

Systematic Review of *Kingella kingae* Musculoskeletal Infection in Children: Epidemiology, Impact and Management Strategies

This article was published in the following Dove Press journal:
Pediatric Health, Medicine and Therapeutics

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Abstract: *Kingella kingae*, a pathogen often responsible for musculoskeletal infections in children is the most common cause of septic arthritis and osteomyelitis in children 6 to 36 months of age. The aim of this study was to perform a systematic review of previous studies to determine the proportion of *K. kingae* in bacteriologically proven musculoskeletal infections among the pediatric population. A secondary objective was to describe the diagnostic strategies and outcome of patients with musculoskeletal infections caused by *K. kingae*. A systematic review was conducted to identify publications that report on musculoskeletal infections caused by *K. kingae* in the pediatric population (patients 0 to <18 years old with microbiologic culture and/or polymerase chain reaction (PCR) confirmation of *K. kingae* and a description of the musculoskeletal infection involved). Of 144 studies included in this review, we sought to determine the proportion of *K. kingae* pediatric musculoskeletal infections. A total of 711 (30.8%) out of 2308 pediatric cases with culture and/or PCR proven musculoskeletal infections had *K. kingae* successfully identified from twenty-nine studies. Of the 1070 patients who were aged less than 48 months, *K. kingae* was the organism identified in 47.6% of infections. We found the average age from the collated studies to be 17.73 months. Of 520 pediatric musculoskeletal patients in which *K. kingae* infections were identified and where the studies reported the sites of infection, a large proportion of cases (65%) were joint infections. This was followed by 18.4% osteoarticular infection (concomitant bone and joint involvement), with isolated bone and spine at 11.9% and 3.5%, respectively. Twenty-one papers reported clinical and laboratory findings in children with confirmed *K. kingae* infection. The median temperature reported at admission was 37.9°C and mean was 38.2°C. Fourteen studies reported on impact and treatment, with the majority of children experiencing good clinical outcome and function following antibiotic treatment with no serious orthopaedic sequelae.

Keywords: *Kingella kingae*, osteoarticular infection, septic arthritis, osteomyelitis, spondylodiscitis

Introduction

Since the 1990s there has been increasing recognition of *Kingella kingae* as an emerging cause of osteoarticular infections in young children. This, coupled with the decline of skeletal infections caused by *Haemophilus influenzae* due to widespread vaccination has resulted in an increased proportion of musculoskeletal infections in young children caused by *K. kingae*.^{1,2}

Previously known as *Moraxella kingii*, *K. kingae* was first described in the 1960s. It is a beta-hemolytic encapsulated coccobacillus belonging to the *Neisseriaceae* family

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of gram-negative bacteria found colonizing the oropharynx of healthy young children.^{3,4} The pathogen is transmitted by close contact between young children with a recent reported increase in oropharyngeal carriage rates and outbreaks of invasive disease involving the skeletal system in daycare centers.^{5–8} The colonized oropharyngeal surfaces are the source of droplet transmission and the respiratory mucosa is the gateway for the bacterium into the bloodstream where it disseminates to distant sites. Bone and joint infections including spondylodiscitis are the most commonly reported *K. kingae* infections in the paediatric population. However, soft tissue infections, occult bacteraemia, endocarditis and rarely lower respiratory tract, meningeal and ocular infections have also been reported in children.^{5,9–12} Epithelium breach may facilitate invasion of *K. kingae* into the circulation.^{13,14} *K. kingae* invasive infections have been associated with hand-foot-mouth disease, herpes simplex virus causing stomatitis, varicella zoster virus and human rhinovirus.^{13,15,16}

K. kingae exhibits virulence factors which include RTX (repeat-in-toxin), polysaccharide capsule and pili. Pili enable adherence of the organism to the respiratory and synovial epithelium.¹⁷ The polysaccharide capsule protects the organism from phagocytosis and the cell-mediated immune system of the host.⁵ Munoz et al highlighted a novel interplay between the capsule and exopolysaccharide, where the capsule interfered with neutrophil response and the exopolysaccharide promotes evasion of neutrophil killing through complementary mechanisms while also promoting virulence.¹⁸ Kehl-Fie et al suggested that *K. kingae* may damage the epithelial layer of the upper respiratory tract due to the broad spectrum cytotoxicity of RTX that lyses epithelial cells, leukocytes and facilitates upper respiratory colonization and induction of buccal ulcers, enabling survival of the bacterium in the bloodstream and invasion of skeletal tissues. The toxin also damages synoviocytes to allow seeding into joint spaces.¹⁹

