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Abstract: Background: Ceftobiprole is a fifth-generation cephalosporin that has been approved in Europe solely for the treatment of community-acquired and nosocomial pneumonia. The objective was to analyze the use of ceftobiprole medocaril (Cefto-M) in Spanish clinical practice in patients with infection in hospital or outpatient parenteral antimicrobial therapy (OPAT). Methods: This retrospective, observational, multicenter study included patients treated from September 1, 2021 to December 31, 2022. Results: 249 individuals were enrolled, aged 66.6±15.4 years, 59.4% male, with Charlson index of 4 (IQR 2-6); 13.7% had COVID-19, and 4.8% were in intensive care unit (ICU). The most frequent type of infection was respiratory (55.8%), followed by skin and soft tissue infection (21.7%). Cefto-M was administered to 67.9% as empirical treatment, being in monotherapy for 7 days (5-10) in 53.8% of cases. The infection-related mortality was 11.2%.The highest mortality rates were for ventilator-associated pneumonia [40%], and infections due to methicillin-resistant *S. aureus* (20.8%) and *Pseudomonas aeruginosa* (16.1%). Mortality-related factors were age (OR: 1.1, 95%CI [1.04-1.16]), ICU admission (OR:42.02, 95%CI[4.49-393.4]), and sepsis/septic shock (OR:2.94, 95%CI [1.01-8.54]).Conclusions: In real life, Cefto-M is a safe antibiotic, with only half of prescriptions in respiratory infections, mainly administered as rescue therapy in pluripathological patients with severe infectious diseases.

Keywords: ceftobiprole; sepsis; older; Real-World Data; OPAT

1. Introduction

There has been a disturbing increase in multi-resistant microorganisms worldwide over the past decade (1), presenting clinicians with major diagnostic and therapeutic challenges. This phenomenon has been associated with a rise in the failure of empirical antibiotic therapies (2) and in the delay

before administration of an effective drug (3), increasing mortality rates (4). The rate of carbapenemase-resistant *Pseudomonas* spp. is currently >20% in Spain (1), mainly due to efflux pumps and porin losses. Lower mortality rates have been obtained with meropenem than with piperacillin/tazobactam in patients with ceftriaxone-resistant *E coli* or Klebsiella pneumoniae bloodstream infection (5). This has fostered the administration of bactericide antibiotics other than piperacillin/tazobactam to treat Gram-negative bacteria such as *P. aeruginosa*, including ceftobiprole.Ceftobiprole medocaril (Cefto-M) is a broad-spectrum, fifth-generation cephalosporin against Gram-negative cocci and bacilli, ranging from methicillin-resistant *S. aureus* (MRSA) to ampicillin-susceptible *Enterococcus faecalis* and *faecium* and *P. aeruginosa*, and it is not affected by efflux pumps or porin losses (6). It has a spectrum of potential interest for the treatment of catheter-related bacteremia, endocarditis, or complicated urine infections. In an experimental study, the bactericide capacity of Cefto-M in biofilm was higher than that of linezolid, vancomycin, or daptomycin in infections caused by MRSA, methicillin-susceptible *S. aureus* (MSSA), or coagulase-negative *staphylococci* (CNS) (7). It may therefore be useful to treat infections related to devices (intracardiac, cranial leads, etc.), prosthetic valves, endoprostheses, or osteosynthesis material. It has demonstrated a similar effectiveness to that of other antibiotics in skin and soft-tissue infections (8). Nevertheless, it has only been approved in Europe for the treatment of community-acquired (CAP) and nosocomial (NP) pneumoniae, excluding ventilator-associated pneumonia (VAP).

Clinical trials are the gold standard for approving novel pharmaceutical products or therapies but can differ from actual clinical experience due to their strict eligibility criteria and optimal conditions. Real World Data can help to bridge this gap, thereby supporting and accelerating the incorporation of effective new therapies and technologies into routine clinical practice (9). With this background, this real-life study in Spain was designed to examine the routine administration of Cefto-M to patients with any type of infection in hospital or receiving outpatient parenteral antimicrobial therapy (OPAT), considering health and safety outcomes and mortality-related factors.

2. Results

2.1. Cohort description.

The study included 249 individuals with a mean age of 66.6±15.4 years; 59.4% were male and 92.8% Caucasian, with a mean age-adjusted Charlson index of 4 (IQR 2-6); 49.4% had cardiovascular risk factors, mainly cardiovascular disease (31.3%), arterial hypertension (29.3%), and diabetes mellitus (28.1%); 20.9% were immunosuppressed, 14.1% had chronic kidney failure, and 11.6% chronic obstructive pulmonary disease (COPD) (also see table 1). Infection origin was nosocomial/healthcare-related in 57% of patients. Cefto-M was administered in-hospital in 95.6% of patients (medical department in 80.4%) and as outpatient parenteral antimicrobial therapy in 4.4%. Sepsis was present in 26.5%, septic shock in 4.4%, and concomitant COVID-19 infection in 13.7%. The median number of foci was 1 (IQR: 1-1). The type of infection was respiratory in 55.8% (CAP in 24.1%, NP in 24.9%, and VAP in 2%); skin and soft-tissue infection (SSTI) in 21.7%; and bacteremia in 17.7% (catheter-related in 2.8% and no focus in 14.9%) (also see Table 1)

