International Journal of Antimicrobial Agents 54 (2019) 562–571

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Review

Off-label use of ceftaroline fosamil: A systematic review

Arianna Pani[a,e,*], Fabrizio Colombo[b], Francesca Agnelli[b], Viviana Frantellizzi[c], Francesco Baratta[d], Daniele Pastori[d], Francesco Scaglione[a,e]

[a] Clinical Pharmacology Unit, ASST Grande Ospedale Metropolitano Niguarda, Italy
[b] Internal Medicine Department, ASST Grande Ospedale Metropolitano Niguarda, Italy
[c] Department of Radiological, Oncological and Anatomical Pathological Sciences, University of Rome Sapienza, Italy
[d] Department of Internal Medicine and Medical Specialties, University of Rome Sapienza, Italy
[e] Department of Oncology and Onco-Hematology, Postgraduate School of Clinical Pharmacology and Toxicology University of Milan Statale, Italy

ARTICLE INFO

Article history:
Received 14 December 2018
Accepted 28 June 2019

Editor: Stefania Stefani

Keywords:
Ceftaroline fosamil
MRSA
Bacteremia
Endocarditis
Meningitis
Off-label

ABSTRACT

Ceftaroline fosamil is a fifth-generation cephalosporin with anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity. It has been approved by the EMA and FDA for the treatment of adults and children with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). However, ceftaroline fosamil has a broad spectrum of activity, and a good safety and tolerability profile, so is frequently used off-label.

The aim of this systematic review was to summarize the safety and efficacy of off-label use of ceftaroline.

The review was conducted according to PRISMA guidelines. MEDLINE, EMBASE and CENTRAL databases (2010-2018) were searched using as the main term ceftaroline fosamil and its synonyms in combination with names of infectious diseases of interest.

A total of 21 studies with 1901 patients were included: the most common off-label indications for ceftaroline use were bacteremia (n=595), endocarditis (n=171), osteoarticular infections (n=368), hospital-acquired pneumonia (n=115) and meningitis (n=23). The most common reasons for off-label use were persistent or recurrent infection after standard treatment or non-susceptibility to vancomycin and daptomycin.

Clinical success was evaluated in 933 patients, and 724 (77%) of these reached this positive outcome. Incidence of adverse events (AEs) was reported in 11 studies. In 83 (9%) cases there were AEs related to the use of ceftaroline; the most common reported AEs were nausea, vomiting, diarrhea, rash and neutropenia.

The review results show that ceftaroline may be used in clinical settings other than those currently approved; however, the use of ceftaroline in these contexts deserves further investigation.

1. Introduction

Ceftaroline fosamil is a fifth-generation cephalosporin with broad spectrum bactericidal activity. It was approved in October 2010 by the Food and Drug Administration (FDA) for the treatment of adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). In 2015 the FDA approved a label expansion for the treatment of *Staphylococcus aureus* bacteremia associated with ABSSSI in adults. In 2016 it was approved for pediatric use with the same indications.

Abbreviations: MRSA, Methicillin-resistant *Staphylococcus aureus*; PBP2a, Penicillin binding protein 2a; VRSA, Vancomycin-resistant *S. aureus*; hVISA, Heterogeneous vancomycin intermediate-resistant *S. aureus*; MRSA-RVS, reduced vancomycin susceptibility phenotype; EOT, End of therapy; AOR, Adjusted odds ratio; CKD, Chronic kidney disease; CABP, Community-acquired bacterial pneumonia; ABSSSI, Acute bacterial skin and skin structure infections; NP, Nosocomial pneumonia; HAP, Hospital-acquired pneumonia; HCAP, Health-care associated pneumonia; VAP, Ventilator-associated pneumonia; ICU, Intensive care unit; OAIs, Osteoarticular infections; GISA, Glycopeptide-intermediate *S. aureus*; IRR, Infection-related readmission; CCI, Charlson Comorbidity Index; OAI, Osteoarticular infection; $\%fT_{MIC}$, Percentage of time of free drug concentration above the MIC; LOS, length of stay; IQR, interquartile ratio; CI, confidence interval.

* Corresponding author: Arianna Pani, Postgraduate school of Clinical Pharmacology and Toxicology, Via Vanvitelli 32, 20129 - Milan, Italy Tel: +39 3314858040; Fax: +39 02 6444.2957.

