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ORIGINAL RESEARCH



Ceftolozane/Tazobactam treatment for patients with hospital-acquired and ventilatory-associated bacterial pneumonia in Canada in 2022–2024: results from the CLEAR registry

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ABSTRACT

Background: We report results from the national CLEAR (Canadian Leadership on Antimicrobial Real-Life Usage) registry on the usage of ceftolozane/tazobactam in Canada from 2022 to 2024.

Research design and methods: The authors reviewed the final data using the national ethics approved CLEAR study. Thereafter, the literature is surveyed regarding the usage of ceftolozane/tazobactam to treat patients with HABP and VABP via PubMed (up to May 2024).

Results: Ceftolozane/tazobactam was primarily used as directed therapy to treat HABP and VABP caused by *Pseudomonas aeruginosa*. It was primarily used alone, or in combination with another agent, to treat resistant and multidrug-resistant (MDR) *P. aeruginosa* infections. Despite primarily being used to treat severely ill patients in intensive care units, its use was associated with relatively high microbiological/clinical cure rates, along with an excellent safety profile. Several reports attest to the microbiological/clinical efficacy and safety of using ceftolozane/tazobactam to treat HABP and VABP.

Conclusions: In Canada, ceftolozane/tazobactam is primarily used as directed therapy alone, or in combination, to treat MDR *P. aeruginosa* infections. Though mostly used to treat severely ill patients in the ICU, ceftolozane/tazobactam use in HABP and VABP is associated with relatively high microbiological/clinical cure rates and an excellent safety profile.

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1. Introduction

Ceftolozane/tazobactam is a broad-spectrum bactericidal cephalosporin/established β -lactamase inhibitor combination with well-established *in vitro* activity against Gram-positive and Gram-negative organisms [1,2]. The potent activity of ceftolozane/tazobactam against *Pseudomonas aeruginosa*, especially multidrug-resistant (MDR) and extremely-drug-resistant (XDR) strains, distinguishes it from many other β -lactams [1–4]. In Canada, the United States and Europe, ceftolozane/tazobactam has been approved to treat complicated urinary tract infections, complicated intra-abdominal infections, as well as hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) [1,2,5]. Earlier reports attest to ceftolozane/tazobactam's attainment of high concentrations in epithelial lining fluid (ELF) and resultant clinical efficacy and safety in treating HABP and VABP [6–32]. Limited published data exist regarding the usage of ceftolozane/tazobactam to treat HABP and VABP

in Canada, thus, we endeavored to assess how ceftolozane/tazobactam was used by clinicians to treat these infections across Canada.

Infections caused by antimicrobial-resistant Gram-negative bacilli are a global problem [33,34]. Extended-spectrum β -lactamase (ESBL)-producing and carbapenem-resistant Enterobacterales (CRE) continue to increase globally [33–38]. In addition, infections caused by carbapenem-resistant, MDR and XDR *P. aeruginosa* are also escalating worldwide [39,40]. Resistance among Gram-negative bacilli continues to generate a need for newer intravenous (IV) antimicrobials with activity versus gram-negative bacilli including resistant strains, despite several agents being recently approved and marketed in the United States, Europe, and elsewhere [41–48].

In Canada, as in other countries, newer IV antimicrobials once approved by regulatory agencies and introduced into the clinical marketplace are used primarily by infectious diseases/medical microbiology clinical services [41–48].

Article highlights

- Real-world clinical usage data for ceftolozane/tazobactam in Canada are limited.
- A description of ceftolozane/tazobactam usage in patients with hospital-acquired bacterial pneumonia (HABP) and ventilatory-associated bacterial pneumonia (VABP) in Canada from 2022 to 2024 using data captured by the national CLEAR registry.
- Ceftolozane/tazobactam was primarily used alone, or in combination with another agent, as directed therapy to treat infections caused by resistant and multidrug-resistant *Pseudomonas aeruginosa*.
- Although primarily used to treat severely ill patients in intensive care units, ceftolozane/tazobactam use in HABP and VABP was associated with relatively high microbiological and clinical cure rates, along with an excellent safety profile.
- Several small and large peer-reviewed reports attest to the microbiological and clinical efficacy of using ceftolozane/tazobactam for treating HABP and VABP.
- Outside of Canada, ceftolozane/tazobactam is used as directed therapy and empirically in selected patients with HABP and VABP as part of treatment algorithms.

Regrettably, limited data sharing occurs among clinicians regarding why they chose to use a newer IV antimicrobial agent (i.e. due to clinical failure of previously used agents, resistance to existing agents, or adverse effects associated with other antimicrobial agents), the types of infections treated, the dosage, and duration of therapy, and whether the newer agent was combined with other agents. The CLEAR registry is a program coordinated by the Canadian Antimicrobial Resistance Alliance (CARA; <http://www.can-r.ca/index.php>). CLEAR, initiated in late 2019, is a voluntary, national, usage registry platform that enables the collection of information regarding the clinical usage of new IV antimicrobials recently introduced into the Canadian clinical marketplace. In addition to ceftolozane/tazobactam, CLEAR also collects data on the clinical usage of ceftobiprole, IV fosfomycin and dalbavancin in Canada [49–51].

In this paper we report the results of clinical usage of ceftolozane/tazobactam in patients with HABP and VABP in Canada from January 2022 to April 2024 using data obtained from the national CLEAR (Canadian Leadership on Antimicrobial Real-Life Usage) registry. We previously reported 2019–2020 data on ceftolozane/tazobactam usage in a limited number of patients with a variety of infections including bone and joint infections, complicated intra-abdominal infections, complicated skin and skin structure infections, and pneumonia [32]. In this study, we solely focus on outcomes in pneumonia and in a greater number of patients.

