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PII: S2590-1702(22)00006-1
DOI: https://doi.org/10.1016/j.clinpr.2022.100138
Reference: CLINPR 100138

To appear in: *Clinical Infection in Practice*

Received Date: 2 November 2021
Revised Date: 25 January 2022
Accepted Date: 4 February 2022

Please cite this article as: J. William Goodall, B. James Patterson, J. Barrett, M. Colquhoun, S. Williamson, A. Clayton-Smith, G. Koh, T. Corrah, A comparison of tuberculous and bacterial native joint septic arthritis infections in a retrospective cohort: presentation characteristics, outcomes and long term follow up, *Clinical Infection in Practice* (2022), doi: https://doi.org/10.1016/j.clinpr.2022.100138

Title Page

Full Title

A comparison of tuberculous and bacterial native joint septic arthritis infections in a retrospective cohort: presentation characteristics, outcomes and long term follow up

Running Title

Comparing bacterial and tuberculous septic arthritis

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Declarations of interest

None

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Introduction

Septic arthritis (SA) refers to infection of the normally sterile joint space by bacteria, mycobacteria, or fungi. The consequences of such infection can be severe, with mortality estimated at 11%, and 25-50% experiencing irreversible loss of joint function.[1]
SA typically presents with a hot, swollen, and painful joint. Although SA is most commonly a monoarticular infection, in up to 22% of cases more than one joint may be involved.[1–3]
Non-mycobacterial bacteria (hereafter referred to as bacteria) typically enter the joint space by haematogenous spread, following acute bacteraemia. More rarely, infection can occur through direct inoculation following trauma.[4] Bacterial SA occurs more frequently at extremes of ages and has a slight male predominance.[1,5]

The most common species identified is *Staphylococcus aureus*, followed by various *Streptococcus* species (of which the most common is *S. pyogenes*). [3,4,6–8] Gram-negative bacteria are less commonly encountered than Gram-positive, but occur at higher frequency in older patients and those who are immunocompromised.[3,6]

It is estimated that 10 million people globally became unwell with tuberculosis in 2019.[9] In England in 2019 there were 4,725 notifications of tuberculosis. This was the first time since 2011 that the number of notifications increased compared to the previous year.[10] Incidence varies significantly across the country and cases are generally clustered in urban centres, with the capital, London, accounting for a third of all cases in England.[10]

Septic arthritis is a relatively uncommon manifestation of tuberculosis infection and was reported in 5% of cases in the UK in 2019.[10] The pathogenesis of tuberculosis SA is not fully understood, but is hypothesised to represent reactivation of bacilli lodged in the highly vascularised vertebrae and long bone growth plates during the primary infection. This initial infectious focus in the bone is thought to then infect the joint space by direct extension.[11]

Given its relative rarity, tuberculosis is not often considered in the differential diagnosis of a hot swollen joint in low endemic settings such as the UK. This can lead to significant diagnostic delays; median time from symptom onset to initiation of anti-tuberculous treatment was nine months in one study.[12] The few studies that have directly compared tuberculous to bacterial SA have found the former presents more sub-acutely with lower inflammatory markers. However, the clinical overlap between the two conditions is significant.[13–15]

Determining the aetiology of a hot, swollen joint in the acute setting can be problematic and no single test has adequate predictive power to safely exclude bacterial SA from the differential. Previous studies have suggested that markers such as C-reactive protein and procalcitonin may be helpful in guiding clinical decision making.[14,16–19] However, it is widely noted that the opinion of an experienced clinician is likely to be the most reliable discriminator.[1,3]

In this study we aimed to characterise and compare the clinical features of patients with SA caused by either bacteria or *Mycobacterium tuberculosis*. In particular we aimed to explore the differences in outcomes, about which little is currently reported.

Methods

Patient selection

This retrospective cohort study included all patients with a microbiologically confirmed tuberculous or bacterial, native, large joint septic arthritis between 1 January 2012 and 1 October 2018. The study was conducted at London Northwest University Healthcare NHS Trust, which includes Northwick Park Hospital and Ealing Hospital. Both hospitals are in north London, England and serve the boroughs of Brent, Harrow, and Ealing. These boroughs have some of the highest incidence rates of tuberculosis in London.[20]

Bacterial septic arthritis (BSA) cases were identified by positive bacterial culture from joint aspirate on the hospital's electronic results database.

Tuberculous septic arthritis (TBSA) cases were identified from those patients who had cultured *Mycobacterium tuberculosis* or had the organism identified by Polymerase Chain Reaction (PCR) in a sample from a joint.

