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Susceptibility testing of *Kingella kingae* to cefazolin

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Running title: *Kingella kingae* susceptibility to cefazolin

Key words: *Kingella kingae*, osteo-articular infections, antimicrobial susceptibility test,
antibiotic therapy, children

18 Sir,

19 We read with great interest the article entitled “Antimicrobial susceptibility testing of
20 *Kingella kingae* with broth microdilution and disk diffusion using EUCAST recommended
21 media” published by Matuschek et al ¹. *Kingella kingae*, is now recognized as the first
22 pathogen causing septic arthritis and osteomyelitis in children between 6 months and 4 years
23 of age in several countries, preceding *Staphylococcus aureus* ². Empiric treatment should
24 therefore cover both pathogens and amoxicillin plus clavulanate or second or third generation
25 cephalosporins have been recommended ^{2, 3}. Moreover, *K. kingae* is not fully susceptible to
26 oxacillin (minimum inhibitory concentration [MIC]: MIC₅₀ = 3 mg/L and MIC₉₀ = 6 mg/L) ²,
27 which is frequently used as first line treatment in some countries. First generation
28 cephalosporins such as cefazolin are recognized for a long time to cure bone and joint
29 infections due to *S. aureus* and are even recommended in prosthetic joint infection treatment
30 due to methicillin-susceptible *S. aureus* ⁴. However, the susceptibility of *K. kingae* to this
31 drug has not been investigated yet, and neither breakpoints were provided in the recent
32 publication of the European Committee on Antimicrobial Susceptibility Testing (EUCAST,
33 Clinical Breakpoint Tables v7.1, March 2017, <http://www.eucast.org/>) nor MICs distribution
34 by Matuschek et al ¹.

35 Forty clinical *K. kingae* isolates from various geographical locations and representative of the
36 diversity of the species in terms of pathogenicity and genotypes, based on multilocus
37 sequence typing (MLST) analysis ⁵, were selected for susceptibility testing. The reference
38 type strain ATCC 23330 from Norway was also included. The 40 clinical isolates were from
39 the USA (n=5), Canada (n=5), Spain (n=6), Israel (n=10), Iceland (n=2) and France (n=12).
40 The major sequence type complexes STc-6, 14, 23, 25, 33, and 35 were represented with 11,
41 8, 5, 6, 3 and 5 strains respectively. Twenty-nine strains were involved in osteo-articular
42 infections, 4 in occult bacteraemia, 3 in endocarditis, 1 in infection of unknown site, and

43 finally 3 were isolated from healthy carriers. Nine strains produced a penicillinase and were
44 from the USA, Iceland, Israel and France ⁶. Cefazolin MICs using E-test method were
45 determined on Mueller-Hinton-F agar (Biomerieux, Marcy-l'Etoile, France) with an
46 inoculum of McFarland 0.5 (corresponding to 10⁸ CFU/ml), as recommended by EUCAST.
47 The reference strains *Escherichia coli* ATCC 25922 and *S. aureus* ATCC 29213 were used as
48 control.

49 MIC₅₀ and MIC₉₀ were 0.38 and 0.5 mg/L respectively (range 0.19 to 0.75 mg/L). The nine
50 beta-lactamase-producing *K. kingae* isolates had similar cefazolin MICs compared to their
51 non-producers counterparts (MIC₅₀ = 0.50 mg/L [range: 0.25-0.75 mg/L] vs. MIC₅₀ = 0.38
52 mg/L [range: 0.19-0.75 mg/L], respectively, p=0.31 by Mann-Whitney U test). The cefazolin
53 MICs of the reference strains *Escherichia coli* ATCC 25922 and *S. aureus* ATCC 29213 were
54 2 and 0.38 mg/L, respectively. All the *K. kingae* strains had a cefazolin MIC under the “non-
55 species related” MIC breakpoints (1 mg/L) as proposed by EUCAST. Moreover the cefazolin
56 MICs of the *K. kingae* isolates were lower than those of *S. aureus*, for which the
57 epidemiological cut-off is 2 mg/L.

58 The recent description of penicillinase-producing *K. kingae* strains with the potential risk of a
59 global emergence and dissemination ⁶, as well as the necessity to cover *S. aureus* in case of
60 culture and PCR negative septic arthritis, lead to reconsider the first-line treatment. Cefazolin
61 appears well active among *K. kingae* beta-lactamase producers.

62 Although beta-lactamase producing *K. kingae* strains remain uncommon, international
63 collaboration to monitor their spread is crucial. The present study investigated a sample of *K.*
64 *kingae* strains representative of the diversity of the species throughout the world. Our results
65 indicate that *in vitro* susceptibility of *K. kingae* to cefazolin is compatible with the use of this
66 drug in probabilistic treatment of bone and joint infections in young infants.

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