EXTENDED REPORT

Prospective comparative study of patients with culture proven and high suspicion of adult onset septic arthritis

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Objective: To investigate whether patients with acute septic arthritis (SA) diagnosed by positive synovial fluid (SF) culture (Newman grade A) have different clinical and serological features from those with sterile SF in whom there is nonetheless a high suspicion of SA (Newman grades B and C).
Patients and methods: A prospective 12 month multicentre hospital based study of adult patients with SA recruited 47 patients with culture positive SA and 35 patients with clinically suspected SA but sterile SF.
Results: Patient demography, clinical and laboratory features at presentation were similar irrespective of the underlying diagnosis, SF culture, and the presence of prosthetic joints. Medical and surgical treatment and outcome were comparable in the two patient groups. Patients with both suspected and proven SA were more likely to be from the more socially deprived areas of our community ($p<0.0001$).
Conclusion: Patients in whom there is a high clinical suspicion of SA are comparable to those patients with SA with a positive SF culture and have similar morbidity and mortality on follow up. Therefore, if clinical suspicion of SA is high then it is correct to treat as SA in the absence of bacterial proof.

Septic arthritis (SA) is a clinical emergency with considerable morbidity and mortality.[1 2] Antibiotic treatment should be started as soon as the diagnosis is suspected[3 4] and modified once the organism isolated from the synovial fluid (SF) has been characterised. We have recently shown that prognosis has not improved despite optimisation of conventional treatment.[5] Unfortunately, in many cases, despite a high clinical suspicion of SA, the diagnosis cannot be confirmed because the SF is sterile on bacterial culture. This may lead to difficulties in patient management.

Newman retrospectively reviewed SA over a 30 year period and classified this condition using the following criteria: grade A—organism isolated from the joint; grade B—organism isolated from elsewhere; grade C—no organism isolated but histological or radiological evidence of infection or turbid fluid aspirated from the joint.[6]

To date there have been no prospective studies examining these groups of patients. It is important to be sure that the prolonged inpatient treatment regimens used in patients with SA can be justified in those cases where a diagnostic dilemma is caused by the absence of bacterial proof. In this one year prospective study we therefore compared 47 patients with SA diagnosed by positive SF culture (Newman grade A) with 35 patients in whom there was a high clinical suspicion of SA but in whom the SF culture was negative (Newman grades B and C). We investigated clinical characteristics, treatment, and outcome in order to evaluate whether patients with proven SA (Newman grade A) are identical to those with suspected SA (Newman grades B and C) and whether all such patients should therefore be managed in the same way.

METHODS

This was a prospective, comparative, multicentre study over a 12 month period of adult patients (aged over 16) with proven and suspected SA. Patients were identified by weekly telephone contact with rheumatologists and orthopaedic surgeons across the west of Scotland. In addition, patients admitted to other wards were notified to us by bacteriologists in participating hospitals.

A single observer (MNG) interviewed patients and collected details of presenting features, laboratory indices, prior use of antibiotics and immunosuppressant drugs, comorbid conditions, inpatient treatment, complications, and outcome.

Bacteriological analysis

SF specimens were collected in sterile universal containers and transported to the bacteriology laboratory within two hours. Where undertaken, a Gram stain was performed by routine methods. SF was cultured on the same day in 10% carbon dioxide on chocolate agar and anaerobically for 24 hours as previously reported.[7]

Statistical analysis

Data were analysed using the Mann-Whitney U test and χ^2 test. Where comparison of multiple variables was undertaken it was necessary to correct the p value using the Bonferroni correction.

RESULTS

Patient demography

Over 12 months, 82 patients with septic arthritis were examined. Forty seven had culture positive SA (Newman grade A) and 35 patients had suspected SA (seven patients in Newman grade B and 28 patients in grade C—one with suggestive synovial membrane histology, three with suggestive serial radiographs, and the rest with turbid SF).