The electronic notes of all potential TBSA and BSA cases were reviewed and were included if they involved a large joint, without prosthetic material. Large joints considered were the shoulder, elbow, wrist, hip, knee, and ankle. Bacterial cases were excluded from the dataset if the result had contemporaneously been deemed to be a contaminant. Cases were excluded if their culture grew both *M tuberculosis* and a pathogenic bacterial species.

Data were collected as part of a Service Evaluation (defined by the National Health Service Health Research Authority and the Medical Research Council) and therefore did not require research ethics committee approval. All data gathered were retrospective and anonymised and therefore no informed consent was required. Local approval was obtained by the trust's research and development department prior to data collection.

Variables

Basic demographics, treatment, follow-up, and outcomes were recorded from electronic patient records. The first set of blood tests available at initial presentation were recorded, including: C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), albumin, neutrophil count, and lymphocyte count.

Clinic letters, general-practice referrals and readmission documentation were screened for evidence of ongoing morbidity or need for surgical intervention. Records were last screened in January 2020. Patients were considered lost to follow up if they were not seen in a relevant clinic after discharge.

Those patients who had ongoing morbidity at the point of last follow up, required surgical intervention (other than initial surgical washout), or died during their admission were classified as having an adverse outcome and were analysed together.

Statistical analysis

Binary variables were reported with percentages and compared with chi-squared tests. All continuous variables were visually assessed for normality with Q-Q plots and with Shapiro-Wilk tests and were found to have non-normal distributions; continuous variables were all therefore reported as medians and interquartile ranges and comparisons were made with Mann-Whitney U tests. Odds ratios were ascertained with univariable logistic regression with binary independent variables.

All statistical analyses were performed, and graphics generated using R version 4.0.0 (R Foundation for Statistical Computing; http://www.r-project.org/).

Results

Comparisons between TB and bacterial infections

We identified 64 BSA and 29 TBSA meeting our criteria. The median age of BSA cases was higher than TBSA cases (63 [IQR 33-81] versus 35 [27-49], $p = 0.0024$). Both groups had a slight male preponderance (61% male in BSA versus 55% male in the TBSA, $p = 0.77$).

For the TBSA cases the diagnostic sample was taken at the bedside in 12 cases, under radiological guidance in 11 cases and surgically in 6 cases. For the BSA cases the sample was taken at the bedside in 60 cases and surgically in 3 cases (one sample was unknown). The higher proportion of TBSA samples acquired surgically or radiographically likely reflects the lower levels of inflammation and consequent smaller volumes of joint fluid typically seen in this condition.

The comparative distributions of the five laboratory parameters considered are shown in Figure 1.

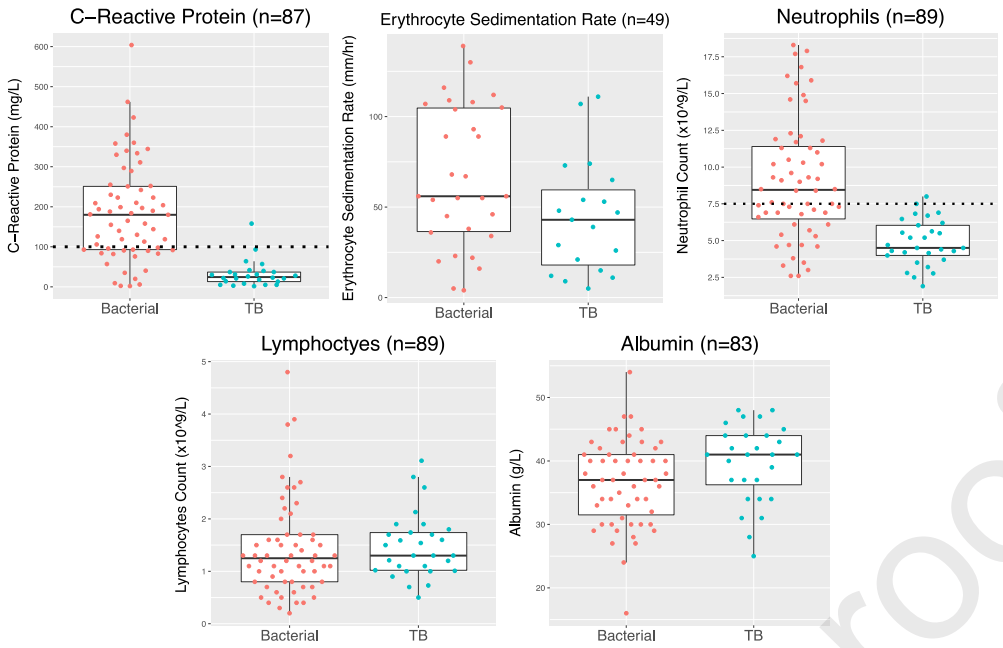

Figure 1: Comparison between laboratory tests for bacterial and tuberculous septic arthritis. n is the number of total cases with data available for each parameter.

