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In Vitro Activity of Ceftolozane-Tazobactam in Comparison with Ceftazidime-Avibactam Versus Antimicrobial Non-Susceptible *Pseudomonas aeruginosa* Clinical Isolates, Including Multidrug-Resistant and Extensively Drug-Resistant Subsets: CANWARD, 2007-2017

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Abstract

Background: *Pseudomonas aeruginosa* (PA) an important nosocomial pathogen. Unfortunately, treatment options for infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates remain limited. Ceftolozane-tazobactam (C/T) and ceftazidime-avibactam (CZA) are two newer antimicrobials with antipseudomonal activity. The purpose of this study was to directly compare the *in vitro* activity of C/T and CZA versus antimicrobial non-susceptible (NS) PA clinical isolates obtained as part of the CANWARD study.
Methods: Annually from 2007 to 2017, sentinel hospitals across Canada submitted blood, respiratory, urine, and wound isolates (consecutive, one per patient/infection site) from patients attending ERs, medical and surgical wards, hospital clinics, and ICUs (CANWARD). Susceptibility testing was performed using broth microdilution as described by CLSI. MDR PA were defined as isolates that tested NS to at least one antimicrobial from ≥3 classes. XDR PA were defined as isolates that tested NS to at least one antimicrobial from ≥5 classes.
Results: 4224 PA clinical isolates were obtained as a part of CANWARD. 628 (14.9%) were MDR, and 129 (3.1%) were XDR. The *in vitro* activity of C/T and CZA (plus relevant comparators) is presented in the accompanying table and figures.
Conclusions: The *in vitro* activity of C/T was superior to CZA versus antimicrobial NS PA clinical isolates (including MDR and XDR isolates) recovered from patients across Canada.

Introduction

Background: *Pseudomonas aeruginosa* is frequently implicated as a cause of nosocomial bloodstream, respiratory tract, urine, and wound infections.[1] *P. aeruginosa* clinical isolates are intrinsically resistant to antimicrobials from several classes. Additionally, they may acquire resistance to the limited antimicrobials that do possess antipseudomonal activity, leaving clinicians with few therapeutic options from which to choose.[2] Infections caused by multidrug-resistant (MDR) *P. aeruginosa* have been associated with adverse patient outcomes, including increased mortality.[3]
Ceftazidime-avibactam and ceftolozane-tazobactam are two novel antimicrobials with *in-vitro* activity versus *P. aeruginosa*.[4] There are few published reports directly comparing the activity of these agents. The purpose of this study was to evaluate the *in vitro* activity of ceftazidime-avibactam in comparison with ceftolozane-tazobactam against antimicrobial non-susceptible *P. aeruginosa* clinical isolates obtained from patients in Canadian hospitals as part of the CANWARD study (2007-2017).

Materials and Methods

Bacterial Isolates: From January 2007 to December 2017, inclusive, 10 to 15 sentinel hospitals across Canada submitted clinical isolates from patients attending emergency rooms, medical and surgical wards, hospital clinics, and intensive care units (CANWARD). On an annual basis, each center was asked to submit clinical isolates (consecutive, one per patient/infection site) from blood, respiratory, urine, and wound infections. The medical centers submitted clinically significant isolates, as defined by their local site criteria. Isolate identification was performed by the submitting site and confirmed at the reference site as required (i.e., when morphological characteristics and antimicrobial susceptibility patterns did not fit the reported identification). Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skim milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out.
Antimicrobial Susceptibilities: Following 2 subcultures from frozen stock, the *in vitro* activity of ceftazidime-avibactam, ceftolozane-tazobactam, and relevant comparators was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines.[5,6] In-house-prepared 96-well broth microdilution panels were used to test all antimicrobial agents. Antimicrobial MICs were interpreted using CLSI breakpoints.[5] MDR *P. aeruginosa* isolates were defined as isolates testing non-susceptible to at least one antimicrobial from 3 or more different classes. Extensively drug-resistant (XDR) *P. aeruginosa* isolates were defined as a subset of MDR isolates that tested non-susceptible to at least one antimicrobial from five different classes. For the purpose of this report, the five antimicrobial classes considered were aminoglycosides (gentamicin, tobramycin, amikacin), fluoroquinolones (ciprofloxacin), antipseudomonal cephalosporins (ceftazidime), antipseudomonal penicillins (piperacillin-tazobactam), and carbapenems (meropenem).

Results

In total, 4224 *P. aeruginosa* clinical isolates were obtained as a part of the CANWARD Study between January 2007 and December 2017. Isolates were collected from patients on medical wards (n = 1437, 34.0%), hospital clinics (n = 1035, 24.5%), intensive care units (n = 933, 22.1%), emergency rooms (n = 511, 12.1%), and surgical wards (n = 308, 7.3%). The distribution of isolates by specimen source was 2829 (67.0%) respiratory, 765 (18.1%) blood, 432 (10.2%) wound, and 198 (4.7%) urine. The *in vitro* activity of ceftolozane-tazobactam, ceftazidime-avibactam, and comparators versus all isolates and antimicrobial non-susceptible subsets is presented in Table 1 and Figure 1. The MIC distribution of ceftolozane-tazobactam and ceftazidime-avibactam versus all isolates, and the MDR and XDR subsets is presented in Figures 2 and 3, respectively.

