International Journal of Antimicrobial Agents 62 (2023) 106817

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

CEFTO-CURE study: CEFTObiprole Clinical Use in Real-lifE – a multi-centre experience in Italy

Ivan Gentile[a,*], Antonio Riccardo Buonomo[a], Silvia Corcione[b], Laurenza Paradiso[c,d], Daniele Roberto Giacobbe[e,f], Davide Fiore Bavaro[g], Giusy Tiseo[h], Francesca Sordella[i], Michele Bartoletti[q,r], Giulia Palmiero[j], Antonietta Vozza[k], Antonio Vena[e,f], Francesca Canta[b], Nicola Schiano Moriello[a], Paola Congera[a], Arta Karruli[d], Carlo Tascini[l], Pierluigi Viale[q,r], Valerio Del Bono[i], Marco Falcone[h], Sergio Carbonara[m], Malgorzata Karolina Mikulska[n,o], Matteo Bassetti[e,f], Emanuele Durante-Mangoni[d], Francesco Giuseppe De Rosa[b], Alberto Enrico Maraolo[p]

[a] *Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy*
[b] *Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy*
[c] *Ninth Division of Infectious Diseases, Cotugno Hospital, Azienda Ospedaliera dei Colli, Naples, Italy*
[d] *Department of Precision Medicine, University of Campania 'L. Vanvitelli' and AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy*
[e] *Department of Health Sciences, University of Genoa, Genoa, Italy*
[f] *Clinica Malattie Infettive, Ospedale Policlinico San Martino, IRCCS, Genoa, Italy*
[g] *Clinic of Infectious Diseases, University of Bari, University Hospital Policlinico, Bari, Italy*
[h] *Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[i] *Infectious Diseases Unit, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy*
[j] *Fourth Division of Infectious Diseases, Cotugno Hospital, Azienda Ospedaliera dei Colli, Naples, Italy*
[k] *Division of Pharmacy, AOU Federico II, Naples, Italy*
[l] *Division of Infectious Diseases, University Hospital ASUFC, Udine, Italy*
[m] *Infectious Diseases Unit, V. Emanuele II Hospital, Bisceglie, Italy*
[n] *Infectious Diseases Unit, Department of Health Sciences, University of Genoa, Genoa, Italy*
[o] *Infectious Diseases Unit, Ospedale Policlinico San Martino, IRCCS for Oncology and Neurosciences, Genoa, Italy*
[p] *First Division of Infectious Diseases, Cotugno Hospital, Azienda Ospedaliera dei Colli, Naples, Italy*
[q] *Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[r] *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*

ARTICLE INFO

Article history:
Received 5 October 2022
Accepted 7 April 2023

Editor: Dr Jim Gray

Keywords:
Ceftobiprole
Pneumonia
MRSA
Bloodstream infection

ABSTRACT

Background: Ceftobiprole is approved in Europe for treatment of community-acquired pneumonia and non-ventilator-associated hospital-acquired pneumonia (HAP) in adults. Real-world data are limited.
Methods: This multi-centre, observational, ambispective investigator-initiated study was undertaken in Italy from January 2018 to December 2019 in order to evaluate the use of ceftobiprole in a real-world setting.
Results: Overall, 195 patients from 10 centres were evaluated (68% retrospectively). Male sex was prevalent (n=121, 62%). Median age was 67 [interquartile range (IQR) 53–75] years. Median Charlson Comorbidity Index score was 5 (IQR 3–7). The most common indication was pneumonia (151/195, 77%), especially HAP. Other uses were skin and soft tissue infections (5%), endocarditis (4%) and bone infections (4%). Ceftobiprole was usually an empiric choice (65%), in combination with other drugs (66%) and as second-line therapy (58%). A causative agent was found in 39% of cases. A diagnosis of sepsis was made in 59 cases (30%). Success in the clinically evaluable population (excluding 12 cases due to isolation of pathogens outside ceftobiprole's spectrum of activity) was obtained in 79% of cases, with all-cause mortality of 20%. On multi-level analysis, three predictors were positively associated with clinical success:

* Corresponding author at: Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Sergio Pansini 5, I-80131, Naples, Italy.
E-mail address: ivan.gentile@unina.it (I. Gentile).

https://doi.org/10.1016/j.ijantimicag.2023.106817

male gender, pneumonia and detection of causal agent. Sepsis was a negative predictor. Nine factors were independently associated, favourably or unfavourably, with fatal outcome.
Conclusions: Ceftobiprole is a safe and effective therapeutic choice, even in a real-world setting. More data are needed to establish its efficacy in patients with sepsis.

1. Introduction

Ceftobiprole, the active form of the water-soluble prodrug ceftobiprole medocaril, is a fifth-generation cephalosporin that is approved for community-acquired pneumonia (CAP) and non-ventilator-associated hospital-acquired pneumonia (HAP) [1]. It can bind to and inhibit several penicillin binding proteins (PBPs) that confer resistance or reduced susceptibility to conventional β-lactams, including PBP2a of methicillin-resistant *Staphylococcus aureus* (MRSA) and PBP2x of penicillin-resistant pneumococci [2]. Ceftobiprole has a broad spectrum of antimicrobial activity, covering difficult-to-treat Gram-positive bacteria, such as resistant staphylococci and pneumococci [2], but also most Enterobacterales and *Pseudomonas aeruginosa*. Ceftobiprole is stable towards chromosomal AmpC-type β-lactamases [2].

Ceftobiprole exhibits high bactericidal and anti-biofilm activity *in vitro* and in animal models; synergy has been demonstrated with several antibiotics; and it is well tolerated, mirroring the typical safety profile of β-lactams [3]. All these features render ceftobiprole an attractive option for the treatment of many types of infection beyond the approved indications, either as monotherapy or in combination with other drugs [4].

