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Colonization by *Escherichia coli* strains with increased minimal inhibitory concentration for cefiderocol: when resistance anticipates drug use

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Dear editor

Emergence of carbapenem-resistant Gram negatives (GN) is a global concern [1]. Cefiderocol is a siderophore cephalosporin active against carbapenem-resistant Enterobacterales (CRE) approved by US FDA in 2019 for treatment of complicated urinary tract infections. The catechol moiety on the 3-position chain of this molecule contributes the entry through the outer membrane of GN iron transport systems [2]. An outbreak of New Delhi metallo-β-lactamase-producing carbapenem-resistant Enterobacterales (NDM-CRE) was recorded in Tuscan-Italy, in November 2018-October 2019 with 1645 cases [3]. Most of these cases were intestinal colonization: 77.2% *K. pneumoniae* and 4.2% *E. coli*.

We observed two children with CRE with reduced sensitivity to cefiderocol, related with this outbreak.

First patient, born in 2017, was hospitalized in 2018 and 2019 in a Tuscan pediatric center to perform cardiac surgery and urological procedures for congenital malformations. In November 2020, she was admitted for further treatment at Istituto Giannina Gaslini, Genoa, Liguria-Italy. Screening rectal swab for detection of CRE was performed according to internal protocol [4]. A NDM producing *E. coli* was isolated. Cefiderocol susceptibility testing (kindly provided by Shionogi) was performed by broth microdilution (BMD) and disk diffusion assay with the disk of 30 μg (Kirby-Bauer method, KB) according to EUCAST recommendations [5]; for BMD, a lyophilized plate (Sensititre™Termo Fisher Scientific™) was used, while KB was performed on a Mueller-Hinton agar plate (bioMeriéux), with BMD clinical breakpoints [6] of S≤2 and R>2mg/L, with an epidemiological cut-off value (ECOFF) of 0.25mg/L, and KB breakpoints S≥22 and R<22mm with 24mm ECOFF. Cefiderocol MIC was 1 mg/L and inhibition diameter was 22mm. Subsequently, another patient was identified from Tuscany, who was hospitalized several times in a pediatric center in her region due to complications of a Rett syndrome. She was then admitted in November 2020 to our hospital to carry out neurological assessment. Screening rectal swab for CRE was performed with isolation of *E. coli* Verona integron-encoded-metallo-β-lactamase (VIM) producer. KB test showed inhibition diameter of 22mm, BMD was not performed.

Confirmatory tests were performed for both patients.

Mechanism of reduced susceptibility is unclear: it could be related to reduced influx for iron transport or to the co-expression of serine-type-β-lactamases, although no one has identified them [7]. NDM-producing *E.*

coli strains with reduced susceptibility to cefiderocol has been already identified [7], but to the best of our knowledge, these are the first *E. coli* strains isolated in pediatric patients with carbapenemases and cefiderocol MIC>ECOFF, in spite of its compassionate availability in Italy for adults and absence of any clinical use and recommendation in pediatrics. These findings pose a double question: on one hand, an increase in *E. coli* ECOFF for cefiderocol could be considered, on the other, cross-resistance mechanisms could be involved as well.

Our report emphasize the need for screening and isolation protocols in CRE-positive pediatric patients [4], even in presence of simple epidemiological suspicion. Antibiotic stewardships programs are also mandatory to promote correct use reducing the possibility for further resistance.

Conflict of interest: All authors have no conflict of interest to declare.

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