



In Vitro activity of ceftobiprole against 20,255 recent clinical bacterial isolates in Canada (CANWARD 2015-2023)

Élodie Gemme^a, Andrew Walkty^{a,b}, Melanie Baxter^a, Heather J. Adam^{a,b},
Philippe Lagacé-Wiens^{a,b}, Karl Weiss^{c,d}, James A. Karlowsky^{a,b}, George G. Zhanel^{a,*}, the
Canadian Antimicrobial Resistance Alliance (CARA)^a

^a Department of Medical Microbiology and Infectious Diseases, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba

^b Clinical Microbiology, Diagnostic Services Manitoba/Shared Health, Winnipeg, Manitoba

^c Department of Medical Microbiology and Infectious Diseases, McGill University, Montreal, Quebec

^d Division of Infectious Diseases, Jewish General Hospital, Montreal, Quebec

ARTICLE INFO

Keywords:

Ceftobiprole

MRSA

Staphylococcus aureus

Streptococcus pneumoniae

Enterobacteriaceae

Pseudomonas aeruginosa

ABSTRACT

Background: Ceftobiprole is a fifth-generation cephalosporin active against methicillin-resistant *Staphylococcus aureus* (MRSA). In this study, we determined the *in vitro* activities of ceftobiprole and comparator agents against 20,225 common Gram-positive and Gram-negative bacteria isolated from patients who presented for care at 16 tertiary-care hospitals across Canada between 2015 and 2023.

Methods: Minimum inhibitory concentrations (MICs) were determined using the Clinical and Laboratory Standards Institute (CLSI) reference M07 broth microdilution method. MICs were interpreted using CLSI M100 breakpoints where available. As CLSI does not publish MIC breakpoints for ceftobiprole, ceftobiprole MICs were interpreted using United States Food and Drug Administration (FDA), European Committee on Antimicrobial Susceptibility Testing (EUCAST), and Health Canada breakpoints.

Results: Ceftobiprole inhibited 100 % of MRSA at ≤ 4 $\mu\text{g/ml}$; 100 % of methicillin-susceptible *S. aureus* (MSSA) and 99.8% of MRSA at ≤ 2 $\mu\text{g/ml}$; 100 % of *Streptococcus pneumoniae* and *Streptococcus pyogenes* at ≤ 0.5 $\mu\text{g/ml}$; and 97.9 % of ESBL-negative *Escherichia coli*, 97.4 % of ESBL-negative *Klebsiella pneumoniae*, 97.8 % of *Proteus mirabilis*, 89.3 % of *Serratia marcescens*, 78.2 % of *Enterobacter cloacae*, 55.7 % of *Klebsiella oxytoca* at ≤ 0.25 $\mu\text{g/ml}$. Ceftobiprole was inactive against ESBL-positive *E. coli* and ESBL-positive *K. pneumoniae*.

Conclusions: Ceftobiprole demonstrated potent *in vitro* activity against MRSA, MSSA, *S. pneumoniae*, *S. pyogenes*, ESBL-negative *E. coli* and *K. pneumoniae*, and *P. mirabilis* isolated from clinical specimens of patients seeking care at Canadian tertiary-care hospitals.

1. Introduction

Ceftobiprole is a cephalosporin active against methicillin-resistant *Staphylococcus aureus* (MRSA) [1–3]. Its spectrum of activity also includes other Gram-positive cocci and Gram-negative bacilli, similar to third-generation cephalosporins, as well as methicillin-resistant *Staphylococcus epidermidis*, penicillin-resistant *Streptococcus pneumoniae*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* [1–3].

In Europe and Canada, ceftobiprole is indicated for treatment of community-acquired and hospital-acquired pneumonia (excluding ventilator-associated pneumonia) [4,5]. More recently, in April 2024, it

was approved by the United States Food and Drug Administration (FDA) for three major indications: adults with bloodstream infections, including right-sided infective endocarditis, caused by *S. aureus*; adults with acute bacterial skin and skin structure infections; and adults and children with a community-acquired bacterial pneumonia [6].

Given its broad-spectrum activity, including against important resistant pathogens such as MRSA, and its strong safety profile, ceftobiprole is positioned to become a widely used agent [7,8]. In this study, we determined the *in vitro* activities of ceftobiprole and relevant comparator antimicrobial agents against a very large (20,255) recent collection of common Gram-positive and Gram-negative bacteria

* Corresponding author: Department of Medical Microbiology and Infectious Diseases Max Rady College of Medicine, University of Manitoba 502 Basic Medical Sciences Building, University of Manitoba, 745 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E 0J9.

E-mail address: ggezhan@pcsinternet.ca (G.G. Zhanel).

<https://doi.org/10.1016/j.diagmicrobio.2025.116838>

Received 7 March 2025; Received in revised form 31 March 2025; Accepted 8 April 2025

Available online 11 April 2025

0732-8893/© 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

causing infections in patients who presented for care at 16 tertiary-care hospitals across Canada between 2015 and 2023. We then compared our results to previously published studies from other countries and review current and potential clinical uses for ceftobiprole.

2. Material and methods

2.1. Bacterial isolates

20,225 isolates were collected by clinical microbiology laboratories at 16 tertiary-care hospitals distributed across Canada between January 2015 and December 2023. All isolates were determined to be clinically significant based upon algorithms in place in each participating laboratory and were collected consecutively. Duplicate isolates (same patient, same organism, same year) were excluded from testing. Isolate sample collection locations were: 6,913 (34.2 %) from patients admitted to medical wards; 4,744 (23.5 %) from patients seen in an emergency department; 3,858 (19.1 %) from patients in intensive care units; 3,226 (16.0 %) from patients assessed in outpatient clinics; and 1,484 (7.3 %) from patients admitted to surgical wards. Eye, ear, nose and surveillance swabs, pathology isolates, gastrointestinal and genital tract specimens, and anaerobes were excluded. Each participating laboratory shipped samples to the Canadian Ward (CANWARD) surveillance study coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) on Amies charcoal swabs. 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 stocked in skim milk at -80 °C until antimicrobial susceptibility testing was performed.

