Outbreaks of Invasive *Kingella kingae* Infections in Daycare Facilities: Approach to Investigation and Management

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In recent decades, the number of young children attending out-of-home daycare has increased in Western countries.[1] This shift to out-of-home childcare had a substantial public health impact because transmission of agents of human disease, and particularly of pathogens of respiratory origin, is enhanced greatly in this setting. Clusters of severe *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis* diseases have occurred in daycare facilities.[2-4] Over the last few years, outbreaks of bacteremia, skeletal system infections, endocarditis, and fatal meningitis caused by the emerging pediatric pathogen *Kingella kingae* have been detected in daycare centers.[5-11] This Gram-negative coccobacillary member of the upper respiratory tract microbiota increasingly is being recognized as the most common agent of skeletal system infections in children aged 6-36 months in countries in which improved culture methods and sensitive nucleic acid amplification tests (NAATs) routinely are used for detecting the organism.[12-15] The aims of this review are to describe the clinical and epidemiologic features of *K kingae* outbreaks in daycare centers, to delineate the microbiologic tools available for detecting the organism, and to summarize the current approach to investigate and manage these events.

K kingae Carriage

K kingae is carried on the oropharyngeal epithelium,[14] and the colonized mucosal surface is the source of person-to-person transmission,[16] as well as the portal of entry of the organism to the bloodstream, from which it may disseminate to joints, bones, or the endocardium, for which the bacterium exhibits particular tropism.[17,18] Genotyping of *K kingae* organisms by pulsed-field gel electrophoresis or multilocus strain typing (MLST) demonstrated that the species exhibits remarkable genomic heterogeneity and strains show wide differences in their virulence.[19] Although some strains frequently are isolated from healthy carriers but seldom cause clinical infections, others are responsible for most of the disease burden and are associated significantly with bacteremia, osteoarthritis, or endocarditis.[20-22]

Studies have revealed that 10%-12% of the healthy pediatric population in Israel and Switzerland harbors the organism between the ages of 12 and 24 months,[23-25] coinciding with the peak attack rate of invasive infections.[26] A recent study carried out in New Zealand, where the attack rate of *K kingae* endocarditis is unusually high, found that 23% of children 6 months to 4 years of age are colonized by the organism.[27] Pharyngeal carriage of *K kingae* and occurrence of disease before 6 months of age are exceptional, suggesting protection conferred by maternal immunity and limited social contacts.[28] The colonization rate significantly decreases in children older than 3 years and adults, indicating cumulative immunity after repeated exposure and carriage.[24,29]

The colonization rate is enhanced substantially among daycare center attendees. In an 11-month longitudinal study, 35 of 48 (73%) children attending a daycare facility carried *K kingae* at least once, with an average point prevalence of 28%[14]; typing of the isolates showed genotypic identity, demonstrating interpersonal spread of the organism.[16] The link between out-of-home childcare and *K kingae* colonization was confirmed in a large prospective study in which daycare attendance was strongly and independently associated with *K kingae* carriage.[23]

Invasive *K kingae* Infections

More than 90% of all invasive *K kingae* infections are diagnosed in otherwise-healthy children 6-36 months of age.[26,29] Disease in older children and adults frequently is associated with chronic debilitating diseases, immunodeficiency, or underlying cardiac valve pathology.[29] Affected children frequently present with antecedent or concomitant signs of a nonspecific upper respiratory tract infection,[29,30] stomatitis caused by a primary herpetic infection or varicella[31,32] or, more commonly, by hand, foot, and mouth disease (HFMD)[6,8,11,33] or herpangina,[8] emphasizing the role played by breach of the mucosal barrier in pathogenesis of the disease.

With the notorious exception of patients with endocarditis, most children with invasive *K kingae* infections exhibit mild clinical illness characterized by good general condition, normal body temperature or low-grade fever, and normal or

BCV	Blood culture vial
DUS	DNA uptake sequences
HFMD	Hand, foot, and mouth disease
MLST	Multilocus strain typing
NAAT	Nucleic acid amplification test

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moderately elevated acute-phase reactants, thus requiring a high clinical index of suspicion.[26,29,34]

Osteoarticular involvement (mostly septic arthritis) is observed in more than one-half of sporadic pediatric infections, followed by bacteremia with no focus in 40% and endocarditis in <2%.[26,29] More rare presentations include tenosynovitis, spondylodiscitis, meningitis, and ocular infections.[29]

