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RESEARCH ARTICLE

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The AO trauma CPP bone infection registry: Epidemiology and outcomes of *Staphylococcus aureus* bone infection

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Abstract

Bone infection represents a serious complication of orthopedic surgery and *Staphylococcus aureus* is the most common pathogen. To improve the understanding of host-pathogen interaction, we developed a biospecimen registry (*AO Trauma CPP Bone Infection Registry*) to collect clinical data, bacterial isolates, and serum from patients with *S. aureus* bone infection. A prospective multinational registry with a

Abbreviations: AEs, adverse events; FRI, fracture-related infection; FU, follow-up; Katz ADL, Katz Index of independence in activities of daily living; LMIC, low- and middle-income countries; MCS, mental component summary scores; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; PCS, physical component summary scores; PMS, Parker Mobility Score; SD, standard deviation; SF-36, Short Form-36.

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12-month follow-up was created to include adult patients (18 years or older) with culture-confirmed *S. aureus* infection in long bones after fracture fixation or arthroplasty. Baseline patient attributes and details on infections and treatments were recorded. Blood and serum samples were obtained at baseline, 6, and 12 months. Patient-reported outcomes were collected at 1, 6, and 12 months. Clinical outcomes were recorded. Two hundred and ninety-two patients with fracture-related infection (n = 157, 53.8%), prosthetic joint infection (n = 86, 29.5%), and osteomyelitis (n = 49, 16.8%) were enrolled. Methicillin-resistant *S. aureus* was detected in 82 patients (28.4%), with the highest proportion found among patients from North American sites (n = 39, 48.8%) and the lowest from Central European sites (n = 18, 12.2%). Patient outcomes improved at 6 and 12 months in comparison to baseline. The SF-36 physical component summary mean (95% confidence interval) score, however, did not reach 50 at 12 months. The cure rate at the end of the study period was 62.1%. Although patients improved with treatment, less than two-thirds were cured in 1 year. At 12-month follow-up, patient-reported outcome scores were worse for patients with methicillin-resistant *S. aureus* infections.

KEYWORDS

bone infection registry, fracture-related infection, MRSA, implant-related infection, *Staphylococcus aureus*

1 | INTRODUCTION

Infection represents a feared complication after orthopedic surgery.[1] The emergence of multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) have made infection treatment more challenging.[2] Multiple revision surgeries and long-term antimicrobial therapy are often needed to treat infection and restore function. Although surgical treatment options have improved over time, a considerable knowledge gap remains with respect to the relationship between treatment protocols, risk factors, and patient outcomes.[3,4]

A recently published systematic literature review (93 studies and 3701 patients) analyzed the treatment concepts and outcomes of fracture-related infection (FRI).[5] The authors reported an overall treatment success rate of 85% and a recurrence rate of 9%. This review underscored the heterogeneity in treatment protocols and the lack of accepted standardized outcome parameters (eg, quality of life) and showed that study of critical data such as patient factors, causative pathogens, and treatment details were needed for a better understanding of the relationship between FRI treatment protocols and patient outcomes. Further, the 2018 International Consensus Meeting on Musculoskeletal Infection (ICM 2018), comprised of 869 delegates from 92 countries,[6] failed to reach an agreement that "moderate" evidence exists on the subjects of immunotherapy and immunoprophylaxis for the treatment of implant-associated infections, and concluded that the elucidation of patient-specific host-pathogen interactions is a research priority in this field.[7]

To help understand the interplay among patient demographics, comorbidities, treatment modalities, patient-specific host immunity against the causal pathogen(s), and outcomes, we established an international multicenter biospecimen registry of *S. aureus* infection in long bones and joints (the *AO Trauma CPP Bone Infection Registry*) to collect clinical data, bacterial isolates, whole blood, and sera. The development and challenges in setting up this registry have been reported,[8] and the manuscript on the microbiological and immunological results of this registry has been submitted for publication. The aim of this article is to describe the results of the *AO Trauma CPP Bone Infection Registry*: its patient population, baseline characteristics, infection details, cryopreserved biomaterials, treatment details, complications, functional outcomes, and quality of life after treatment.

2 | METHODS

The study was a prospective, observational, nonrandomized case-series of patients with bony infections (registered in ClinicalTrials.gov: NCT01677000). Study conduct, data management, patient consent (including the use of collected biomaterials for future studies), and ethics approval were as described previously.[8] Baseline assessments were collected when patients consented to participate in the study. The follow-up (FU) period was 12 months with planned visits at 1, 6, and 12 months. The study was approved by our University Institutional Review Board and at each site's local ethics committee. Written informed consent was obtained from all individual participants included in the study. Level of evidence 2b, prognostic study. The AO Foundation via the AO Trauma Clinical Priority Program on "Bone Infection" funded this study.

2.1 | Inclusion and exclusion criteria

Adult patients (18 years or older) with confirmed *S. aureus* (either methicillin-resistant or sensitive) infection involving a long bone (femur, tibia, fibula, humerus, radius, ulna, and clavicle) due to fracture fixation, osteomyelitis, or arthroplasty were eligible[8] regardless of the stage of disease progression and prior treatment history. *S. aureus* infection was confirmed by positive deep wound cultures from baseline examinations or by a prior definitive diagnosis of ongoing *S. aureus* infection (deep wound culture) from the surgical site by the treating surgeon. Prisoners or patients unable to give consent or attend the FU visits were excluded. Patients with active substance abuse that would preclude reliable assessments were excluded.

