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1589. Ceftolozane–Tazobactam Activity Against Difficult-to-Treat Resistance in *Pseudomonas aeruginosa* from Bloodstream Infections in US Hospitals

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. Infections caused by *Pseudomonas aeruginosa* (PSA) resistant to first-line agents are difficult to treat and require using more toxic antimicrobials, such as amikacin (AMK) and colistin (COL). Kadri et al. recently described the category of difficult-to-treat resistance (DTR) as intermediate or resistant to all tested first-line agents (fluoroquinolones, carbapenems, and extended-spectrum cephalosporins). Ceftolozane–tazobactam (C-T) is an antibacterial combination of an antipseudomonal cephalosporin and a β-lactamase inhibitor. C-T has been approved in >60 countries to treat complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections. The filing is in progress for treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia. The Program to Assess Ceftolozane–Tazobactam Susceptibility (PACTS) monitors gram-negative (GN) isolates resistant to C-T worldwide. In this study, the activity of C-T and comparators against PSA bloodstream isolates that are DTR, multidrug-resistant (MDR), or extensively drug-resistant (XDR) were analyzed.

Methods. A total of 922 PSA isolates from BSI were collected between 2011 and 2018 from 35 PACTS hospitals in the United States. Isolates were tested for C-T susceptibility (S) by the CLSI broth microdilution method. Other antibiotics tested included cefepime (FEP), ceftazidime (CAZ), ciprofloxacin, levofloxacin (LEV), doripenem, imipenem, meropenem (MEM), piperacillin–tazobactam (PIP-TAZ), AMK and COL. Antibiotic-resistant phenotypes analyzed using CLSI (2019) breakpoints included MDR (nonsusceptible to ≥ 1 agent in ≥ 3 drug classes), XDR (susceptible to ≤ 1 agent in ≤ 2 drug classes), or DTR.

Results. The percent of DTR isolates was 4.8% when compared with 15.2% MDR and 9.3% XDR. The %S for C-T and other first- and second-line agents are shown in the table for each phenotype.

Conclusion. C-T demonstrated 97.1%S overall for BSI isolates, similar to AMK (97.8%) and COL (99.5%). C-T had better coverage than first-line drugs against MDR (81.4%) and XDR (72.1%), and 50% for the DTR isolates, which represented only 4.8% of isolates. Only AMK and COL had > 75%S for DTR isolates.

		% susceptible[a]							
	n	C-T	FEP	CAZ	MEM	PIP-TAZ	LVX	AMK	COL
PSA	922	97.1	87.2	86.1	81.9	82.2	70.9	97.8	99.5
MDR	140	81.4	32.1	31.4	17.9	16.4	10.7	86.4	100.0
XDR	86	72.1	12.8	20.9	4.7	4.7	0.0	80.2	100.0
DTR	44	50.0	0.0	0.0	0.0	4.5	0.0	79.5	100.0

[a] CLSI (2019).

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1590. Updated Aminoglycoside (AG) MIC Breakpoints (BP) to Minimize Adverse Events and Improve Outcome: Impact on Susceptibility (S) Rates

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. In 2016 USCAST, the National Advisory Committee (NAC) for the United States (US) to EUCAST, undertook the re-evaluation of the in vitro susceptibility (AST) test interpretive criteria (IC) for gentamicin (GM), tobramycin (TO) and amikacin (AK) against Enterobacteriaceae (ENT), P. aeruginosa (PSA) and *S. aureus* (SA) based on an analysis of contemporary microbiology and PK/PD data. In 2019 USCAST posted the third version (www.uscast.org) of AG IC document and CLSI and EUCAST has published AG IC in CLSI M100-S29 and EUCAST v 9.0 documents. USCAST ICs for S were generally lower than those proposed by CLSI for all organism/drug combinations. PK/PD emphasized high, extended interval dosing (5 renal function groups) to reduce nephro-vestibular toxicity and a stasis exposure endpoint. Here, we evaluate the impact on S rates for US AST data that these IC changes created.

Methods. Clinical isolates from 2010 to 2018 US SENTRY Program (reference broth microdilution AST) were analyzed for S based on current and previous IC values. AG results for GM, TO and AK were evaluated against 66,280 ENT, 13,959 PSA and 51,950 SA. Benchmark S data for meropenem, cefepime, piperacillin–tazobactam and new AG, plazomicin (PZM) were included as well as ESBL and carbapenem-resistant ENT (CRE; 805 isolates).

