Original Article

Clinical and laboratory profile in confirmed *vs.* suspected septic arthritis patients and its relevance in decision making: A comparative cross-sectional study

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ABSTRACT

Purpose: There were 10%–30% of patients with adult-onset septic arthritis (SA) exhibiting sterile synovial fluid (SF), and the uncertainty in the determining diagnosis of these patients posed a challenge in management. The purpose of this study was to investigate the differences between confirmed (Newman A) and suspected (Newman B & C) SA in adults.
Methods: This was a descriptive study with a cross-sectional study design conducted at a tertiary referral centre from July 2016 to February 2019. Patients aged over 18 years presented to the emergency department with clinical features suggestive of SA and were scheduled to undergo arthrotomy and joint lavage by the treating surgeon were included in the study. Patients with prosthetic joint infections and open joint injuries were excluded. Patients' demographic data, clinical features and laboratory parameters were collected. The clinical and laboratory profile (blood and SF) of the adult patients presenting with features suggestive of SA based on Newman criteria was statistically analyzed by SPSS version 20 software and Microsoft Excel. The categorical variables were expressed as proportions while the continuous variables were expressed as mean (SD) or median (IQR) depending upon the normality of distribution. The difference between the two groups for categorical variables was assessed using the Chi-square test and the difference for continuous variables was assessed using the unpaired *t*-test and the Mann-Whitney test depending upon normality. A *p* value < 0.05 was considered significant.
Results: Thirty-six patients were divided into confirmed ($n = 19$) or suspected ($n = 17$) SA for assessment based on SF culture. The median (IQR) age of the patients was 50 years (37–60 years). There was no significant difference in demographic, clinical and laboratory parameters between the concerned groups. Eight patients presented with fever. Among the confirmed SA cases, 8 were negative for C-reactive protein and 6 had synovial white blood cell count <50,000. *Staphylococcus* species were isolated in 8 cases. The most common risk factors for SA were chronic kidney disease (25.0%), diabetes mellitus (25.0%), pharmacologic immunosuppression (16.7%), recent joint surgery (11.1%) and distant site infection (11.1%).
Conclusion: SA is an orthopaedic emergency that needs prompt and aggressive treatment to prevent catastrophic complications. Confirmed and suspected cases of SA exhibit similar demography, clinical features and laboratory parameters at presentation which may mislead the treating surgeon. Management should be based on sound clinical judgment in the event of failure to culture microorganisms.

Introduction

Septic arthritis (SA) is an orthopaedic emergency that necessitates timely diagnosis and intervention to prevent irreversible damage to the articular cartilage and permanent disability. Apart from the significant morbidity, the mortality in SA is estimated to be approximately 11%.[1] Newman et al.[2] retrospectively analysed the patients with SA over 30 years old and classified them into three

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groups based on the isolation of microorganism from the synovial fluid (SF): Newman A-isolation of microorganism from the SF of involved joint, Newman B-isolation of microorganism from elsewhere, Newman C-no microorganism isolated but histological and radiological evidence of infection or turbid fluid aspirated from the joint.[2] It has been reported that 10%–30% of patients with adult-onset SA have been found to have sterile SF and the management of these patients is challenging due to the uncertainty in diagnosis.[1,3] Coupled with the diagnostic dilemma is the paucity of previously published prospective studies that have analysed this patient group and its characteristics, especially in Indian population. The purpose of this study was to investigate the differences in patient demography, clinical features and laboratory parameters between confirmed (Newman A) and suspected (Newman B & C) SA in adult Indian population. We also aimed to evaluate the risk factors associated with adult-onset SA in our study population.

