Septic arthritis: a 5-year review of admissions to the Orthopedic Department

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ABSTRACT

Objectives: Characterization of sociodemographic and clinical aspects of patients admitted to the Orthopedic Department (OD) after observation in the Emergency Room (ER) with the diagnosis of septic arthritis (SA).
Material and Methods: A retrospective, monocentric study was conducted. Sociodemographic and clinical data on patients admitted to the OD with suspected SA between April 2014 and September 2019 were collected.
Results: One-hundred and ten patients were included. In the overall sample, most patients were male (n=61; 55.5%) with a median age of 70 (IQR=20) years old. Thirty-six patients (32.7%) had a previous history of hyperuricemia or gout, or had this diagnosis established at the time of their hospital admission. Monoarthritis was the most common form of presentation (n=106; 96.4%), with the knee being the most frequently involved joint (n=60; 54.5%). *S. aureus* was the most representative microorganism in synovial fluid (SF) cultures (n=33; 30.6%). SF cultures did not allow the identification of a causative microorganism in 53 cases submitted to arthrotomy (50.5%). Serum C-reactive protein (CRP) was a predictive factor for microorganism identification in SF cultures, with values ≥ 17.6 mg/dl showing instead of presenting a sensibility and specificity of 60.8% and 77.4%, respectively [AUC (CI 95%): 0.70 (0.52 – 0.80)]. Patients with a diagnosis of hyperuricemia or gout presented a higher risk for a negative SF culture result (OR = 4.7 [CI 95% =1.9 - 11.5]).
Conclusions: Elderly subjects with multiple comorbidities, namely cardiovascular risk factors, seem more prone to SA. Serum CRP appears to be a predictive factor for the identification of a causative microorganism. The higher risk of a negative SF culture in patients with hyperuricemia or gout should alert us for the possibility of misdiagnosis of SA in patients with an acute gout attack.

Keywords: Septic arthritis; Gout arthritis; Inflamed synovial fluid.

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INTRODUCTION

Septic arthritis (SA) is an important medical emergency, with known high morbidity and mortality[1,2]. Most cases of SA stem from hematogenous seeding of a joint in the setting of bacteremia[3]. Less frequently, overlying soft tissue infections can spread contiguously to the joint. Direct inoculation of bacteria into a joint can occur through a traumatic arthrotomy, open fracture or dislocation, arthrocentesis, or intraarticular injection, resulting in infection[3].

Although all ages can be affected, SA is a disease that usually arises in elderly people and very young children (up to 2 years-old)[1]. The most robust risk factor for SA is preexisting joint disease - up to 47% of patients with bacterial arthritis have prior joint problems[4,5]. Additionally, previous joint pathology (e.g., rheumatoid arthritis, osteoarthritis, crystal arthropathy, and other forms of inflammatory arthritis) predispose individuals for the development of sepsis[1]. In all age and risk groups, the most frequent causative organisms identified are *Staphylococcus aureus* followed by other gram-positive bacteria, including streptococci[1,6]. In view of the 11% mortality rate for SA, suspected patients should be promptly assessed and admitted to hospital for supportive care and intravenous antibiotic treatment, along with measures to aspirate or drain pus from the joint[1]. Ideally, SA is confirmed by the detection of bacteria in synovial fluid (SF), but the diagnosis is made mainly on clinical assumption[1]; negative

cultures do not exclude SA. In fact, approximately 20% of cases of suspected SA have negative cultures of SF on solid media[4]. Delayed or inadequate treatment can lead to irreversible joint destruction and case-fatality is generally around 11%[1].

Acute arthritis, in particular monoarthritis, has a broad differential diagnosis[1,2], which includes microcrystalline arthropathy and reactive arthritis, besides SA Gout and pseudogout may mimic many of the symptoms associated with SA. However, it must be noted that simultaneous bacterial infection and crystalline disease may occur[6].

The characterization of risk factors and predisposing conditions for SA, as well as the main pathogenic agents could be useful for the refinement of diagnostic and therapeutic strategies.

MATERIAL AND METHODS

STUDY TYPE

We have conducted an observational, monocentric, retrospective study. Clinical and sociodemographic data of patients admitted to the Orthopedic Department (OD) after observation in the Emergency Room (ER) between April 2014 and September 2019 for suspicion of SA were collected.