The median CRP of the BSA group was significantly raised compared to TBSA group (180mg/L [93-250] versus 25mg/L [13-37], $p < 0.001$). The median ESR was non-significantly higher in the BSA group compared to the TBSA group, (56mm/hr [37-105]) versus 54mm/hr [26-89], $p = 0.051$).
The median neutrophil count was significantly greater in the BSA group compared to TBSA group ($8.4x10^9$/L [6.5-11] versus $4.5x10^9$/L [4.0-6.0], $p <0.001$). There was no statistically significant difference between the lymphocyte counts of the BSA and TBSA groups ($1.2 x10^9$/L [0.8-1.1] versus $1.3x10^9$/L [1.0-1.7], $p = 0.28$).
The median albumin of the BSA group was found to be lower than the TBSA group (37g/L [32-41] versus 41g/L [36-44], $p = 0.030$).
The odds ratio for septic arthritis having a bacterial aetiology versus a tuberculous one if the CRP was greater than 100mg/L was 46 [95% confidence interval (CI) 8.5-850], $p = <0.001$. Similarly, the odds ratio for a bacterial versus tuberculous aetiology if the neutrophil count was greater than $7.5x10^9$/L (the upper limit of normal for our laboratory) was 24 [95% CI 6.1-160], $p = <0.001$.
The joint aspirates from the BSA group had significantly greater white cell counts than the aspirates from the TBSA group ($p <0.001$, see Figure 2).

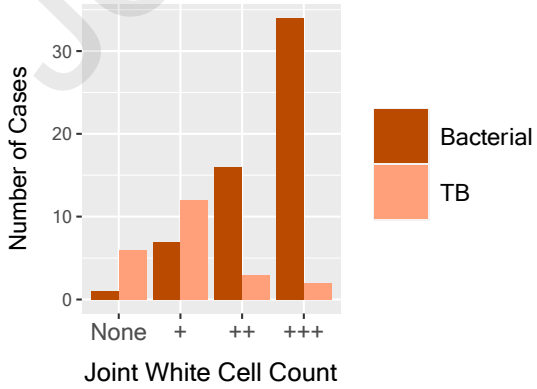

Figure 2: Semiquantitative white cell counts of joint fluid from bacterial and tuberculous cases

The most frequently affected joint for the BSA group was the knee (58%) whereas the most frequently affected joint for the TBSA group was the ankle (38%). The full distributions are shown in Table 1.

Joint Affected	Bacterial, n=64 (%)	Tuberculosis, n=29 (%)
Hip	5 (7.8)	6 (21)
Knee	37 (58)	4 (14)
Ankle	3 (4.7)	11 (38)
Shoulder	13 (20)	3 (10)
Elbow	3 (4.7)	3 (10)
Wrist	3 (4.7)	2 (10)

Table 1: Distribution of affected joints

Microbiology

Of the 64 BSA, 51 (80%) were Gram-positive and 13 (20%) were Gram-negative (see Table 2). *Staphylococcus aureus* was the most frequently encountered pathogen, accounting for 27 infections. Of these, 24 were methicillin sensitive and 3 were methicillin resistant.
The next most frequently encountered organism was *Streptococcus pyogenes* accounting for eight infections during the study period.
Eight infections were attributed to coagulase-negative Staphylococci. Although often identified as a contaminant, these cases were all contemporaneously deemed likely to be infecting by the managing clinical team on account of the clinical presentation and laboratory results. To explore this further, a sensitivity analysis was performed with these cases excluded. This analysis found that excluding these cases did not change the outcomes or significance level of any of the study's findings. The full analysis is available in the supplemental materials.
Nine of the TBSA cases had a polymerase-chain reaction performed on the joint fluid with Xpert® MTB/RIF (Cephid). Of these, 4 (44%) were positive for *Mycobacterium tuberculosis*.

