

Risk Factors, Screening, and Treatment Challenges in *Staphylococcus aureus* Native Septic Arthritis

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Background. *Staphylococcus aureus* is the most common cause of native septic arthritis. Few studies have characterized this disease during the US opioid epidemic. The role of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening in this disease has not been elucidated. We sought to identify risk factors and outcomes for *S. aureus* native septic arthritis and to evaluate MRSA screening in this disease.

Methods. A retrospective cohort study of native septic arthritis patients (2012–2016) was performed. Demographics, risk factors, and outcomes were compared between *Staphylococcus aureus* and other native septic arthritis infections. Sensitivity, specificity, and predictive values of MRSA screening were assessed.

Results. Two hundred fifteen cases of native septic arthritis were included. *S. aureus* was cultured in 64% (138/215). MRSA was cultured in 23% (50/215). *S. aureus* was associated with injection drug use (odds ratio [OR], 4.33; 95% CI, 1.74–10.81; $P = .002$) and switching antibiotics (OR, 3.92; 95% CI, 1.01–21.38; $P = .032$). For every 10-year increase in age, the odds of *S. aureus* decreased (OR, 0.72; 95% CI, 0.60–0.87; $P = .001$). For 1-unit increases in Charlson comorbidity index score, the odds of *S. aureus* decreased (OR, 0.82; 95% CI, 0.73–0.91; $P = .0004$). MRSA screening during admission demonstrated a sensitivity of 0.59, specificity of 0.96, positive predictive value of 0.85, and negative predictive value of 0.84 for MRSA native septic arthritis.

Conclusions. The opioid epidemic may be contributing to a demographic shift in native septic arthritis to younger, healthier individuals. *S. aureus* native septic arthritis has unique risks, including injection drug use. MRSA screening may be useful to rule in MRSA native septic arthritis.

Keywords. native septic arthritis; opioid epidemic; *Staphylococcus aureus*.

Native septic arthritis is a medical emergency characterized by direct invasion or hematogenous spread of microorganisms into the joint space. Inappropriate management can lead to the destruction of joint cartilage, significant morbidity, and mortality reported as high as 13% [1]. *Staphylococcus aureus* is the most common organism isolated from synovial fluid cultures in multiple prior studies worldwide [2–8] and has been associated with poorer joint outcomes compared with other organisms [2]. Furthermore, the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) septic arthritis has increased in recent years [9]. There is a paucity of studies characterizing native septic arthritis

in the United States in the past decade. As such, there is a need for data that reflect the impact of major ongoing events on the risk factors for and outcomes of native septic arthritis, such as the advent of multidrug-resistant organisms (eg, MRSA) and the opioid epidemic. Indeed, our institution in Pittsburgh, Pennsylvania, is at the center of a well-known opioid crisis. According to the Centers for Disease Control and Prevention's (CDC's) report on Drug and Opioid-Involved Overdose Deaths, Pennsylvania had the third highest rate of age-adjusted drug overdose deaths between 2013 and 2017 in the country [10].

In response to the emergence of MRSA, nasal screening for MRSA colonization has become commonly utilized to facilitate antimicrobial stewardship, infection prevention and control, and targeted decolonization strategies [11]. Current investigations seek to understand the role of this screen in predicting MRSA infection and guiding empiric antibiotic selection. MRSA nasal screening within 14 days of a positive culture has been shown in multiple studies to have a negative predictive value >90% in the setting of respiratory, blood, and wound infections [11]. However, there is no research investigating the role of this screening tool for MRSA in native septic arthritis.

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Given the lack of data describing native septic arthritis in the United States and the unknown utility of current MRSA screening practices, we asked the following questions at our institution: (1) What are the epidemiological characteristics of individuals with *S. aureus* native septic arthritis compared with native septic arthritis with other organisms in our population? (2) What are the differences in treatment and outcomes in *S. aureus* native septic arthritis compared with native septic arthritis with other organisms? (3) Does MRSA screening before or during admission predict MRSA culture positivity from joint aspirates?