K. kingae frequently colonises the oropharynx (but not the nasopharynx) of young children from 6–48 months.²⁰ While there are significant variations in reported carriage rates which can be attributed to both host and technical factors, age is a major predictor of carriage in all studied populations.²¹ Carriage rates greatly exceed rates of invasive disease with <1% of carriers developing invasive disease over a one-year period.²²

K. kingae is fastidious, slow growing and exhibits preferred growth at 35°C under aerobic conditions. Growth is enhanced in a 5% CO₂ atmosphere.²³ It is notoriously

difficult to culture from synovial fluid and bone aspirate.¹¹ Recent knowledge has initiated the use of blood culture vials inoculated with synovial fluid or bone aspirate. Inoculation of the synovial fluid into a large volume of nutrient broth dilutes the concentration of harmful factors in the aspirates, thus enhancing the recovery of *K. kingae*.²⁴ The addition of broad spectrum polymerase chain reaction (PCR) use since the mid-90s in laboratory analysis has increased the diagnosis of musculoskeletal infections caused by *K. kingae* especially in affluent countries where more advanced laboratory technology is available. Nucleic acid amplification (NAA) assays that target genes encoding the RTX toxin (rtxA and rtxB) are highly sensitive and can be used on multiple clinical specimens. NAA techniques enable the identification of a significant number of additional cases even when using the most sensitive conventional culture techniques.²⁵ Molecular tests that only target the RTX locus do not distinguish between *K. kingae* and the recently described *K. negevensis* species.²⁶ A novel *K. kingae* specific RT-PCR assay that amplify the more specific cpn60 and malate dehydrogenase genes has demonstrated high specificity and sensitivity.²⁷

Over the last decade, *K. kingae* has gained a reputation as being the major pathogen of osteoarticular infection in children 6–36 months following the optimization of conventional culture methods and the development of current molecular techniques such as real-time PCR.^{28,29}

The aim of this study was to perform a systematic review to determine the proportion of *K. kingae* in bacteriology proven musculoskeletal infections in the pediatric population. A secondary objective was to describe the clinical findings, diagnostic strategies and outcome of patients with musculoskeletal infections caused by *K. kingae*.

Methods

Search Strategy

A systematic review was conducted to identify publications that report on musculoskeletal infections caused by *K. kingae* in the paediatric population (patients 0 to <18 years old with microbiologic culture and/or PCR confirmation of *K. kingae* and a description of the musculoskeletal infection involved). An exhaustive, comprehensive search without data restriction was conducted up to March 6th 2019 using Ovid Medline, Embase, Cinahl, PubMed and Cochrane Central. Search items included “*Kingella kingae*” OR “*Moraxella kingii*” AND “musculoskeletal infection” OR “bone” OR “joint” OR “skeletal” OR “osteoarticular” OR “osteoarthritis” OR

“osteomyelitis” OR “spondylodiscitis” OR “tenosynovitis” AND “infant” or “children” or “adolescent” or “pediatrics” or “juvenile” NOT (animals or adults).

Inclusion and Exclusion Criteria

Studies were included in the critical appraisal process if they were written in English and retrievable through the South Australian Health Library Service. The authors used the CoCoPop (condition, context, population) to identify the included articles. Citations selected were included in the final analysis if these following data were available: documentation of musculoskeletal infection in children (septic arthritis, osteomyelitis, osteoarticular, spondylodiscitis, tenosynovitis) and confirmation of *K. kingae* detection by cultures or molecular methods (PCR test). Studies were excluded if they were of the adult population, literature synthesis or expert reviews. Two reviewers were involved in the article selection process, and full agreement was reached on the included articles.

Critical Appraisal Process

The critical appraisal tool known as the critical appraisal instrument for studies reporting prevalence data from Joanna Briggs Institute was used to review the methodology and summarize the findings of the selected studies.³⁰ A set of nine questions with “yes”, “no” or “unclear” responses are used to guide the reviewer which then leads to the final decision to “include” or “exclude” a study if a minimum score of five out of nine is achieved for each study.