Laboratory Detection of *K kingae*

K kingae is a fastidious bacterium, and cultures of synovial fluid and bone exudates on standard agar media have low sensitivity.[35] The yield can be increased significantly by inoculating these specimens into aerobic blood culture vials (BCVs),[29,35] indicating that dilution of exudates in a large volume of nutrient broth decreases the concentration of inhibitory factors, improving recovery of the bacterium.[29,35] When synovial fluid aspirates from French and Israeli children with arthritis were inoculated routinely into BCVs, *K kingae* was detected in one-half of patients with culture-proven bacterial arthritis.[36,37] Conversely, when BCVs are not used, many cases of *K kingae* infection can be overlooked and labeled as "culture-negative septic arthritis."[38] The organism also can be isolated from the oropharynx by the use of a selective vancomycin-containing medium designed to suppress the competing Gram-positive flora.[7,39]

In recent years, development of NAATs has improved further the detection of *K kingae* from blood, osteoarticular exudates, and oropharyngeal specimens. The initial approach involved the use of universal primers that amplify the 16S rRNA gene, followed by sequencing of the amplicon and comparison of results with those kept in a broad free-access database (such as GenBank) to enable full identification. Use of this novel technology improved the detection of *K kingae* 2-fold compared with the BCV method, reduced time-to-detection, and allowed bacteriological diagnosis in patients being treated with antibiotics.[29] More recently, use of *K kingae*-specific primers that target the RTX toxin-encoding gene or the chaperonin-encoding *cpn*60 gene exhibit even greater sensitivity, increasing detection of the organism 5-fold compared with BCV culture.[29] Published reports comparing the performance of *K kingae*-specific DNA targets vs cultures show that the former detected 238 of 239 (99.6%) positive specimens vs 42 of 255 (16.5%) with positive culture isolation.[28] Use of *K kingae*-specific NAATs has confirmed that this bacterium is the most common etiology of septic arthritis in children <3 years of age and has shortened the time required to detect and identify the bacterium from 3-4 days to <24 hours.[13,15,29,40-43] In-house NAATs for the detection of *K kingae* infections in the osteoarticular infections have been used in France and Switzerland for a few years.[29] Although commercial tests currently are being developed, they are not yet available and, therefore, the use of molecular diagnostic tools outside Europe is somewhat limited. Data from North America are particularly scarce, but recent evidence indicates that *K kingae* also is a common cause of septic arthritis and osteomyelitis in the US[44,45] and Canada.[46]

It should be pointed out, however, that cultures have the advantage of detecting living bacteria, whereas the viability of *K kingae* organisms in NAATs-positive but culture-negative specimens is questionable, and cultivation permits complete characterization of the strain, including determination of antibiotic susceptibility.

Outbreaks of Invasive *K kingae* Infections among Daycare Center Attendees

Following the first recognition of a cluster of invasive *K kingae* infections in a Minneapolis daycare center,[5] similar events have been detected in the US,[6] Israel,[9-11] and France[7,8] (**Table I**). It is noteworthy that 8 of these 10 outbreaks were reported by researchers already involved in the study of *K kingae* and its diseases that routinely used BCV cultures and NAATs, indicating that awareness and use of sensitive improved laboratory procedures are crucial components of the recognition of these events.[7-11]

Because of the suboptimal isolation of *K kingae* from osteoarticular exudates, the case definition of an invasive infection has evolved over time, reflecting improvements in laboratory methods, and, currently, diagnosis of the disease is not restricted to patients in whom the organism is isolated from a normally sterile specimen such as blood, joint aspirate, or

Table I. Summary of the 10 reported outbreaks of invasive *K kingae* infections in daycare center facilities

Year	Location	Closed community	Cases (n)			Age range, mo	Attack rate	Outbreak duration, d	Authors	Year
			Proven	Highly probable	Presumptive					
2003	Minnesota	No	2	0	1	17-21	3/21 (14%)	<14	Kiang et al[5]	2005
2005	Military base A	Yes	1	0	2	8-12	3/14 (21%)	15	Yagupsky et al[9]	2006
2007	Durham	No	1	1	1	11-25	3/14 (21%)	11	Seña et al[6]	2010
2011	Paris	No	1	0	4	10-16	5/24 (21%)	30	Bidet et al[7]	2013
2012	Eilat	No	1	0	1	10-16	2/36 (6%)	7	Yagupsky[10]	2014
2013	Uum-el-Fahm	No	2	0	0	12	2/16 (15%)	7	Yagupsky[10]	2014
2013	Marseille	No	3	1	1	11-16	5/21 (24%)	16	El Houmami[8]	2015
2014	Military base B	Yes	0	0	2	11-14	2/14 (14%)	21	Yagupsky et al[11]	2016
2014	Nir-Itzhak	Yes	1	0	1	8-16	2/12 (17%)	3	Yagupsky et al[11]	2016
2014	Military base C	Yes	0	2	0	14-17	2/12 (17%)	5	Yagupsky et al[11]	2016
Total		4/10 (40%)	12	4	13	8-25	29/184 (16%)	3-30		