2. Patients and methods

In the methods, we describe the final data using the national ethics approved CLEAR study. Thereafter, the literature was also surveyed regarding the usage of ceftolozane/tazobactam to treat patients with HABP and VABP via PubMed (up to May 2024). For the CLEAR registry, a usage questionnaire for IV ceftolozane/tazobactam was developed using the input of infectious disease/medical microbiology specialists (physicians and pharmacists) across Canada. The CLEAR registry protocol/

questionnaire was submitted, reviewed, and received Human Ethics Committee approval at the University of Manitoba (HS22785-H2019:156 Winnipeg, Canada; in 2019). Using the web-based research data management program, REDCapTM (Research Electronic Data Capture), clinicians (physicians and clinical pharmacists) have responded directly to usage questionnaires online starting in late 2019 [52]. The REDCapTM online survey (<https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=WHWT7RDK7X>) was distributed via e-mail to > 400 CLEAR participants (members of the Association of Medical Microbiology and Infectious Diseases Canada [AMMI] and Canadian Society of Hospital Pharmacists [CSHP]) [32]. Every 2–3 months clinicians were sent an e-mail encouraging their voluntary participation in CLEAR. A series of drop-down menus and short answer questions allowed for rapid (~3 min) completion of the survey. Clinicians were invited to voluntarily complete usage questionnaires for as many patients as possible. The data in this report were previously presented at the national Association for Medical Microbiology and Infectious Diseases (AMMI) meeting in Vancouver, April 9–12, 2024 [53]. It was decided to develop a standardized questionnaire that would take clinicians a very short time (~3 min) to complete in order to encourage clinicians to voluntarily complete as many surveys as possible and to also have standardized answers. The intent of the CLEAR registry was not to dictate to Canadian clinicians when and how to use ceftolozane/tazobactam to treat pneumonia, but rather to encourage clinicians to describe when, why, how they treat pneumonia using ceftolozane/tazobactam.

All microbiological lab assessments (e.g. identification and antimicrobial susceptibility testing) were performed in each hospital as per their individual hospital protocols. Ceftolozane/tazobactam microbiological success was defined as eradication or presumed eradication of the pathogen in clinically evaluable cases, while microbiological failures were defined as persistence of bacteria. Clinical success was defined as cure (absence of signs/symptoms) or improvement (reduction or absence of some signs/symptoms) in clinically evaluable cases.

3. Results

3.1. Patient demographics and clinician responders

Fifty-four patient questionnaires were completed from 1 January 2022 to 3 April 2024; 37.0% of patients treated with ceftolozane/tazobactam were from western Canada, 63.0% from central Canada, and 0% from eastern Canada (data not shown); and 72.3% of patients were aged 18–64 years and 27.8% were ≥65 years (data not shown). Responders to the survey were clinicians from various institutions across Canada and mostly represented large tertiary-care institutions in major cities. The responders were medical microbiology/infectious diseases specialists (~40%) and clinical pharmacists (~60%).

3.2. Therapeutic use

Ceftolozane/tazobactam was used for HABP in 42.6% of surveys, for VABP in 46.3% of surveys and for ventilated HABP

(vHABP) in 11.1% of surveys (Table 1). A minority (7.4%) of the 54 patients had bacteremia and 81.5% started or completed their therapy in an intensive care unit (ICU). Ceftolozane/tazobactam was used as directed (non-empirical) therapy in 79.6% of patients while empirical therapy was used in 20.4% of patients. Cultured pathogens treated included *P. aeruginosa* (96.2%), with one patient having a mixed infection (*P. aeruginosa* and *Enterococcus faecium*). Initiation of ceftolozane/tazobactam treatment occurred due to resistance to initially prescribed antimicrobial agents (94.4%), clinical failure of previous antimicrobial therapy (3.7%), or adverse effects associated with use of previous antimicrobial agents (1.9%) (Table 2). Antimicrobial susceptibility testing with ceftolozane/tazobactam was performed in 90.7% of cases; disk diffusion was used in 70.4% and Etest in 29.6% of cases. No isolates of *P. aeruginosa* resistant to ceftolozane/tazobactam were reported.

3.3. Dosage and administration

The most common ceftolozane/tazobactam dosages prescribed were: 2 g-ceftolozane (1 g-tazobactam) q8h (36.4%), 1 g (0.5 g) q8h (27.8%) and 450 mg (225 mg) q8h (22.2%) (Table 3). Clinicians assessed renal function using creatinine clearance in all patients, thus the various dosages listed in Table 3 reflect dosage adjustment for patients' individual renal function. In 9.1% of cases ceftolozane/tazobactam was administered using a prolonged infusion (2 h or more) and in one patient the drug was administered using continuous

infection (Table 3). Ceftolozane/tazobactam's usage as prolonged infusion is consistent with optimizing β -lactam pharmacodynamics [54–56].

Ceftolozane/tazobactam was used in the vast majority of cases (94.4%) because of resistance to other antimicrobials and the *P. aeruginosa* strains being MDR (data not shown). In 37.0% of cases, clinicians used concomitant therapy with ceftolozane/tazobactam. It was the individual clinicians' decision whether to use ceftolozane/tazobactam alone or to combine the agent with a second agent with activity versus Gram-negative bacilli. When clinicians chose to use a second agent active against Gram-negative bacilli, it included, aminoglycosides (8 cases IV only and 1 case aerosol only), colistin (one case IV only and three cases aerosol only), a fluoroquinolone (three cases), a carbapenem (two cases) and trimethoprim/sulfamethoxazole (one case). Duration of treatment was <7 days in 16.7%, 7–10 days in 37.0% and ≥ 10 days in 44.4% of known cases.

