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Predictors of treatment failure and mortality in native septic arthritis

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Abstract The aims of this study are to analyse the characteristics of septic arthritis stratified by age and to identify the predictors of treatment failure and mortality in septic arthritis. A retrospective single-centre study was conducted in patients with native septic arthritis between 1994 and 2012. The primary outcome was treatment failure. Secondary outcomes included mortality, complications, endocarditis, bacteraemia, hospital readmission and the duration of the hospital stay. Logistic regression analyses with a propensity score were performed to identify the predictors of response and mortality. Additional analyses were performed according to age and the initial treatment (surgery or conservative). A total of 186 patients were studied. The median (interquartile range) age was 64 (46, 74) years, and the percentage of male patients was 68.9 %. A logistic regression analysis showed that *Staphylococcus aureus* infection [OR 2.39 (1.20–4.77), $p=0.013$], endocarditis [OR 4.74 (1.16–19.24), $p=0.029$] and the involvement of joints difficult to access with needle drainage [OR 2.33 (1.06–5.11), $p=0.034$] predict treatment failure

and that age [OR 1.27 (1.07=1.50), $p=0.005$], the leucocyte count at baseline [OR 1.01 (1.00–1.02), $p=0.023$], bacteraemia [OR 27.66 (1.39–551.20), $p=0.030$], diabetes mellitus [OR 15.33 (1.36–172.67), $p=0.027$] and chronic renal failure [OR 81.27 (3.32–1990.20), $p=0.007$] predict mortality. No significant differences in treatment failure by age were found. In septic arthritis, the predictors of mortality and the predictors of treatment failure differ. The predictors of treatment failure concern local factors and systemic complications, whereas conditions related to the host's immune competence, such as age and comorbidities that hamper the host's response, predict mortality.

Keywords Age · Joint drainage · Mortality · Septic arthritis · Treatment

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Introduction

Septic arthritis is a serious and potentially life-threatening condition. Delays in its diagnosis and treatment can lead to irreversible joint damage with consequent functional loss and death [1]. The administration of intravenous antibiotics coupled with drainage of the joint through needle aspiration or surgery (arthroscopy or arthrotomy) are the standard treatments. A better understanding of the diagnosis and management of septic arthritis is still needed to improve the prognosis of this disorder.

Previous studies that analysed the predictors of outcome and mortality in septic arthritis included a small number of patients or patients with septic arthritis of a joint prosthesis [2, 3]. However, this type of septic arthritis presents substantial differences in its clinical and microbiological data and in its management compared with native septic arthritis. Both the age of the population and the comorbidities are increasing in current clinical practice. Age may be considered to be not only

a risk factor for septic arthritis but also may be an important prognostic factor of response to treatment [4, 5]. However, reports of the characteristics of septic arthritis in the older population and information about the differences in response to treatment compared with younger patients are limited. Small case series [2, 5, 6] and one large descriptive study that included native and prosthetic septic arthritis analyse these differences [7].

The selection of the type of joint drainage is generally based on the individual physician's experience. The data that describe the effectiveness of these interventions are based on small descriptive studies that yielded conflicting results. Some comparative studies show that surgical treatment is not superior to daily needle aspiration [8–11]. In contrast, one study shows the superiority of early surgical intervention over closed daily needle aspiration [12]. Thus, the role of needle aspiration, arthrotomy, or arthroscopy in the treatment of septic arthritis is not clear [13]. A careful selection of treatment for each patient may be essential to improve the prognosis of septic arthritis.

The aims of the present study are to analyse the characteristics and differences in responses stratified by age and to identify the predictors of treatment failure and mortality in native septic arthritis, with special attention to the type of drainage.

Materials and methods

This is a single-centre retrospective observational study of patients with a diagnosis of septic arthritis and a synovial fluid culture yielding bacterial growth identified via the coding system in a university hospital from 1994 to 2012. The data were obtained from the hospital's database records. This study was performed using a checklist based on the preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology [14]. The study protocol was approved by the Clinical Research Ethic Committee of Galicia. Informed consent from the patients was not required owing to the nature of the study.