2.2. Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed by the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method [9]. Minimum inhibitory concentrations (MICs) were interpreted using CLSI M100 breakpoints [10], where available. CLSI does not publish MIC breakpoints for ceftobiprole, thus ceftobiprole MICs were interpreted using United States Food and Drug Administration (FDA), European Committee on Antimicrobial Susceptibility Testing (EUCAST), and Health Canada breakpoints. FDA publishes susceptible MIC breakpoints for ceftobiprole for the following bacteria/bacterial groups: *S. aureus* (including MRSA), ≤ 2 µg/ml; *S. pneumoniae*, ≤ 0.5 µg/ml; *Streptococcus pyogenes*, ≤ 0.5 µg/ml; *Enterobacterales*, ≤ 0.25 µg/ml; and *Haemophilus influenzae* and *Haemophilus parainfluenzae*, ≤ 0.25 µg/ml [11; last updated April 3, 2024]. EUCAST publishes susceptible MIC breakpoints for ceftobiprole for the following bacteria/bacterial groups: *S. aureus*, ≤ 2 µg/ml; *S. pneumoniae*, ≤ 0.5 µg/ml; and *Enterobacterales*, ≤ 0.25 µg/ml [12; last updated January 1, 2025]. Health Canada publishes susceptible MIC breakpoints for ceftobiprole for the following bacteria/bacterial groups: *S. aureus* (including MRSA), ≤ 4 µg/ml; *S. pneumoniae*, ≤ 0.5 µg/ml; and *Enterobacteriaceae*, ≤ 1 µg/ml that were last updated October 30, 2017 [13]. Regarding Health Canada MIC breakpoints for ceftobiprole, the Family *Enterobacteriaceae* includes the genera *Escherichia*, *Klebsiella*, and *Enterobacter* and excludes the genera *Proteus* (Family *Morganellaceae*) and *Serratia* (Family *Yersiniaceae*) [13].

S. pneumoniae isolates susceptibility to penicillin was determined using the CLSI oral penicillin breakpoints (susceptible, ≤ 0.06 µg/ml; intermediate, 0.12–1 µg/ml; resistant, ≥ 2 µg/ml); susceptibility to ceftriaxone was defined based on non-meningitis breakpoints (susceptible, ≤ 1 µg/ml; intermediate, 2 µg/ml; resistant, ≥ 4 µg/ml) [10].

Escherichia coli and *Klebsiella pneumoniae* isolates with ceftriaxone and/or ceftazidime MICs ≥ 1 µg/ml were tested for extended-spectrum β -lactamases (ESBL) production using the CLSI phenotypic confirmatory disk test [10]. Presumptive AmpC-positive *E. coli* were defined as isolates with ceftriaxone and/or ceftazidime MICs ≥ 1 µg/ml and a

cefoxitin MIC ≥ 32 µg/ml and a negative ESBL confirmatory test.

3. Results

3.1. Epidemiology

Patients ranged in age from 0 to 105 years old; 47.1 % ($n = 9,530$) of patients were aged 65 years or older, 43.8 % ($n = 8,854$) were aged 18 to 64 years; and 9.1 % ($n = 1,841$) were pediatric patients. Male patients (54.8 %, $n = 11,088$) were more numerous than female patients (45.2 %, $n = 9,136$): biological sex was not provided for one patient. Isolate sources were: 40.7 % ($n = 8,240$) from blood; 37.2 % ($n = 7,526$) from respiratory tract samples; 11.5 % ($n = 2,327$) from urine; and 10.5 % ($n = 2,132$) from wound samples.

3.2. Ceftobiprole activity against Gram-positive organisms

All isolates of methicillin-susceptible *S. aureus* (MSSA) tested were susceptible to ceftobiprole (MIC, ≤ 2 µg/ml) by FDA, EUCAST, and Health Canada MIC breakpoints (Table 1). MRSA were 99.8 % susceptible by both the FDA and EUCAST MIC breakpoint (MIC, ≤ 2 µg/ml) and 100 % susceptible to ceftobiprole by the Health Canada MIC breakpoint (MIC, ≤ 4 µg/ml). Two MRSA isolates (of 990) had a reproducible ceftobiprole MIC of 4 µg/ml. Percent susceptible values for both MSSA and MRSA exceeded 99 % for linezolid, vancomycin, daptomycin and dalbavancin; susceptibility to doxycycline and trimethoprim-sulfamethoxazole was > 97 %. Ceftobiprole had an MIC₉₀ of 1 µg/ml for *S. epidermidis* suggesting it possesses *in vitro* activity against the majority of isolates of this staphylococcal species even though MIC breakpoints are not published for this organism.

All isolates of *S. pneumoniae* tested, including those resistant to penicillin, were ceftobiprole-susceptible (MIC ≤ 0.5 µg/ml) by FDA, EUCAST, and Health Canada MIC breakpoints (Table 1). Ceftriaxone inhibited all penicillin-susceptible and penicillin-intermediate *S. pneumoniae* and 92.5 % of penicillin-resistant *S. pneumoniae* at ≤ 1 µg/ml (nonmeningitis ceftriaxone-susceptible MIC breakpoint). All isolates of *S. pyogenes* were ceftobiprole-susceptible (MIC ≤ 0.5 µg/ml, FDA MIC breakpoint). The ceftobiprole MIC₉₀ value and MIC range for *S. agalactiae* were ≤ 0.03 µg/ml and ≤ 0.03 – 0.06 µg/ml, respectively, suggesting it possesses *in vitro* activity against all isolates of this β -hemolytic streptococcus even though MIC breakpoints are not published.

Ceftobiprole was more active *in vitro* against *E. faecalis* (MIC₉₀, 1 µg/ml) than against *Enterococcus faecium* (MIC₉₀, > 32 µg/ml) consistent with the well-established pattern for other β -lactam antimicrobial agents.

