Kingella kingae Displaced *S. aureus* as the Most Common Cause of Acute Septic Arthritis in Children of All Ages

Catarina Gouveia, MD,† Mariana Duarte, MD,* Susana Norte, MD,‡ Joana Arcangelo, MD,‡ Margarida Pinto, MD,§ Cristina Correia, PhD,¶ Maria João Simões, PhD,¶ Helena Canhão, PhD,† and Delfin Tavares, MD‡*

Background: Acute septic arthritis (SA) still remains a challenge with significant worldwide morbidity. In recent years, *Kingella kingae* has emerged and treatment regimens have become shorter. We aim to analyze trends in SA etiology and management and to identify risk factors for complications.
Methods: Longitudinal observational, single center study of children (<18 years old) with SA admitted to a tertiary care pediatric hospital, from 2003 to 2018, in 2 cohorts, before and after implementation of nucleic acid amplification assays (2014). Clinical, treatment and disease progression data were obtained.
Results: A total of 247 children were identified, with an average annual incidence of 24.9/100,000, 57.9% males with a median age of 2 (1–6) years. In the last 5 years, a 1.7-fold increase in the annual incidence, a lower median age at diagnosis and an improved microbiologic yield (49%) was noticed. *K. kingae* became the most frequent bacteria (51.9%) followed by MSSA (19.2%) and *S. pyogenes* (9.6%). Children were more often treated for fewer intravenous days (10.7 vs. 13.2 days, $P = 0.01$) but had more complications (20.6% vs. 11.4%, $P = 0.049$) with a similar sequelae rate (3.7%). Risk factors for complications were C-reactive protein ≥80 mg/L and *Staphylococcus aureus* infection, and for sequelae at 6 months, age ≥4 years and CRP ≥ 80 mg/L.
Conclusions: The present study confirms that *K. kingae* was the most common causative organism of acute SA. There was a trend, although small, for decreasing antibiotic duration. Older children with high inflammatory parameters might be at higher risk of sequelae.

Key Words: acute septic arthritis, complications, *Kingella kingae*

(*Pediatr Infect Dis J* 2021;40:623–627)

Acute septic arthritis (SA) is an acute infection of the joints, often localized in the knee and hip, with significant worldwide morbidity.[1,2] The long-term sequelae can be overwhelming, with adverse consequences on growth. In Europe, the incidence varies from 2 to 22 per 100,000 children,[3,4] most common being in young boys, with a male/female rate of 1.2–3.7.[2,3] Etiology is changing and dependent on age, comorbidities and geographic origin.[3–5] *Staphylococcus aureus* is one of the most common bacteria causing SA in children[1,6,7]; however, in recent years, *Kingella kingae*, a Gram-negative coccobacillus, has been recognized as the *major* cause of SA in children younger than 5 years, responsible for 30–93.8% of cases.[1,8,9] These infections are usually mild, although atypical presentations have been described.[1,9,10] Differentiating *K. kingae* from pyogenic pathogens is fundamental for management, and although some algorithms have been proposed, they are still controversial.[11] In Europe, the basis of therapy includes a β-lactam, however, the antibiotic length, route of treatment and surgery type is changing, with a trend for less aggressive, shorter treatments.[12–15]

The yield of microbiology bacterial identification, specifically for *K. kingae*, a fastidious organism, has been significantly improved by the inoculation of clinical species into aerobic blood culture bottles and also by advanced molecular diagnosis methods.[2] The 16sRNA gene assay and the real-time polymerase chain reaction (PCR) assays to amplify *K. kingae*-specific targets, such as *rtxA*, *rtxB*, *groEL, mdh* genes, have been developed with high sensitivity.[8,9,16–18]

Our aims were to evaluate trends in etiology after systematic use of molecular tests for *K. kingae*, to analyze changes in management practices and to compare differences between *K. kingae* and *S. aureus* infections.

PATIENT AND METHODS

We performed a longitudinal, observational data analysis of children (<18 years old) with SA admitted to a tertiary care pediatric hospital from January 2003 to December 2018. Children were registered retrospectively until 2014 and prospectively since then. A new management protocol was implemented in 2014, based on bacterial identification by culture, collecting synovial fluid directly into blood culture bottles, and by molecular tests for *K. kingae* identification. Patient evaluation was done by a multidisciplinary team composed of an infectious disease, orthopedic and radiology pediatric consultant. The recommended first-line antibiotics were high-dose flucloxacillin or cefuroxime for children ≤3 years intravenous (IV), due to *K. kingae* decreased susceptibility to oxacillin.[13,19] A switch to oral therapy was considered after a minimum of 3 days, if the patient was improving clinically and analytically [50% decrease of C-reactive protein (CRP) or CRP below 20 mg/L].[3,13]

Clinical, microbiologic, imaging findings, treatment regimens, complications and sequelae data were obtained from medical charts. All patients under 3 months of age and with previous surgery or open fracture at the infection site were excluded.

