720. Efficacy of Fosfomycin for Injection (FOS) vs. Piperacillin–Tazobactam (PIP-TAZ) in Adults with Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP): ZEUS Study Outcomes in Patients With Reduced Study Drug Susceptibility

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. FOS is being pursued for US registration in cUTI/AP. Safety and efficacy of FOS vs. PIP-TAZ were demonstrated in the noninferiority ZEUS trial in hospitalized patients with cUTI/AP. Although FOS resistance has been observed in several *in vitro* studies, resistance rates in clinical settings have remained relatively stable despite >40 years of clinical use of FOS outside of the United States. Here we report outcomes in patients who developed reduced susceptibility to study drug (FOS or PIP-TAZ) after enrollment in ZEUS.

Methods. Patients received IV FOS 6g q8h or PIP-TAZ 4.5g q8h for 7 days (no oral switch allowed). The primary endpoint was overall success (clinical cure + microbiologic eradication) in microbiologic modified intent-to-treat (m-MITT) population at test-of-cure (TOC; Day 19–21). Reduced susceptibility to FOS or PIP-TAZ was defined as a ≥4-fold increase from baseline in minimum inhibitory concentration (MIC) at Day 5, end of treatment (EOT; Day 7–8), TOC, or late follow-up (LFU; Day 26 ± 2). Microbiologic eradication/persistence of baseline and postbaseline pathogens was confirmed post hoc by pulsed-field gel electrophoresis (PFGE).

Results. In all m-MITT patients, overall success/clinical cure/microbiologic eradication rates (with PFGE) at TOC were 69.0/90.8/70.7% (FOS) and 57.3/91.6/60.1% (PIP-TAZ). Reduced study drug susceptibility was identified in 7/184 (3.8%) FOS and 8/178 (4.5%) PIP-TAZ patients; all had monomicrobial infections (Table 1). Of these patients, almost all were aged ≥50 years (93%), male (73%), white (100%), and had a screening diagnosis of cUTI (93%). At TOC, 7/7 FOS patients and 7/8 PIP-TAZ patients had microbiologic persistence but all patients were clinical cures; these responses were all sustained through LFU (Table 1).

Conclusion. In the ZEUS study, few patients had urine isolates with reduced postbaseline susceptibility to either FOS or PIP-TAZ. No trend was observed in isolate species associated with decreased susceptibility to FOS or PIP-TAZ, including various *Enterobacteriaceae* species and *Pseudomonas aeruginosa*. Despite microbiologic persistence at TOC in a small number of patients, all of these patients were clinical cures at TOC and sustained cures at LFU.

Table 1. Summary of Outcomes in Patients With Reduced Study Drug Susceptibility (m-MITT population*)

Treatment Group Patient	Visit	Pathogen	Uropathogen Identity Based on Molecular Typing (With PFGE Analysis)			Responses at TOC/LFU (With PFGE Analysis)		
			Baseline MIC (µg/mL)	Post-Baseline MIC (µg/mL)	Fold Change†	Clinical	Microbiologic	Overall
FOS (n=7)								
1	LFU	*Pseudomonas aeruginosa*	64	>512	>8	C/SC	P/CP	F/F
2	LFU	*Escherichia coli*	0.5	64	128	C/SC	P/CP	F/F
3	Day 5	*Klebsiella pneumoniae*	4	32	8	C/SC	P/CP	F/F
4	Day 5, EOT, TOC, LFU	*Enterobacter cloacae* species complex	64	≥512	>8	C/SC	P/CP	F/F
5	EOT, TOC	*Pseudomonas aeruginosa*	64	>512	>8	C/SC	P/CP	F/F
6	TOC	*Pseudomonas aeruginosa*	64	>512	>8	C/SC	P/CP	F/F
7	EOT, TOC	*Klebsiella pneumoniae*	16	>512	>32	C/SC	P/CP	F/F
PIP-TAZ (n=8)								
8	TOC	*Escherichia coli*	1	4	4	C/SC	P/CP	F/F
9	TOC	*Klebsiella pneumoniae*	4	64	16	C/SC	P/CP	F/F
10	LFU	*Klebsiella pneumoniae*	1	4	4	C/SC	P/CP	F/F
11	TOC	*Escherichia coli*	16	>64	>4	C/SC	P/CP	F/F
12	LFU	*Klebsiella pneumoniae*	2	>64	>32	C/SC	E/R	S/F
13	LFU	*Klebsiella pneumoniae*	2	64	32	C/SC	P/CP	F/F
14	LFU	*Klebsiella pneumoniae*	8	32	4	C/SC	P/CP	F/F
15	TOC	*Escherichia coli*	2	8	4	C/SC	P/CP	F/F

C=cure; CP=continued persistence; E=eradication; EOT=end of treatment; F=failure; FOS=fosfomycin for injection; LFU=late follow-up; MIC=minimum inhibitory concentration; m-MITT=microbiologic modified intent to treat; P=persistence; PFGE=pulsed-field gel electrophoresis; PIP-TAZ=piperacillin-tazobactam; R=recurrence; S=success; SC=sustained cure; TOC=test-of-cure
*All randomized patients who received study drug and had ≥1 baseline Gram-negative pathogen from an appropriately collected pretreatment baseline urine or blood sample.
†Ratio of post-baseline MIC value to baseline MIC value.