METHODS

Study Design

A retrospective cohort study of patients diagnosed with native septic arthritis between 2012 and 2016 was performed at our institution, which comprises 2 large academic hospitals with 750 total beds and offers multiple specialty and subspecialty services and serves as a tertiary care center for the Pittsburgh, Pennsylvania, area. Institutional board review approval was obtained, and data were acquired through the electronic medical record. A list of all patients with positive synovial fluid cultures identified by our microbiology lab was cross-checked with a list of patients who had ICD codes 9 (711.0) and 10 (M00.9) for septic arthritis. Additionally, a Boolean search for the term “septic arthritis” was performed in all patient charts between January 2012 and December 2016 at the University of Pittsburgh Presbyterian and Montefiore Hospitals. Only inpatient encounters were included.

The following patient categories were excluded: age <18 years, prosthetic joint infections, patients with bursitis, and patients with synovial fluid analysis not fitting the clinical and laboratory criteria for native septic arthritis outlined below.

Data Collection

All patient records were reviewed, and data were collected from electronic medical records, including demographics at presentation such as age, gender, ethnicity, body mass index (BMI); social risk factors such as smoking history, alcohol use, history of or active use of intravenous drugs; clinical factors such as Charlson comorbidity index (CCI), history of liver cirrhosis, diabetes mellitus, chronic kidney disease, end-stage renal disease, rheumatoid arthritis, heart disease, osteoarthritis, chronic obstructive pulmonary disease, bacteremia, presence of infective endocarditis at index admission, and prior local irradiation at affected joint; immune suppression due to transplant, active malignancy, or other cause; and laboratory values including serum albumin, total leukocyte count, erythrocyte sedimentation rate, C-reactive protein, joint leukocyte count, percentage of neutrophils, and the presence of crystals. Joint infections were classified as monoarticular or polyarticular, and locations

of infection were recorded. The presence of concomitant spinal osteomyelitis was noted. Affected joints were reviewed for local risk factors such as trauma, joint injection, prior surgery, and prior infection. Causative organisms from joint cultures, gram stain, and blood cultures were recorded. MRSA nasal screening any time before index admission and during index admission was also reviewed. If a patient was screened before and during admission, each instance was counted as a separate event. If a patient was screened more than once before admission, the screen closest in time to the admission was used. If a patient was screened more than once during an admission, the screen performed closest to the diagnosis of septic arthritis was used.

The treatment plan was recorded, including antibiotic type, duration, and route; extension of antibiotic treatment, switching of antibiotics, reason for the switch, and any surgical procedures done were also documented. All MRSA nasal screening was performed using CHROMagar culture medium; however, there is no official protocol in place for when screening is performed at our institution.

Statistical Analysis

Continuous variables were summarized with mean and standard deviation for symmetrical distribution or median and interquartile range for skewed distribution. Categorical variables were summarized with frequencies and proportions. For the purpose of analysis, race was dichotomized into 2 categories: Caucasian and other. A univariate logistic regression was used to test for differences between *S. aureus* and non-*S. aureus* in clinical characteristics, treatments, and outcomes. Confidence intervals for odds ratios were calculated using the Wald method if cell sizes were sufficient and exact methods otherwise. Values for diagnostic properties were calculated from 2 × 2 tables. Analysis was conducted in SAS, version 9.4, and statistical significance was set at .05.