3.4. Microbiological and clinical outcomes

Ceftolozane/tazobactam microbiological success, defined as eradication or presumed eradication of the pathogen in evaluable cases, was 50.0%; 40.5% (22/54) of patients were classified as microbiological failures due to the persistence of bacteria; and microbiological outcome was unknown for 18.8% of patients (Table 4). Of the 22 microbiological failures, 10 (45.5%) were HABP patients, 10 (45.5%) were VABP patients and two (9.0%) were hHABP patients; 77.3% of microbiological failures were treated in an ICU and 59.1% had moderate-to-severe renal dysfunction (creatinine clearance <49 mL/min); 45.5% of microbiological failures received ≥ 10 days of ceftolozane/tazobactam treatment with concomitant therapy (ceftolozane/tazobactam and a second agent active against Gram-negative bacilli) in 7 (31.8%) patients. Nine (40.9%) of the 22 microbiological failures were clinically cured or improved, seven (31.8%) were deemed clinical failures and six (27.3%) died.

Clinical success, defined as cure or improvement in evaluable cases, occurred in 61.2% (30/49) of patients; clinical outcome was unknown for 9.2% of patients (Table 5). Clinical failure occurred in nine patients (16.7%). Five of the nine patients with clinical failure had HABP and four had VABP.

Table 1. Infections treated with ceftolozane/tazobactam.

Infection treated	% of patients (n = 54)
Hospital-acquired bacterial pneumonia (HABP)	42.6% (n = 23)
Ventilator-associated bacterial pneumonia (VABP)	46.3% (n = 25)
Ventilated hospital-acquired bacterial pneumonia (vHABP)	11.1% (n = 6)

Table 2. Reasons for using ceftolozane/tazobactam.

Infection treated	% of patients (n = 54)
Resistance to initially prescribed antimicrobial agents	94.4% (n = 51)
Clinical failure of previous antimicrobial therapy	3.7% (n = 2)
Adverse effects associated with use of previous antimicrobial agents	1.9% (n = 1)

Table 3. Ceftolozane/Tazobactam dosing and infusion time.

	% of patients (n = 54)
Ceftolozane/tazobactam dose	
2 g (1 g) q8h	36.4% (n = 20)
1 g (0.5 g) q8h	27.8% (n = 15)
450 mg (225 mg) q8h	22.2% (n = 12)
750 mg (375 mg) q8h	7.9% (n = 4)
150 mg (75 mg) q8h	1.9% (n = 1)
1 g (0.5 g) q12h	1.9% (n = 1)
3 g (1.5 g) continuous infusion	1.9% (n = 1)
Infusion Time	
Short (15 min–1 h)	90.7% (n = 49)
Prolonged (≥ 2 h)	7.4% (n = 4)
Continuous infusion	1.9% (n = 1)

Table 4. Microbiological outcomes with ceftolozane/tazobactam treatment.

Outcome	% of patients (n = 54)
Eradication	11.1% (n = 6)
Presumed eradication	29.6% (n = 16)
Persistence	40.5% (n = 22)
Unknown	18.8% (n = 10)

Table 5. Clinical outcomes with ceftolozane/tazobactam treatment.

Outcome	% of patients (n = 54)
Cure	16.7% (n = 9)
Improvement	38.9% (n = 21)
Failure	16.7% (n = 9)
Death due to all causes	18.5% (n = 10)
Death due to infection	9.2% (n = 5)
Unknown	9.2% (n = 5)

Seven of the nine patients were treated in the ICU and all nine patients had infections with MDR *P. aeruginosa* strains. One of the nine (11.1%) patients was treated with ceftolozane/tazobactam and a concomitant therapy (an aminoglycoside). Five of the nine patients had moderate-to-severe renal dysfunction (creatinine clearance ≤ 30 mL/min in three patients and 30–49 mL/min in two patients). Seven of the nine patients had persistent infection (two patients had presumed eradication). Assessment of the various ceftolozane/tazobactam dosage regimens did not result in establishment of a relationship between dosage and microbiological or clinical outcome. In addition, no relationship was documented between usage of ceftolozane/tazobactam monotherapy or combination therapy (ceftolozane/tazobactam used with a second agent active versus Gram-negative bacilli) and microbiological and clinical outcome.

Mortality overall was 18.5% with five (9.2%) patients dying as a result of their infection (Table 5). Of these five patients, four (80%) were treated in the ICU and four (80%) had VABP. All five patients had infections caused by MDR *P. aeruginosa* strains. Two of five patients were treated with concomitant therapy of ceftolozane/tazobactam with either a carbapenem or aminoglycoside. Four of the five patients had moderate-to-severe renal dysfunction (creatinine clearance ≤ 30 mL/min in two patients and 30–49 mL/min in two patients). All five patients were deemed microbiologically to have persistent infection and clinical failure.

3.5. Adverse effects

Of the 54 patients, 4 (7.4%) patients reported adverse effects including: gastrointestinal (1 patient), hypersensitivity (1 patient) and 2 patients with neutropenia. One patient had to discontinue ceftolozane/tazobactam treatment due to severe neutropenia.

3.6. Limitations of CLEAR registry study

This CLEAR registry study has limitations. We have only reported our experience with 54 patients which provides data on a relatively small number of patients. In addition, all 54 patients were treated in western and central Canada and none in eastern Canada. All clinician reports of ceftolozane/tazobactam treatment of patients with pneumonia are voluntary. Whether this voluntary data submission is more likely to have clinicians report clinical successes or failures is unknown. Although duplicate patient cases are possible, they are very unlikely as all submitted ceftolozane/tazobactam treated pneumonia patient cases were closely reviewed to make sure that submission date, patient age, gender, submitting clinician, infection treated, pathogen treated were different. Lastly, the outcomes of all patients were not known, as some patients were lost to follow up.