2.2. Microbiological isolation

Microbiological isolates were obtained from 138 patients (55.4%) and were polymicrobial in 56 (40.6%). Among the isolates, 87 (35.3%) were Gram-positive cocci (GPC), 20 (22.9%) of which were coagulase-negative staphylococci (CoNS), including 13 (65%) that were methicillin-resistant; 46 (18.4%) *S. aureus*, including 21 (45.6%) methicillin-susceptible *S. aureus* (MSSA) and 24 (52.3%) methicillin-resistant *S. aureus* (MRSA) isolates; 9 (10.3%) were Enterococcus spp., including 8 (88.9%) *E. faecalis* and 1 (11.1%) ampicillin-susceptible *E. faecium* isolates; 10 (11.5%) were *Streptococcus* spp., including 5 (50%) *S. pneumoniae* and 5 (50%) *streptococci* of other species; 48 were Gram-negative bacilli (GNB), including 13 (26.5%) multi-susceptible *Enterobacteriaceae*, 31 (64.7%) nonfermenting GNB (100% *P. aeruginosa*), and 5 (10.2%) GNB of other species (*Hemophilus influenzae* [2], *Morganella* spp. [2], and *Moraxella* spp. [1]). Supplementary Table 1 lists the other variables.

All isolated microorganisms treated with Cefto-M were susceptible to this drug (3 MRSA, 3 MSSA, 1 enterococcus, 1 streptococcus, and 10 GNB, including 4 *P. aeruginosa*). Among GPC, 97.2% (n=35) were susceptible to vancomycin (100% of MRSA, 93.3% of MSSA, and 100% of both enterococci and streptococci). In terms of GNB susceptibility, 83.3% of *P. aeruginosa* isolates were susceptible to meropenem, 40% to cefepime, and 70% to piperacillin/tazobactam (Table 2).

2.3. Outcomes

The median (IQR) stay was 20 (13-32) days. Total Cefto-M dose per patient was 10.5 (7.5-15) g for 7 days (5-10), being administered in monotherapy to 134 patients (53.8%). It was prescribed as empirical antibiotic treatment in 67.9% of patients, being appropriate in 82.8% of these. It was first-line antibiotic in 74 (29.7%) patients and second-line or more in 176 (70.3%). It was administered for failure of previous antibiotic therapy in 33.7% of patients and after receiving microbiology results in 26.1%. The death of 54 patients (21.7%) during the 6-month follow up was directly attributable to infection in 28 (11.2%) patients, 17 (60.7%) of whom died during the first 14 days, 9 (32.1%) between days 15 and 28, and 2 (7.1%) between day 29 and 6 months. Readmission for the same reason was recorded in 15 patients (6%) and recurrence during the first month of follow-up in 3 (1.2%).

The mortality rate by infection type was 16.7% (10/60) for CAP, 14.5% (9/62) for NP, 40% (2/5) for VAP, 11.4% (5/44) for bacteremia, 5.6% (3/54) for SSTI, and 20% (7/34) for concomitant COVID-19 infection (also see Figure 1).

The mortality rate was 9.1% (8/88) for infections by GPC (MRSA 20.8% [5/24], *E. faecalis* 12.5% [1/8], MSSA 9.5% [2/21], CNS-MR 0% [0/13], *Pneumococcus* 0% [0/5], *E. faecium* S-ampicillin 0% [0/1], *S. pneumoniae* 0% [0/5], and *Streptococcus* spp. 0% [0/5]). It was 11.8% (6/51) for infections by GNB (*P. aeruginosa* 16.1% [5/31], multi-susceptibility *Enterobacteriaceae* 0% [0/12], and other nonfermenting GNB 0% [0/2]), and 0% in infections by Gram-positive bacilli (0/1) (Figure 2).

2.4. Adverse effects

No adverse effect was recorded in 96.4% of treated patients, a mild effect in 1.6% and a moderate effect in 1.6%. No patient abandoned treatment due to adverse effects; mild hypertransaminasemia was reported in 1.2%, diarrhea, nausea, and vomiting in 0.8%, and skin rash in 0.4% (Table 4).

2.5. Bi- and multivariate analyses of mortality-related factors

In the bivariate analysis, mortality was associated with higher age (76.7±13.3 *vs*. 65.3±15.2 yrs.; p=0.0001), ICU admission (28.6 *vs*. 2.1%; p= 0.001), cardiovascular risk factors (78.6 *vs*. 45.7%, p =0.001), underlying neurological disease (21.4 *vs*. 6.8%; p=0.019); immunodepression (35.7 *vs*. 19%; p= 0.04); sepsis/septic shock (57.1 *vs*. 27.6%; p=0.0001), VAP (7.1 *vs*. 1.4%, p=0.04), fewer days of Cefto-M treatment (6 [P25-P75: 3-8.5] *vs*. 7 [P25-P75: 5-10] days, p=0.029), and lower total dose (in mg) of Cefto-M (9 [4.5-12.75] *vs*. 10.5 [7.5-15], p=0.049). Hospitalization in a Department/Unit of Infectious Diseases emerged as a protective factor (24.9% *vs*. 7.1%; p=0.035).

In the multivariate analysis, factors associated with infection-related mortality were age (OR: 1.1 95% CI [1.04-1.16]), sepsis/septic shock (OR 2.94, 95% CI [1.01-8.54]), and ICU admission (OR 42.02, 95% CI [4.49-393.4]) (Table 5).

2.6. Figures, Tables and Schemes

Table 1. Epidemiological characteristics, comorbidities, and infection pathways.