Diagnosis of acute SA and osteomyelitis was based on classical clinical findings [nonweight bearing, limited range of movement (ROM), pain, local inflammatory signs, fever] present for less than 14 days, plus suggestive imaging with or without microbiologic isolation.[1,2] Complications included dislocation, avascular necrosis, abscesses, pyomyositis, deep venous thrombosis, disseminated infection, pathologic fractures, or chronic osteomyelitis. Sequelae considered were pain, limping, ROM limitation, stiffness, angular deformity, or limb length discrepancy caused by SA with more than 6 months' duration. Good outcome measures included clinical recovery at discharge, CRP < 20 mg/L and no complications or sequelae. Days of admission and treatment duration were also considered.

Accepted for publication January 25, 2021
From the *Infectious Diseases Unit, Hospital de Dona Estefânia, CHULC—EPE, Lisbon, Portugal; †Nova Medical School, Faculdade de Ciências Médicas, Lisbon, Portugal; ‡Pediatric Orthopedic Unit, Hospital de Dona Estefânia, CHULC—EPE, Lisbon, Portugal; §Patologia Clinica, Hospital de Dona Estefânia, CHULC—EPE, Lisbon, Portugal; and ¶Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Lisboa, Portugal.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Catarina Gouveia, MD, Hospital Dona Estefânia, CHULC—EPE, Rua Jacinto Marto, 1169-045 Lisbon, Portugal. E-mail:cmfgouveia@gmail.com.

ISSN: 0891-3668/21/4007-0623
DOI: 10.1097/INF.0000000000003105

Organism isolation and antimicrobial susceptibility were performed on the BacT/ALERT microbial detection system by the hospital microbiology laboratory. Real-time PCR for *K. kingae* identification was implemented in 2014 using primers and a TaqMan probe specific for *rtxA* gene[17] for SA diagnosis in children ≤4 years of age. Values were expressed as percentages for qualitative variables or as means or medians and standard deviations or interquartile ranges (IQR) for continuous variables. Continuous variables were compared using Student *t* test, Mann-Whitney *U* test, or Kruskal Wallis test and categorical variables with χ^2 test or Fisher exact test. A logistic regression for multivariate analysis was performed to determine possible risk factors associated with complications, complaints at discharge and sequelae according to univariate analyses. SPSS Statistics version 24 (IBM Corp, NY) was used to perform data analysis. $P < 0.05$ was considered statistically significant.

Data were collected and retained in accordance with the General Regulation on Data Protection (EU) 2016/679 of April 27, 2016. The study was subject for approval to the local ethics committee. No samples were collected as part of this study.

RESULTS

Overall Study Population

A total of 247 cases of SA were identified, mostly males (57.9%) with a median age of 2 years (1–6 years). There were 5–25 cases per year, with an average annual incidence of 24.9/100,000 children<18 years per year (20/100,000 emergency department admissions per year) with a 1.7-fold increase (from 20.5 to 34.5/100,000) in the annual incidence in the last 5 years. Fifty-eight (23.5%) children reported preceding respiratory tract infection, 23 (9.3%) had trauma, 16 (6.5%) a cutaneous wound and 7 (2.8%) chickenpox. Fifteen had chronic disease (sickle cell disease 7, primary immunodeficiency 3 and cardiac disease 1). The most frequent findings were pain and ROM limitation (87.9%), fever (tympanic ≥38.2º) (64%), local inflammatory signs (64.8%) and toxic appearance (6.9%). Clinical presentation data are detailed in Table 1.

The most common affected joints were the hip (38.9%), knee (36.4%), ankle (9.7%), elbow (5.3%) and shoulder (5.3%). Forty-two (17%) patients presented with concomitant osteomyelitis, and the bones more commonly involved were the femur (26.2%), iliac bone (14.3%), tibia (9.5%) and humerus (9.5%).

We observed good protocol adherence with most patients being empirically treated with either flucloxacillin (63.6%) or cefuroxime (25.1%). After 2014, 74.3% of children under 4 years received cefuroxime. Days of IV treatment and length of stay (LOS) were reduced in recent years (Table 1). Most (87.9%) were submitted to surgery, mainly arthrocentesis alone (90%), and 22.3% had more than 1 intervention (Table 1).