The selection criteria were defined as follows: (1) men or women of at least 18 years of age, (2) diagnosis of septic or infectious arthritis and (3) synovial fluid culture yielding bacterial growth. Septic arthritis related to prosthetic materials was not included.

Patients were treated with early surgery, including either arthroscopy or arthrotomy (in the first 72 h after diagnosis) or daily closed needle aspiration, selected at the physician's discretion.

The primary endpoint was treatment failure, which was operatively defined as death, admission to the intensive care unit, the need for surgery after 72 h of initial treatment or readmission to the hospital for the same reason. The investigated secondary endpoints were mortality during hospitalisation and mortality in the first year after the diagnosis, the number of hospitalised days, and complications, such as endocarditis or bacteraemia. The data collected included age, gender, joints involved, presence of comorbidities, admitting department, number of hospitalised days, joint and blood culture results, baseline leucocyte counts, baseline erythrocyte sedimentation rate (ESR), baseline C-reactive protein (CRP) levels, treatment and development of complications, such as endocarditis or bacteraemia. Special attention was paid to the data on early surgery, including arthroscopy or arthrotomy (in the first 72 h after diagnosis) or closed needle aspiration.

Statistical analysis

A descriptive analysis was stratified by the age (70 years or older vs. younger than 70 years). Significant differences in the baseline characteristics and differences in the response were analysed in both populations. A second analysis was performed to identify the differences in the baseline characteristics and the differences in response according to the type of early intervention, i.e. early surgical intervention (in the first 72 h after admission) or conservative medical treatment with repetitive joint taps as needed. Dichotomous variables were analysed using the chi-squared or Fisher's exact test and continuous variables were analysed using the Wilcoxon-Mann-Whitney test. A $p < 0.05$ was considered to be statistically significant.

Logistic regression analyses were performed to identify the predictors of treatment failure and mortality. Dichotomous variables included in the univariate analyses were the gender, joint, *Staphylococcus aureus*, early surgical intervention, comorbidities (described in Table 1), endocarditis, bacteraemia and admission to the rheumatology unit. This variable was included to take into account that the rheumatology unit is more experienced than other departments in the treatment of septic arthritis in our hospital. Continuous variables included in the univariate analyses were the age, baseline leucocytes, ESR baseline and CRP baseline. Variables in the univariate analysis with a $p < 0.10$ were included in the multivariate analysis. Finally, a propensity score model was created to correct for the confounding factors. The quality of the propensity score model was assessed using a Hosmer-Lemeshow test (statistical test for goodness of fit for logistic regression models) [15]. A logistic regression analysis that included the propensity score was performed to identify the predictors of treatment failure and mortality. Stata version 11.1 (Stata/IC 11.1 for Windows, StataCorp LP, Texas, USA) was used in all of the statistical analyses.