	Cohort N=249
Age, mean (years), (± SD)	66.6 (±15.4)
Charlson index, median (IQR)	4 (2-6)
Sex, n (%) • Male • Female	148 (59.4) 101 (40.6)

Ethnicity, n (%)	
• Caucasian	231 (92.8)
• Latin	17 (6.8)
• African	1 (0.4)
Acquisition of the infection, n (%)	
• Community-acquired infection	107 (43)
• Nosocomial/Nosohusial infection	142 (57)
Presence of Sepsis or Septic Shock, n (%)	
• Sepsis	66 (26.5)
• Septic Shock	11 (4.4)
Inpatient department, n (%)	
• Medical Services	200 (80.4)
• Intensive care	12 (6)
• Surgical Services	38 (15.2)
Outpatient antibiotic treatment, n (%)	11 (4.4)
Coinfection with SARS-COV2 (COVID-19), n (%)	34 (13.7)
Comorbidities	
• Cardiovascular Risk Factors, n (%)	123 (49.4)
- Hypertension	73 (29.3)
- Dyslipidemia	11 (4.4)
- Obesity	1 (0.4)
- ≥ 2 Risk Factors	38 (15.2)
• Cardiovascular disease, n (%)	78 (31.3)
- Ischemic Heart Disease	26 (33.3)
- Heart Failure	9 (11.5)
- Atrial Fibrillation/Flutter	15 (19.2)
- Pacemaker Carrier	1 (1.3)
- Dilated Cardiomyopathy	1 (1.3)
- Other Conditions	9 (11.5)
- ≥ 2 Conditions	17 (21.8)
• Respiratory diseases, n (%)	74 (29.7)
- Chronic Obstructive Pulmonary Disease (COPD)	29 (39.2)
- Obstructive Sleep Apnea (OSA)	9 (12.2)
- Thromboembolic Pulmonary Vascular Disease (TPVD)	4 (5.4)
- Bronchiectasis	8 (10.8)
- Asthma	4 (5.4)
- Interstitial Lung Disease	3 (4.1)
- Other Conditions	6 (8.1)
- ≥ 2 Conditions	11 (14.9)
• Gastrointestinal and hepatic diseases, n (%)	45 (18.1)
- Chronic Liver Disease	18 (40)
- Liver Cirrhosis	8 (17.8)
- Peptic Ulcer Disease	6 (13.3)
- Inflammatory Bowel Disease	3 (6.7)
- Liver Transplantation	3 (6.7)
- Other Conditions	7 (15.6)
• Chronic Kidney Disease, n (%)	35 (14.1)
• Active Solid Malignancy, n (%)	20 (8)
• Active Hematologic Malignancy, n (%)	33 (13.3)
• Metabolic disorders, n (%)	83 (33.3)
- Diabetes Mellitus	70 (84.3)
- Hypothyroidism	11 (13.3)

- Adrenal Insufficiency	2 (2.4)
• Neurological diseases, n (%)	21 (8.4)
• Stroke, n (%)	14 (5.6)
• Psychiatric conditions, n (%)	9 (3.6)
• Immunocompromised patients, n (%)	52 (20.9)
• Immunosuppressant drugs therapy, n (%)	43 (17.3)
Infection Pathway	
• Bloodstream infection, n (%)	44 (17.7)
• Primary Bacteremia	37 (14.9)
• Catheter-associated Bloodstream Infection	7 (2.8)
• Infective Endocarditis, n (%)	3 (1.2)
• Respiratory Tract Infections, n (%)	139 (55.8)
- Nosocomial pneumonia	62 (24.9)
- Community-acquired pneumonia	60 (24.1)
- Ventilator-associated pneumonia	5 (2)
• Soft Tissue and Skin infection, n (%)	54 (21.7)
- Diabetic Foot Infection	20 (37)
- Cellulitis	10 (18.5)
- Soft Tissue Abscess	7 (13)
- Infected Pressure-Ulcer	7 (13)
- Surgical Wound Infection	6 (11.1)
- Myositis	2 (3.7)
- Other type	2 (3.7)
• Urinary Tract Infection, n (%)	10 (4)
- Complicated UTI (pyelonephritis)	5 (50)
- Non-complicated UTI	3 (30)
- Renal Abscess	2 (20)
• Central Nervous System infection, n (%)	8 (3.2)
- Ventriculoperitoneal Shunt Infection	3 (37.5)
- Epidural Abscess	2 (25)
- Cerebral Abscess	2 (25)
- Meningitis	1 (12.5)
• Intra-abdominal infection, n (%)	9 (3.6)
• Bone and Joint infection, n (%)	14 (5.6)
- Prosthetic Joint Infection	6 (42.9)
- Osteomyelitis	4 (28.6)
- Infectious Tenosynovitis	3 (21.4)
- Septic Arthritis	1 (7.1)
• Spondylodiscitis, n (%)	3 (1.2)
• Other type of infection, n (%)	4 (1.6)

Table 2. Susceptibility of microbial isolates.