Methods

A descriptive study using a cross-sectional study design was conducted from July 2016 to February 2019 at a tertiary referral centre for the treatment of bone and joint disorders in south India. Institutional ethical board clearance was obtained and a convenient method of sampling was employed. The patients were enrolled in the study after obtaining a written informed consent. Patients aged over 18 years presented to emergency department with clinical features suggestive of SA, who were scheduled to undergo arthrotomy and joint lavage by the treating surgeon were included in the study. Patients with prosthetic joint infections (PJI) and open joint injuries were excluded. The initial assessment of those included detailed history, demographic profile and clinical examination. The parameters extracted from the patient's history were duration of symptoms (in days), co-morbid conditions, prior antibiotics dosages and duration of immunosuppressive medications. Before surgery blood samples were collected to assess the baseline white blood cell count, erythrocyte sedimentation rate, C-reactive protein (CRP) and blood culture. The SF and tissue sample obtained during arthrotomy was collected in a sterile container and transported to microbiology and biochemistry labs within 2 h and was analysed as a standard protocol.

Based on the analysis report of SF and tissue obtained during arthrotomy, the patients were divided into two groups: group I - SF culture-positive adult-onset SA (Newman A/confirmed); group II - SF culture-negative adult-onset SA (Newman B and Newman C/suspected).

Suspicious cases with sterile SF culture were included in the study based on SF white blood cell count being > 50,000 cells/mm³ with predominant neutrophils which suggesting septic joint, joint aspiration revealing frank pus, a synovial histology suggestive of acute suppurative infection or a positive blood or exudate culture from a nearby wound.

Post-operatively, the patients received empirical broad-spectrum intravenous antibiotics (Cloxacillin 1 mg Q6H and Gentamycin 80 mg Q8H) as per hospital protocol, which was subsequently changed according to the antibiotic sensitivity report of microorganisms cultured from SF. Antibiotic sensitivity of microorganism cultured from blood culture or wound exudate was used in SF culture sterile patients. According to the hospital policy, an intravenous antibiotic was administered for 2 weeks followed by oral antibiotics for 4 weeks. In patients with diabetes mellitus (DM) and chronic kidney disease (CKD) the antibiotic protocol was modified based on hospital recommendations after consultation with physician and nephrologist for dose titration. All patients were observed until discharge from the hospital.

The data obtained from the two groups were analysed by SPSS version 20 and Microsoft Excel. The categorical variables were expressed as proportions, while the continuous variables were expressed as mean (SD) or median (IQR) depending upon the normality of distribution. The difference between the two groups for categorical variables was assessed using the Chi-square test and the difference for continuous variables was assessed using the unpaired *t*-test and the Mann-Whitney test depending upon normality. A *p* value < 0.05 was considered significant. A sample size of 55 for a finite population of 60, with a confidence interval of 95% and a relative precision of 20% keeping a ratio of 1:1 between the two groups was calculated using an expected prevalence of fever in proven and suspected SA patients as 34% and 57%.

Results

Demographic variables

A total of 38 patients underwent arthrotomy but 36 were considered for final evaluation with 19 belonging to group I (Newman A) and 17 to group II (Newman B & C) (Fig. 1). The demographic variables between the two groups were comparable and are summarised in Table 1. The median (IQR) age for the study population was 50 years (37–60 years) with a fair majority being male in both groups (89% and 76%). Most patients were found to have SA of one knee joint with a right-sided preponderance. An isolated case of bilateral knee involvement was noted in group II. This patient suffered from chronic pancreatitis with features suggestive of sepsis and nothing to indicate systemic or inflammatory arthritis. Another patient having polyarticular disease demonstrated growth of *Burkholderia pseudomallei* from the synovial culture (group I) of the knee and ankle. The mean duration of hospital stay was 18 days ranging from 8 to 38 days across both of the groups.

Clinical and biochemical profile

The data on the clinical and laboratory profile of the two groups is summarised in Tables 2 and 3. The median time to presentation was 5 days (3–7 days). Pain (100%) was the most common presenting symptom followed by swelling around the affected joint. Twenty-eight patients presented with swelling (excluding hip and shoulder), but significant swelling (>1 cm difference in circumference) was present in only 23 cases. Fever at the time of admission was noted in 22.2% of cases.

