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ORIGINAL ARTICLE

Clinical characteristics of patients with polymicrobial septic arthritis

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Abstract

Little is known about the incidence, risk factors, clinical characteristics, and outcomes of patients with polymicrobial SA (PMSA). We aimed to determine the unique characteristics of patients with PMSA by comparing them to patients with monomicrobial SA (MMSA). We conducted a retrospective cohort study of patients 18 years and older admitted to a single tertiary care medical center, between 1998 and 2015, with surgically treated culture–positive SA affecting one or more joints. Patients were separated into two groups by the presence of one (MMSA) or more organisms (PMSA). A total of 441 patients with MMSA and 47 with PMSA were identified. Prior history of SA was more common among the PMSA group (31.9% vs. 18.6%; $p = 0.03$) as well as higher rates of prosthetic joint involvement (48.9% vs. 36.1%; $p = 0.06$). Patients with PMSA were sicker with higher rates of shock at presentation (14.9% vs. 5.5%; $p = 0.02$), intensive care unit admissions (39.1% vs. 18%; $p < 0.001$), and longer mean length of stay (16.1 vs. 10.9 days; $p < 0.001$). The most prevalent pathogens in the PMSA group were coagulase-negative *Staphylococcus* (31%), followed by methicillin-sensitive *Staphylococcus aureus* (29%), and *Enterococcus* (24%). To our knowledge, this is the first study to determine the clinical and microbiologic profiles of patients with PMSA. Important differences were noted such as more frequent involvement of atypical and prosthetic joints in PMSA. PMSA should be suspected in patients with these clinical features, and broad-spectrum antibiotics should be considered as these patients appear to be sicker and have worse outcomes.

Keywords Septic arthritis · Polymicrobial infection · Prosthetic joint · *Staphylococcus aureus*

Introduction

The incidence of septic arthritis (SA) is rising due to aging of the population and an increase in the rates of joint replacement surgeries [1]. SA is usually monomicrobial and predominantly caused by *Staphylococcus aureus* [1].

Polymicrobial SA (PMSA) is uncommon, especially in the absence of direct inoculation or contiguous spread from osteomyelitis or soft tissue infection. Limited case reports and case series on PMSA are available in the published literature [2–5]. One recent series demonstrated the importance of molecular identification of PMSA in 61 cases of post-surgical joint infections [2]. Other series establish intravenous drug use [3] and atypical joint involvement, including pubic symphysis and facet joints [5, 6], as factors that should raise suspicion for PMSA. Unusual pathogens, such as *Clostridium* species [7], may be found in PMSA. One series demonstrated polymicrobial isolates in 37% of cases among diabetic patients with bone, joint, and soft tissue infections [8]. One case of PMSA was reported in patient with Wilsons' disease [9]. Finally, higher rates of PMSA have been observed in patients with prosthetic joint SA and are associated with worse outcomes [10].

The existing literature on this condition is limited, and it is unknown how patients with PMSA may differ from their counterparts with MMSA. To our knowledge, this is the largest and most detailed study designed to address this poorly understood entity.

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Methods and study design

Study design

We conducted a retrospective study of patients with SA admitted to a single tertiary care center from 1998 to 2015. Permission to review data was obtained from the Beth Israel Deaconess Medical Center Institutional Review Board. All authors vouch for the accuracy of the reported data and analyses.

Study population

Eligible patients 18 years old or older were identified using an ICD9 code for SA. Only patients with positive synovial fluid or synovial tissue or blood cultures in the setting of arthritis who were surgically treated were included. Patients with PMSA were characterized by isolation of multiple organisms from synovial fluid in one or more joints, or documentation of clinical evidence of inflammatory arthritis in the setting of polymicrobial bacteremia. Those with MMSA were characterized by isolation of a single organism from synovial fluid or documentation of clinical evidence of inflammatory arthritis in the setting of monomicrobial bacteremia. We excluded patients with osteomyelitis, septic bursitis, and culture-negative SA.