E-mail addresses: arianna.pani@unimi.it (A. Pani), fabrizio.colombo@ospedaleniguarda.it (F. Colombo), francesca.agnelli@ospedaleniguarda.it (F. Agnelli), viviana.frantellizzi@uniroma1.it (V. Frantellizzi), francesco.baratta@uniroma1.it (F. Baratta), daniele.pastori@uniroma1.it (D. Pastori), francesco.scaglione@unimi.it (F. Scaglione).

https://doi.org/10.1016/j.ijantimicag.2019.06.025
0924-8579/

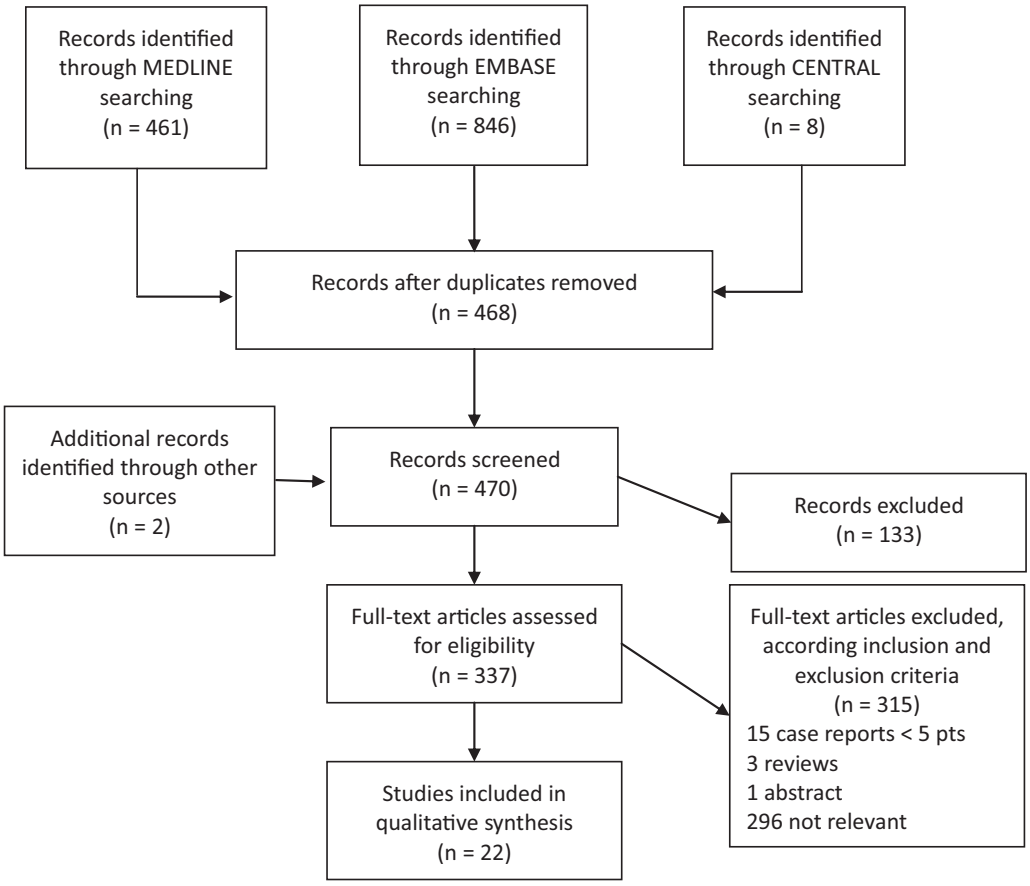

Fig. 1. Flowchart summarizing the selection process of included studies.

Ceftaroline, like other β-lactams, inhibits bacterial cell wall transpeptidation by irreversibly binding penicillin-binding protein (PBP). In addition, ceftaroline is a unique cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) through binding PBP2a.

Ceftaroline is also active against other common bacteria, such as *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae* and *Moraxella catarrhalis*, including resistant phenotypes. Furthermore, ceftaroline has activity against Gram-negative bacteria, including *Klebsiella species* and *Escherichia coli*. Notably, ceftaroline retained activity against heterogeneous vancomycin-intermediate *S. aureus* and showed activity against significant penicillin- and cephalosporin-resistant *S. pneumoniae* strains [1,2].

Ceftaroline has been widely used off-label in adult and pediatric patients since its approval because of its activity on MRSA, broad spectrum of activity, pharmacokinetic profile, good tolerability and handling typical of a β-lactam.

The aim of this systematic review was to summarize the safety and efficacy of off-label use of ceftaroline.

