CLINICAL ARTICLE

Adult septic arthritis in a tertiary setting: A retrospective analysis

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Abstract

Purpose of the study:
Septic arthritis (SA) constitutes an orthopaedic emergency as it can rapidly lead to progressive and irreversible joint destruction with loss of function. We aim to identify our microbiological spectrum and sensitivity profiles, and compare it to our empirical antimicrobial choice in the management of septic arthritis in the adult population.

Description of methods:
A retrospective analysis was performed on patients admitted from June 2005 to March 2009. The study population consisted of all patients over the age of 14 years admitted for either arthrotomies or joint aspirations, yielding positive cultures of either joint fluid or pus swabs taken intra-operatively. A data analysis was also done on serum CRP and WCC on all the patients.

Summary of results:
Gram-positive organisms were cultured in only 53% of isolates, and *Staphylococcus aureus* accounted for only 25% of all isolates. Of all the Gram-positive organisms, 38% were multi-drug resistant, only sensitive to vancomycin. Gram-negative organisms constituted 36% of isolates, showing resistance in 55%. The remainder of isolates consisted of anaerobic organisms.

Conclusion:
Gram-negative and resistant strains are becoming more important as an aetiological agent in adult septic arthritis. The current use of cloxacillin as empiric antibiotic therapy only covers 32% of all isolates in our setting. Based on these findings, use of co-amoxyclav as empiric antibiotic will increase the cover to 46%. The emergence of resistant strains remains a challenge, as evidenced by this study. Patients not responding to initial empiric therapy should be considered for early use of extended spectrum antimicrobials.

Introduction

Septic arthritis (SA) constitutes an orthopaedic emergency as it can rapidly lead to progressive and irreversible joint destruction with loss of function.[1] In adult patients, an acutely swollen and inflamed joint needs to be distinguished from various other causes (*Table I*) as different epidemiological and patient factors render SA in adult patients a completely distinct condition from that in children.

Classically, SA is associated with abnormalities in the peripheral white cell count (WCC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), although the use of these as specific diagnostic markers for SA is restricted due to the low specificity.[2] The diagnosis of SA can, in certain instances, pose a diagnostic dilemma and Newman *et al*[4] reviewed cases over a 30-year period, classifying this condition based on 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 joint.

Various co-morbid conditions have been identified as risk factors for more severe SA. These include:

- diabetes mellitus[5,6]
- rheumatoid arthritis and osteoarthritis[7-11]
- prosthetic joint[12-14]
- recent joint surgery[12]
- previous intra-articular corticosteroid injection[15]
- skin infection and ulcers[2,13]
- intravenous drug abuse[1,6]
- alcohol and tobacco use[16]
- sickle cell anaemia[17]
- immunocompromised states
  - elderly[18]
  - HIV.[16]

Table I: Differential diagnosis of an acute monoarthritis in an adult patient *(adapted from reference 2)*

- Infection
- Gout
- Pseudogout
- Apatite-related arthropathy
- Reactive arthritis
- Systemic lupus erythromatosis
- Dialysis-related amyloidosis
- Metastatic carcinoma
- Haemarthrosis
- Neuropathic arthropathy
- Osteoarthritis
- Intra-articular injury
- HIV-associated arthritis[3]

The knee is almost universally quoted as the most common site of infection, with other joints affected including the hip, shoulder, wrist, ankle, elbow and sternoclavicular joint. Poly-articular infection is not uncommon, shown to affect as many as 10% of cases.[1]

A recent systematic review found staphylococci and streptococci to be the aetiological agent in up to 91% of cases. The empiric antibiotic of choice in uncomplicated cases is cloxacillin 2 g qid intravenous. Patients at high risk for Gram-negative sepsis are treated with a third generation cephalosporin (cefuroxime 1.5 g tds) with or without cloxacillin. If the patient is at risk for developing SA due to methicillin-resistant *Staphylococcus aureus* (MRSA), use vancomycin with a third generation cephalosporin. With a suspected gonococcal or meningococcal infection, use of a third generation cephalosporin is indicated.[19] This is the policy followed by our department.

With the changing epidemiology in our patient population, we found it essential to retrospectively review all cases of SA among our adult patients. This was performed to ensure that our expected microbiological spectrum and sensitivity profiles correspond to our empiric antimicrobial choices in this patient population.

Materials and methods

This retrospective study was performed on patients admitted to the Steve Biko Academic Hospital, Pretoria, South Africa, from June 2005 to March 2009 (46 months). All patients over the age of 14 years, with a possible diagnosis of SA, who had an arthrotomy or joint aspiration, were included in the study (i.e. Newman Grade A).