Gram-positive	**Count**
Staphylococcus aureus	27
Streptococcus pyogenes	8
Coagulase-negative Staphylococcus*	9
Streptococcus pneumoniae	2
Group G β-haemolytic Streptococci	2
Streptococcus agalactiae	2
Viridians group Streptococcus*	1
Gram-negative	
Escherichia coli	6
Pseudomonas aeruginosa	4
Citrobacter koseri	1
Enterococcus faecalis	1
Haemophilus influenzae	1
Klebsiella species	1

*Table 2: Species distribution of bacterial isolates. *One patient's sample grew both viridians group Streptococcus and coagulase-negative Staphylococcus*

Follow up and outcomes

After discharge, 21 (33%) of the BSA were not seen in a relevant clinic and hence were considered lost to follow up. All of the TBSA were followed up after discharge.
For those not lost to follow up, the median duration of follow up was 110 days (IQR 63-280). On average, patients with TBSA were followed up for longer than those with BSA (280 days versus 86 days, $p < 0.001$).
All patients underwent acute management with either joint aspiration or washout. Three subsequent joint replacements were required for symptomatic control in the cohort: one hip and one knee replacement in the BSA group, and one knee replacement in the TBSA group.
Of all patients with follow up data (n = 72), 51% of the BSA group were asymptomatic at last follow up compared to 72% of the TBSA group (Figure 3). All-cause in-hospital mortality was 14% of those with BSA, whereas no deaths were observed in those with TBSA.

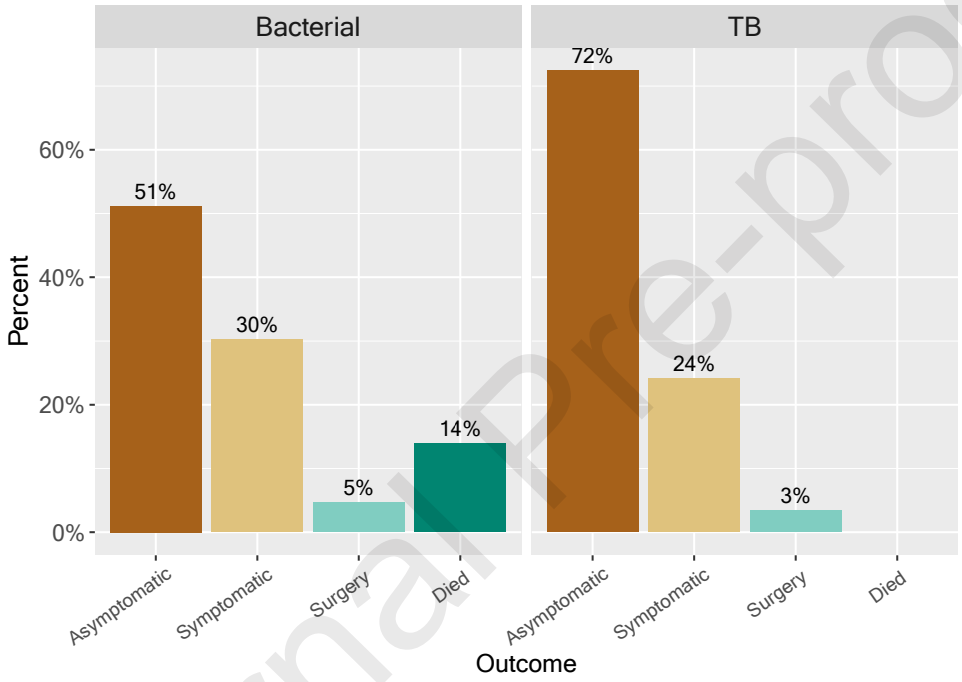

Figure 3: Outcome of patients by septic arthritis aetiology. BSA n = 43 (21 with no follow up data). TBSA n = 39 (all patients had follow up data)

Discussion

Both bacterial and tuberculous SA are significant diagnoses that can be hard to differentiate clinically. Both mandate urgent, but entirely distinct, antimicrobial management. Due to the high tuberculosis incidence in the hospitals' catchment areas compared to the UK average, we were able to identify a significant number of patients with TBSA, allowing for comparisons to be made between TBSA and BSA.
The average age of patients with bacterial SA was significantly greater than those with tuberculous SA. This is in line with previous research which also notes that recent immigrants to high-income countries, tend to present younger with TBSA than those who were born in high-income countries.[1,11]
Albumin levels were lower in those with BSA, possibly reflecting the more inflammatory nature of this condition, but also likely influenced by the older average age of this group.[21]

On average, CRP values and neutrophil counts were higher in the BSA group than the TBSA group. This is consistent with how the two conditions are expected to present, with the former typically representing a more acute and proinflammatory condition.