2.2 | Outcome measures

Patient attributes, medical history, comorbidities (Charlson comorbidity index),[9] medications, treatment approaches, and hospital course were recorded at baseline. Nasal swabs, deep wound cultures, serum, and whole blood samples were taken only at baseline; laboratory blood tests performed through the study sites were recorded. Serum samples collected for later testing in the central laboratory were obtained at baseline, 6, and 12 months. Short Form-36 version 2 (SF-36 v2),[10,11] Parker Mobility Score (PMS),[12] and Katz Index of independence in activities of daily living (Katz ADL) questionnaires[13,14] were used to assess patients' physical and mental health, their mobility, and their degree of independence at baseline and at all FU visits.

All patients received standard care chosen by their treating surgeon. Procedure-related adverse events (AEs) such as complications caused by collection of blood, nasal, and aerobic bacterial samples were documented. In-hospital complications that led to prolonged hospitalization or readmission were documented in the complication form; predefined events of medical relevance that required hospital admission or prolonged hospitalization were also recorded. Other AEs as defined by ISO 14155 were not recorded.

2.2.1 | Short Form-36

SF-36 questionnaire consists of 36 questions in eight different scales assessing both physical and mental health status.[10,11] The scores range from 0 to 100 with higher scores representing better health status.

2.2.2 | Parker Mobility Score

The PMS assesses patient mobility. The final score ranges from 0 to 9 points, with higher scores indicating higher function.[12] If any of the three questions were missing, the total score was also set to missing.

2.2.3 | Katz Index of independence in activities of daily living

Katz ADL is a 6-item questionnaire that assesses the independence in activities of daily living (bathing, dressing, toileting, transferring, continence, and feeding).[13,14] If any of the six items were missing, the total grade was also marked as missing.

2.2.4 | Healing status

Healing status was recorded at each FU as cured, healing, or other by the individual investigational sites according to their standard of care.

2.3 | Establishment of the annotated biorepository and clinical laboratory tests

S. aureus strains were identified from the wound samples taken at baseline, and characterized as MRSA, and/or methicillin-sensitive *S. aureus* (MSSA) by local laboratories. The individual strains were cultured, cryopreserved at −80°C, and labeled with the patient's alphanumeric registry number for subsequent analyses. Serum samples (~10 mL per patient) collected at baseline and FU visits were cryopreserved at −80°C and labeled with the alphanumeric registry number for subsequent analyses.

Descriptive analyses of the level of glycated hemoglobin, C-reactive protein, white blood cell count, and erythrocyte sedimentation rate were performed by the local laboratories. Since these values were not particularly informative, they are not presented in this study.

2.4 | Statistical analysis

The current study aimed to characterize the patient demographics, disease and treatment characteristics, and clinical outcomes, therefore no sample size calculation was required. The target sample size of 300 was calculated to allow the possibility of building a prognostic model with nine variables of interest assuming a binary outcome with an incidence of 30 events per 100 patients.

The “full analysis population” was defined as all eligible patients who gave written consent and commenced treatment within the study. The “per-protocol population” was defined as patients who completed all FU visits.

Patient baseline characteristics, type of infection, hospitalization, and treatment details were analyzed using descriptive analyses. Continuous variables were summarized using mean and standard deviation (SD) for normally distributed data, whereas median and interquartile range (IQR) as well as minimum and maximum, were used for nonnormally distributed data. Number and percentages were used for categorical variables.

SF-36 and PMS scores were analyzed using both descriptive statistics and mixed-effects models for repeated measures with an

unstructured covariance. Katz ADL scores were analyzed by descriptive statistics and the changes from baseline were analyzed using the Wilcoxon sign rank test. Outcome scores were analyzed for both the full analysis population and the per-protocol population.

The aggregated SF-36 physical and mental component summary scores (PCS and MCS, respectively) were transformed using the norm-based scoring with mean = 50 and SD = 10 using the US population norm because its documentation of the algorithm is the best. In short, all scores above 50 can be interpreted as being above the US population average and all scores below 50 can be interpreted as being below the US population average. Although our study population was global, this norm-based scoring helped simplify the interpretation of the scores. The questionnaire used for this study was the standard (4-week recall) form.

The healing status was analyzed for both full analysis population and complete cases, that is, patients whose assessment was available at all FU visits. SAS software (V9.4 Analytics Software & Solutions, Cary, NC) was used to perform all statistical analyses.