Complications (15.4%) were more frequent after 2014 (20.6%) (Table 1) and included sepsis (21.4%), avascular necrosis (17.9%), intraosseous or subperiosteal abscesses (14.3%), prolonged arthritis (14.3%), myositis (9.3%, more frequent after 2014), subluxation (7%), fasciitis (7%) and deep venous thrombosis (0.4%). Only 1.6% needed intensive care unit admission. At discharge 23% had symptoms, mostly ROM limitation (17.4%), edema (4%) or pain (1.2%). Nine patients lost follow-up. At 6 months' follow-up, 13 (5.4%) patients had sequelae: limited ROM (3.8%), stiffness (0.8%), limb length discrepancy (0.4%) and angular deformity (0.4%). After a 12-month follow-up, 9 (3.7%) had sequelae, mostly ROM limitation and only 1 angular deformity.

Microbiology

Before 2014, microbiologic etiology was found in 49/133 (37%) cases, all with positive blood or synovial fluid cultures. Blood cultures were performed in 75.7% of patients and 29.2% were positive (Table 1). The identified bacteria were *S. aureus* (32/49; 65.3%), *S. pyogenes* (6/49; 12.2%), *S. pneumoniae* (5/49; 10.2%), *K. kingae* (1/49; 2%), *H. influenza b* (1/49; 2%), *N. meningitidis*

TABLE 1. Overall Study Population

	TOTAL (n = 247)	2003–2013 (n = 140)	2014–2018 (n = 107)	*P*
Age, yrs, mean (SD)	4.1 (4.1)	4.5 (4.2)	3.5 (3.8)	0.05
Male gender, n (%)	143 (57.9%)	76 (54.3%)	67 (62.6%)	0.19
Underlying chronic disease, n (%)	15 (6.1%)	7 (5%)	8 (7.5%)	0.37
Duration of symptoms at admission, d, mean (SD)	4.9 (5.8)	5 (6.5)	4.9 (4.6)	0.8
Fever on presentation, n (%)	158 (64%)	100 (71.4%)	58 (54.2%)	0.025
Leukocytes peak, mean (SD)	13,942 (5154)	13,500 (5210)	14,665 (5007)	0.1
CRP peak, mean (SD)	86.6 (84.2)	91.5 (90.1)	80.3 (75.7)	0.3
ESR peak, mean (SD)	60.3 (29.6)	62.8 (32.8)	57.6 (25.7)	0.2
Positive pathogen, n (%)	101/239 (42.3%)	49/133 (36.8%)	52/106 (49%)	0.031
Positive blood culture, n (%)	45/209 (21.5%)	31/106 (29.2%)	14/103 (13.6%)	0.006
Positive synovial fluid culture, n (%)	56 /217 (25.8%)	31/128 (24.2%)	25/89 (28.1%)	0.798
PCR for *K. kingae*,n (%)	21/32 (69%)	0/2 (0%)	21/30 (73%)	<0.001
Complications, n (%)	38 (15.4%)	16 (11.4%)	22 (20.6%)	0.049
Myositis, n (%)	23 (9.3%)	7(5%)	16 (15%)	0.02
Concomitant osteomyelitis, n (%)	42 (17%)	20 (14.3%)	22 (20.6%)	0.19
Empiric IV cefuroxime, n (%)	62 (25.1%)	4 (2.9%)	58 (54.2%)	<0.001
Days IV antibiotic, mean (SD)	12.1 (8.1)	13.2 (9.2)	10.7 (6.1)	0.01
Days Total antibiotic, mean (SD)	27.6 (17.4)	26.9 (21)	28.4 (12.1)	0.5
Days hospitalization, mean (SD)	12.9 (8.9)	14.2 (10.3)	11.2 (6.3)	0.01
Surgical procedures, n (%)*	214 (86.6%)	126 (90%)	89 (83.2%)	0.07
Arthocentesis alone, n (%)*	193 (90.2%)	120 (95.2%)	73/89 (82%)	
Arthrotomy alone, n (%)*	11 (5%)	2 (1.6%)	9 (10%)	
Both Arthocentesis and arthrotomy. n (%)	13 (6.1%)	6 (4.8%)	7 (7.9%)	
Sequelae 6M FU, n (%)	13 /239 (5.4%)	8/133 (6%)	5/106 (4.7%)	0.66
Sequelae 12M FU, n (%)	9 /238 (3.7%)	6/133 (4.5%)	3/105 (2.9%)	0.5

*% of patients submitted to surgery.
CRP indicates C-reactive protein; ESR, eritrocyte sedimentation rate; IV, intravenous; FU, Follow-up.

(1/49; 2%), *E. coli* (1/49; 2%), *S. mitis* (1/49; 2%) and *Salmonella spp* (1/49; 2%). Among *S. aureus,* 90.6% were methicillin-susceptible *S. aureus* (MSSA).

