Epidemiology and Clinical Manifestations of *Kingella kingae* Disease

Kevin J. Downes

Abbreviation

OAI Osteoarticular infection

Epidemiology

A precise description of the epidemiology of *Kingella kingae* disease was limited historically by the inability of standard culture techniques to reliably isolate the organism from tissue, body fluids, and blood. *K. kingae* is a facultative anaerobic β-hemolytic gram-negative bacterium that grows poorly on standard solid media [1, 2]. Until recently, most data regarding *K. kingae* disease stemmed from case reports and small case series. However, over the past 20 years, with the more routine use of selective culture media and molecular diagnostics by microbiology laboratories, the clinical relevance of this emerging pathogen has become more fully appreciated.

Age

Age is the most important factor influencing *K. kingae* oropharyngeal carriage [3, 4] and hence *K. kingae* invasive disease. *K. kingae* is carried on the tonsillar surfaces of young children, generally without producing symptoms [2]. Carriage is rare in the first few months of life [4–6] and begins to appear around 6 months of age, achieving rates of approximately 3–12 % in children 6–48 months old [3–7]. In a random sample of patients undergoing throat culture in Southern Israel from 1998 to 2001, Yagupsky and colleagues found carriage rates of 3.2 % in children

K.J. Downes (✉)
Division of Infectious Diseases, The Children's Hospital of Philadelphia,
3535 Market Street, Suite 1409, Philadelphia, PA 19104, USA
e-mail: downeskj@email.chop.edu

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0–3 years of age, 1.5 % in children 4–17 years of age, and 0.8 % in individuals 18 years and older [3]. More recent studies have reported higher rates of pharyngeal carriage among young children [4, 7]. For example, Amit and colleagues found that carriage ranged between 5 and 12 % in children 6–30 months of age in Southern Israel [4]. Similarly, Anderson de la Llana et al. found that the mean prevalence of carriage was 8.7 % (range 7.6–10.4 %) in a cohort of healthy, asymptomatic Swiss children 7–48 months of age, with no differences across subgroups of age [7].

Oropharyngeal carriage is believed to be the first step in the pathogenesis of invasive disease, a conclusion supported by studies that have detected universal carriage in patients with invasive disease [8]. Yagupsky et al. observed that nearly all cases (98.6 %) of *K. kingae* invasive disease occurred in children younger than 48 months of age, with an incidence that was more than four times higher among children aged 7–12 and 13–24 months of age than among children 25–36 months of age [3]. In a nationwide study of *K. kingae* invasive disease in Israel, almost all children (96 %) were between 6 and 29 months of age, as highlighted in Fig. 1, which displays the age distribution among the 290 children [9]. The higher incidence of invasive disease among children 6–24 months old may coincide with decreased humoral immunity against the pathogen [10].

Osteoarticular infections (OAIs) are the most common form of *K. kingae* invasive disease [9]. In a recent review of 566 cases of *K. kingae* OAI reported in the English literature from 2000 to 2014, 80 % occurred in children between the ages of 4 months and 4 years [11]. In a cohort of children in France with OAIs, the median age of patients with *K. kingae* infection was 14.6 months (range 6.8 months to 6.8 years), with 95 % of these *K. kingae* infections occurring in children younger than 3 years [12]. Similarly, in a prospective cohort study of children 7–48 months of age in Geneva, Switzerland with confirmed OAIs due to *K. kingae,* children 7–24 months of age had an increased odds of OAIs [7].

