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ORIGINAL RESEARCH



How is ceftobiprole used in Canada: the CLEAR study final results

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ABSTRACT

Background: We report the final results of the clinical usage of ceftobiprole in patients in Canada from data in the national CLEAR (Canadian Leadership on Antimicrobial Real-Life Usage) registry.

Research design and methods: The authors review the final data using the national ethics approved CLEAR study. Thereafter, the literature is surveyed regarding the usage of ceftobiprole to treat patients with infectious diseases via PubMed (up to March 2024).

Results: In Canada, ceftobiprole is primarily used as directed therapy to treat a variety of severe infections caused by MRSA. It is primarily used in patients failing previous antimicrobials, is frequently added to daptomycin and/or vancomycin with high microbiological and clinical cure rates, along with an excellent safety profile. Several reports attest to the microbiological/clinical efficacy and safety of ceftobiprole. Ceftobiprole is also reported to be used empirically in select patients with community-acquired bacterial pneumonia (CABP), as well as hospital-acquired bacterial pneumonia (HABP).

Conclusions: In Canada, ceftobiprole is used mostly as directed therapy to treat a variety of severe infections caused by MRSA, in patients failing previous antimicrobials. It is frequently added to, and thus used in combination with daptomycin and/or vancomycin with high microbiological/clinical cure rates, and an excellent safety profile.

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1. Introduction

Ceftobiprole is a novel advanced-generation cephalosporin with *in vitro* activity against both Gram-negative bacilli (Enterobacterales and *Pseudomonas aeruginosa*), [excluding extended-spectrum β -lactamase (ESBL)-producing and carbapenem-resistant Enterobacterales], and Gram-positive cocci including penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-resistant *Staphylococcus epidermidis* (MRSE) [1–3]. In Canada and Europe, it has been approved to treat community-acquired bacterial pneumonia (CABP) and hospital-acquired bacterial pneumonia (HABP), excluding ventilator-associated bacterial pneumonia (VABP), and reported to have a role in selected patients as empiric treatment of CABP and HABP [4–9]. Ceftobiprole has been documented to effectively treat a wide variety of other infections including acute bacterial skin and skin structure infections [10–18]. Ceftobiprole, like ceftaroline, is active versus MRSA, and ceftobiprole has demonstrated bactericidal activity versus MRSA, including heteroresistant vancomycin-intermediate *S. aureus* (hVISA) and

vancomycin-intermediate *S. aureus* (VISA) strains, and showed efficacy in animal studies, patient case reports, and small patient cohorts with MRSA infections [19–26]. In addition, ceftobiprole is active versus *Enterococcus faecalis* [1]. Limited published data exist in Canada regarding the usage of ceftobiprole, thus we endeavored to assess how ceftobiprole was used by clinicians across Canada.

Antimicrobial-resistant pathogens such as MRSA and ESBL-producing and carbapenem-resistant Enterobacterales continue to increase across the globe [27–32]. As a result, many new intravenous (IV) antimicrobials have been approved and marketed in the United States, Europe, and elsewhere [33–37]. Frequently when these new IV antimicrobials are approved for use and introduced into the market, they are used primarily by infectious diseases/medical microbiology specialists and frequently used to treat 'off-label' infectious indications [33–37]. Unfortunately, limited data sharing between clinicians occurs regarding why they chose to use these new IV antimicrobials (i.e. because of clinical failure of previously used agents, resistance, or adverse effects associated with use of other

Article highlights

- Clinical usage data of ceftobiprole are limited.
- We report the final results of ceftobiprole usage in patients in Canada using data captured by the national CLEAR registry.
- Of the first 100 patients reported, the most common infections treated with ceftobiprole were endocarditis, bone/joint infection, and hospital-acquired bacterial pneumonia (HABP) with almost all patients having a concomitant bacteremia.
- Ceftobiprole was primarily used as directed therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infections and added to failing vancomycin and/or daptomycin regimens.
- Ceftobiprole usage was associated with high rates of microbiological and clinical success along with a good safety profile.
- In Canada to date, ceftobiprole is used as directed therapy to treat a variety of severe infections caused by MRSA.
- Outside of Canada, ceftobiprole is used as directed therapy and empirically in select patients with a variety of infections, especially community-acquired bacterial pneumonia (CABP) and HABP as part of treatment algorithms.

antimicrobial agents), the types of infections treated, and how (i.e. dosage regimen, duration of therapy, as monotherapy or in combination with one or more other antimicrobial agents) they use new IV antimicrobial agents in their practice. The CLEAR (Canadian LEadership on Antimicrobial Real-life Usage) 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 accumulation of information regarding the clinical usage of new IV antimicrobials recently introduced into the Canadian marketplace. CLEAR is currently acquiring data on clinical usage of ceftolozane/tazobactam, IV fosfomycin, and dalbavancin [38,39]; however, this paper presents data on the usage of IV ceftobiprole in Canada among participating clinicians in the first 100 patient treatment surveys (as of November 2023).

