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Comparative Activity of Ceftolozane-Tazobactam (C/T) and Ceftazidime-Avibactam (CZA) against *Pseudomonas aeruginosa* (PSA) from Patients with Cystic Fibrosis (CF)

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ABSTRACT

Background: Acute pulmonary exacerbations (APE) are a frequent cause of hospitalization for patients with CF. PSA is among the most common pathogen implicated in CF APE. Due to repetitive antibiotic courses, multidrug resistance (MDR) must be considered leaving few available intravenous antibiotic options. CZA and C/T are newer anti-PSA antibiotics that have been used to treat CF APE, but little data are available to compare their *in vitro* activity.

Methods: Non-duplicate, contemporary, clinical PSA (n=105) isolates were acquired from 85 patients during CF APE from 3 US hospital systems. MICs were assessed in at least triplicate by reference broth microdilution for C/T, CZA, aztreonam (ATM), cefepime (FEP), ceftazidime (CAZ), ciprofloxacin (CIP), levofloxacin (LVX), meropenem (MEM), piperacillin/tazobactam (TZP), and tobramycin (TOB). Current CLSI breakpoints were used to define susceptibility. Activity was further assessed in MDR, CAZ and MEM non-susceptible (NS) phenotypes.

Results: The mean patient age at isolate retrieval was 31 years (IQR: 21-43), and 20% were under 18 years. Mucoid morphology was observed in 48 (46%) isolates, and MDR defined in 41 (39%). Rates of susceptibility (MIC_{50}/MIC_{90}/%S) were: C/T (1/4/92%), CZA (2/8/90%), CAZ (4/64/68%), TZP (8/256/67%), TOB (2/32/63%), MEM (1/32/58%), ATM (8/64/58%), FEP (8/≥128/50%), CIP (2/8/27%), and LVX (4/16/24%). A mucoid phenotype did not alter %S (non-mucoid vs. mucoid) for C/T (93 vs. 92%) or CZA (91 vs. 88%). Among the 41 MDR PSA, activity was 2/16/83% and 4/16/76% for C/T and CZA, respectively. C/T, CZA, and MEM %S was 77, 69, and 23% for the 35 CAZ-NS isolates. C/T, CZA, and CAZ %S was 84, 77, and 39% for MEM-NS isolates.

Conclusion: These contemporary PSA from patients with CF displayed low susceptibility rates to most β-lactams, fluoroquinolones, and tobramycin, and MDR was common. C/T and CZA retained similarly high susceptibility against these isolates, including MDR strains and CAZ-NS/MEM-NS phenotypes. These data justify that both C/T and CZA may be considered for CF APE due to PSA non-susceptible to current standard of care treatment options.

INTRODUCTION

- *Pseudomonas aeruginosa* is a frequent cause of acute pulmonary exacerbation in Cystic Fibrosis (CF)[1]
- Multidrug resistance (MDR) is common in patients with CF
- Ceftazidime-avibactam and ceftolozane-tazobactam are newer beta-lactam/beta-lactamase inhibitor combination antibiotics with potent activity against *P. aeruginosa*
- Data comparing *in vitro* activity of these antibiotics against CF isolates are lacking

OBJECTIVE

To evaluate *in vitro* activity of ceftazidime-avibactam and ceftolozane-tazobactam compared with commonly used antibiotics against a contemporary set of *P. aeruginosa* isolated from CF acute pulmonary exacerbation

METHODS

Antibiotics

- Analytical powders purchased for preparation of MIC trays
  - Aztreonam (ATM)
  - Cefepime (FEP)
  - Ceftazidime (CAZ)
  - Ceftazidime-avibactam (CZA)
  - Ceftolozane-tazobactam (C/T)
  - Ciprofloxacin (CIP)
  - Levofloxacin (LVX)
  - Meropenem (MEM)
  - Piperacillin-tazobactam (TZP)
  - Tobramycin (TOB)

Isolates

- Non-duplicate clinical *P. aeruginosa* were collected from patients during CF pulmonary exacerbation at CF centers
  - Hartford, CT
  - Baltimore, MD
  - Indianapolis, IN
- Collected information:
  - Patient age at time of exacerbation
  - Mucoid/non-mucoid phenotype

Broth Microdilution

- Broth microdilution (BMD) trays were prepared using a Biomek 3000 (Beckman Instruments, Inc., Fullerton, CA)
- BMD was completed in triplicate for each isolate as described in CLSI M100[2]
- PSA 27853 was used as quality control each experimental day