2. Methods

2.1. Inclusion and exclusion criteria

The following were included in the review: clinical trials, cohort studies, case-control studies and case series with more than 5 patients in which patients were treated with off-label ceftaroline without time restrictions. Reviews, case series with less than 5 patients, in vitro studies and studies on animals, abstracts and unpublished data were excluded.

2.2. Literature search

A literature search was conducted of MEDLINE, EMBASE and CENTRAL databases (2010-2018). Keywords were “ceftaroline”, “teflaro”, “zinforo” alone and in combination with infectious diseases of interest names: “bacteremia”, “endocarditis”, “hospital-acquired pneumonia”, “osteomyelitis”, “osteoarticular infection”, “*Staphylococcus aureus* infection”, “methicillin resistant *Staphylococcus aureus* infection”, “meningitis”, “septic arthritis”, “prosthetic joint infection”, and “hospital acquired pneumonia”.

2.3. Study selection and data extraction

Study selection and data extraction were performed by two independent reviewers (A.P. and V.F.). The articles produced by the literature search were screened for off-label uses of ceftaroline and potentially relevant articles were selected. The full text of selected articles was assessed and all articles that respected the inclusion and exclusion criteria previously described were considered eligible. The selection process is shown in the flowchart in Fig. 1. The characteristics of included studies are listed in Table 1.

The following were reported for each study: disease indication, study design, reason for off-label use, days of ceftaroline therapy, age of patients, dose of ceftaroline, Charlson comorbidity index (CCI), and year of publication.

3. Results

Table 1 shows the study characteristics of the 22 included studies. Ten of the studies were retrospective, 3 were case-control studies, and 9 were case series with more than 5 patients. Indication

Table 1
Characteristics of included articles

Disease	Study design	Reason for off-label use	Length of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCIMean/ median (SD) [range]	Year of publication
Bacteremia, pneumonia, bone and joint infection (66.8% off-label prescription)	Retrospective, multicenter	Persistent or recurrent infection after standard treatment or non-susceptibility to vancomycin and daptomycin, simplified regimen for multiple indications, adverse reaction or allergy, preferred empirical coverage for MRSA	(median) 6 [IQR 4-9]	527	(median) 60 [IQR 49-72]	600 mg q12 (85.8%) 600 mg q8 (14.4%)	(median) 2 [IQR 1-4]	2014 [12]
Bacteremia and sepsis, bone and joint infection, pneumonia, endocarditis, meningitis, device infections	Retrospective, population-based, epi-demiological	NR	(median) 3 [IQR 3-12]	764	(median) 61 [IQR 54-67]	NR	(median) 6 [IQR 3-8]	2017 [17]
Bacteremia	Case series	Persistent or recurrent MRSAB after standard treatment or non-susceptibility to vancomycin and daptomycin	(median) 30.4 [7-60]	31	(median) 49 [22-86]	NR	NR	2013 [6]
Bacteremia	Case series	Persistent bacteremia after treatment with other therapies	(mean) 16	26	(mean) 60 [27-86]	600 mg q24 600 mg q12 600 mg q8	NR	2013 [14]
Bacteremia	Retrospective, multicenter, matched case-control	Persistent bacteremia after treatment with vancomycin or preferred empirical coverage for MRSA	NR	16	(median) 75 [28-92]	600 mg q12 (13/16) 600 mg q8 (3/16)	NR	2014 [10]
Bacteremia	Case series	Failure of prior therapies	NR	5	(mean) 57.2 [42-82]	600 mg q8 (1/5) 600 mg q 12 (1/5) 400 mg q12 (1/5) 200 mg q12 (2/5)	NR	2016 [18]
Bacteremia	Retrospective, multicenter	Perceived failure of prior therapy or elevated vancomycin MIC	(median) 11 [IQR 5-15]	211	(median) 59 [IQR 45.5-66.8]	Ceftaroline dosing frequency: Every 8 h; Every 12 h; Every 24 h Ceftaroline dose: 600 mg; 400 mg; 300 mg; 200 mg	(median) 3 [IQR 2-5]	2017 [11]
Bacteremia	Retrospective, single center, matched cohort	Persistent bacteremia after standard treatment or non-susceptibility to vancomycin and daptomycin	NR	30	(mean) 55.9 (12.7)	NR	NR	2017 [1]
Bacteremia and endocarditis	Case series	Failure of vancomycin therapy	(mean) 27 [10-42]	6	NR	600 mg q8 (5/6) 600 mg q12 (1/6)	NR	2012 [15]
Bacteremia and endocarditis	Retrospective	NR	(median) 16 [IQR 8-35]	29	(median) 54 [IQR 47-62]	600 mg q8 400 mg q8 300 mg q8 400 mg q12	NR	2014 [13]
Bacteremia, endocarditis, pneumonia, septic arthritis, osteomyelitis	Case series	Persistent or recurrent infection after standard treatment or non-susceptibility to vancomycin, adverse reaction or allergy	NR	10	NR	800 mg q12 600 mg q12 600 mg q8 400 mg q12 400 mg q8 200 mg q12	NR	2013 [16]

