Kingella kingae: An Emerging Cause of Invasive Infections in Young Children

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Kingella kingae, a fastidious hemolytic gram-negative bacillus once considered to be an exceptional cause of disease, has emerged in recent years as an important invasive pathogen in children. When synovial fluid and other exudates were inoculated into blood culture bottles, enhanced recovery of the organism was observed, and an annual incidence of invasive K. kingae infections of 27.4 per 100,000 children younger than age 24 months was demonstrated in southern Israel. Skeletal infections are the most common clinical presentation of K. kingae, and studies conducted in that region have shown that this organism is the most common etiology of septic arthritis in children below the age of 24 months. Other invasive diseases caused by K. kingae include bacteremia, endocarditis, and infections involving the lower respiratory tract, the eyes, or the central nervous system. Recent studies have demonstrated that K. kingae is part of the normal oropharyngeal flora of young children. Clinical data suggest that the organism may gain access to the bloodstream in the course of an upper respiratory infection or stomatitis. The organism is susceptible to a wide range of antimicrobial drugs, and with the exception of some cases of endocarditis, K. kingae infections in children usually run a benign clinical course.

In the 1960s, King described a β-hemolytic fastidious gram-negative microorganism that was similar in morphological and cultural characteristics to the Moraxella genus and designated it Moraxella n. sp. 1 [1]. A few years later, the organism was allocated in a separate genus and renamed Kingella kingae in honor of King’s pioneering investigation [2]. For most of the 3 decades since the first description of K. kingae, the organism was considered a rare cause of infection, infrequently isolated from patients with endocarditis or skeletal infections [3–10].

In recent years, however, there have been an increasing number of reports on infections caused by the organism in children in the United States, Europe, and Israel, indicating that K. kingae is a more common invasive pathogen than has been traditionally appreciated [5, 9, 11, 12]. In 1985, Claesson et al. reported 10 Swedish patients with skeletal infections, bacteremia, or endocarditis caused by the organism, of whom seven were children [5]. Three years later, de Groot et al. published a report on six additional cases of bone or joint infections caused by the organism [9].

In 1991 Goutzmanis et al. reported on 10 pediatric patients of their own and summarized other cases published since 1975; a total of 19 children had septic arthritis, 23 had osteomyelitis, 8 had diskitis, and 11 had endocarditis [11]. Between 1988 and 1992, invasive K. kingae infections in 25 pediatric patients and one adult were diagnosed and reported from southern Israel [12], and an additional 22 children were treated between 1993 and 1996.

This rapidly enlarging body of information does not necessarily imply that K. kingae truly is a new pathogen. It appears that the organism is being recognized with greater frequency as the result of improved culture methods and increasing familiarity with its peculiar bacteriologic characteristics [11]. In this synopsis we will summarize the epidemiological and clinical features of invasive infections caused by K. kingae in young children.

Microbiological Characteristics of K. kingae

K. kingae is a nonmotile gram-negative β-hemolytic bacterium that appears as pairs or short chains of short bacilli with tapered ends. The organism tends to resist decolorization and thus might be misclassified as gram-positive. K. kingae grows on trypticase soy agar with added hemoglobin (routine blood agar medium) and chocolate agar, but it fails to grow on MacConkey or Krigler agar. It is oxidase-positive, as are other members of the Neisseriaceae family, and exhibits negative catalase, urease, and indole reactions.

K. kingae produces acid from glucose and maltose but not from other sugars [13]. The organism is usually susceptible to β-lactam drugs, macrolides, cotrimoxazole, tetracycline, and chloramphenicol and resistant to vancomycin. Occasional in vitro resistance to erythromycin, clindamycin, trimethoprim, and ciprofloxacin has been reported [8, 11, 14]. Production of β-lactamase by a single isolate of K. kingae recovered from an HIV-positive patient has been reported [15].

Detection of K. kingae: Recent Advances

In the past, K. kingae was unfamiliar to most personnel in clinical microbiology laboratories and as such was frequently
misidentified or dismissed as a contaminant [11, 16]. Studies conducted at the Soroka Medical Center (SMC), in Beer-Sheva in southern Israel, have shown that the primary isolation of \textit{K. kingae} from synovial fluid is strongly dependent on the bacteriologic methodology used [16].