Results

Search Findings

A total of 682 studies were located (Ovid-265, Embase-339, Cochrane Central-3, Cinahl-46, PubMed-27, other-2). All 682 identified citations were loaded into EndNote X9.1.1 (2019) and 299 duplicates removed. Titles and abstracts were screened for assessment against the inclusion criteria for the review and another 239 screened abstracts removed, leaving a final result of 144 studies to be critically appraised independently by two reviewers. These 144 potentially relevant papers were retrieved in full text and assessed in detail against the inclusion criteria by two independent reviewers. Studies were excluded if they were of the adult population, literature synthesis or expert reviews. Any disagreements that arose between the reviewers at each stage of the selection process were resolved through discussion. The results of the

search were reported in full in the final report and presented according to the Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram (Figure 1).³¹

Twenty-nine articles were considered relevant with respect to identifying the number of confirmed infections with *K. kingae* in bacteriologically proven musculoskeletal infections in children (Table 1).^{2,22,28,29,32–51,66–70} This was further studied to summarize the frequency of *K. kingae* infections among children under 48 months old (Table 2). Additional epidemiological data extracted and collated included musculoskeletal infection sites, gender, age and seasonality. Twenty-one articles reported on clinical findings (Table 3)^{4,7,35,36,39,41,51–64,71} and fourteen articles reported on the impact or outcome as well as management strategies (Table 4)^{4,25,35,51,52,55–61,65,71} in children who had *K. kingae* musculoskeletal infection.

Study Characteristics

Epidemiology

To determine the proportion of *K. kingae* cases, we collected all studies which reported on bacteriologically confirmed (positive culture and/or PCR test) musculoskeletal infection in children, from any organism. Out of 2308 cases of paediatric (below 18 years old) musculoskeletal infections collated from 29 reports (see Table 1), a total of 711 (30.8%) patients had *K. kingae* successfully identified. These reports were further examined to summarize the frequency of *K. kingae* infections among children aged below 48 months (Table 2). We found 47.6% of 1070 children under 48 months old were diagnosed with *K. kingella* infections. Moumille et al reported 14% *K. kingae* in a retrospective study of a French cohort of diagnosed bacterial osteoarticular infection in children (n=74). The authors noted *Staphylococcus aureus* was the most isolated bacterium among older children who were over 36 months whereas *K. kingae* was isolated only from children under 36 months old.⁴⁹ In a separate French paediatric centre, Verdier et al reported 14% *K. kingae* osteoarticular infection, with *Staphylococcus aureus* (47%) and *Streptococcus pyogenes* (16%) in children whose age ranges from 9–90 months with a median of 17.9 months. The authors also confirmed the classical occurrence of osteoarticular infection due to *K. kingae* in children between 6 months and 4 years of age.^{4,28,57,72} More recent studies using both conventional culture and PCR combined showed *K. kingae* to be the most common cause of osteoarticular infection in children <4 years of age. We found the average age from the collated studies to be 17.73 months.