3.3. Ceftobiprole activity against Gram-negative organisms

Among ESBL-negative isolates, ceftobiprole inhibited 97.9 % of *E. coli* and 97.4 % of *K. pneumoniae* at the FDA and EUCAST *Enterobacterales* MIC susceptible breakpoint (≤ 0.25 µg/ml) (Table 2). Ceftobiprole was inactive against most ESBL-positive *E. coli* and ESBL-positive *K. pneumoniae* similar to third-generation cephalosporins like ceftriaxone and ceftazidime. Piperacillin-tazobactam inhibited 83.3 % of ESBL-positive *E. coli* and 52.5 % of ESBL-positive *K. pneumoniae*. For AmpC-positive *E. coli*, percent susceptible values for ceftobiprole ranged from 66.7 % (FDA and EUCAST MIC breakpoint) to 85.2 % (Health Canada *Enterobacteriaceae* MIC breakpoint, ≤ 1 µg/ml) depending upon the MIC breakpoint used. Percent susceptible values for ceftriaxone, piperacillin-tazobactam, cefepime, and meropenem were 40.7 %, 73.3 %, 91.9 % and 97.8 %, respectively, for AmpC-positive *E. coli*. Ceftobiprole percent susceptible values for *K. oxytoca* ranged from 55.7 % (FDA and EUCAST MIC breakpoint) to 83.5 % (Health Canada MIC breakpoint) and for *E. cloacae* ranged 78.2 % (FDA and EUCAST MIC breakpoint) to 83.8 % (Health Canada MIC breakpoint). Ceftobiprole percent susceptible values for *P. mirabilis* and *S. marcescens* were 97.8 % and 89.3

Table 1

In vitro activity of ceftobiprole and comparator agents against 8,078 isolates of aerobic Gram-positive cocci isolated from patients in Canadian hospitals from 2015 to 2023.

Organism (no. tested) ^a / antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
<i>S. aureus</i> , MSSA (4,038)				
ceftobiprole ^b	0.5	0.5	≤0.06 - 2	100, 100, 100
clarithromycin	0.25	>32	≤0.03 - >32	76.3
clindamycin ^c	≤0.12	≤0.12	≤0.12 - >8	95.7
dalbavancin (2985)	0.06	0.12	≤0.03 - 0.25	100
daptomycin	0.25	0.5	≤0.03 - 2	99.9
doxycycline	≤0.12	0.25	≤0.12 - 32	98.8
linezolid	2	4	≤0.12 - 8	>99.9
trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12 - >8	99.3
vancomycin	0.5	1	≤0.12 - 2	100
<i>S. aureus</i> , MRSA (990)				
ceftobiprole ^b	1	2	0.25 - 4	99.8, 99.8, 100
clarithromycin	>32	>32	0.06 - >32	26.2
clindamycin ^c	≤0.12	>8	≤0.12 - >8	73.9
dalbavancin (713)	0.06	0.12	≤0.03 - 1	99.6
daptomycin	0.25	0.5	0.12 - 4	99.7
doxycycline	≤0.12	0.25	≤0.12 - 16	97.9
linezolid	2	4	0.5 - > 16	99.9
trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 - >8	97.3
vancomycin	1	1	0.25 - 4	99.8
<i>S. epidermidis</i> (539)				
ceftobiprole ^b	0.5	1	≤0.06 - 8	NA, NA, NA
clarithromycin	16	>32	≤0.03 - >32	37.8
clindamycin ^c	≤0.12	>8	≤0.12 - >8	66.6
dalbavancin (395)	≤0.03	0.06	≤0.03 - 1	NA
daptomycin	0.25	0.5	≤0.03 - 2	99.6
doxycycline	0.5	2	≤0.12 - >32	94.2
linezolid	1	2	≤0.12 - >4	100
trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12 - >8	66.4
vancomycin	1	2	≤0.12 - 4	100
<i>S. pneumoniae</i> , penicillin-susceptible (647)				
ceftobiprole ^b	≤0.03	≤0.03	≤0.03 - 0.06	100, 100, 100
penicillin	≤0.03	≤0.03	≤0.03 - 0.06	100
ceftriaxone	≤0.12	≤0.12	≤0.12 - 0.5	100
clarithromycin	≤0.03	2	≤0.03 - >32	84.1
clindamycin	≤0.12	≤0.12	≤0.12 - >64	97.8
dalbavancin (115)	≤0.03	≤0.03	≤0.03 - 0.06	NA
doxycycline	≤0.25	≤0.25	≤0.25 - 16	94
levofloxacin	1	1	≤0.06 - 2	100
linezolid	1	2	≤0.12 - 4	99.8
trimethoprim-sulfamethoxazole	0.25	0.5	≤0.12 - >8	90.4
vancomycin	0.25	0.5	≤0.12 - 1	100
<i>S. pneumoniae</i> , penicillin-intermediate (97)				
ceftobiprole ^b	≤0.03	0.25	≤0.03 - 0.5	100, 100, 100
penicillin	0.12	1	0.12 - 1	0
ceftriaxone	≤0.12	0.5	≤0.12 - 0.5	100

Table 1 (continued)