Attempts to isolate the organism from synovial fluid or bone exudates on routine solid media succeeded in only two of 25 cases, whereas inoculation of these clinical specimens into aerobic BACTEC (Becton Dickinson, Cockeysville, MD) blood culture bottles yielded the organism in all cases after a median incubation of 4 days [16]. It is postulated that pus exerts an inhibitory effect upon \textit{K. kingae} and that dilution of the synovial fluid specimen in a large volume of broth decreases the concentration of unknown detrimental factors and facilitates recovery of the organism [16, 17].

**Epidemiology of Invasive Diseases in Children**

Until recently, no firm data on the incidence of invasive \textit{K. kingae} infections were available because most reports consisted of single cases or series compiled from different institutions and lacked data on the size of the population from which these patients derived. We have recently studied the incidence of invasive infections among children in southern Israel. The fact that practically all children in the region are born and receive inpatient health services at a single hospital (SMC) allowed us to calculate the incidence of invasive \textit{K. kingae} infection in this population [12].

The disease showed a remarkable age distribution: 19 (45%) of the 42 children whose disease was diagnosed during an 8-year period were infants aged 6–12 months, 19 (45%) were 13–24 months old, 2 (5%) were 25–36 months old, and the remaining 2 were 37 and 40 months old. The calculated annual incidence of invasive infections caused by the organism during the 5-year period 1988–1992 was 14.3, 27.4, and 31.9 cases per 100,000 children ≤4 years, ≤24 months, and ≤12 months old, respectively. The attack rate of \textit{K. kingae} detected among children younger than age 24 months represented one-quarter of that of invasive \textit{Haemophilus influenzae} type b found in the same population prior to the introduction of the vaccine [18].

The peculiar age-distribution of cases of \textit{K. kingae} infection also shows striking similarities with that of cases of \textit{H. influenzae} type b infection [11, 12, 18]. Almost 90% of all patients with invasive \textit{K. kingae} infections have been children younger than 5 years of age, and >60% of episodes of invasive disease have occurred before the age of 2 years (table 1). It should also be pointed out that occurrence of the disease in infants younger than 6 months of age has not been described [11, 12]. Whether this negative finding represents lack of exposure of young infants to the organism and/or indicates the presence of transient immunity that fades in the course of the first year of life is unknown.

Overall, the 43 children with invasive \textit{K. kingae} infections diagnosed in southern Israel in the 9-year period of 1988–1996 represent almost half of all cases of pediatric infections caused by the organism that have been described in the literature so far. Although it is possible that the observed high incidence of \textit{K. kingae} infections is related to unknown factors peculiar to the area or to our pediatric population, this seems improbable. \textit{K. kingae} has been reported worldwide, and the organism is a normal component of the normal respiratory flora.

On the other hand, recovery of the organism is highly dependent on the methodology used, and correct identification requires familiarity with its unusual bacteriologic characteristics [16]. Increased use of blood culture systems for routine culture of normally sterile body fluids and growing experience in the identification of the organism will probably result in improved recognition of \textit{K. kingae} infections.

**Seasonal distribution.** Thirty-one (72%) of the 43 pediatric cases of invasive \textit{K. kingae} infection treated at the SMC since 1988 were diagnosed between July and December (\(P < .01\)). A similar seasonal cluster has also been noted by Claesson et al. among Swedish patients [5]. Although the explanations for this peculiar distribution are merely speculative at this stage of our knowledge, an increase in the incidence of invasive infections caused by other respiratory pathogens such as \textit{H. influenzae} type b and \textit{Streptococcus pneumoniae} during the fall and winter has been described in Israel [18, 50].

**Clinical presentation.** The medical literature on the subject consists of reports of single cases or short series of patients with specific entities, in which unusual clinical manifestations are frequently overrepresented, making it difficult to establish the true relative frequency of the different syndromes caused by the organism [3–10, 19, 29, 51].

Among 77 \textit{K. kingae} isolates sent to the Centers for Disease Control between 1953 and 1980 for identification or confirmation, 38 (49%) were recovered from blood cultures, 21 (27%) from joint fluid or bone cultures, and 14 (18%) from upper respiratory tract specimens [51]. Based on the large experience accumulated at the SMC in the last few years, a more accurate picture can be drawn. Clinical disease among the 43 children whose blood and other normally sterile body fluids or exudates yielded \textit{K. kingae} included skeletal infections in 30 (70%; septic arthritis in 24, osteomyelitis in 4, septic arthritis and osteomyelitis of the adjacent bone in 1, and dactylitis in 1), occult bacteremia in 10 (23%), and bacteremic lower respiratory tract infection in 3 (7%).