After 2014, microbiologic etiology was found in 52/106 (49%) cases, from positive cultures (75%) and molecular amplification (40%). Blood cultures were performed in 96% of patients and 14% were positive. The identified bacteria were *K. kingae* (27/52; 51.9%) followed by *S. aureus* (10/52; 19.2%; all MSSA), *S. pyogenes* (5/52; 9.6%), *S. pneumoniae* (3/52; 5.8%), *N. meningitidis* (3/52; 5.8%), *H. influenza b* (1/52; 1.9%), *Enterobacter spp* (2/52; 3.8%) and *Brucella* (1/52; 1.9%). After 2014, *K. kingae* molecular tests were only performed in 30/75 (40%) children under 4 years and 21/30 (70%) were positive.

Comparing data between negative versus positive pathogen isolation, negative cases were more common in children under 4 years (66.2 % vs. 33.7%, $P=0.003$), who had fewer days of fever (median 0 vs. 2 days, $P=0.001$) did not present a toxic appearance (99% vs. 82.6%, $P<0.001$) and had a CRP < 80 mg/L (76.8% vs. 39.8%, $P<0.001$). Only 8% of these cases were tested for *K. kingae*. Nonpositive cases had fewer complications (4.1% vs. 31.7%, $P<0.001$) were more frequently treated for less than 7 IV days (38.3% vs. 18.9%, $P=0.001$) and 28 days total (75.8% vs. 50%, $P<0.001$) and had a shorter LOS (median 9 [7–13] vs. 14 [8–21] days, $P<0.001$).

K. kingae was identified by molecular amplification in 21/28 cases (16 from synovial fluid and 5 only from oropharyngeal swab), synovial fluid culture in 10/28 and blood culture in 1/28. Patients with *K. kingae* infection (Table 2) were all under 3 years old, 78.6% referred preceding viral upper respiratory tract infections such as rhinitis, pharyngitis and stomatitis. The seasonal distribution of *K. Kingae* was 14.3% in winter, 17.9% in spring, 7.1% summer and 60.7% in fall. All had monoarticular involvement and the most frequently affected joints were the knee (39.3%), ankle (21.4%) and hip (17.9%). The majority of patients (70.4%) were afebrile, only 6 (23%) had fever for more than 2 days and the peak CRP was below 80 mg/L in 77.8% but below 20 mg/L in only 7.4%. Two (7%) had concomitant tenosynovitis, 3 (10.7%) myositis and 3 (10.7%) osteomyelitis. Eight (28.6%) needed more than 1 surgical intervention due to persistent arthritis and 2 (7.1%) had complications: 1 hip subluxation and 1 intraosseous abscess. However, most (86%) were treated for less than 4 weeks, had a shorter LOS and no sequelae at 6 months (Table 2).

Data comparing *S. aureus* (N = 42) and *K. kingae* arthritis are presented in Table 2. *S. aureus* patients were significantly older than 4 years (81% vs. 0%, $P<0.001$), had CRP ≥ 80 mg/L (73.8% vs. 22% $P<0.001$) and had more often hip involvement (57% vs. 17.9%, $P=0.001$), osteomyelitis and complications (Table 2), namely myositis (3), abscesses (2), fasciitis (2), sepsis (5), hip dislocation (2) and avascular necrosis (1). They were treated with longer antibiotic courses and 16 (38.1%) needed more than 1 surgical intervention. Four had ROM limitation at 12 months.

Age Distribution

Children younger than 4 years more often had CRP < 80 mg/L (69.5% vs. 45.2%, $P=0.001$), culture and PCR negative infection (66.2% vs. 47.3%, $P=0.003$), less bacteremia (9.7% vs. 32.3%, $P<0.001$) and were treated for less than 28 days total (64.9% vs. 48.4%, $P=0.012$).

Bacteremia and Osteomyelitis

Patients with bacteremia were more likely to have *S. aureus* infection (57.8% vs. 9.8%, $P<0.001$), concomitant osteomyelitis (35.5% vs. 14.6%, $P=0.002$), longer treatment courses and more complications (40% vs. 6.7%, $P<0.001$) and sequelae at 6 months (Table 3).

Forty-two patients (17%) had concomitant osteomyelitis and these were older (6 vs. 2 years, $P<0.001$), more often had pathogen isolation (57.1% vs. 36.1%, $P=0.011$), more likely *S. aureus* infection (35.7% vs. 13.2%, $P<0.001$), and CRP ≥ 80 (52.4% vs. 34.1%, $P=0.037$), associated complications (40,5% vs. 5.9%, $P<0.001$) and sequelae at 6 months (14.3% vs. 3.4%, $P=0.004$). They needed longer duration of treatment, either IV (15 vs. 9 days, $P=0.003$) or total course (36 vs. 23 days, $P<0.001$).