Seven patients in our study (3 patients in group I, 4 patients in group II) presented with a discharging wound near the joint. This was constituted by 2 patients with pin tract infection following Ilizarov ring fixator application, 2 with cellulitis of lower limb with a discharging wound (1 with thigh cellulitis and the other with leg cellulitis), 1 patient with serous discharge from tibial tunnel screw site post anterior cruciate ligament reconstruction, another with necrotising fasciitis of leg and 1 patient with a deltoid abscess following intramuscular injection. The microorganisms cultured from the joint in these patients were *Methicillin-sensitive Staphylococcus aureus* (MSSA), *Klebsiella* and *Enterococcus faecalis*. MSSA and *Klebsiella* were also isolated from the discharging wounds in these cases.

Six patients (2 patients in group I and 4 patients in group II) in our study received antibiotic treatment before SF culture or joint lavage. This consisted of 3 patients who had sepsis at presentation and were started on broad-spectrum antibiotic treatment, 1 patient with SA of shoulder who had received intravenous linezolid for osteomyelitis of the proximal humerus before the presentation, one
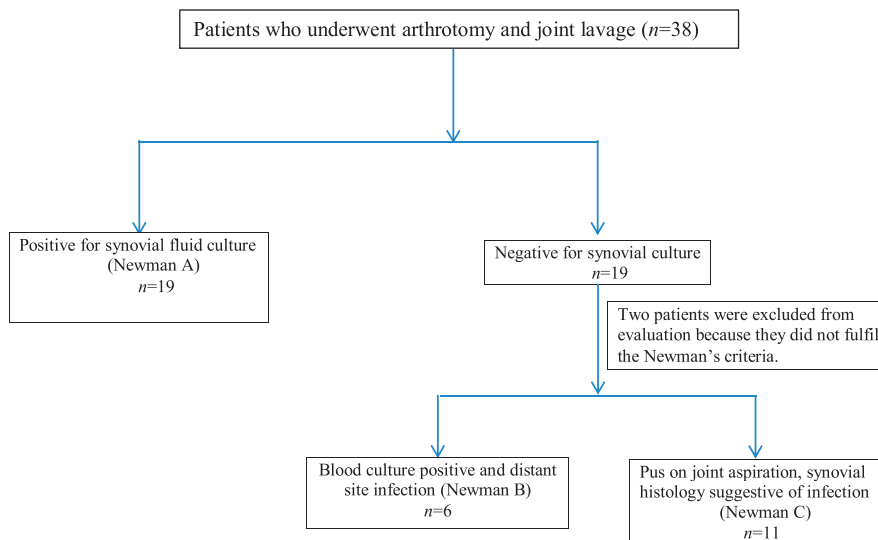
Fig. 1. Flow diagram representing the recruitment of patients into the study.

Table 1
Demographic variables between group I and group II.

Variables	Group I ($n = 19$)	Group II ($n = 17$)	p value
Age, median (IQR) (year)	42 (27.5—56.5)	54.5 (39.8—65.0)	0.150
Sex, n (%)			0.296
Male	17 (89.5)	13 (76.5)	
Female	2 (10.5)	4 (23.5)	
Joint involved, n (%)			0.895
Knee	13 (68.4)	15 (88.2)	
Hip	1 (5.3)	0 (0)	
Shoulder	3 (15.8)	2 (11.8)	
Elbow	1 (5.3)	1 (5.9)	
Wrist	1 (5.3)	0 (0)	
Ankle	1 (5.3)	0 (0)	
Side, n (%)			0.317
Right	15 (78.9)	10 (58.8)	
Left	3 (15.8)	6 (35.3)	
Two or more joints involved, n (%)	1 (5.3)	1 (5.9)	
Duration of hospital stay, median (IQR) (day)	17 (11.5—24.0)	17.5 (14.3—23.8)	0.899

Table 2
Comparison of clinical features between group I and group II.