Median age was comparable in the two groups (66.5 years, interquartile range (IQR) 58–74 in those with proven SA; 64 years, IQR 45–71 in suspected SA). Twenty two (63%) of those with suspected SA were female compared with 27 (57%) of those with culture positive SA. Most patients in both groups had primary joint disease (table 1). Four patients with proven SA (9%) and one patient with suspected SA (3%) had had a previous episode of culture positive SA.

Abbreviations: CRP, C reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, interquartile range; IV, intravenous; MRSA, multiply resistant *Staphylococcus aureus*; RA, rheumatoid arthritis; SA, septic arthritis; SF, synovial fluid; WCC, white cell count

Table 1 Clinical features in septic arthritis. Results are given as No (%) unless stated otherwise

	Proven SA (n=47)	Suspected SA (n=35)
Primary joint disease		
Overall	32 (68)	18 (51)
Rheumatoid arthritis	19 (40)	15 (43)
Osteoarthritis	8 (17)	2 (6)
Seronegative spondyloarthropathy	3 (6)	0
Crystal arthropathy	2 (4)	0
Undifferentiated polyarthropathy	0	1 (3)
Presenting feature		
Median symptom duration (days)	13	7.5
Pain	39 (83)	31 (89)
Swelling	37 (79)	28 (80)
Sweats	7 (15)	12 (34)
Fever	16 (34)	20 (57)
Rigors	3 (6)	6 (17)
Investigations		
Temperature at presentation (°C) (range, IQR)	37.5 (35.5–40.0, 36.8–38.0)	38.0 (36.0–39.1, 37.1–38.5)
Median CRP (mg/l) (range, IQR)	175 (6–440, 102–239)	224 (37–494, 121–252)
Median ESR (mm/1st h) (range, IQR)	71.5 (12–135, 42–102)	84 (30–136, 62–110)
Median WCC ($\times 10^9$/l) (range, IQR)	14.4 (6–38, 9–18)	14 (6–53, 11–21)

Symptoms, signs, and investigations at presentation

Median time to presentation in patients with proven SA was 13 days, compared with 7.5 days in suspected SA (table 1). Of the clinical features at presentation, pain and swelling were the commonest symptoms in both groups. Patients with suspected SA were more likely to complain of sweats and to feel feverish, and to have a slightly higher temperature, but after correction for multiple comparisons there was no significant difference in the incidence of any of these features. Interestingly, 40% of patients with proven SA and 14% of those with suspected SA were apyrexial at presentation. More patients in the group with suspected SA (29%) had received antibiotics in the preceding week than in the group with proven SA (15%). Neither of these differences was statistically significant.

Biochemical and haematological investigations at presentation showed that the C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white cell count (WCC) were slightly higher in the patients with suspected SA (table 1). Although the ESR was raised in all patients and the CRP in all but one, the WCC at presentation was normal in 37% of patients with proven SA, and 24% of those with suspected SA.

Coexistent conditions

Table 2 lists a number of coexistent conditions which were commonly identified. Eighteen patients (38%) with proven SA and seven (20%) with suspected SA had prosthetic joint infection. Other local causes for infection (trauma, primary periarticular abscess, recent intra-articular steroid injection, and recent joint surgery) were identified in 11 (23%) proven and eight (23%) suspected cases of SA. Distant sites of infection (intravenous drug injections, leg ulcers, chest infection, etc) were present in 23 (49%) patients with proven SA and 14 (40%) of those with suspected SA.

