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In vitro activity of mecillinam against urine isolates of Escherichia coli from outpatient departments in Germany

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Background: *Escherichia coli* is the leading pathogen of community-acquired urinary tract infections (UTI). The management of UTI in the community is empirically in most cases, but acquired antimicrobial resistance in *E. coli* is a growing serious problem that complicates effective treatment of UTI. In this context, pivmecillinam, a prodrug of the penicillin derivative mecillinam, has become an attractive drug for oral first-line treatment of acute uncomplicated UTI. The purpose of this study was to evaluate the *in vitro* activity of mecillinam against a German collection of *E. coli* urine isolates prior to its introduction.

Material/methods: Bacterial strains were obtained from patients in outpatient departments and collected during a laboratory surveillance study conducted by the Paul-Ehrlich-Society between October and December 2013. Twenty-five laboratories across Germany were requested each to collect 20 consecutive non-duplicate urine isolates. Organisms were shipped to a coordinating laboratory for species confirmation and susceptibility testing. Species identification was confirmed by MALDI-TOF. Minimal inhibitory concentrations (MICs) of mecillinam were determined using the agar dilution method according to the CLSI standard M07-A10, while MICs of other antibacterial agents were determined using the microdilution method according to the standard ISO 20776-1. Results were interpreted according to EUCAST criteria (version 6.0). Breakpoints of mecillinam for susceptibility and resistance were ≤8 mg/l (susceptible) and >8 mg/l (resistant). Extended-spectrum beta-lactamase (ESBL) screening and confirmatory tests were performed according to the guideline of the CLSI.

Results: A total of 494 isolates were tested. An ESBL phenotype was confirmed for 23 (4.7%) isolates. 484 (98%) isolates were mecillinam-susceptible and 10 (2%) were mecillinam-resistant. In comparison, rates of resistance to fosfomycin and nitrofurantoin were 0.8% and 1%, respectively. Applying the EUCAST epidemiological cut-off value of mecillinam (1 mg/l), 121 (24.5%) isolates

showed acquired resistance mechanisms (non-wild type) to the agent, but were classified as mecillinam-susceptible (i. e. MICs 2-8 mg/l). All but three of these isolates were resistant to amoxicillin. MIC-50/90 values of mecillinam for ESBL isolates were 1/4 mg/l, as compared to 0.25/4 mg/l for non-ESBL isolates.

Conclusions: This study demonstrated that the susceptibility of *E.coli* to mecillinam is high and at the same level as fosfomycin and nitrofurantoin in Germany. Pivmecillinam may thus (still) be a first-line oral therapeutic option in the treatment of acute uncomplicated UTI caused by *E. coli*, as recommended by international guidelines.