The protocol of the study has been approved by the Ethics Committee of Unidade Local de Saúde do Alto Minho (protocol number 58/2019).

STATISTICAL ANALYSIS

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Normal distribution of data was tested using the Shapiro-Wilk test or the asymmetry and kurtosis value analysis for psychometric variables.

Hyperuricemia was defined as a serum urate concentration of more than 7mg/dL for men, and more than 6mg/dL for women.

Independent T-test or Mann Whitney test were used to evaluate differences in inflammatory serum parameters and SF biochemical parameters within gender; between patients with and without hyperuricemia/gout; and between patients with and without SF positive cultures. The one-way analysis of variance (ANOVA) was used to determine associations between the involved joint, gender, inflammatory serum parameters and SF biochemical parameters. The Chi-Square statistic was used for testing relationships between categorical variables, namely involved joint and gender; SF cultures result and gender; and the presence of hyperuricemia/gout and SF cultures result.

Pearson's correlation coefficient or Spearman correlation was used to assess the correlation between inflammatory serum parameters, age and number of antibiotics. The value of *r* 0.00-0.19 was accepted as very weak, 0.20-0.39 as weak, 0.40-0.59 as moderate, 0.60-0.79 as strong, and 0.80-1.00 as very strong[7].

A logistic regression model was adjusted with stepwise data entry to determine predictors of microorganism identification in SF cultures. The accuracy of these predictors was assessed using the area under the ROC curve (AUC).

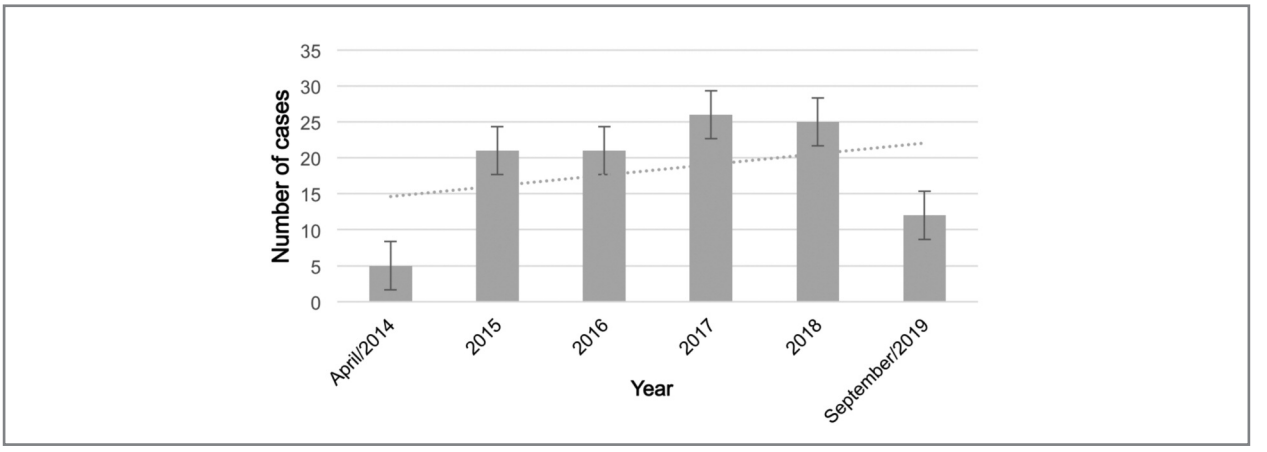

FIGURE 1. Search strategy for the systematic literature review

TABLE I. SOCIODEMOGRAPHIC CHARACTERISTICS OF SA PATIENTS

Male, n (%)	61 (55.5%)
Age in years (median; IQR)	70; 20
Education Level in years (median; IQR)	4; 6
Employment status, n (%)	
Retired	60 (55.0%)
Employed	30 (27.5%)
Unemployed	16 (14.7%)
Student	2 (1.8%)
Other	1 (0.9%)
Missing	1
Residence, n (%)	
Own residence/Relative's residence	102 (92.7%)
Nursing home	5 (4.5%)
Day care	2 (1.8%)
Host family	1 (0.9%)

