diseases such as rheumatoid arthritis may present with acutely inflamed joint mimicking the clinical presentation of septic arthritis [28].

In addition, this study shows that patients with acutely inflamed joints with a negative synovial fluid culture and accompanying extra-articular infection were more likely to have a higher morbidity and mortality during a prolonged inpatient hospital stay in comparison with patients without accompanying extra-articular infection.

There are limitations to our study. The most important one being the retrospective design and the second one being that data extraction took a significant amount of time and effort and was not always readily available in the medical records. However, following this study we have established a prospective database for collecting data on this group of patients. We would also certainly recommend further prospective studies to develop algorithms for appropriate management of this challenging cohort of patients.

Conclusion

Patients with an acutely inflamed joint and a negative synovial fluid culture are difficult to diagnose and treat. Our study shows that when diagnosis can be established in this group of patients, they are less likely to suffer from morbidity, mortality, medical intervention, and a longer hospital stay. Patients without an established diagnosis tend to present with a worse clinical picture and potentially have a higher morbidity and mortality during their prolonged inpatient hospital stay especially when an extra-articular infection is present. Based on these observations, we recommend that the orthopaedic surgeons treating these patients should work closely with the infectious diseases and microbiology teams to reach a prompt diagnosis and formulate an appropriate management plan to reduce the risk of an adverse outcome.

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