TABLE 2. Clinical and Laboratory Presentation of SA According to Bacterial Etiology (*S. aureus* vs. *K. kingae*)

	S. aureus **(n = 42)**	***K. kingae*** **(n = 28)**	*P*
Age, yrs, mean (SD)	8.3 (4.3)	1.4 (0.5)	<0.001
Male gender, n (%)	27 (64.3%)	19 (67.8%)	0.8
Duration symptoms at presentation, d, mean (SD)	4.6 (3.1)	3.9 (3.1)	0.59
Fever on presentation, n (%)	35 (83.3%)	8 (28.6%)	<0.001
Duration of fever, mean (SD)	6.2 (5.8)	0.67 (1.1)	<0.001
Bacteriemia, n (%)	26 (61.9%)	1 (3.6%)	<0.001
Concomitant osteomyelitis, n (%)	15 (35.7%)	3 (10.7%)	0.025
Complications, n (%)	17 (40.5%)	5 (17.9%)	<0.001
Leukocytes count, cells/mm^3, mean (SD)	11,939 (4918)	15,306 (4635)	0.011
CRP peak, mg/L, mean (SD)	175 (100)	58.2 (32.6)	<0.001
Normal CRP, d, mean (SD)	21.4 (15.6)	7.31 (5.1)	0.05
ESR peak, mm/h, mean (SD)	69.9 (26.7)	58.5 (20.1)	0.06
Days IV antibiotic, mean (SD)	19.8 (11.8)	9.8 (4.7)	<0.001
Days total antibiotic, mean (SD)	39.3 (32.1)	25.2 (6.9)	0.01
Hospital Stay, d, mean (SD)	18.3 (9.2)	9.9 (4.7)	<0.001
Sequelae 6 M FU, n (%)*	6/39 (15.4%)	0/28 (0%)	0.036
Sequelae 12 M FU, n (%)*	3/39 (7.7%)	0/28 (0%)	0.134

*% of patients submitted to surgery.

CRP indicates C-reactive protein; ESR, eritrocyte sedimentation rate; IV, intravenous; FU, Follow-up.

TABLE 3. Differences in Demographic, Clinical and Lab Parameters Between Patients With or Without Sequelae

Clinical Characteristics	With Sequelae 6M **N = 13**	Without Sequelae **N = 226**	***P***
Male gender, n (%)	9 (69.2)	132 (58,4)	0.57
Age, yrs, mean (SD)	8.7 (4.8)	3.8 (3.8)	<0.001
Underlying chronic disease, n (%)	5 (38.5%)	10 (4.4)	<0.001
Duration of symptoms at admission, d, mean (IQR)	4.4 (4.8)	5 (5.9)	0.7
Leukocytes peak, mean (SD)	15,103 (5418)	13,874(5155)	0.46
CRP peak, median (SD)	216 (109)	78.9 (76.1)	<0.001
CRP ≥80, n (%)	10 (76.9%)	79 (35.9%)	0.002
Normal CRP, d, mean (SD)	36.4 (19.1)	8.7 (7.1)	0.032
ESR peak, mean (SD)	75.2 (34)	59 (28.9)	0.65
Positive pathogen, n (%)	9 (69.2%)	87 (38.5%)	0.04
S. aureus positive, n (%)	6 (46%)	33 (14.6%)	0.009
Positive blood cultures, n (%)	7/12 (58.3%)	35/190 (18.4%)	0.004
Complications, n (%)	11 (84.6%)	24 (10.6%)	<0.001
Days IV antibiotic, mean(SD)	24.9 (12.3)	11.1 (7.1)	<0.001
Days total antibiotic, mean(SD)	56 (52.1)	26 (11.5)	<0.001
Days of hospitalization, mean(SD)	28 (16.1)	11.9 (7.6)	<0.001

CRP indicates C-reactive protein; ESR, eritrocyte sedimentation rate; IV, intravenous.

Risk Factors for Worse Outcome

The LOS was related to fever duration (Pearson correlation r = 0.3, $P = 0.000$), inflammatory parameters on admission, such as CRP (Pearson correlation r = 0.45, $P = 0.000$) or ESR (Pearson correlation r = 0.3, $P = 0.000$) and number of surgical interventions (Pearson correlation r = 0.4, $P = 0.000$).

Risk factors for complications were age ≥4 years (OR 3 [1.5–6.2]), intensive care unit admission (OR 14 CI (1.8–106]), CRP ≥ 80 mg/L (OR 4.2 [2–8.9]), *S. aureus* infection (OR 1.2 [0.7–2.1]). On multivariate analyses, only CRP ≥ 80 mg/L and *S. aureus* infection were significant. Risk factors for sequelae at 6 months were age ≥4 years, underlying chronic disease, CRP ≥ 80 mg/L, *S. aureus* infection, positive blood cultures and complications (Table 3). On multivariate analyses, only age ≥4 years (10.4 [2.3–48.2]) and CRP ≥ 80 mg/L (OR 8.9 [1.9–41.7]) were significant.