3 | RESULTS

Patients were enrolled between November 2012 and August 2017 in 18 centers from ten countries in Europe (Germany, Switzerland, Austria, Belgium, and Denmark), Asia (China and Japan), North America (the United States and Canada), and South America (Argentina). Three hundred and sixty-two patients were consented for the study of which 48 did not commence treatment in the study (Figure 1). The culture results were negative for *S. aureus* in another 22 patients. These patients were not included in this registry. In total, 292 patients met inclusion criteria, gave written consent, and commenced treatment within the study (the full analysis population).[8] Of the 292 patients, 147 (50.4%) were recruited from Europe, 80 (27.4%) from North America, 62 (21.2%) from Asia, and 3 (1.0%) from South America. A patient recruitment diagram shows the details of patient recruitment from the initial screening to the end of the study (Figure 1). A detailed description of patient dropouts and deaths is provided in our previous publication.[8]

3.1 | Baseline information and infection details

The patient population was predominantly male (n = 203, 69.5%), and otherwise healthy as indicated by the low Charlson comorbidity index (median = 0.0, range = 0.0-10.0) (Table 1). More than half of the patients (n = 175; 59.9%) had previously (within the 3 years prior to their inclusion in the current study)

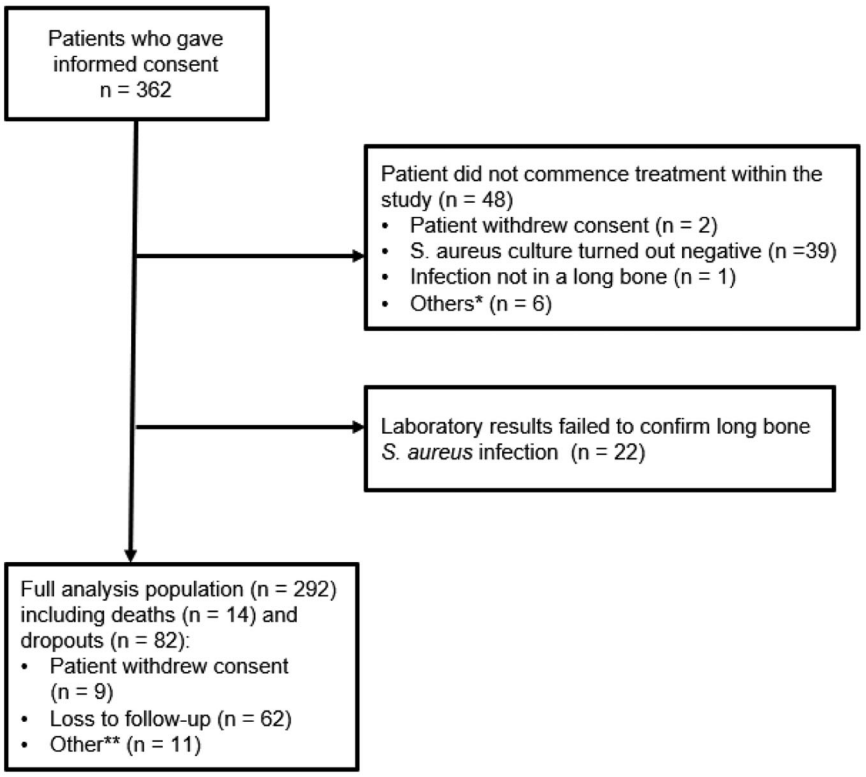

FIGURE 1 Patient recruitment diagram* Reasons include: infection did not involve a long bone, culture-negative for *Staphylococcus aureus* infection, and patient moved to a different hospital** Reasons include: patients did not plan on coming back for follow-ups, patient withdrawal, insurance coverage issue, and unknown exclusion

TABLE 1 Patient characteristics according to healing status at 1-year follow-up (FU) (full analysis population with healing status at 1 year available)

Variables	Healing status at 1 year FU (cured vs healing/other) Healing/other N = 72	Cured N = 118	Total N = 190
Age, y[a]			
n	72	118	190
Mean (SD)	49.0 (16.3)	52.7 (16.0)	51.3 (16.2)
Median (Q1; Q3)	50.0 (40.0; 60.5)	51.0 (43.0; 64.0)	51.0 (41.0; 62.0)
Min; max	18.0; 93.0	18.0; 85.0	18.0; 93.0
Gender, n (%)	72	118	190
Female	26 (36.1)	33 (28.0)	59 (31.1)
Male	46 (63.9)	85 (72.0)	131 (68.9)
Body mass index, kg/m^2			
n	72	117	189
Mean (SD)	28.5 (8.6)	27.7 (6.1)	28.0 (7.2)
Median (Q1; Q3)	26.0 (22.6; 32.8)	26.9 (23.4; 30.9)	26.1 (23.4; 31.5)
Min; max	16.6; 68.1	18.0; 50.4	16.6; 68.1
Body mass index (kg/m^2), n (%)	72	117	189
<18.5	5 (6.9)	1 (0.9)	6 (3.2)
18.5 to <25.0	23 (31.9)	47 (40.2)	70 (37.0)
25.0 to <30.0	21 (29.2)	32 (27.4)	53 (28.0)
30.0 to <35	9 (12.5)	20 (17.1)	29 (15.3)
35.0 to <40	9 (12.5)	12 (10.3)	21 (11.1)
≥40	5 (6.9)	5 (4.3)	10 (5.3)
Body mass index (kg/m^2), n (%)	72	117	189
<25.0	28 (38.9)	48 (41.0)	76 (40.2)
25.0 to <30.0	21 (29.2)	32 (27.4)	53 (28.0)
30.0 to <35	9 (12.5)	20 (17.1)	29 (15.3)
≥35	14 (19.4)	17 (14.5)	31 (16.4)
Origin of infection, n (%)	72	118	190
Osteomyelitis	12 (16.7)	18 (15.3)	30 (15.8)
Fracture fixation infection	39 (54.2)	75 (63.6)	114 (60.0)
Prosthetic joint infection	21 (29.2)	25 (21.2)	46 (24.2)
Diabetes, n (%)	72	118	190
No	64 (88.9)	94 (79.7)	158 (83.2)
Yes	5 (6.9)	17 (14.4)	22 (11.6)
Not assessed	3 (4.2)	7 (5.9)	10 (5.3)
Diabetes, n (%)	69	111	180
No	64 (92.8)	94 (84.7)	158 (87.8)
Yes	5 (7.2)	17 (15.3)	22 (12.2)
Charlson comorbidity index[b]			
n	65	111	176
Mean (SD)	0.6 (0.9)	0.6 (1.3)	0.6 (1.2)
Median (Q1; Q3)	0.0 (0.0; 1.0)	0.0 (0.0; 1.0)	0.0 (0.0; 1.0)
Min; max	0.0; 3.0	0.0; 6.0	0.0; 6.0
Charlson comorbidity index[b], n (%)	65	111	176
0	40 (61.5)	80 (72.1)	120 (68.2)
1	12 (18.5)	19 (17.1)	31 (17.6)
2	11 (16.9)	3 (2.7)	14 (8.0)
3	2 (3.1)	1 (0.9)	3 (1.7)
4	0 (0.0)	5 (4.5)	5 (2.8)
5	0 (0.0)	0 (0.0)	0 (0.0)
6	0 (0.0)	3 (2.7)	3 (1.7)
8	0 (0.0)	0 (0.0)	0 (0.0)
10	0 (0.0)	0 (0.0)	0 (0.0)
Region, n (%)	72	118	190
Central Europe	26 (36.1)	75 (63.6)	101 (53.2)
Asia	20 (27.8)	27 (22.9)	47 (24.7)
America	26 (36.1)	16 (13.6)	42 (22.1)