4. Discussion

In this report from the CLEAR registry, we observed that in Canada, ceftolozane/tazobactam is used primarily to treat

HABP, VABP, and vHABP in critically ill patients with microbiologically confirmed MDR *P. aeruginosa*. Several other studies have reported similar efficacy and safety data to ours for ceftolozane/tazobactam in the treatment of patients with HABP and VABP, both as empiric and directed therapy [6–8,10–12,14,15,17–22,24–26,28–31]. Clinical cure using ceftolozane/tazobactam to treat *Pseudomonas aeruginosa* HABP and VABP, including resistant, MDR and XDR strains has ranged from 49.0% to 81.3% in earlier studies [6–8,10–12,14,15,17–22,24–26,28–31]. Reported patient mortality from all causes in these studies has ranged from 0% to 36.5% [6–8,10–12,14,15,17–22,24–26,28–31]. Not surprisingly, as ceftolozane/tazobactam is a cephalosporin, studies have consistently documented low adverse effects, describing the drug as well tolerated [6–8,14,21,28,29,31]. Researchers have also studied the lung penetration of ceftolozane and tazobactam in healthy volunteers and patients with pneumonia assessing achievable concentrations in ELF and subsequently making assessments of the probability of pharmacodynamic target attainment (PTA) [9,13,16,27]. From these studies, it is clear that after the administration of ceftolozane/tazobactam 2 g/1 g q8h, both drugs achieved >50% penetration into ELF (relative to achievable serum concentrations). With these high concentrations in ELF, it is not surprising that a PTA of >90% is achieved for isolates with ceftolozane/tazobactam MICs of 8 µg/ml and for many isolates with MICs of 16 µg/ml [9]. An unresolved issue in the literature is whether when treating patients with HABP or VABP due to resistant, MDR or XDR *P. aeruginosa*, should ceftolozane/tazobactam be used alone as monotherapy or in combination with a second agent that also has activity against Gram-negative bacilli [8,20,25]. Similar to our findings in the CLEAR registry, we believe that the majority of the literature does not support using combination therapy with ceftolozane/tazobactam when treating resistant, MDR or XDR *P. aeruginosa* causing HABP or VABP and that monotherapy with ceftolozane/tazobactam is sufficient bacilli [8,20,25]. Lastly, regarding the issue of resistance developing during treatment with ceftolozane/tazobactam, when treating resistant *P. aeruginosa* causing HABP or VABP, the literature suggests there is little to no emergence of resistance on therapy [7]. Limited data suggest that ceftolozane/tazobactam treatment of HABP and VABP, including infections caused by *P. aeruginosa*, is a cost-effective strategy when compared to meropenem [23].

It seems clear that ceftolozane/tazobactam is used in many medical centers primarily as directed therapy to treat HABP and VABP caused by resistant, MDR and XDR *P. aeruginosa*, whereas in other centers it may also be used as an empiric treatment. Based on our encouraging results of the CLEAR ceftolozane/tazobactam HABP/VABP registry study, and the favorable ceftolozane/tazobactam data in the published literature, we recently published potential empiric treatment algorithms for HABP and VABP in Canada [5] where we identified potential roles for ceftolozane/tazobactam (Tables 6 and 7). It requires stating that these potential empiric antimicrobial treatments of HABP and VABP in Canada are influenced in part by the availability and lack of availability of certain antimicrobials. In Canada, ceftiderocol, ceftaroline, ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam and

Table 6. Potential empiric antimicrobial treatment of hospital-acquired bacterial pneumonia (HABP).

Group 1 (mild-moderate presentation ^a) with No Risk Factors for Antimicrobial Resistance ^c	Group 2 (mild-moderate presentation ^a) with Risk Factors for Antimicrobial Resistance ^c	Group 3 (severe presentation ^b) with/without Risk Factors for Antimicrobial Resistance ^c
MONOTHERAPY Cefepime, Cefotaxime, Ceftobiprole, Ceftriaxone, Ceftolozane/tazobactam OR Piperacillin-tazobactam OR Levofloxacin or Moxifloxacin	MONOTHERAPY Ceftobiprole ^e OR COMBINATION THERAPY Cefepime, Ceftolozane/tazobactam OR Piperacillin-tazobactam OR Imipenem or Meropenem OR Levofloxacin PLUS Vancomycin or linezolid (if MRSA present or suspected)	COMBINATION THERAPY Cefepime, Ceftazidime, Ceftolozane/tazobactam OR Piperacillin-tazobactam OR Imipenem or Meropenem PLUS Ciprofloxacin or Levofloxacin ^d OR Gentamicin, Tobramycin or Amikacin PLUS Vancomycin or Linezolid (if MRSA present or suspected)

^amild – moderate presentation: no hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end organ dysfunction.

^bsevere presentation: hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end organ dysfunction.

^crisk factors for antimicrobial resistance include: prior antimicrobial therapy in past 90 days and late-onset during hospitalization (≥5 days).

^dfluoroquinolone preferred over aminoglycoside due to atypical coverage (eg. *Legionella* spp) and reduced toxicity.

^eif ceftobiprole used there is no need to add vancomycin or linezolid for MRSA (present or suspected).

Table 7. Empiric antimicrobial treatment of ventilator-associated bacterial pneumonia (VABP).