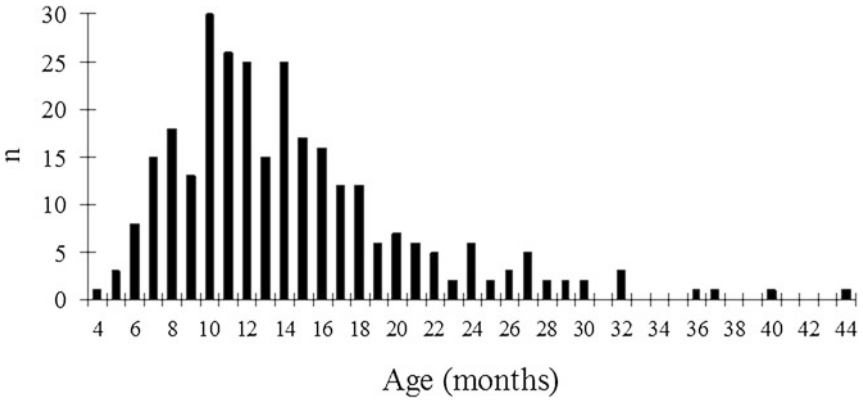

Fig. 1 Age distribution of invasive *K. kingae* infection in otherwise healthy children. Reproduced with permission from Dubnov-Raz et al. [9]. Copyright © Wolters Kluwer Health, Inc.

Few studies have reported the population incidence of *K. kingae* disease [9, 13, 14]. Among children 6–48 months of age in Geneva, the annual incidence of OAIs due to *K. kingae* was estimated to be less than 1 % (0.0664 %) [13]. Based on the population-based studies in Southern Israel, the annual incidence of invasive *K. kingae* disease was 9.4 per 100,000 in children age 0–4 years [9] and roughly 20 per 100,000 in children less than 2 years of age [14].

Gender

The influence of gender on the risk of oropharyngeal carriage and invasive disease with *K. kingae* varies among studies. In a study of asymptomatic Swiss children, Anderson de la Llana and colleagues reported that males were more likely than females to be carriers (10.9 % vs. 6.4 %, $p < 0.05$) [7]. However, other studies have found similar rates of carriage among male and female children [3]. Some studies have reported that invasive disease develops more often in males [3, 15], as highlighted in a cohort of 74 children with invasive disease in Southern Israel that included 50 males ($p < 0.045$) [3]. In contrast, the series of 566 *K. kingae* OAIs reported between 2000 and 2014 identified an equal gender distribution of cases: 1.14 male per 1 female [11].

Seasonality

There may be a seasonal pattern to the development of invasive disease due to *K. kingae*. In the large study by Anderson de la Llana et al., the rate of asymptomatic pharyngeal carriage did not differ by time of year, but nearly two-thirds of OAIs occurred between July and November [7]. Similarly, in a series of studies in Israel, more cases of invasive disease occurred between July and December [3, 9, 14]. In a single-center study from France, the peak incidence of *K. kingae* septic arthritis was in October [16]. The frequent presence of upper respiratory tract symptoms in children with *K. kingae* invasive disease suggests that viral coinfections may predispose children to the development of invasive disease [14, 17–19]. Thus, the seasonal distribution of invasive *K. kingae* disease may mirror that of viral upper respiratory pathogens.

Geographic Location

Investigators in Israel, Switzerland, and France have contributed disproportionately to the current understanding of the epidemiology of *K. kingae* carriage and disease. It can be argued that the populations studied from these regions are diverse,

allowing findings to be extrapolated to other pediatric populations. The similar rates of pharyngeal carriage [3, 4, 7] and invasive disease [9, 12, 13] across these countries support the conclusion that *K. kingae* is a universal pathogen in young children. Yet, there has been a relative paucity of systematic investigation from other countries. Undoubtedly, young children are at highest risk for invasive *K. kingae* disease globally, but the prevalence of disease and the influence of specific risk factors (e.g., gender and season) on carriage and disease may differ among geographic regions.

Recent data indicate that β-lactamase production varies among *K. kingae* isolates from different countries [20, 21], highlighting the possibility that there are important genetic differences in the circulating strains that are associated with carriage and that cause disease in different geographic locations [22]. Additional data indicate that specific clinical syndromes [23], transmissibility [24], and colonization [25] vary based on the *K. kingae* clone involved. Thus, until systematic epidemiologic investigations are conducted in more parts of the world, the global impact of this pathogen cannot be fully understood.