Organism (no. tested) ^a / antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
clarithromycin	1	>32	≤0.03 - >32	41.2
clindamycin	≤0.12	>64	≤0.12 - >64	67
dalbavancin (25)	≤0.03	≤0.03	≤0.03 - ≤0.03	NA
doxycycline	0.5	16	≤0.25 - >16	49.5
levofloxacin	1	1	0.5 - 16	99
linezolid	1	2	0.25 - 2	100
trimethoprim-sulfamethoxazole	0.25	8	≤0.12 - >8	67
vancomycin	0.25	0.25	≤0.12 - 0.5	100
<i>S. pneumoniae</i> , penicillin-resistant (40)				
ceftobiprole ^b	0.5	0.5	0.12 - 0.5	100, 100, 100
penicillin	2	4	2 - 8	0
ceftriaxone	1	1	0.25 - 4	92.5
clarithromycin	8	>32	≤0.03 - >32	15
clindamycin	>64	>64	≤0.12 - >64	42.5
dalbavancin (4)	≤0.03	≤0.03	≤0.03 - ≤0.03	NA
doxycycline	4	16	≤0.25 - 16	22.5
levofloxacin	1	1	0.25 - 2	100
linezolid	1	2	0.25 - 2	100
trimethoprim-sulfamethoxazole	8	>8	≤0.12 - >8	42.5
vancomycin	0.25	0.5	0.25 - 0.5	100
<i>S. pyogenes</i> (318)				
ceftobiprole ^b	≤0.03	≤0.03	≤0.03 - 0.5	100, NA, NA
clarithromycin	≤0.03	1	≤0.03 - >32	87.7
clindamycin ^c	≤0.12	≤0.12	≤0.12 - >64	95.9
dalbavancin (53)	≤0.03	≤0.03	≤0.03 - ≤0.03	100
daptomycin (179)	0.06	0.12	≤0.03 - 0.25	100
doxycycline	≤0.25	8	≤0.25 - >16	NA
levofloxacin	0.5	1	0.12 - 16	99.7
linezolid	1	2	≤0.12 - 4	98.4
vancomycin	0.25	0.5	≤0.12 - 1	100
<i>S. agalactiae</i> (370)				
ceftobiprole ^b	≤0.03	≤0.03	≤0.03 - 0.06	NA, NA, NA
clarithromycin	≤0.03	>32	≤0.03 - >32	57.8
clindamycin ^c	≤0.12	>64	≤0.12 - >64	75.9
dalbavancin (59)	≤0.03	≤0.03	≤0.03 - ≤0.03	100
daptomycin (200)	0.25	0.25	0.06 - 1	100
doxycycline	8	16	≤0.25 - >16	NA
levofloxacin	1	1	≤0.06 - >32	95.9
linezolid	1	2	≤0.12 - 4	96.5
vancomycin	0.5	0.5	≤0.12 - 1	100
<i>E. faecalis</i> (683)				
ceftobiprole ^b	0.5	1	≤0.06 - >32	NA, NA, NA
dalbavancin (473)	0.06	0.12	≤0.03 - 0.25	100
daptomycin	1	2	≤0.03 - 4	98.1
doxycycline	8	16	≤0.12 - 32	33.2
linezolid	2	4	0.25 - 4	87.1
vancomycin	1	2	0.5 - 4	100
<i>E. faecium</i> (356)				

(continued on next page)

Table 1 (continued)

Organism (no. tested) ^a / antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
ceftobiprole ^b	>32	>32	0.5 - >32	NA, NA, NA
dalbavancin (252)	0.12	>16	≤0.03 - >16	NA
daptomycin	2	2	≤0.03 - >16	NA
doxycycline	8	16	≤0.12 - >16	48.9
linezolid	2	4	0.5 - >16	88.2
vancomycin	0.5	>32	≤0.12 - >32	73.0

^a Each antimicrobial agent was tested against all isolates except where indicated by a lesser number in brackets following an individual antimicrobial agent.

^b Percent susceptible values for ceftobiprole are shown using FDA, EUCAST, and Health Canada MIC breakpoints, where available.

^c Testing for inducible clindamycin resistance was not performed.

%, respectively, using the FDA and EUCAST MIC breakpoint.

MIC breakpoints for ceftobiprole tested against *P. aeruginosa* are not currently published, however, of note, the MIC₅₀ and MIC₉₀ for ceftobiprole against *P. aeruginosa* were the same as determined for cefepime (4 and 16 µg/ml, respectively). Ceftobiprole was inactive against *Stenotrophomonas maltophilia* but did demonstrate more potent activity than ceftriaxone and cefepime, and similar activity to meropenem (ceftobiprole MIC₅₀ 0.5 µg/ml and MIC₉₀ 4 µg/ml), for *Acinetobacter baumannii*.

4. Discussion

We observed that the *in vitro* activity of ceftobiprole against MRSA was similar (> 99 % susceptible) to dalbavancin, daptomycin, linezolid, and vancomycin and slightly better (a 2-3 % higher percent susceptible value) than doxycycline and trimethoprim-sulfamethoxazole (Table 1). Our results are consistent with earlier publications that reviewed ceftobiprole activity [14–17]. Canton et al., tested 3,502 MRSA isolates from 17 European countries and reported that 99.5 % were ceftobiprole-susceptible (MIC ≤ 2 µg/ml) [14]. In 2019, Pfaller et al., published that 99.3 % of 1,260 MRSA isolates from the United States were ceftobiprole-susceptible (MIC ≤ 2 µg/ml) [15]. Another, more recent study from the United States published in 2025 by Sader et al., reported that 99.3 % of 9,184 MRSA isolates were susceptible to ceftobiprole [16]. An earlier study by the same research group reported that 97.2 % of globally-collected MRSA isolates with reduced susceptibility to daptomycin, linezolid or vancomycin were susceptible to ceftobiprole [17].

All isolates of *S. pneumoniae* tested in the current study, including those resistant to penicillin, were susceptible to ceftobiprole (Table 1). High *in vitro* percent susceptible values for ceftobiprole tested against clinical isolates of *S. pneumoniae* have also been reported by Canton et al. (97.8 % of 3,007 isolates tested ceftobiprole susceptible) and Pfaller et al. (99.7 % of 698 isolates tested ceftobiprole susceptible) [14,15].

Our study also confirmed that the *in vitro* activity of ceftobiprole is comparable to cefepime and ceftriaxone against ESBL-negative *E. coli* and *K. pneumoniae*, that it possesses limited activity against AmpC-producing *E. coli*, and that it is inactive against ESBL-positive *E. coli* and *K. pneumoniae*, as per previous studies [18]. Cefepime (91.9 % susceptible) was superior to ceftobiprole for AmpC positive *E. coli* isolates (Table 2).

No breakpoints have been established for ceftobiprole use against *P. aeruginosa*, however, our study did show that it had similar MICs to cefepime (77.9 % susceptible). Further clinical data are required to determine whether ceftobiprole may have a role in the treatment of infections caused by *P. aeruginosa*.

Table 2

In vitro activity of ceftobiprole and comparator agents against 12,147 aerobic Gram-negative bacilli isolated from patients in Canadian hospitals from 2015 to 2023.