DISCUSSION

In the current study, nucleic acid amplification assays have changed the knowledge of SA epidemiology, probably justifying a significant increase in the rise and upsurge of *K. kingae*, now the most common cause of SA in Lisbon. In fact, the incidence of SA has increased in recent years and ranges between 1 and 30.8/100,000.[2,16] Samara et al[9] in a 20-year retrospective Swiss study that included 369 children, report a 79% increase in the mean annual incidence, from 18.3 to 32.7/100,000, but only in young children, being unchanged in teens. Likewise, in our study, there was a 68% rise in the incidence of children in the last 5 years, mostly in children under 2 years.

The present study confirms that *K. kingae* is the most common bacteria causing SA in recent years in Lisbon (51.9%), mainly in young children. In most European countries, *K. kingae* is the main cause of osteoarticular infections in children between 6 and 48 months (30–93.8%).[9,16] Furthermore, in Switzerland, France, and even in the United States, *K. kingae* has been reported as the leading cause of OAI in all age groups.[18,20,21] As suggested by Juchler et al,[20] it is probable that this incidence is even underestimated. Actually, our pathogen negative infections were more common in children younger than 4 years, who had CRP less than 80 mg/L, fewer complications and only a few (8%) tested for *K. kingae*, it being possible that a reasonable proportion of these younger children would have *K. kingae* SA. This low rate of molecular testing in our study (40%), much lower than the 76.7% reported by Ceroni et al[22] because of insufficient synovial fluid or protocol incompliance, might justify our low rate of positive pathogen (49%) when compared with other studies (61–62.7%).[9,20,23] Also, the implementation of new, highly sensitive molecular tests will probably increase our *K. kingae* sensitivity.[9,24] In 5 children, *K. kingae* OAI was diagnosed only based on oropharyngeal swab and clinical grounds. Although in these cases, oropharyngeal colonization, present in 8–12% of Swiss and Israeli young children, cannot be excluded, *K. kingae* OAI was assumed based on previous high sensibility data (90.5%).[25,26] According to the literature, *K. kingae* SA has a clear seasonal pattern, with a higher incidence during fall and early winter.[18] This is probably related to the overlapping occurrence of viral upper respiratory tract infections, such as rhinitis, pharyngitis and stomatitis, that usually precede *K. kingae* infection.[18,23] *K. kingae* SA are typically milder and monoarticular and have few complications, with rare or even no sequelae.[16,18,20,27] These characteristics were also present in our 28 *K. kingae* SA, with 78.8% of patients reporting previous respiratory infections, 60.7% in fall. Most were mild and monoarticular, affecting more commonly the knee and hip as described[16,23,27] but with less limbs extremities affection and tenosynovitis than reported by others.[22,28] This is probably related to the strict inclusion of acute SA cases in nonoutbreak settings. These children were treated with shorter antibiotic courses and had no sequelae, consistent with other studies. However, 8 (28.6%) needed repeated arthrocentesis, which is unusual[16] and much higher than reported by Basmaci et al,[27] where only 1/64 (1.6%) patients with *K. kingae* SA needed a second surgical drainage. Also, although intraosseous abscesses and chronditis[10,22] have been reported to the best of our knowledge no hip subluxation has been described secondary to *K. kingae* infection. Concomitant osteomyelitis, age less than 6 months, and inadequate or delayed treatment have all been clear risk factors, none present in this patient. In fact, *K. kingae* infections can be atypical and have complications and this might justify similar management care to other SA.[10]

S. aureus is worldwide responsible for 36.5–70% of cases.[1,5–7] In our study, in recent years, it represented only 19% yet the second most frequent, all MSSA. *S. aureus* infections were associated with a higher frequency of fever, mean CRP value, concomitant osteomyelitis, complications and longer antibiotic courses and LOS, as observed.[5,6,29,30]

Our rate of positive blood cultures (overall 21.5% but only 14% after 2014) and synovial fluid or bone cultures (30%) were comparable with the rate of positive blood cultures (12.9%) and synovial fluid/bone cultures (30.3%), respectively, reported in the Swiss[9] and Spanish multicenter study.[29] However, lower than reported by Bransson et al[5] in Texas, United States, where 37% and 55.8% of blood and synovial fluid cultures were, respectively, positive. It is probable that differences in molecular testing and in the rate and virulence of pyogenic bacteria, mostly *S. aureus,* account for these data.