Socioeconomic Factors and Childcare Attendance

The socialization of young children likely contributes to *K. kingae* carriage and disease. As with other bacteria that reside in the upper respiratory tract, child-to-child transmission is believed to be the primary mechanism of spread [1]. During an 11-month longitudinal study of 48 daycare attendees, nearly three quarters of the children studied (n = 35, 73 %) carried *K. kingae* at least once [6]. In a more recent study of carriage among children followed in well-newborn clinics in Israel, only 40 % (283 or 716) of children 2–30 months of age carried the organism one or more times [4]; half of the children in this study attended day care. The difference in carriage rates between these two studies raises the possibility that daycare attendance increases the risk of *K. kingae* acquisition. This conclusion is supported by other studies that found daycare attendance to be a strong independent risk factor for *K. kingae* carriage [5]. Reports of outbreaks of invasive *K. kingae* disease in daycare settings suggest that child-to-child transmission of virulent strains also occurs [26–28].

Amit et al. compared the epidemiology of *K. kingae* invasive disease between Jewish children and Bedouin children less than 4 years of age during a 23-year period in Southern Israel [15]. Despite the fact that both populations lived in the same part of the country and received medical care from the same tertiary care center through the same insurance, Jewish children had a significantly higher incidence of invasive disease (12.21 vs. 5.53/100,000, $p < 0.05$). According to the authors, children of these two ethnicities have similar carriage rates, implying that other factors must play a role in the discrepant rates of invasive disease. There were important differences in age (Jewish children were younger) and socioeconomic status (Bedouin children more often live in poverty and crowded conditions) that

could explain the difference in rates between the two populations. However, Jewish children also had a clustering of *K. kingae* strains, with a single clone accounting for more than 40 % of infections. Other studies from these investigators have demonstrated that daycare attendance is a risk factor for carriage among Jewish children but not among Bedouins [5], suggesting the possibility that social factors and the amount of close contact with other young children play a role in the transmission of strains causing invasive disease.

Clinical Manifestations

Kingella kingae causes a number of different types of invasive disease. The most common forms of *K. kingae* disease are OAIs and bacteremia. Endocarditis is rare but can be severe [9, 29]. As with asymptomatic carriage, invasive disease occurs almost exclusively in previously healthy young children [9, 30]. Children with underlying chronic health conditions who develop invasive *Kingella* infections tend to be older: mean age 51.6 ± 51.9 months versus 14.3 ± 6.4 months in otherwise healthy children [9]. Table 1 displays presenting clinical and laboratory data from the largest case series to date of children with invasive *K. kingae* disease (n = 322) [9].

The pathogenesis of invasive disease likely involves bacterial translocation across the oropharyngeal mucosal barrier and entry into the bloodstream [2]. Children with *K. kingae* invasive disease frequently have concurrent or preceding symptoms of other acute infections, such as upper respiratory tract infections, aphthous stomatitis, or acute gastroenteritis [9, 17, 19, 31]. Compromise of the normally protective respiratory epithelium can lead to dissemination of the bacterium to various sites in the body, including joints, bones, and endocardium. The capacity of *K. kingae* to cause invasive disease may vary based on the specific clone involved, resulting in different clinical syndromes [23].

Osteoarticular Infections

Osteoarticular infections (OAIs) are the most prevalent form of invasive disease caused by *K. kingae* [9]. Septic arthritis, osteomyelitis, and spondylodiscitis make up the majority of *K. kingae*-associated OAIs. In a systematic review of *K. kingae* OAI cases reported between 2000 and 2014, septic arthritis accounted for 73.1 % (n = 404/553) of cases, osteomyelitis for 15.7 % of cases, and spondylodiscitis for 5.4 % of cases [11]. Less common forms of osteoarticular disease include cartilage matrix infections [32] and tenosynovitis [33].

With incorporation of specialized culture techniques and molecular diagnostic methods into routine clinical microbiology laboratory practices, several studies have reported that *K. kingae* is the leading cause of OAIs in children less than four

Table 1 Clinical and laboratory data of children with invasive *K. kingae* infections

