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Low-level amikacin resistance induced by AAC(6′)-Ib and AAC(6′)-Ib-cr in extended-spectrum β-lactamase (ESBL)-producing Enterobacterales isolated from urine in children

Editor: S. Stefani

Sir,

Amikacin is commonly used in children in combination with other agents as a last-resort treatment for severe infections caused by multidrug-resistant Gram-negative bacteria. Amikacin is also prescribed empirically in febrile neutropenia in children with cancer and in acute pulmonary exacerbations in cystic fibrosis patients [1]. Over the past few years, however, amikacin has been increasingly used to treat urinary tract infections (UTIs) in children caused by Enterobacterales producing extended-spectrum β-lactamases (ESBLs), given the low resistance rates to this agent among ESBL-producing uropathogens worldwide [2–5]. Resistance to amikacin in Enterobacterales can be caused by multiple mechanisms, including 16S rRNA methyltransferases [6]. However, the most common cause is the aminoglycoside *N*-acetyltransferase AAC(6′)-Ib, which acetylates amikacin, tobramycin, kanamycin and netilmicin but spares gentamicin, while its bifunctional variant AAC(6′)-Ib-cr also modifies ciprofloxacin and norfloxacin [7]. AAC(6′)-Ib-cr is frequently co-produced by CTX-M-type ESBL-producing isolates, particularly CTX-M-15, conferring low-level resistance to amikacin with minimum inhibitory concentrations (MICs) that do not exceed susceptible breakpoints [7].

In this study, we assessed the amikacin MIC in CTX-M-type ESBL-producing Enterobacterales harbouring *aac(6′)-Ib* or *aac(6′)-Ib*-cr genes recovered from urine specimens from children diagnosed with UTI between 2017–2019 at Hamad Medical Corporation and Sidra Medicine, two tertiary-care academic institutions that provide health care for the entire paediatric population in Qatar. Amikacin MICs were determined by Etest, while the presence of *aac(6′)-Ib* or *aac(6′)-Ib*-cr genes was determined by whole-genome sequencing or Sanger sequencing (Supplementary methods).

A total of 123 isolates were studied, including 109 *Escherichia coli* (88.6%) and 14 *Klebsiella pneumoniae* (11.3%). None of the isolates co-existed in the same patient. All isolates except one were susceptible to amikacin. The *aac(6′)-Ib* and the -cr variant genes were detected in 69 isolates (56.1%), including 61/69 *E. coli* (56.0%) and 8/14 *K. pneumoniae* (57.1%). Of these 69 isolates, 65 (94.2%) harboured the *aac(6′)-Ib*-cr gene. All isolates were susceptible to amikacin, except for one *E. coli* carrying *aac(6′)-Ib*-cr that was intermediate. Moreover, 46 amikacin-susceptible isolates (67.7%) harbouring *aac(6′)-Ib* or the -cr variant genes had MICs for amikacin of ≥4 mg/L, including 27 isolates (39.1%) with MICs of ≥8 mg/L. In contrast, 8 (14.8%) of 54 strains lacking *aac(6′)-Ib* and the -cr variant had amikacin MICs between 4–8 mg/L. An interval-censored regression model fitted to amikacin MICs to assess the difference between the groups (Fig. 1) showed that the presence of *aac(6′)-Ib* and the -cr variant genes is associated with an increase in the $\log_2$(MIC) of 1.11 (95% confidence interval 0.77–1.45; $P = 1.3 \times 10^{-10}$), which corresponds to ≥2-fold higher MICs.

A ratio of the peak serum concentration (C_{peak}) divided by the MIC for the target pathogen is the best pharmacokinetic/pharmacodynamics (PK/PD) parameter to predict bacterial killing and to prevent the selection of resistance to aminoglycosides. The desirable C_{peak}/MIC ratio for amikacin to achieve therapeutic success is >8 [1,8–10]. Knowledge of amikacin pharmacodynamics in children beyond the neonatal period and without cystic fibrosis or burns is scarce. However, limited studies performed in children without cystic fibrosis or burns using doses ranging from 15–30 mg/kg/day administered through once-daily or multiple-daily regimens showed that a C_{peak}/MIC ratio >8 was only achieved in isolates with MIC < 4 mg/L. In fact, C_{peak}/MIC > 8 was not achieved in any of the isolates with an MIC > 8 mg/L owing to the difficulty in attaining C_{peak} > 40 mg/L even with once-daily dosing regimens to optimise maximum plasma concentrations [8–10].

Although the vast majority of our isolates harbouring *aac(6′)-Ib* and the -cr variant genes were susceptible to amikacin, they exhibited an ~2-fold increase in amikacin MIC compared with isolates lacking these genes. Therefore, if amikacin had been used, there would have been a failure in achieving C_{peak}/MIC > 8 in two-thirds of isolates with MIC ≥ 4 mg/L assuming hypothetical peak concentrations between 20 mg/L and 30 mg/L, and in almost one-half of the isolates exhibiting MIC ≥ 8 mg/L even with serum peak concentrations of 40 mg/L.