Microorganisms, n (%)	Cohort N=249	Vanco-S	Cloxa-S	Dapto-S	Ceftobi-S	Cefe-S	Mero-S	Pip/Taz-S
Staphylococcus aureus	46 (18.4)	35 (97.2)	14 (41.2)	21 (67.7)	6 (100)			
- MRSA	24 (9.6)	21 (100)	0 (0)	16 (80)	3 (100)			
- MSSA	21 (8.4)	14 (93.3)	14 (100)	5 (45.5)	3 (100)			
Enterococcus spp.	10 (4)	5 (100)	NT	0 (0)	1 (100)			
Streptococcus spp.	10 (4)	3 (100)	NT	NT	1 (100)			

GNB						
Enterobacterales	51 (20.5)		10 (100)	4 (33.3)	5 (83.3)	16 (84.2)
Pseudomonas	13 (5.2)		5 (100)	1 (50)	NT	6 (100)
aeruginosa	31 (12.4)		4 (100)	2 (40)	5 (83.3)	7 (70)
Haemophilus	2 (0.4)		1 (100)	1 (100)	NT	NT
influenzae						

GNB: gram-negative bacilli. Vanco-S: vancomycin-susceptible; Cloxa-S: cloxacillin-susceptible; Dapto-S: daptomycin-susceptible; Ceftobi-S: ceftobiprole-susceptible; Cefe-S: cefepime-susceptible; Mero-S: meropenem-susceptible; Pip/Taz-S: piperacillin-tazobactam-susceptible. NT: not tested.

EUCAST cutoff points

Staphylococci

- Vancomycin (*S. aureus*): 2
- Vancomycin (CoNS): 4
- Oxacillin *(S. aureus)*: 2
- Oxacillin (CoNS): 0.25

Enterococci

- Vancomycin: 4

Pneumococci

- Cefepime: 1
- Ceftobiprole: 0.5
- Vancomycin: 2
- Meropenem: 2

Enterobacteriaceae

- Cefepime: 1
- Ceftobiprole: 0.25
- Meropenem: 2

Pseudomonas

- Cefepime: 0.001
- Ceftobiprole: insufficient evidence
- Meropenem: 2

Table 3. Outcomes.

	N=249
Total dose of ceftobiprole, median (IQR)	10.5 (7.5-15)
Duration of antibiotic therapy, median (IQR)	7 (5-10)
Treatment regimen, n (%)	
• Ceftobiprole Monotherapy	134 (53.8)
• Antibiotic combination	115 (46.2)
- Ceftobiprole + Daptomycin	27 (23.5)
- Ceftobiprole + Vancomycin	4 (3.5)
- Ceftobiprole + Linezolid	8 (7)

- Ceftobiprole + Dalbavancin	1 (0.9)
- Ceftobiprole + Clindamycin	2 (1.7)
- Ceftobiprole + Tigecycline	4 (3.5)
- Ceftobiprole + Cloxacillin	3 (2.6)
- Ceftobiprole + Ceftazidime	1 (0.9)
- Ceftobiprole + Ceftaroline	2 (1.7)
- Ceftobiprole + Ceftriaxone	2 (1.7)
- Ceftobiprole + Ceftazidime/Avibactam	2 (1.7)
- Ceftobiprole + Meropenem	9 (7.8)
- Ceftobiprole + Levofloxacin	10 (8.7)
- Ceftobiprole + Ciprofloxacin	4 (3.5)
- Ceftobiprole + Piperacillin/Tazobactam	2 (1.7)
- Ceftobiprole + Amikacin	6 (5.2)
- Ceftobiprole + Azithromycin	10 (8.7)
- Ceftobiprole + Metronidazole	13 (11.3)
- Ceftobiprole + Trimethoprim/Sulfamethoxazole	7 (6.1)
- Ceftobiprole + Doxycycline	2 (1.7)
- Ceftobiprole + Fosfomycin	1 (0.9)
- Ceftobiprole + Antifungal agents	6 (5.2)
- Ceftobiprole + Antiviral agents	2 (1.7)
Length of hospital stay, median (IQR)	20 (13-32)
Ceftobiprole as empirical treatment, n (%)	169 (67.9)
Appropriate empirical treatment, n (%)	140 (82.8)
Prescription of Ceftobiprole, n (%)	
• As first-line treatment	74 (29.7)
• As second-line or more	175 (70.3)
Reason for switching to Ceftobiprole, n (%)	
• Failure of previous antibiotic treatment	84 (48)
• Toxicity/adverse effects of previous antibiotic treatment	3 (1.7)
• Guided by microbiological results	65 (37.1)
• Other reasons (or combination of previous)	23 (13.1)
Recurrence and readmission, n (%)	
• Recurrence of infection (in first month)	3 (1.2)
• Hospital readmission	15 (6)
Mortality, n (%)	
• Total mortality	54 (21.7)
• Non-related-to-infection mortality	26 (10.4)
• Related-to-infection mortality	28 (11.2)
Related-to-infection mortality, n (%)	
• 14-day mortality	17 (60.7)
• 28-day mortality	9 (32.1)
• 6-month mortality	2 (7.1)

Table 4. Mortality risk factors: bivariate and multivariate analyses.