	Occult bacteremia (n = 145)	Bacterial endocarditis (n = 8)	Skeletal infections (n = 169)
Age (mo)	13.2 ± 6.3 (4–176)	25.4 ± 21.7* (10–66)	15.5 ± 7.2* (5–40)
Maximal temperature (°C)	38.8 ± 0. 8 (36.7–40.0)	39.6 ± 0.7* (38.5–40.5)	38.3 ± 1.0* (36.0–40.0)
Symptom duration before diagnosis (d)	3.7 ± 2.2 (1–14)	7.8 ± 6.0 (1–14)	4.0 ± 4.6 (1–31)
Symptom duration after diagnosis (d)	3.0 ± 2.4 (1–14)	13.5 ± 11.8* (5–30)	6.7 ± 5.2* (1–30)
Blood WBC count (cells/mm^3)[a]	14,350 ± 6170 (1200–41,300)	18,600 ± 13,200 (5660–47,040)	14,797 ± 4383 (5860–28,450)
CRP (mg/dL)[a]	2.3 ± 1.9 (0.4–6.6)	11.0 ± 8.7* (6.0–24.7)	3.7 ± 3.8 (0.15–17.0)
ESR (mm/h)[a]	32 ± 20 (4–115)	90 ± 25* (60–120)	44 ± 25* (5–140)
Synovial WBC count (cells/mm^3)[a]	–	–	105,368 ± 72,296 (800–325,000)

Reproduced from Dubnov-Raz et al. [9], with permission from Wolters Kluwer Health, Inc.
Values are expressed as mean ± SD. Values in parenthesis mean range
*Values that differ significantly ($p < 0.05$) from those found in the occult bacteremia group
[a]Upon diagnosis

years of age, responsible for 40–70 % of confirmed cases [8, 12, 16, 34, 35]. Ferroni and colleagues found that *K. kingae* was the cause of 53 % (n = 44/83) of proven OAIs in children <15 years of age [34]; *K. kingae* was the most common pathogen isolated and was found exclusively in children less than 4 years of age. Similarly, in a study examining OAIs in patients at DeBrousse Hospital in Lyon, France, Chometon and coworkers discovered that *K. kingae* was the predominant pathogen in children less than 4 years of age, with *Staphylococcus aureus* assuming a dominant role in older children (see Fig. 2) [12]. In another case series of children <16 years of age hospitalized for infectious and non-infectious arthritis in France, *K. kingae* was the most common cause of septic arthritis (69 %) and the most common cause of arthritis of any form, infectious or non-infectious [16]. In a recent report from the University of Texas Southwestern Medical Center, *K. kingae* was the second most common cause of septic arthritis among children less than 18 years of age over a 2-year period [36].

Symptoms of *K. kingae* OAI can be insidious, particularly in patients with osteomyelitis or spondylodiscitis. In a cohort study of consecutive cases of OAIs, the mean duration from onset of symptoms to hospitalization among the 23 cases of *K. kingae* infection was 9.3 days [35]. In the large case series by Dubnov-Raz et al., the mean time to presentation was 3.2 ± 3.0 days for patients with septic arthritis and 9.2 ± 9.4 days ($p < 0.001$) for patients with osteomyelitis [9]. A study by Gene et al. reported an average time to diagnosis of *K. kingae* osteomyelitis of more than two weeks [30]. Thus, diagnosis of *K. kingae* OAI may be delayed due to the subacute nature of infection with this pathogen, especially in cases of *K. kingae* osteomyelitis.

K. kingae may elicit a less intense inflammatory response compared with other pathogens. In a retrospective study comparing 30 children with *K. kingae* OAIs to