Further data collected included admission laboratory infectious markers (white cell count and C-reactive protein). In cases where MRSA was cultured, sufficient data could not be collected to establish whether the infection was acquired in the community or in a health care setting. Cases where organisms of doubtful clinical significance were isolated (e.g. coagulase negative staphylococcus) were included as they could act as pathogens in select patient populations.

Results

Patient demographics

During the study period, a total of 125 patients were admitted for signs and symptoms suggestive of SA; of the culture positive patients, the majority was male (34/60) with a male to female ratio of 1.3:1. Ages varied from 16 to 72 years (*Figure 1*). Unfortunately, less than a quarter of patients were tested for HIV infection, but from the total population, 13% were HIV-positive and 8% HIV-negative.

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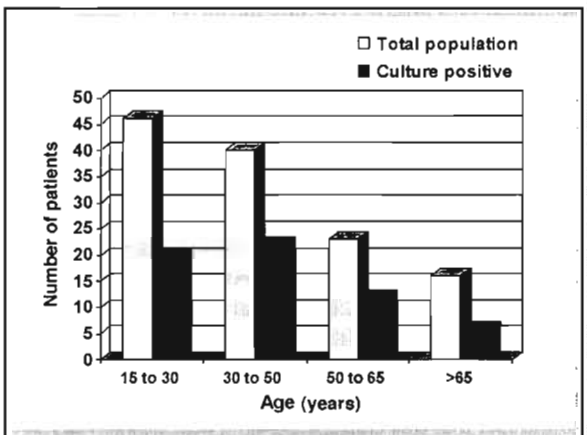

Figure 1: Age distribution of patients expressed as total and culture-positive population groups

Clinical findings

Knee joints were involved in a significant proportion of patients, accounting for 73% of cases (*Figure 2*).

Microbiological data

In total, 125 patients were admitted with the clinical diagnosis of SA. In 77 patients, the diagnosis was evident and arthrotomies were performed. In 48 patients, the clinical diagnosis was in doubt, and aspirations were performed.

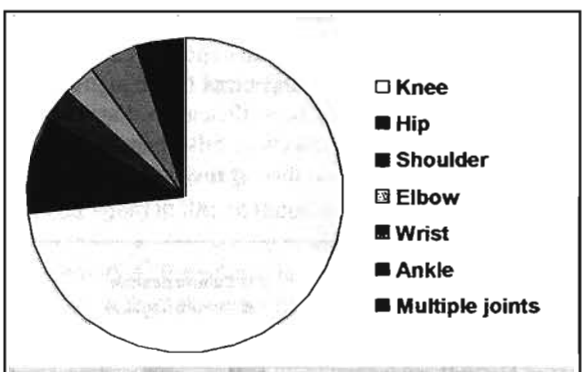

Figure 2: Joint distribution of SA in adult patients

Table II: Organisms isolated with the respective sensitivity profiles

Organisms isolated	Cases (No)	Sensitivity profile S	I_1	I_2	R
Gram-positives	**42**				
Staphylococcus aureus	20	**13**	0	0	**7**
Coagulase negative staphylococcus	11	**4**	**1**	0	**6**
Streptococcus pneumoniae	1	**1**	0	0	0
Alpha-haemolytic streptococcus	5	**5**	0	0	0
Beta-haemolytic streptococcus	5	**5**	0	0	0
Gram-negatives	**29**				
Acinetobacter baumannii	4	0	**1**	0	**3**
Klebsiella pneumoniae	4	**1**	**1**	0	**2**
Klebsiella oxytoca	2	**1**	0	0	**1**
Enterobacter spp	5	0	0	**5**	0
Eschericiae coli	4	**4**	0	0	0
Serratia marscesence	1	0	0	**1**	0
Proteus mirabilis	1	**1**	0	0	0
Proteus vulgaris	1	**1**	0	0	0
Pseudomonas aeruginosa	6	**5**	0	0	**1**
Pseudomonas stutzeri	1	0	**1**	0	0
Other	**9**				

S - Sensitive to cloxacillin in Gram-positive organisms and sensitive to co-amoxyclav in both Gram-positive and Gram-negative cases.
I_1 - Sensitive to third generation cephalosporins
I_2 - Sensitive to fourth generation cephalosporins
R - Sensitive to extended spectrum antimicrobials. In the Gram-positive group this refers to vancomycin and in the Gram-negative group, the carbapenems

Of the total samples submitted for microbiological analysis, 60 rendered positive cultures with 80 isolates (44 patients with single isolates, 15 with double and two with triple isolates). *Staphylococcus aureus* was the most prominent causative organism (*Table II*).