Definitions

Native Septic Arthritis was defined as the presence of a pathogenic organism isolated from synovial fluid or joint culture samples obtained directly from the joint space, bacteremia with either positive joint fluid gram stain or culture that was concordant with the blood pathogen present, or joint fluid neutrophils >50 000 cells/μL with signs/symptoms of native septic arthritis in the absence of any other etiology. *Immunosuppression* included any of the following conditions: congenital immunodeficiency, functional asplenia or splenectomy, solid organ or bone marrow transplant recipients, active malignancy (with or without chemotherapy) within 1 year of diagnosis or latest therapy, active prednisone use (≥7.5 mg/d), the use of any immunosuppressive therapy (biologics, other steroids, chemotherapy, etc.) either for >1 month or within 6 months of clinical presentation, infection with HIV, or presence of left ventricular assist device

[12]. *Active Intravenous Drug Use* (IDU) was defined as IDU occurring within the 4 weeks preceding the onset of infection via chart review [13] or a positive urine drug screen (UDS) on clinical presentation combined with confirmed injection drug use by the patient in the chart [13].

Recurrence was defined as infection with a preceding episode that had been adequately treated and the patient free of symptoms for an intervening period of at least 3 months. *Relapse* of infection was defined as persistent infection despite completion of adequate treatment. *Readmission* was defined as hospitalization within 30 days of hospital discharge. *Mortality* was defined as death during index hospitalization or within 30 days of hospital discharge. *Antibiotic Extension* was defined as antibiotic treatment that extended beyond the planned treatment duration.

RESULTS

Microbiology and Joint Characteristics

Microbiological and joint characteristics of our cohort are summarized in Table 1A–B. A total of 215 patients with 260 separate cases of native septic arthritis were identified. *S. aureus* was cultured in 64% (138/215) of patients,

while MRSA was cultured in 23% of patients (50/215). *Streptococcus* spp. were grown in 14.8% (32/215). The most common gram-negative organisms were *Escherichia coli* with 3.3% (7/215) and *Pseudomonas aeruginosa* with 2.3% (5/215). In patients with a history of IDU or current IDU, *S. aureus* was the most common organism (59/69), followed by *Enterococcus* spp. (3/69) and *Candida* spp. (2/69). Notably, we did not have any instances of gonococcal septic arthritis. There were 11 cases of polymicrobial native septic arthritis. In 41.4% (89/215) of cases, antibiotics were initiated before arthrocentesis. All cases were either joint fluid culture positive, joint tissue culture positive, or had joint fluid white blood cell count elevation in conjunction with bacteremia and compatible clinical signs/symptoms. Therefore, there were no completely culture negative cases in our cohort. Overall, the knee was the most common joint involved (81/260), followed by the shoulder (34/260) and the hip (25/260). In patients who grew *S. aureus*, the knee was also the most common joint involved (54/260), followed by the shoulder (24/215), the hip (14/215), and the sacroiliac joint (14/215). In patients who grew non-*S. aureus* organisms, the knee was again the most common site involved (27/215),

Table 1. Microbiological and Joint Characteristics of Native Septic Arthritis Cohort

A, Microbiology of the Native Septic Arthritis Cohort			
n = 215			
Gram Positive, No. (%)		Gram Negative, No. (%)	
<i>Staphylococcus aureus</i>	138 (64.2)	<i>Escherichia coli</i>	7 (3.3)
MRSA	50 (23.2)	<i>Pseudomonas aeruginosa</i>	5 (2.3)
Coagulase-negative <i>Staphylococcus</i>	5 (2.3)	<i>Bacteroides</i> spp.	4 (1.9)
Group B streptococci	12 (5.6)	<i>Prevotella</i> spp.	3 (1.4)
<i>Streptococcus viridans</i>	8 (3.7)	Other ^b	8 (3.7)
Group A streptococci	5 (2.3)		
Group C streptococci	4 (2.0)	Other	
<i>Streptococcus pneumoniae</i>	3 (1.4)	<i>Mycobacteria</i>	2 (1.0)
<i>Enterococcus</i> spp.	9 (4.2)	<i>Candida</i> spp.	9 (4.2)
Other ^a	10 (4.7)	Fungus	2 (1.0)
B, Joints Affected in the Native Septic Arthritis Cohort			
Joint, No. (%)	All (n = 260)	<i>S. aureus</i> (n = 174)	Non- <i>S. aureus</i> (n = 86)
Knee	81 (31.1)	54 (31.0)	27 (31.4)
Shoulder	34 (13.0)	24 (13.8)	10 (11.6)
Hip	25 (9.6)	14 (8.0)	11 (12.8)
Sternoclavicular	22 (8.5)	10 (5.7)	12 (14.0)
Wrist	23 (8.9)	13 (7.4)	10 (11.6)
Sacroiliac	16 (6.2)	14 (8.0)	2 (2.3)
Ankle	14 (5.3)	11 (6.3)	3 (3.5)
Facet	11 (4.2)	10 (5.7)	1 (1.2)
Elbow	9 (3.4)	8 (4.6)	1 (1.2)
Symphysis pubis	2 (1.0)	1 (0.01)	1 (1.2)
MCP	9 (3.4)	7 (4.0)	2 (2.3)
MTP	5 (1.9)	3 (1.7)	2 (2.3)
Other	11 (4.2)	5 (2.9)	4 (4.7)