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
<i>E. coli</i> (4,714)				
ceftobiprole ^a	≤0.06	>32	≤0.06 - >32	85.4, 85.4, 86.4
ceftriaxone	≤0.25	>64	≤0.25 - >64	84.7
ceftazidime	≤0.25	16	≤0.25 - >32	87.4
cefepime	≤0.25	4	≤0.25 - >64	88.7
ceftolozane-tazobactam	0.25	0.5	≤0.12 - >64	98.9
amoxicillin-clavulanate	8	32	0.5 - >32	69.5
piperacillin-tazobactam	2	4	≤1 - >512	94.3
meropenem	≤0.03	≤0.03	≤0.03 - >32	99.9
ciprofloxacin	≤0.06	>16	≤0.06 - >16	72.4
tobramycin	≤0.5	4	≤0.5 - >64	88.1
trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 - >8	72.2
<i>E. coli</i> , ESBL-negative (4,109)				
ceftobiprole ^a	≤0.06	≤0.06	≤0.06 - >32	97.9, 97.9, 98.9
ceftriaxone	≤0.25	≤0.25	≤0.25 - >64	97.2
ceftazidime	≤0.25	0.5	≤0.25 - >32	97.2
cefepime	≤0.25	≤0.25	≤0.25 - >64	99.3
ceftolozane-tazobactam	0.25	0.5	≤0.12 - >64	99.4
amoxicillin-clavulanate	8	>32	0.5 - >32	73.9
piperacillin-tazobactam	2	4	≤1 - >512	96.0
meropenem	≤0.03	≤0.03	≤0.03 - >32	99.9
ciprofloxacin	≤0.06	>16	≤0.06 - >16	81
tobramycin	≤0.5	2	≤0.5 - >64	92.5
trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12 - >8	77.7
<i>E. coli</i> , ESBL-positive (604)				
ceftobiprole ^a	>32	>32	0.25 - >32	0.7, 0.7, 1.8
ceftriaxone	>64	>64	1 - >64	0.3
ceftazidime	32	>32	0.5 - >32	20.5
cefepime	16	>64	≤0.25 - >64	16.2
ceftolozane-tazobactam	0.5	1	≤0.12 - >64	95.7
amoxicillin-clavulanate	16	32	2 - >32	38.8
piperacillin-tazobactam	2	16	≤1 - >512	83.3
meropenem	≤0.03	0.06	≤0.03 - >32	99.3
ciprofloxacin	>16	>16	≤0.06 - >16	14.4
tobramycin	1	32	≤0.5 - >64	58.1
trimethoprim-sulfamethoxazole	>8	>8	≤0.12 - >8	35.3
<i>E. coli</i> , AmpC-positive (135)				
ceftobiprole ^a	0.12	8	≤0.06 - >32	66.7, 66.7, 85.2
ceftriaxone	8	>64	≤0.25 - >64	40.7

(continued on next page)

Table 2 (continued)

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
ceftazidime	16	>32	≤0.25 - >32	32.6
cefepime	≤0.25	2	≤0.25 - >64	91.9
ceftolozane-tazobactam	0.5	4	≤0.12 - >64	87.4
amoxicillin-clavulanate	>32	>32	2 - >32	8.4
piperacillin-tazobactam	8	128	≤1 - >512	73.3
meropenem	≤0.03	0.12	≤0.03 - >32	97.8
ciprofloxacin	0.12	>16	≤0.06 - >16	60.7
tobramycin	1	4	≤0.5 - >64	85.9
trimethoprim- sulfamethoxazole	≤0.12	>8	≤0.12 - >8	65.9
<i>K. pneumoniae</i> (1,731) ceftobiprole ^a	≤0.06	0.5	≤0.06 - >32	89.5, 89.5, 90.6
ceftriaxone	≤0.25	1	≤0.25 - >64	90.3
ceftazidime	≤0.25	2	≤0.25 - >32	91.1
cefepime	≤0.25	0.5	≤0.25 - >64	91.5
ceftolozane-tazobactam	0.25	1	≤0.12 - >64	96.9
amoxicillin-clavulanate	4	16	≤0.06 - >32	87.0
piperacillin-tazobactam	4	8	≤1 - >512	90.9
meropenem	≤0.03	0.06	≤0.03 - >32	99.2
ciprofloxacin	≤0.06	1	≤0.06 - >16	86.2
tobramycin	≤0.5	1	≤0.5 - > 64	93.3
trimethoprim- sulfamethoxazole (1,730)	≤0.12	>8	≤0.12 - >8	86.8
<i>K. pneumoniae</i> , ESBL-negative (1,590) ceftobiprole ^a	≤0.06	≤0.06	≤0.06 - >32	97.4, 97.4, 98.5
ceftriaxone	≤0.25	≤0.25	≤0.25 - >64	98.1
ceftazidime	≤0.25	1	≤0.25 - >32	98.1
cefepime	≤0.25	≤0.25	≤0.25 - >64	99.0
ceftolozane-tazobactam	0.25	1	≤0.12 - >64	98.9
amoxicillin-clavulanate	4	8	≤0.06 - >32	93.2
piperacillin-tazobactam	2	8	≤1 - >512	94.3
meropenem	≤0.03	0.06	≤0.03 - >32	99.6
ciprofloxacin	≤0.06	0.25	≤0.06 - >16	92.7
tobramycin	≤0.5	≤0.5	≤0.5 - >64	98.4
trimethoprim- sulfamethoxazole (1,589)	≤0.12	0.5	≤0.12 - >8	93.4
<i>K. pneumoniae</i> , ESBL-positive (141) ceftobiprole ^a	>32	>32	0.12 - >32	0.7, 0.7, 2.1
ceftriaxone	>64	>64	≤0.25 - >64	2.1
ceftazidime	>32	>32	1 - >32	12.1
cefepime	>64	>64	≤0.25 - >64	6.4

Table 2 (continued)

