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Abstract

Potential impact of low ciprofloxacin concentrations in the promotion of resistance in *Aliarcobacter butzleri*

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Abstract: Although antimicrobial resistance has traditionally been associated with exposure to high therapeutic concentrations of antibiotics, the contribution of subclinical concentrations has recently been demonstrated to select for multidrug-resistant mutants. Nonetheless, this is an unexplored topic under gastrointestinal pathogens. In this respect, the reports of multidrug resistance rates for *Aliarcobacter butzleri*, an emerging enteropathogen whose ubiquity represents a significant concern for public health, translate into a potential compromise in the treatment of infections caused by this microorganism. Fluoroquinolones are one of the recommended classes of antibiotics for infections by this bacterium. However, ciprofloxacin is classified by the WHO as having the highest priority among the critically important antimicrobials and is a member of the Watch category. Aiming to unveil the role of low antibiotic concentrations on the resistance potential of *A. butzleri*, three strains isolated from distinct origins were phenotypically characterized regarding resistance to ciprofloxacin and submitted to a 12-day adaptative laboratory evolution in the presence of subinhibitory concentrations of this fluoroquinolone. Following experimental evolution, the susceptibility of the evolved populations to ciprofloxacin was assessed, as was their cross-resistance profile to antibiotics belonging to classes, biocides, heavy metals, and ethidium bromide. In all cases, multidrug-resistant mutants emerged upon exposure to concentrations below the levels reported in ciprofloxacin-polluted ecosystems, with changes in the susceptibility to ethidium bromide observed, suggesting that the efflux pumps activity is involved in the resistance phenotypes. From a One-Health perspective, these findings support the relevance that low antibiotic concentrations may have in worsening the antibiotic resistance problem, especially for environmental pathogens such as *A. butzleri*.

Keywords: *Aliarcobacter butzleri*; antimicrobial resistance; experimental evolution; low antibiotic concentrations.

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