Table 1 Baseline characteristics

	Total (n=186)	Age ≥70 years (n=69)	Age <70 years (n=117)	p
Age, median (IQR)	64 (46,74)	77 (73,80)	53 (39,62)	–
Female, n (%)	58 (31.1)	25 (36.2)	33 (28.2)	0.254
Joint, n (%)				
Knee, n (%)	77 (41.4)	22 (31.8)	55 (47.0)	0.043
Small joint, n (%)	21 (11.2)	9 (13.0)	12 (10.2)	0.562
Shoulder, n (%)	19 (10.2)	11 (15.9)	8 (6.8)	0.047
Hip, n (%)	16 (8.6)	6 (8.7)	10 (8.5)	0.971
Polyarticular, n (%)	15 (8.0)	8 (11.5)	7 (5.9)	0.174
Elbow, n (%)	13 (6.9)	7 (10.1)	6 (5.1)	0.195
Wrist, n (%)	10 (5.3)	3 (4.3)	7 (5.9)	0.634
Sternoclavicular, n (%)	10 (5.3)	0 (0.0)	10 (8.5)	0.012
Ankle, n (%)	5 (2.6)	3 (4.3)	2 (1.7)	0.282
Baseline leukocytes, median (IQR); (n=179)	10,120 (6850,14,230)	10,430 (7400,15,820)	9980 (6600,13,690)	0.108
Baseline ESR, median (IQR); (n=147)	86 (51,104)	88 (56,101)	84 (42,105)	0.862
Baseline CRP mg/dl, median (IQR); (n=80)	13.5 (5.3,23.2)	15.6 (5.1,23.3)	12.0 (5.8,23.1)	0.992
Early surgery, n (%)	32 (17.2)	12 (17.3)	20 (17.0)	0.959
Admission in rheumatology department, n (%)	99 (53.2 %)	38 (55.07)	61 (52.1)	0.701
Comorbidities, n (%)				
Osteoarthritis, n (%)	36 (19.3)	21 (30.4)	15 (12.8)	0.003
Diabetes, n (%)	27 (14.5)	11 (15.9)	16 (13.6)	0.672
Treatment with steroids, n (%)	26 (13.9)	14 (20.2)	12 (10.2)	0.057
Cardiovascular disease, n (%)	24 (12.9)	18 (26.0)	6 (5.1)	<0.001
Malignancies, n (%)	21 (11.2)	12 (17.3)	9 (7.6)	0.043
Rheumatoid arthritis, n (%)	20 (10.7)	13 (18.8)	7 (5.9)	0.006
Chronic renal failure, n (%)	18 (9.6)	9 (13.0)	9 (7.6)	0.233
Cirrhosis, n (%)	18 (9.6)	3 (4.3)	15 (12.8)	0.073
Obstructive pulmonary disease, n (%)	17 (9.1)	12 (17.3)	5 (4.2)	0.003
Parenteral drug addiction, n (%)	5 (2.6)	0 (0.0)	5 (4.2)	0.159
Haemodialysis, n (%)	5 (2.6)	0 (0.0)	5 (4.2)	0.159
HIV, n (%)	3 (1.6)	0 (0.0)	3 (2.5)	0.296

IQR interquartile range

Results

A total of 186 patients with native septic arthritis were included in the study. The median (interquartile range) age was 64 (46, 74) years, and the percentage of male patients was 68.9 %. The knee was the most commonly involved joint, and it was significantly more frequently involved in patients aged less than 70 years (younger population) than in the population aged 70 years or older (older population) (p= 0.043). The sternoclavicular joint was also affected more frequently in the younger population than in the older population (p=0.012). In contrast, the shoulder was more frequently affected in the older population than in the younger population (p=0.047). Osteoarthritis (p=0.003), cardiovascular disease (p<0.001), malignancies (p=0.043), rheumatoid arthritis (p=0.006) and chronic obstructive pulmonary disease

(p=0.003) were more frequent in the older population than in the younger population. Details of the baseline characteristics are described in Table 1.

Staphylococcus aureus was the most common microorganism in all populations (63.8 % of infections). The frequency of *Staphylococcus aureus* in the older group was 68.1 and 61.5 % in the younger group. *Streptococcus pneumoniae* was statistically more prevalent in the older population than in the younger population (p=0.043). No other differences were found (see details in Table 2).

The frequency of treatment failure in all populations was 39.7 %. No significant differences were found between the older and younger populations (47.8 vs. 35.0 %, p=0.085). The mortality was 8.6 % in the global population. The mortality was higher in the older population than in the younger population (20.2 vs. 1.7 %, p<0.001). The mortality

Table 2 Table of microbiology results

Microbiology, n (%)	Total (n=186)	Age ≥70 years (n=69)	Age <70 years (n=117)	p
Staphylococcus aureus	119 (63.8)	47 (68.1)	72 (61.5)	0.366
Staphylococcus aureus OR	10 (5.38)	2 (2.9)	8 (6.8)	0.253
Other *Staphylococcus*	11 (5.9)	5 (7.2)	6 (5.1)	0.553
Streptococcus	28 (15.0)	12 (17.3)	16 (13.6)	0.494
Streptococcus pneumoniae	5 (2.6)	4 (5.8)	1 (0.85)	0.043
Gram negative	13 (15.0)	2 (2.9)	11 (9.4)	0.093
Polymicrobial	6 (3.2)	3 (4.3)	3 (2.5)	0.504
Mycobacterium tuberculosis	4 (2.1)	0 (0.0)	4 (3.42)	0.120
Other	3 (1.6)	0 (0.0)	3 (2.5)	0.185
Neisseria meningitides	2 (1.0)	0 (0.0)	2 (1.7)	0.276