	Non-survivor N= 31	Survivor N= 219	Bivariate p*	Multivariate OR, 95% CI
Epidemiological characteristics				
• Age (± DS)	76.7 (±13.3)	65.3 (±15.2)	0.0001	
• Charlson index, median (IQR)	4.5 (4-6.75)	4 (2-6)	0.253	1.1 (1.04-1.16)
• Sex, n (%)				
- Male	20 (71.4)		0.17	

- Female	8 (28.6)	128 (57.9)		
• Ethnicity n (%)		93 (44.1)		
- Caucasian	27 (96.4)			
- Latin	1 (3.6)	204 (92.3)	0.718	
- African	0 (0)	16 (7.2)		
		1 (0.5)		
Inpatient department, n (%)				
• Medical Departments				
- Infectious Diseases	2 (7.1)	55 (24.9)	0.035	
- Internal Medicine	9 (32.1)	43 (19.5)	0.12	0.19 (0.03-1.2)
- Pneumology	2 (7.1)	37 (16.7)	0.27	
- Intensive Care Unit	8 (28.6)	4 (1.8)	0.001	
- Hematology	1 (3.6)	10 (4.5)	0.25	42.02 (4.49-393.4)
- Oncology	2 (7.1)	14 (6.3)	0.27	
• Surgical Departments	2 (7.1)	36 (16.3)	0.27	
OPAT, n (%)	2 (7.1)	9 (4.1)	0.36	
				1.67 (0.49-5.62)
Comorbidities, n (%)				
• Cardiovascular Risk Factors	22 (78.6)	101 (45.7)	0.001	
• Cardiovascular Disease	6 (21.4)	72 (32.6)	0.231	
• Lung Disease	10 (35.7)	64 (29)	0.461	0.94(0-21-4.33)
• Gastrointestinal and Liver Disease	5 (17.9)	40 (18.1)	0.975	
• Chronic Kidney Disease	4 (14.3)	31 (14)	0.97	1.81 (0.289-11.41)
• Active Solid Malignancy	3 (10.7)	17 (7.7)	0.526	
• Hematological Malignancy	4 (14.3)	29 (13.1)	0.864	1.21 (0.24-6.16)
• Metabolic Disorder	11 (39.3)	72 (32.6)	0.478	
• Neurological Disease	6 (21.4)	15 (6.8)	0.019	
• Psychiatric Disorder	0 (0)	9 (4.1)	0.6	2.59 (0.69-9.85)
• Stroke	3 (10.7)	11 (5)	0.199	
• Immunosuppression	10 (35.7)	42 (19)	0.04	
				2.03 (0.52-7.88)
COVID-19 superinfection	7 (25)	27 (12.2)	0.063	2.08 (0.43-10.12)
Number of infection pathways, median (IQR)	1 (1-1)	1 (1-1)	0.945	
Pathway Infection, n (%)				
• Bloodstream infection	5 (17.9)	39 (17.6)	0.978	
• Infective endocarditis	1 (3.6)	2 (0.9)	0.223	
• Community-acquired pneumonia	10 (35.7)	50 (22.6)	0.127	
• Nosocomial pneumonia	9 (32.1)	53 (24)	0.347	
• Ventilator-associated pneumonia	2 (7.1)	3 (1.4)	0.04	0.12 (0.004-3.89)
• Skin and Soft Tissue infection	3 (10.7)	51 (23.1)	0.135	
• Urinary Tract infection	0 (0)	10 (4.5)	0.251	
• Central Nervous System infection	0 (0)	8 (3.6)	0.306	
• Intra-abdominal infection	1 (3.6)	8 (3.6)	0.99	
• Bone and Joint infection	1 (3.6)	13 (5.9)	0.617	
• Spondylodiscitis	0 (0)	3 (1.4)	0.535	
• Other type of infection	0 (0)	4 (1.8)	0.473	
• Sepsis or Shock	16 (57.1)	61 (27.6)	0.0001	

|				
				2.94 (1.01-8.54)
Microbiology and acquisition of infection, n (%)				
• Microbial isolation			0.758	
- Monomicrobial infection	9 (32.1)	84 (38)		
- Polymicrobial infection	6 (21.4)	50 (22.6)		
• Setting of infection acquisition			0.762	
- Community-acquired infection	12 (42.9)	95 (43)		
- Nosocomial infection	10 (35.7)	90 (40.7)		
- Nosohusial infection	6 (21.4)	36 (16.4)		
• GPC	8 (28.6)	80 (36.2)	0.426	
• MRSA	5 (17.9)	19 (8.6)	0.118	
• MSSA	2 (7.1)	19 (8.6)	0.794	
• CoNS	0 (0)	20 (9)	0.097	
• *Enterococcus faecalis*	1 (3.6)	7 (3.2)	0.909	
• *Streptococcus pneumoniae*	0 (0)	5 (2.3)	0.421	
• GNB	6 (21.4)	45 (20.4)	0.895	
• *Pseudomonas aeruginosas*	5 (17.9)	26 (11.8)	0.358	
Antimicrobial Therapy				
• Total dose of Ceftobiprole (mg), median (IQR)	9 (4.5-12.75)	10.5 (7.5-15)	0.049	0.91 (0.73-1.12)
• Length of Ceftobiprole therapy (days), median (IQR)	6 (3-8.5)	7 (5-10)	0.029	1.08 (0.82-1.4)
• Therapy regimen:			0.708	
- Monotherapy, n (%)	16 (57.1)	118 (53.4)		
- In combination, n (%)	12 (42.9)	103 (46.6)		
• Prescription of Ceftobiprole:			0.308	
- First-line, n (%)	6 (21.4)	68 (30.8)		
- Rescue therapy, n (%)	22 (78.6)	153 (69.2)	0.183	1.34 (0.4-4.49)
• Empirical treatment, n (%)	22 (78.6)	146 (66.1)		

OPAT: outpatient parenteral antibiotic therapy; GPC: gram-positive cocci; CoNS: coagulase-negative staphylococcus; GNB: gram-negative bacilli; MRSA: methicillin-resistant *Staphylococcus aureus;* MSSA: methicillin-susceptible *S. aureus*. HR: ratio, 95% CI: 95% confidential interval. *P<0.05 as significant.

