The biochemical, microbiological and histological findings in native joint septic arthritis in adults

Dane Maimin,[1]* Vijay Martin,[1] Kaylin Williams,[1] Roopam Dey,[1,4-7] Sipho Dlamini,[3] Sithombo Maqungo[1,2]

[1] Orthopaedic Research Unit, Division of Orthopaedic Surgery, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa
[2] Division of Global Surgery, University of Cape Town, Cape Town, South Africa
[3] Division of Infectious Diseases, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa
[4] Division of Biomedical Engineering, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa
[5] Division of Physiological Sciences, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa
[6] Biomedical Engineering Research Centre (BMREC), University of Cape Town, South Africa
[7] Health through Physical Activity, Lifestyle and Sport (HPALS), University of Cape Town, South Africa

Corresponding author: danemaimin@gmail.com

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Abstract

Background

Septic arthritis is an orthopaedic emergency with an incidence of 2 to 10 per 100 000 patients in the general population. Mortality rates between 3 and 29% can be expected. Local knowledge of microorganisms and antibiotic sensitivities will facilitate expedited and effective treatment. The aim of the study was to review and analyse the microbiological, histological and biochemical findings in patients taken to theatre for the purposes of treating a septic arthritis of native joints in adult patients at our institution.

Methods

A retrospective case series analysis was performed. We included only adult patients that were taken to theatre for treatment of a presumed septic joint. We excluded paediatric patients, joints distal to the elbow or ankle, and the spine. Preoperative blood tests and samples obtained intraoperatively for microbiological and histological testing were analysed. Inflammatory markers were compared against culture results. Bacteria trends and antibiotic sensitivities were assessed. Histological findings were analysed against positive cultures.

Results

In our study, 104 patients were taken to theatre for the treatment of presumed septic arthritis during the data collection period. Eighty-six (81%) were found to have septic arthritis based on cultures and/or histology. The knee was the most affected joint (67%). A regression analysis suggested that high erythrocyte sedimentation rate and high C-reactive protein levels were better predictors for septic arthritis compared to white cell count. Methicillin-sensitive *Staphylococcus aureus* (31%), *Staphylococcus epidermidis* (10%) and *Enterobacter cloacae* complex (8%) were the most common organisms identified. Multidrug-resistant organisms were cultured in 19% (9/48) cases, in the form of methicillin-resistant *Staphylococcus aureus*, *Proteus mirabilis* and *Acinetobacter baumannii*.

Conclusion

Septic arthritis remains a diagnostic challenge and organism and antibiotic patterns vary. We present a review and summary of all septic joints over a seven-year period at a tertiary level orthopaedic service.

Level of evidence: Level 4

Keywords: acute septic arthritis, biochemistry, histology, microbiology

Introduction

Septic arthritis (SA) is an orthopaedic emergency with an incidence of 2 to 10 per 100 000 patients in the general population.[1,2] Mortality rates between 3 and 29% can be expected.[3,4] *Staphylococcus aureus* (*S. aureus*) is the most common pathogen identified on culture of septic knee aspirate.[1,3-8] The knee is the most commonly affected joint in adults[1,2,4] and is associated with significant morbidity when not treated correctly and expeditiously.[1,3,4,8,9] A combination of the host immune response and bacterial toxins and enzymes damage the intra-articular cartilage matrix within three hours and lead to its destruction and subchondral bone loss in as little as three days.[4,5]

This study aims primarily to review microbiological, histological and biochemical findings in native joint SA in adults taken to theatre at our institution. Our results will be compared against relevant existing international and local literature. Secondary aims are to assess prevalence of organisms as well as antibiotic sensitivities, and resistance patterns will be assessed. Relevant blood results will be analysed, and the most useful biochemical markers will be

identified. Positive blood and synovial fluid culture rates will be reviewed. These findings could aid in the diagnosis of SA for future patients as well as help tailor empiric antibiotic regimens.

There has been limited recent research on SA in adults in South Africa. Only three previous studies could be found from this century, from only two institutions, both of which are in Gauteng.[10-12] SA data trends have not been explored at our institution.