No microbiological data was available in 10 patients from the arthrotomy group and 20 patients from the aspiration group. The reasons for this are unclear but may include laboratory errors, sampling problems or the treating surgeon's clinical assessment.

A noteworthy feature was the lack of any cases of *Neisseria gonorrhoea*, as this is an important cause of SA, especially among young adult patients.[20] Although routine culture techniques should be sufficient to diagnose the presence of gonococcal infection, false negative results are frequently a problem, as this organism can be very difficult to culture.[21]

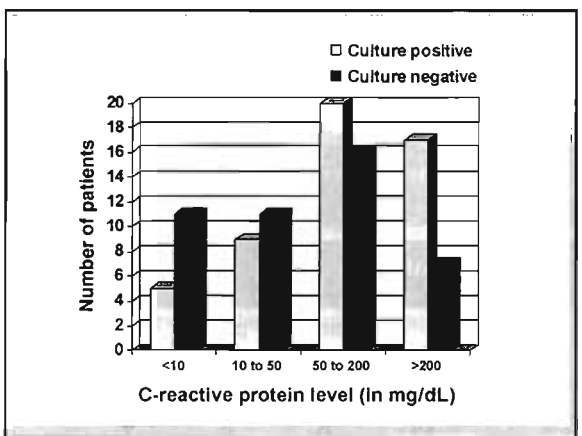

Figure 3: CRP levels, reported in mg/ml, in patients with infectious and non-infectious arthritis

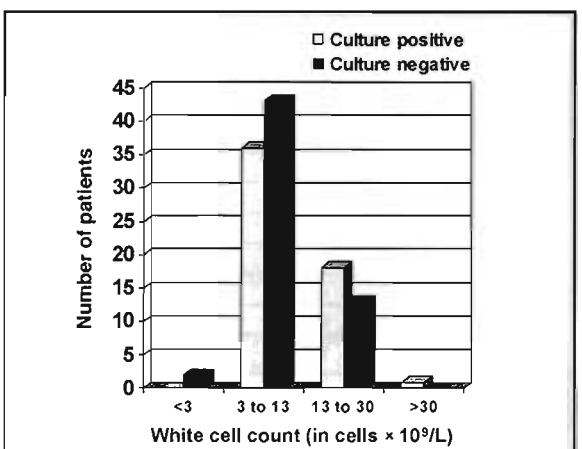

Figure 4: WCC levels in patients with infectious and non-infectious acute arthritis, reported in x 10^9 cells/L

Laboratory data

C-reactive protein (CRP) levels were performed in 96 cases and white cell counts (WCC) were determined 113 cases. CRP results are summarised in *Figure 3* with WCC results summarised in *Figure 4*, differentiating between patients with an established SA (culture positive) versus non-infectious arthritis (culture negative).

Discussion

In adult patients presenting with an acutely inflamed joint or joints, the diagnosis can be complicated, as various conditions can present in a similar way. The clinical diagnosis consists of a tender, swollen, hot joint with a limited range of movement.[19] Septic arthritis as the cause of an acutely swollen joint, has been shown to account for 8% of cases in Israel,[22] 27% in Taiwan,[23] 29% in Saudi Arabia,[16] 33% in the UK[8] and 35% in Australia.[24] In this study the rate was substantially higher, at 48%. This high prevalence of infectious arthritis can in part be attributed to the fact that this study was performed in a tertiary setting. It should be noted that a negative culture does not exclude the presence of SA as various factors may render a false negative microbiological result,[25] including pre-emptive initiation of antibiotics prior to sampling, etc. This should be considered and empiric antibiotics are therefore advocated in cases prior to establishment of a clear diagnosis.

Where the diagnosis was in doubt, aspirations of the joint fluid were performed, which if upon inspection seemed purulent, would then be converted to a formal arthrotomy. In total, 48 aspirations were not converted to formal arthrotomies. Of these, only 28 were submitted for microbiological culturing. The reasons why all samples were not submitted are unclear, but may be due to laboratory error or due to the discretion of the surgeon. Of the 28 samples that were submitted for microbiological culturing, eight (29%) yielded positive results. This suggests that visual inspection is not adequate to determine submission for culture, and that it should be considered a standard operating procedure to submit all aspirations to microbiology.