Table 5. Adverse drug effects.

	N = 249
Total adverse effects, n (%)	9 (3.6)
Severity of adverse effects, n (%)	
• Mild	4 (1.6)
• Moderate	4 (1.6)
• Severe	1 (0.4)
Adverse effects by symptoms, n (%)	
• Acute kidney failure	5 (2)
• Elevated liver enzymes	3 (1.2)
• Gastrointestinal symptoms	2 (0.8)
• Urticaria-like cutaneous rash	1 (0.4)
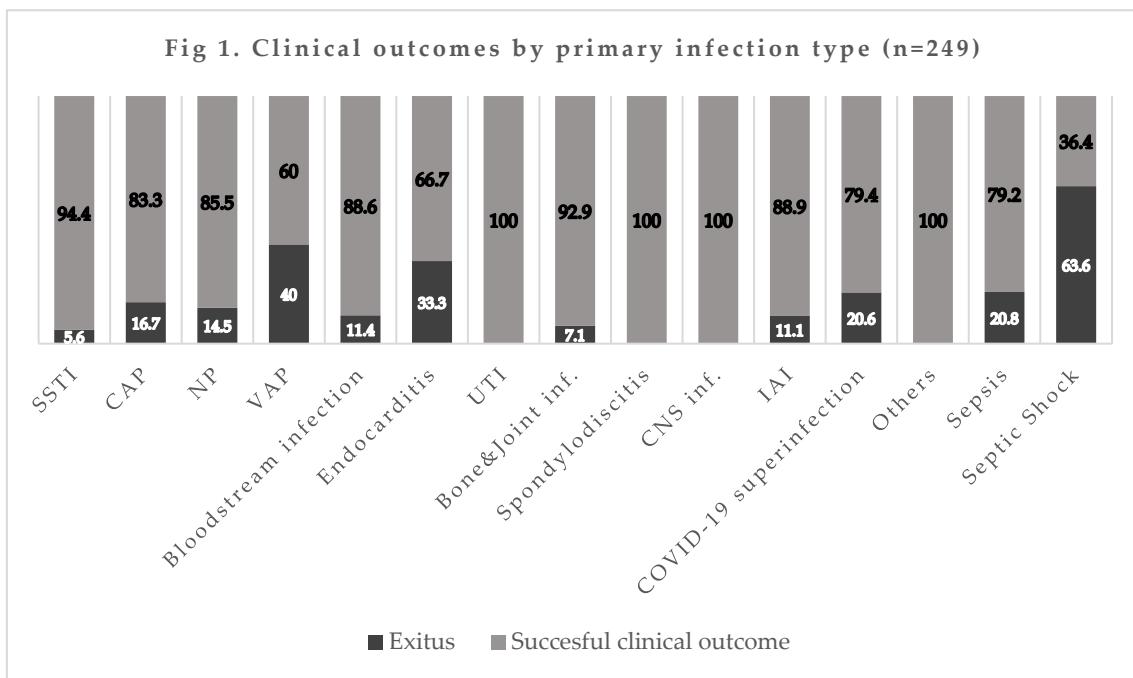
Figure 1. SSTI: Skin and Soft Tissue infection, CAP: Community-acquired pneumonia; NP: Nosocomial pneumonia; VAP: Ventilator-associated pneumonia; UTI: Urinary Tract infection; CNS: Central Nervous System; IAI: Intra-abdominal infection.
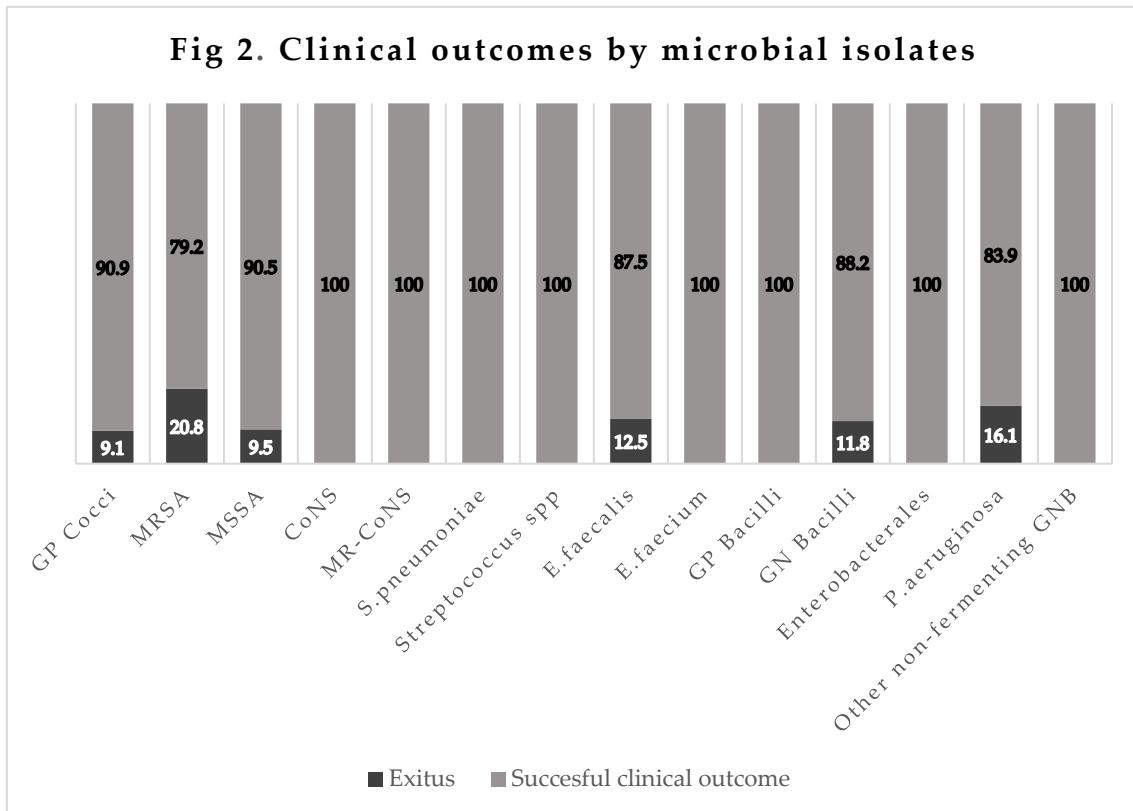
Figure 2. GP: Gram-Positive; MRSA: Methicilin-Resistant *Staphylococcus aureus*; MSSA: Methicilin-Susceptible *Staphylococcus aureus*; CoNS: Coagulase-Negative *Staphylococcus* spp; MR-CoNS: Methicilin-Resistant Coagulase-Negative *Staphylococcus* spp; GN: Gram-Negative; GNB: Gram-Negative Bacilli.