Materials and methods

The authors obtained relevant institutional and ethical review board approval. An observational, retrospective, descriptive case series review was performed on a prospectively collected database at a single tertiary level institution in South Africa. The Department of Orthopaedic Surgery's REDCap database was reviewed for all patients taken to theatre for an arthrotomy or joint washout with a provisional diagnosis of SA. The data collection period was January 2016 to December 2021. We excluded all patients under the age of 16 years, those with a prosthetic joint in-situ and those who appeared in the surgical database but did not have any corresponding laboratory data. Demographic data was collected, and patients were anonymised with only folder numbers used for identification purposes. The local laboratory services (Disa-Labs and National Health Laboratory Service) were used to obtain microbiological, histological and biochemical results.

White cell count (WCC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were noted as the most relevant and available inflammatory markers. Normal value cutoffs were used as 4.5×10^9/L − 11.0×10^9/L, 20 mm/hr, and 10 mg/L respectively.

Culture specimens were reviewed either as blood cultures or as intraoperative specimens sent for culture. Intraoperative culture specimens were either swabs of the intra-articular fluid or periarticular tissue. Due to the retrospective design, it was not possible to standardise the nature of the specimens sent to the laboratory. In samples where bacteria were cultured, the organism was classified by Gram stain and reviewed by the senior authors. Antibiotic resistance and unusual organisms were noted.

Histology reports tended to be non-standardised and varied in their use of language. There were, however, several terms that were repeated throughout the reports, and these were used to form four major categories: acute synovitis/arthropathy, acute-on-chronic synovitis, chronic synovitis, and granulomatous inflammation. All reports were assessed on an individual basis by the two senior authors and grouped into one of the major categories. For the purposes of statistics, both acute and acute-on-chronic findings were deemed to support a diagnosis of acute pyogenic SA, even if no organisms were cultured at the same sample setting. Chronic synovitis and granulomatous inflammation were findings that did not support a diagnosis of acute pyogenic SA.

For statistical analysis, the diagnosis of pyogenic SA was confirmed if either histology was supportive, or an organism was cultured or both.

Since this was an exploratory retrospective study, a priori sample size analysis was not performed. Odds ratios were calculated using logistic regression. Percentage positive predictive values were calculated as the ratio of the true positives and the total number of patients classified to have SA. The statistical tests were performed in SPSS v.28 and the limit for statistical significance was set as $p < 0.05$.

Results

At the time of sampling the database had 104 patients over 16 years of age who had been to theatre for washout of a native joint. One patient's results could not be traced at the laboratory, leaving a final sample size of 103. Most of our sample was under 65 years old (86%) with a mean age of 46.5 years (± 19.2 years). The ages ranged from 16 to 91 years. Males accounted for 64% (n = 65).

Eighty-one per cent (n = 84) of our cohort had microbiological or histological results from theatre that confirmed the diagnosis of SA. Of this group, an organism was cultured in 56% and the remainder were culture-negative but had histology in keeping with pyogenic infection. The knee was the most prevalent joint involved in 69% (n = 58) of cases. The shoulder (11%, n = 9) and the hip (9%, n = 8) were the next most common joints affected. Five per cent (n = 4) of patients had multiple joints washed out simultaneously. Twenty-seven per cent (n = 23) of patients required more than one theatre episode for repeat arthrotomies.

Although not every patient had had all three of the analysed culture methods (periarticular tissue cultures, intra-articular fluid swabs and blood cultures) when an organism was cultured, it was more likely to be from synovial tissue samples. In cases where an organism was cultured, it was found in the synovial tissue in 82% of the time. This was followed by 46% on fluid swab, with blood cultures only yielding 15% positive results. Blood cultures and tissue cultures were both done on 64% (n = 62) of patients diagnosed with SA. Of these 62 patients, five patients had blood culture results that differed from tissue culture results; four of these had positive blood cultures and negative tissue cultures, and one blood culture grew a different bacterium to the theatre culture (*Streptococcus viridans* on blood and *Streptococcus agalactiae* on tissue).