Group 4 (mild-moderate presentation ^a) with No Risk Factors for Antimicrobial Resistance ^c	Group 5 (severe presentation ^b) with/without Risk Factors for Antimicrobial Resistance ^c
MONOTHERAPY Cefepime, Ceftolozane/tazobactam OR Piperacillin-tazobactam OR Imipenem or Meropenem OR Levofloxacin or Moxifloxacin	COMBINATION THERAPY Cefepime, Ceftazidime, Ceftolozane/tazobactam OR Piperacillin-tazobactam OR Imipenem or Meropenem PLUS Ciprofloxacin or levofloxacin ^d OR Gentamicin, Tobramycin or Amikacin PLUS Vancomycin or Linezolid (if MRSA present or suspected)

^amild – moderate presentation: no hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end organ dysfunction.

^bsevere presentation: hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end organ dysfunction.

^crisk factors for antimicrobial resistance include: prior antimicrobial therapy in past 90 days and late-onset during hospitalization (≥5 days).

^dfluoroquinolone preferred over aminoglycosides due to atypical coverage (eg. *Legionella* spp) and reduced toxicity.

plazomicin are not Health Canada approved and marketed. Thus, the reader needs to consider these potential empiric antimicrobial treatments of HABP and VABP to be Canada specific (Tables 6 and 7). Each individual country requires an individualized assessment of potential empiric treatments of HABP and VABP and what role ceftolozane/tazobactam may have based on a variety of factors including the list of antimicrobial agents approved for use in their country.

Ceftolozane is stable against multiple resistance mechanisms present in *P. aeruginosa* and other Gram-negative bacteria, including overexpression of AmpC, porin loss and efflux pumps [1–4,11]. Microbiological studies, including our own data consistently show that ceftolozane/tazobactam is more active *in vitro* than other β -lactam/ β -lactamase inhibitor combinations and carbapenems against *P. aeruginosa*, including MDR and XDR isolates [1–4,11]. Although ceftolozane/tazobactam is active against ESBL-producing Enterobacterales it lacks activity against all carbapenemases-producing strains (both metallo- β -lactamases and serine carbapenemases) of *P. aeruginosa* and Enterobacterales [1]. Ceftolozane/tazobactam has been shown to be non-inferior to meropenem in the

treatment of nosocomial pneumonia and superior in post-hoc studies in the subgroup of patients with VABP, all without the emergence of resistance during treatment and these data are consistent in real-world studies as well [10,12,14,15,18,19,21,28,31]. Ceftolozane/tazobactam is typically dosed 2 g/1 g q8h when used to treat HABP and VABP, including infections caused by *P. aeruginosa* [10,12,14,15,18,19,21,28,31].

5. Conclusion

We describe ceftolozane/tazobactam usage in patients with HABP and VABP in Canada using data captured by the national CLEAR registry from 2022 to 2024. In Canada, ceftolozane/tazobactam is primarily used as directed therapy alone, or in combination, to treat infections caused by resistant and MDR *P. aeruginosa*. Although it is most commonly used to treat severely ill patients in the ICU, ceftolozane/tazobactam use in HABP and VABP is associated with good microbiological and clinical cure rates, along with an excellent safety profile. A variety of small and large peer-reviewed and published

reports also attest to the microbiological and clinical efficacy of using ceftolozane/tazobactam for treating HABP and VABP.

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Declaration of interest

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Author contributions statement

All authors contributed in the conception, study design, execution, acquisition of data, analysis and interpretation. In addition, all authors were involved in drafting, revising the article and agreed on the journal to which the article was submitted. All authors, reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. Lastly all authors take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest () to readers.**

- Zhanel GG, Chung P, Adam HJ, et al. Ceftolozane/Tazobactam: a novel cephalosporin/ β -lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. *Drugs*. 2014;74(1):31–51. doi: [10.1007/s40265-013-0168-2](https://doi.org/10.1007/s40265-013-0168-2)
- Excellent review of the various in vitro and in vivo properties of ceftolozane/tazobactam.**
- Walkty A, Lagace-Wiens PRS, Adam H, et al. Antimicrobial susceptibility of 2906 *Pseudomonas aeruginosa* clinical isolates obtained from patients in Canadian hospitals over a period of 8 years: results of the Canadian Ward surveillance study (CANWARD), 2008–2015. *Diag Microbiol Infect Dis*. 2017;87(1):60–63. doi: [10.1016/j.diagmicrobio.2016.10.003](https://doi.org/10.1016/j.diagmicrobio.2016.10.003)
- Walkty A, Adam H, Baxter M, et al. In vitro activity of ceftolozane/tazobactam versus antimicrobial non-susceptible *Pseudomonas aeruginosa* clinical isolates including MDR and XDR isolates obtained from across Canada as part of the CANWARD study, 2008–16. *J Antimicrob Chemother*. 2020;73(3):703–708. doi: [10.1093/jac/dkx468](https://doi.org/10.1093/jac/dkx468)
- Walkty A, Karlowicz JA, Lagacé-Wiens PRS, et al. Moving towards a standardized definition of antimicrobial resistance: a comparison of the antimicrobial susceptibility profile of difficult to treat resistance (DTR) versus multi-drug resistant (MDR) *Pseudomonas aeruginosa* clinical isolates (CANWARD 2016–2021). *Diagnostic Microbiol Infect Dis*. 2024;108:116130.
- Rotstein C, Lynch JP, Zhanel GG. Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in Canada: treatment update and the role of new IV