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
ceftolozane-tazobactam	1	32	0.25 - >64	73.8
amoxicillin-clavulanate	16	>32	4 - >32	18.0
piperacillin-tazobactam	8	>512	≤1 - >512	52.5
meropenem	0.06	0.12	≤0.03 - >32	94.3
ciprofloxacin	4	>16	≤0.06 - >16	12.8
tobramycin	8	32	≤0.5 - > 64	34.8
trimethoprim- sulfamethoxazole	>8	>8	≤0.12 - >8	12.1
<i>K. oxytoca</i> (492) ceftobiprole ^a	0.25	>32	≤0.06 - >32	55.7, 55.7, 83.5
ceftriaxone	≤0.25	8	≤0.25 - >64	88.4
ceftazidime	≤0.25	1	≤0.25 - >32	96.5
cefepime	≤0.25	0.5	≤0.25 - >64	96.1
ceftolozane-tazobactam	0.25	1	≤0.12 - 64	97.8
amoxicillin-clavulanate	4	16	0.5 - >32	86.6
piperacillin-tazobactam	2	32	≤1 - >512	89.0
meropenem	≤0.03	0.06	≤0.03 - 2	99.8
ciprofloxacin	≤0.06	≤0.06	≤0.06 - >16	96.5
tobramycin	≤0.5	1	≤0.5 - 64	96.1
trimethoprim- sulfamethoxazole	≤0.12	0.25	≤0.12 - >8	93.7
<i>E. cloacae</i> (777) ceftobiprole ^a	≤0.06	4	≤0.06 - >32	78.2, 78.2, 83.8
ceftriaxone	≤0.25	>64	≤0.25 - >64	69.0
ceftazidime	0.5	>32	≤0.25 - >32	73.1
cefepime	≤0.25	2	≤0.25 - >64	90.5
ceftolozane-tazobactam	0.5	8	≤0.12 - 64	81.1
piperacillin-tazobactam	2	128	≤1 - >512	76.6
meropenem	0.06	0.12	≤0.03 - 32	99.4
ciprofloxacin	≤0.06	0.12	≤0.06 - >16	93.6
tobramycin	≤0.5	1	≤0.5 - >64	96.1
trimethoprim- sulfamethoxazole	≤0.12	0.5	≤0.12 - >8	91.8
<i>P. mirabilis</i> (401) ceftobiprole ^a	≤0.06	≤0.06	≤0.06 - >32	97.8, 97.8, NA
ceftriaxone	≤0.25	≤0.25	≤0.25 - >64	97.3
ceftazidime	≤0.25	≤0.25	≤0.25 - >32	98.3
cefepime	≤0.25	≤0.25	≤0.25 - >64	98.5
ceftolozane-tazobactam	0.5	1	0.25 - 8	98.8
amoxicillin-clavulanate	1	8	0.5 - >32	85.5
piperacillin-tazobactam	≤1	≤1	≤1 - >512	99.3
meropenem	0.12	0.25	≤0.03 - 1	100
ciprofloxacin	≤0.06	2	≤0.06 - >16	82.5
tobramycin	1	2	≤0.5 - >64	91.8

(continued on next page)

Table 2 (continued)

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml)			MIC interpretation % Susceptible
	MIC ₅₀	MIC ₉₀	MIC range	
trimethoprim- sulfamethoxazole	≤0.12	>8	≤0.12 - >8	80.8
<i>S. marcescens</i> (449) ceftobiprole ^a	0.12	0.5	≤0.06 - >32	89.3, 89.3, NA
ceftriaxone	≤0.25	2	≤0.25 - >64	89.3
ceftazidime	0.5	1	≤0.25 - >32	97.6
cefepime	≤0.25	0.5	≤0.25 - >64	98.2
ceftolozane/tazobactam	1	2	0.25 - 64	94.9
piperacillin/tazobactam	2	8	≤1 - 128	94.4
meropenem	0.06	0.12	≤0.03 - >4	99.6
ciprofloxacin	≤0.06	1	≤0.06 - >16	84.2
tobramycin	2	4	≤0.5 - >64	74.6
trimethoprim- sulfamethoxazole	0.25	1	≤0.12 - >8	96.4
<i>P. aeruginosa</i> (2,784) ceftobiprole ^a	4	16	≤0.06 - >32	NA, NA, NA
aztreonam (1464)	8	32	≤0.12 - >64	69.0
ceftazidime	4	>32	≤0.25 - >32	72.3
cefepime	4	16	≤0.25 - >64	77.9
ceftolozane-tazobactam	1	4	≤0.12 - >64	94.7
piperacillin-tazobactam	8	128	≤1 - >512	75.0
meropenem	1	16	≤0.03 - >32	74.2
ciprofloxacin	0.25	4	≤0.06 - >16	73.6
tobramycin	≤0.5	2	≤0.5 - >64	85.6
<i>S. maltophilia</i> (670) ceftobiprole ^a	>32	>32	≤0.06 - >32	NA, NA, NA
cefepime	64	>64	≤0.25 - >64	NA
ciprofloxacin	4	16	0.12 - >16	NA
trimethoprim- sulfamethoxazole	0.25	1	≤0.12 - >8	97.2
<i>A. baumannii</i> (129) ceftobiprole ^a	0.5	4	≤0.06 - >32	NA, NA, NA
ceftriaxone	16	64	≤0.25 - >64	37.2
ceftazidime	8	16	0.5 - > 32	75.2
cefepime	4	16	≤0.25 - >64	82.2
ceftolozane-tazobactam	1	8	≤0.12 - >64	NA
piperacillin-tazobactam	8	128	≤1 - >512	74.4
meropenem	0.5	2	≤0.03 - 32	94.6
ciprofloxacin	0.25	0.5	≤0.06 - >16	93.0
tobramycin	≤0.5	1	≤0.5 - >64	95.3

^a Percent susceptible values for ceftobiprole are shown using FDA, EUCAST, and Health Canada MIC breakpoints, where available.