Table 2 Potential risk factors for septic arthritis*. Results are given as No (%)

Risk factor	Number of patients with proven SA (n=47)	Number of patients with suspected SA (n=35)
Local factors		
Primary joint disease	32 (68)	18 (51)
Prosthetic joint	18 (38)	7 (20)
Blunt trauma	1 (2)	1 (3)
Penetrating trauma	0	1 (3)
Primary periarticular abscess	2 (4)	1 (3)
Recent intra-articular steroid†	3 (6)	3 (9)
Recent joint surgery‡	5 (11)	2 (6)
Previous septic arthritis	4 (9)	1 (3)
Distant sites of infection		
Intravenous drug abuse	5 (11)	3 (9)§
Leg ulceration	5 (11)	3 (9)
Chest infection	7 (15)	4 (11)
Cholangitis	2 (4)	0
Cellulitis	0	1 (3)
Infected finger	0	1 (3)
Permanent pacemaker¶	2 (4)	0
Gonococcal urethritis	0	1 (3)
Pharyngitis	2 (4)	1 (3)
Systemic diseases		
Diabetes mellitus	2 (4)	2 (6)
Alcoholic liver disease	2 (4)	1 (3)

*No statistically significant differences found; †within three months; ‡within six months; §one patient hepatitis C positive; ¶within two weeks.

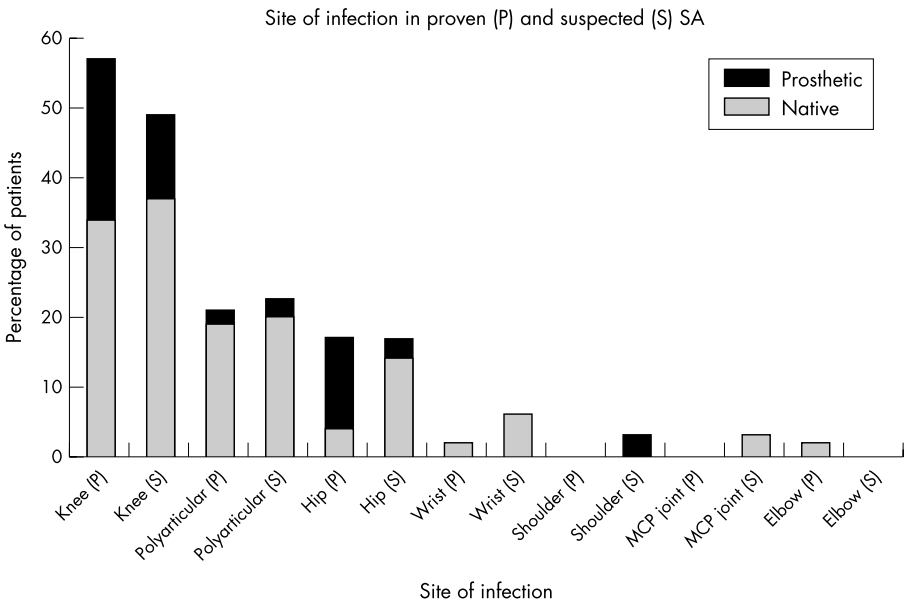

Figure 1 Sites of infection in patients with proven (n=47) and suspected (n=35) septic arthritis.

Use of disease modifying antirheumatic drugs (DMARDs) and immunosuppressant drugs

Analysis of the use of disease modifying antirheumatic drugs (DMARDs) in the patients with rheumatoid arthritis (RA) showed that 9/19 (47%) and 4/15 (27%) patients with RA with proven and suspected SA, respectively, were taking prednisolone or methotrexate alone or in combination. In the cohort with proven SA, one patient was taking methotrexate for seronegative spondyloarthropathy and one was taking prednisolone for autoimmune nephritis. Two patients with suspected SA were taking prednisolone for exacerbation of chronic obstructive airways disease. However, almost half the patients with RA with proven SA and one third of the patients with RA with suspected SA were not taking DMARDs at the time of admission.

Social deprivation

Socioeconomic status was assessed using the Carstairs index[8]—a composite score derived from the postcode and calculated on the basis of social class, male unemployment, overcrowding, and car ownership. Patients with proven and suspected SA lived in the more socially deprived areas. Twenty one (45%) patients with proven SA and 14 (40%) of those with suspected SA lived in the most socially deprived categories (groups 6 and 7) compared with only 27% of the west of Scotland population in general (n=2.3 million, $p<0.0001$ for both groups of patients).