Rates of contiguous osteomyelitis in the background of SA have been more often reported in recent years and varies from 20.8% to 68%.[5,30] In our study, it was only 17%, similar to the 12% of the Spanish cohort,[29] but with a rising trend recently (20.6%), although not significant. This is probably related to the low *S. aureus* rate in our cohort. Indeed, Montgomery et al[31] found that concomitant SA and osteomyelitis were more common in *S. aureus* infections and in older children with longer duration of symptoms. Also, longer duration of fever at admission and higher inflammatory parameters were associated with contiguous infection, as observed in our study.[5,30]

In our study, length of treatment was too long, although modestly reduced in recent years, similar to the Spanish cohort,[29] but still far from that proposed by Peltola et al[13] with a short 2–4 days' intravenous course followed by 10 days' oral treatment. Other authors have also reported an important reduction in the mean IV duration and LOS to less than 7 days.[32,33] Although, we expected to have the same decrease in recent years, only a slight difference in IV treatment and LOS was noticed. Undeniably, we have the need to improve. Immediate drainage and irrigation of *major* joints are still considered the standard of care for SA.[2] Indeed, most of our cases were submitted to a surgical procedure, 90% arthrocentesis and only 5% arthrotomy, it being impossible to compare both procedures.

In our study, we had 3.7% long-term adverse outcomes, all minor, which is in accordance with data from the literature pointing for sequelae occurring in 1.1–4.5% of cases related to strain virulence, severe disease, delayed therapy, infection location and concomitant hip or shoulder infection.[1–3]

Few studies analyze risk factors for complications and sequelae in SA.[34] As previously reported, older age, positive bacterial isolate (mostly *S. aureus)*, and in some series,[29] higher CRP at admission were associated with complications and sequelae.[5,35] Calvo et al[29] reported an association with hip involvement; however, in our study, long-term sequelae were only associated with older age, comorbidities and bacteremia. This age difference in sequelae is probably related to a milder nature of *K. kingae* infections, more frequent in toddlers, and to the aggressive nature of other pyogenic infections, more common in older children.[9,11]

Our study has several limitations, including being a single center partial retrospective study, missing some data points. However, all patients were cared for by the same multidisciplinary team and recorded prospectively after 2014, which improves patient knowledge and follow-up. Regardless of its limitations, this study shows a *major* change in SA etiology in recent years in Lisbon, with *S. aureus* being replaced by *K. kingae* as the main cause of SA. Older children with comorbidities seem at higher risk of sequelae.