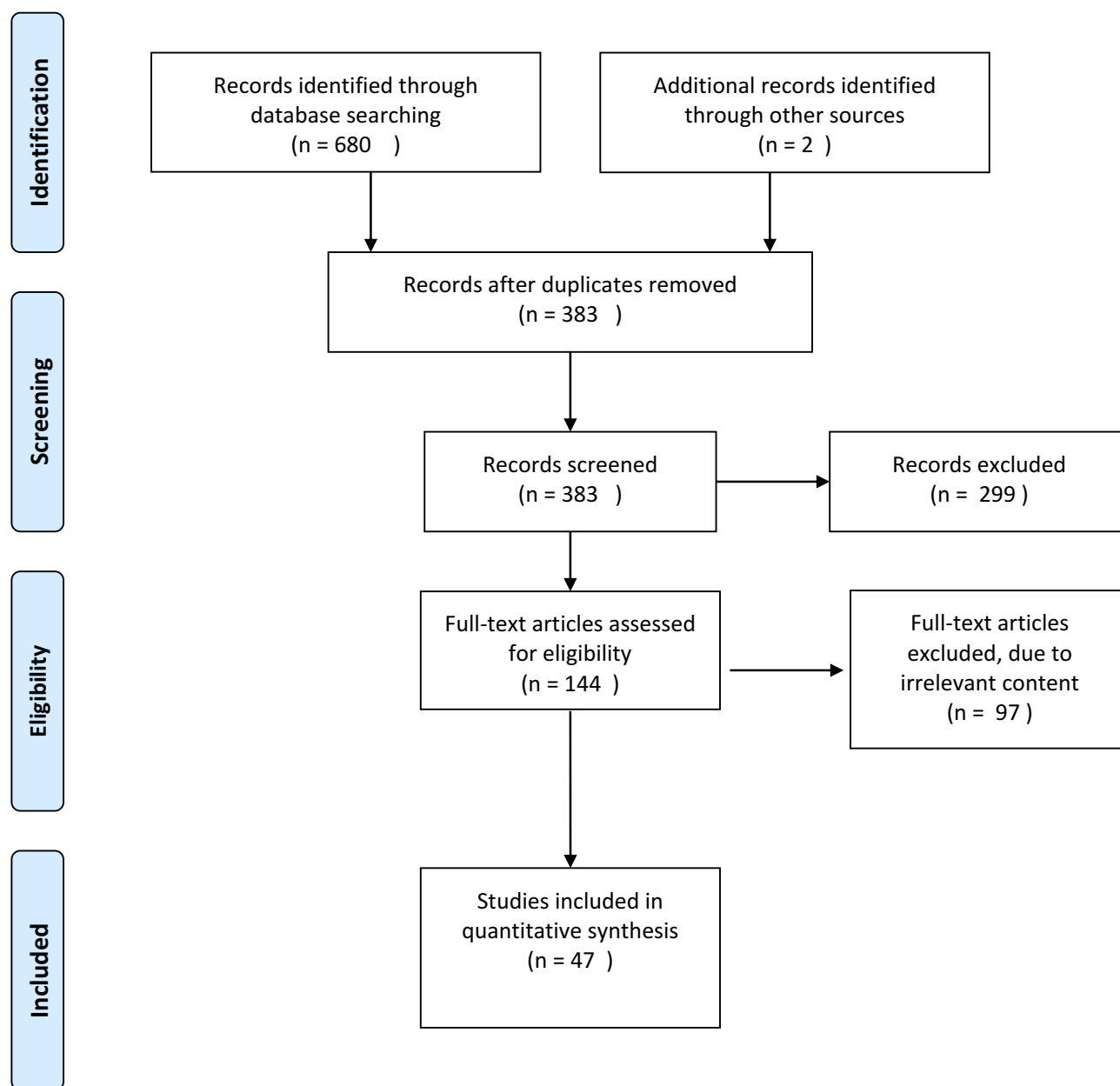


Figure 1 Flow chart of the systematic review search result.

Notes: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.³¹

The sites of musculoskeletal infections included joint and/or bone, spine and tenosynovitis. Of 520 pediatric musculoskeletal patients in which *K. kingae* infections were identified and where the studies reported the sites of infection, a large proportion of reported cases (65%) involved joint infections. This was followed by 18.4% osteoarticular infection (concomitant bone and joint involvement), with isolated bone and spine at 11.9% and 3.5%, respectively. French studies have reported *K. kingae* as the most common pathogen in septic

arthritis (Chometon et al 45%, Ilharreborde et al 52% and Aupiais et al 69%) in young children.^{2,29,39}

Most studies which identified gender reported a male preponderance (60.5%). A large proportion of *K. kingae* patients were also diagnosed in the autumn to winter season. Dubnov-Raz et al confirmed previous observations of a consistent seasonal pattern, characterized by higher incidences between May and January with a nadir between February and April in the northern hemisphere.⁴ As respiratory epithelial carriage of

Table 1 Summary of Characteristics of *Kingella kingae* (KK) Musculoskeletal Infection in Children

Authors	Sample Size	Frequency of KK	Sites of MSK Infections					Age (Months)			Gender (%Male)	Winter-Autumn Seasonality (%)
			Joint	Bone	OAI	Spine	Tenosynovitis	Median	Mean	Range		
Alcobendas (2018) ³²	253	10.28%										
Aupias (2015) ²	75	69.33%	52					18		13–40	75.0%	44.2%
Calvo (2016) ³³	252	13.89%	29	1	5							
Carter (2016) ³⁴	99	10.10%						6.1		0.4–18.2		
Ceroni, Cherkaoui (2010) ²⁸	28	82.14%	11		10	2		18.4	19.6	1–42	52.2%	
Ceroni (2011) ³⁵	60	50.00%	16	3	9	2		15.5		9–42	53.3%	
Ceroni, DF (2012) ²²	64	70.31%										
Ceroni (2013) ³⁶	10	20.00%				2		24.99			100.0%	
Ceroni (2014) ³⁷	14	57.14%		8				27.8		12–54	50.0%	
Ceroni, DF (2013) ³⁸	43	69.77%	19	7	1	3				4–48		
Chometon (2007) ³⁹	86	45.35%	27	7		5		14.6		6.8–80	43.6%	74.4%
Dayer (2018) ⁴⁰	13	23.08%				3				6–48		
Ferroni (2012) ⁴¹	197	22.34%	35	9						<4 yr		
Gene (2019) ⁴²	88	28.41%	23	2				25		1.2–80		
Gravel (2017) ⁴³	77	44.16%								6–48		
Hernandez R (2018) ⁴⁴	40	35.00%	14						13	9.7–14.2	71.4%	78.6%
Ilharreborde (2009) ²⁹	60	51.67%						16		8–68	58.1%	
Juchler (2018) ⁴⁵	138	47.83%			66			11.5	19.7	6–48		
Kanavaki (2012) ⁴⁶	31	67.74%	10	11							81.0%	
Lironi (2017) ⁴⁷	11	54.55%					6	14.5		8–22	50.0%	
Lundy (1998) ⁴⁸	60	16.67%	7	3				16.3		0.9–23.4	70.0%	80.0%
Moumle (2005) ⁴⁹	74	14.86%	11									