- antimicrobials. *Exp Rev Antiinfect Ther*. 2023;21(11):1213–1225. Online ahead of print. doi: [10.1080/14787210.2023.2268287](https://doi.org/10.1080/14787210.2023.2268287)
- Thorough review of the empiric treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.**
- Timsit JF, Moutien J, Akhrich B, et al. Ceftolozane/Tazobactam for the treatment of complicated infections in hospital settings—A French real-world study. *Open Forum Infect Dis*. 2024;11(2):ofae037. doi: [10.1093/ofid/ofae037](https://doi.org/10.1093/ofid/ofae037)
- Martin-Loeches I, Bruno CJ, DeRyke CA. Perspectives on the use of ceftolozane/tazobactam: a review of clinical trial data and real-world evidence. *Fut Microbiol*. 2024;19(6):465–480. Online ahead of print. doi: [10.2217/fmb-2023-0197](https://doi.org/10.2217/fmb-2023-0197)
- Neves CS, Moura LBCRV, Lima JLDC, et al. Clinical outcomes of intensive care unit patients infected with multi-drug resistant gram-negative bacteria treated with ceftazidime/avibactam and ceftolozane/tazobactam. *Braz J Microbiol*. 2024;55(1):333–341. doi: [10.1007/s42770-023-01193-x](https://doi.org/10.1007/s42770-023-01193-x)
- Shen Y, Kuti JL. Optimizing antibiotic dosing regimens for nosocomial pneumonia: a window of opportunity for pharmacokinetic and pharmacodynamic modeling. *Exp Opin Drug Metab Toxicol*. 2023;19(1):13–25. doi: [10.1080/17425255.2023.2178896](https://doi.org/10.1080/17425255.2023.2178896)
- Martin-Loeches I, Shorr AF, Wunderink RG, et al. Outcomes in participants with ventilated nosocomial pneumonia and organ failure treated with ceftolozane/tazobactam versus meropenem: a subset analysis of the phase 3, randomized, controlled ASPECT-NP trial. *Ann Inten Care*. 2023;13(1):8. doi: [10.1186/s13613-022-01084-8](https://doi.org/10.1186/s13613-022-01084-8)
- Bassetti M, Magnè F, Giacobbe DR, et al. New antibiotics for gram-negative pneumonia. *Eur Respir Rev*. 2022;31(166):220119. doi: [10.1183/16000617.0119-2022](https://doi.org/10.1183/16000617.0119-2022)
- Excellent comparative review of new intravenous antibiotics used for gram-negative bacterial pneumonia.**
- Kollef M, Timsit JJ, Martin-Loeches I, et al. Outcomes in participants with failure of initial antibacterial therapy for hospital-acquired/ventilator-associated bacterial pneumonia prior to enrolment in the randomized controlled phase 3 ASPECT-NP trial of ceftolozane tazobactam versus meropenem. *Crit Care*. 2022;26(1):373. doi: [10.1186/s13054-022-04192-w](https://doi.org/10.1186/s13054-022-04192-w)
- Gao W, Patel YT, Zhang Z, et al. Ceftolozane tazobactam probability of target attainment in patients with hospital-acquired or ventilatory-associated bacterial pneumonia. *J Clin Pharmacol*. 2023;63(3):352–357. doi: [10.1002/jcph.2165](https://doi.org/10.1002/jcph.2165)
- Holger DJ, Rebold NS, Alosaimy S, et al. Impact of ceftolozane-tazobactam vs. Best alternative therapy on clinical outcomes in patients with multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa* lower respiratory tract infections. *Infect Dis Ther*. 2022;11(5):1965–1980. doi: [10.1007/s40121-022-00687-9](https://doi.org/10.1007/s40121-022-00687-9)
- Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/Tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis*. 2020;71(2):304–310. doi: [10.1093/cid/ciz816](https://doi.org/10.1093/cid/ciz816)
- Gao W, Passarelli J, Patel YT, et al. Exposure-efficacy analyses support optimal dosing regimens of ceftolozane/tazobactam in participants with hospital-acquired/ventilator-associated bacterial pneumonia in ASPECT NP. *Antimicrob Agents Chemother*. 2022;66:1–10. doi: [10.1128/aac.01399-21](https://doi.org/10.1128/aac.01399-21)
- Bassetti M, Mularoni A, Giacobbe DR. New antibiotics for hospital-acquired pneumonia and ventilator-associated pneumonia. *Semin Respir Crit Care Med*. 2022;43(2):280–294. doi: [10.1055/s-0041-1740605](https://doi.org/10.1055/s-0041-1740605)
- Mogyorodi B, Czseko AB, Hermann C. Ceftolozane/Tazobactam versus colistin in the treatment of ventilator-associated pneumonia to extensively drug-resistant *Pseudomonas aeruginosa*. *Sci Rep*. 2022;12:1–10. doi: [10.1038/s41598-022-08307-9](https://doi.org/10.1038/s41598-022-08307-9)
- Timsit JF, Huntington JA, Wunderink RG, et al. Ceftolozane/Tazobactam versus meropenem in patients with ventilated hospital-acquired pneumonia: subset analysis of the ASPECT-NP randomized controlled phase 3 trial. *Crit Care*. 2021;25(1):1–14. doi: [10.1186/s13054-021-03694-3](https://doi.org/10.1186/s13054-021-03694-3)