IQR – interquartile range

TABLE II. COMORBIDITIES AND OTHER CLINICAL ASPECTS OF SA PATIENTS

Comorbidities, n (%)	
Hypertension	55 (50.0%)
Dyslipidemia	39 (35.5%)
Hyperuricemia/gout	36 (32.7%)
Diabetes mellitus	31 (28.2%)
Cancer	14 (12.7%)
Alcoholism	13 (11.8%)
Kidney chronic disease	12 (10.0%)
Calcium pyrophosphate deposition disease	4 (3.6%)
Chronic liver disease	4 (3.6%)
Psoriatic arthritis	2 (1.8%)
Rheumatoid arthritis	1 (0.9%)
Immunosuppressive drugs, including GC, n (%)	6 (5.5%)
Invasive joint procedure in the previous 6 months, n (%)	17 (15.5%)
Any surgery in the previous 6 months, n (%)	5 (4.5%)
Hospital admission in the previous 6 months, n (%)	26 (23.6%)
Any infection in the previous 6 months, n (%)	19 (17.3%)
Joint trauma in the previous 6 months, n (%)	15 (13.6%)

GC - glucocorticoids

All reported *p*-values were two-tailed, with a 0.05 significance level (α). Data analysis was carried out using Statistical Package for the Social Sciences (SPSS) software, version 23.

RESULTS

One-hundred and ten patients were included. In the overall sample, most patients were male (n=61; 55.5%) with a median age of 70 (IQR=20) years old. Table I shows the sociodemographic characteristics of the sample. Figure 1 demonstrates a growing tendency of SA cases. Hypertension (n=55; 50.0%), dyslipidemia (n=39; 35.5%) and diabetes *mellitus* (n=31; 28.2%) were the most frequent comorbidities. Thirty-six patients (32.7%) had a previous history of hyperuricemia/gout, or had this entity diagnosed at the time they were admitted to the hospital (Table II). In the previous 6 months, 17 (15.5%) patients had been submitted to an invasive joint procedure (surgery, joint aspiration, and/or corticoid injection), 26 (23.6%) had been hospitalized and 19 (17.3%) had been treated for any kind of infection (Table II).

Monoarthritis was the most common form of presentation (n=106; 96.4%), with the knee being the most frequently involved joint (n=60; 54.5%). One-hundred and six patients (96.4%) underwent arthrotomy. We obtained a total of 108 SF cultures: 105 after arthrotomy and 3 after joint aspiration in patients who did not undergo surgery. *S. aureus* was the most representative microorganism identified in SF cultures (n=33; 30.6%) (Table III). SF cultures did not allow the identification of a causative microorganism in 53 cases submitted to arthrotomy (50.5%). All patients were treated with antimicrobial agents. Vancomycin was the most common antibiotic (n=77; 70.0%), in monotherapy or in association with other antibiotics (Table III). Twenty-seven (24.8%) patients underwent a second surgical intervention of the same joint and 5 (4.5%) were readmitted within 6 months after the first admission for a new SA suspicion.

Involved joint, inflammatory serum parameters, SF total cell count (TCC) and polymorphonuclear neutrophils percentage (%PMN) were not different within gender and age groups.

Serum CRP (mg/dl) and SF TCC were higher in the cases with positive SF cultures (22.7 *vs* 14.4; $p<0.001$ and 22.4 *vs* 14.5; $p=0.026$, respectively). Patients with hyperuricemia/gout presented 5-fold higher odds