Abbreviations: MCP, metacarpophalangeal joint; MRSA, methicillin-resistant *S. aureus*; MTP, metatarsophalangeal joint.

^aOrganisms in this category had ≤2 occurrences and included diptheroids, *S. intermedius*, *P. acnes*, *S. anginosus*, group G & group F streptococci.

^bOrganisms in this category had ≤2 occurrences and included *E. corrodens*, *H. influenzae*, *E. cloacae*, *Serratia* spp., *M. morgani*, *P. multocida*.

followed by the sternoclavicular joint (12/215) and the hip (11/215). There were 35 cases of polyarticular native septic arthritis, with 25 being in the *S. aureus* group. No joints were excluded.

Patient Demographics and Clinical Characteristics

Table 2 summarizes the demographic and clinical characteristics of our study population. The average age of presentation (SD) was 53.6 (16.6) years. For every 10-year increase in age, the odds of native septic arthritis with *S. aureus* decreased by 28% compared with other organisms (OR, 0.72; 95% CI, 0.60–0.87; $P = .001$). *S. aureus* was associated with Caucasian race as opposed to all other races (OR, 3.42; 95% CI, 1.41–8.28; $P = .006$). Other risk factors associated with *S. aureus* included history of IDU (OR, 4.33; 95% CI, 1.74–10.81; $P = .002$) and current IDU (OR, 3.45; 95% CI, 1.11–14.30; $P = .029$). For a 1-unit increase in CCI, the odds of *S. aureus* decreased by 18% (OR, 0.82; 95% CI, 0.73–0.91; $P = .0004$). Interestingly, immunosuppression was associated with lower odds of *S. aureus* native septic arthritis compared with non-*S. aureus* organisms (OR, 0.30; 95% CI, 0.16–0.56; $P = .0002$). Compared with other organisms, *S. aureus* infections were more commonly associated with concomitant spinal osteomyelitis (OR, 5.64; 95% CI, 2.08–19.23; $P = .0001$).

Treatment and Outcomes

Treatment and outcomes are summarized in Table 3. Overall, 15% (32/215) of patients underwent extended antibiotic treatment, while 10% (22/215) of patients had their initial antibiotic switched to another agent. The most common reason for switching in the *S. aureus* group was attributed to an adverse event associated with the original antibiotic (13/19, 68%).

Vancomycin was attributed to 3 of these adverse events. Other reasons included inadequate treatment (3/19, 16%), social factors such as injection drug use requiring discharge on oral medication (2/19, 11%), and lack of insurance coverage (1/19, 5%). All 3 instances of antibiotic switching in the non-*S. aureus* group were attributed to an antibiotic-associated adverse event. Switching antibiotics during treatment was more commonly associated with *S. aureus* native septic arthritis (OR, 3.92; 95% CI, 1.01–21.38; $P = .032$) compared with native septic arthritis with other organisms. A higher number of relapses was found in patients with *S. aureus* compared with patients with non-*S. aureus* (OR, 4.40; 95% CI, 1.25–23.85; $P = .015$). We were not able to detect a statistically significant association between hospital mortality, readmission, recurrence, or length of stay and having *S. aureus* vs non-*S. aureus* native septic arthritis.