Interpretation

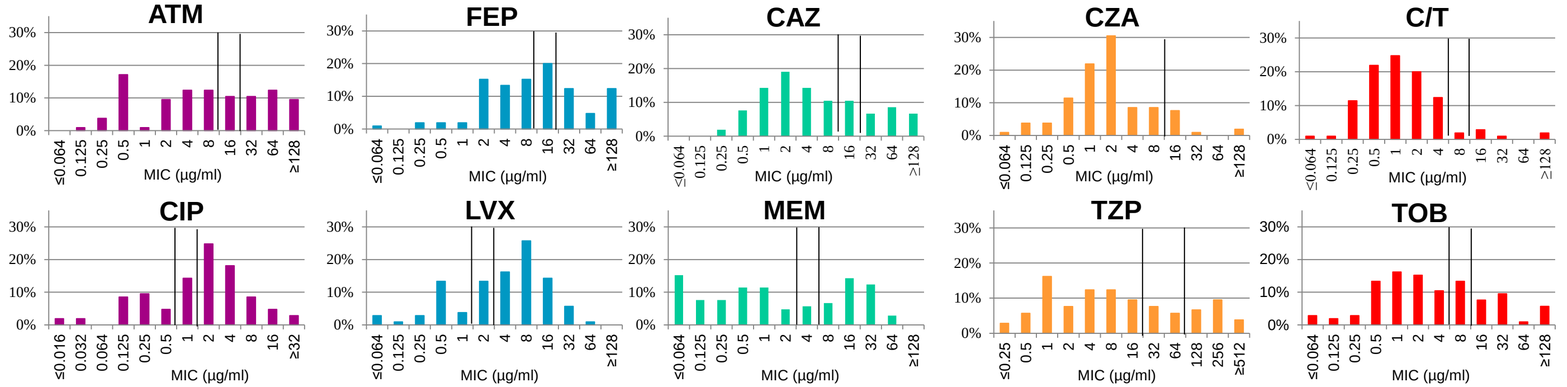
- Modal MICs were used for category interpretation using CLSI breakpoints[2]
- Multi-drug resistance was defined as resistant to ≥3 antibiotic classes
- C/T and CZA activity was compared by:
  - Non-mucoid vs. mucoid phenotype
  - MDR isolates
  - CAZ non-susceptible isolates
  - MEM non-susceptible isolates

RESULTS

Table 1. Isolate characteristics (n=105)

Site of Collection	
Hartford, CT	35 (33%)
Baltimore, MD	33 (32%)
Indianapolis, IN	37 (35%)
Median age	31 (IQR: 21-43)
Under 18	21 (20%)
Mucoid phenotype	48 (46%)

Figure 1. MIC distributions for 10 anti-pseudomonal antibiotics against 105 *P. aeruginosa* from patients with CF (horizontal lines represent CLSI breakpoints)



ATM, aztreonam; FEP, cefepime; CAZ, ceftazidime; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; CIP, ciprofloxacin; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin-tazobactam; TOB, tobramycin;

Table 2. MIC_{50}, MIC_{90}, and categorical interpretation for 10 antibiotics against 105 CF *P. aeruginosa*

Antibiotic	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	S/I/R (%)
ATM	8	64	58/10/32
FEP	8	≥128	50/20/30
CAZ	4	64	68/10/22
CZA	2/4	8/4	90/-/10
C/T	1/4	4/4	92/2/6
CIP	2	8	27/14/59
LEV	4	16	24/13/63
MEM	1	32	58/6/36
TZP	8/4	256/4	67/13/20
TOB	2	32	63/13/24

S, susceptible; I, intermediate; R, resistant;
MIC_{50}, minimum inhibitory concentration of 50% of isolates;
MIC_{90}, minimum inhibitory concentration of 90% of isolates

Table 3. CZA and C/T potency against MDR-*P. aeruginosa*

MDR Isolates (n=41)		
Category	Count	Percent
CZA S	31	76%
CZA R	10	24%
CZA MIC_{50} (μg/ml)	4	
CZA MIC_{90} (μg/ml	16	
C/T S	34	83%
C/T R	5	12%
C/T MIC_{50} (μg/ml)	2	
C/T MIC_{90} (μg/ml)	16	

Table 4. CZA, C/T, CAZ, and MEM potency against CAZ- and MEM-NS *P. aeruginosa*

CAZ NS (n=35)			MEM NS (n=44)		
Category	Count	Percent	Category	Count	Percent
CZA S	24	69%	CZA S	34	77%
CZA R	11	31%	CZA R	10	23%
CZA MIC_{50} (μg/ml)	4		CZA MIC_{50} (μg/ml)	2	
CZA MIC_{90} (μg/ml)	16		CZA MIC_{90} (μg/ml)	16	
C/T S	27	77%	C/T S	37	84%
C/T R	7	20%	C/T R	6	14%
C/T MIC_{50} (μg/ml)	4		C/T MIC_{50} (μg/ml)	2	
C/T MIC_{90} (μg/ml)	16		C/T MIC_{90} (μg/ml)	16	
MEM S	8	23%	CAZ S	17	39%
MEM R	26	74%	CAZ R	19	43%
MEM MIC_{50} (μg/ml)	16		CAZ MIC_{50} (μg/ml)	16	
MEM MIC_{90} (μg/ml)	32		CAZ MIC_{90} (μg/ml)	≥128	

Table 5. CZA and C/T potency against non-mucoid and mucoid *P. aeruginosa*

Non-Mucoid NS (n=57)			Mucoid NS (n=48)		
Category	Count	Percent	Category	Count	Percent
CZA S	52	91%	CZA S	42	88%
CZA R	5	9%	CZA R	6	12%
C/T S	53	93%	C/T S	44	92%
C/T R	4	7%	C/T R	2	4%

DISCUSSION & CONCLUSION

- Low susceptibility was observed for the fluoroquinolones, tobramycin, and older β-lactam antibiotics against these CF *P. aeruginosa* isolates
- C/T and CZA retained high rates of susceptibility, including sub-groups of:
  - MDR *P. aeruginosa*
  - CAZ non-susceptible *P. aeruginosa*
  - MEM non-susceptible *P. aeruginosa*
- Both C/T and CZA may be viable considerations for CF *P. aeruginosa* acute pulmonary exacerbations when non-susceptibility to meropenem or ceftazidime is suspected

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2. Clinical and Laboratory Standards Institute M100. 30th Edition

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