1521. Heterogeneity of Recent Phase 3 cUTI Clinical Trials with New Antibiotics

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Background. For new antibiotics to treat Gram-negative infections, one regulatory pathway includes complicated urinary tract infections (cUTI) clinical trials. Although individual clinical trials comply with regulatory guidelines, they may differ substantially in design and execution. Six recent cUTI trials that supported or are likely to support FDA regulatory review were compared to determine variables that impacted patient selection and outcome parameters.

Methods. cUTI trials for six new antibiotics developed to treat multi-drug-resistant Gram-negative infections were obtained from publicly disclosed information including FDA documents, publications, or presentations at scientific meetings. Antibiotics included were: ceftolozane-tazobactam (CTL-TAZ), ceftazidime–avibactam (CTZ-AVI), meropenem-vaborbactam (MER-VAB), cefiderocol, plazomicin, and fosfomycin. Comparison variables included: mMITT sample size, age, % female patients, % acute pyelonephritis, % *E. coli* and other pathogens at baseline, switch to PO antibiotic, and the non-inferiority margin. Other variables as well as the microbiologic eradication, clinical response, and the combined outcomes will be included in the poster.

Results.

	CTL-TAZ	CTZ-AVI	MER-VAB	Cefiderocol	Plazomicin	Fosfomycin
mMITT (*n*)	800	810	374	371	388	362
Non-inferiority margin (%)	10	10	15	15	15	15
Age, years (mean)	48.6	52.4	54.3	62	59.4	Not Reported
% female	74	69.8	65.5	55	52.8	63.5
Acute pyelonephritis (%)	82	72	59	27	42	53
E. coli (%)	78.6	73.8	64.7	62.3	69.6	73.4
IV-to-PO	no	Yes	yes	no	yes	no

Conclusion. Study design and eligibility criteria significantly influences patient characteristics. The proportion of acute pyelonephritis varied greatly and influenced population demographics (age, gender) and baseline microbiology. Studies with a smaller proportion of acute pyelonephritis resulted in an older patient population, fewer females and less *E. coli*. Larger sample size did not impact outcomes.

Disclosures. **A. Bass**, Shionogi Inc.: Employee, Salary. **R. Echols**, Shionogi Inc.: Consultant, Consulting fee. **S. Portsmouth**, Shionogi Inc: Employee, Salary. **A. Howell**, Shionogi Inc.: Employee, Salary.

1522. Initial Clinical Response of Children with Extended-Spectrum Cephalosporin-Resistant Urinary Tract Infections (ESC-R UTI's) Started on Discordant Antibiotics

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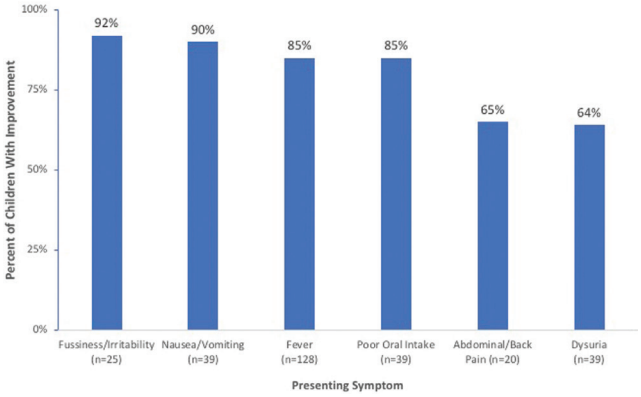
Background. ESC-R UTI's in children are often resistant to common empiric regimens. Our objective was to describe the initial clinical response of children with ESC-R UTI's while on discordant antibiotics.

Methods. We conducted a multicenter retrospective chart review of children <18 years with ESC-R UTI's presenting to an acute care setting of 5 children's hospitals and a large managed care organization from 2012 to 2017. ESC-R UTI was defined as having a urinalysis with positive leukocyte esterase or >5 white cells per high-power field and urine culture with ≥50,000 colony-forming units per milliliter of *E. coli* or *Klebsiella* spp. nonsusceptible to ceftriaxone. Children were included if they received initial discordant antibiotics (an agent to which their isolate was nonsusceptible) and had phone or in-person follow-up when urine culture susceptibilities resulted. Children with urologic surgery, immunosuppression and nonrenal chronic conditions were excluded. Outcomes were: (1) Escalation of care, defined as an emergency room visit, hospital admission or intensive care unit (ICU) transfer while on discordant therapy and (2) clinical response at the time of follow-up, classified as improved (complete or partial resolution of presenting symptoms) or not improved (persistence of symptoms) and assessed by a second reviewer in 20% of charts to determine inter-rater reliability.

Results. Of 253 children with ESC-R UTI's, 76% were female, median age was 2 years (interquartile range [IQR] 0.5–6.5) and 88% were started on cephalosporins. Median time to follow-up was 3 days (IQR 2–3). Nine children (4%) had escalation of care without ICU transfer. Follow-up records with clinical response information were available for 187 children (74%); 154 (83%) were improved and 33 (17%) were not improved ($\kappa = 0.80$). Figure 1 shows improvement by symptom. In children with repeat urine testing while on discordant therapy, pyuria improved in 12/15 and urine cultures sterilized in 10/13.