Clinical features	Group I ($n = 19$)	Group II ($n = 17$)	p value
Duration of symptoms, median (IQR) (day)	5 (3—11)	6.5 (3—7.8)	0.5
Pain, n (%)	19 (100)	17 (100)	—
Swelling, n (%)			0.228
Yes	12 (63.2)	16 (94.1)	
No	7 (36.8)	1 (5.9)	
Significant swelling, n (%)	9 (47.4)	14 (82.4)	0.153
Fever, n (%)			0.858
Yes	4 (21.1)	4 (23.5)	
No	15 (78.9)	13 (76.5)	
Discharge, n (%)			0.847
Yes	3 (15.8)	4 (23.5)	
No	16 (84.2)	13 (76.5)	

with necrotizing fasciitis and one with a history of recurrent pyogenic infection (abscess).

Microbiology

The microorganisms cultured in Newman A/confirmed adult SA patients were *Staphylococcus* species ($n = 8$), *Enterococcus faecalis*

($n = 1$), *Pseudomonas aeruginosa* ($n = 3$), *Klebsiella* species ($n = 3$), *Gram negative rods* ($n = 3$) and mixed infection ($n = 1$). Other organisms isolated were *Proteus, Acinetobacter* and *Streptococcus agalactiae*. All patients in whom gram negative organism were isolated were immunocompromised.

The SF gram stain was positive in only 5 cases after aspiration, 3 of which subsequently yielded a micro-organism (group I). Five

Table 3
Comparison of biochemical parameters (blood and synovial fluid) between group I and group II.

pcParameters	Group I ($n = 19$)	Group II ($n = 17$)	p value
Blood parameters			
ESR, median (IQR) (mm/h)	52 (41—98)	70 (61—93)	0.29
CRP, n (%)			0.77
Positive	11 (57.9)	8 (47.1)	
Negative	8 (42.1)	9 (52.9)	
Blood TLC, median (IQR) (cells/mm^3)	10,090 (6910—12550)	10,465 (7260—14280)	0.34
Elevated TLC, n (%)			1.00
Yes	8 (42.1)	8 (47.1)	
No	11 (57.9)	9 (52.9)	
Blood culture, n (%)			0.85
Positive	5 (26.3)	4 (23.5)	
Negative	14 (73.6)	13 (76.4)	
Synovial fluid parameters			
Gram stain, n (%)			0.73
Positive	3 (15.8)	2 (11.8)	
Negative	16 (84.2)	15 (88.2)	
Synovial fluid color (purulent)	16 (84.2)	6 (35.3)	0.01
Synovial TLC, median (IQR) cells/mm^3	41,155 (4115—65350)	18,800 (1300—32000)	0.43
Synovial protein, median (IQR) (g/mL)	0.03 (0.03-0.04)	0.05 (0.03-0.05)	0.46
Synovial sugar, median (IQR) (mg/mL)	0.08 (0.06-0.11)	0.07 (0.04-0.11)	0.56
Synovial LDH, median (IQR) (IU/L) ($n = 12$)	5525 (5000—6099)	2442 (662—5604)	0.23
USG echoes			0.65
Positive	13 (68.4)	14 (82.4)	
Negative	6 (31.6)	3 (17.6)	

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TLC: total leucocyte count, LDH: lactate dehydrogenase, USG: ultrasonogram.

patients in group I had positive blood cultures and among these, 4 cases matched with the organism grown in SF. One patient whose blood culture showed a mixed infection (*Streptococcus agalactiae* and *Enterococcus*) grew *Burkholderia* species in SF culture. Four patients in group II yielded positive blood cultures.

Host related factors and co-existing conditions

The co-morbid conditions in both groups are summarised in Table 4. CKD and DM were present in 50% of confirmed SA cases. Among the 9 patients with CKD, 5 concurrently had DM, 2 had systemic lupus erythematosus (SLE) and one each had co-existing juvenile idiopathic arthritis and chronic liver disease. While diabetes was more prevalent among group I as opposed to group II, the difference was statistically insignificant. The other major co-existing factors noted in our study were chronic alcoholism ($n = 3$), steroid and immunosuppressive therapy ($n = 6$), systemic sepsis ($n = 3$) and malignancy ($n = 2$). Both groups had 2 patients

with underlying joint disease wherein 3 patients had osteoarthritis and 1 suffered from juvenile idiopathic arthritis.