OR oxacillin-resistant

12 months after the diagnosis was 16.6 %, with a significantly higher frequency in the older population than in the younger population (28.9 vs. 9.4 %, $p=0.001$). The frequency of complications in the global population was 45.1 %. Complications were also more frequent in the older than the younger population (59.4 vs. 36.7 %, $p=0.003$). The frequency of hospital readmission in the global population was 12.3 %, and readmission was more frequent in the younger group than in the older population (17.0 vs. 4.3 %, $p=0.011$). No significant differences in endocarditis ($p=0.059$), bacteraemia ($p=0.073$) or the duration of the hospital stay ($p=0.458$) were found in the two groups.

Thirty-two patients had early surgery, and 154 received conservative treatments (see Tables S1 and S2 in the online supplementary material). Groups did not differ statistically except for the frequency of infected hips, which was more commonly treated with surgery ($p=0.024$). Furthermore, patients hospitalised in the rheumatology unit habitually underwent conservative treatment ($p<0.001$), and patients hospitalised in the orthopaedic surgery unit underwent early surgery ($p<0.001$). The groups treated surgically and conservatively did not differ statistically in the rates of treatment failure (53.1 % in the early surgery-treated group vs. 37.0 % in the conservatively treated group, $p=0.090$). In addition, the other secondary outcomes were not significantly different.

A propensity score model identified the admitting department as a confounding factor (Hosmer-Lemeshow chi-square result of 90.21, $p<0.001$). A logistic regression analysis that included the propensity score model showed that endocarditis [OR 4.74 (1.16–19.24), $p=0.029$], *Staphylococcus aureus* infection [OR 2.39 (1.20–4.77), $p=0.013$], and involved joints with more difficult access to drainage, including the hip and small joints of the hands and feet [OR 2.33 (1.06–5.11), $p=0.034$], predict treatment failure (see Table 3). Additionally, a logistic regression analysis that included the propensity score model showed that age [OR 1.27 (1.07–1.50), $p=0.005$], the leucocyte count at baseline [OR 1.01 (1.00–1.02), $p=0.023$],

bacteraemia [OR 27.66 (1.39–551.20), $p=0.030$], diabetes mellitus [OR 15.33 (1.36–172.67), $p=0.027$] and chronic renal failure [OR 81.27 (3.32–1990.20), $p=0.007$] predict mortality (see Table 4).

Discussion

In the present study of septic arthritis, treatment failure is predicted by the type of joint involved and the bacteria, and mortality is predicted by age, chronic comorbidities, the presence of an important inflammatory response and disseminated infection and the experience of the admitting unit.

Overall, the population in our study does not differ from that in other studies. The percentage of males and the proportion of patients with rheumatoid arthritis are higher than expected in the general population. A higher percentage of males with septic arthritis have been previously reported, especially in the younger population [7]. The risk of septic arthritis in patients with RA is increased several-fold [16–18]. This higher risk is explained by the reduced bactericidal activity of the synovial fluid and the defective phagocytosis related to the disease and/or to the medications [19–21]. In addition, rheumatoid arthritis patients treated with TNF antagonists are particularly susceptible to septic arthritis [22, 23]. The predominance of the knee infections characteristic in our study has been recurrently reported. Sternoclavicular septic arthritis is uncommon, and in previous studies, it has been more frequently reported in younger patients with risk factors [24]. In our study, sternoclavicular septic arthritis was also more frequent in the younger population, and 60 % of these patients had comorbidities. Other joints with similar structural characteristics, such as the pubic symphysis or sacroiliac joint, were commonly infected in the younger population [9, 25]. In the elderly, these joints are sclerosed and difficult for microorganisms to access due to poor vascularisation. In contrast, septic shoulder arthritis is more common in older patients who