In this paper, we report the final results of the clinical usage of ceftobiprole in patients in Canada using data obtained by the national CLEAR (Canadian Leadership on Antimicrobial Real-Life Usage) registry. We previously reported preliminary data on this same study utilizing the same methods [26].

2. Patients and methods

A usage questionnaire for IV ceftobiprole 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) responded directly to the usage questionnaire online starting in late 2019. The REDCapTM online survey (<https://rcsurvey.radyfhs.umanitoba.ca/surveys/?s=A8EHM8JJRF>) 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]) [40].

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. We previously reported data on the first 38 CLEAR ceftobiprole patient treatment surveys [26]. The CLEAR ceftobiprole questionnaires received by 15 March 2024 were tabulated, and the final results presented here are based on the first 100 patient treatment surveys received.

3. Results

3.1. Patient demographics and clinician responders

One-hundred patient usage questionnaires were completed as of 15 March 2024 across Canada; 37% of patients treated were from western Canada, 58% from central Canada, and 5% from eastern Canada (data not shown). Most patients (79%) were aged 18–64 years, 19% were ≥65 years, and 2% were ≤17 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

Usage of ceftobiprole was for a variety of infections including endocarditis (39% of patients) followed by bone/joint infections (24%), HABP (8%), CABP (8%), acute bacterial skin and skin structure infections (ABSSSI) (8%) and device-related infection (6%) (Table 1). Ninety-four (94%) of the 100 patients had bacteremia and 32% started or completed their therapy in an intensive care unit (ICU). Ceftobiprole was mostly used (95%) as directed (meaning non-empiric) therapy. Cultured pathogens treated included MRSA (95%), one patient each with *Enterococcus faecalis*, *Enterococcus faecium*, or MRSE and two cases of mixed infection (each with a Gram-positive coccus and a Gram-negative bacillus). Initiation of ceftobiprole treatment occurred due to clinical failure of previous antimicrobial therapy (73%), resistance to initially prescribed antimicrobial agents (12%), or adverse effects associated with use of previous antimicrobial agents (13%). Antimicrobial susceptibility testing (AST) with ceftobiprole was performed in 32% of cases, each time using Etest. No isolates tested resistant to ceftobiprole.

Table 1. Infections treated with ceftobiprole.

Infection Treated	% of Patients (n = 100)
Endocarditis	39%
Bone and Joint Infections	24%
Community-Acquired Bacterial Pneumonia	8%
Hospital-Acquired Bacterial Pneumonia	8%
Acute Bacterial Skin and Skin Structure Infection	8%
Device-Related Infection	6%
Bacteremia	3%
Central Nervous System Infection	2%
Complicated Intraabdominal Infection	1%
Enteritis	1%

3.3. Dosage and administration

The most common ceftobiprole dosages prescribed were as follows: 500 mg q8h (67%), 500 mg q12h (12%), 250 mg q24h (12%), and 250 mg q12h (5%). Renal function was assessed (creatinine clearance) in all patients with dosages adjusted based upon renal function (Table 2). In 83% of cases, ceftobiprole was administered using a prolonged infusion (2 h or more) [Table 2]. Ceftobiprole's usage as prolonged infusion is consistent with optimizing β -lactam pharmacodynamics [41–43]. Ceftobiprole was added after initial clinical failure with daptomycin and/or vancomycin, and thus used concomitantly with daptomycin (46% of patients) or vancomycin (20% of patients), daptomycin and vancomycin in 5%, or as monotherapy (in 23% of patients). Duration of treatment was primarily >10 days (66% of patients).

Table 2. Ceftobiprole dosing and infusion.