Three patients in the study were diagnosed with systemic sepsis at presentation. One was on corticosteroid-based treatment for thrombotic thrombocytopenic purpura; the second had alcoholic liver disease and the last was a diabetic with CKD.

Similarly, a total of 6 patients were on immunosuppressive agents for various ailments (thrombotic thrombocytopenic purpura, SLE, polymyositis, immune thrombocytopenic purpura, post-renal transplant) at the time of presentation. Two patients were on monotherapy with Methylprednisolone (12—16 mg/day) while the other 4 were on Prednisolone (5—40 mg/day) in combination with either Azathioprine (50 mg/day) or Tacrolimus (4 mg twice a day). Among these patients, 4 yielded positive SF cultures wherein 1 grew MRSA and the rest grew gram-negative organisms.

Table 4
Co-existent risk factors in group I and group II, n (%).

Co-existing risk factors	Group I ($n = 19$)	Group II ($n = 17$)	p value
Systemic diseases			
Chronic kidney disease	5 (26.3)	4 (23.5)	0.590
Diabetes mellitus	8 (42.1)	1 (5.9)	0.120
Chronic liver disease	2 (10.5)	1 (5.9)	0.615
Others	6 (31.6)	10 (58.8)	0.153
Local factors			
Primary joint disease	2 (10.5)	2 (11.8)	0.906
Peri-articular infection	0 (0)	2 (11.8)	0.124
Recent intra-articular steroid	0 (0)	0 (0)	−
Previous septic arthritis	1 (5.3)	0 (0)	0.284
Recent joint surgery	3 (15.8)	1 (5.9)	0.494
Distant sites of infection			
Cellulitis	1 (5.3)	1 (5.9)	
Leg ulcers	0 (0)	1 (5.9)	
Intravenous drug abuse	0 (0)	0 (0)	
Urinary tract infection	1 (5.3)	0 (0)	

Discussion

Despite all efforts at diagnosis and treatment, SA persists to be a cause of significant morbidity and mortality.[4] While the prompt institution of treatment and successful functional outcome are the goals of management in SA, one must first overcome the diagnostic conundrum associated with it. Clinical features, SF analyses and culture reports may paint contrasting pictures between inflammatory arthritis and SA thereby, delaying diagnosis. This ambiguity often hinders the institution of early aggressive treatment by the surgeon due to lack of justification for the same and the subsequent need for prolonged treatment duration and hospital stay.

Our study aimed to analyse the differences in patients' demography, clinical features and laboratory parameters between confirmed (Newman A) and suspected (Newman B and C) SA in adult Indian population. We did not find any difference in the demography, clinical presentation and biochemical profile between the two groups. These findings were similar to published studies on Caucasians, where the authors failed to conclusively report differences between suspected and confirmed cases of SA in adults.[4,5] A study reported an age over 80 years to be an independent risk factor for SA in adults.[6] While the other risk factors were comparable, the mean age of onset of SA in adults was reported to be higher by other investigators in contrast to our study. We attribute this to the lower life expectancy and socioeconomic factors prevalent in our sub-continent.

In a meta-analysis of 14 studies, Margaretten et al.[7] reviewed the accuracy and diagnostic precision of clinical history and examination. The investigators reported pain (85%), swelling (78%) and fever (57%) to be sensitive for the diagnosis of SA in adults whereas chills and rigors had a low diagnostic yield. The pain was a constant feature in all our patients and swelling was present in a fair majority (80%). We had a mere 22% of patients in either group who presented with a fever on admission. Fever and acute phase reactants have been reported as unreliable indicators of SA in adults.[4,7] Furthermore, disagreement on the cut-off temperature to define fever has been reported by various studies.[7] While Gupta et al.[1,4] reported CRP to be a better indicator for the diagnosis of SA, 8 confirmed cases in our study were negative for CRP. A subgroup of 7 patients who presented with a discharging wound near the joint were all expected to be confirmed cases because the foci of infection in the vicinity was believed to have precipitated the joint infection. However, 4 of these belonged to group II and only 3 belonged to group I. The organisms cultured from the SF and the discharging wound in confirmed cases of this sub-group were the same. The 4 cases of suspected SA in this subgroup had frank pus on aspiration at the time of arthrotomy. The most likely explanation for the failure to culture organisms in this subgroup may be attributed to their immunocompromised state and antibiotic administration before SF analysis.

