Table 1. Cardiac TEAEs and Postbaseline ECG Changes in Patients at Risk for Cardiac Safety Concerns

Patients with history of hypertension, *n* (%)	**LEF (*n*=246)**	**MOX (*n*=252)**
TEAEs in cardiac SOC*	8 (3.3)	8 (3.2)
TE-AESIs in QT prolongation category†	1 (0.4)	4 (1.6)
Patients with both baseline and postbaseline values of QTcF	(*n*=244)	(*n*=251)
Increase in QTcF	215 (88.1)	223 (88.8)
Increase >30 msec in QTcF	45 (18.4)	57 (22.7)
Increase >60 msec in QTcF	4 (1.6)	8 (3.2)
Value QTcF >480 msec	10 (4.1)	9 (3.6)
Value QTcF >500 msec	1 (0.4)	2 (0.8)
Baseline QTcF ≤480 msec and postbaseline QTcF >480 msec	9 (3.7)	7 (2.8)
Baseline QTcF ≤500 msec and postbaseline QTcF >500 msec	1 (0.4)	1 (0.4)
Patients with history of arrhythmia, *n* (%)	**LEF (*n*=42)**	**MOX (*n*=30)**
TEAEs in cardiac SOC‡	4 (9.5)	3 (10.0)
TE-AESIs in QT prolongation category†	2 (4.8)	1 (3.3)
Patients with both baseline and postbaseline values of QTcF	(*n*=42)	(*n*=30)
Increase in QTcF	36 (85.7)	22 (73.3)
Increase >30 msec in QTcF	10 (23.8)	8 (26.7)
Increase >60 msec in QTcF	1 (2.4)	3 (10.0)
Value QTcF >480 msec	2 (4.8)	3 (10.0)
Value QTcF >500 msec	0	1 (3.3)
Baseline QTcF ≤480 msec and postbaseline QTcF >480 msec	2 (4.8)	2 (6.7)
Baseline QTcF ≤ 500 msec and postbaseline QTcF >500 msec	0	0
Patients aged ≥65 y, *n* (%)	**LEF (*n*=267)**	**MOX (*n*=248)**
TEAEs in cardiac SOC§	3 (1.1)	3 (1.2)
Patients with both baseline and postbaseline values of QTcF	(*n*=266)	(*n*=247)
Increase in QTcF	234 (88.0)	218 (88.3)
Increase >30 msec in QTcF	52 (19.5)	49 (19.8)
Increase >60 msec in QTcF	4 (1.5)	7 (2.8)
Value QTcF >480 msec	11 (4.1)	14 (5.7)
Value QTcF >500 msec	1 (0.4)	6 (2.4)
Baseline QTcF ≤480 msec and postbaseline QTcF >480 msec	10 (3.8)	10 (4.0)
Baseline QTcF ≤500 msec and postbaseline QTcF >500 msec	1 (0.4)	4 (1.6)

ECG=electrocardiogram; LEF=lefamulin; MOX=moxifloxacin; QTcF=QT interval corrected according to Fridericia; SMQ=Standardized Medical Dictionary for Regulatory Activities query; SOC=system organ class; TEAE=treatment-emergent adverse event; TE-AESI=treatment-emergent adverse event of special interest.
*Specific preferred terms that occurred in >1 patient were myocardial infarction (*n*=2 LEF), acute myocardial infarction (*n*=2 MOX), and atrial fibrillation (*n*=3 MOX). All other cardiac TEAEs occurred in ≤1 patient per treatment group.
†QT prolongation category included broad SMQ search for "Torsades des Pointes/QT Prolongation."
‡Specific preferred terms that occurred in >1 patient were atrial fibrillation (*n*=2 LEF). All other cardiac TEAEs occurred in ≤1 patient per treatment group.
§All cardiac TEAEs occurred in ≤1 patient per treatment group.