(Continued)

Table 1 (Continued).

Authors	Sample Size	Frequency of KK	Sites of MSK Infections					Age (Months)			Gender (%Male)	Winter-Autumn Seasonality (%)
			Joint	Bone	OAI	Spine	Tenosynovitis	Median	Mean	Range		
Nguyen (2018) ⁵⁰	85	10.59%	3	1		1		16		9–38	33.3%	
Nielsen (2019) ⁶⁶	64	25.00%	13	3								
O'Rourke (2019) ⁶⁷	41	12.20%			5							
Rasmont (2008) ⁶⁸	13	23.08%	3									
Slinger (2016) ⁶⁹	17	41.18%	7					19		0.86–74		
Spyropoulou (2016) ⁷⁰	65	33.85%										
Williams (2014) ⁵¹	68	39.71%	27					18.6		4–63	51.9%	

K. kingae is fairly stable throughout the year, the seasonal variation is likely to reflect an association with upper respiratory viral infections and stomatitis, allowing for passage of the colonizing *K. kingae* through the breached epithelium.

Management Strategies and Impact

Out of a collection of twenty-one papers which reported on clinical and laboratory findings (Table 3), a total of 569 paediatric patients with musculoskeletal infections caused by *K. kingae* were identified. The median temperature reported at admission was 37.9°C and mean temperature was 38.2°C. The range of temperature for patients on admission ranged between 36.2°C and 40.0°C. A trend could not be identified in the white blood cell count, C-reactive protein test (CRP) and the erythrocyte sedimentation rate (ESR) diagnostic tests of patients upon admission; however, some studies based on patients from France and Israel generally reported a milder clinical picture with normal to mildly raised inflammatory markers.^{4,35,71}

Fourteen papers, including 382 pediatric patients reported the duration of antibiotic treatment and the outcome of treatment in children with *K. kingae* infections (Table 4). The antibiotic treatment ranged from 7 to 21 days both for median and mean for both intravenous (IV) and oral treatments. IV antibiotics were administered between 7 to 14 days whereas oral antibiotics between 14 and 21 days. Most of the studies report good clinical and functional outcome following antibiotic treatment with no serious orthopaedic sequelae.

Discussion

The increasing knowledge surrounding musculoskeletal infection caused by *K. kingae* in paediatric patients reflects increasing awareness of the organism and ability to isolate it in the laboratory. Studies published mainly from Western Europe, North America as well as Australia have placed the bacterium as a major pathogen causing osteoarticular infection in healthy children below the age of 4 years.^{2,4} *K. kingae* is the leading pathogen for septic arthritis in this age group as reported in Europe.^{2,29,39,71} Soft tissue infection caused by *K. kingae* has also been reported, including a Swedish report of a fluctuant mass anterior to tendon Achilles insertion and 6 cases of pyogenic hand tenosynovitis from Switzerland.^{9,47,73} Three centers from France, Israel and Switzerland collaborated in 2018 to report on ten children (ages 6–22 months, mean 12.1) with *K. kingae* hand and wrist tenosynovitis. The authors recommended children aged below 48 months with at least