20. Puzniak L, Dillon R, Palmer T, et al. Systematic literature review of real-world evidence of ceftolozane/tazobactam for the treatment of respiratory infections. *Inf Dis Ther.* 2021;10(3):1227–1252. doi: 10.1007/s40121-021-00491-x
21. Giaccari LG, Pace MC, Passavanti MB, et al. Ceftolozane/Tazobactam for resistant drugs *Pseudomonas aeruginosa* respiratory infections: a systematic literature review of the real-world evidence. *Life.* 2021;11(6):474–482. doi: 10.3390/life11060474
22. Castan B, Akrih B, Levy-Bachelot L, et al. Real-world evaluation of ceftolozane/tazobactam therapy and clinical outcomes in France. *Infect Dis Now.* 2021;51(6):532–539. doi: 10.1016/j.idnow.2021.05.003
23. Naik J, Puzniak L, Critchlow S, et al. Cost effectiveness of ceftolozane/tazobactam compared to meropenem for the treatment of patients with ventilated hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Infect Dis Ther.* 2021;10(2):939–954. doi: 10.1007/s40121-021-00436-4
24. Hart DE, Gallagher JC, Puzniak LA, et al. Multi centre evaluation of ceftolozane/tazobactam treatment outcomes in immunocompromised patients with multi-drug resistant *Pseudomonas aeruginosa* infections. *Open Form Infect Dis.* 2021;8:1–6.
25. Fiore M, Corrente A, Pace MC, et al. Ceftolozane-tazobactam combination therapy compared to ceftolozane-tazobactam monotherapy for the treatment of severe infections: a systematic review and meta-analysis. *Antibiotics.* 2021;10(1):1–4. doi: 10.3390/antibiotics10010079
26. Balandin B, Ballesterio D, De Luna R, et al. Multicenter study of ceftolozane/tazobactam for treatment of *Pseudomonas aeruginosa* infections in critically ill patients. *Int J Antimicrob Agents.* 2021;57(3):106270. doi: 10.1016/j.ijantimicag.2020.106270
27. Caro L, Nicolau DPO, DeWaele JJ, et al. Lung penetration bronchopulmonary pharmacokinetic pharmacodynamic profile and safety of 3 g of ceftolozane/tazobactam administered to ventilated critically ill patients with pneumonia. *J Antimicrob Chemother.* 2020;75(6):1546–1553. doi: 10.1093/jac/dkaa049
28. Almangour TA, Aljabri A, Musawa MA, et al. Ceftolozane/Tazobactam vs colistin for the treatment of infections due to multidrug-resistant *Pseudomonas aeruginosa*: a multicenter cohort study. *J Glob Antimicrob Resist.* 2022;28:288–294. doi: 10.1016/j.jgar.2022.01.023
29. Maraolo AE, Mazzitelli M, Trecarichi EM, et al. Ceftolozane/Tazobactam for difficult-to-treat *Pseudomonas aeruginosa* infections: a systematic review of its efficacy and safety for off-label indications. *Int J Antimicrob Agents.* 2020;55(3):105891. doi: 10.1016/j.ijantimicag.2020.105891
30. Vena A, Giacobbe DR, Mussini C, et al. Clinical efficacy of ceftolozane-tazobactam versus other active agents for the treatment of bacteremia and nosocomial pneumonia due to drug-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis.* 2020;71(7):1799–1801. doi: 10.1093/cid/ciaa003
31. Kollef MH, Novacek M, Kivistik U, et al. Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis.* 2019;19(12):1299–1311. doi: 10.1016/S1473-3099(19)30403-7
32. Zhanell GG, Dharmi R, Baxter M, et al. Real life experience with ceftolozane/tazobactam in Canada: results from the CLEAR (Canadian leadership on antimicrobial real-life usage) registry. *J Glob Antimicrob Resist.* 2021 Jun;25:346–350. doi: 10.1016/j.jgar.2021.03.025
- **Real life clinical usage data of ceftolozane/tazobactam used alone and in combination to treat patients with infections in Canada.**
33. Zhanell GG, Adam HJ, Baxter MR, et al. 42936 pathogens from Canadian hospitals: 10 years of results (2007–16) from the CANWARD surveillance study. *J Antimicrob Chemother.* 2019;74(Supplement 4):5–21. doi: 10.1093/jac/dkz283
- **Excellent review discussing the activity of > 20 antimicrobials versus ~50,000 pathogens causing infections in patients receiving care in Canadian hospitals.**
34. Denisuik AJ, Garbutt LA, Golden AR, et al. Antimicrobial resistant pathogens in Canadian ICUs: results of the CANWARD 2007–2016 study. *J Antimicrob Chemother.* 2019;74(3):645–653. doi: 10.1093/jac/dky477
35. Lagace-Wiens PRS, Adam HJ, Poutanen S, et al. Trends in antimicrobial resistance over 10 years among key bacterial pathogens from Canadian hospitals: results on the CANWARD study 2007–2016. *J Antimicrob Chemother.* 2019;74(Supplement 4):22–31. doi: 10.1093/jac/dkz284
36. Denisuik AJ, Karlowksy JA, Adam HJ, et al. Dramatic rise in the proportion of esbl-producing *Escherichia coli* and *Klebsiella pneumoniae* among clinical isolates identified in Canadian hospital laboratories from 2007–2016. *J Antimicrob Chemother.* 2019;74(Supplement 4):64–71. doi: 10.1093/jac/dkz289
37. Karlowksy JA, Walkty A, Golden AR, et al. Esbl-positive *Escherichia coli* and *Klebsiella pneumoniae* isolates from across Canada: CANWARD surveillance study, 2007–18. *J Antimicrob Chemother.* 2021;76(11):2815–2824. doi: 10.1093/jac/dkab269
38. Lynch JP, Clark NM, Zhanell GG. Escalating antimicrobial resistance among Enterobacteriaceae: focus on carbapenemases. *Exp Opin Pharm.* 2021;22(11):1455–1473. doi: 10.1080/14656566.2021.1904891
39. Lynch JP, Zhanell GG. *Pseudomonas aeruginosa* pneumonia: evolution of antimicrobial resistance and implications for therapy. *Sem Resp Crit Care Med.* 2022;43(2):97–124. doi: 10.1055/s-0041-1740109
40. Lynch JP, Clark NM, Zhanell GG. Infections due to *Acinetobacter baumannii*–calcoaceticus complex: escalation of antimicrobial resistance and evolving treatment options. *Sem Resp Crit Care Med.* 2022;43(1):97–124. doi: 10.1055/s-0041-1741019
41. Zhanell GG, Golden AR, Zelenitsky S, et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multi-drug resistant gram-negative bacilli. *Drugs.* 2019;79(3):271–289. doi: 10.1007/s40265-019-1055-2
42. Zhanell GG, Zhanell MA, Karlowksy JA. Intravenous fosfomycin: an assessment of its potential for use in the treatment of systemic infections in Canada. *Can J Infect Dis Med Microbiol.* 2018;2018:1–13. doi: 10.1155/2018/8912039
- **Thorough review of the various in-vitro and in-vivo properties of fosfomycin when used intravenously including clinical efficacy and safety data when used alone and in combination**
43. Zhanell GG, Lawson CD, Adam H, et al. Ceftazidime-avibactam: a novel cephalosporin/β-lactamase inhibitor combination. *Drugs.* 2013;73(2):159–177. doi: 10.1007/s40265-013-0013-7
44. Zhanell GG, Lawrence CK, Adam H, et al. Imipenem–relebactam and meropenem–Vaborbactam: two novel Carbapenem–β-Lactamase inhibitor combinations. *Drugs.* 2018;78(1):65–98. doi: 10.1007/s40265-017-0851-9
45. Zhanell GG, Cheung D, Adam H, et al. Review of eravacycline: a novel fluorocycline antibacterial agents. *Drugs.* 2016;76(5):567–588. doi: 10.1007/s40265-016-0545-8
46. Zhanell GG, Lawson CD, Zelenitsky S, et al. Comparison of the next generation aminoglycoside plazomicin to gentamicin, tobramycin and amikacin. *Expert Rev Antiinfect Ther.* 2012;10(4):459–473. doi: 10.1586/eri.12.25
47. Zhanell GG, Snizek G, Schweizer F, et al. A review of ceftaroline: a novel broad-spectrum cephalosporin with activity against MRSA. *Drugs.* 2009;69(7):809–831. doi: 10.2165/00003495-200969070-00003
48. Zhanell GG, Lam A, Schweizer F, et al. Ceftobiprole: a review of a broad spectrum and anti-mrsa cephalosporin. *Amer J Clin Dermatol.* 2008;9(4):245–254. doi: 10.2165/00128071-200809040-00004
- **Excellent review of the various in-vitro and in-vivo properties of ceftobiprole including clinical efficacy and safety data.**
49. Zhanell GG, Baxter M, Wong M, et al. Real-life experience with IV fosfomycin in Canada: results from the CLEAR (Canadian leadership on antimicrobial real-life usage) registry. *J Glob Antimicrob Resist.* 2023;33:171–176. doi: 10.1016/j.jgar.2023.03.010