Data collection

Following identification of eligible patients, the electronic medical record for each patient was reviewed to obtain demographic data and comorbidities at the time of the index admission, presenting clinical and laboratory features, sites of joint involvement, synovial fluid data, microbial data, and timing of antibiotic administration and operative intervention. Length of hospital stay (LOS), discharge to a rehabilitation facility, 60-day readmission rates, repeated surgery, and 30-day mortality rates also were determined. De-identified data were stored securely in Research Electronic Data Capture (REDCap), an institutionally available web–based data repository.

Groups

Patients with SA were stratified into two comparison groups: patients with MMSA and PMSA. Patients with PMSA were compared to those with MMSA with respect to presenting features, joint distribution, microbial profile, and patient outcomes.

Statistical analysis

Quantitative variables were described by mean and standard deviation. Qualitative variables were described by frequencies and percentages. Differences between continuous variables were analyzed using the Student's two-sample t test or the Mann-Whitney U test where appropriate. Differences between categorical variables were analyzed using the Chi-square test or Fisher's exact test where appropriate. A p value of < 0.05 was considered to be significant, 2-sided p value was noted, unless otherwise specified. Analyses were conducted using IBM SPSS Statistics, release 19.0.

Table 1 Baseline characteristics of the study population

	Monomicrobial ($N = 441$)	Polymicrobial ($N = 47$)	p value
Age, y, mean ± SD	61.4 ± 15.6	58.8 ± 13.5	0.28
Male, no. (%)	248 (56.2)	27 (57.4)	0.87
Cancer, no. (%)	77 (17.5)	2 (4.3)	0.02
Chronic kidney injury, no. (%)	71 (16.1)	7 (14.9)	0.84
Dialysis, no. (%)	27 (6.1)	3 (6.4)	0.99
Diabetes mellitus, no. (%)	141 (32)	19 (40.4)	0.25
Past history of endocarditis, no. (%)	8 (1.8)	0 (0)	0.99
Current diagnosis of endocarditis, no. (%)	18 (4%)	1 (2%)	0.07
Liver cirrhosis, no. (%)	16 (3.6)	1 (2.1)	0.99
Gout, no. (%)	24 (5.4)	1 (2.1)	0.5
HIV, no. (%)	13 (2.9)	2 (4.3)	0.64
Current immunosuppression, no. (%)	74 (16.8)	7 (14.9)	0.83
IVDU, no. (%)	28 (6.3)	2 (4.3)	0.75
Kidney transplant, no. (%)	9 (2)	1 (2.1)	0.99
Rheumatoid arthritis, no. (%)	30 (6.8)	5 (10.6)	0.36
History of septic arthritis, no. (%)[a]	82 (18.6)	15 (31.9)	0.03