[a]Calculated as (date of informed consent minus date of birth) divided by 365.25 (subsequently rounded off); date of birth was approximated using year of birth and 30th June as the day and month.
[b]The minimum possible score is 0 and maximum of 29. A higher score indicates a greater burden of comorbid conditions.

undergone orthopedic treatment related to the bone infection with a median number of treatments of 2.0 (range = 1.0-20.0).

The origin of infection was fracture fixation for open or closed fracture (n = 157, 53.8%), prosthetic joint infection (PJI) (n = 86, 29.5%), or osteomyelitis (n = 49, 16.8%) (Table 1).

Aside from *S. aureus* infection (MSSA or MRSA), 46 patients (15.8%) had infections involving additional organisms. The proportion of MRSA infection was the highest in patients recruited from North American study sites (n = 39, 48.8%), followed by the ones recruited from Asian study sites (n = 25, 40.3%) and lowest in European sites (n = 18, 12.2%).

3.2 | Hospitalization and treatment details

The median time from onset of infection symptoms until baseline hospitalization was 14 days. Urgent (within 1 day) hospital admission was required in 43.5% (n = 127) and emergency (same day) admission in 21.6% (n = 63) and 60% of the patients had already had some orthopedic treatment related to infection prior to recruitment. (Table 2). The remaining patients (n = 102; 34.9%) were admitted semi-electively. Only three patients (1.0%) received an ambulatory treatment. The median time between admission and surgery was one day (Table 2). All but seven patients (2.4%) received surgical treatment; in more than half of the cases (n = 151; 53.2%) a multistage procedure was used. Surgical debridement was performed in most cases (n = 264; 92.6%). The mean duration of hospital stay was 29.9 days (SD = 31.9), ranging from one to 247 days. Systemic antibiotics were prescribed for all but eleven patients, and the median (Q1; Q3) treatment length was 24.0 (12.0; 42.0) days. Among the 277 patients with recorded antibiotic treatment details, the predominant route of administration was intravenous (n = 251; 90.6%). Treatment details are summarized in Table 2.

TABLE 2 Details of infection, hospitalization, and treatment

Infection and hospitalization details	
Onset of symptoms of infection (days before hospital admission), n	292
Mean (SD)	359.2 (1795.7)
Median (Q1; Q3)	14.0 (4.0; 80.0)
Min; max	0.0; 17885.0
Origin of infection, n (%)	292
Osteomyelitis	49 (16.8)
Fracture fixation infection	157 (53.8)
Prosthetic joint infection	86 (29.5)
Days between admission and surgery (days), n	285
Mean (SD)	4.8 (17.3)
Median (Q1; Q3)	1.0 (0.0; 4.0)
Min; max	0.0; 230.0
Duration of hospital stay (nights), n	290
Mean (SD)	29.9 (31.9)
Min; max	0.0; 247.0
Admission type, n (%)	292
Emergency	63 (21.6)
Urgent	127 (43.5)
Elective	102 (34.9)
Discharge destination n (%)	289
Home	215 (74.4)
Nursing home	40 (13.8)
Residential home	3 (1.0)
Hospice care	1 (0.3)
Transfer to other hospital	30 (10.4)
Treatment details	
Duration of surgery (skin-to-skin time) (min), n	282
Mean (SD)	96.9 (68.7)
Median (Q1; Q3)	80.0 (43.0; 132.0)
Min; max	0.0; 539.0
Which surgical procedures were performed? n (%)	285
Debridement	264 (92.6)
Implant removal	132 (46.3)
Local antibiotic treatment	121 (42.5)
Spacer placement	78 (27.4)
Implant exchange	43 (15.1)
Amputation	1 (0.4)
Revision of fixation	14 (4.9)
Osteotomy	17 (6.0)
Other*	68 (24.1)

The lower leg (tibia/fibula) was the most frequently affected (n = 116; 40.7%) body region, followed by the knee (n = 60; 21.1%), the femur (n = 51; 17.9%), and the hip (n = 44; 15.4%). The infection was less commonly seen in the upper extremity (clavicle: n = 1, 0.4%; shoulder: n = 5, 1.8%; humerus: n = 10, 3.5%; forearm: n = 15, 5.3%). In 26 patients (8.9%), more than one body region was involved.