TABLE III. CLINICAL CHARACTERISTICS OF SA PATIENTS

Arthrotomy, n (%)	**106 (96.4%)**
Monoarthritis at presentation, n (%)	106 (96.4%)
Involved Joint, n (%)	
Knee	60 (54.5%)
Shoulder	14 (12.7%)
Hip	11 (10.0%)
Elbow	7 (6.4%)
Ankle	6 (5.5%)
Sternoclavicular joint	4 (3.6%)
Wrist	4 (3.6%)
Acromioclavicular joint	2 (1.8%)
Fingers	2 (1.8%)
Microorganism identified in SF cultures, n (%)	
Microorganism not identified	54 (50.0%)
Staphylococcus aureus	33 (30.6%)
Streptococcus agalactiae	5 (4.6%)
Escherichia coli	3 (2.8%)
Pseudomonas aeruginosa	2 (1.9%)
Staphylococcus haemolyticus	1 (0.9%)
Pasteurella multocida	1 (0.9%)
Staphylococcus warneri	1 (0.9%)
Serratia marcescens	1 (0.9%)
Enterococcus faecalis	1 (0.9%)
Corinebacterium amycolatum/striatum	1 (0.9%)
Streptococcus acidominimus	1 (0.9%)
Streptococcus constellatus	1 (0.9%)
Staphylococcus capitis	1 (0.9%)
Enterobacter cloacae	1 (0.9%)
Streptococcus mitis group	1 (0.9%)
Missing	2
Antibiotic therapy, n (%)	
None	2 (1.8%)
Vancomycin	77 (70.0%)
Ceftriaxone	31 (28.2%)
Ciprofloxacin	25 (22.7%)
Cefazolin	20 (18.2%)
Clindamycin	14 (12.7%)
Flucloxacillin	11 (10.0%)
Imipenem	11 (10.0%)
Sulfamethoxazole + Trimethoprim	7 (6.4%)
Amoxicillin + clavulanic acid	9 (8.2%)
Gentamicin	6 (5.5%)
Metronidazole	4 (3.6%)
Levofloxacin	4 (3.6%)
Piperacillin + tazobactam	4 (3.6%)

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TABLE III. CONTINUATION

Penicillin	1 (0.9%)
Cefixime	1 (0.9%)
Ceftazidime	1 (0.9%)
Monotherapy, n (%)	37 (33.9%)
2nd arthrotomy in the same joint within 6 months, n (%)	27 (24.8%)
2nd arthrotomy in a different joint within 6 months, n (%)	5 (4.5%)
Hospital stay in days (median; IQR)	18; 24
Hospital readmission within 6 months, n (%)	5 (4.5%)

IQR – interquartile range; SF - synovial fluid

TABLE IV. SYNOVIAL FLUID BIOCHEMICAL CHARACTERISTICS

Total cell count (median; IQR)	93114; 92300
% PMN (median; IQR)	92,5; 7
Monosodium urate crystals, n (%)	7 (17.9%)
Calcium pyrophosphate crystals, n (%)	7 (17.9%)

IQR – interquartile range; PMN - % Polymorphonuclear neutrophils

of obtaining a negative SF culture (OR = 4.7 [CI 95%= 1.9-11.5]). However, SF biochemical parameters, serum leukocytosis and CRP levels were not different between patients with or without hyperuricemia/gout. Patients with higher serum CRP values (r = 0.21; p=0.031) and SF TCC (r =0.52; p<0.001) needed a higher number of antibiotics.

A binary logistic regression model was created to assess potential predictor variables of microorganism identification in SF cultures (Table V). Only CRP (p = 0.019) showed a statistically significant association with a SF positive culture.

ROC curve analysis revealed an AUC of 0.70, with serum CRP values ≥17.6 mg/dl presenting a sensitivity and specificity of 60.8% and 77.4%, respectively [AUC (CI 95%): 0.70 (0.52 – 0.80)].

DISCUSSION

Besides the known risk of SA in subjects older than 60 years-old and with recent bacteriemia, other medical

TABLE V. LOGISTIC REGRESSION MULTIVARIABLE MODEL FOR PREDICTOR VARIABLES OF MICROORGANISM IDENTIFICATION IN SF CULTURES

	B	S.E.	p-value	OR	95% C.I. for OR	
					Lower	Upper
Hyperuricemia/gout	-3.437	3.315	0.300	0.032	0.000	21.327
C-reactive protein	0.210	0.089	0.019	1.234	1.036	1.470
Total cell count	0.000	0.000	0.249	1.000	1.000	1.000
% PMN	-0.022	0.580	0.698	0.978	0.874	1.095
Constant	-2.850	5.961	0.633	0.058		

SF - synovial fluid; PMN - polymorphonuclear neutrophils; OR - odds ratio

conditions are considered risk factors for joint infection, namely rheumatoid arthritis, osteoarthritis and the treatment with immunosuppressive drugs[1]. In this study, the elderly were the most representative group. However, in our sample, the prevalence of diseases such as rheumatoid arthritis and immunosuppressive drugs was low. Similarly, despite the risk classically attributed to intravenous drug abuse6, none of our cases had a previous history of drug abuse. Authors believe that such finding may be related to unreported cases instead of a real absence of intravenous drug users. The same would be true for the low number of reported cases of alcoholism and liver cirrhosis. Up to 22% of SA patients do not have any known risk factor for SA or a previous history of joint disease[8].