HIV human immunodeficiency virus, *IVDU* intravenous drug use

[a] Within a year

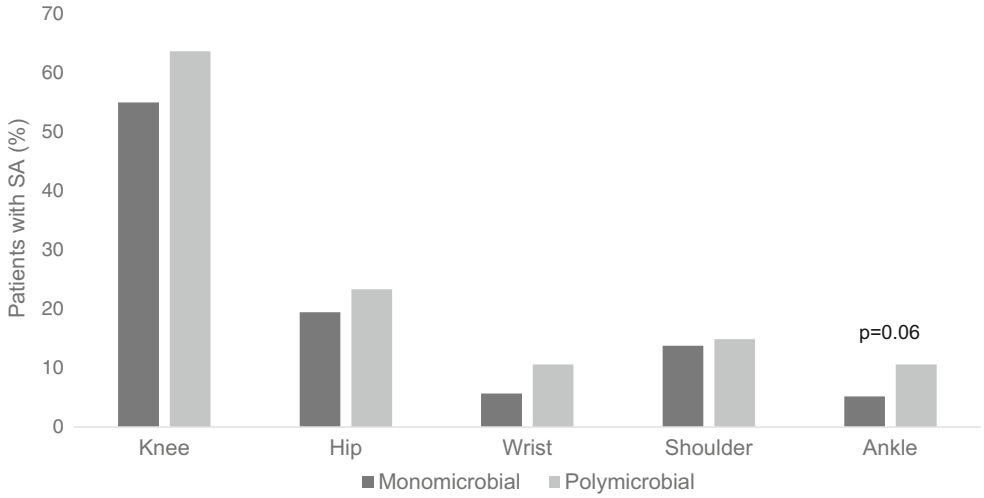

Fig. 1 Joint distribution among patients with culture-positive septic arthritis

Results

Characteristics of the study population

Over a period of 17 years (1998–2015), a total of 488 patients with culture-positive SA were identified. Among these patients, 441 (90.3%) had MMSA while 47 (9.7%) had PMSA. The groups were similar with respect to age, gender, and ethnicity. Cancer diagnosis was more prevalent among patients with PMSA (17.5% vs. 4.3%; $p = 0.02$), as well as history of SA in the in the involved joint during the past year (31.9% vs. 18.6%; $p = 0.03$). There were no other significant differences in the prevalence of other comorbidities or known risk factors for SA (Table 1).

Characteristics of joint involvement

The most commonly affected joint in both groups was the knee, followed by the hip and the shoulder (Fig. 1). Involvement of the ankle joint was more commonly seen in patients with PMSA (10.6 vs. 5.2%, $p = 0.06$). Nearly 50% of patients with PMSA had prosthetic joint involvement (48.9% vs. 36.1%, $p = 0.06$) while recent joint trauma was more prevalent in the MMSA group (15% vs. 4.3%; $p = 0.04$) (Table 2).

Characteristics of the clinical presentation

Fever at the time of hospital admission was significantly more prevalent among the patients with PMSA (57.4% vs. 39.9%; $p = 0.02$), and these patients had higher rates of septic shock at presentation (14.9% vs. 5.5%; $p = 0.02$). Results of standard blood tests and synovial fluid analysis were similar between the two groups (Table 3).

Microbiology profile

The rates of positive blood cultures and positive synovial fluid gram stains were similar between the PMSA and MMSA groups. Significantly higher rates of positive synovial fluid cultures were observed in the MMSA group compared with the PMSA group (87.1% vs. 46.5% respectively; $p < 0.001$). In cases where synovial tissue was obtained, significantly higher rates of synovial gram stain (43.3% of vs 25.7%; $p = 0.05$) and culture positivity (96.7% vs 78.4%; $p = 0.02$) were observed among the patients with PMSA (Fig. 2). The most common pathogens in the PMSA group were coagulase-negative *Staphylococcus aureus* (CoNS), which was 3 times more prevalent when compared to the MMSA group (38.8% vs. 12.1%; $p < 0.001$), followed

Table 2 Characteristics of joint involvement stratified by the study groups

	Monomicrobial ($N = 441$)	Polymicrobial ($N = 47$)	p value
Previous pathology in joint, no. (%)	292 (66.2)	33 (70.2)	0.63
Gout, no. (%)	17 (3.9)	3 (6.4)	0.43
Osteoarthritis, no. (%)	133 (30.2)	18 (38.3)	0.32
Rheumatoid arthritis, no. (%)	30 (6.8)	5 (10.6)	0.36
Recent trauma in joint, no. (%)*	66 (15)	2 (4.3)	0.04
Prosthesis in the involved joint, no. (%)	159 (36.1)	23 (48.9)	0.06**

*Within a year

**1-sided

Table 3 The clinical presenting features stratified by the study groups

	Monomicrobial ($N = 441$)	Polymicrobial ($N = 47$)	p value
Fever (> 100 °F), no. (%)	164 (39.9)	27 (57.4)	0.02
Shock, no. (%)	22 (5.5)	7 (14.9)	0.02
Sepsis (defined by SIRS criteria), no. (%)	154 (38)	22 (46.8)	0.27
Mean peripheral WBC (in thousands) ± SD	11.87 ± 5.4	12.22 ± 8.3	0.77
Mean peripheral PMN (%) ± SD	78.7 ± 11.2	75.99 ± 7.9	0.04
Mean ESR (mm/h) ± SD	77.6 ± 38.2	72.7 ± 37.7	0.54
Mean CRP (mm/dL) ± SD	150.5 ± 107.8	126.2 ± 105.1	0.28
Mean synovial fluid WBC (in thousands) ± SD	100.2 ± 154.5	121.9 ± 283.7	0.66
Mean synovial fluid PMN (%) ± SD	89.1 ± 13.5	81.5 ± 27.4	0.373
Synovial fluid crystals, no. (%)	29 (10.9)	1 (4.5)	0.71