Table 2. Hepatobiliary TEAEs and Postbaseline Liver Enzyme Changes in Patients at Risk for Hepatic Safety Concerns

Patients with baseline liver enzyme elevation (AST or ALT >ULN)	**LEF (*n*=119)**	**MOX (*n*=144)**
TEAEs in hepatobiliary SOC,* *n* (%)	4 (3.4)	3 (2.1)
TE-AESIs in liver safety,† *n* (%)	2 (1.7)	9 (6.3)
Any postbaseline value, *n/N* (%)		
ALT >3 ×ULN	2/36 (5.6)	5/34 (14.7)
ALT >5 ×ULN	1/36 (2.8)	1/34 (2.9)
ALT >10 ×ULN	0/36	0/34
AST >3 ×ULN	0/23	0/39
AST >5 ×ULN	0/23	0/39
AST >10 ×ULN	0/23	0/39
Total bilirubin value >2 ×ULN	1/102 (1.0)	1/124 (0.8)
ALT or AST >3 ×ULN and total bilirubin value >2 ×ULN	0/55	1/64 (1.6)
Patients aged ≥65 y	**LEF (*n*=267)**	**MOX (*n*=248)**
TEAEs in hepatobiliary SOC,* *n* (%)	2 (0.7)	1 (0.4)
Any postbaseline value, *n/N* (%)		
ALT >3 ×ULN	11/262 (4.2)	8/242 (3.3)
ALT >5 ×ULN	3/262 (1.1)	4/242 (1.7)
ALT >10 ×ULN	1/262 (0.4)	0/242
AST >3 ×ULN	6/262 (2.3)	4/242 (1.7)
AST >5 ×ULN	2/262 (0.8)	2/242 (0.8)
AST >10 ×ULN	1/262 (0.4)	0/242
Total bilirubin value >2 ×ULN	0/262	1/242 (0.4)
ALT or AST >3 ×ULN and total bilirubin value >2 ×ULN	0/262	1/242 (0.4)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; LEF=lefamulin; MOX=moxifloxacin; SMQ=Standardized Medical Dictionary for Regulatory Activities query; SOC=system organ class; TEAE=treatment-emergent adverse event; TE-AESI=treatment-emergent adverse event of special interest; ULN=upper limit of normal.
*No hepatobiliary TEAE occurred in more than one patient per treatment group.
†TE-AESIs in the liver safety SMQ included broad searches for "liver related investigations, signs, symptoms" and "biliary related investigations, signs, symptoms."

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718. Activity of Ceftolozane–Tazobactam and Ceftazidime–Avibactam Against Clinical *P. aeruginosa* Isolates Collected in United States and Canada—SMART 2018

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
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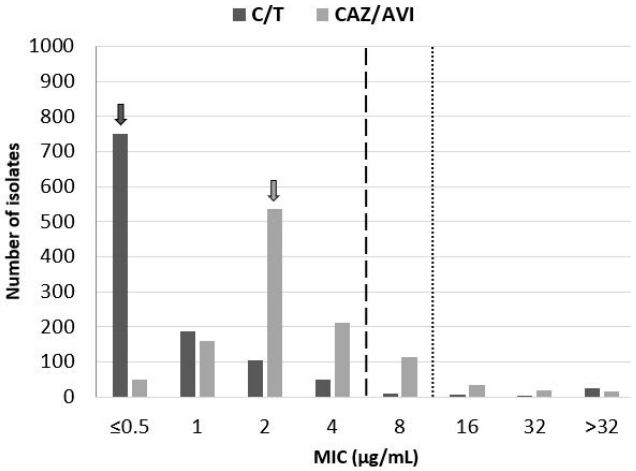
Background. Ceftolozane–tazobactam (C/T) is an antipseudomonal cephalosporin combined with a β-lactamase inhibitor. The combination was cleared by FDA and EMA and is approved in the United States and over 60 countries worldwide. Using clinical isolates collected in the United States and Canada as part of the global SMART surveillance program, we compared the activity of C/T and ceftazidime–avibactam (CAZ/AVI) against *P. aeruginosa* isolates and subsets nonsusceptible (NS) to selected antimicrobial agents.

Methods. In 2018, 31 clinical laboratories from United States and Canada collected up to 250 consecutive, aerobic or facultatively anaerobic, Gram-negative pathogens (GNP) from blood, intra-abdominal, urinary, and lower respiratory tract infections. A total of 6,178 GNP were collected, of which 1,138 (18.4%) were *P. aeruginosa*. MICs were determined using CLSI broth microdilution and interpreted with CLSI 2019 breakpoints.