Table 3 Logistic regression analysis of treatment failure in septic arthritis

Variable	Univariate OR (95 % CI)	Multivariate OR (95 % CI)	Propensity score OR (95 % CI)
Age (years)	1.01 (0.99, 1.03), p=0.109	–	–
Early surgery (present/absent)	1.93 (0.89, 4.14), p=0.093	1.54 (0.64, 3.73), p=0.333	1.73 (0.59, 5.11), p=0.314
Endocarditis (present/absent)	5.03 (1.31, 19.25), p=0.018	4.95 (1.24, 19.70), p=0.023	4.74 (1.16, 19.24), p=0.029
Bacteraemia (present/absent)	1.70 (0.89, 3.25), p=0.105	–	–
Cardiovascular disease (present/absent)	1.96 (0.83, 4.64), p=0.128	–	–
Chronic renal failure (present/absent)	2.03 (0.76, 5.41), p=0.157	–	–
Osteoarthritis (present/absent)	0.51 (0.23, 1.15), p=0.105	–	–
Cirrhosis (present/absent)	0.40 (0.13, 1.27), p=0.119	–	–
Staphylococcus aureus (present/absent)	2.42 (1.26, 4.63), p=0.008	2.41 (1.20, 4.79), p=0.012	2.39 (1.20, 4.77), p=0.013
Admission in rheumatology unit (yes/no)	0.47 (0.26, 0.84), p=0.012	0.64 (0.31, 1.26), p=0.197	–
Difficult drainage joints (present/absent)	2.74 (1.31, 5.72), p=0.007	2.29 (1.05, 4.98), p=0.036	2.33 (1.06, 5.11), p=0.034

Only variables with $p<0.02$ in univariate analysis are showed. The propensity score is adjusted by the admitting department. Difficult drainage joints included hip and small joints of hands and feet

have predisposing factors, such as structural damage or co-morbidities [26].

The logistic regression analysis showed that *Staphylococcus aureus* infection, endocarditis and joints with more difficult access to drainage (the hip and the small joints of the hands and feet) predict treatment failure. In addition, age, leucocytosis at the baseline, bacteraemia and comorbidities are predictors of mortality. *Staphylococcus aureus* was the most commonly isolated pathogen in the joint independent of age, as reported by many investigators. Previous reports have shown that *Staphylococcus aureus* is associated with a poor prognosis in septic arthritis [13]. *Staphylococcus aureus* is also a leading cause of community- and hospital-acquired bacteraemia. *Staphylococcus aureus* bacteraemia can often occur and ubiquitously seed the bacteria, resulting in severe disease and significant morbidity and death [27]. The frequency of endocarditis in patients with *Staphylococcus aureus* bacteraemia is high (~30 %). This is consistent with our data that identified *Staphylococcus aureus* as a predictor of a poor

response and endocarditis and bacteraemia as predictors of both poor response and mortality, respectively. *Streptococcus pneumoniae* septic arthritis is considered uncommon and is more frequently reported in older patients with comorbidities [28, 29]. In our study, pneumococcal septic arthritis was more common in the older population with cardiovascular disease, rheumatoid arthritis, diabetes mellitus or cirrhosis but did not in itself predict a poor outcome. The most effective method of joint drainage has yet to be clearly delineated, given the paucity of quality studies. There is no definitive evidence to recommend one method over another, and most studies focus on a specific joint [30, 31]. Traditionally, infected hip joints are drained by open arthrotomy, but arthroscopy appears to be as effective as open drainage [32]. Herein, the type of joint drainage was influenced by the department that the patient entered, and this difference was related to the decision of the physician in the emergency department. Only infected hips were more frequently treated with early surgery. This difference was expected because the hip is not easily accessible by