3.3 | Outcomes

Table 3 summarizes the results of the mixed-effects model analyses on the SF-36 and PMS scores of the full analysis population. At 1 month, both the SF-36 mean (95% confidence interval [CI]) PCS score (30.5 [29.5; 31.5]) and the PMS mean (95% CI) score (4.2 [3.9; 4.6]) were lower than the baseline scores (30.9 [29.7; 32.0] and 4.8 [4.4; 5.1], respectively); the difference was statistically significant for the PMS scores ($P = .002$), but not statistically significant for the SF-36 PCS scores ($P = .447$). At 6 months, the SF-36 mean (95% CI) scores were PCS, 35.5 (34.2; 36.7) and MCS, 47.1 (45.4; 48.7); by 12 months, these were 37.9 (36.4; 39.3) and 46.7 (45.0; 48.5), respectively; the improvements from baseline were statistically significant ($P < .001$). Both PCS and MCS mean (95% CI) scores at 12 months were lower than 50, that is, the US population norm.

Statistically significant improvements were also observed in PMS scores at 6 and 12 months.

Analyses performed on the data from the "per-protocol population" produced results with no qualitative differences from those performed on the data from the "full analysis population" (data not shown).

Table 4 summarizes the results of Katz ADL scores over the course of follow-up for patients with and without MRSA. Table 5 summarizes the changes in Katz ADL scores between FU visits and baseline using data from patients with scores available both at baseline and at the relevant follow-up. Similar to the results from SF-36 PCS and PMS, the mean (SD) score at 1 month (4.4 [2.0]) decreased slightly from the baseline (4.7 [1.9]), and as in the case of SF-36 PCS scores, the decrease was not statistically significant ($P = .070$) (Table 5). At 6 and 12 months (full analysis population) the mean (SD) scores rose from 4.6 (1.9) at baseline to 5.3 (1.5) and 5.5 (1.2), respectively ($P < .001$ in both cases). At the individual patient level, approximately half of the patients maintained their independence level at each FU; some became more independent at 6 and 12 months (n = 76, 38.4% and n = 71, 39.4%, respectively) whereas a few worsened and became more dependent (n = 20, 10.1% at 6 months and n = 15, 8.3% at 12 months) compared with baseline (Table 5).

Treating surgeons recorded the cure rate at 1, 6, and 12 months as 4.5% (12/265), 36.8% (78/212), and 62.1% (118/190), respectively. At one year, 75 (63.6%) of FRIs, 25 (21.2%) of PJI's, and 18 (15.3%) cases of osteomyelitis were described as cured (Table 1).

3.4 | In-hospital complications and rehospitalization

Forty-one patients experienced in-hospital complications that led to prolonged hospitalization or readmission; 10 patients died of such in-hospital complications and 14 patients who enrolled for the study died. The details of the patients who died are found in Table S1. The risk (% [95% CI]) of in-hospital complication was 14.1% (10.3; 18.7) based on the number of the full analysis population and 18.9% (13.9; 24.7) based on the sensitivity analysis (ie, analysis including only patients who either completed the 1-year FU or who experienced at least one in-hospital complication).