Although real-world experiences with ceftobiprole have been published, these are limited to single-centre studies [5,6] or small registries [7], translating into a paucity of data regarding the efficacy and safety of the drug in the framework of real-world evidence.

As such, this multi-centre study was undertaken in Italy to report the characteristics of the clinical use of ceftobiprole, describing the outcome of patients receiving the drug.

2. Methods

2.1. Description of the study: design and setting

This multi-centre, observational, ambispective study was conducted across 10 hospital centres in Italy over 2 years. Specifically, the study included a retrospective cohort comprising all patients who received ceftobiprole between January 2018 and December 2018, and a prospective cohort of patients who received ceftobiprole during the 12 months after study initiation (1 January 2019) in the participating hospitals. A 1-month follow-up was planned to collect both retrospective and prospective data on clinical management and outcome of patients who received ceftobiprole alone or in combination with other antimicrobials. The 1-month follow-up went beyond the limit of enrolment if the time of enrolment occurred close to the deadline for both the retrospective and prospective cohorts. Patients were treated according to standard hospital practice. The decision to use ceftobiprole was at the physician's discretion and was made before study inclusion.

2.2. Inclusion and exclusion criteria

The main inclusion criteria were adult patients undergoing a course of therapy with ceftobiprole (at least three doses) during the study periods. Reasons for exclusion were: lack of informed consent (prospective cohort); and incomplete medical charts or non-provision of data to assess the outcome (retrospective cohort).

2.3. General definitions and outcomes

Infections requiring treatment based on ceftobiprole were defined according to the updated terminology provided by the National Healthcare Safety Network Patient Safety Component Manual [8]. The main indications were CAP, HAP, bloodstream infection (BSI), skin and soft tissue infection (SSTI) and endocarditis. Infections were further categorized as follows [9,10]:

- nosocomial, if onset ≥48 h after admission;
- healthcare-associated, if not nosocomial but at least one of the following conditions was fulfilled: admission to an acute care facility within 90 days of the infective episode, residence in a nursing home or rehabilitation facility in the preceding 30 days, receipt of renal replacement therapy in the preceding 30 days, or receipt of wound care or specialized nursing care in an outpatient setting or at home in the preceding 30 days; and
- Community-acquired, if neither nosocomial nor healthcare-associated.

The severity of patients' clinical condition was assessed using the Sepsis-3 criteria in order to establish if the patient had sepsis or septic shock [11]. The burden of comorbidities was evaluated using the Charlson Comorbidity Index (CCI) [12]. Chronic kidney disease as a baseline condition was defined according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria [13].

Ceftobiprole administration without microbiological data was deemed empiric therapy, and treatment initiated on the basis of microbiological data was deemed targeted treatment [14]. Ceftobiprole administered as stand-alone treatment was considered monotherapy, and ceftobiprole given in conjunction with other agents was defined as combination therapy. Ceftobiprole used as initial treatment was defined as first-line therapy, and treatment instituted later was considered as rescue therapy.

If susceptibility testing in a patient on empiric ceftobiprole therapy showed susceptible strains alone, treatment was deemed microbiologically appropriate. Susceptibility to the drug was evaluated according to the indications provided by the European Committee on Antimicrobial Susceptibility Testing.

Primarily, this study had a qualitative outcome, namely description of the real-world use of ceftobiprole: clinical indications, monotherapy vs combination therapy, empiric vs targeted therapy, and first-line vs rescue therapy.

The primary quantitative outcomes were clinical success, being a composite of clinical cure, improvement or de-escalation feasibility in the framework of a 30-day follow-up (where day 1 was the first day of ceftobiprole treatment); and all-cause mortality. Secondary outcomes were attributable mortality, microbiological cure, recurrence, toxicity and incidence of *Clostridioides difficile* infection (CDI). Outcomes were assessed by site investigators.

Clinical cure was defined as a composite endpoint including clinical resolution (disappearance of signs and symptoms, normalization of laboratory parameters) with no further need for antibiotic, clinical improvement (reduction of signs and symptoms intensity, amelioration of laboratory parameters), or clinical improve-

ment with concurrent finding of a causative agent allowing for de-escalation to a narrower-spectrum agent (possibly through the oral route) [15]. Treatment failure was defined as where the index infection required a change in antibacterial therapy due to documented lack of clinical response or need for therapy escalation, or if premature drug discontinuation was required due to safety issues. All-cause mortality was a composite outcome of 30-day and inpatient all-cause mortality. Patients who were discharged before 30 days were deemed survivors without other information, as were those who died in hospital after 30 days (patients who were discharged before 30 days, re-admitted, and died within 30 days of the infection were included as negative outcomes). Mortality attributable to infection was where site investigators assessed that the patient would not have died in the absence of infection. Microbiological eradication was defined as absence of the pathogen(s) from follow-up samples taken from the original site of infection. Infection relapse was defined as recurrence of infection with the same pathogen at the same site within the pre-established follow-up period after ceftobiprole discontinuation. Toxicity was defined according to international standard terminology [16], and CDI was diagnosed according to standard criteria [17].

Notably, as far as the primary quantitative outcomes were concerned, analysis focused on the clinically evaluable (CE) population, excluding patients whose infections were due to pathogens outside ceftobiprole's spectrum of activity (e.g. nosocomial pneumonia caused by carbapenemase-producing Enterobacterales). Drug safety was assessed in all included patients.