% of Patients (n = 100)	Ceftobiprole Dose
67%	500 mg q8h
12%	500 mg q12h
12%	250 mg q24h
5%	250 mg q12h
2%	1 g q8h
1%	1 g q12h
1%	500 mg q24h
	Infusion Time
83%	Prolonged (≥ 2 h)
15%	Short (15 min–1 h)
2%	Unknown

3.4. Microbiological and clinical outcomes

Ceftobiprole microbiological success, defined as eradication or presumed eradication of the pathogen in evaluable cases, was 96% (85/89); microbiological outcomes were unknown for 11 patients (Table 3). Four patients were classified as microbiological failures due to the persistence of bacteria (Table 3). The first of the four patients had a bone and joint infection and concomitant bacteremia both due to *E. faecium*. Ceftobiprole was chosen due to resistance to prior antibiotics. The patient was treated with ceftobiprole (250 mg q24h hours using a 2-h infusion; creatinine clearance <30 ml/min) and a fluoroquinolone for >10 days but the pathogen persisted and was associated with clinical failure. The second patient had endocarditis due to MRSA, was treated for >10 days with ceftobiprole and daptomycin with microbiological failure and death due to infection. The third patient had a bone/joint infection and was bacteremic due to MRSA, was treated for >10 days with ceftobiprole and daptomycin with microbiological failure and an unknown clinical outcome. The fourth patient had a bacteremic CABP due to MRSA, was treated for <7 days with ceftobiprole with microbiological failure and death due to infection.

Table 3. Microbiological outcomes with ceftobiprole treatment.

Outcome	% of Patients (n = 100)
Eradication	46%
Presumed Eradication	39%
Persistence	4%
Unknown	11%

Defined as cure or improvement in evaluable cases, clinical success occurred in 85% (75/88) of patients; clinical outcome was unknown for 12 patients (Table 4). Clinical failure occurred in two patients. The first patient had an *E. faecium* bone/joint infection with concomitant bacteremia, was treated with >10 days of ceftobiprole and a fluoroquinolone but was deemed a microbiologic and clinical failure. The second patient had a central nervous system infection with MRSA and concomitant MRSA bacteremia. Ceftobiprole was chosen due to clinical failure of prior antibiotics. The patient was treated with a combination of ceftobiprole (500 mg q12h using a 30 min infusion; creatinine clearance 30–49 ml/min) and vancomycin for >10 days, and showed microbiological eradication, but clinically did not improve and manifested with irreversible neurological sequelae. Clearly, more data are required into ceftobiprole's penetration into the central nervous system (CNS) in humans with CNS infections.

Mortality overall was 11%, with 8% of patients (n = 8) dying as a result of their infection (Table 4). The first of the eight patients who died had MRSA endocarditis/bacteremia, with ceftobiprole treatment chosen due to clinical failure to prior antibiotics. The patient was treated with ceftobiprole (500 mg q8h using a 2 h infusion) alone for 7–10 days resulting in eradication of the pathogen; however, the patient deteriorated clinically, died and the death was attributed to the infection. The second patient had MRSA HABP with bacteremia. Ceftobiprole was used due to clinical failure to prior antibiotics. The patient was treated with ceftobiprole (500 mg q8h using a 2 h infusion) along with vancomycin for <7 days. The microbiological outcome in this patient was unknown but the patient deteriorated clinically, died and the death was attributed to the infection. The third patient had MRSA endocarditis which was eradicated by ceftobiprole but developed septic emboli/heart failure and death was attributed to the infection. The fourth patient had MRSA endocarditis and persistent bacteremia despite concomitant ceftobiprole and daptomycin therapy, and died as a result of his infection. The fifth patient had MRSA endocarditis and bacteremia treated with ceftobiprole and daptomycin for <7 days, died, and the death was attributed to the infection. The sixth patient had a complicated intraabdominal infection caused by MRSA, was treated with ceftobiprole for 7–10 days and died with death attributed to the infection. The seventh patient had MRSA CABP with bacteremia, was treated with ceftobiprole alone for <7 days with persistence and died with death attributed to the infection. Lastly, the eighth patient had MRSA endocarditis and persistent bacteremia despite ceftobiprole and daptomycin therapy for >10 days with bacterial eradication but the patient died and the death was attributed to the infection. Assessment of the various ceftobiprole dosage regimens did not result in the relationship between dosage and microbiological or clinical outcome. In addition, no relationship was documented between

Table 4. Clinical outcomes with ceftobiprole treatment.