TABLE 3 SF-36 summary scores and Parker Mobility Score over follow-up

Outcome	Visit	n	Mean (95% CI)	Change (95% CI)	*P* value	MRSA vs no MRSA *P* value
SF-36 physical component summary (PCS)	Baseline	271	30.9 (29.7; 32.0)			
	1 month	253	30.5 (29.5; 31.5)	−0.4 (−1.4; 0.6)	.447	
	6 months	210	35.5 (34.2; 36.7)	4.6 (3.3; 5.9)	<.001	
	12 months	191	37.9 (36.4; 39.3)	7.0 (5.6; 8.4)	<.001	
SF-36 mental component summary (MCS)	Baseline	271	42.5 (40.8; 44.2)			
	1 month	253	43.1 (41.4; 44.8)	0.6 (−1.0; 2.1)	.458	
	6 months	210	47.1 (45.4; 48.7)	4.5 (2.9; 6.2)	<.001	
	12 months	191	46.7 (45.0; 48.5)	4.2 (2.5; 6.0)	<.001	
SF-36 PCS No MRSA	Baseline	200	31.5 (30.2; 32.9)			.047
	1 month	187	31.2 (30.0; 32.3)	−0.4 (−1.6; 0.9)	.574	.037
	6 months	156	36.5 (35.0; 38.0)	5.0 (3.5; 6.5)	<.001	.018
	12 months	144	39.3 (37.6; 41.0)	7.7 (6.1; 9.4)	<.001	.003
SF-36 PCS + MRSA	Baseline	79	29.0 (26.9; 31.1)			
	1 month	71	28.9 (27.0; 30.7)	−0.1 (−2.1; 1.8)	.902	
	6 months	55	33.0 (30.5; 35.5)	4.0 (1.6; 6.5)	.001	
	12 months	49	34.3 (31.5; 37.1)	5.3 (2.6; 8.0)	<.001	
SF-36 MCS No MRSA	Baseline	200	43.3 (41.3; 45.3)			
	1 month	187	43.5 (41.4; 45.5)	0.2 (−1.7; 2.0)	.844	.097
	6 months	156	47.7 (45.8; 49.7)	4.5 (2.6; 6.4)	<.001	.423
	12 months	144	47.6 (45.5; 49.6)	4.3 (2.2; 6.3)	<.001	.167
						.130
SF-36 MCS + MRSA	Baseline	79	40.1 (37.0; 43.3)			
	1 month	71	41.9 (38.6; 45.2)	1.7 (−1.2; 4.7)	.244	
	6 months	55	45.1 (42.0; 48.3)	5.0 (1.9; 8.1)	.002	
	12 months	49	44.5 (41.1; 47.9)	4.4 (1.0; 7.7)	.011	
Parker Mobility Score	Baseline	285	4.8 (4.4; 5.1)			
Summary	1 month	259	4.2 (3.9; 4.6)	−0.5 (−0.9; −0.2)	.002	
	6 months	210	6.2 (5.9; 6.6)	1.5 (1.0; 1.9)	<.001	
	12 months	187	6.9 (6.6; 7.2)	2.1 (1.8; 2.5)	<.001	
	Baseline	204	5.0 (4.6; 5.4)			
Parker Mobility Score	1 month	184	4.4 (3.9; 4.8)	−0.7 (−1.0; −0.3)	.001	
No MRSA	6 months	153	6.4 (6.0; 6.8)	1.4 (0.9; 1.9)	<.001	
	12 months	137	7.1 (6.8; 7.5)	2.1 (1.7; 2.5)	<.001	
Parker Mobility Score	Baseline	78	4.0 (3.3; 4.7)			.013
With MRSA	1 month	72	3.9 (3.3; 4.6)	−0.1 (−0.7; 0.6)	.812	.273
	6 months	56	5.8 (5.1; 6.4)	1.8 (1.0; 2.6)	<.001	.110
12 months	48	6.3 (5.7; 6.9)	2.3 (1.6; 3.1)	<.001	.028	

Note: Estimates, confidence intervals, and *P* values were derived from a mixed-effect model for repeated measures with an unstructured covariance

Not counting the hospitalization at baseline, patients were re-hospitalized due to infection at a median (Q1; Q3) of 1.0 (0.0; 1.0) time during the study period and received surgical treatments at a median (Q1; Q3) of 1.0 (0.0; 3.0) time. The overall risk (% [95% CI]) of patients being rehospitalized during the study period was 53.8% (47.9; 59.6). Sensitivity analysis of patients who had completed the 1-year FU and/or with a record of rehospitalization showed a slightly higher rehospitalization risk of 63.4% (57.1; 69.4).

3.4.1 | Comparison of MSSA vs MRSA infections

The patient's age, body mass index, and Charlson Comorbidity Index did not differ between MSSA and MRSA infections.

At 12-month follow-up, 64.7% (90/139) of the MSSA infections and 57.1% (28/49) of the MRSA infections were cured ($P = .161$). The healing status did not differ between the two groups at 1- and 6-month follow-up (Table 6).

TABLE 4 KATZ ADL over follow-up for patients with and without MRSA (full analysis population)

	MRSA infection present?		
KATZ ADL sum score	No N = 207	Yes N = 82	*P* value
Baseline			.001§
n	203	76	
Mean (SD)	4.8 (1.8)	4.0 (2.1)	
Median (Q1; Q3)	6.0 (4.0; 6.0)	4.5 (2.0; 6.0)	
Min; max	0.0; 6.0	0.0; 6.0	
1 month			.004§
n	184	68	
Mean (SD)	4.7 (1.8)	3.8 (2.2)	
Median (Q1; Q3)	6.0 (3.5; 6.0)	4.0 (2.0; 6.0)	
Min; max	0.0; 6.0	0.0; 6.0	
6 months			.020§
n	150	54	
Mean (SD)	5.5 (1.3)	4.8 (1.9)	
Median (Q1; Q3)	6.0 (6.0; 6.0)	6.0 (4.0; 6.0)	
Min; max	0.0; 6.0	0.0; 6.0	
12 months			.175§
n	136	49	
Mean (SD)	5.6 (1.1)	5.3 (1.4)	
Median (Q1; Q3)	6.0 (6.0; 6.0)	6.0 (5.0; 6.0)	
Min; max	0.0; 6.0	0.0; 6.0	

Abbreviations: KATZ ADL, Katz Index of independence in activities of daily living; max, maximum; min, minimum; MRSA, methicillin-resistant *Staphylococcus aureus*.
§*P* value calculated according to the Wilcoxon sign rank test.

The PMS score and SF-36 outcomes with subscale and summary scores of the full analysis population are shown separately for patients with or without MRSA infection in Table 3.