According to our own experience and published reports, the vast majority of patients had been healthy before the acute \textit{K. kingae} infection. In a few instances the disease affected persons with systemic lupus erythematosus [12, 44, 52], liver cirrhosis [53], rheumatoid arthritis [54], sickle cell anemia [53], renal transplants [8], solid tumors [14], hematologic malignancies [5, 19], and AIDS [15, 55].

Pediatric patients with invasive \textit{K. kingae} infections frequently present with minimal or no constitutional symptoms: fever is frequently absent on admission, and the vast majority of affected children are considered to be only mildly or moder-
The site of anatomical involvement in 25 pediatric patients with osteomyelitis included the femur in 11 [5-7, 9, 11, 12, 25, 29-31], the tibia in 3 [5, 25, 29], and the ulna [33] and radius [34] in 1 each, as well as unusual locations such as the calcaneus in 4 [9, 32], the thalamus [5, 8] and the sternum [24, 35] in 2 each, and the clavicle in 1 [36]. Onset of *K. kingae* osteomyelitis is generally insidious, and the disease is frequently diagnosed with considerable delay (after ≥1 week for 70% of patients) [11]. The long-term prognosis is favorable in all cases, including those with involvement of the epiphyses of the long bones [11, 29].

Hematogenous invasion of the intervertebral disk by *K. kingae* in 15 children (all but one aged 1–5 years) and a single adult has been reported [11, 60]. Diskitis caused by *K. kingae* usually runs a relatively indolent and benign clinical course [11]. The organism has been isolated from disk-space aspirates, bone curettage specimens, and blood. The disk infection involved lumbar intervertebral spaces in 9 children [5, 6, 11, 25, 34, 35, 38], the thoracic [3, 38], lumbar [6, 35], or thoracolumbar spaces [3, 30] in 2 patients each, and a cervical disk in 1 child [39]. Involvement of two noncontiguous spaces in one child has been reported [38].

**Endocarditis.** In contrast to other clinical manifestations of invasive *K. kingae* infections, bacterial endocarditis has also been noted with some frequency in adult patients and school-age children [11, 61]. A total of 10 children and 10 adults with native valve endocarditis have been described in the medical literature; most of these cases involved the mitral valve [4, 8, 11, 26, 44–47, 52, 55, 62–67]. Predisposing factors included congenital cardiac malformations, rheumatic valvular disease,
and systemic lupus erythematosus. In four children the disease affected previously normal valves [8, 11, 23, 26, 47].

In addition, five adults and two children, aged 9 and 16 years, with prosthetic valve endocarditis have been reported [5, 48, 49, 61, 62, 66]. Clinical findings for all 12 pediatric patients with native and prosthetic valve endocarditis are summarized in table 2.

Despite the overall benign course observed in most other K. kingae infections and the wide range of antimicrobial drugs to which the organism is susceptible, the complication rate observed among pediatric patients with native valve infection is high: cerebrovascular accidents occurred in two children, and femoral embolism, mycotic aneurism, cardiogenic shock, and tricuspid insufficiency with pulmonary infarction were diagnosed in one child each [8, 23, 26, 44-46].

This unusual morbidity appears to be related in part to the difficulties in recovering and identifying K. kingae, problems often encountered with other members of the HACEK group of organisms. Because of the serious nature of K. kingae endocarditis, evaluation of all adult patients with K. kingae bacteremia to exclude endocardial invasion has been strongly advocated [67].

Bacteremia. This presentation has been observed in 24 children without evidence of endocarditis [5, 7, 8, 10-12, 19, 22, 26, 68, 69]. Eleven of them had concomitant infection of the skeletal, respiratory, or central nervous systems (see table 1), and the remaining had occult bacteremia. A maculopapular rash mimicking disseminated meningococcal or gonococcal infection in a few children and adults with K. kingae bacteremia has been described [11, 19, 53, 70, 71].

Demographic, clinical, and laboratory data regarding the 13 bacteremic children without suppurative focal infections are summarized in table 3. Among the 13 children with K. kingae bacteremia diagnosed at the SMC since 1988, only three had a documented focal infection involving the lower respiratory tract, and the remaining had occult bacteremia. No bacteremia was demonstrated among the 30 children admitted with skeletal infections. In our experience, bacteremic children are usually younger than those without bacteremia [68]. Among 20 infants admitted with invasive K. kingae infections, 9 (45%) were bacteremic, as opposed to only 4 (17%) of 23 children older than 12 months of age.