Outcome	% of Patients (n = 100)
Cure	46%
Improvement	29%
Failure	2%
Death due to infection	11%
Unknown	12%

usage of ceftobiprole, monotherapy or combination therapy and microbiological and clinical outcome.

3.5. Adverse effects

Of the 100 patients, one patient reported gastrointestinal adverse effects associated with ceftobiprole but the drug was continued. Four patients demonstrated hypersensitivity reactions with discontinuation in one patient due to blisters.

3.6. Limitations of CLEAR

The CLEAR study is not without limitations. We have only reported our experience with the first 100 patient treatment surveys which provides data on a relatively small number of patients especially for certain infections. All clinician reports of ceftobiprole treated patients 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 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 Canada, we observed that ceftobiprole usage is primarily as directed therapy against documented severe MRSA infections including endocarditis, bone/joint infections, CABP, and HABP with the majority of patients having a concomitant bacteremia. Published clinical data using ceftobiprole in other countries also attest to its high clinical cure rates in a variety of infections caused by *S. aureus* including MRSA [17,18,20,22–24]. Like our study, other investigators have also documented that the use of ceftobiprole is frequently in combination with daptomycin or vancomycin; these combinations demonstrate synergistic activity and maximize the opportunity for clinical cure [18,21,25]. Tascini et al. recently reported their experience with ceftobiprole treating 12 patients with infective endocarditis caused by *Staphylococcus* spp. including MRSA [18]. Of the 12 patients treated with ceftobiprole, 11 were treated in combination with daptomycin. The majority of patients (75%) were switched to ceftobiprole due to patients clinically failing previous antimicrobial therapy. Similar to our observations in the current study, these researchers reported a clinical cure rate of 83% and concluded that ceftobiprole especially when used in combination with daptomycin is a promising alternative treatment for infective endocarditis [18].

Other investigators report using ceftobiprole as both directed therapy and empiric therapy due to its proven efficacy in treating a variety of infections and *in vitro* activity against common Gram-positive and Gram-negative pathogens [7,12–16]. Durante-Mangoni et al. reported their real-life experience of treating 29 patients with ceftobiprole in a tertiary-care hospital [12]. The majority of infections were nosocomial in origin, primarily pneumonia and bloodstream infections. These investigators documented using ceftobiprole empirically in 31% of patients and as

directed therapy in 69%. A favorable clinical outcome was reported in 69% of patients. The investigators concluded that ceftobiprole is a safe and effective treatment for resistant Gram-positive infections when other agents are inactive or poorly tolerated or for salvage therapy [14]. Crapis et al. reported their real-life experience using ceftobiprole to treat patients with severe pneumonia admitted to the emergency department [7]. Of the 48 treated patients, 46% received ceftobiprole as empiric therapy, 27% as escalation therapy following failure with ceftriaxone and amoxicillin/clavulanate, 19% as de-escalation following piperacillin/tazobactam plus linezolid and 8.3% as targeted therapy based on microbiological results [7]. The mean duration of ceftobiprole therapy was 10 days. The researchers documented that 96% patients demonstrated early clinical improvement within 72 hours after the start of ceftobiprole therapy [7]. The clinical cure rate was 85% and 30-day crude mortality was 10%. The researchers concluded that ceftobiprole was effective therapy for severely ill patients with pneumonia at risk for poor outcomes. Bellut et al. recently described the experience of real-life use of ceftobiprole treatment of severe infections of critically ill patients with multiple infected sites in a French ICU [13]. The main indication for ceftobiprole was pneumonia (51%) and most patients presented with a concomitant bacteremia (72%). Interestingly, all infections were polymicrobial and yet clinical cure was achieved for nearly 80% of the patients [13]. The researchers concluded that in their experience, treatment of ICU patients with ceftobiprole for severe polymicrobial infections is mostly associated with clinical cure. Spanish researchers recently assessed the clinical usage of ceftobiprole both in patients with infections treated in hospital or as outpatient parenteral antimicrobial therapy (OPAT) [14]. Of the 249 individuals studied, mostly the infections were respiratory (55.8%) and skin and soft tissue (21.7%). Ceftobiprole was administered primarily as empirical treatment and mostly as monotherapy for 7 days. The infection-related mortality was 11% and highest in patients with ventilator-associated pneumonia, MRSA infections, and in infections caused by *P. aeruginosa* [14]. The researchers concluded that ceftobiprole is a safe and effective antibiotic mainly administered as rescue therapy in pluripathological patients with severe infectious diseases. Recently, in an Italian study, clinicians assessed the use of ceftobiprole in a real-world setting [16]. 195 patients from 10 centers were treated mostly for HABP, but also skin and soft tissue infections, endocarditis and bone infections. Usage of ceftobiprole was empiric in 65% of patients, in combination with other antimicrobials (66%) and frequently as second-line therapy (58%). The researchers concluded that ceftobiprole was both effective and safe when used to treat a variety of infections.