3. Discussion

Patients in this real-life study were elderly and largely male and pluripathological, with a high comorbidity index and predominance of cardiovascular risk factors. Around one in five were immunodepressed, one in seven had kidney failure, and one in ten had COPD. More than half of infections were nosocomial or healthcare-related, and around 5% received outpatient antibiotic treatment. As in the case of other beta-lactams, the pharmacokinetics and pharmacodynamics of Cefto-M favor its infusion for 24 h, making it a potentially useful antibiotic for OPAT regimens in patients with infections by GPC, including MRSA and ampicillin-susceptible *Enterococcus* spp., and non-ESLB-producing GNB such as *Pseudomonas* spp. (15).

More than one-third of participants had sepsis/septic shock, and one-seventh were co-infected with SARS-COV2 (COVID-19). Septic shock has been described as an independent mortality risk factor, with an increase in risk of up to 12% for every hour in shock, regardless of the focus, isolate, type of poly-/mono-microbial infection, or presence/absence of bacteremia (16). A multicenter study of more than 5,000 individuals with septic shock reported a mortality rate of around 50% when the antibiotic treatment was appropriate and 89% when it was not (17). Coinfection with SARS-COV2 in critical patients with NP or VAP is known to worsen the prognosis, although it does not increase the rate of invasive fungal infection or change the type of microorganism isolated at respiratory level (18).

In the present study, only around half of the patients received Cefto-M for respiratory infection (half NP and half CAP), which is the sole indication for this antibiotic in Spain (19). One-fifth of patients were treated for skin/soft tissue infection and one-sixth for bacteremia. Cefto-M was effective against *Enterococcus* in a murine model of UTI (20) and has been proposed as a possible option in complicated UTI produced by *Pseudomonas* spp. (21). Three non-inferiority clinical trials in patients with skin and soft tissue infections reported no difference between Cefto-M and comparators in clinical or microbiological response or safety profile (22). Decisions of clinicians to prescribe Cefto-M to the remaining patients in this real-life study are supported by pharmacokinetic (23) and *in vitro* (24) studies and by a real-life study with a small sample size (25).

The total crude infection-related mortality in these patients was 11.2%, most frequently due to VAP (40%), followed by pneumonia with COVID-19 coinfection (20%), CAP requiring hospitalization (16.7%), NP (14.5%), bacteremia (11.4%), and skin/soft-tissue infections (5.6%). Among microorganisms, the highest mortality rates were for MRSA (20.8%) and *P. aeruginosa* (16.1%). The mortality rate was <1% in clinical trials of Cefto-M in patients with CAP. The difference with the present finding might be explained by their stricter eligibility criteria, with the exclusion of patients receiving an antibiotic for >24 h in the previous three days and those with aspiration pneumonia, viral respiratory infection, polymicrobial infection, or radiological or clinical suspicion of atypical pneumonia (26). In the trial in patients with NP, the total mortality rate was 16.7% and the infection-attributed rate was 5.9%. This major discrepancy with the present findings can again be attributed to the trial eligibility criteria, which excluded patients receiving systemic antibiotic treatment for >24 h in the previous two days and those with severe kidney failure or liver failure, evidence of infection with ceftazidime- or Cefto-M-resistant pathogens, and clinical circumstances potentially hampering the evaluation of effectiveness, e.g., sustained shock, active tuberculosis, pulmonary abscess or postobstructive pneumonia (27).

Only one patient (0.4%) had a severe complication, and the treatment was not withdrawn from any patient due to an adverse effect, similar to the findings of a single-center real-life study on the use of Cefto-M in 29 patients with infections in a third-level hospital (28).

Finally, the main factors related to mortality in this cohort of Cefto-M-treated patients were older age (the mean age of patients was 76.7 years), the presence of sepsis/septic shock, and ICU admission, which have all been independently related to higher infection-related mortality rates in previous studies (29).