The WCC was raised in only 59% of patients who were taken to theatre. We found a positive predictive value of 62% for WCC and confirmed SA. It was found that high ESR and CRP had positive predictive values of 100% and 95% respectively. Patients with a raised ESR (95% CI: 0.995–1.016. p-value 0.279) and raised CRP levels (95% CI: 0.997–1.004. p-value 0.850) were more likely to be diagnosed with SA, although these trends did not reach statistical significance. Patients with a low or raised WCC showed no significant difference in their odds of being diagnosed with SA.

The most common organism in our cohort was methicillin-sensitive *S. aureus*, found in 31% of our positive cultures. Sixty-four per cent of the bacteria cultured were Gram positive. Other common Gram-positive organisms included various staphylococcal and streptococcal species. Gram negatives were cultured in only 16% (n = 17) cases, and were typically *Escherichia coli*, *Pseudomonas* species, *Klebsiella pneumoniae* or *Enterobacter* species. Methicillin-resistant *Staphylococcus aureus* (MRSA) was found in 2% of cases. Uncommon organisms were mostly Gram negative and included *Citrobacter braakii*, *Shewanella algae*, *Stenotrophomonas maltophilia* and *Acinetobacter* species. *Bacillus cereus* was the only uncommon Gram-positive organism that was cultured in this series. Organisms that were found to be resistant to standard empiric antibiotic therapy were cultured in 9% of cases. *Mycobacterium tuberculosis* was cultured in two samples: one hip and one shoulder joint.

In our cohort, 65% were tested for HIV either previously, or during their admission, and 21% (n = 14) were HIV positive. Although this is a small sample, non-parametric statistical analysis showed that the HIV-positive group had significantly lower ($p < 0.05$) WCC levels than the HIV-negative groups. Such significant differences were not observed in the ESR and CRP levels. Patients who were HIV positive were more likely to grow an unusual organism, seen in more than half (n = 8) of cases. These organisms were, however, not more likely to be resistant to standard antibiotic therapy than those patients who were HIV negative.

ESR were found to be raised in those patients over the age of 65 years regardless of a positive or negative diagnosis of SA. The mean ESR level for patients above the age of 65 years was

34.4 (SD: 49.3; 95% CI: 9.6–58.7). Eighteen patients over 65 years of age were taken to theatre for arthrotomy with only 33% (n = 6) returning positive cultures or histology. Those that did return positive cultures had similar microbiological findings to other age groups.

Discussion

Eighty-one per cent of our cohort had their preliminary clinical diagnosis of SA confirmed by their microbiological and histological finding. To date there is no single reliable method to diagnose SA. Helito et al. found a leukocytosis rate of under 50% in their knee SA series review.[1] Both CRP and ESR have also reportedly been unreliable in confirmed cases of SA. These acute phase reactants cannot distinguish between septic and other forms of acute inflammatory arthritis.[1,4,5] Our series found that a raised or low WCC had no bearing on the likelihood of confirming SA. ESR and CRP were found to be more useful in predicting the diagnosis of SA although we did not reach statistical significance in this cohort. HIV-positive patients showed a trend towards having lower inflammatory markers although the sample size was too small to prove significant. It is noted that ESR values in HIV-positive patients may be unreliable due to the HIV infection itself causing a raised ESR level.[13] On average, elderly patients were more likely to have a raised ESR, even in cases with no microbiological or histological evidence of SA.

Our series had a positive culture rate of 56% across all methods of sampling. We found that tissue from the affected joint was the most likely to yield a positive culture. Helito et al. identified an organism in 77% of their series on knee SA, but contrasted their work to Madruga Dias et al. with only a 22.8% positive organism rate.[1] A similar study to ours from Chris Hani Baragwanath Academic Hospital had 55% positive cultures.[11] Hindle and colleagues found organisms on Gram stain and microscopy in 22% and in 44% of cultures respectively. They went on to find that 0% of cases identified an organism on microscopy, as well as a statistically significant lower rate of organisms on cultures if antibiotics had been given prior to sampling.[2] Peres et al. found 48% culture positive rates in their series.[8]

In our cohort, blood cultures were only positive in 15% of cases in which a synovial sample was also positive. Weston et al. found positive blood cultures in only 24% of cases in which an organism was cultured from subsequent synovial fluid analysis.[14] Diagnosis is further complicated by administration of antibiotics prior to samples being taken for culture. Hindle et al. found a significant decrease in culture sensitivity when empiric antibiotics had been administered prior to microbiological culture sampling.[2] There were four instances in our cohort where the initial blood culture was positive and the subsequent samples from theatre showed no growth. It is possible that this may be due to early administration of antibiotics before theatre samples were taken.