Comparison Between Methicillin-Sensitive and Methicillin-Resistant *S. aureus*

We compared demographics and risk factors between MSSA and MRSA native septic arthritis. MRSA was cultured in 50 patients, while MSSA was cultured in 88 patients. Individuals who smoked had increased odds of developing MRSA as opposed to MSSA native septic arthritis (OR, 2.22; 95% CI, 1.07–4.62; $P = .033$). For every 10-year increase in age, the odds of MRSA native septic arthritis decreased by 20% compared with MSSA native septic arthritis (OR, 0.80; 95% CI, 0.64–1.00; $P = .050$). Patients with a recurrent infection had 8 times the odds of having MRSA vs MSSA, compared with patients without a recurrent infection (OR, 8.06; 95% CI, 1.52–81.21; $P = .009$). The median length of stay for MRSA vs MSSA native septic arthritis (interquartile range [IQR]) was found to be 16.5 (15.0) days vs 12.0 (13.5) days, respectively. Length of stay was longer in individuals with MRSA (OR, 1.03; 95% CI, 1.00–1.05; $P = .036$).

Table 2. Comparison of Patient Demographics and Clinical Characteristics Between *S. aureus* and Non-*S. aureus* Native Septic Arthritis

	All (n = 215)	<i>S. aureus</i> (n = 138)	Non- <i>S. aureus</i> (n = 77)	OR	95% CI	P Value
Demographics						
Age, mean (SD), y	53.6 (16.6)	50.6 (16.0)	58.9 (16.4)	0.72 ^a	(0.60–0.87)	.001
Caucasian, No. (%) ^b	177 (88)	119 (93)	58 (79)	3.42	(1.41–8.28)	.006
Female gender, No. (%)	79 (37)	51 (37)	28 (36)	1.03	(0.58–1.83)	.931
BMI, mean (SD), kg/m ²	29.3 (8.6)	29.8 (8.0)	28.4 (9.6)	1.02	(0.99–1.06)	.260
Clinical characteristics						
Smoking, No. (%)	61 (28)	45 (32)	16 (21)	1.84	(0.96–3.55)	.067
Alcohol use, No. (%)	18 (8)	13 (9)	5 (7)	1.50	(0.48–5.58)	.640
Current IDU, No. (%)	26 (12)	22 (16)	4 (5)	3.45	(1.11–14.30)	.029
History of IDU, No. (%)	43 (20)	37 (27)	6 (8)	4.33	(1.74–10.81)	.002
CCI, median (IQR)	2.0 (4.0)	2.0 (4.0)	4.0 (4.0)	0.82	(0.73–0.91)	.0004
Endocarditis, No. (%)	43 (20)	33 (24)	10 (13)	2.11	(0.97–4.55)	.058
Osteoarthritis, No. (%)	35 (16)	21 (15)	14 (18)	0.81	(0.38–1.70)	.573
Total immunosuppressed, No. (%)	54 (25)	23 (17)	31 (40)	0.30	(0.16–0.56)	.0002
Spinal osteomyelitis, No. (%)	44 (21)	39 (28)	5 (7)	5.64	(2.08–19.23)	.0001

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; IDU, injection drug use; IQR, interquartile range; OR, odds ratio.

^aOR calculated for a change of 10 years.

^bRace data were not available for every patient. For this category: all (n = 201), *S. aureus* (n = 128), non-*S. aureus* (n = 73).