Systemic inflammatory response syndrome (SIRS), criteria: (1) Body temperature of < 36 °C (96.8 °F) or > 38 °C (100.4 °F); (2) Heart rate > 90 beats per minute; (3) Tachypnea (high respiratory rate), > 20 breaths per minute, or an arterial pressure of carbon dioxide < 4.3 kPa (32 mmHg); (4) White blood cell count < 4000 cells/mm3 (4 × 109 cells/L) or > 12,000 cells/mm^3 (12 × 109 cells/L), or the presence of > 10% immature neutrophils (band forms). *WBC* white blood cell, *PMN* polymorphonuclear neutrophils, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

by methicillin-sensitive *Staphylococcus aureus* (36.2% vs. 35%; $p = 1$) and *Enterococcus* (29.8% vs. 2.9%; $p < 0.001$) (Fig. 3). The other two pathogens that were more commonly isolated from patients with PMSA were *Escherichia coli* (19.1% vs. 2.5%; $p < 0.001$) and *Proteus* (17% vs. 0.2%; $p < 0.001$) (See complete list of all isolated pathogens in Online Resource 1 and Online Resource 2). Interestingly, we found a tendency for certain bacteria isolated from patients with PMSA to be found together. For example, *Enterococcus* species were isolated with MRSA in 57% of the cases, and *Pseudomonas* was isolated with MRSA in 43% of cases.

Selection of antibiotics

Vancomycin was the most common initial antibiotic treatment in both the PMSA and MMSA groups (64%). The majority of patients were prescribed multiple antibiotics during their admission.

Vancomycin was the most commonly prescribed antibiotic in both MMSA patients (81%) and PMSA patients (83%), followed by ceftriaxone which was used in 27.7% of MMSA patients and 34% of PMSA patients. Cefepime was more commonly prescribed in patients with PMSA (25.5%) than those with MMSA (7%) ($p < 0.001$) (See list of all prescribed initial and overall antibiotics in Online Resource 3 and 4).

Surgical intervention

An arthroscopic intervention was performed at similar rates in both MMSA and PMSA patients (Online Resource 5). Pus was detected during operative intervention in 70.3% of the MMSA and in 63.9% of PMSA patients ($p = 0.44$). The majority of PMSA patients had more than one procedure, with multiple procedures occurring more frequently in PMSA relative to MMSA (52.3% vs. 24%, $p < 0.001$).

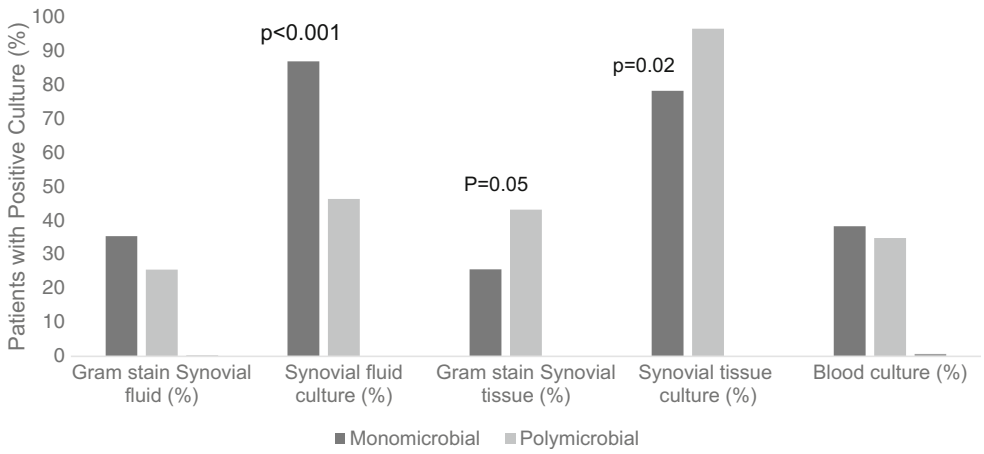

Fig. 2 Rates of culture positivity among patients with septic arthritis, stratified by modality and by bacterial growth patterns (monomicrobial vs. polymicrobial)