S. aureus is the most common pathogen identified on culture of septic knee aspirate.[1,3-8,10-12] After *S. aureus*, streptococcal bacterial strains are the second most common. Gram-negative bacteria account for 10–20% of the remaining infections.[5] There are reported cases of highly unusual pathogens identified on culture which are not covered by typical empiric antibiotic regimens and may not be identified by routine culture methods. A search of recent literature shows that these may include *Parvimonas micra*, *Fusobacterium necrophorum* and *Corynebacterium striatum*.[15-17]

S. aureus accounted for 33% of our positive cultures which is similar to findings from other South African research with 29%, 25% and 42% respectively.[10-12] The majority (31%) were sensitive to methicillin with only 2% found to be resistant (MRSA). The rate of MRSA was significantly lower in our cohort when compared to other local literature. Other staphylococcus species accounted for 13%, streptococcal species were 13%. Overall Gram positives were 84% of our sample and Gram negatives were 16%. This was again not in keeping with the abovementioned studies where Gram negatives represented much larger portions of their positive cultures (47 and 40% respectively).[10,12] Twelve per cent of organisms were unusual bacteria, and this included *Enterobacter* species, *Acinetobacter* species, *Bacillus* species and *Bacteroides* species. A case of *Stenotrophomonas maltophilia* and one of *Shewanella algae* (this patient was HIV positive) were cultured. Both have been the subject of only a handful of case reports in the past two decades.[18,19] *Citrobacter braakii* was cultured in a 25-year-old female with SA of her knee, who was diagnosed with HIV infection on admission. The researchers were unable to find any other reports of this organism causing SA in the literature.

Limitations of this study include a small cohort confined to a single facility in a single geographic location in our country, although this tertiary level hospital does drain a very large population across a major metropolitan area in South Africa. Our small sample size may have prevented some of our analyses from reaching statistical significance. Due to the retrospective nature of the study, there is no standardisation in the investigations of each patient including what blood tests were performed, what types of cultures were taken as well as the surgical technique used when sampling. The administration of antibiotics prior to sampling for cultures was not assessed and may affect results.

Conclusion

Septic arthritis remains a challenging condition to diagnose with no gold standard method available at present. Our analysis showed that the serum WCC was unhelpful in making the diagnosis of SA, and CRP and ESR were both better options. ESR was, however, also less reliable in the elderly patient.

Although our HIV-positive cohort was small, a statistically significant lower absolute WCC was found in HIV-positive patients. HIV-positive patients were more likely to culture an unusual organism. Antibiotic resistance was not affected by HIV status.

Tissue cultures were found to have the highest yield and should be included if the patient is taken to theatre for arthrotomy. Blood cultures were found to have the lowest rate of culture yield.

Most cultured organisms were Gram-positive staphylococcal and streptococcal species. Gram-negative organisms were cultured in 16% of positive cultures.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Prior to commencement of the study, ethical approval was obtained from the following ethical review board: University of Cape Town Human Research Ethics Committee, reference number 511/2018.

For this study, formal consent was not required. There is no identifying information about participants available in the article.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

DM: data analysis, first draft preparation, manuscript revision
VM: data collection, first draft preparation
KW: data collection, first draft preparation
RD: study design, data analysis
SD: manuscript review
SM: study conceptualisation and design, data analysis, manuscript revision

ORCID

Maimin D https://orcid.org/0000-0002-1106-9930

Martin V https://orcid.org/0009-0007-2876-2997
Williams K https://orcid.org/0009-0003-0736-4667
Dey R https://orcid.org/0000-0002-3616-1995
Dlamini S https://orcid.org/0000-0003-0582-5987
Maqungo S https://orcid.org/0000-0002-8735-8341

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