The PMS scores (95% CI) were significantly lower in patients with a MRSA infection at baseline (4.0 [3.3; 4.7]) and 12-month follow-up (6.3 [5.7; 6.9]) compared with MSSA infections (5.0 [4.6; 5.4] [*P* = .013] and 7.1 [6.8; 7.5] [*P* = .028] respectively). At 1 and 6 months, the PMS scores did not differ between methicillin-resistant and susceptible infections.

The difference in SF-36-PCS scores between the two groups was statistically significant at baseline and all time points. The most pronounced differences were at 12 months, with the mean (95% CI) score of 34.3 (31.5; 37.1) for the MRSA positive patients in comparison to 39.3 (37.6; 41.0) for the MRSA negative patients (*P* = .003). The difference in MCS scores between the two groups was not statistically significant.

The mean (SD) Katz ADL scores were lower in MRSA infections at all time points, whereas the difference was significant only at baseline, 1- and 6-month (Table 4). Univariate analysis and multivariate logistic regression models were performed to look for predictors of being cured at 1 year (Tables 7 and 8). Age, gender, body mass index, Charlson score, diabetes, and origin of infection were not predictive for cure. Only treatment delivered in Europe was statistically significant as a predictor of 1-year cure on univariate and multivariate logistical regression models.

4 | DISCUSSION

The *AO Trauma CPP Bone Infection Registry* offers insight into the epidemiology and outcomes of *S. aureus* infections

TABLE 5 Change in Katz ADL sum scores

Variables	Baseline	1 month	Change from baseline	*P* value
KATZ ADL sum score				.070*
n	250	250	250	
Mean (SD)	4.7 (1.9)	4.4 (2.0)	−0.2 (2.0)	
Median (Q1; Q3)	6.0 (4.0; 6.0)	5.0 (3.0; 6.0)	0.0 (−1.0; 0.0)	
Min; max	0.0; 6.0	0.0; 6.0	−6.0; 6.0	
	Baseline	**6 months**	**Change from baseline**	***P* value**
KATZ ADL sum score				<.001*
n	198	198	198	
Mean (SD)	4.6 (1.9)	5.3 (1.5)	0.7 (2.1)	
Median (Q1; Q3)	6.0 (3.0; 6.0)	6.0 (5.0; 6.0)	0.0 (0.0; 2.0)	
Min; max	0.0; 6.0	0.0; 6.0	−6.0; 6.0	
	Baseline	**12 months**	**Change from baseline**	***P* value**
KATZ ADL sum score				<.001*
n	180	180	180	
Mean (SD)	4.6 (1.8)	5.5 (1.2)	0.9 (1.9)	
Median (Q1; Q3)	6.0 (3.0; 6.0)	6.0 (6.0; 6.0)	0.0 (0.0; 2.0)	
Min; max	0.0; 6.0	0.0; 6.0	−6.0; 6.0	

Note: Only data from patients with scores available both at baseline and at the relevant follow-up were used for analysis.
Abbreviations: KATZ ADL, Katz Index of independence in activities of daily living; max, maximum; min, minimum.
**P* value calculated according to the Wilcoxon sign rank test.

TABLE 6 Summary of healing status assessment over time (full analysis population)

Variables	Visit			
	Baseline N = 292	1 month N = 265	6 months N = 216	12 months N = 196
Healing status				
n	...	265	212	190
Cured, n (%)	...	12 (4.5)	78 (36.8)	118 (62.1)
Healing, n (%)	...	229 (86.4)	122 (57.5)	57 (30.0)
Other, n (%)	...	24 (9.1)	12 (5.7)	15 (7.9)
No MRSA present				
n	...	188	155	139
Cured, n (%)	...	9 (4.8)	57 (36.8)	90 (64.7)
Healing, n (%)	...	163 (86.7)	89 (57.4)	36 (25.9)
Other, n (%)	...	16 (8.5)	9 (5.8)	13 (9.4)
MRSA present				
n	...	74	56	49
Cured, n (%)	...	3 (4.1)	21 (37.5)	28 (57.1)
Healing, n (%)	...	63 (85.1)	33 (58.9)	19 (38.8)
Other, n (%)	...	8 (10.8)	2 (3.6)	2 (4.1)

involving long bones and joints. A few key aspects are addressed below.

The study showed that nearly 60% of the patients had been treated for the same infection within the three years before they were enrolled in the current study. These patients had received a median number of two prior treatments. At least one patient had received as many as 20 prior orthopedic treatments, demonstrating the chronic nature of *S. aureus* long-bone infection. This clinical finding is consistent with the recent discoveries on the unique pathogenic mechanisms of *S. aureus* in orthopedic infections. These include (a) biofilm formation on the implant[15] and necrotic bone,[16,17] (b) generation of staphylococcal abscess communities (SACs) in soft tissues and bone marrow,[18-20] (c) intracellular infection,[1] and (d) the ability to colonize the osteocyte-canalicular network of live cortical bone.[21,22]

Less than two-thirds of the patients were judged by their treating surgeon to be "cured" 12 months after treatment. This underscores the chronic nature of long-bone infections. Although the current cure rate was low in comparison to what has been reported historically (ie, 80% to 100% for both FRIs and PJI),[5,23] a true comparison is not possible because there is no objective definition of "cure". Caution is necessary when interpreting the current cure rate because of the heterogeneity of the patient population in terms of the infection stage upon enrollment in the study.