Table 2 Fraction of *K. kingae* (KK) infections among children aged <48 months

Author	Age <48m (n)	KK cases <48m (n)	Frequency of KK
Alcobendas (2018) ³²	136	25	18.38%
Aupiais (2015) ²	75	52	69.33%
Calvo (2016) ³³			
Carter (2016) ³⁴			
Ceroni, Cherkaoui (2010) ²⁸	28	23	82.14%
Ceroni (2011) ³⁵	60	30	50.00%
Ceroni, DF (2012) ²²	64	45	70.31%
Ceroni (2013) ³⁶	10	2	20.00%
Ceroni (2014) ³⁷			
Ceroni, DF (2013) ³⁸	43	30	69.77%
Chometon (2007) ³⁹	53	39	73.58%
Dayer (2018) ⁴⁰	13	3	23.08%
Ferroni (2012) ⁴¹	63	44	69.84%
Gene (2019) ⁴²	31	25	80.65%
Gravel (2017) ⁴³	77	34	44.16%
Hernandez R (2018) ⁴⁴	40	14	35.00%
Ilharreborde (2009) ²⁹			
Juchler (2018) ⁴⁵	138	66	47.83%
Kanavaki (2012) ⁴⁶	31	21	67.74%
Lironi (2017) ⁴⁷	11	6	54.55%
Lundy (1998) ⁴⁸	60	10	16.67%
Moumle (2005) ⁴⁹	31	11	35.48%
Nguyen (2018) ⁵⁰	85	9	10.59%
Nielsen (2019) ⁶⁶			
O'Rourke (2018) ⁶⁷			
Rasmont (2008) ⁶⁸			
Slinger (2016) ⁶⁹			
Spyropoulou (2016) ⁷⁰	21	20	95.24%
Williams (2014) ⁵¹			

one Kanavel sign, a recent viral infection and no prior penetrating hand injury should be highly suspected for *K. kingae* tenosynovitis. Seven children were confirmed by culture or PCR of the synovial fluid or blood, while three were presumed infected because of positive oropharyngeal PCR.⁷³ The authors suggested that the index of presumptive diagnosis for *K. kingae* infection in non-operated cases were high if the pathogen is detected in the oropharyngeal swabs by PCR. This was earlier reported (Ceroni et al, 2013) that detection of *K. kingae* in the oropharynx of ill children has a positive predictive value of 91% for *K. kingae* infection.³⁸

K. kingae is a recognized commensal in the oropharynx of young children particularly in ages 6 to 48 months, which

is considered a prerequisite for invasive disease which is commonly triggered by viral infections.⁷⁴ Children aged less than 6 months benefited from maternal protective antibodies; whereas at 6–48 months, susceptibility is due to relative immaturity of the immune system particularly with respect to the development of antibodies directed against the polysaccharide capsule.⁸ This observation also indicates that isolation of *K. kingae* from a normally sterile site in older children should alert the clinician to the possibility of underlying immunodeficiency or endocarditis indicating the need for cardiologic evaluation.⁷⁵

Yagupsky et al stressed the importance of blood cultures in a young child with unexplained skeletal system complaints even in the absence of fever or constitutional symptoms in areas of high prevalence of *K. kingae* infections.⁷⁶ Increasing awareness regarding this elusive emerging pathogen has led Lebel et al adopt a more aggressive approach in an attempt to aspirate and culture all suspected joint fluid in this age group.⁶³

In general, *K. kingae* musculoskeletal infections are reported to present with a milder clinical picture as compared to typical pathogens which present with high fever, elevated leukocyte count and inflammatory markers.^{35,71} Ceroni et al in their attempt to identify predictors for *K. kingae* osteoarticular infection when compared to typical pathogens found that 13 out of 30 (43.3%) of proven *K. kingae* cases remained afebrile with normal CRP and only two (15.4%) had an elevated leukocyte count. The authors concluded that a normal body temperature at admission, a normal WBC count and CRP do not exclude the diagnosis of *K. kingae*.³⁵ This is similar to Dubnov-Raz et al who reported that children frequently presented with body temperature of <38°C and lacked objective signs of osteoarthritis and leukocytosis.⁴ Chometon et al reported only 33.3% of *K. kingae* skeletal infection cases had fever on admission.³⁹ This current review found both mean and median temperature at presentation at 38.2°C and 37.9°C, respectively.