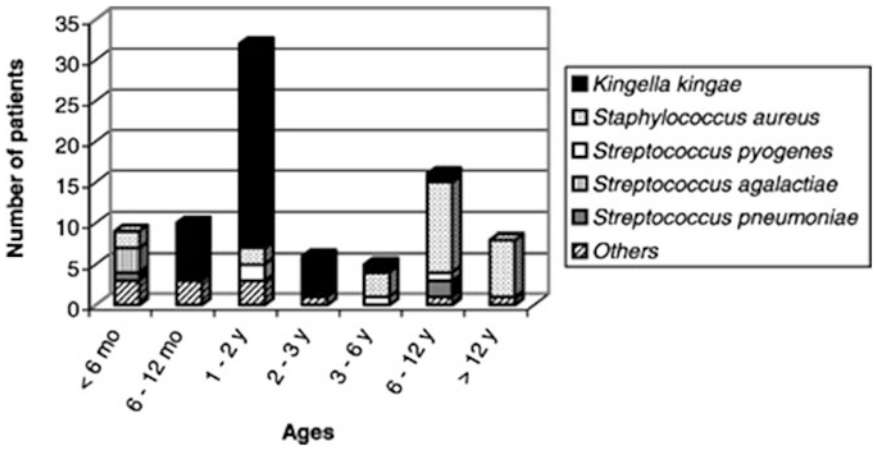

Fig. 2 Distribution of pathogens of 86 bacteriologically documented osteoarticular infections according to the age of patients. Reproduced with permission from Chometon et al. [12]. Copyright © Wolters Kluwer Health, Inc.

30 children with OAIs due to other pathogens [37], only 10 % of children with *K. kingae* infection had a fever (>38 °C) at admission compared to 96.7 % of children with other pathogens. The area under the receiver operator curve for temperature at admission was 0.981 to distinguish OAIs due to *K. kingae* from OAIs due to other pathogens [37]. The laboratory evidence of infection in *K. kingella* OAIs is also more often absent. Dubnov-Raz et al. found that fewer than 50 % of patients with *K. kingella* OAIs had a peripheral white blood cell count above 15,000 cells/mm^3 [9]. Of 23 OAIs caused by *K. kingae* reported by Ceroni et al. [35], only 2 had an elevated peripheral white blood cell count. In a prospective cohort of children with varying OAIs of all causes, CRP was lower in children with documented *K. kingae* infections compared with infections due to other pathogens: mean 4.2 mg/dL versus 8.2 mg/dL, $p < 0.005$ [34]. Similarly, Chometon reported only a modest increase in CRP (mean 3.2 mg/dL) at admission among 33 patients with *K. kingae* OAIs [12].

The outcomes of children with *K. kingae* OAIs are generally favorable [11, 34, 38]. In a study comparing children with *K. kingae* septic arthritis and children with *S. aureus* septic arthritis [38], patients in both groups were similar with regard to numerous factors at initial presentation: symptom duration, fever, CRP, WBC count. However, patients with *K. kingae* had more rapid resolution of fever and normalization of CRP and fibrinogen than did patients with *S. aureus* septic arthritis, suggesting a more rapid response to therapy. Additionally, patients with *K. kingae* had significantly fewer complications (<2 % vs. 23 %), although the types of complications were not defined in this study [38]. Severe cases of *K. kingae* OAI appear to be uncommon [39].

Septic Arthritis

Septic arthritis is the most common type of OAI due to *K. kingae* [9, 11, 12]. In a large case series of invasive *K. kingae* infections from 8 centers in Israel, septic arthritis accounted for 83 % (140/169) of all OAIs [9]. Lower extremities tend to be affected most often [12, 35], with the knee the most commonly infected joint [9, 11, 40]. In a case series from France, *K. kingae* more often caused septic arthritis of the knee, while other organisms more commonly infected the hip and ankle ($p < 0.01$) [16]. Figure 3 displays the cumulative site distribution of *K. kingae* septic arthritis cases as reported by Al-Qwbani et al. in their systematic review [11].

Similar to patients with other etiologies of septic arthritis, children with *K. kingae* septic arthritis present with localized pain, joint swelling, erythema, immobility, and evidence of joint effusion [30]. Fever may be a less pronounced presenting symptom than in *S. aureus* septic arthritis [36]. When present, fever resolves more quickly after initiation of appropriate treatment in patients with *K. kingae* than *S. aureus* septic arthritis. In a single center's experience, the mean duration of fever was 0.2 days (range: 0–3) in children with *K. kingae* septic arthritis versus 3.5 days (range: 0–27) in children with *S. aureus* septic arthritis ($p < 0.0001$) [38]. Synovial fluid aspiration generally reveals inflammation