In the present study, cardiovascular risk factors (CVRF) such as hypertension and diabetes *mellitus,* were the main comorbidities. Diabetes *mellitus* is a known risk factor for SA[6]. The high prevalence of hyperuricemia/gout could be a consequence of the significant prevalence of metabolic syndrome, which, although not extensively studied in this investigation, is partially corroborated by the high prevalence of CVRF, as mentioned above.

Previous studies reported a high prevalence of elevated serum acid uric in patients with established cardiovascular disease or CVRF, such as arterial hypertension, coronary artery disease, stroke and metabolic syndrome[9]. Also, acute gout is a common cause of ED admission[10], and its presentation could be indistinguishable from that of SA[11]. In this study, patients with hyperuricemia/gout presented a 5-fold higher risk of a negative result in SF cultures. Therefore, it should alert us for a possible misdiagnosis of SA, since some of the negative cultures could be in fact, acute gout crisis, even though gout does not rule out a concomitant joint infection. In the present study, inflammatory serum parameters and biochemical SF parameters were no different within patients with or without hyperuricemia/gout. Therefore, these parameters do not seem to be useful for the differential diagnosis between these two entities. Previous data[1,4,12] indicate that SF TCC above 50 000 cells/ L suggest the possibility of SA, but cannot differentiate between SA and microcrystalline arthropathies. The distinction between the two diseases is based mainly on patient anamnesis, namely the presence of risk factors and previous acute gout episodes. Nonetheless, this study demonstrated that a higher serum CRP (≥18mg/dl) could be a predictive factor of microorganism isolation, therefore demonstrating potential value in therapeutic decisions in borderline cases.

Only half of the patients who underwent arthrotomy had a causative microorganism identified, which is significantly higher than the 20% of negative cases previously described[4].

Given the association we found between hyperuricemia/gout and the higher number of negative cultures mentioned above, the possibility of a mistaken diagnosis of septic arthritis in patients with acute gout, might be the main explanation.

Other possible explanations include: SF may have been collected after the antibiotic start in some patients; small numbers of bacteria were present, perhaps because of brisk neutrophil phagocytosis; the quantity of SF plated was inadequate or infecting bacteria may have had fastidious growth requirements[4].

Leroux *et al.*[13] in a retrospective study that included 398 diagnosed and treated as SA, found that at least 14% of patients diagnosed with SA with negative bacteriological results subsequently developed a rheumatic disease. The authors advise that when no microor-

ganism is identified, the diagnosis should remain presumptive and follow-up is necessary to screen for other diseases, especially rheumatic diseases.

This study demonstrated a growing tendency of SA cases. Such tendency could be a consequence of the rising life expectancy within the older population itself, which increase the number and proportion of people at very old ages. We should also consider the greater number of diabetic patients and other conditions, such as a greater number of orthopedic surgeries and invasive joint procedures, that also can predispose to SA.

This study has some potential limitations. First, being a retrospective study, some key statistics cannot be measured; researchers relied on others for accurate recordkeeping, and some data are missing; the retrospective aspect may also introduce selection bias and mis-classification or information bias. Second, our sample is quite small and from only one center, and it would be advisable to collect data from larger samples and from multiple centers. Finally, the inclusion of additional variables, namely in what concerns other risk factors, such as osteoarthritis, human immunodeficiency virus infection and other chronic infections, would be important for a better characterization of SA.

CONCLUSION

Elderly subjects with multiple comorbidities, namely cardiovascular risk factors, seem more prone to SA. Hyperuricemia/gout is a common condition within patients observed for suspected SA. Serum CRP can be the most important predictive factor for the identification of a microbial agent. SF analysis and inflammatory serum parameters are of no value in the distinction between SA and gout.

The fact that patients with hyperuricemia/gout present higher odds of obtaining a negative SF culture should alert us to the possibility of a mistaken diagnosis of septic arthritis in patients with acute gout, which may have important treatment and prognostic implications.

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