The study is limited by its retrospective design and possible selection bias. Its strengths include its multicenter design, sample size (largest to date) and real-life nature, reflecting as faithfully as possible the utilization of Ceftobiprole-M in routine clinical practice in Spain.

4. Materials and Methods

Study design

This real-life, retrospective, multicenter, observational, and descriptive study on the use of Cefto-M included patients in hospital or receiving OPAT with nosocomial/nosohusial or community-acquired infections from 12 Spanish centers in six autonomous communities (Andalusia, Madrid, Cataluña, Valencia, Murcia, and Cantabria). The study period was from the time of the drug's approval in 2021 to December 31, 2022. The study was approved by the Provincial Ethics Committee of Granada (ref: 0095-N-22), with no requirement for the informed consent of patients. All data were gathered in accordance with Spanish personal data protection legislation (Organic Law 3/2018 December 5) and the Helsinki declaration.

This descriptive study did not involve a pharmacological intervention. Treatments were always prescribed by attending physicians according to their clinical practice.

Inclusion criteria: age >17 years, receipt of Cefto-M as first-line or rescue treatment for ≥48 h (≥6 vials in patients with normal renal function, creatinine clearance-adjusted in patients with kidney failure); and ≥30 days of follow-up post-discharge or, in the case of patients with osteomyelitis o endocarditis, ≥ 6 months post-discharge.

Exclusion criteria: pregnancy, allergy to beta-lactams or any formulation excipient.

Variables and definitions.

Age, sex, ethnicity, days of hospitalization (dates of admission and discharge); prescribing hospital department., age-adjusted Charlson index, comorbidities.

Infection type: bacteremia (complicated/non-complicated], endocarditis (definite/probable/suspected, native/early prosthetic/late prosthetic/on pacemaker, respiratory infection (upper tract/CAP/NP/VAP), urinary tract infection (UTI), central nervous system infection, spondylodiscitis, osteoarticular infection, intraabdominal infection, or other foci of infection. Infection origin: community or nosocomial/nosohusial/healthcare-related. Sepsis or septic shock. Monomicrobial/polymicrobial infection. Co-infection with SARS-CoV-2 (COVID-19).

Cefto-M administration in monotherapy or combination therapy (for the same infection); empirical or targeted administration; first-line or rescue (due to poor response to previous antibiotherapy, microbiology results, or toxicity with previous antibiotherapy); days of administration and dose; and adverse events.

Previous antibiotic (for same infection) with treatment duration.

Microbiology: microorganism causing the infection and antibiogram according to EUCAST criteria (10).

Infection-related mortality at 14 and 28 days (at 6 months for endocarditis or osteomyelitis).

Readmission for the same reason during first month.

Relapse/recurrence of the infection.

Definitions.

- Nosocomial infection: onset >72 h after hospitalization.

- Nosohusial/nosocomial infection: healthcare-related (day hospital, residence, daycenter for elderly).

- The age-adjusted Charlson comorbidity index was used to estimate the 10-year life expectancy of patients as a function of their age and the presence of comorbidities at admission for the infectious episode (11).

- Sepsis/septic shock: refractory hypotension and end-organ perfusion dysfunction despite adequate fluid resuscitation (12).

- Immunodepression: congenital or acquired immunodeficiency or receipt of immunosuppressive treatment (13).

- Relapse/recurrence of the infection was defined by a second episode within three months (14).

- Adverse effect classification.

Mild: requires no antidote or treatment; brief hospitalization.

Moderate: requires treatment modification (e.g., dose adjustment, combination with another drug) but no interruption of drug administration; longer hospitalization or prescription of a specific treatment may be needed.

Severe: threatens the life of the patient and mandates interruption of drug administration and prescription of a specific treatment.

Lethal: can directly or indirectly contribute to the death of a patient.

Sample size

A sample size of around 250 individuals was estimated to be adequate to analyze the use of Cefto-M-in routine clinical practice with a confidence interval of 95% and error of 5%. Information was obtained from the electronic records of the different Hospital Pharmacy Departments, gathering the number of patients administered the drug by type of infection. These data were introduced into an anonymized database in SPSS format, following national data protection legislation and the principles of the Helsinki declaration.

Statistical analysis

In a descriptive analysis, absolute and relative frequencies (%) were calculated for qualitative variables. Means with standard deviation were calculated for quantitative variables with normal distribution and medians with interquartile range (IQR) for those with non-normal distribution (Kolmogorov–Smirnov test).

In bivariate analyses of mortality-related factors, the chi-squared test was used to compare qualitative variables, the Student's t-test for quantitative variables with normal distribution, and the Mann Whitney U test for those with non-normal distribution. Multivariate logistic regression analysis considered variables that were statistically significant in bivariate analysis or deemed relevant (i.e., chronic kidney failure, active hematological or solid organ neoplasia, coinfection by SARS-COV-2, rescue/first-line treatment).

Ethics approval and consent to participate: This study was approved by the ethics committee of the coordinating center and was exempted from the need to obtain informed consent due to its retrospective design and large size. All data were gathered in accordance with Spanish personal data protection legislation.

5. Conclusions

Ceftobiprole-M is a safe antibiotic, with only half of prescriptions for patients with respiratory infection, mainly administered as rescue therapy in pluripathological patients with severe infections. The infection-attributable mortality was 11.2%, largely associated with higher age, presence of sepsis/septic shock, and ICU admission.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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