Recently, Giuliano et al. assessed whether ceftobiprole had a potential role to treat *E. faecalis* bacteremia and endocarditis [44]. Ceftobiprole *in-vitro* activity against *E. faecalis* is due to binding to penicillin-binding proteins (PBP), PBP4 and PBP5, in addition to PBP2 and PBP3. Ceftobiprole used along with ampicillin might be an alternative to ceftriaxone in difficult to treat *E. faecalis* severe infections [44].

Thus, it is clear that ceftobiprole is used in certain medical centers primarily as directed therapy to treat severe infections caused by *Staphylococcus* spp., including MRSA, whereas in other centers it is also used as an empiric treatment to treat

many different infections but especially respiratory tract infections. Based on the favorable results of the CLEAR ceftobiprole study, and the favorable ceftobiprole data in the published literature, we were motivated to publish a recent invited review on the potential empiric treatment of HABP in Canada (6). We presented potential empiric treatments of

HABP in Canada where we identified potential roles for ceftobiprole [6]. It needs to be mentioned that these potential empiric treatments of HABP in Canada shown in Table 5 and Figure 1 are influenced in part, by the availability of certain antimicrobials but especially the lack of availability of other agents in Canada including: cefiderocol, ceftaroline,

Table 5. 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, Ceftobiprole 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).

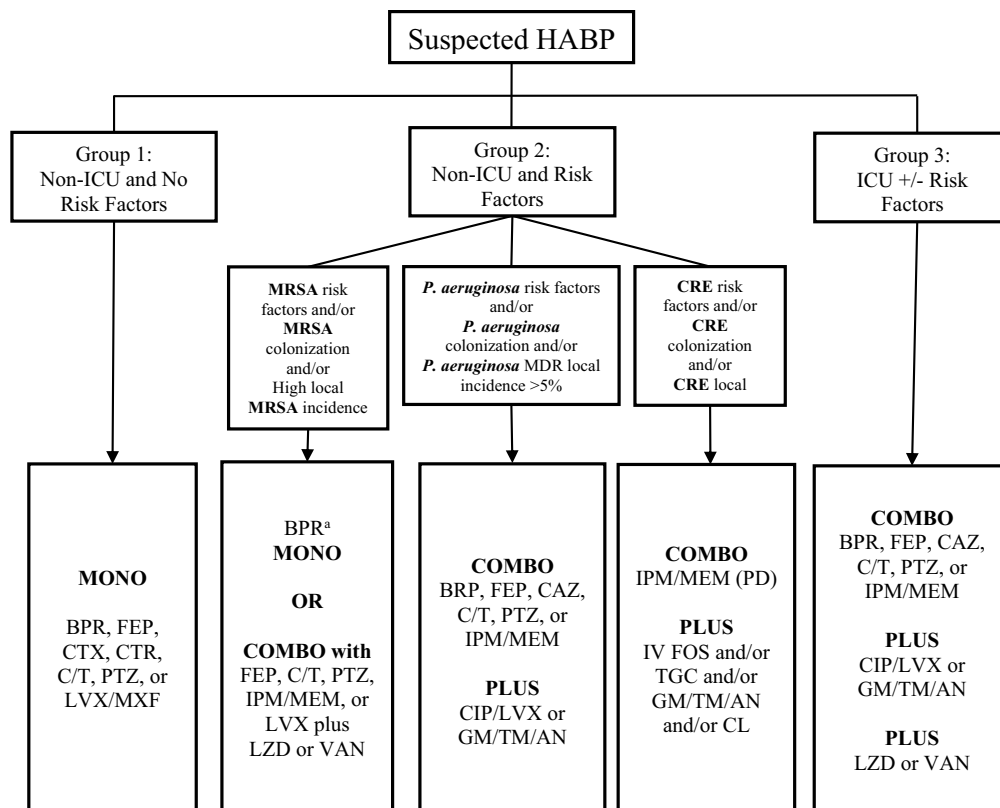


Figure 1. Algorithm of empiric antimicrobial hospital-acquired bacterial pneumonia (HABP) treatment.