Experienced centers stress the importance of sampling and inoculation of aspirates into blood culture vials, ie, BACTEC blood culture system before transport to the laboratory. Successful isolation of *K. kingae* from bone and joint aspirates is strongly dependent on bacteriologic methodology used and PCR identifies multiple cases of *K. kingae* infection in “culture negative” cases.^{24,57} *K. kingae* is reportedly susceptible to most antibiotics including penicillin and cephalosporin, with resistance to vancomycin, clindamycin and fusidic acid.⁶¹ It is interesting to note there were four children who had

Table 3 Clinical Features of *Kingella kingae* Musculoskeletal Infection in Children

Author	KK Patients	Duration Before Diagnosis (Days)	At Admission – Median (Range)			
		Median (Range)	Temperature	CRP (mg/L)	ESR (mm/h)	Blood WCC (WBC/mm ³)
Basmaci (2011) ⁷¹	64	NA	37.7 (36.2–39.9)	39 (9–151)	NA	12.4 (7.8–27.9)
Ceroni (2011) ³⁵	30	NA	36.8 (36.2–38.6)	16 (10–140)	36 (11–102)	19.5 (10–140)
Ceroni (2013) ³⁶	10	NA	NA	18.1*	34.3*	9.3*
Chometon (2007) ³⁹	39	NA	NA	32.9*	NA	12.5*
Dubnov-Raz (2010) ⁴	169	(1–31)	38.3* (36–40)	38* (1.5–170)	25* (5–140)	4.4* (5.9–28.5)
Ferroni (2012) ⁴¹	44	NA	NA	42* (6–132)	NA	NA
Garron (2002) ⁵²	6	22.3 (8–60)	NA	NA	NA	NA
Gene (2004) ⁵³	9	16* (2–28) bone (n=6) 3.3* (2–5) joint (n=3)	NA	NA	NA	NA
Luegmair (2008) ⁵⁴	6	10.5 (3–15)	NA	16.7 (5–34)	NA	14.67 (8.01–22.8)
Mallet (2014) ⁵⁵	10	11 (4–30)	37.3 (36.2–39)	12 (10–31)	NA	10.3 (4.9–15.1)
Moumle (2003) ⁵⁶	18	(2–28)	37.6*	22.5 (6–41)	NA	13.3 (6.3–20.6)
Verdier (2005) ⁵⁷	24	8*	NA	32.9*	NA	13.2*
Williams (2014) ⁵¹	27	3 (0.5–5)	37.1	24 (8–47)	55 (48–60)	12.4 (9.9–13.8)
Basmaci (2013) ⁵⁸	2	7.5 (5, 10)	38.3(36.9–39.7)	NA	NA	14 (13.6–14.4)
Moylett (2000) ⁵⁹	3	4 (1–7)	NA	NA	69 (36–112)	NA
Birgisson (1997) ⁶⁰	5	5 (1–14)	37.9 (37.5–38.6)	13 (11–37)	15 (10–64)	13.8 (10.5–14)
Dubnov-Raz (2008) ⁶¹	20	1 (1–7)	38.6	3.3 (0.4–17)	48.5 (18–92)	14.8 (7.8–21)
El-Houmami (2016) ⁷	12	NA	NA	NA	NA	15 (7.7–23)
Gamble (1988) ⁶²	22	3 (1–60)	38.5 (36.5–40)	NA	40 (19–109)	10 (5.2–22.3)
Lebel (2006) ⁶³	15	NA	37.7* (36.6–39.1)	NA	30* (15–50)	15.5* (10.5–20.7)
Yagupsky (2014) ⁶⁴	34	2 (1–14)	38.5 (37.5–40)	NA	28.5 (5–85)	14.2 (6.6–25.7)

Note: *Mean.

K. kingae proven osteoarticular infection and recovered completely despite never receiving antibiotics.⁶³ There were also two irritable hip cases with *K. kingae* isolated from blood but were self-limiting, without antibiotic treatment.⁶⁴

This raises the question about the implications of misdiagnosing a suppurative joint infection caused by *K. kingae* since it appears to be self-limiting in certain cases. Some authors have even questioned the need to treat *K. kingae* due to these self-limiting reports, and it has been suggested that invasive procedures are not necessary. In contrast, there have been reported cases of severe infections which involved abscess formation, growth plate damage and valgus deformity of

lower limbs. Narrowed disc spaces in the spine were reported but without any functional or clinical morbidity.^{24,55,77} In another report, five children had more than one presentation to emergency department while one child required two arthroscopic knee washouts in order to gain control of the infection. These reports suggest that infection with *K. kingae* should not be generally considered benign or self-limiting.⁵¹ β -lactamase production is a survival strategy shared by many pathogens of respiratory origin in order to colonize the human mucosal surface. Common pathogens of the upper respiratory tract, ie, *Staphylococcus aureus*, *Haemophilus influenzae* are repeatedly exposed to antimicrobials resulting in high rates of

Table 4 Impact and Management Strategies of *Kingella kingae* Musculoskeletal Infection in Children