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721. *In Vitro* Activity of Cefiderocol Against Gram-Negative Clinical Isolates From New York City

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Background. Multidrug-resistant Gram-negative bacteria have become a serious problem in hospitals worldwide. Cefiderocol (CFDC) is a novel siderophore cephalosporin with activity against a wide range of carbapenemase- and ESBL-producing bacteria. We tested the activity of CFDC against (1) a recent collection of clinical isolates and (2) a separate collection of carbapenem-resistant isolates gathered from NYC hospitals.

Methods. Susceptibility testing was performed on isolates of *E. coli*, *K. pneumoniae*, *Enterobacter* spp., *P. aeruginosa*, and *A. baumannii* gathered in 2017 from 7 hospitals in Brooklyn, NY. Consecutive unique patient clinical isolates from all sources were collected for a three month period. Testing was also done on a collection of carbapenem-resistant isolates from a similar surveillance study conducted in 2013–2014. MICs were performed with iron-depleted cation-adjusted Mueller–Hinton broth for CFDC and agar dilution for other antibiotics according to CLSI methodology. The provisional CLSI breakpoint (≤4 µg/mL susceptible) was used for CFDC. Cephalosporin-resistant isolates were tested for common carbapenemases by PCR.

Results. The susceptibility results for CFDC and meropenem for the isolates gathered in 2017 are listed in the Table. All of the Enterobacteriacae were susceptible to CFDC including KPC-possessing *E. coli* (n = 4), *K. pneumoniae* (n = 20), and *Enterobacter* spp (n = 3). 99.6% of *P. aeruginosa* and 100% of *A. baumannii* (including 8 with bla_{OXA-23}, 2 with bla_{OXA-24}, and 1 with bla_{KPC}) were susceptible to CFDC. For the collection of carbapenem-resistant isolates gathered in 2013–14, 100% of *K. pneumoniae* (n = 111), 100% of *P. aeruginosa* (n = 130), and 90% of *A. baumannii* (n = 78) were susceptible to CFDC.

Conclusion. CFDC has excellent *in vitro* activity against Gram-negative clinical isolates from NYC, including a large collection of carbapenem-resistant Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii*.

	MIC_{50}	MIC_{90}	Range	Percent susceptible
	µg/ml			
E. coli (n=1869)				
Meropenem	≤0.125	≤0.125	≤0.125 - 4	99.9%
Cefiderocol	0.125	0.5	≤0.03 - 2	100%
K. pneumoniae (n=518)				
Meropenem	≤0.125	≤0.125	≤0.125 - >8	96.5%
Cefiderocol	0.125	0.5	≤0.03 - 2	100%
Enterobacter spp. (n=172)				
Meropenem	≤0.125	≤0.125	≤0.125 - >8	97.6%
Cefiderocol	0.125	0.5	≤0.03 - 1	100%
P. aeruginosa (n=269)				
Meropenem	1	8	≤0.125 - >8	76%
Cefiderocol	0.25	0.5	≤0.03 - 8	99.6%
A. baumannii (n=46)				
Meropenem	8	>8	≤0.125 - >8	48%
Cefiderocol	0.25	1	0.06 - 4	100%

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722. Pharmacokinetics (PK) and Safety of Lefamulin (LEF) After Single Intravenous Dose Administration in Subjects With Impaired Hepatic Function

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Background. Patients with chronic liver disease (CLD) have impaired immune function, are prone to community-acquired bacterial pneumonia (CABP), and experience greater morbidity/mortality and healthcare costs than CABP patients without CLD. LEF, a novel pleuromutilin antibiotic (IV/oral) with primary liver elimination, was generally well tolerated and noninferior to moxifloxacin in two phase 3 studies of adults with CABP. We investigated the PK and safety of LEF and its main metabolite, BC-8041, in subjects with hepatic impairment.

Methods. In this open-label study, subjects were allocated to 1 of 3 groups based on hepatic function level; Moderate (Child-Pugh score 7–9) or Severe subjects (Child-Pugh score ≥10) were matched (gender, age, and weight) to subjects in the Normal group (normal hepatic function, no liver cirrhosis). Subjects received a single 1-hour 150 mg LEF infusion. Blood and urine samples were collected predose and over a 48-hour period postdose for PK analysis; plasma and urine were assayed for LEF and BC-8041 using validated assays. Safety assessments included treatment-emergent adverse events (TEAEs), labs, vital signs, and electrocardiograms.

Results. 27 subjects enrolled in and completed the study (n = 11, Normal; n = 8, Moderate; n = 8, Severe). Mean LEF and BC-8041 plasma concentration profiles were comparable across all hepatic function groups through the first 12 hours following the start of infusion. Subjects with hepatic impairment had slightly slower rates of elimination in the later elimination phases. LEF and BC-8041 exposures were similar across all hepatic function groups (table), and the majority of LEF and BC-8041 were excreted nonrenally. TEAEs were reported in 2 (18.2%) subjects in the Normal group, 2 (25%) in the Moderate group, and 1 (12.5%) in the Severe group. None of the TEAEs were serious or led to study drug discontinuation. No subject met Hy's law criteria. Within 4 hours postdose, the maximum mean change from baseline in the QTcF interval was 12.4, 19.2, and 14.1 msec in the Normal, Moderate, and Severe groups, respectively.

Conclusion. No dosage adjustment for LEF appears to be required when treating subjects with hepatic impairment. LEF was generally well tolerated in all subjects regardless of hepatic functional status.