REFERENCES

1. Arnold JC, Bradley JS. Osteoarticular infections in children. *Infect Dis Clin North Am.* 2015;29:557–574.
2. Krogstad P. Septic arthritis. In: Feigin RD, Cherry JD, Kaplan SL, et al, eds. *Textbook of Pediatric Infectious Diseases*. 8th ed. Saunders Elsevier; 2018:529–534.e2
3. Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, et al. Bone and joint infections. *Pediatr Infect Dis J.* 2017;36:788–799.
4. Gafur OA, Copley LA, Hollmig ST, et al. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. *J Pediatr Orthop.* 2008;28:777–785.
5. Branson J, Vallejo JG, Flores AR, et al. The contemporary microbiology and rates of concomitant osteomyelitis in acute septic arthritis. *Pediatr Infect Dis J.* 2017;36:267–273.
6. Bocchini CE, Hulten KG, Mason EO Jr, et al. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous *Staphylococcus aureus* osteomyelitis in children. *Pediatrics.* 2006;117:433–440.
7. Dohin B, Gillet Y, Kohler R, et al. Pediatric bone and joint infections caused by Panton-Valentine leukocidin-positive *Staphylococcus aureus*. *Pediatr Infect Dis J.* 2007;26:1042–1048.
8. Ceroni D, Kampouroglou G, Valaikaite R, et al. Osteoarticular infections in young children: what has changed over the last years? *Swiss Med Wkly.* 2014;144:w13971.
9. Samara E, Spyropoulou V, Tabard-Fougère A, et al. *Kingella kingae* and osteoarticular infections. *Pediatrics.* 2019;144:20191509.
10. Alcafache M, Ramos S, Alves P, et al. Uncommon *Kingella kingae* lytic bone lesions in children. *Pediatr Int.* 2016;58:244–245.
11. Ceroni D, Cherkaoui A, Combescure C, et al. Differentiating osteoarticular infections caused by *Kingella kingae* from those due to typical pathogens in young children. *Pediatr Infect Dis J.* 2011;30:906–909.
12. Darley ES, MacGowan AP. Antibiotic treatment of Gram-positive bone and joint infections. *J Antimicrob Chemother.* 2004;53:928–935.
13. Peltola H, Pää Kkö Nen M, Kallio P, et al. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short- term course of parenteral therapy, for childhood septic arthritis. *Clin Infect Dis*. 2009;48:1201–1210.
14. Jagodzinski NA, Kanwar R, Graham K, et al. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. *J Pediatr Orthop.* 2009;29:518–525.
15. Pääkkönen M, Peltola H. Management of a child with suspected acute septic arthritis. *Arch Dis Child.* 2012;97:287–292.
16. Ilharreborde B, Bidet P, Lorrot M, et al. New real-time PCR-based method for *Kingella kingae* DNA detection: application to samples collected from 89 children with acute arthritis. *J Clin Microbiol.* 2009;47:1837–1841.
17. Lehours P, Freydière AM, Richer O, et al. The rtxA toxin gene of *Kingella kingae*: a pertinent target for molecular diagnosis of osteoarticular infections. *J Clin Microbiol.* 2011;49:1245–1250.
18. Chometon S, Benito Y, Chaker M, et al. Specific real-time polymerase chain reaction places *Kingella kingae* as the most common cause of osteoarticular infections in young children. *Pediatr Infect Dis J.* 2007;26:377–381.
19. Yagupsky P. Antibiotic susceptibility of *Kingella kingae* isolates from children with skeletal system infections. *Pediatr Infect Dis J.* 2012;31:212.
20. Juchler C, Spyropoulou V, Wagner N, et al. The contemporary bacteriologic epidemiology of osteoarticular infections in children in Switzerland. *J Pediatr.* 2018;194:190–196.e1.
21. Aupiais C, Ilharreborde B, Doit C, et al. Aetiology of arthritis in hospitalised children: an observational study. *Arch Dis Child.* 2015;100:742–747.
22. Ceroni D, Cherkaoui A, Ferey S, et al. *Kingella kingae* osteoarticular infections in young children: clinical features and contribution of a new specific real-time PCR assay to the diagnosis. *J Pediatr Orthop.* 2010;30:301–304.
23. Hernández-Rupérez MB, Suárez-Arrabal MDC, Villa-García Á, et al. *Kingella kingae* as the main cause of septic arthritis: importance of molecular diagnosis. *Pediatr Infect Dis J.* 2018;37:1211–1216.
24. El Houmami N, Durand GA, Bzdrenga J, et al. A new highly sensitive and specific real-time PCR assay targeting the malate dehydrogenase gene of *Kingella kingae* and application to 201 pediatric clinical specimens. *J Clin Microbiol*. 2018;56:e00505–18.
25. Gravel J, Ceroni D, Lacroix L, et al. Association between oropharyngeal carriage of *Kingella kingae* and osteoarticular infection in young children: a case-control study. *CMAJ.* 2017;189:E1107–E1111.
26. Ceroni D, Dubois-Ferriere V, Cherkaoui A, et al. Detection of *Kingella kingae* osteoarticular infections in children by oropharyngeal swab PCR. *Pediatrics.* 2013;131:e230–e235.
27. Basmaci R, Lorrot M, Bidet P, et al. Comparison of clinical and biologic features of *Kingella kingae* and *Staphylococcus aureus* arthritis at initial evaluation. *Pediatr Infect Dis J.* 2011;30:902–904.
28. El Houmami N, Yagupsky P, Ceroni D. *Kingella kingae* hand and wrist tenosynovitis in young children. *J Hand Surg Eur Vol.* 2018;43:1001–1004.
29. Calvo C, Núñez E, Camacho M, et al; Collaborative Group. Epidemiology and management of acute, uncomplicated septic arthritis and osteomyelitis: Spanish Multicenter Study. *Pediatr Infect Dis J.* 2016;35:1288–1293.
30. Monsalve J, Kan JH, Schallert EK, et al. Septic arthritis in children: frequency of coexisting unsuspected osteomyelitis and implications on imaging work-up and management. *AJR Am J Roentgenol.* 2015;204:1289–1295.
31. Montgomery CO, Siegel E, Blasier RD, et al. Concurrent septic arthritis and osteomyelitis in children. *J Pediatr Orthop.* 2013;33:464–467.
32. Bréhin C, Claudet I, Dubois D, et al. Assessing the management of pediatric bone and joint infections according to French guidelines. *Med Mal Infect.* 2020;50:515–519.
33. Filleron A, Laurens ME, Marin G, et al. Short-course antibiotic treatment of bone and joint infections in children: a retrospective study at Montpellier University Hospital from 2009 to 2013. *J Antimicrob Chemother.* 2019;74:3579–3587.
34. Chiappini E, Krzysztofiak A, Bozzola E, et al. Risk factors associated with complications/sequelae of acute and subacute haematogenous osteomyelitis: an Italian multicenter study. *Expert Rev Anti Infect Ther.* 2018;16:351–358.
35. Martin AC, Anderson D, Lucey J, et al. Predictors of outcome in pediatric osteomyelitis: five years experience in a Single Tertiary Center. *Pediatr Infect Dis J.* 2016;35:387–391.