It appears that young infants with K. kingae bacteremia are referred to the hospital early in the course of the disease, whereas older children with bacteremia are probably asymptomatic or not sick enough to be brought to medical attention, and their illnesses are diagnosed only after the bacterium has invaded the skeletal system. At this stage, the organism is only rarely isolated from the blood, indicating that the bacteremic phase of the disease is of short duration. Whether symptomatic bacteremic young infants would have developed secondary foci of infection if left untreated remains entirely speculative.

Lower respiratory tract infections. K. kingae has been isolated from the blood or respiratory secretions of previously healthy and immunocompromised adult and pediatric patients with lower respiratory tract conditions such as laryngotracheobronchitis, epiglottitis, pneumonia, and pyothorax [12, 14, 61, 72]. A case of K. kingae pneumonia complicating measles has also been reported [72].

Table 2. Summary of data regarding 12 pediatric patients with bacterial endocarditis caused by K. kingae.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient's sex/age</th>
<th>Predisposing factor</th>
<th>Involvement</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>[8]</td>
<td>F/8 y</td>
<td>...</td>
<td>MV</td>
<td>Myotic aneurism of iliac artery</td>
</tr>
<tr>
<td>[11]</td>
<td>F/14 mo</td>
<td>PDA</td>
<td>MV</td>
<td>PA</td>
</tr>
<tr>
<td>[23]</td>
<td>M/4 y</td>
<td>Complex</td>
<td>VSD</td>
<td>...</td>
</tr>
<tr>
<td>[26]</td>
<td>M/14 mo</td>
<td>...</td>
<td>MV</td>
<td>CVA, mitral stenosis and insufficiency</td>
</tr>
<tr>
<td>[44]</td>
<td>F/16 mo</td>
<td>TOF</td>
<td>VSD</td>
<td>CVA (twice)</td>
</tr>
<tr>
<td>[45]</td>
<td>F/11 y</td>
<td>MVP</td>
<td>MV</td>
<td>Tricuspid insufficiency, pulmonary infarction</td>
</tr>
<tr>
<td>[46]</td>
<td>M/4 y</td>
<td>VSD</td>
<td>VSD</td>
<td>Tricuspid insufficiency, pulmonary infarction</td>
</tr>
<tr>
<td>[47]</td>
<td>M/1 y</td>
<td>...</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>[48]</td>
<td>F/9 y</td>
<td>Truncus arteriosus I, prosthetic AV, graft</td>
<td>AV</td>
<td>...</td>
</tr>
<tr>
<td>[49]</td>
<td>M/16 y</td>
<td>Bicuspid AV, prosthetic AV</td>
<td>AV</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE. AV = aortic valve; complex = complex cardiac malformation; CVA = cerebrovascular accident; MV = mitral valve; MVP = mitral valve prolapse; PA = pulmonary artery; PDA = patent ductus arteriosus; TOF = tetralogy of Fallot; VSD = ventricular septal defect.
Table 3. Summary of data regarding 13 children with occult bacteremia caused by K. kingae.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient’s sex/age (mo)</th>
<th>Stomatitis</th>
<th>URTI</th>
<th>No. of WBCs/mL</th>
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<tbody>
<tr>
<td>[12, 68]</td>
<td>F/8</td>
<td>+</td>
<td>–</td>
<td>14,000</td>
</tr>
<tr>
<td></td>
<td>M/10</td>
<td>–</td>
<td>–</td>
<td>19,900</td>
</tr>
<tr>
<td></td>
<td>M/10</td>
<td>–</td>
<td>+</td>
<td>15,700</td>
</tr>
<tr>
<td></td>
<td>M/7</td>
<td>+</td>
<td>–</td>
<td>21,900</td>
</tr>
<tr>
<td></td>
<td>M/8</td>
<td>+</td>
<td>+</td>
<td>16,100</td>
</tr>
<tr>
<td>PR</td>
<td>M/23</td>
<td>–</td>
<td>–</td>
<td>9,700</td>
</tr>
<tr>
<td></td>
<td>M/11</td>
<td>–</td>
<td>+</td>
<td>18,700</td>
</tr>
<tr>
<td></td>
<td>F/12</td>
<td>–</td>
<td>–</td>
<td>10,100</td>
</tr>
<tr>
<td></td>
<td>M/16</td>
<td>+</td>
<td>–</td>
<td>8,500</td>
</tr>
<tr>
<td></td>
<td>M/21</td>
<td>+</td>
<td>–</td>
<td>18,100</td>
</tr>
<tr>
<td></td>
<td>F/7</td>
<td>–</td>
<td>–</td>
<td>17,300</td>
</tr>
<tr>
<td>[69]</td>
<td>F/32</td>
<td>+</td>
<td>–</td>
<td>9,500</td>
</tr>
</tbody>
</table>

NOTE. PR = present report; URTI = upper respiratory tract infection; + = yes; – = no.