2.4. Data collection

Anonymized demographic and clinical information was collected using REDCap (Research Electronic Data Capture), a secure, web-based application conceived to support data gathering for research studies [18]. An electronic case report form was used to collect data.

Demographic data pertaining to age, sex and body mass index were collected. Admission dates, reasons for hospitalization, and wards where ceftobiprole was started were recorded. Recent histories of patients (in the 90 days preceding admission) were also collected, including previous hospitalizations, surgery, and endoscopy or dialysis within that period. The CCI score was calculated for all patients, defining the presence of each comorbidity (neurological disease, diabetes mellitus, cardiovascular disease, respiratory disease, neoplasia, liver disease, kidney disease) in detail. Other relevant data at baseline were renal function, presence/absence of neutropenia, sepsis/septic shock, mechanical ventilation, and presence of central venous catheter.

Infection characteristics, including microbiological findings if present, and details of prior antibiotic treatments were collected. Ceftobiprole treatment data related to dose, frequency, duration, indication at treatment initiation, targeted or empiric prescription, first-line or rescue therapy (with reason for switching), and presence of a companion antibiotic were gathered.

2.5. Statistical analysis

As the main goal of the study was to describe the clinical use of ceftobiprole in a real-world setting, a predefined sample size was not required.

Descriptive summary data were expressed as count and percentage for categorical variables, and median [interquartile range (IQR)] for continuous variables.

Predefined key demographic and clinical variables were first tested for their association with the two primary outcomes in univariable logistic regression models.

Factors potentially associated with the two main outcomes of interest on univariable analysis ($P<0.10$) were included in a multivariable, generalized, linear mixed model (defined as Model A, with centre as a random effect and logit as the link function). Multi-level modelling has the advantage of better partitioning sources of variation between levels (e.g. patient level vs hospital level) [19].

As sensitivity analysis, all variables included in Model A were also tested for their association with the primary outcomes in an additional traditional multi-variable regression model (Model B). Discrimination of the model was expressed as the area under the receiver-operating curve for a logistic model or the equivalent c-index in a survival model. A c-index of 0.5 represents no discriminative ability, whereas a c-index of 1.0 indicates perfect discrimination [20].

Variable selection was implemented in a backward stepwise fashion. All significant variables identified on univariate analysis were screened for multi-collinearity. The variance inflation factor (VIF) was calculated to control the influence of collinearity. A lack of multi-collinearity was assumed if all variables had VIF <2. Due to the collinearity between invasive sepsis and septic shock, only the variable 'sepsis' was used in the multi-variable model, because the occurrence of sepsis was more common, and sepsis is the prerequisite of septic shock.

Adjusted odds ratios (aOR) and their 95% confidence intervals (CI) based on these regression models have been reported as appropriate. Two-tailed P-values <0.05 were considered to indicate significance.

As post-hoc analysis, a comparison was conducted between patients receiving ceftobiprole as monotherapy and patients receiving ceftobiprole in a combination regimen. Given predictable differences regarding characteristics between these two groups, inverse probability of treatment weighting (IPTW) was applied to control for confounding [21]. The propensity score, defined as the conditional probability of monotherapy compared with combination regimens based on ceftobiprole, was estimated using a multi-level random-effects model in the context of multi-level data [22], with ceftobiprole monotherapy as the dependent variable and the baseline key features related to the therapeutic choice (monotherapy or not) and to the outcomes (clinical success and all-cause mortality) in the two groups as covariates. Features of the propensity score model, including their component variables and their respective weights, are presented in Table S1 (see online supplementary material). The so-called 'common support', namely the overlap in the range of propensity scores across groups, was assessed subjectively through a density plot (Fig. S1, see online supplementary material). The balance of covariates after weighting is depicted in Fig. S2 (see online supplementary material) by plotting the standardized mean differences of all covariates, and setting values >0.1 as a threshold for declaring imbalance [23]. A clustered-weighted estimator was used to obtain the average treatment effect [24].

All the analyses were carried out using R Version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with packages such as 'finalfit', 'lme4', 'survey' and 'twang'.

2.6. Ethics

This study was conducted in compliance with the Declaration of Helsinki and the principles of good clinical practice. The collection of anonymized data was approved by the Ethics Committee of the University of Naples 'Federico II' at the coordinating investigator's study centre which signed the study protocol (Record No. 297-2018).

Table 1
Description of the main demographic and baseline characteristics of the study population.

Variable of interest	No. of patients n=195 (100%)
Demographics	
Male gender	121 (62%)
Age in years, median (IQR)	67 (53-75)
Comorbidities	
Heart failure	41 (21%)
COPD	52 (27%)
Liver disease	31 (16%)
Diabetes mellitus	50 (26%)
Kidney disease	44 (23%)
Solid cancer	41 (21%)
Haematological malignancy	27 (14%)
Charlson Comorbidity Index score, median (IQR)	5 (3-7)
Previous healthcare exposure (<90 days)	
Surgery	72 (37%)
Dialysis	12 (6%)
Endoscopy	33 (17%)
Hospitalization	78 (40%)
ICU stay	56 (28%)
Antimicrobial administration	124 (64%)
Features at the time of ceftobiprole prescription	
CVC presence	95 (49%)
Severe neutropenia (<500 neutrophils/μL)	14 (7%)
Dialysis	18 (9%)
ICU stay	26 (13%)
Mechanical ventilation	21 (11%)
Sepsis	59 (30%)
Septic shock	17 (9%)
Clinical indication for ceftobiprole prescription (sum is higher than 195 as patients could have more than one infectious syndrome at the same time)	
Pneumonia	151 (74%)
BSI	37 (19%)
SSTI	9 (5%)
Endocarditis	7 (4%)
Bone infection	7 (4%)
Other	9 (5%)
Epidemiology of infectious process	
Communitarian	41 (21%)
Healthcare-associated	17 (9%)
Nosocomial	137 (70%)
Features of ceftobiprole prescription	
Empiric	127 (65%)
Empiric with subsequent confirmation as targeted	6 (3%)
Targeted	62 (32%)
First-line	78 (40%)
Renally adjusted dose	54 (28%)
Duration, median (IQR)	10 (7-14)
Dose modification	8 (4%)
Monotherapy	66 (34%)
Microbiological findings	
Identification of a causative agent	76 (39%)
If causal agent identified, monomicrobial infection	57/76 (75%)
If causal agent identified, MRSA involvement	29/76 (38%)
If causal agent identified, MRNAS involvement	16/76 (21%)

BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range; MRNSA, methicillin-resistant non-*aureus* staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection. Results are reported as *n* (%) unless otherwise specified.

3. Results

Overall, 195 patients were included, among whom an evaluable clinical endpoint was attained in 182 patients (CE population). In detail, patients were enrolled in 10 Italian centres. Data were collected retrospectively for the majority of subjects (133/195, 68%).

Patients' demographic and clinical characteristics are presented in Table 1.

The primary indication for ceftobiprole administration was pneumonia (151/195, 74%), followed by bloodstream infection (BSI) (37/195, 19%). Some patients had multiple infected samples (e.g. bacteraemic pneumonia was detected in 12 subjects), so the total number of clinical indications exceeded the number of patients. Although 11% of subjects were mechanically ventilated, ventilator-associated pneumonia (VAP) was the reason for ceftobiprole administration in two patients.

Ceftobiprole was administered as monotherapy in one-third of cases (66/195, 34%), and almost always in subjects with pneumonia (60/66, 91%). Monotherapy was empiric in 39 of 66 patients.

When used in combination regimens (129/195, 66%), the most common companion drug of ceftobiprole was meropenem (40/129, 31%), and it was used empirically in nearly all instances (36/40). Combination regimens were also mostly empiric (88/129, 68%). The main clinical indications in this context were pneumonia (91/129, 71%) and BSI (26/129, 20%). The full microbiological profile of the identified causative agents is described in Table S2 (see online supplementary material). A breakdown of combination therapy regimens is provided in Table S3 (see online supplementary material).

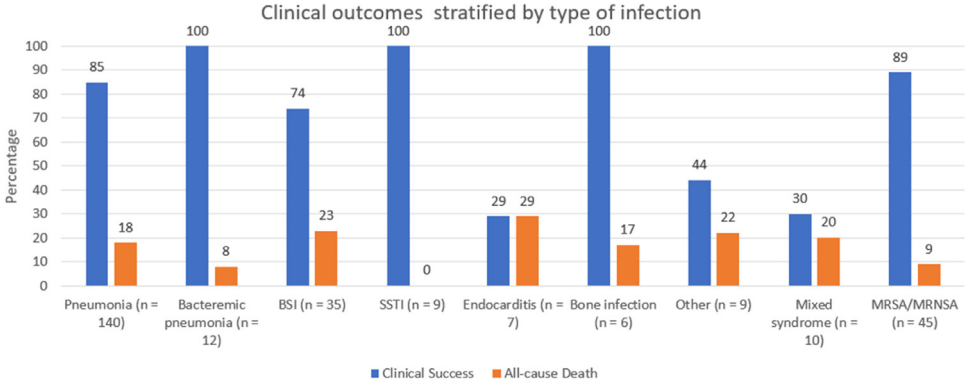

Fig. 1. Summary of clinical outcomes stratified by type of infection. BSI, bloodstream infection; MRNSA, methicillin-resistant non-*aureus* staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection.

Twelve patients treated empirically with ceftobiprole were excluded from assessment of the primary outcomes because their infections were found to be caused by ceftobiprole-resistant bacteria. Twenty-five percent (3/12) of these patients died. No ceftobiprole-related toxicity was reported among these 12 patients, but patient had after treatment of nosocomial pneumonia caused by multi-drug-resistant *P. aeruginosa* with meropenem and then ceftazidime-avibactam.

In the CE population, the crude failure rate was 21% (39/183) and the crude all-cause fatality rate was 19.6% (36/183). The attributable mortality rate was 6% (11/183). There were six cases of toxicity, including rash (n=2), myoclonus (n=2), allergic reaction (n=1) and seizures (n=1). The four patients with rash or myoclonus were all receiving combination therapy with daptomycin. There were eight recurrent infections (seven pneumonia, one BSI) and only one case of CDI infection. Microbiological eradication was achieved in the majority of cases with culture follow-up (34/39, 87%).

A summary of the results related to the two primary outcomes, stratified by type of infection and main type of pathogen targeted by ceftobiprole (methicillin-resistant staphylococci), is illustrated in Fig. 1. Clinical success in patients with pneumonia was 85% (119/140), and this reached 100% for bacteraemic forms (12/12). The lowest success rate was observed in the endocarditis subgroup, where only two of seven (29%) patients were cured and survived.