We found that having a neutrophil count above $7.5x10^9$/L had an odds ratio of 24 for bacterial versus tuberculous infection. Similarly, a CRP of greater than 100mg/L conferred an odds ratio of 46 for bacterial infection. This finding is of clinical relevance as the approach and urgency of the interventions required differs greatly between the two conditions. Either of these two criteria being met would imply a high risk for a bacterial aetiology and would likely mandate urgent surgical intervention. The converse, however, is not true, as many confirmed bacterial infections had lower CRP values and normal neutrophil counts at first presentation. Previous studies have found a significant difference between CRP levels in BSA and TBSA in a paediatric cohort in South Africa;[14] in spinal infections;[15] and in ankle infections.[13]

We found that, where it was performed, TB PCR had a relatively low sensitivity of 44% for *M tuberculosis* in joint aspirates. No cases were found where TB PCR was positive but Mycobacterial cultures were ultimately negative. It should be noted that newer generations of TB PCR have subsequently become available and that this test is not validated on synovial fluid. There is, however, a clear clinical advantage to securing a diagnosis in advance of the weeks that mycobacterial cultures typically require.

All patients with TBSA remained under follow up, reflecting the need for lengthy treatment courses. However, a notable proportion of BSA patients (33%) were not seen again after discharge. Although it is likely that many of these patients were either not invited or opted not to attend follow up due to the absence of ongoing morbidity at the point of discharge, this cannot be confidently stated. Given the relatively high levels or morbidity in those who did remain under follow up it seems prudent to review all patients after discharge.

The major limitations of this study come from its retrospective nature, meaning that there are missing data in the admission characteristics and follow up data.

It is possible that the lower number of TBSA who were symptomatic at the point of last follow up may partly be an artefact of their longer average follow up duration. Equally, the outcomes may have been biased by the unequal levels of loss to follow up in each group, as those with BSA who were asymptomatic at discharge may be less likely to be seen again in clinic. It is possible too that some patients would have moved area and their subsequent management would not have been captured in our follow up data.

As the cases were managed by a variety of clinicians, using their clinical judgement rather than a pre-determined protocol, there is inevitably some heterogeneity in management approaches, which may have influenced the outcomes.

To ensure that the groups were comparable, we excluded all patients treated for a TBSA who did not have a microbiologically confirmed diagnosis. As *Mycobacterium tuberculosis* is a more fastidious organism than the common causes of bacterial SA, a higher proportion of TBSA are diagnosed empirically. Exclusion of these cases may be a source of bias as the failure to culture the organism may in some instances be attributable to milder infections with low numbers of Mycobacteria or smaller effusions.

In conclusion, we found that SA with either typical bacteria or tuberculosis often had severe negative sequalae. Those with BSA had higher inpatient mortality rates and suffered more long-term sequalae. There are notable trends in the presentation characteristics and blood tests between bacterial and tuberculosis SA, although none strong enough to obviate the need for microbiological confirmation by joint aspiration or biopsy. This endorses the current UK guidelines for the management of the hot swollen joint, which advocates for the measurement of inflammatory markers primarily to monitor response to treatment.[2]

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Highlights

- Patients with bacterial versus tuberculous septic arthritis had significantly higher CRP levels and neutrophil counts
- A CRP level above 100mg/L conferred an odds ratio of 46 for bacterial infection
- 51% of bacterial septic arthritis cases were asymptomatic at last follow up compared to 72% of tuberculous cases

Abstract

Objectives

This retrospective observational cohort study aimed to characterise and compare the demographics, initial laboratory tests and outcomes between patients with large-joint bacterial septic arthritis (BSA) and tuberculous septic arthritis (TBSA).

Methods

All patients with a culture from a large, native joint growing either non-mycobacterial bacteria or *Mycobacterium tuberculosis* between 1 January 2012 and 1 October 2018 in our institution were included. Clinical details and admission laboratory values were obtained from patient records. Comparisons were made by Mann-Whitney U, chi-squared tests, and logistic regression analysis.

Results

We identified 64 BSA and 29 TBSA. On average, the BSA cases were older, had higher CRP levels and neutrophil counts and lower albumin levels. The odds ratio for having a BSA was 46 in cases with a CRP greater than 100mg/L (95% confidence interval (CI) 8.5-850, $p < 0.001$) and 24 with a neutrophil count greater than 7.5×10^9 (95% CI 6.1-160, $p < 0.001$). 51% of BSA were asymptomatic at last follow up compared to 72% of TBSA. 14% of the BSA cases died during admission; there were no deaths in the TBSA group.

Conclusions

Significant differences exist between patients with BSA and TBSA. Whilst no test is sufficient to exclude BSA, a raised neutrophil count or a CRP greater than 100mg/L significantly increases the odds of a bacterial aetiology. Patients with BSA had worse long-term outcomes and higher incidence of inpatient mortality.