Bacteriological investigations

Figure 1 shows the knee as the commonest site of infection in both patient groups (57% in proven SA, 49% in suspected SA), followed by hip infection (17% both cohorts). Polyarticular sepsis, affecting two or more joints was detected in 21% and 23% respectively.

Foreign material is preferentially colonised and the presence of prosthetic joints leads to a predisposition to SA. Prosthetic joint infection was seen in 38% of patients with proven SA and 20% of those with suspected SA. Although the median time of infection after joint replacement was 10 years (IQR 15–33) in the patients with suspected SA and only 6 months (IQR 4 months–three years) in those with proven infection, this did not reach significance after correction for multiple comparisons. Similarly, we were unable to show any significant differences in clinical, serological, or bacteriological features when comparing the groups with native joint infection and those with infection in prosthetic joints. In particular, mortality did not differ.

Table 3 Pathogens in 47 adult patients with proven septic arthritis

Bacterium	Number (%) of patients
*Staphylococcus aureus**	26 (55)
Staphylococcus epidermidis	6 (13)
Streptococcus species	11 (23)
Gram negative bacilli	3 (6)
Mixed infection†	1 (2)

*Three patients with MRSA; †*Staphylococcus aureus* and group A streptococcus.

The SF was sent for a Gram stain in 24 (51%) patients with proven SA and was positive for bacteria in 15 (63%) of these cases. This positive yield is higher than previously reported.[9] In the suspected SA cohort we were unable to trace the Gram stain results in three patients. There were data therefore for 32/35 patients with suspected SA. A Gram stain was undertaken in 16 (50%)patients, but a Gram positive coccus was identified in only one case. Subsequent bacterial culture was, however, negative and therefore the patient did not fulfil Newman grade A criteria.

Table 3 shows the bacteria isolated from the SF of patients with proven SA. Staphylococci and streptococci accounted for more than 90% of infections. Multiply resistant *Staphylococcus aureus* (MRSA) was detected in 6% of all infections (12% of *Staphylococcus aureus* infections) in keeping with the increased detection of MRSA in the community. One patient had a mixed *Staphylococcus aureus* and group A streptococcal infection. Although bacteria were not found in the SF of patients with suspected SA, organisms were isolated from other sites in a number of cases. Blood cultures in two patients yielded *Staphylococcus epidermidis*. In one patient, mixed infection with *Staphylococcus aureus* and group C streptococcus was detected, and in another, *Staphylococcus aureus* alone. Yeasts were isolated from the blood of one further patient.

Additionally, there was a mixed growth of staphylococcus and Gram negative bacilli in the wound swab from an elderly woman who had received a dynamic hip screw after a fractured neck of femur. One young man with a knee monarthritis and pyrexia had confirmed gonococcal urethritis. Histological examination of hip material obtained at a Girdlestone procedure for a pyrexial woman with rapid destruction

in a native hip joint, showed microabscesses which were subsequently sterile. Frank pus was obtained from the joint in two patients but was also sterile on culture.

Antibiotic treatment

Antibiotic treatment was comparable in the groups. Median duration of intravenous (IV) antibiotics was 14 days (IQR 7–28) in the patients with suspected SA compared with 16 days (IQR 14–23 days) in the group with proven SA. Subsequent oral antibiotic median duration was longer in the patients with proven SA (25 days, IQR 10–42) than in the suspected cases (14 days, IQR 0–35 days), but this was not statistically significant. Most patients received IV and then oral antibiotic treatment.

Most patients in both groups received empirical treatment with flucloxacillin in combination with gentamicin, cephalosporin, benzylpenicillin or erythromycin. Vancomycin alone was more likely to be prescribed after recent joint surgery or in suspected prosthetic joint infections, but the difference was not significant. One patient with suspected SA who had a tooth embedded in his metacarpophalangeal joint after a disagreement with a neighbour was treated with IV clarithromycin and metronidazole. There was no difference between the two groups of patients in the antibiotics prescribed.