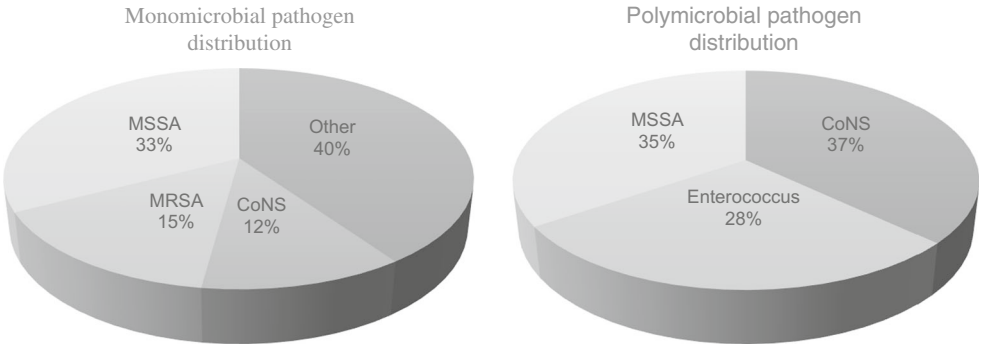

Fig. 3 Monomicrobial and polymicrobial pathogen distribution. MSSA, *methicillin-sensitive Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulase-negative *Staphylococcus*

Outcomes

The outcomes of the patients are described in Table 4. ICU admissions rates were significantly higher in the PMSA group (39.1% vs. 18%; $p < 0.001$) and length of stay was longer (16.1 vs. 10.9 days; $p < 0.001$).

Discussion

Little is known about patients with PMSA and how they differ from their MMSA counterparts. To our knowledge, this is the largest and most detailed study addressing the demographics, clinical characteristics, management, and outcomes of patients with PMSA.

In our cohort, we found that patients with a prior history of SA and those with a prosthetic joint were more prone to develop PMSA. Higher rates of PMSA observed in those with a prosthetic joint infection have been previously suggested by studies using molecular identification to identify causative organisms in this population [2, 10]. While intravenous drug use is an important risk factor for PMSA [3] in our cohort, it had less impact, perhaps due to the small number of intravenous drug users. Previous studies have demonstrated that PMSA is associated with infections of atypical joints [5, 6], consistent with what we observed in our cohort (e.g., higher prevalence of PMSA among patients with ankle joint SA).

In addition to having a distinct risk profile, PMSA also had a distinctive clinical presentation in our cohort. Patients with PMSA were sicker and more commonly febrile (57.4%) and presented with higher rates of shock (14.9%), requiring higher rates of ICU admission (39.1%) and more frequently multiple surgical interventions.

There are several limitations to this study. The study population was derived from a single tertiary referral center, which limits the diversity of the study population, with likely higher prevalence of sick and complex patients. Another limitation, common to retrospective studies reliant on medical chart review, was potentially incomplete or variable reporting of clinically relevant data and we had limited availability of long-term follow-up.

Despite these limitations, this study provides a detailed overview of patients with PMSA and is among the largest and most detailed analysis of this condition. We identified clinical, microbiologic, and prognostic features that differed between patients with PMSA and MMSA. These findings could help physicians recognize PMSA patients sooner so that appropriate treatment can be initiated.

Conclusion

PMSA may be more common than previously appreciated as it accounted for nearly 10% of our patient cohort with culture-positive SA. It should be considered in patients with suspected SA and involvement of atypical joints, prior history of SA, presence of prosthesis, and when the patient is in shock at presentation. In these cases, empiric coverage with vancomycin alone may not be sufficient, and prompt administration of broad-spectrum antibiotic therapy may improve clinical outcomes in these patients.

Table 4 Outcomes of patients with monomicrobial versus polymicrobial septic arthritis

	Monomicrobial ($N = 441$)	Polymicrobial ($N = 47$)	p value
ICU, no. (%)	79 (18)	18 (39.1)	0.001
Rehabilitation, no. (%)	238 (57.8)	27 (61.4)	0.75
Readmission within 30 days, no. (%)	85 (20.6)	10 (22.2)	0.85
Death within 30 days, no. (%)	27 (6.2)	1 (2.2)	0.50

ICU intensive care unit

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the BIDMC IRB committee, study protocol: 2013P000367.

Informed consent This is a retrospective data based study, which did not require an informed consent.

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