The Contemporary Bacteriologic Epidemiology of Osteoarticular Infections in Children in Switzerland

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Objectives To assess the contemporary bacteriologic epidemiology of pediatric osteoarticular infection with particular regard to children's ages, because *Kingella kingae* has gained increasing recognition as the predominant pathogen for osteoarticular infection in young children.

Study design Retrospective file review of enrolled children from 0 to 15 years of age, admitted to our institution from 2007 to 2015 for suspected osteoarticular infection (217 cases). Information on age, sex, the bone or joint infected, imaging studies, and laboratory data (including bacterial investigations) were collected for analysis.

Results Microorganism identification was possible for 138 infected children (63.6%), through blood (cultures or polymerase chain reaction [PCR]) and/or operative samples (cultures or PCR). Thirty-one patients (14.3%) were found to both have positive blood cultures and operative samples. The results of positive bacteriology specimens identified the most common causative pathogen for osteoarticular infection as *K kingae* (47.8% of microbiologically confirmed osteoarticular infections of all ages, and 87.7% in children between the ages of 6 and 48 months), significantly more common than *Staphylococcus aureus* (35.5% of microbiologically confirmed osteoarticular infections of all ages, and 78.2% in children >4 years of age).

Conclusions Use of the appropriate PCR assays demonstrated that *K kingae* currently is the major bacterial cause of pediatric osteoarticular infection, especially in children <4 years of age in whom *K kingae* is more common than *S aureus*. PCR assays should be used in routine microbiologic laboratory evaluation to improve diagnostic performance. However, despite the use of molecular methods, there are many osteoarticular infections in which no microorganism is detected, which suggests that these infections may be caused by other as yet unrecognized fastidious microorganisms. *(J Pediatr 2017;■■:■■-■■).*

Osteoarticular infection remains a serious pediatric diagnosis, with potentially severe consequences for bone development and function.[1] Rapid diagnosis and appropriate treatment are paramount to minimizing complications and optimizing outcomes.[2] Identification of the causative organism is required to confirm the diagnosis and to adjust antibiotic therapy,[3] but remains challenging, with high rates of negative cultures.[4]

Classically, *Staphylococcus aureus* has been described as the most common infective bacterial pathogen for osteoarticular infection in all age groups.[2,5-8] However, since the 1980s, the reported number of cases of osteoarticular infection owing to *Kingella kingae* has increased markedly[9] owing to improvements in culture techniques[10] and the more widespread use of molecular diagnostics.[11] This fastidious microorganism is difficult to isolate on solid media,[4] and cultures often are negative,[12] indicating that its role in osteoarticular infection has probably been underestimated in the past.[12] Recently, with real-time polymerase chain reaction (PCR) methods, *K kingae* has been demonstrated to be the predominant cause of osteoarticular infection in young children in European countries, especially around the Mediterranean basin.[4,12-18] The present study aimed to assess the current epidemiology of osteoarticular infection in a single Swiss health district, with particular regard to incidence, patient age, types of osteoarticular infection, bacteriologic etiology, clinical features, and markers of inflammatory response at admission.

Methods

After approval from the Children's Hospital Ethics Review Committee (CE 14-102R), we retrospectively reviewed the medical charts of all children from 0 to 15 years of age admitted to our institution between January 2007 and December 2015 for

CA	Community-acquired
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
PCR	Polymerase chain reaction*
WBC	White blood cell

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suspected osteoarticular infection. Our children's hospital is a 111-bed tertiary care pediatric hospital serving Geneva and its surrounding area, and is the only medical facility providing inpatient and specialized medical services, especially for pediatric osteoarticular infection, to the 460 000 inhabitants of the district of Geneva. The annual population of children ranging from 0 to 15 years of age was extracted from statistics published by the regional population's office,[19] and an estimated 80 000 children (annual mean 76 507 children) from this age group were present every year in the district of Geneva and the surrounding area. In Switzerland, vaccination coverage for classical pathogens responsible for osteoarticular infection was very high during the study's period; immunization against *Haemophilus influenzae* type b reached 93%-95% in infants of 2 years of age, 89%-93% in children of 8 years of age, and 16%-81% in adolescents 16 years of age.[20] The 7-valent and 13-valent pneumococcal conjugate vaccines were introduced in Switzerland in 2006 and 2011, respectively. During the study period, PCV vaccination rates varied between 75% and 89%.[21,22] January 2007 was chosen as the starting point for this study, because this time was when large-scale PCR assays began to be used in our institution, especially a novel real-time PCR assay specific for *K kingae*. All files were identified through a computerized search by codes with respect to the following primary diagnoses: acute hematogenous osteomyelitis, subacute osteomyelitis, septic arthritis, acute osteomyelitis with concomitant arthritis, primary spine infection (spondylodiscitis, vertebral osteomyelitis), pyomyositis, and septic tenosynovitis. Clinical features, such as fever before and at the time of admission and final diagnosis, were recorded for each patient. Laboratory investigations included white blood cell (WBC) count, platelet count, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).