Synovial total leucocyte count > 50,000 cells/mm^3 with neutrophilic predominance (>75%) has been reported in 50%—70% of SA cases in adults, but immunocompromised individuals tend to have lower counts.[7,8] The confirmed and suspected SA cases in our study had a median synovial total leucocyte count of 41,155 cells/mm^3 and 18,800 cells/m^3. While this may indicate that higher counts increase the likely hood of a positive culture, we found 6 patients with counts <50,000 cells/mm^3 among the confirmed group I cases. The rate of positive blood culture (9 patients, 22.9%) and gram stain (5 patients, 23.5%) was lower in our study group in comparison to various other studies.[4,5,7]

Four of 6 patients on prior antibiotic treatment were categorised into group II. History of prior antibiotic usage is associated with sterile SF culture in SA.[1,6] The factors responsible for sterile culture in group II are the host innate defence mechanism and adaptive immunity. Studies have demonstrated that a minimum inoculum of 10^7 bacteria is required to produce clinical signs and symptoms.[9] Early initiation of antibiotic treatment in these patients may give a picture of arthritis similar to Newman B and C. Weston et al.[10] reported the sensitivity of gram stain and SF culture to be 50% and 67%. They reported that antibiotic treatment before culture and the presence of atypical organisms in SF resulted in 30%—80% false-negative culture outcomes. Essen et al.[11] in another study reported that a high volume of inoculum and the type of culture medium might increase the chance of detecting the microorganism on SF culture. Sorlin et al.[12] reported that the use of commercial blood culture systems ("BACTEC plus Aerobic/F" medium) might increase the chance of microorganism detection in antibiotic-treated suspected SA cases. Few authors have recommended inoculation in blood culture bottles in addition to solid culture media to increase the yield of fastidious bacteria.[11] The SF samples were inoculated on MacConkey and blood agar in our study. Cultures that were negative after 48 h of incubation were then inoculated on brain heart infusion broth for an additional 7 days. Polymerase chain reaction does not provide an added advantage over SF culture in the detection of microorganisms.[13]

Multiple studies have reported the presence of primary joint disease, a prosthetic joint and pharmacologic immunosuppression to be the major risk factors for SA.[4–6] In our study, we observed CKD, DM, and pharmacologic immunosuppression to be co-existent in a vast majority and the most contributory towards SA. A recent surgery near the joint was one of the risk factors for SA in our study group and the microorganism profile of these patients was consistent with that of hospital-acquired infection. Our study excluded patients with PJI because we observed that they tend to skew the data from native joint infections. A high incidence of SA, both SF culture-positive and sterile, has been documented in the presence of prosthetic joints.[4,5] However, Gupta et al.[4] failed to demonstrate significant differences in clinical, serological, bacteriological profile and mortality rates between native joint infection and PJI.

The limitations of this study were its small sample size and short study duration. A prospective study design could have provided more insight into the eventual fate of Newman A and Newman B and concerning differences in functional outcome and mortality.

In this study, confirmed and suspected SA patients based on Newman's criteria in adult Indian population exhibit similar demography, clinical features and laboratory parameters at presentation. However, a prospective study design with a larger sample size could provide more insight into the differences between the two groups. While risk factors between the two groups show a similarity, SA persists to be an orthopaedic emergency that necessitates prompt and aggressive treatment to prevent catastrophic complications. The management should consider a constellation of factors and not just be based on any one criterion. Sound clinical judgement should guide treatment in the event of failure to culture micro-organisms.

Ethical statement

Institutional ethical board clearance was obtained. A written informed consent was obtained from the patient enrolled in the study.

Declaration of competing interest

The authors do not have any conflict of interests.

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