with dose-escalated oral monotherapy was observed at ISA 224 mg/kg Q12h (50% survival) and Q8h OG (60%) compared with other monotherapy or combination, or untreated groups (18–20%). The residual fungal burden in kidney between monotherapy and combination therapy groups was 5.81 10Log (untreated), 4.03 10Log (ISA 224 mg/kg, OG Q12h), 5.19 10Log (ISA 224 mg/kg Q12h + MICA 10 mg/kg, Q12h), 4.67 10Log (ISA 224 mg/kg, Q24h), and 4.82 10Log (ISA 224 mg/kg Q24h + MICA 10 mg/kg, Q12h).

Conclusion. High doses of isavuconazole (exceeding currently approved human dosages) in combination with micafungin improved survival in experimental murine disseminated fusariosis. Given the excellent safety profile of ISA, exploration of higher dosages that are necessary to achieve this antifungal effect is warranted for successful management of disseminated fusariosis.

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1586. *In Vitro* Activity of Rifampin, Rifabutin, Rifapentine, and Rifaximin Against Biofilms Formed by Staphylococci Isolated from Prosthetic Joint Infection

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Background. Prosthetic joint infections (PJIs) are serious complications after total joint arthroplasty. *Staphylococcus aureus* and *Staphylococcus epidermidis*, which are proficient biofilm-formers, account for ~60% of PJI cases. Therapy often includes rifampin because of its anti-biofilm activity; the activity of other rifamycins against staphylococcal biofilms is poorly defined. This study evaluated the *in vitro* activity of rifampin, rifabutin, rifapentine, and rifaximin against *S. aureus* and *S. epidermidis* biofilms formed by isolates from patients with PJI.

Methods. 200 staphylococcal isolates were tested (111 *S. aureus* and 89 *S. epidermidis*). All *S. aureus* isolates, and all except 7 *S. epidermidis* isolates, were rifampin susceptible. Rifampin, rifabutin, rifapentine, and rifaximin minimum biofilm inhibitory concentrations (MBICs) and minimum biofilm bactericidal concentration (MBBCs) were determined using a pegged lid microtiter plate assay.

Results. Rifampin-resistant isolates had MBICs and MBBCs ≥16 µg/mL. Results for the rifampin-susceptible isolates are shown. All 193 rifampin-susceptible isolates had rifampin MBICs ≤1 µg/mL (rifampin-susceptible breakpoint for planktonic susceptibility testing), with 1, 2, and 2 isolates having MBICs > 1 µg/mL for rifabutin, rifapentine and rifaximin, respectively. *S. aureus* $MBBC_{50}$ values were 8, 1, 2 and 4 µg/mL for rifampin, rifabutin, rifapentine and rifaximin, respectively. *S. epidermidis* $MBBC_{50}$ values were 2, 0.06, 0.25, and 0.5 µg/mL for rifampin, rifabutin, rifapentine and rifaximin, respectively, for rifampin-susceptible isolates.

Conclusion. Rifabutin and rifapentine, and to a lesser extent, rifaximin, show promising *in vitro* activity against rifampin-susceptible staphylococcal biofilms formed by isolates associated with PJI; studies evaluating *in vivo* activity are warranted.

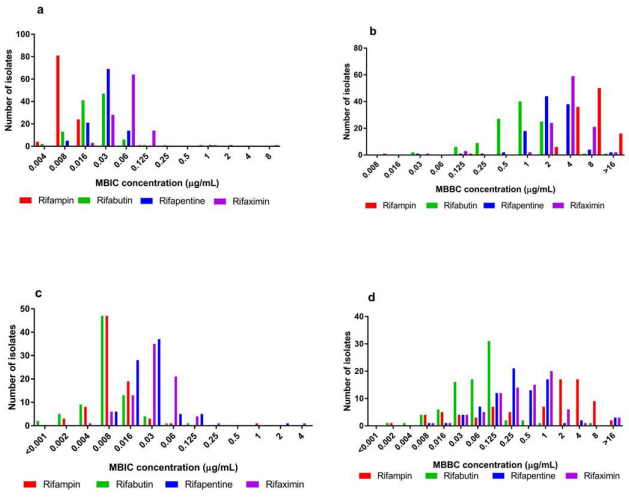

Figure. Distribution of rifampin, rifabutin, rifapentine and rifaximin MBICs and MBBCs for rifampin-susceptible *S. aureus* (a and b, respectively) and *S. epidermidis* (c and d, respectively).

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1587. Comparative *In Vitro* Antipseudomonal Activity of Ceftolozane/Tazobactam Against *Pseudomonas aeruginosa* Isolates from Children with Cystic Fibrosis

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Background. Ceftolozane/tazobactam (C/T) is a relatively new antipseudomonal cephalosporin combined with a β-lactamase inhibitor approved by the FDA in 2014. The study goal was to evaluate its *in vitro* activity vs. comparator agents against a pre-selected panel of *Pseudomonas* isolates obtained from pediatric patients with cystic fibrosis.