Our data, and reports from other investigators, support the clinical utility of ceftobiprole in treating patients with MRSA infections; pneumococcal infections, including penicillin-resistant *S. pneumoniae* infection concurrently not susceptible to ceftriaxone (7.5 % of penicillin-resistant isolates in the current study; Table 1); polymicrobial infections involving MRSA and *S. pneumoniae* where monotherapy with ceftobiprole would suffice; or for patients with contraindications for alternate antimicrobial agents. Ceftobiprole's broad-spectrum activity may enable use as monotherapy [19,20]. It presents a good safety profile and is usually well tolerated compared to other cephalosporins, linezolid, and vancomycin. Ceftobiprole has been associated with higher rates of nausea and emesis in comparison with daptomycin and ceftriaxone, but those effects were usually mild [8,21]. Serious adverse effects are less common [8]. While cephalosporin use can result in patients developing *Clostridioides difficile* infection, ceftobiprole may be associated with a relatively lower risk due to its primary renal excretion, low interference with the intestinal microbiota and its direct activity against *Clostridioides* and *Clostridium* species [22].

The clinical efficacy of ceftobiprole has been reported for common infections [21]. As previously mentioned, the FDA has recently approved the use of ceftobiprole for three main indications: Adults with *S. aureus* bloodstream infections, including right-sided infective endocarditis, adults with acute bacterial skin and skin structure infections and adults and children with a bacterial community-acquired pneumonia [6]. The FDA based their approval on three different studies: ERADICATE, TARGET and an additional randomized controlled trial by Nicholson et al [23]. ERADICATE demonstrated that ceftobiprole was non-inferior to daptomycin in the treatment of adults with *S. aureus* bloodstream infections, including right-sided infective endocarditis in terms of clinical success, mortality and microbiologic eradication [24]. Clinical and microbiological success of ceftobiprole in the treatment of acute bacterial skin and skin structure infections was non-inferior to vancomycin combined with aztreonam in the TARGET study [25]. Similarly, a randomized trial performed by Noel et al. found that clinical cure and microbiologic eradication rates for ceftobiprole were comparable to vancomycin combined with ceftazidime in the treatment of a broad range of complicated skin and skin structure infections [26]. Nicholson et al. evaluated the efficacy of ceftobiprole in comparison with ceftriaxone (with or without linezolid) in a randomized, double-blind trial of adult patients with community-acquired bacterial pneumonia (CABP) [27]. Clinical and microbiological outcomes were comparable between the two treatment arms [27]. In Canada, the CLEAR registry found that ceftobiprole was primarily used against MRSA, and most commonly in the context of endocarditis, bone and joint infections and hospital-acquired bacterial pneumonia (HABP), where most cases had a concomitant bacteremia [4]. Recent data concluded that ceftobiprole is a good option for empiric treatment of CABP and HABP due in part to its broad spectrum activity against common pneumonia pathogens and even polymicrobial pneumonia but cautioned that in patients at high risk of ESBL-producing organisms or MDR *Pseudomonas aeruginosa* infections, that combination therapy is recommended [28,29].

There are several important limitations to the data presented here that deserve attention. The clinical significance of isolates included in the CANWARD study is determined by protocols in place at the submitting laboratories. It is possible that some of the isolates were actually contaminants rather than true pathogens. Due to space limitations on the broth microdilution panels, some clinically relevant antimicrobials were not tested versus certain species (e.g., ampicillin was not evaluated versus *E. faecalis* isolates). Finally, the ceftobiprole susceptibility data presented here for some species may not be applicable to countries that have a higher prevalence of certain antimicrobial-resistant pathogens (e.g., carbapenemase-producing *Enterobacterales*) than what is seen in Canada [4].

5. Conclusions

We conclude that ceftobiprole demonstrates potent *in vitro* activity against MSSA, MRSA, *S. pneumoniae*, *S. pyogenes*, ESBL-negative *E. coli* and *K. pneumoniae*, and *P. mirabilis* isolated from clinical specimens of patients seeking care at Canadian tertiary-care hospitals. Data from this very large study testing ceftobiprole against 20,255 isolates, supports ceftobiprole usage in patients with indicated infections with these bacterial pathogens susceptible to ceftobiprole [4,14–17].

Funding

No funding was received in association with the writing of this manuscript. The CANWARD study was supported in part by the University of Manitoba, Shared Health, the National Microbiology Laboratory, Avir, Merck, Paladin Labs.

CRediT authorship contribution statement

Élodie Gemme: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Andrew Walkty:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Melanie Baxter:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Heather J. Adam:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Philippe Lagacé-Wiens:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Karl Weiss:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **James A. Karlowsky:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **George G. Zhanel:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influence on the work reported in this paper

Acknowledgements

The authors thank the participating sites in the CANWARD surveillance study.