A comparison of patients who achieved clinical success in the CE population with those who did not achieve clinical success is reported in Table 2. Results of multi-variable analyses exploring the association of relevant variables with clinical success are described in Table 3, showing findings from the main multi-level model (Model A) and the traditional multi-variable logistic regression model in the framework of a sensitivity analysis (Model B); results of Model A are also depicted in graphical form in Fig. S3 (see online supplementary material). According to the main model, sepsis was the strongest independent predictor of treatment failure (aOR for clinical success 0.25, 95% CI 0.09–0.63), whereas the following factors were independently associated with clinical success: male gender (aOR 4.55, 95% CI 1.69–12.50), pneumonia (aOR 14.29, 95% CI 3.03–50.00) and identification of causal agent (aOR 25.00, 95% CI 4.35–100). The sensitivity analysis yielded similar results, confirming the same predictors, and endocarditis also negatively impacted clinical success in Model B (aOR 0.11, 95% CI 0.01–0.90). Endocarditis was not retained in the final multi-level model as it did not meet the predefined criterion of significance level <0.05, and endocarditis tended to be a predictor of treatment failure in full Model A (aOR for clinical success 0.09, 95% CI 0.01–1.00; P=0.05). Of note, endocarditis was always related to methicillin-resistant staphylococci, namely MRSA (2/7) and methicillin-resistant non-*aureus* staphylococci (5/7), and ceftobiprole was never administered as monotherapy. Ceftobiprole was administered with daptomycin in the majority of cases (6/7), and with linezolid in the remaining case.

Comparison of patients who met the mortality endpoint with survivors in the CE population is reported in Table 4. Results of multi-variable analyses exploring the association of relevant predictors with all-cause mortality are described in Table 5, which shows the findings from the main multi-level model (Model A) and the traditional multi-variable logistic regression model in the framework of a sensitivity analysis (Model B); the results of Model A are also depicted in graphical form in Fig. S4 (see online supplementary material), and mortality outcome was presented as its inverse (i.e. survival) for ease of interpretation. In the multi-level model, several factors were independently associated with all-cause mortality. Specifically, there were six predictors of unfavourable outcome: age (aOR 1.06 per 1-year increase, 95% CI 1.05–1.07), CCI score (aOR 1.16 per point increase, 95% CI 1.14–1.17), mechanical ventilation (aOR 2.47, 95% CI 2.45–2.50), nosocomial origin of infection (aOR 3.65, 95% CI 3.61–3.68), sepsis (aOR 3.99, 95% CI 3.95–4.03) and clinical failure (aOR 7.19, 95% CI 2.69–19.19). On the other hand, there were three predictors of reduced all-cause mortality: chronic obstructive pulmonary disease (COPD; aOR 0.98, 95% CI 0.97–0.99), duration of ceftobiprole treatment (aOR 0.95 per 1-day increase, 95% CI 0.94–0.96), and identification of causal agent (aOR 0.41, 95% CI 0.40–0.41). In Model B, only age, mechanical ventilation and clinical failure were independently and negatively associated with mortality.

Given the difference in baseline covariates between patients who received ceftobiprole as monotherapy and patients who received ceftobiprole in a combination regimen, an IPTW analysis was performed. We found no significant difference between these two groups, showing that combination strategy does not imply a better outcome in terms of clinical success (IPTW OR of monotherapy vs combination therapy 1.19, 95% CI 0.40–3.45) or all-cause mortality (IPTW OR of monotherapy vs combination therapy 0.76, 95% CI 0.22–2.69).

4. Discussion

Real-world evidence is essential to understand the generalizability of randomized clinical trial (RCT) results to routine clinical practice. In fact, the sole national registry identified in the available literature, which comes from Canada, consists of only 38 patients; among them, the on-label indication (pneumonia) was present in just 16% of cases, and the most common (42%) indication for use of ceftobiprole was endocarditis. Microbiological and clinical success were observed in 97% and 85% of subjects, respectively [7].

Table 2
Comparison of patients who achieved clinical success with those who did not in the clinically evaluable population of patients undergoing therapy with ceftobiprole.

Variable of interest	Patients who achieved clinical success (n=144)	Patients who did not achieve clinical success (n=39)	P-value
Demographics			
Male gender	98 (68%)	15 (40%)	0.002
Age in years, median (IQR)	66 (52–75)	73 (59–81)	*0.064*
Comorbidities			
Heart failure	26 (18%)	14 (40%)	0.032
COPD	35 (25%)	13 (33%)	0.377
Liver disease	23 (16%)	6 (15%)	1.000
Diabetes mellitus	39 (27%)	10 (26%)	1.000
Kidney disease	28 (19%)	11 (28%)	0.335
Solid cancer	32 (22%)	7 (18%)	0.721
Haematological malignancy	18 (13%)	7 (18%)	0.538
Charlson Comorbidity Index score, median (IQR)	5 (3–7)	6 (4–8)	*0.052*
Previous healthcare exposure (<90 days)			
Surgery	61 (42%)	9 (23%)	0.044
Dialysis	7 (5%)	3 (8%)	0.770
Endoscopy	25 (18%)	6 (16%)	0.983
Hospitalization	59 (41%)	15 (39%)	0.921
ICU stay	40 (28%)	13 (33%)	0.632
Antimicrobial administration	95 (66%)	21 (54%)	0.227
Features at the time of ceftobiprole prescription			
CVC presence	66 (46%)	19 (49%)	0.918
Severe neutropenia (<500 neutrophils/μL)	9 (6%)	4 (10%)	0.608
Dialysis	11 (8%)	5 (13%)	0.486
ICU stay	10 (7%)	8 (21%)	0.008
Mechanical ventilation	14 (10%)	8 (21%)	0.119
Sepsis	34 (24%)	21 (54%)	0.001
Septic shock	9 (27%)	8 (38%)	0.544
Clinical indication for ceftobiprole prescription (sums are higher than 144 and 39 as some patients had more than one infectious syndrome at the same time)			
Pneumonia	119 (83%)	21 (54%)	<0.001
BSI	26 (18%)	9 (23%)	0.633
SSTI	9 (6%)	0 (0%)	0.237
Endocarditis	2 (1%)	5 (13%)	0.005
Bone infection	6 (4%)	0 (0%)	0.430
Other	4 (3%)	5 (13%)	0.031
Epidemiology of the infectious process			
Communitarian	29 (20%)	8 (21%)	0.664
Healthcare-associated	14 (10%)	2 (5%)	
Nosocomial	101 (70%)	29 (74%)	
Features of ceftobiprole prescription			
Empiric	93 (65%)	25 (64%)	0.400
Empiric with subsequent confirmation as targeted	6 (4%)	0 (0%)	
Targeted	45 (31%)	14 (36%)	
First-line	59 (41%)	16 (41%)	0.995
Duration, median (IQR)	10 (7-15)	9 (5-11)	0.038
Dose modification	8 (6%)	0 (0%)	0.282
Monotherapy	52 (36%)	13 (33%)	0.894
Microbiological findings			
Identification of a causative agent	62 (43%)	7 (18%)	0.007
If causal agent identified, monomicrobial infection	50 (81%)	3 (43%)	0.076
MRSA involvement in case of *S. aureus* infection	28 (90%)	1 (100%)	1.000
MRNAS involvement in case of non-*aureus* staphylococci infection	12 (80%)	4 (100%)	0.839

BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range; MRNSA, methicillin-resistant non-*aureus* staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection.
Results are reported as n (%) unless otherwise specified. Factors potentially associated with the outcome of interest on univariable analysis (P<0.10) were included in a multi-variable model, and corresponding P-values are reported in bold (in italic if not <0.05).

The most numerous observational case series to date comes from Italy: a single-centre study whose data collection preceded the present cohort. In 48 subjects with severe pneumonia, ceftobiprole showed a high clinical cure rate (85%) and low 30-day mortality (10%), notably used as an empiric choice in less than half (45%) of cases [25]. In another Italian case series of 25 patients with non-ventilator-associated HAP, clinical cure was observed in 20 (80%) cases; the mortality rate was 16% [26]. These series and reports of other small cohorts or case series do not provide sufficient information on the real-world use of ceftobiprole. As such, guidelines on the use of ceftopibrole outside approved indications (CAP and HAP) are based largely on expert opinion [27].

The most recent published RCT (TARGET) (n=679) showed that ceftobiprole was non-inferior to a combination of vancomycin and aztreonam for the treatment of acute bacterial SSTI [28]. A recent meta-analysis of data from three RCTs on acute bacterial SSSI confirmed that ceftobiprole has a similar efficacy and safety profile to its comparators [29]. Results from a just-completed RCT comparing ceftobiprole with daptomycin for the treatment of S. *aureus* BSI, including infective endocarditis, are eagerly awaited (clinicaltrials.gov identifier: NCT03138733) [30].

In the present study, ceftobiprole was mainly used on label for pneumonia, mostly nosocomial, achieving a high clinical cure rate

Table 3
Multi-variable analysis of independent predictors of clinical success in patients undergoing ceftobiprole treatment.

Model A (c-statistic: 0.859)	Adjusted OR (95% CI)	*P*-value
Male gender	4.55 (1.69–12.50)	0.003
Sepsis	0.25 (0.09–0.63)	0.004
Pneumonia	14.29 (3.03–50.00)	0.001
Identification of causal agent	25.00 (4.35–100.00)	<0.001
Model B (c-statistic: 0.847)		
Male gender	4.55 (1.81–11.11)	0.001
Sepsis	0.26 (0.10–0.66)	0.005
Pneumonia	9.09 (2.38–50.00)	0.003
Endocarditis	0.11 (0.01–0.90)	0.046
Identification of causal agent	25.00 (5.88–100.00)	<0.001

Model A, multi-level model; Model B, multi-variable logistic regression model; OR, odds ratio; CI, confidence interval.

of 85%. In comparison, in the registration RCT, the clinical cure rates with ceftobiprole were 87% in CAP [31] and 69% in HAP [32].

In the current cohort, the diagnosis of pneumonia itself was a strong predictor of clinical success, along with identification of the causal agent, represented by methicillin-resistant staphylococci in nearly two-thirds of cases. Surprisingly, male gender also predicted clinical success, but as there was no imbalance of key covariates between males and females (data not shown), it is likely that some unidentified variable may have acted as a confounder. On the contrary, sepsis was a driver of clinical failure and mortality. In this respect, older age and higher CCI score also had a negative impact on survival, as did nosocomial infection and mechanical ventilation. The strongest predictor of mortality was failure of ceftobiprole treatment, but the evidence that sepsis alone was a predictor of clinical failure, whereas other factors associated with

Table 4
Comparison of survivors and non-survivors in the clinically evaluable population of patients undergoing ceftobiprole treatment.