Results. The MIC distributions of C/T and CAZ/AVI against 1,138 *P. aeruginosa* are shown below. The modal MIC value for C/T was ≥2 doubling dilutions lower than that for CAZ/AVI, and it was ≥3 dilutions lower than the C/T CLSI susceptible breakpoint, whereas the modal MIC value for CAZ/AVI was 2 dilutions lower than its susceptible breakpoint. Among all *P. aeruginosa* isolates, percentages of susceptibility were 96.0% (C/T), 93.8% (CAZ/AVI), 76.6% (CAZ and cefepime), 67.0% (imipenem [IMI]), 74.0% (meropenem [MEM]), 71.5% (piperacillin–tazobactam [TZP]), and 64.9% (aztreonam). Among subsets of nonsusceptible isolates, susceptibilities to C/T and CAZ/AVI were 83.5% and 74.4%, respectively (CAZ-NS subset, *n* = 266), 91.0% and 85.1% (IMI-NS, *n* = 376), 87.5% and 80.1% (MEM-NS, *n* = 296), 87.0% and 79.6% (TZP-NS, *n* = 324), and 72.4% and 57.8% among isolates nonsusceptible to all tested β-lactams (*n* = 116).

Conclusion. The activity of C/T exceeded that of CAZ/AVI and other tested comparators against a recent collection of clinical isolates of *P. aeruginosa*, including subsets of isolates nonsusceptible to other β-lactams. Susceptibilities to C/T were 6–14 percentage points higher than observed for CAZ/AVI among β-lactam-NS subsets. C/T promises to be an important treatment option for patients with antimicrobial-resistant *P. aeruginosa* infections.



Arrows indicate the modes of the respective MIC distributions. Dashed line represents the C/T CLSI susceptible breakpoint, dotted line the CAZ/AVI CLSI susceptible breakpoint

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719. Cefiderocol Retains Anti-Biofilm Activity in MDR Gram-Negative Pathogens

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Background. Cefiderocol is a siderophore cephalosporin with potent antibacterial activity against a broad range of Gram-negative pathogens. Microorganisms forming biofilm, e.g., cUTI, utilize bacterial siderophores to access free iron. A siderophore antibiotic may have unique antimicrobial properties in the setting of biofilm. In this study, we compared antimicrobial activity of cefiderocol to comparator antibiotics in well-characterized multi-drug-resistant pathogens. We determined the activity of cefiderocol and comparator antibiotics in the biofilm setting.

Methods. Minimum inhibitory concentrations (MICs) in Mueller–Hinton II broth (MHII) and iron-depleted cation-adjusted MHII (ID-CAMHB) were determined for cefiderocol and seven comparator antibiotics in multidrug-resistant isolates of *P. aeruginosa*, *Burkholderia cepacia* complex (Bcc), *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter baumannii*. MBEC (minimum biofilm eradication concentration) assays were used to test cefiderocol's activity in biofilms formed on pegs. Total biofilm biomass and viable cell number were measured.

Results. The MIC_{90} of cefiderocol ranged from 0.125 μg/mL (Bcc) to 1 μg/mL (*P. aeruginosa*) in ID-CAMHB. MIC_{90} values were consistently lower for cefiderocol in all strains tested compared with other agents (ceftolozane-tazobactam, ceftazidime–avibactam, ceftazidime, pipercallin-tazobactam, imipenem, tobramycin, clarithromycin). Twenty-four hour *P. aeruginosa* biofilms (strains ATCC 9027, MB640, MB771, MB580A, MB730) were treated every 12 hours with 4 μg/mL of cefiderocol or comparator antibiotics. Cefiderocol treatment displayed a superior reduction in biofilm based on colony counts (>90%; $P < 0.0001$ vs. untreated control) compared with comparator drugs (50 to 80% reduction). Crystal violet staining revealed a dose-dependent response of cefiderocol in the reduction of biofilm. Reduction of biofilm was not significantly altered by the growth media that was used; however, *P. aeruginosa* strains form more biofilm in MHII.

Conclusion. Cefiderocol effectively reduces biofilm in multidrug-resistant strains of *P. aeruginosa* and is a potent inhibitor of planktonic growth across a range of Gram-negative medically important pathogens.

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