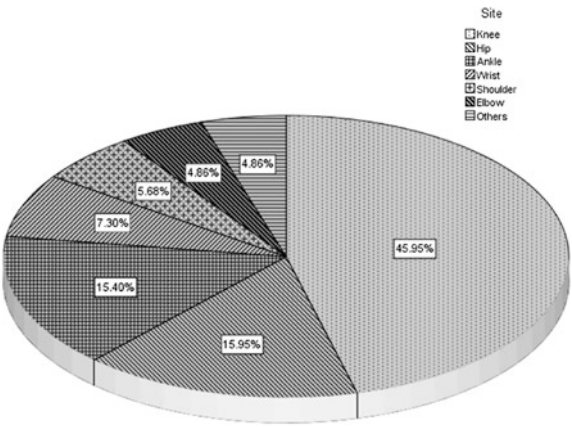

Fig. 3 Site distribution of septic arthritis caused by *K. kingae*. Reproduced from Al-Qwbani et al. [12]. Copyright © SAGE Publications

consistent with pyogenic arthritis [11]. However, among 78 children with septic arthritis who had synovial fluid sampling in the large nationwide study in Israel by Dubnov-Raz et al. [9], 18 (23 %) had synovial fluid WBC with <50,000 cells/mm^3 (mean 105,368 ± 72,296).

Osteomyelitis

Osteomyelitis is less common than septic arthritis as a manifestation of *K. kingae* infection [9, 11, 39]. Infections may develop in any bone, but there are numerous reports describing atypical locations such as the calcaneus [9, 41], sternum [42], and clavicle [43]. Figure 4 displays the site distribution of *K. kingae* osteomyelitis cases as reported by Al-Qwbani et al. [11]. Most cases present subacutely [9], sometimes resulting in formation of a Brodie abscess by the time the diagnosis is made [9, 18, 44]. Although uncommon, severe cases of osteomyelitis with metaphyso-epiphyseal or epiphyseal abscess formation can occur [39]. *K. kingae* has also been described as the most common cause of primary epiphyseal or apophyseal subacute osteomyelitis in children less than 4 years of age [45]. This form of subacute osteomyelitis affects the epiphysis and generally presents as an indolent process with few laboratory signs of infection. The femur (70 %) and tibia are involved most often [45].

Spondylodiscitis

Spondylodiscitis is an infection of the intervertebral disk space and adjacent vertebral bodies. Diagnosis can be challenging in young children whose symptoms can include refusal to sit or walk, abnormal gait, or back stiffness [46]. *K. kingae* is among the most common causes of spondylodiscitis in children, accounting for at

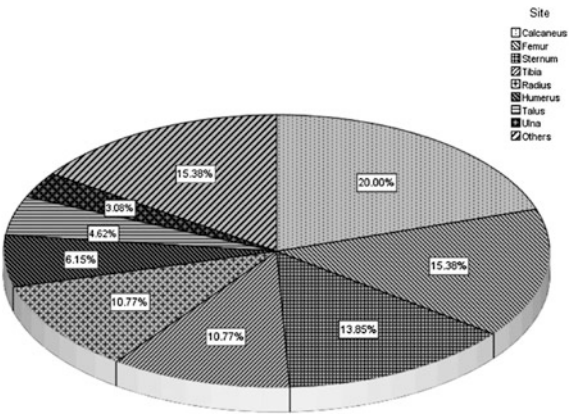

Fig. 4 Site distribution of osteomyelitis caused by *K. kingae*. Reproduced from Al-Qwbani et al. [12]. Copyright © SAGE Publications

least 25 % of confirmed cases [46]. Similar to other OAIs due to *K. kingae*, spondylodiscitis occurs predominantly in young children and presents in an indolent manner [46–48]. The lumbar spine is affected most often, and asymptomatic narrowing of the disk space is the expected long-term outcome, as with all causes of spondylodiscitis [47].

Bacteremia

Bacteremia can occur concurrently with other invasive infections [9, 49] or in isolation as occult bacteremia [9, 31]. Positive blood cultures are obtained in about one in four patients with OAIs in general and are a prerequisite for the diagnosis of bacterial endocarditis [9]. Because of the inferiority of culture methods compared to DNA-based techniques to detect *K. kingae*, accurate estimates of the population incidence of bacteremia are not known. Over an eleven-year period (1996–2006) at Schneider Children's Medical Center of Israel, a tertiary care pediatric hospital in central Israel, there were 42 bloodstream infections with *K. kingae*, including 4 that occurred during cases of endocarditis and none associated with osteomyelitis [31]. In a study of 53,503 blood cultures obtained over a 35-month period in the pediatric emergency department at Soroka University Medical Center in Southern Israel [50], 16 were positive for *K. kingae.* At the Children's Hospital of Philadelphia, 301,716 blood cultures were obtained from 53,544 children between 2004 and 2014, including 5 that were positive for *K. kingae* (unpublished data). Thus, there may be regional differences in rates of *K. kingae* bacteremia, although this issue has not been formally investigated.