- **Real life clinical usage data of IV fosfomycin used alone and in combination to treat patients with infections in Canada.**
50. Zhanel GG, Kosar J, Baxter M, et al. Real-life experience with ceftobiprole in Canada: results from the CLEAR (Canadian leadership on antimicrobial real-life usage) registry. *J Glob Antimicrob Res.* 2021;24:335–339. doi: [10.1016/j.jgar.2021.01.014](https://doi.org/10.1016/j.jgar.2021.01.014)
 - **Real life clinical usage data of ceftobiprole used alone and in combination to treat patients with infections in Canada.**
 51. Zhanel GG, Kosar J, Baxter M, et al. Real-life experience with dalbavancin in Canada: results from the CLEAR (Canadian leadership on antimicrobial real-life usage) registry. *J Glob Antimicrob Res.* 2024 (submitted). 38:154–157. doi: [10.1016/j.jgar.2024.06.002](https://doi.org/10.1016/j.jgar.2024.06.002)
 52. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377–381. doi: [10.1016/j.jbi.2008.08.010](https://doi.org/10.1016/j.jbi.2008.08.010)
 53. Zhanel GG, Dhimi R, Baxter M, et al. Treating hospital-acquired, ventilated hospital-acquired and ventilator-associated bacterial pneumonia in Canada with ceftolozane/tazobactam: final results from the CLEAR (Canadian leadership on antimicrobial real-life usage) registry. In: Association of Medical Microbiology and infectious disease (AMMI), Poster WP020; Vancouver, Canada; 2024 Apr 9–12.
 54. Bavaro DF, Belati A, Diella L, et al. Loading dose plus continuous/extended infusion versus intermittent bolus of β -lactams for the treatment of gram-negative bacteria bloodstream infections: a propensity score-adjusted retrospective cohort study. *J Antimicrob Chemother.* 2023;78(9):2175–2184. doi: [10.1093/jac/dkad215](https://doi.org/10.1093/jac/dkad215)
 55. Roberts JA, Croom K, Adamakoh N. Continuous infusion of beta-lactam antibiotics: narrative review of systematic reviews, and implications for outpatient parenteral antibiotic therapy. *Exp Rev Antiinfect Ther.* 2023;21(4):375–385. doi: [10.1080/14787210.2023.2184347](https://doi.org/10.1080/14787210.2023.2184347)
 56. Gatti M, Pea F. Jumping into the future: overcoming pharmacokinetic/pharmacodynamic hurdles to optimize the treatment of severe difficult to treat-gram-negative infections with novel beta-lactams. *Expert Rev Anti Infect Ther.* 2023;21(2):149–166. doi: [10.1080/14787210.2023.2169131](https://doi.org/10.1080/14787210.2023.2169131)
 - **Excellent review of PK/PD with beta-lactams when used to treat resistant and multidrug-resistant (MDR) infections.**