Table 3. Comparison of Treatment and Outcomes Between *S. aureus* and Non-*S. aureus* Native Septic Arthritis

	All (n = 215)	<i>S. aureus</i> (n = 138)	Non- <i>S. aureus</i> (n = 77)	OR	95% CI	P Value
Treatment						
Antibiotic switching, No. (%)	22 (10)	19 (14)	3 (4)	3.92	(1.01–21.38)	.032
Antibiotic extension, No. (%)	32 (15)	19 (14)	13 (17)	0.79	(0.37–1.69)	.539
Antibiotic duration, median (IQR), wk	6.0 (0.0)	6.0 (0.0)	6.0 (2.0)	1.01	(0.93–1.11)	.776
Outcomes						
Hospital mortality, No. (%)	24 (11)	14 (10)	10 (13)	0.76	(0.32–1.80)	.527
Readmission, No. (%)	53 (25)	35 (25)	18 (23)	1.11	(0.58–2.14)	.746
LOS, median (IQR), d	12.0 (15.0)	13.5 (15.0)	11.0 (13.0)	1.01	(0.99–1.03)	.574
Recurrence, No. (%)	13 (6)	10 (7)	3 (4)	1.92	(0.48–11.21)	.501
Relapse, No. (%)	24 (11)	21 (15)	3 (4)	4.40	(1.25–23.85)	.015

Abbreviations: IQR, interquartile range; LOS, length of stay; OR, odds ratio.

MRSA Nasal Screening

A total of 116 patients with *S. aureus* native septic arthritis underwent MRSA nasal screening before or during index admission for septic arthritis, with a total of 138 recorded screens. Of the patients with MRSA native septic arthritis, 41 underwent MRSA nasal screening, with a total of 49 screens performed on these patients. In this group, 51% of screens were positive for MRSA native septic arthritis (25/49). Of the patients with MSSA native septic arthritis, 75 patients underwent MRSA nasal screening, with 89 screening procedures performed. In this group, 5.6% screened positive for MRSA. When screening was performed before index admission, the sensitivity and specificity were 0.42 and 0.91, respectively. The positive predictive value was 0.80, while the negative predictive value was 0.66. When screening was performed during the index admission for native septic arthritis, the sensitivity was 0.59 and the specificity was 0.96. The positive predictive value was found to be 0.85, while the negative predictive value was found to be 0.84.

DISCUSSION

Although *S. aureus* is the most common cause of native septic arthritis in adult populations around the world [2–8], few studies have investigated the risk factors and outcomes associated with these infections over the past decade in US populations. Our study sought to characterize native septic arthritis risk factors and outcomes at our institution in Western Pennsylvania, an area impacted by the opioid epidemic. In 2017, Pennsylvania had the third highest rate of age-adjusted drug overdose deaths between 2013 and 2017 in the country according to the CDC [10]. Given the increasing incidence of community- and hospital-acquired MRSA infections [9], we also evaluated the common practice of MRSA nasal screening in predicting MRSA native septic arthritis.

Our study found that current injection drug use and history of injection drug use were associated with higher odds of *S. aureus* native septic arthritis, as opposed to native septic arthritis with other organisms. Native septic arthritis is known to be associated with injection drug use via hematogenous spread of

organisms from the skin or injected material. Since the 1980s, *S. aureus* has become the most common cause of septic arthritis in people who use injection drugs and is thought to be related to the rise of heroin use and its method of preparation [14]. The opioid epidemic's effect on Western Pennsylvania may contribute to this finding, which was also reinforced in our study. The trend toward an overall increasing incidence of *S. aureus* infections in the hospital and community may also play a role [9]. The high amount of injection opioid use in this region may put individuals who inject drugs at higher risk for *S. aureus* native septic arthritis. This may be useful in guiding empiric treatment in this patient population in regions with high rates of injection drug use. *S. aureus* native septic arthritis was also associated with spinal osteomyelitis in our study, which is known to be associated with injection drug use [15]. We believe that the increased propensity for *S. aureus* septic arthritis, spinal osteomyelitis, and other *S. aureus* infections in injection drug users provides further support to the argument for harm reduction policies and interventions such as safe injection sites and needle exchanges, as well as allocations of increased resources toward opioid treatment programs as ways to reduce morbidity and mortality from injection drug use.