Variable of interest	Survivors (*n*=147)	Non-survivors (*n*=36)	*P*-value
Demographics			
Male gender	91 (62%)	22 (61%)	1.000
Age in years, median (IQR)	65 (51–74)	76 (67–82)	< 0.001
Comorbidities			
Heart failure	29 (20%)	11 (31%)	0.246
COPD	33 (23%)	15 (42%)	0.037
Liver disease	24 (16%)	5 (14%)	0.917
Diabetes mellitus	40 (27%)	9 (25%)	0.953
Kidney disease	28 (19%)	11 (31%)	0.199
Solid cancer	31 (21%)	8 (22%)	1.000
Haematological malignancy	19 (13%)	6 (17%)	0.753
Charlson Comorbidity Index score, median (IQR)	5 (3–7)	7 (5–9)	0.001
Previous healthcare exposure (<90 days)			
Surgery	57 (39%)	13 (36%)	0.918
Dialysis	7 (5%)	3 (8%)	0.663
Endoscopy	24 (17%)	7 (20%)	0.814
Hospitalization	60 (41%)	14 (39%)	0.983
ICU stay	41 (28%)	12 (33%)	0.660
Antimicrobial administration	94 (64%)	22 (61%)	0.902
Features at the time of ceftobiprole prescription			
CVC presence	65 (45%)	20 (57%)	0.316
Severe neutropenia (<500 neutrophils/μL)	10 (7%)	3 (8%)	1.000
Dialysis	10 (7%)	6 (17%)	0.121
ICU stay	13 (8%)	5 (14%)	0.366
Mechanical ventilation	12 (8%)	10 (28%)	0.003
Sepsis	34 (23%)	21 (58%)	<0.001
Septic shock	7 (21%)	10 (48%)	*0.071*
Clinical indication for ceftobiprole prescription (sums are higher than 147 and 36 as some patients had more than one infectious syndrome at the same time)			
Pneumonia	115 (78%)	25 (69%)	0.371
BSI	27 (18%)	8 (22%)	0.771
SSTI	9 (6%)	0 (0%)	0.275
Endocarditis	5 (3%)	2 (6%)	1.000
Bone infection	5 (3%)	1 (3%)	1.000
Other	7 (5%)	2 (6%)	0.905
Epidemiology of the infectious process			
Communitarian	33 (22%)	4 (11%)	*0.078*
Healthcare-associated	15 (10%)	1 (3%)	
Nosocomial	99 (67%)	31 (86%)	
Features of ceftobiprole prescription			
Empiric	93 (63%)	25 (70%)	0.447
Empiric with subsequent confirmation as targeted	4 (3%)	2 (6%)	
Targeted	50 (34%)	9 (25%)	
First-line	60 (41%)	15 (42%)	0.926
Duration, median (IQR)	10 (8-15)	7.5 (5-11)	0.019
Dose modification	7 (5%)	1 (3%)	0.934
Monotherapy	54 (37%)	11 (31%)	0.617
Microbiological findings			
Identification of a causative agent	61 (42%)	8 (22%)	*0.078*
If causal agent identified, monomicrobial infection	48 (79%)	5 (63%)	0.566
MRSA involvement in case of *S. aureus* infection	27 (90%)	2 (100%)	1.000
MRNAS involvement in case of non-aureus staphylococci infection	14 (82%)	2 (100%)	1.000

BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range; MRNSA, methicillin-resistant non-*aureus* staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection.
Results are reported as *n* (%) unless otherwise specified. Factors potentially associated with the outcome of interest on univariable analysis ($P<0.10$) were included in a multi-variable model, and corresponding *P*-values are reported in bold (in italic if not <0.05).

Table 5
Multi-variable analysis of independent predictors of all-cause mortality in patients undergoing ceftobiprole treatment.

Model A (c-statistic: 0.914)	Adjusted OR (95% CI)	*P*-value
Age (median, per 1-year increase)	1.06 (1.05–1.07)	<0.001
Chronic obstructive pulmonary disease	0.98 (0.97–0.99)	<0.001
Charlson Comorbidity Index score (median, per point increase)	1.16 (1.14–1.17)	<0.001
Nosocomial infection (opposed to communitarian)	3.65 (3.61–3.68)	<0.001
Mechanical ventilation	2.47 (2.45–2.50)	<0.001
Identification of causal agent	0.41 (0.40–0.41)	<0.001
Sepsis	3.99 (3.95–4.03)	<0.001
Duration of ceftobiprole therapy (median, per 1-day increase)	0.95 (0.94–0.96)	<0.001
Clinical failure	7.19 (2.69–19.19)	<0.001
Model B (c-statistic: 0.835)		
Age (median, per 1-year increase)	1.07 (1.03–1.11)	0.001
Mechanical ventilation	6.00 (1.78–20.94)	0.004
Clinical failure	8.03 (3.26–20.66)	<0.001

Model A, multi-level model; Model B, multi-variable logistic regression model; OR, odds ratio; CI, confidence interval.

higher all-cause mortality did not influence the success of ceftobiprole treatment, may suggest that fatalities were driven more by baseline conditions than infection in many cases. Indeed, only 11 of 36 deaths were defined as infection-related.

The issue of sepsis deserves further attention. A post-hoc analysis of the registration trials on CAP [32] and HAP [33] showed no differences in terms of outcome between ceftobiprole and comparators in most severe patients, including patients with sepsis [34], but the definition of sepsis used in the two pivotal RCTs was not the latest definition according to the Sepsis-3 criteria [11]. Particularly for MRSA infection, higher exposure (100% time above minimum inhibitory concentration) is associated with strong bactericidal action, but the probability of attaining this goal with the current dosage is probably lower, leaving room for improvement by prolonging infusion time (to >4 h) or increasing the dosage (500 mg/6 h or 1 g/8–12 h) [35,36].

Another variable warranting more consideration is mechanical ventilation, which was associated with death but not with clinical failure of ceftobiprole treatment. In the registration RCT on HAP, non-inferiority of the drug was not found in the VAP subgroup, being the difference in clinical cure rates equal to -18.2% (favouring the comparator arm) [33]. A multi-variate logistic regression analysis did not find that any individual or combination of patient-related variables explained the differential outcome in patients with VAP [33], and no differences in ceftobiprole pharmacokinetics between non-VAP and VAP groups were highlighted [2]. Furthermore, in mechanically ventilated patients with non-VAP, clinical outcomes were in favour of ceftobiprole [33].