Although patients' mental and physical state generally improved by the end of the study period based on the SF-36, PMS, and Katz ADL scores, the health status of the patients was still worse than the average of the normal US population as measured by the SF-36 scores. This underscores the negative effect of *S. aureus* bone infection on the patient's quality of life. Additionally, 4.8% of patients died during the first year after enrollment underscoring the serious nature of *S. aureus* infection of long bones and joints.

4.1 | Limitations

The current study has several limitations. (a) Since we chose to accept patients previously diagnosed with long-bone infection, the baseline status of the patient population was heterogeneous with regard to the chronicity and progression of the infection. Although we have presented the outcome of the patients after the current treatments, the readers should interpret the timing of the outcomes with caution, keeping in mind that the starting population was heterogeneous. (b) Although the current study aimed to capture a global picture of long-bone infections, the study patient population was not evenly distributed among the geographical locations. Some regions were underrepresented (eg, South America, Middle East, and Southeast Asia) or not represented at all (eg, Africa and Australia). Due to the high incidence and widespread nature

TABLE 7 Analysis of potential predictors for cure at 1-year follow-up—results from univariable logistic regression models

Variable	Details	Unadjusted odds ratio	95% CI	*P* value
Age, y	Per 10 years increase	1.16	(0.96; 1.39)	.118
Gender	Male vs female	1.46	(0.78; 2.72)	.240
Body mass index, kg/m^2	25.0 to <30.0 vs <25.	0.89	(0.43; 1.83)	.714
	30.0 to <35 vs <25.0	1.30	(0.52; 3.23)	
	≥35 vs <25.0	0.71	(0.30; 1.65)	
Charlson comorbidity index	Per 1 point increase	0.98	(0.76; 1.28)	.908
Diabetes	Yes vs no	2.31	(0.81; 6.59)	.116
Origin of infection	Osteomyelitis vs fracture fixation infection	0.78	(0.34; 1.78)	.391
	Prosthetic joint infection vs fracture fixation infection	0.62	(0.31; 1.24)	
Region	America vs Central Europe	0.21	(0.10; 0.46)	<.001
	Asia vs Central Europe	0.47	(0.23; 0.97)	

TABLE 8 Analysis of potential predictors for being cured at the 1-year follow-up—results from multivariable logistic regression models

Variables	Details	Adjusted odds ratio	95% CI	*P* value
Age, y	Per 10 years increase	1.19	(0.94; 1.51)	.149
Gender	Male vs female	1.34	(0.63; 2.85)	.445
Body mass index, kg/m^2	25.0 to <30.0 vs <25.0	0.68	(0.31; 1.52)	.665
	30.0 to <35 vs <25.0	1.31	(0.42; 4.11)	
	≥35 vs <25.0	0.91	(0.30; 2.80)	
Charlson comorbidity index	Per 1 point increase	0.74	(0.51; 1.06)	.098
Diabetes	Yes vs no	3.73	(0.86; 16.27)	.079
Origin of infection	Osteomyelitis vs fracture fixation infection	0.92	(0.37; 2.28)	.729
	Prosthetic joint infection vs fracture fixation infection	1.50	(0.51; 4.40)	
Region	America vs Central Europe	0.22	(0.09; 0.58)	.008
	Asia vs Central Europe	0.61	(0.26; 1.43)	

of antimicrobial-resistant infections, bone and joint infections are a major healthcare burden in low- and middle-income countries (LMIC),[24] therefore, the underrepresentation of LMIC is particularly noticeable. (c) For the sake of having a patient population with some degree of homogeneity, the current study focused on *S. aureus* infections. Although *S. aureus* is the most common causative pathogen, many bone and joint infections are associated with other pathogens,[3,25-27] which were not represented in this registry. (d) Although the current study showed that more than half of the patients (n = 151, 53.2%) received a multistage procedure, which is concordant with the literature,[5] this number should be taken with caution because the reporting was not consistent among the investigational sites. Some sites reported a multistage surgery as one surgery, while others may have reported the baseline surgery of a multistage surgery as the first surgery and all subsequent stages as additional surgeries. (e) The *AO Trauma CPP Bone Infection Registry* suffered from a high dropout rate.[28] Nevertheless, per-protocol analyses and sensitivity analyses produced qualitatively similar results. We presume that the high dropout rate did not affect the interpretation of the data.

5 | CONCLUSION

The *AO Trauma CPP Bone Infection Registry* demonstrated a highest proportion of MRSA vs MSSA long bone and joint infection in North America, followed by Asia and then Central Europe. Of this population, nearly 60% of the patients had been previously treated for reasons related to the current infection. One year after the treatment, less than two-thirds of the patients were reported to be clinically cured, and both the mental and health status of the patients were, on average, worse than the general US population. At 12-month follow-up, SF-36 (PCS component) and PMS scores were reported to be worse for patients with MRSA infections than for MSSA infection. The *AO Trauma CPP Bone Infection Registry* is an annotated biospecimen repository that can be utilized to elucidate relationships between patient demographics, comorbidities, treatment modality, patent-specific host immunity to the causal pathogen (s), and outcomes, in prospective studies.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

SLK: design and oversight of the study, drafting and review of manuscript. MM: Principal investigator at study site, drafting of the manuscript. WJM, MB, FL, DS, JS, MS, RB, VA, KY, JB, MN, KS, XZ, BQ, and YL: Principal investigator at study site. Review/corrections of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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