Other infections. In addition, K. kingae has been isolated from patients with a wide spectrum of clinical conditions, including meningitis [41, 42, 73], a cervical abscess [74], and a variety of ocular infections such as eyelid abscess, endophthalmitis, and corneal abscess [11, 40, 43, 74].

Treatment. Except for some cases of endocarditis, invasive K. kingae infections generally follow a benign clinical course and resolve completely after administration of antibiotic therapy [11]. This encouraging experience is consistent with the exquisite in vitro susceptibility of the organism to antimicrobial drugs (including β-lactam drugs) that are empirically given to ill-looking young infants or patients with signs of joint or bone infection [75–77].

Carriage state. It has long been presumed that K. kingae may be part of the normal respiratory flora of humans, and this possibility is supported by several lines of evidence. In a study conducted in the early 1970s, Henriksen isolated K. kingae in five (1%) of 437 nasal and pharyngeal cultures [74]. Other members of the Neisseriaceae family such as Moraxella and Neisseria species are well-known respiratory commensals. Symptoms of upper respiratory infections have been consistently noted in children with invasive K. kingae infections, suggesting a respiratory portal of entry of the organism [11, 12]. In addition, K. kingae has been implicated in the causation of lower respiratory tract infections [12, 14, 61, 72].

To investigate the niche of the organism in the respiratory tract and its prevalence in the normal flora of children, tonsillar and nasopharyngeal culture specimens were obtained at the time of enrollment from a cohort of 28 children (aged 19–48 months) attending a day-care center in southern Israel [78]. In addition, to determine the age-related prevalence of K. kingae, throat culture specimens were obtained from 81 healthy infants (aged <6 months) attending a day-care center for routine immunization and from 100 children (aged 6 months to 14 years) hospitalized for elective surgery who had not received antibiotics during the previous 30 days [78].

Specimens were inoculated onto a selective medium consisting of blood agar with vancomycin [79]. K. kingae grew in up to 33% of the cultures of tonsillar specimens obtained from the children attending the day-care center; almost three-quarters of them carried the organism in the pharynx at least once, and one-half carried it for at least 2 of 11 months of follow-up. The prevalence rate of K. kingae found in the respiratory tract of these youngsters is within the range of carriage of S. pneumoniae and much higher than that of H. influenzae type b or hemolytic streptococci [80]. The organism appears to have a narrow anatomic niche, however, in that it colonized only the tonsilar surface and was not isolated in any nasopharyngeal culture.

The carriage rate among surgical patients younger than age 4 years was 10%—coinciding with the age at which the attack rate of invasive disease increases—and 6% among older children. The organism was not isolated from any of the infants younger than 6 months of age attending the well-baby-care clinic, a finding paralleling the lack of morbidity caused by K. kingae noted in young infants.

Mechanism of infection. Because K. kingae has been considered until recently as an exceptional human pathogen, our understanding of the pathogenesis of invasive infections caused by this bacterium is incomplete. It is worth mentioning that concomitant stomatitis, including varicella-induced buccal ulcers, and symptoms of upper respiratory tract infection have been frequently noted in children with bacteremia and other invasive K. kingae infections [3, 5, 7, 9, 11, 68, 69].

On the basis of the clinical and epidemiological information available, it is speculated that K. kingae organisms colonizing the oropharynx may penetrate the damaged mucosal layer. The organism might then progress throughout the airways, causing laryngotracheobronchitis or pneumonia, and/or invade the bloodstream. Transient benign bacteremia may follow or the organism might be seeded in the endocardium, joint space, bone, or intervertebral disks, resulting in a focal supplicative infection. The reason for the striking predilection of K. kingae for these sites remains beyond our current knowledge.

In summary, K. kingae is emerging as an important etiologic agent of invasive infections in young children, particularly of those affecting the skeletal system. The clinical presentation of the disease is often subtle, and auxiliary laboratory tests are frequently normal. Although isolation and recognition of the organism are not difficult, clinicians and microbiologists should be aware of its fastidious nature. To maximize the recovery of K. kingae, inoculation of synovial fluid specimens into blood culture bottles is strongly recommended.

References