Interestingly, being immunocompromised was not associated with a higher risk of acquiring *S. aureus* native septic arthritis compared with native septic arthritis with other organisms. This may be because immunocompromised individuals are at higher risk for less common or opportunistic organisms [16], which our sample may reflect. However, it should be noted that the number of immunosuppressed patients in our population was relatively small, which may make our observations less robust than other dedicated studies involving native septic arthritis and immunosuppression.

The average age in our cohort was 53 years, which seems to follow overall demographic trends of septic arthritis presenting at an average age of 51 in 2002 [15]. However, it should be noted that for patients with non-*S. aureus* native septic arthritis, the age of presentation was found to be significantly higher. Interestingly, we also found that patients with fewer

comorbidities had significantly higher odds of infection with *S. aureus*. We also found that *S. aureus* was associated with being Caucasian, which is likely representative of the local population in Western Pennsylvania. Combined with our above findings, this may reinforce the notion that the opioid epidemic, which has affected primarily a younger patient population with fewer comorbidities, has affected the demographic risk factors associated with native septic arthritis.

To our knowledge, this is the first study to investigate the relationship of joint culture positivity and MRSA nasal screening in MRSA native septic arthritis. We found that MRSA nasal screening has a low sensitivity (59%) and high specificity (96%) for MRSA native septic arthritis during index admission. The negative predictive value (NPV) and positive predictive value (PPV) were 84% and 85%, respectively. These values were lower if screening was done before admission. Of note, Uckay and colleagues' study of MRSA nasal screening in *S. aureus* prosthetic joint infection (PJI) also found that screening by culture poorly predicted the presence of MRSA in individuals with *S. aureus* PJI, with a sensitivity of 58%, specificity of 90%, PPV of 79%, and NPV of 76% [17]. The poor correlation with MRSA colonization and MRSA native septic arthritis may in part be due to the fact that joint spaces are closed structures that typically lack direct communication with the overlying skin, where MRSA often colonizes. Furthermore, the presence of MRSA in the nares may not be fully representative of MRSA colonization in other parts of the body, such as the skin, through which other mechanisms of infection could be introduced (ie, joint injections, injection drug use) [11, 15]. In support of this concept, MRSA nasal screening has the most utility in ruling out MRSA pneumonia (NPV >95%) with evidence for use in narrowing antibiotic treatment in pneumonia [11, 18]. In part, this may be related to the nares being in communication with the lungs. However, given that MRSA colonization is generally associated with increased risk of MRSA infection [19], we believe it is reasonable to use a positive MRSA nasal screen as an adjunct to clinical suspicion in ruling in MRSA native septic arthritis while sterile site cultures of blood, synovial fluid, or joint tissue samples are pending. This screen may be more clinically applicable and useful for selection of empiric antibiotics targeted toward MRSA when used in conjunction with a formal assessment of other MRSA risk factors [11] but cannot be reliably used alone to rule in/out MRSA native septic arthritis. Furthermore, this screen should not be used to de-escalate MRSA-targeted therapy, such as in the case of pneumonia. Sterile site cultures are necessary for targeted septic arthritis treatment.

We found that *S. aureus* native septic arthritis was more commonly associated with antibiotic switching during treatment and relapse of infection when compared with native septic arthritis with other organisms. Although our confidence intervals showed statistical significance for both outcomes, there

is a range of variability that requires cautious interpretation of these results. However, we have several plausible explanations for these differences. A higher rate of infection relapse in our *S. aureus* cohort may be related to higher rates of IDU, as repeated injections after the original infection may reseed the joint. Of the patients who had antibiotics switched, the majority were due to a side effect of the original antibiotic. Other reasons included social factors, such as lack of insurance coverage and inadequacy of original treatment, as well as the need to convert patients who were actively using injection drugs to an oral regimen for discharge.