Methods. Clinical *Pseudomonas* isolates from 2 free-standing pediatric centers were obtained from respiratory samples from patients with cystic fibrosis during 2015–2017. Stored isolates were cultured on blood agar (Thermo Fisher Scientific) at 35±1°C for 18–24 hours. A 0.5 McFarland suspension was prepared with Sensititre® demineralized water. Final inocula of 5 × $10E^5$ CFU/mL were prepared in Sensititre® Mueller–Hinton broth. Custom-prepared Sensititre® MIC plates (Thermo Fisher Scientific) containing C/T and 10 comparator antimicrobials were inoculated and incubated at 35±1°C for 18–24 hours. MICs were determined via Sensititre Vizion® system. MIC endpoints (susceptibilities) were interpreted by CLSI (2018) breakpoint criteria.

Results. Data from 83 unique isolates from 2 sites (Missouri: 38 and Texas: 45) for the years 2015–2017 are reported. Overall, 90% of the tested isolates were C/T susceptible (MIC ≤4 µg/mL), while susceptibility for colistin, meropenem, and ciprofloxacin were 93%, 88%, and 86%, respectively (Table 1). C/T exhibited high overall activity (MIC50/90, 1/4 µg/mL) against these *Pseudomonas* isolates. C/T was more active than amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, gentamycin, meropenem, piperacillin–tazobactam and tobramycin against tested *Pseudomonas* isolates but less active than colistin.

Conclusion. C/T had broad-spectrum activity and high potency against most *Pseudomonas aeruginosa* from 2 geographically diverse pediatric US medical centers.

Table 1: Susceptibility results against *Pseudomonas aeruginosa* isolates from pediatric patients with cystic fibrosis

Name	% Susceptible	MIC_{50}	MIC_{90}
Amikacin	82	8	64
Aztreonam	69	8	32
Cefepime	83	4	32
Ceftazidime	78	4	32
Ceftolozane/Tazobactam	90	1	4
Ciprofloxacin	86	0.12	8
Colistin	93	2	2
Gentamicin	72	2	64
Meropenem	88	0.25	4
Piperacillin/Tazobactam	81	4	64
Tobramycin	76	1	32

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1588. Delafloxacin Activity Against *Staphylococcus aureus* with Reduced Susceptibility or Resistance to Methicillin, Vancomycin, Daptomycin, or Linezolid

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Background. Delafloxacin is a recently approved anionic fluoroquinolone antibiotic with broad-spectrum activity against Gram-positive and Gram-negative organisms. The drug has been approved for patients with acute bacterial skin and skin structure infections including those caused by methicillin-resistant *S. aureus*. There is limited data available against methicillin-resistant *S. aureus* blood isolates (MRSABI), vancomycin intermediate strains (VISA), vancomycin-resistant strains (VRSA), daptomycin non-susceptible strains (DNSSA) and linezolid-resistant *S. aureus* (LRSA).

Methods. Antimicrobial activity of delafloxacin, levofloxacin, vancomycin, daptomycin, ceftaroline, and linezolid was determined against recent (2016–2018) MRSABI (110), VRSA (15), VISA (35), DNSSA (40), and LRSA (6). Broth microdilution testing using Mueller–Hinton broth was used to determine minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) according to CLSI guidelines. FDA breakpoints were used to determine delafloxacin susceptibility, and CLSI breakpoints were used for all other antibiotics.

Results. Antimicrobial MIC_{90} expressed in mg/L and (% susceptible)

	MRSABI	*VISA*	*VRSA*	*DNSSA*
Delafloxacin	1 (68)	1 (40)	4 (7)	1 (38)
Levofloxacin	>16 (38)	>16 (9)	> 16 (0)	>16 (15)
Vancomycin	1 (99)	8 (0)	>64 (0)	8 (35)
Daptomycin	1 (96)	4 (26)	1 (100)	4 (0)
Ceftaroline	1 (99)	1 (100)	1 (100)	1 (100)
Linezolid	2 (100)	2 (100)	2 (100)	2 (100)

None of the LRSA were susceptible to delafloxacin or levofloxacin. All strains that were susceptible to the antimicrobial agents above had an MBC that was the same as the MIC or one dilution greater except for linezolid which demonstrated an MBC that was more than eight-fold greater than the MIC. For MRSABI isolates with a levofloxacin MIC ≥ 8 mg/L (55/110) suggesting multiple mutations in the quinolone-resistant determining region, the delafloxacin MIC_{90} was 1 mg/L with a 36.4% susceptibility rate.

Conclusion. Delafloxacin demonstrates superior activity to levofloxacin against recent MRSA blood isolates, VISA, VRSA, and DNSSA.

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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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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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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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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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