Author	KK Cases	Antibiotic Duration Days median (range) ^a		Outcome (Complication and/or Sequelae)
		IV	Oral	
Basmaci (2011) ⁷¹	64	NA	NA	One child had repeated drainage
Ceroni (2011) ³⁵	30	4.5*	22.2*	NA
Dubnov-Raz (2010) ⁴	169	(7–21)	(14–28)	NA
Garron (2002) ⁵²	6	10	21	Full clinical recovery
Mallet (2014) ⁵⁵	10	8* (2–15)	27* (21–30)	2 had growth plate damage
Moumille (2003) ⁵⁶	18	6* (4–10)	56	Full recovery at 6 months follow-up
Verdier (2005) ⁵⁷	24	12	(15–45)	Clinically good at 30 days
Williams (2014) ⁵¹	27	6 (2–28)	NA	One child had repeated knee arthroscopic washouts
Basmaci (2013) ⁵⁸	2	5	20	Full recovery 3 months
Cherkaoui (2009) ²⁵	2	6	14	Full recovery at 2 months
Dodman (2000) ⁶⁵	2	7	17.5	NA
Moylett (2000) ⁵⁹	3	14 (7–21)	7	NA
Birgisson (1997) ⁶⁰	5	14 (0–21)	14 (7–28)	All recovered, including one self-limiting ankle arthritis
Dubnov-Raz (2008) ⁶¹	20	(14–21)	(14–21)	NA

Notes: For articles where median is not reported, data for mean was available and this was included into the table and marked with *. ^aDemonstrated therapeutic approach in terms of duration of antibiotics given, the IV portion showing the days of hospitalisation.

therapy resistance. *K. kingae* which is usually susceptible to common antibiotics β -lactamase production and spread has been detected in the USA since 1993, Iceland since 1995 and Israel since 2001.⁷⁸ Production of β -lactamase has important therapeutic implications as this may cause severe skeletal system morbidity and fatal endocarditis.

Despite the recognition of self-limiting cases, reports of significant complications would indicate that at a minimum, appropriate antibiotics should be administered to patients when the organism is recovered from a normally sterile body site. Patients with *K. kingae* isolated from blood should be immediately suspected of bacterial endocarditis and treated at once with antibiotics. Septicaemia with endocarditis is the most severe form of infection caused by *K. kingae* with reported fatalities.^{4,79}

K. kingae is resistant to clindamycin, fusidic acid and vancomycin, which are used in the treatment of osteomyelitis and MRSA related infections.⁶¹ Hence, the further relevance of identifying *K. kingae* in order to commence an appropriate antibiotic.

A limitation of this current review is that most data were sourced from affluent countries with access to routine PCR

investigation. Microbiological confirmation of skeletal infection enables early diagnosis, identification of the pathogen and antibiotic susceptibility to achieve a good outcome. Molecular technology has reduced the number of false-negative cases in cases of transient synovitis and reactive arthritis which are frequently treated at home with rest and analgesia, usually without antibiotics.⁶⁴ A high index of suspicion is required for *K. kingae* infection in children 6–48 months with suggestive clinical features and aspirate samples should be inoculated and transported in blood culture vials if PCR is not available. Some authors suggest total antibiotic duration 2–3 weeks for septic arthritis, 3–6 weeks for osteomyelitis and 3–12 weeks for spondylodiscitis in cases where *K. kingae* is isolated.^{72,80} These were accumulated experiences based on collection of individual case reports or case series with several expert reviews regarding *K. kingae*. Experience from other parts of the world is required to examine the changing epidemiology of this musculoskeletal pathogen to complete a worldwide prevalence picture. Treatment strategies lack solid recommendations, duration of treatment is not well defined and all these should be studied in larger prospective studies.

Conclusion

The practical implication of this study is that a high index of suspicion is needed due to the subtle presentation of *K. kingae* musculoskeletal infection in young children below 48 months. Increased clinician awareness of this age group, enhanced laboratory protocols, and communication between clinicians and laboratory staff is critical to achieve a better understanding of the true burden of musculoskeletal infections caused by *K. kingae*. The need for appropriate culture media that can detect *K. kingae* namely blood culture bottles and the availability of molecular testing cannot be overemphasized. Failure to take this approach may lead to inappropriate diagnosis of culture-negative arthritis in cases of *K. kingae* infection.

Acknowledgments

The authors thank Natalie Dempster for assistance with the database search.

Disclosure

The authors report no conflicts of interest in this work.

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