In comparing MRSA native septic arthritis with MSSA native septic arthritis, we found that MRSA was significantly associated with smoking, which is a known risk factor for MRSA colonization [20]. Perhaps targeted MRSA nasal screening and decolonization of inpatients identified as smokers with other risk factors for septic arthritis (eg, bacteremia, IDU) could be useful in preventing these infections.

In our study, the age of presentation of MRSA native septic arthritis was found to be lower than that of MSSA, although this association was not deemed to be statistically significant. Prior literature also has not supported a clear association between age and MRSA vs MSSA infection across multiple infection types, including pneumonia and infective endocarditis [21–23]. Notably, a prior review of the literature comparing MRSA septic arthritis with MSSA septic arthritis did show that MRSA patients tended to be older than those with MSSA in several studies [24]. However, this review spanned several different countries. Our results may be reflective of our local population's relatively high rate of injection drug use, which may be contributing to a decrease in age of presentation.

In our study, MRSA native septic arthritis was also associated with a slightly longer length of stay during index admission, with no significant differences detected between comorbidities (via CCI), antibiotic duration, or antibiotic extension between the 2 groups. This trend may reflect a delay in diagnosis or delay in starting the appropriate antibiotic in the MRSA group, which has been found to be more common in MRSA septic arthritis when compared with MSSA septic arthritis [25]. This further reinforces the need for prompt initiation empiric MRSA therapy in appropriate candidates and presents another target for future research.

There are several limitations to our study. First, it is a retrospective cohort analysis; therefore, we were not able to reliably assess risk. Data collection was at times limited by the availability of the medical record, and certain demographic criteria were missing for several of our patients in this study. Furthermore, the study sample and local population are primarily Caucasian with high local rates of injection drug use. Therefore, the results may not be generalizable to racially or ethnically diverse populations in the United States. Regarding MRSA nasal screening, positive and negative predictive values

depend on local prevalence of MRSA [11]. Our results will not be generalizable to populations with different MRSA prevalence rates. Additionally, our institution used chromogenic culture instead of polymerase chain reaction for MRSA nasal screening during the time period of the study. Generally, culture is subject to more variability depending on time, initiation of antibiotics, and contamination of the sample [11]. Finally, we did not have standardized time periods for pre-admission screening, nor did we account for the presence of antibiotic initiation during admission screening, which may affect the reliability of the screening results.

Our study sought to characterize native septic arthritis at our institution in Western Pennsylvania, an area deeply affected by the opioid epidemic. Our findings regarding *S. aureus* native septic arthritis will have the most relevance in clinical practice, as *S. aureus* is the most common organism causing these infections. We believe that the ongoing opioid epidemic may be contributing to a demographic shift in native septic arthritis to younger, healthier individuals. We found that *S. aureus* native septic arthritis has unique risk factors compared with native septic arthritis with other organisms, including IDU and spinal osteomyelitis, supporting this overall conclusion. With these risk factors in mind, we hope that these data can help guide clinical suspicion for native septic arthritis in patients with these risk factors, direct further research in selection of empiric therapy, and help guide harm reduction policy. Further investigation with larger samples will be needed to better characterize these risk factors and identify other risk factors in more diverse populations. Regarding treatment, the antibiotics used for *S. aureus* native septic arthritis may be more likely to result in adverse events or necessitate an alteration in treatment for social reasons. In identifying these challenges, there is an opportunity to investigate the optimization of treatment regimens to limit morbidity and establish follow-up that meets social needs. Finally, we believe that MRSA nasal screening may be a useful adjunct in ruling in MRSA native septic arthritis. Further research will be needed to determine how this screen can be combined with clinical risk factors to be more clinically useful as a predictive tool and to guide empiric treatment decisions.

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Patient consent. This study was approved by the University of Pittsburgh's Institutional Review Board and conforms to ethical

standards. As it was based on retrospective chart review, patient consent was not needed.

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