Several studies have reported favourable clinical outcomes and high microbiological cure rates using once-daily amikacin (dosages ranged from 15–25 mg/kg/day) to treat children with lower and upper UTI caused by ESBL-producers with amikacin MIC ≤ 4 mg/L [4,5]. However, the community prevalence of AAC(6′)-Ib, in particular AAC(6′)-Ib-cr, is increasing worldwide, driven by the global dissemination and dominance of CTX-M-15 [7]. Thus, there is a trend towards an increased prevalence of amikacin-susceptible ESBL-producers with MIC > 4 mg/L in the community that may pose a therapeutic challenge for the use of this agent as a carbapenem-sparing option in the treatment of children with UTI caused by ESBL-producers.

Therefore, well-designed clinical trials considering serum PK/PD parameters along with clinical and microbiological outcomes are needed to determine the efficacy of once-daily amikacin in isolates with MICs of 4–16 mg/L due to the production of AAC(6′)-Ib and its –cr variant.

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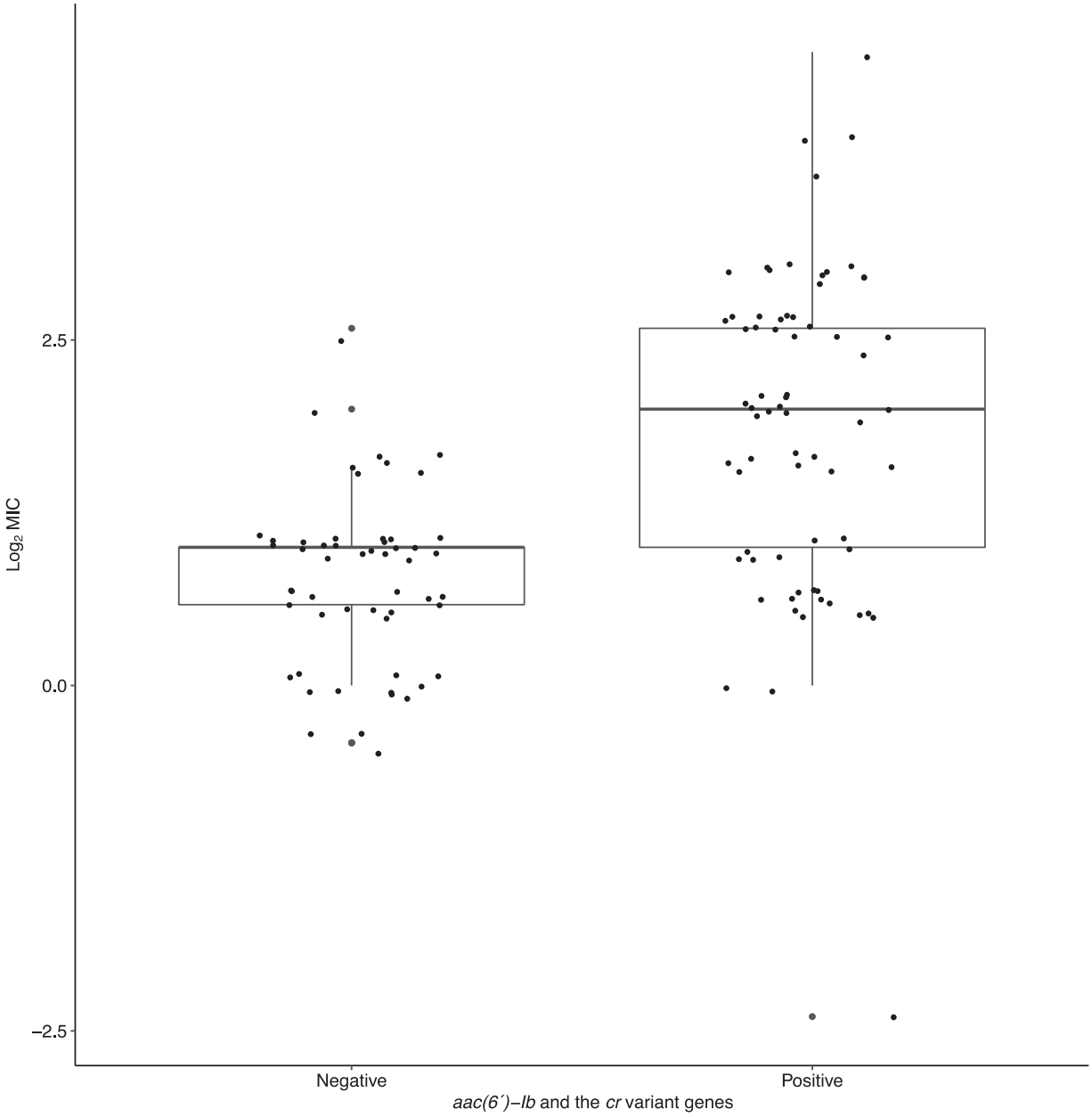

Fig. 1. Box plot showing the distributions of the $\log_2$ MICs for amikacin among isolates carrying and lacking *aac(6′)-Ib* and the -cr variant genes. MIC, minimum inhibitory concentration.

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Competing interests

None declared.

Ethical approval

This study was carried out under Protocol number: 180402214, which was granted exempt status by the Institutional Review Board of Sidra Medicine as it only involved pathology specimens.

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