Results. S rates for ENT as determined by USCAST IC were reduced by 4.2/1.2/3.1% for AK/GM/TO (CLSI) and by 3.3% for AK (EUCAST); no S rate difference for GM and TO as determined by USCAST/EUCAST. For PSA, S decreased by 46.8/6.2% for AK/TO (EUCAST) and 51.6/6.2% (CLSI). S for SA vs. GM declined by only 0.2% (CLSI). No AG IC could be calculated/offered for Acinetobacter or GM X PSA or AM/TO X SA. Best S overall coverage X ESBL (99.2%) or CRE (97.2%) isolates was by PZM.

Conclusion. USCAST IC updates for AG lead to reduced values for some organism/drug combinations among ENT and PSA compared with those proposed elsewhere. The USCAST-recommended ICs were based on achieving AUC/MIC ratio target associated with net bacterial stasis. Given the assumption of AG combination therapy, stasis was considered a reasonable endpoint when evaluating AG ICs to improve both safety and efficacy. Some organism X drug exposures could not be calculated and lower IC for pneumonia isolates (GM, TO) was recommended.

Organism (no. tested)/ Antimicrobial	Percent Susceptible (Applied criteria)		
	USCAST	EUCAST	CLSI
Enterobacteriaceae (66,280)			
Amikacin	94.9	98.2	99.1
Gentamicin	90.1	90.1	91.3
Tobramycin	87.9	87.9	91.0
CRE (805)			
Plazomicin	97.2	-	-
Amikacin	39.0	-	-
Gentamicin	43.9	-	-
Tobramycin	18.5	-	-
P. aeruginosa (13,959)			
Amikacin	44.7	91.5	96.3
Tobramycin	86.7	92.9	92.9
S. aureus (51,950)			
Gentamicin	97.5	97.5	97.7

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1591. Updated Fluoroquinolone MIC Breakpoints: Impact on Susceptibility Rates in the United States

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. In 2015 USCAST, the National Advisory Committee for the United States (US) to EUCAST, produced a report (Version 1.0) on their website (www.uscast.org) re-evaluating fluoroquinolone (FQ) breakpoint interpretive criteria (IC) based on analysis of current microbiology and pharmacokinetic/pharmacodynamic (PK/PD) data. EUCAST initiated a consultative process using USCAST analyses in an effort to update FQ IC, released in 2017. CLSI formed an ad-hoc working group in late 2015 to review the USCAST FQ document and formulate questions about content. In 2018, USCAST released V1.3 of the FQ document and CLSI subsequently published updated FQ MIC IC in the M100-S29 (2019) document. This study evaluated the impact on susceptibility (S) rates for US surveillance data that these IC changes created.

Methods. Clinical isolates (reference broth microdilution MIC) from 2016–2018 US SENTRY Program were analyzed for S based on current and previous IC. FQ results for ciprofloxacin (CIP), levofloxacin (LEV), and moxifloxacin (MOX) were evaluated. Benchmark S comparison data for meropenem, cefepime, piperacillin–tazobactam and delafloxacin (new FQ) were also included.

Results. S rates for *Enterobacteriaceae* (ENT;Figure) were reduced by 3.8/3.7% for CIP/LEV (CLSI) and 2.3/2.5% (EUCAST). MOX-S rate vs. ENT declined 5.7% (EUCAST). Although reductions in S occurred for most organism groups, *K. pneumoniae* (6.0/5.5% for CIP/LEV [CLSI] and 4.0/4.2% [EUCAST]) and *S. marcescens* (7.4/4.1% for CIP/LEV [CLSI] and 4.1/5.0% [EUCAST]) reductions were among the largest changes. For *Pseudomonas aeruginosa* (PSA), CIP-S decreased 6.8% and LEV-S 10.1% (CLSI); but potential for false-S results remain using CLSI IC (5 pathogens).

Conclusion. USCAST's comprehensive analyses of FQ IC in 2015 led to revised breakpoints for most organism/drug combinations among ENT and PSA compared with those being used before. USCAST analysis was most influenced by PK/PD *in vivo* data as current clinical outcomes data by MIC was limited. Awareness and interactions (both formal and informal) among breakpoint setting organizations has modified FQ ICs which are lower than previously recommended, and although not perfectly harmonized in time and detail, this represents a successful model.

Organism (no. tested)/ Antimicrobial	Percent Susceptible (applied criteria)		
	USCAST	EUCAST (2019/2016)	CLSI (2019/2018)
Enterobacteriaceae (29,336)			
Ciprofloxacin	78.1	78.1/80.4	78.1/81.9
Levofloxacin	79.8	79.8/82.3	79.8/83.5
Moxifloxacin	70.3	70.3/76.0	N/A
P. aeruginosa (6,253)			
Ciprofloxacin	71.8	71.8/71.8	71.8/78.6
Levofloxacin	63.6	63.6/63.6	63.6/73.7

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