Side effects of antibiotic treatment were analysed to investigate whether blind treatment led to unacceptable risks in patients with suspected SA. In this group one patient receiving IV ceftazidime developed *Clostridium difficile* infection and a second had reversible renal impairment after IV gentamicin. Side effects were no more common and of similar severity in patients with proven SA, of whom two developed abnormal liver function tests (one who was receiving fusidic acid and one receiving flucloxacillin), one discontinued gentamicin treatment because of renal impairment, and one stopped flucloxacillin because of a rash.

Surgical treatment

Twelve patients (26%) and three (9%) with proven and suspected SA, respectively, required surgical intervention. In the patients with proven SA, 6/18 patients with infected prosthetic joints required removal of the prosthesis and five underwent open washout (one with the insertion of a spacer). In those with suspected SA, 1/7 patients with infected prostheses underwent prosthetic knee joint removal. One had a native hip excision arthroplasty and another had an open washout. Patients on surgical wards or those with prosthetic joints were more likely to undergo surgery.

Outcome

Median inpatient stay was 30 days (IQR 12–47) in those with suspected SA and 27 days (IQR 18–46) in those with proven sepsis. Table 4 details the complications and supportive measures required. Mortality was 15% (two men, five women) in those with proven SA and 11% (one man, three women) in those with suspected SA. There was no difference in early mortality between the patients with native and prosthetic joint infection. Half the patients that died in each group had primary joint disease, all but one of these having RA. One patient with RA with suspected SA had recently received an intra-articular steroid injection. Two patients with RA with proven SA were taking immunosuppressant drugs (prednisolone or methotrexate), and three had coexistent leg ulcers.

All the patients who died had a raised WCC ($p<0.02$). Additionally, 86% and 50% respectively, of those who succumbed to acute proven or suspected SA, developed renal impairment before death ($p<0.05$).

Table 4 Complications and supportive treatment in proven and suspected SA. Results are given as No (%)

	Proven SA (n=47)	Suspected SA (n=35)
Complication		
Liver derangement	8 (17)	2 (6)
Renal impairment	13 (28)	4 (12)
Confusion	5 (11)	2 (6)
Osteomyelitis	1 (2)	0
Pulmonary haemorrhage	0	1 (3)
Supportive treatment		
Admission to ITU	3 (6)	3 (9)
Central venous line	9 (19)	8 (23)
Artificial feeding	4 (9)	2 (6)
Dialysis	2 (4)	1 (3)
Pulmonary ventilation	0	2 (6)

DISCUSSION

SA continues to be associated with significant morbidity and mortality even with effective treatment.[3] A dilemma arises when the clinical features suggest SA but bacteria cannot be identified within the joint because justification for aggressive treatment and prolonged inpatient stay is required. As far as we know, this is the first study to compare patients with SA in whom bacteria can be identified with those in whom the clinical characteristics are suggestive of SA but in whom the SF culture is sterile. We have demonstrated that all parameters (demographic, clinical, and laboratory) in these two groups are similar at presentation. However, it is of interest that so many patients with SA had a normal temperature (24/82) and WCC (25/82), indicating that these measurements alone cannot be relied on for diagnosis. However, the CRP was raised in all patients but one in both groups, indicating that the acute phase response may be a better indicator of early SA. A high WCC at presentation was notable as a predictor of poor outcome.