The use of serum acute phase reactants as surrogate markers for infection has been shown to be inaccurate.[2] This study confirms this result. More useful tests have been sought, specifically on synovial fluid, of which the most promising seems to be joint fluid white cell and differential counts.[2] Synovial WCC greater than 100 000/µl is associated with a 28 times higher likelihood ratio (CI = 12.0-66.0).[22,26-28] Furthermore, a differential count on the fluid showing polymorphonuclear cells of greater than 90% has been said to indicate a higher likelihood of an infectious cause,[2] but may also be as high in crystal arthropathies.[27] A low synovial glucose level (40 mg/dl or less than half the serum value) is suspicious of a bacterial joint infection.[34]

Table III: Key concepts in adult septic arthritis

- **An acutely inflamed joint in an adult patient may have various aetiologies.**
  - A higher portion of patients in the South African cohort had positive synovial fluid cultures.
  - There may also be underlying conditions predisposing the joint to sepsis.
- **As the HIV-1 sero-prevalence in South Africa is high, joint fluid should be subject to:**
  - routine cultures with sensitivities
  - fungal cultures
  - TB cultures
  - crystal analysis
  - histology.
- **In our setting, Gram-negative and resistant strains are becoming more important as aetiological agents in adult SA.**
  - The current use of empiric cloxacillin only covers 32% of all isolates.
  - The use of co-amoxyclav as empiric antibiotic will increase the cover to 48%.
- **MRSA seems to be become more important as an infectious agent in SA; continuous surveillance is needed to monitor trends in resistance.**
  - It is questionable whether a change to vancomycin is necessary as the empiric therapy in adult SA.
  - It is, however, advisable that patients not responding to empiric therapy, be considered for a change to more aggressive antimicrobials.
- **The use of serum white cell count and CRP is limited.**
- **All institutions should undertake an active surveillance programme to ascertain appropriate change in empiric antimicrobial therapy.**

Ultimately, proper sampling with positive culture of either joint fluid and/or pus swabs from the joint surface provides the confirmation of SA. This does not however exclude the presence of further pathology, which may have predisposed the joint to infection. It may therefore be prudent to submit all samples for culture, crystal analysis and histology.

With the high rate of HIV-1 sero-positivity in the South African setting,[29] atypical organisms will always have to be suspected. These include various Gram-negative organisms, mycobacteria[26-28] and fungi.[30,31]

In patients with suspected SA, empiric antimicrobial therapy is indicated as part of early management as it can prevent rapidly progressive and irreversible joint destruction.[1] For the empirical treatment of SA, in adolescents or adults, our current departmental protocol includes the administration of cloxacillin 2 g 6-hourly or vancomycin (if MRSA is suspected) 1 gram 12-hourly. If a gonococcal arthritis is suspected, a third generation cephalosporin may be added.[19] Antibiotic therapy should be de-escalated as soon as the culture and sensitivity is available.

In an ideal setting, empiric therapy should fall within the sensitivity spectrum of all organisms associated with the specific condition and population group, but with trends showing increasing resistance worldwide, this is becoming problematic.[5,7,12,14,32-34] Gram-negative and resistant strains were shown to be important aetiological agents in this present study. The current use of cloxacillin as empiric antibiotic therapy only covers 32% of all isolates in our setting. Based on these findings, use of co-amoxyclav as empiric antibiotic will increase the cover to 46%. Septic arthritis is not a registered indication for administration of co-amoxyclav, so use will be on an 'off-label' basis. Dosing will likely be intravenous at doses of 1 000 mg amoxicillin with 200 mg clavulanic acid twice daily, provided renal function is intact. This will, however have to be confirmed by large, randomised control trials within this clinical setting.

The emergence of resistant strains remains a challenge, as evidenced by this study. In this patient population, seven MRSA isolates (11.4% of all samples and 35% of all *Staphylococcus aureus* isolates) were identified, all of which were only sensitive to vancomycin and linezolid, being resistant to clindamycin as well. It is debatable whether these findings warrant alteration in the departmental empiric treatment regimen, because of the concerns with empiric vancomycin treatment. Use of vancomycin in methicillin sensitive organisms is associated with increased morbidity and mortality.[35-37] It is therefore advisable that patients not responding to initial empiric therapy should be considered for early use of extended spectrum antimicrobials.

As this study indicates, it is pertinent that all institutions should undertake an active surveillance programme in which the aetiological agents and their corresponding sensitivity profiles are continuously monitored, with appropriate adjustment in empiric regimens.

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