Occult bacteremia is defined as bacteremia without a focal infection and is the second most common manifestation of invasive *K. kingae* disease [9]. Children with bacteremia may have osteoarticular complaints without overt evidence of bone or joint infection [31]. In a large case series of 322 invasive infections from 8

institutions in Israel, 140 (43.6 %) children had occult bacteremia [9]. Inflammatory markers in this series were generally low: mean CRP 2.3 ± 1.9 mg/dL and ESR 32 ± 20 mm/h. Many children with bacteremia have a concomitant acute illness such as aphthous stomatitis, upper respiratory tract infection, or acute gastroenteritis [9, 31]. One of these conditions was present in 79 % of children with *K. kingae* bacteremia based on the retrospective review by Dubnov-Raz et al. [31].

Endocarditis

Kingella kingae is one of the HACEK organisms (*Haemophilus* species; *Aggregatibacter* species; and *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species), a group of fastidious gram-negative bacilli that are responsible for approximately 5–10 % of native valve endocarditis cases in adults [51] and children [52]. These organisms are also believed to be responsible for a portion of culture-negative endocarditis cases, due to challenges in isolating these organisms using conventional culture techniques. Some case series have detected *K. kingae* in approximately 7 % of cases of pediatric infective endocarditis [53, 54]. Poor dental health and dental procedures are reported risk factors for endocarditis due to HACEK pathogens, including *Kingella* [51, 55]. Prosthetic valve endocarditis due to *K. kingae* is rare and is generally treatable with antibiotics alone, although complications such as paravalvular abscess have been described [56].

Kingella kingae endocarditis in children is uncommon, accounting for 2–7 % of invasive *K. kingae* infections [9, 31]. Whereas *K. kingae* OAIs occur almost exclusively in young children, *K. kingae* endocarditis may affect older children as well [9]. In a recent PubMed review of 42 reported cases of pediatric *K. kingae* endocarditis, 20 % occurred in children >4 years of age [57]. Underlying congenital heart disease may be a risk factor for *K. kingae* endocarditis. In a review by Foster et al., congenital heart disease was described in a third of reviewed cases, although a native valve was infected in 95 % of the cases [57]. *K. kingae* endocarditis in children is often severe, resulting in valve damage [9, 58, 59] or cerebral complications such as meningitis or stroke [57, 60–63].

Other Clinical Manifestations

Case reports have described *K. kingae* as the cause a number of other invasive infections, including soft tissue abscesses [18], meningitis [64], peritonitis [49], urinary tract infection [65], and pericarditis [66]. Ocular infections such as endophthalmitis [67] and keratitis [68] have also been reported. The routine use of molecular diagnostic techniques on various clinical specimens will likely lead to additional reports in the future and a better understanding of the role of *K. kingae* as an invasive pathogen.

Conclusions

Kingella kingae is an emerging pathogen worldwide. With the increasing incorporation of molecular diagnostic tests into routine microbiological practice, knowledge of the impact and clinical relevance of this organism is growing. Although reports of infections in adults exist, oropharyngeal carriage and invasive disease predominantly affect young children. OAIs such as septic arthritis, osteomyelitis, and spondylodiscitis as well as occult bacteremia disproportionately affect children less than 4 years of age. *K. kingae* is a prominent pathogen causing OAIs in young children, and septic arthritis is the most common form of *K. kingae* disease. The time to medical care is often delayed because of the relatively indolent nature of *K. kingae* disease, but outcomes are generally favorable. *K. kingae* endocarditis is a rare but significant infection in patients of all ages and tends to be associated with poor outcomes and significant complications in children.

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