Table 4 Logistic regression analysis of mortality in septic arthritis

Variable	Univariate OR (95 % CI)	Multivariate OR (95 % CI)	Propensity score OR (95 % CI)
Age (years)	1.10 (1.04, 1.16), p=0.001	1.23 (1.07,1.42), p=0.003	1.27 (1.07,1.50), p=0.005
Leucocytes baseline (μl)	1.01 (1.00,1.02), p=0.002	1.01 (1.00,1.02), p=0.020	1.01 (1.00,1.02), p=0.023
Endocarditis (present/absent)	16.40 (4.47,60.13), p<0.001	1.80 (0.19,17.38), p=0.610	1.00 (0.09,11.30), p=0.998
Bacteraemia (present/absent)	4.92 (1.69, 14.30), p=0.003	15.57 (1.47,165.15), p=0.023	27.66 (1.39, 551.20), p=0.030
Diabetes (present/absent)	4.26 (1.40,12.92), p=0.011	11.89 (1.30, 108.99), p=0.029	15.33 (136,172.67), p=0.027
Cardiovascular disease (present/absent)	5.07 (1.65,15.59), p=0.005	0.27 (0.03,2.61), p=0.249	0.26 (0.03,2.36), p=0.231
Chronic renal failure (present/absent)	5.49 (1.66,18.20), p=0.005	50.57 (2.89,886.08), p=0.007	81.27 (3.32, 1990.20), p=0.007
Admission in rheumatology unit (yes/no)	0.18 (0.05,0.65), p=0.009	0.01 (0.01, 0.23), p=0.03	–
Knee (present/absent)	0.30 (0.08,1.09), p=0.067	0.81 (0.12,5.38), p=0.832	0.51 (0.06,4.23), p=0.532
Elbow (present/absent)	3.69 (0.90,15.15), p=0.069	23.97 (0.99,530.25), p=0.051	22.73 (0.75, 690.61), p=0.073

Only variables with $p<0.02$ in univariate analysis are showed. The propensity score is adjusted by admitting department

needle aspiration. Patients hospitalised in the orthopaedic department were more likely to be treated surgically than those who were hospitalised in other departments. Therefore, a propensity score model was used to correct for this confounding factor. No significant differences in response outcomes were identified for the patients who were surgically and conservatively treated. A published systematic review showed that a significantly higher percentage of the conservatively treated patients had successful outcomes compared with the surgically treated patients. The authors of this work recommend the initial use of medical therapy and surgical drainage for unsuccessful or difficult joint drainage via needle aspiration [8]. Interestingly, when only the conservatively treated patients were analysed, mortality was significantly lower in the group of patients hospitalised in the rheumatology unit, where the largest number of patients had been admitted. Therefore, these results suggest that the experience of the admitting department in treating septic arthritis is an important predictor of mortality. Age was also identified as a predictive factor of mortality. In prior studies, the mortality rates of septic arthritis in older patients ranged from 9 to 23 % [2, 5–7]. In one study of septic arthritis including prosthesis infectious arthritis, an age older than 65 years was a risk factor for mortality [2]. In addition, septic arthritis in older patients has a high percentage of complications and risk of mortality in the first 12 months after the diagnosis. In contrast, the readmission rate was higher in the younger populations. However, these results should be interpreted with caution because they could reflect indirectly the higher rate of mortality in older patients instead of hospital readmission. Leucocytosis is an independent predictor for death [33–35]. In one study, leucocytosis ($>10 \times 10^9$/l) at the time of hospital admission for any reason predicts inpatient mortality (OR=2.0; $p<0.0001$) [36]. The basis of this effect remains unknown. In keeping with this report, leucocytosis at the baseline was a predictor of mortality in our study.

Our study presents limitations. Some data were missing, as commonly happens in retrospective studies. Additionally, bias in the treatment choice was clear and related to the admitting unit. Nevertheless, our analysis including a propensity score may have accounted for this variable. The strengths of our work were the inclusion of only the patients with a synovial fluid culture yielding bacteria growth and the exclusion of patients with prosthetic joint infections.

In conclusion, the predictors of mortality and the predictors of treatment failure are different in septic arthritis. Conditions related to the host immune competence as age and comorbidities hamper the host's response to an aggressive pathogen predict mortality. The definition of treatment failure was more comprehensive and included poor local and systemic infection outcomes. Predictors of this composited outcome concerned local factors and systemic complications. Our present work may help to improve therapeutic decisions for high-risk patients.

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