Conclusion. Most children with ESC-R UTI's experienced initial clinical improvement while on discordant antibiotics. Future studies should prospectively evaluate the *in vitro* and clinical effect of discordant therapy in children to assess the need for modified urine-specific breakpoints.

Figure 1. Percentage of Children with ESC-R UTI's with Initial Improvement in Presenting Symptoms While on Discordant Antibiotics



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1523. Antimicrobial Activity of Ceftazidime–Avibactam and Comparator Agents Tested Against Gram-Negative Organisms Isolated from Complicated Urinary Tract Infections: Results from the International Network for Optimal Resistance Monitoring (INFORM) Program

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Background. Urinary tract infections (UTIs) are among the most frequent healthcare-associated infections and represent a major source of Gram-negative (GN) bacteremia. We evaluated the antimicrobial susceptibility (S) of GN bacteria isolated from patients with complicated UTIs (cUTIs) in United States medical centers.

Methods. Unique patient isolates were consecutively collected from patients with cUTIs in 83 medical centers in 2015–2017, and the GN organisms (n = 9,403) were S tested against CAZ-AVI and comparators by reference broth microdilution Methods. Ceftolozane-tazobactam (C-T) was tested in 2017 only. *Enterobacteriaceae* (ENT) with an extended-spectrum β-lactamase (ESBL) phenotype was evaluated by whole genome sequencing for the presence of genes encoding β-lactamases.

Results. The most common organisms were *E. coli* (EC; 53.2%), *K. pneumoniae* (KPN; 12.5%), *E. faecalis* (6.0%), *P. mirabilis* (PM; 5.3%), and *P. aeruginosa* (PSA; 4.9%). An ESBL phenotype was observed among 13.2, 13.4 and 7.0% of EC, KPN, and PM, respectively. CAZ-AVI inhibited >99.9% of all ENT, including all EC, PM and *E. cloacae* (ECL) isolates, at the S breakpoint of ≤8 µg/mL (table). CAZ-AVI was also highly active against KPN, including ESBL-phenotype ($MIC_{50/90}$, 0.25/1 µg/mL; 99.5%S) and meropenem (MEM)-non-S isolates ($MIC_{50/90}$, 1/2 µg/mL; 98.0%S). In contrast, only 72.9 and 73.1% of ESBL-phenotype KPN isolates were S to C-T and MEM, respectively. Only one ENT isolate was CAZ-AVI-resistant, a KPN with a CAZ-AVI MIC of 16 µg/mL that produced a KPC-2 and an SHV-12 and exhibited decreased expression of OmpK36. Among ECL (27.2% CAZ-non-S), S to CAZ-AVI, C-T, and MEM were 100.0, 80.0, and 98.8%, respectively. CAZ-AVI was also highly active against PSA ($MIC_{50/90}$, 2/4 µg/mL; 99.1%S), including isolates expressing a multidrug-resistant (MDR) phenotype ($MIC_{50/90}$, 4/8 µg/mL; 93.8%S). Further 86.2% (25/29) of PSA isolates non-S to MEM, CAZ, and piperacillin–tazobactam were CAZ-AVI-S.

Conclusion. CAZ-AVI demonstrated potent activity against a large collection of contemporary (2015–2017) GN bacteria isolated from patients with cUTIs in US hospitals, including MDR isolates, and provided greater coverage than the agents currently available in the United States for treatment of cUTIs.

Organism / resistant subset (no.)	MIC_{50}/MIC_{90} in µg/mL (%S)				
	CAZ-AVI	C-T[a]	P-T	Cefepime	MEM
E. coli (5,771)	0.12/0.25 (100.0)	≤0.12/0.5 (99.3)	2/4 (97.6)	≤0.12/4 (89.9)	≤0.015/0.03 (>99.9)
K. pneumoniae (KPN; 1,355)	0.12/0.25 (99.9)	0.25/1 (96.1)	2/16 (92.9)	≤0.12/4 (89.7)	0.03/0.03 (96.4)
ESBL-phenotype KPN (182)	0.25/1 (99.5)	1/>16 (72.9)	16/>64 (51.1)	>16/>16 (23.1)	0.03/16 (73.1)
P. mirabilis (572)	0.06/0.06 (100.0)	0.5/0.5 (99.5)	≤0.5/1 (100.0)	≤0.12/≤0.12 (98.5)	0.06/0.12 (100.0)
E. cloacae (254)	0.25/0.5 (100.0)	0.5/8 (80.0)	2/64 (79.9)	≤0.12/2 (92.1)	0.03/0.12 (98.8)
Enterobacteriaceae (8,803)	0.12/0.25 (>99.9)	0.25/0.5 (97.7)	2/8 (96.1)	≤0.12/1 (91.0)	≤0.015/0.06 (99.3)
P. aeruginosa (PSA; 531)	2/4 (99.1)	0.5/1 (99.5)	4/32 (84.6)	2/16 (89.5)	0.5/8 (83.6)
MDR PSA (80)	4/8 (93.8)	2/4 (96.0)	64/>64 (26.2)	16/>16 (38.8)	4/16 (30.0)

[a] Ceftolozane-tazobactam (C-T) was tested against isolates from 2017 only.