Although sites of infection were almost identical, with the knee being the most commonly affected joint, patients with culture proven SA were numerically more likely to have an infected prosthetic joint, which may explain the higher incidence of surgical intervention in this group. However, it was surprising to note that a large number of patients with RA were not receiving any immunosuppressive treatment or DMARD, which supports the theory that primary joint disease may be sufficient in its own right to predispose to articular infection.[10]

Antibiotic treatment was similar in variety and duration between the two groups irrespective of the underlying diagnosis or presence of a prosthetic joint, which given the identical presenting features would seem appropriate. In addition, mortality was in keeping with that previously reported[11] and was similar in the two groups. The complication rate and use of supportive measures were also similar, indicating that the need for hospital resources was independent of the presence of bacteria in the SF. These analyses confirm that the complex treatment regimen necessary for SA is justified even in the absence of bacterial proof.

This prospective study shows an annual incidence of culture proven SA (Newman grade A) of 1 in 49 000. However, we have shown that our two patient cohorts are similar, and the incidence rises to 1 in 28 000 when the proven and suspected SA groups are combined. These figures may still be an underestimate because one local hospital had no rheumatologist, and bacteriology departments may not have been aware of the working diagnosis in some cases of suspected SA. This analysis shows a higher incidence than retrospective studies,[12–14] presumably because of ascertainment bias in these earlier studies.

The reason for the lack of bacterial culture in patients with suspected SA remains a topic for speculation. In the Bremell animal model of SA, clinical signs developed only after intravenous injection of 10^7 staphylococci.[15] Thus the higher rate of

antibiotic use in the group with suspected SA before clinical diagnosis might have altered the balance between bacterial load and host innate and adaptive immunity, thereby inhibiting growth of live bacteria.

Alternatively, the patients with suspected SA might not actually have had SA, but we feel that the efforts made to exclude other diagnoses (including analysis for crystals), and similarities at presentation and in outcome between the two cohorts make this unlikely. Nevertheless, vigilance is imperative if crystal arthropathy,[16 17] reactive arthritis,[18] HIV arthropathy,[19 20] and "recurrent pseudoseptic arthritis" [21] (a monarthritis in patients with RA resembling SA but responding to intra-articular steroid), all of which are reported to mimic SA, are to be adequately excluded. The fact that so few of these conditions are associated with systemic deterioration or require such intensive supportive treatment also makes this less likely. Equally, other infections might not have been detected. Although synovial biopsy was not routinely undertaken, examination for *Mycobacterium tuberculosis* was performed in the cases where a more insidious monarthritis was slow to improve.[22–24]

Similar bacteriological techniques were used in both cohorts, which must make it unlikely that failure to grow live bacteria in the cases of suspected SA was due to improper collection or suboptimal transport conditions.[25] In the mouse model it is essential to inoculate with live bacteria to produce SA.[15] As a Gram stain was more likely to be positive in the face of subsequent positive SF culture in our proven SA cohort than previously reported,[9] the sterile SF culture in our suspected SA cohort may genuinely be due to failure to grow viable bacteria rather than a failure to detect them.

In the future other techniques might prove useful in increasing sensitivity of detection of bacterial infection. Polymerase chain reaction can detect specific bacterial DNA,[26] even after bacterial culture is negative.[27 28] Detection of antibodies against the teichoic acid staphylococcal cell wall component[29] might also increase detection of current and previous bacterial infection. However, the use of these techniques is limited by their specificity and availability.

In conclusion, we show that patients with features of SA are the same demographically, clinically, and by laboratory measurement, irrespective of the presence of bacteria grown from the joint fluid. The similarity in morbidity and short term mortality supports this contention, and our first impressions of outcome on 3–5 year follow up (data not shown) have demonstrated no real differences between the groups. We therefore provide evidence to reassure the clinician faced with the clinical conundrum of a patient with a clinical diagnosis of SA in the absence of bacterial proof that intensive management is justified.

As radiological diagnosis of SA is rare,[30 31] we suggest that two categories of SA are sufficient: category A—clinical diagnosis with bacteria isolated from the joint, and category B—clinical diagnosis with turbid SF aspirated from the joint and/or bacteria isolated from other sites. In the future it may be possible to refine criteria for the diagnosis of SA based on new analyses. This is the subject of continuing investigation.

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