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### MEETING ABSTRACT

#### A2.13

##### Impact of pH on activity of the novel cephalosporine cefiderocol in pooled human urine

Alina Karoline NUSSBAUMER-PRÖLL, Sabine EBERL, Christine SCHOBER, Markus ZEITLINGER\*

Department of Clinical Pharmacology, Medical University of Vienna, Austria

**Background:** Antibiotic activity of different antibiotics can be impacted by pH, enhancing or reducing their bactericidal properties. Cefiderocol, a novel cephalosporine antibiotic is indicated for the treatment of infections caused by gram-negative bacteria such as Enterobacteriaceae and *P. aeruginosa*. These pathogens are also associated with complicated urinary tract infections. To better link *in vitro* experiments to *in vivo* conditions, pooled human urine (iron levels ~ 0.05 mg/l/24 h) and cation-adjusted Mueller-Hinton broth (CAMHB), were used as media to test cefiderocol activity against the aforementioned pathogens at pH 5–8.

**Methods:** Minimal inhibitory concentration (MIC) determinations were done according to CLSI guideline with the broth microdilution method of 17 clinical isolates of *E. coli* and ATCC 25922 (including isolates with extended-spectrum β-lactamase activity (ESBL)), 17 clinical isolates of *K. pneumoniae* and ATCC 700603 (also with ESBL), and 6 clinical isolates of *P. aeruginosa* and ATCC 27853. All MIC determinations (at least 3x up to 18x per strain) were conducted in pooled human urine and CAMHB at pH 5, 7 and 8. Human urine was obtained from young, male, healthy volunteers, frozen, thawed, pooled, sterile filtered (2 µm) and frozen again until usage. The pH was set directly before the start of the experiments with HCl or NaOH.

**Results:** MIC values in urine and CAMHB were overall identical and did only vary sporadically in a 1-fold dilution up or down. The median MIC values of both antibiotics were up to 50-fold higher in pH 5 than in pH 7 for *P. aeruginosa* isolates and 32-fold higher in *E. coli* and *K. pneumoniae* isolates, leading to MIC values above the EUCAST breakpoint (for iron-depleted CAMHB), for systemic infection of > 2 mg/l at an acidic pH (table 1).

**Discussion:** Acidic pH had a significant negative impact on the activity of cefiderocol in pooled human urine and may be explained by an altered availability of free ferric iron (required for optimal uptake into the cell). Moreover, since non-iron-depleted CAMHB was used, overall MICs might be elevated. Nevertheless, after a recommended intravenous administration of 2 g every 8 hours a concentration of 1247 mg/l of cefiderocol can be achieved in urine, suggesting that efficient killing of all tested pathogens could have been achieved even under acidic conditions *in vivo*.

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**Keywords:** cefiderochol – antibiotic activity – pH – minimal inhibitory concentrations – time-kill curves

Table 1: MIC values of cefiderocol for all isolates and ATCC strains

	MIC in CAMHB			MIC in urine		
	pH 5	pH 7	pH 8	pH 5	pH 7	pH 8
<i>P. aeruginosa</i>						
Median MIC of 6 isolates	8	0.15	0.14	7	0.14	0.08
ATCC 27853	8	0.25	0.25	8	0.25	0.125
<i>E. coli</i>						
Median MIC of 17 isolates	4	0.125	0.19	4	0.125	0.09
ATCC 25922	1	0.06	0.125	1.5	0.125	0.06
<i>K. pneumoniae</i>						
Median MIC of 17 isolates	16	0.5	0.31	16	0.5	0.31
ATCC 700603	8	0.25	0.125	8	0.5	0.25

Values are given as mg/l for pH 5, 7 and 8 in cation-adjusted MHB (CAMHB) and in urine.

\*Corresponding author e-mail: [markus.zeitlinger@meduniwien.ac.at](mailto:markus.zeitlinger@meduniwien.ac.at)