Table 1. *In Vitro* Activity of Ceftolozane-Tazobactam, Ceftazidime-Avibactam, and Relevant Comparators Versus Antimicrobial Non-Susceptible *P. aeruginosa* Clinical Isolates

	Ceftolozane-Tazobactam		Ceftazidime-Avibactam		Meropenem		Piperacillin-Tazobactam	
	MIC_{50}/MIC_{90} (mg/L)	% Susceptible	MIC_{50}/MIC_{90} (mg/L)	% Susceptible	MIC_{50}/MIC_{90} (mg/L)	% Susceptible	MIC_{50}/MIC_{90} (mg/L)	% Susceptible
All Isolates (n = 4224)	0.5/2	98.2	2/8	94.1	0.5/8	81.2	4/64	83.8
Amikacin NS (n = 330)	1/8	86.4	4/16	84.8	1/32	61.5	8/256	63.9
Ceftazidime NS (n = 755)	1/4	90.5	8/16	68.9	4/32	48.2	64/512	21.6
CZA NS (n = 248)	2/16	77.8	16/>16	0.0	8/>32	29.4	64/512	17.3
C/T NS (n = 78)	16/>64	0.0	16/>16	29.5	8/>32	38.5	256/>512	23.1
Ciprofloxacin NS (n = 1010)	1/4	94.8	4/16	85.3	2/32	56.9	16/256	64.8
Gentamicin NS (n = 823)	1/4	94.3	4/16	88.7	1/16	62.1	8/128	70.5
Meropenem NS (n = 793)	1/4	93.9	4/16	77.9	8/16	0.0	16/256	52.6
Piperacillin-tazobactam NS (n = 686)	1/4	91.3	8/16	70.1	4/32	45.2	64/512	0.0
Tobramycin NS (n = 283)	1/8	88.0	4/16	83.7	4/32	38.9	16/256	58.0
MDR (n = 628)	1/8	89.8	8/>16	69.4	8/32	22.6	64/512	22.0
XDR (n = 129)	2/16	78.3	8/>16	55.0	16/>32	0.0	128/512	0.0

NS = non-susceptible, CZA = ceftazidime-avibactam, C/T = ceftolozane-tazobactam, MDR = multidrug-resistant, XDR = extensively drug-resistant

Figure 1. *In Vitro* Activity of Ceftolozane-Tazobactam and Ceftazidime-Avibactam Versus Antimicrobial Non-Susceptible *P. aeruginosa* Clinical Isolates

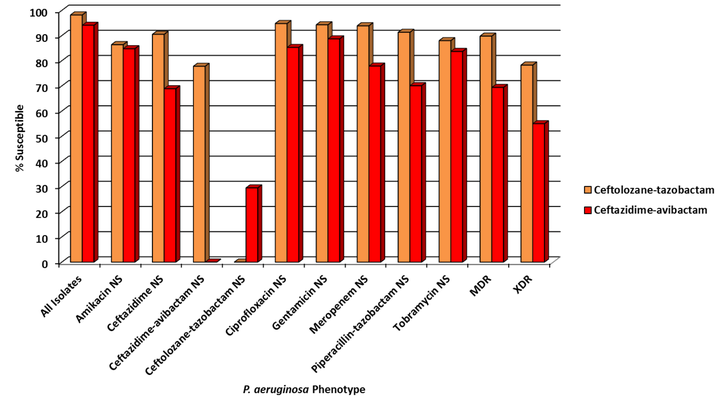


Figure 2. MIC Distribution of Ceftolozane-Tazobactam and Ceftazidime-Avibactam versus *P. aeruginosa* Clinical Isolates

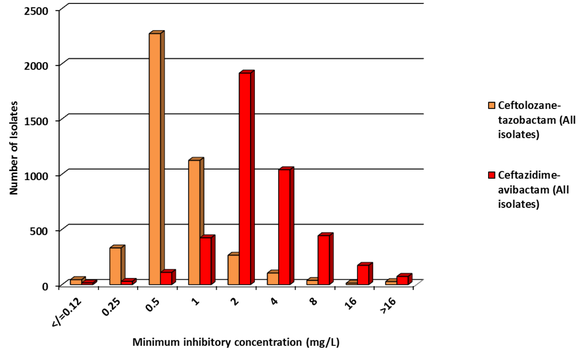
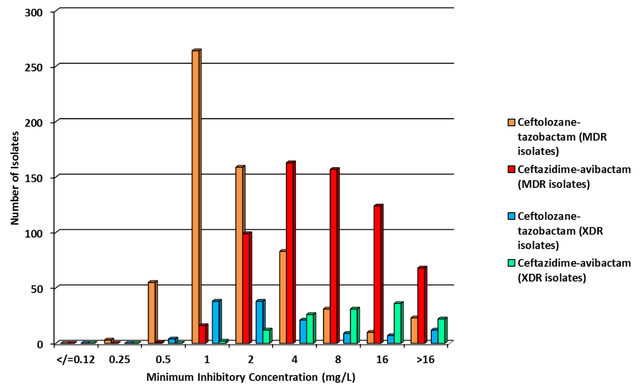


Figure 3. MIC Distribution of Ceftolozane-Tazobactam and Ceftazidime-Avibactam Versus MDR and XDR *P. aeruginosa* Isolates



Conclusions

The *in vitro* activity of ceftolozane-tazobactam was superior to ceftazidime-avibactam versus antimicrobial non-susceptible *P. aeruginosa* clinical isolates (including MDR and XDR isolates) recovered from patients across Canada.

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