Microbiological Methods

Organism identification and antimicrobial sensitivity were performed by the clinical microbiology laboratory during the routine course of care. The blood culture system used was BACTEC 9000 (Becton Dickinson, Franklin Lakes, New Jersey) from 2007 to 2009, followed by an automated BD BACTEC FX system (Becton Dickinson). Joint fluid or bone aspirate samples were sent to the laboratory for Gram staining, cell count, and immediate inoculation onto Columbia blood agar (incubated under anaerobic conditions), Centers for Disease Control & Prevention anaerobe 5% sheep blood agar (incubated under anaerobic conditions), chocolate agar (incubated in a CO_2-enriched atmosphere), and brain–heart infusion medium. The incubation time was 10 days. Since 2007, 2 PCR assays have been used for bacterial identification when standard cultures are negative. A universal, broad-range PCR amplification of the 16S rRNA gene is performed using BAK11w, BAK2, and BAK533r primers (Eurogentec, Seraing, Belgium) and a specific PCR assay targeting the *K kingae* RTX toxin genes. This last assay is designed to detect 2 independent gene targets from the *K kingae* RTX toxin locus, *rtxA* and *rtxB*.[23] It was used to analyze peripheral blood, as well as synovial fluid, bone, or vertebral disc biopsy specimens. Since September 2009, we have been carrying out oropharyngeal swab PCR for children from 6 months to 4 years of age, because this simple technique for detecting *K kingae* RTX toxin genes in the oropharynx has high positive and negative predictive values for detecting osteoarticular infections.[24]

Definitions

The diagnosis of pyogenic or septic arthritis was defined using a combination of classic clinical findings (joint swelling, erythema, tenderness, limited range of motion, etc), radiologic findings, and results of synovial fluid Gram stain and culture. Osteomyelitis was based on a combination of clinical examination findings (such as point tenderness along with fever, erythema, and swelling), radiographic evidence of bone infection (by plain radiographs and magnetic resonance imaging [MRI]), and/or bone culture or histology. The criteria established by Morrey et al were used to estimate children's risk of having an osteoarticular infection.[25,26] Study exclusion criteria included chronic osteomyelitis, rib infections, infections of the skull and the bones of the face, and infections subsequent to a fracture or surgery. According to King and Mayo, any osseous infectious process of >2 weeks' duration without acute symptomatology was categorized as subacute osteomyelitis.[27] Osteomyelitis was considered to be chronic if the duration of the illness was >3 months.[28]

To ensure proper final classification of osteoarticular infection owing to *K kingae*, we classified cases as confirmed, highly probable, and presumptive. Confirmed osteoarticular infection owing to *K kingae* corresponded to cases with positive MRI and positive blood and/or bone and/or joint fluid PCR assays specific for *K kingae*. Highly probable osteoarticular infection owing to *K kingae* were cases with positive MRI, typical clinical and laboratory data of *K kingae* osteoarticular infection, and positive PCR assay on an oropharyngeal specimen. In this group, joint fluid aspiration or bone aspirate samples were not obtained. Presumptive osteoarticular infection owing to *K kingae* were cases affecting children <4 years of age, with a positive MRI, and with typical clinical and laboratory data of *K kingae* osteoarticular infection. In this category, oropharyngeal swab, joint fluid aspiration, and bone aspirate samples were not obtained.

The presentation of *K kingae* osteoarticular infection is often characterized by a mild to moderate clinical and biologic inflammatory response to infection with the consequence that these children present few, if any, criteria evocative of osteoarticular infection. In fact, only 10%-33% of children with osteoarticular infection caused by *K kingae* have a body temperature of ≥38°C at admission, and most patients have a normal or near normal WBC count and CRP level.[15,16,18,29] When *K kingae* osteoarticular infection is present, the ESR and platelet counts seem to be the most sensitive markers of inflammation.[15,18] A model to allow the differentiation of *K kingae* osteoarticular infections from infection owing to typical pathogens has been described and consists of the following 4 findings: temperature at admission of <38°; CRP of <55 mg/L; WBC count of <14 000 leukocytes/mm^3, and bands of <150 forms/mm^3.[18]

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