AN, amikacin; BPR, ceftobiprole; CAZ, ceftazidime; CIP, ciprofloxacin; CL, colistin; COMBO, combination therapy; CRE, carbapenem-resistant Enterobacteriales; C/T, ceftolozane/tazobactam; CTR, ceftriaxone; CTX, cefotaxime; FEP, cefepime; FOS, fosfomycin; GM, gentamicin; IPM, imipenem/cilastatin; IV, intravenous; LVX, levofloxacin; LZD, linezolid; MEM, meropenem; MONO, monotherapy; MRSA, methicillin-resistant *Staphylococcus aureus*; MXF, moxifloxacin; PD, optimize meropenem pharmacodynamics; PTZ, piperacillin/tazobactam; TGC, tigecycline; TM, tobramycin; VAN, vancomycin.

^aIf ceftobiprole is used no linezolid or vancomycin is required.

ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam, and plazomicin; thus, they need to be considered as Canada-specific. Each country needs to assess their potential empiric treatments of HABP and what role ceftobiprole may have based on a variety of factors including what antimicrobial agents are approved for use in their country.

Ceftobiprole is a cephalosporin with activity against both Gram-positive and Gram-negative pathogens. Most importantly, it is active against MRSA. Ceftobiprole and ceftaroline are the only cephalosporins active versus MRSA. Ceftobiprole is available in many countries and appears to be used in one of two ways, most commonly as directed therapy in microbiologically proven MRSA infections including bacteremia, endocarditis, CABP, and HABP, infections of bones and joints, device-related infections, central nervous system infections, and ABSSSI, or empirically as part of hospital treatment algorithms. For most infections, ceftobiprole is used alone; however, in endocarditis, it is frequently used in combination with daptomycin. Ceftobiprole is also used empirically for CABP and HABP and bloodstream infections likely caused by Gram-positive and/or Gram-negative pathogens, especially if there are patient risk factors for MRSA. In each case, ceftobiprole is associated with excellent microbiological and clinical success rates along with an excellent safety profile.

The current study reports the final results of the usage of ceftobiprole in Canada, using the national survey, CLEAR. Our results confirm that ceftobiprole is used primarily as directed therapy for microbiologically diagnosed MRSA infections. Infections treated (on label and off label) included endocarditis, pneumonia, bone and joint, with a consistent feature that the majority of patients were bacteremic. We also observed that bacteremic patients had been previously treated using vancomycin or daptomycin and were experiencing clinical failure or resistance to these therapies thus ceftobiprole was added. Clinicians chose to add ceftobiprole to existing vancomycin and/or daptomycin therapy, likely not only to provide additive and/or synergistic MRSA activity but also likely as a result of ceftobiprole's excellent safety. Ceftobiprole was typically used without antimicrobial susceptibility testing perhaps because a national CARA/Health Canada surveillance study CANWARD previously reported that all MRSA tested in Canada were susceptible to ceftobiprole (<http://www.can-r.ca/index.php>). Ceftobiprole therapy was adjusted for renal function in all patients, and the regimens were pharmacodynamically optimized by extending the infusion to 2–3 hours. In cases of severe infection such as bloodstream infection, potentially using an augmented daily dose (500 mg every 6 h) of ceftobiprole may be an option as recently demonstrated in a study on *S. aureus* bacteremia [20]. Despite patients failing and/or developing resistance to previous therapy and having persistent bacteremia, ceftobiprole was associated with excellent microbiological and clinical success. In addition, like other cephalosporins, and other β -lactams, ceftobiprole, proved to be safe, even though it was used in seriously ill patients.

5. Conclusions

We provide data from the final results of the national CLEAR registry describing the clinical usage of ceftobiprole in Canada

and also compare this usage to other countries. In Canada, ceftobiprole is used mostly as directed therapy to treat a variety of severe infections caused by MRSA. It is primarily used in patients failing previous antimicrobials, is frequently added to, and thus used in combination with daptomycin and/or vancomycin with high microbiological and clinical cure rates, along with an excellent safety profile. In other countries, ceftobiprole is also used as directed therapy for infections caused by *Staphylococcus* spp., especially MRSA, but also empirically for a variety of infections including community-acquired bacterial pneumonia and hospital-acquired bacterial pneumonia.

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Author contributions

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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