References

- [1] Zhanel GG, Lam A, Schweizer F, Thomson K, Walkty A, Rubinstein E, et al. Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol* 2008;9:245–54. <https://doi.org/10.2165/00128071-200809040-00004>.
- [2] Azanza Perea JR, Sádaba Díaz de Rada B. Ceftobiprole: pharmacokinetics and PK/PD profile. *Rev Esp Quimioter* 2019;32(Suppl 3):11–6.
- [3] Merck manual professional version. Cephalosporins; 2024. <https://www.merckmanuals.com/professional/infectious-diseases/bacteria-and-antibacterial-medications/cephalosporins?query=ceftobiprole>. revised May.
- [4] Zhanel GG, Kosar J, Baxter M, Dhani R, Borgia S, Irfan N, et al. How is ceftobiprole used in Canada: the CLEAR study final results. *Expert Rev Anti Infect Ther* 2024;22(8):681–8. <https://doi.org/10.1080/14787210.2024.2374280>. Aug.
- [5] Government of Canada. Drug and health product portal, regulatory decision summary for Zevtera. 2024. <https://dhpp.hpfb-dgpsa.ca/review-documents/resourcel/RDS00063>. revised November 28.
- [6] U.S. Food & Drug Administration. FDA approves new antibiotic for three different uses. 2024. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-three-different-uses>. revised April 03.
- [7] Public Health Agency of Canada. Canadian antimicrobial resistance surveillance system report. 2022. April 04, <https://www.canada.ca/en/public-health/service/s/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-report-2021.html>.
- [8] Grau S. Safety and tolerability of ceftobiprole. *Rev Esp Quimioter* 2019;32(Suppl 3):34–6.
- [9] Clinical and Laboratory Standards Institute. CLSI M07 methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 12th ed. 2024. <https://www.clsi.org/standards/products/microbiology/documents/m07/>. March 19.
- [10] Clinical and Laboratory Standards Institute. CLSI 100, performance standards for antimicrobial susceptibility testing. 34th ed. 2024. <https://www.clsi.org/standards/products/microbiology/documents/m100/>.
- [11] U.S. Food & Drug Administration. Antibacterial susceptibility test interpretative criteria. 2025. <https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretative-criteria>. February 12.
- [12] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, Version 15.0. 2025. <http://www.eucast.org>.
- [13] ZEVTERA (ceftobiprole medocaryl). Product monograph. 2017. https://pdf.hres.ca/dpd_pm/00041903.PDF. October 20.
- [14] Canton R, Hamed K, Wiktorowicz T, Redder N, Jemmely N, Quevedo J, et al. *In vitro* activity of ceftobiprole and comparator antibiotics against contemporary European isolates (2016–19). *JAC Antimicrob Resist* 2022;4:dlac030. <https://doi.org/10.1093/jacamr/dlac030>.
- [15] Pfaller MA, Flamm RK, Mendes RE, Streit JM, Smart JI, Hamed KA, et al. Ceftobiprole activity against Gram-positive and -negative pathogens collected from the United States in 2006 and 2016. *Antimicrob Agents Chemother* 2018;63:e01566. <https://doi.org/10.1128/AAC.01566-18>.
- [16] Sader HS, Smart JI, Mendes RE, Castanheira M. Ceftobiprole activity against multidrug-resistant *Staphylococcus aureus* clinical isolates collected in the United States from 2016 through 2022. *Antimicrob Agents Chemother* 2025;69(2):e0140224. <https://doi.org/10.1128/aac.01402-24>. Feb 13Epub 2025 Jan 13. PMID: 39804046; PMCID: PMC11823664.
- [17] Farrell DJ, Flamm RK, Sader HS, Jones RN. Activity of ceftobiprole against methicillin-resistant *Staphylococcus aureus* strains with reduced susceptibility to daptomycin, linezolid or vancomycin, and strains with defined SCCmec types. *Int J Antimicrob Agents* 2014;43(4):323–7. <https://doi.org/10.1016/j.ijantimicag.2013.11.005>. AprEpub 2013 Dec 11. PMID: 24411474.
- [18] Flamm RK, Duncan LR, Hamed KA, Smart JI, Mendes RE, Pfaller MA. Ceftobiprole activity against bacteria from skin and skin structure infections in the United States from 2016 through 2018. *Antimicrob Agents Chemother* 2020;64:e02566. <https://doi.org/10.1128/AAC.02566-19>. -19.
- [19] Anderson SD, Gums JG. Ceftobiprole: an extended-spectrum anti-methicillin-resistant *Staphylococcus aureus* cephalosporin. *Ann Pharmacother* 2008;42:806–16. <https://doi.org/10.1345/aph.1L016>.
- [20] Duployez C, Wallet F, Migaud H, Senneville E, Loiez C. Ceftobiprole: a potential empirical post-operative monotherapy in prosthetic joint infections. *Ann Clin Microbiol Antimicrob* 2020;19:9. <https://doi.org/10.1186/s12941-020-00351-5>.
- [21] Zimmerman J, Giuliano C, Kale-Pradhan PB. Ceftobiprole medocaryl: a new fifth-generation cephalosporin. *Ann Pharmacother* 2024. <https://doi.org/10.1177/10600280241293773>. Dec 710600280241293773.
- [22] Nerandzic MM, Donskey CJ. Effect of ceftobiprole treatment on growth of and toxin production by *Clostridium difficile* in cecal contents of mice. *Antimicrob Agents Chemother* 2011;55:2174–7. <https://doi.org/10.1128/AAC.01612-10>.
- [23] Medical professionals reference. FDA Approves Antibiotic Zevtera to Treat Multiple Serious Infections. 2024. <https://www.empr.com/home/news/fda-approves-antibiotic-zevtera-to-treat-multiple-serious-infections/>. April 4.
- [24] Holland TL, Cosgrove SE, Doernberg SB, Jenkins TC, Turner NA, Boucher HW, et al. Ceftobiprole for treatment of complicated *Staphylococcus aureus* bacteremia. *N Engl J Med* 2023;389:1390–401. <https://doi.org/10.1056/NEJMoa2300220>.
- [25] Overcash JS, Kim C, Keech R, Gumenchuk I, Ninov B, Gonzalez-Rojas Y, et al. Ceftobiprole compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections: results of a phase 3, randomized, double-blind trial (TARGET). *Clin Infect Dis* 2021;73:e1507–17. <https://doi.org/10.1093/cid/ciaa974>.
- [26] Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaryl with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin Infect Dis* 2008;46:647–55. <https://doi.org/10.1086/526527>.
- [27] Nicholson SC, Welte T, Jr File TM, Strauss RS, Michiels B, Kaul P, et al. A randomised, double-blind trial comparing ceftobiprole medocaryl with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. *Int J Antimicrob Agents* 2012;39:240–6. <https://doi.org/10.1016/j.ijantimicag.2011.11.005>.
- [28] Gentile I, Giuliano S, Corcione S, De Rosa GF, Falcone M, Giacobbe DR, et al. Current role of ceftobiprole in the treatment of hospital-acquired and community-acquired pneumonia: expert opinion based on literature and real-life experiences. *Expert Rev Anti Infect Ther* 2025;5:1–9. <https://doi.org/10.1080/14787210.2025.2461552>. Feb.
- [29] Corcione S, De Benedetto I, Carlin M, Pivetta EE, Scabini S, Grosso C, et al. Real-world experience of ceftobiprole for community- and hospital-acquired pneumonia from a stewardship perspective. *Microorganisms* 2024;12:725. <https://doi.org/10.3390/microorganisms12040725>.