In the current cohort, only two cases of pneumonia qualified as VAP, so the other ventilated patients were diagnosed with non-VAP. Mechanical ventilation did not emerge as a driver of clinical failure of ceftobiprole; however, being strongly linked with mortality, it seemed to be an obvious indicator of very severe general conditions.

Surprisingly, COPD seemed to exert a slight protective effect on mortality. It is likely that this association may be mediated by the higher liability of patients with COPD to develop pneumonia, a predictor of the clinical success of ceftobiprole [37].

Endocarditis impacted negatively on clinical success, in stark contrast to previous reports. Tascini et al. described a clinical cure rate of 83% in 12 patients [6], but all cases in the present cohort were due to methicillin-resistant strains and the sample sizes were very small.

Finally, another result stemming from the present study, although against the backdrop of a post-hoc propensity-score based analysis, is the lack of benefit of combination therapy over monotherapy with ceftobiprole. Interestingly, some authors have speculated on the dichotomy between the role of ceftobiprole as 'sparing' or 'sparring' agent: in essence, ceftobiprole may allow the streamlining of antimicrobial therapies in some instances, not resorting to other antibiotics, or it may be rationally associated with another agent to exert a better therapeutic effect in selected cases [38]. For instance, when approaching a patient with HAP, ceftobiprole can be a reasonable choice as monotherapy if the risk of multi-drug-resistant Gram-negative pathogens is low and the likelihood of MRSA is high [2]. On the other hand, when high-inoculum infections such as endocarditis need to be treated, a logical strategy might be exploitation of the well-known synergism between β-lactams and backbone drugs such as daptomycin [39]. Some experts advocate the use of early combination therapy even for MRSA BSI [40].

In summary, to the best of the authors' knowledge, this is by far the largest observational study regarding the real-world use of ceftobiprole. The drug was well tolerated (adverse events in only 3% of cases) and fairly effective in various clinical scenarios and treatment modalities.

This study has some limitations. First, it was observational in nature, and therefore susceptible to selection bias. However, this risk was minimized by the inclusion of consecutive patients. Second, the impact of unmeasured confounders could represent an issue, as always happens in observational studies. Third, the wide CI associated with some estimates in the multi-variable analyses (e.g. impact on clinical failure by identification of causal agents) make them less precise, warranting studies having larger sample sizes. Fourth, the 'clinical success' outcome may have been liable to ascertainment bias, which is why a hard and objective endpoint such as all-cause mortality was predefined. Fifth, microbiological aetiology was determined in less than half of the cases (39%), which prevented further analysis from being undertaken on the impact of ceftobiprole against given pathogens. Of course, the appropriateness to use a novel antibiotic without microbiological findings may be reasonably questioned; nevertheless, it is well known that the causal agent remains unknown in a not-negligible fraction of CAP and HAP cases. A potential strategy to streamline the place in therapy of an anti-MRSA agent is to exploit the high negative predictive value of MRSA nasal swabs [41]. In addition, the low number of off-label uses curtails the possibility to draw useful inferences when ceftobiprole is used outside the pneumonia framework. Some aspects were not addressed, such as in-vitro synergy of some combinations, and the development of ceftobiprole resistance.

5. Conclusion

Ceftobiprole was found to be a safe and efficacious choice in a large real-world cohort, mainly, but not exclusively, centred on its on-label use, namely pneumonia. More data from RCTs are needed to define its place in therapy addressing other clinical scenarios,

such as BSI, and its role as monotherapy or in combination regimens, as well as its use in patients with sepsis.

CRediT authorship contribution statement

Ivan Gentile: Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Antonio Riccardo Buonomo:** Writing – review & editing, Supervision. **Silvia Corcione:** Writing – review & editing. **Laurenza Paradiso:** Data curation. **Daniele Roberto Giacobbe:** Data curation, Writing – review & editing. **Davide Fiore Bavaro:** Data curation. **Giusy Tiseo:** Data curation. **Michele Bartoletti:** Data curation, Writing – review & editing. **Giulia Palmiero:** Data curation. **Antonietta Vozza:** Data curation. **Antonio Vena:** Data curation. **Francesca Canta:** Data curation. **Nicola Schiano Moriello:** Data curation, Writing – original draft. **Paola Congera:** Data curation. **Pierluigi Viale:** Writing – review & editing. **Valerio Del Bono:** Writing – review & editing. **Marco Falcone:** Writing – review & editing. **Sergio Carbonara:** Writing – review & editing. **Malgorzata Karolina Mikulska:** Writing – review & editing. **Matteo Bassetti:** Data curation. **Emanuele Durante-Mangoni:** Writing – review & editing. **Francesco Giuseppe De Rosa:** Writing – review & editing. **Alberto Enrico Maraolo:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing.

Funding: None.

Competing interests: Outside the submitted work, I.G. reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from Abbvie, Basilea, MSD, Gilead, Pfizer, Angelini, Nordic, Correvio, Abbott, GSK and SOBI. M.B. reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from Bayer, BioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer and Shionogi. D.R.G. reports investigator-initiated grants from Pfizer, Shionogi and Gilead Italia, and speaker fees and/or advisory board fees from Pfizer and Tillotts Pharma.

Ethical approval: The collection of anonymized data was approved by the Ethics Committee of the University of Naples 'Federico II' at the coordinating investigator's study centre, which signed the study protocol (Record No. 297-2018).

Note: This work was presented in preliminary form as an ePoster (#P0292) at the European Congress of Clinical Microbiology and Infectious Diseases 2022 annual meeting.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106817.

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