(*continued on next page*)

Table 1 (*continued*)

Disease	Study design	Reason for off-label use	Length of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCIMean/ median (SD) [range]	Year of publication
Endocarditis	Case series	Clinical failure, microbiological failure, worsening after previous therapies	(mean) 19.5 [7-42]	8	(mean) 73.5 [33-85]	400 mg q12 2/8 600 mg q8 4/8 800 mg q 12 2/8	NR	2014 [20]
Endocarditis	Retrospective	Clinical failure, microbiological failure, worsening after previous therapies	(mean) 13.4 (9.7)	55	52.3 (16.6)	600 mg q12 (15/55) 600 mg q8 (14/55) 400 mg q12 (10/55) 400 mg q8 (6/55) 300 mg q12 (7/55) 300 mg q8 (4/55)	NR	2019 [21]
Hospital-acquired pneumonia	Retrospective, multicenter registry	Discretion of the treating physician	(mean) 6.9 (±3.6) HAP 7.7 (±3.2) VAP	40	(mean) 61.3 (16.8)	NR	NR	2015 [22]
Nosocomial pneumonia	Case series	Persistent infection after prior therapies	From 4 to 28	10	(mean) 69.4 [49-98]	600 mg q12	(mean) 4 [1-10]	2013 [23]
Nosocomial pneumonia	Comparative, retrospective, matched, case-control	NR	(mean) 12.4	40	(mean) 58.8 (16.1)	median dose 600 mg/kg [200-600]	NR	2016 [11]
Nosocomial pneumonia	Retrospective	NR	NR	25	(median) 72 [35-94]	NR	NR	2017 [26]
Osteoarticular infections	Case series	Persistent or recurrent infection after standard treatment or non-susceptibility to vancomycin or daptomycin, adverse reaction or allergy	(median) 45.5 [IQR 7 – 65]	12	(median) 57 [36 -93]	600 mg q 12 11/12 600 mg q8 1/12	NR	2017 [29]
Osteoarticular infections	Matched, retrospective, multicenter	Toxicity of prior therapy, anticipated toxicity risk of vancomycin, empirical therapy	(median) 39 [IQR 31-45]	50	(mean) 56.6 (15.9)	600 mg q12 (82%) 400 mg q12 (8%) 300 mg q12 (3%)	(mean) 2.4 (2.1)	2016 [28]
Osteoarticular infections	Retrospective, multicenter	MRSA infection, adverse reaction or allergy/intolerance to vancomycin, renal failure, polymicrobial infection	(mean) 42 (38.5)	19	(mean) 60 [16-92]	600 mg q 12 11/19 600 mg q 8 8/19	NR	2017 [27]
Osteoarticular infections	Retrospective, multicenter, case-control	Ease of dose, elevated vancomycin MIC, elevated daptomycin MIC, lower cost vs. alternative drug, adverse reaction to other drug(s), failure of prior therapy, empirical, savage therapy	(mean) 52.49 (23.41)	37	(mean) 57.76 (16.5)	600 mg q12 (62%) 23/37 600 mg q8 5/37 (14%) 300 mg q12 (3/37) 8% 200 mg q12 (3/37) 8% 800 mg q12 1/37 (3%)	NR	2018 [26]
Meningitis	Case series	Unknown	(mean) 15,6 [10-21]	5	NR	600 mg q8 4/5 600 mg q12 1/5	NR	2015 [32]

CS, case series; CR, case report; CCI, Charlson Comorbidity Index; HAP, hospital-acquired pneumonia; IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSAB, methicillin-resistant *Staphylococcus aureus* bacteremia; NR, not reported; SD, standard deviation; VAP, ventilator-acquired pneumonia

for off-label use for bacteremia was investigated in 12 studies, endocarditis in 12, osteoarticular infections in 12, hospital-acquired pneumonia in 4 and meningitis in 2.

Efficacy and safety results are reported in Table 2. The studies included in this review reported different endpoints for measuring ceftaroline efficacy. Clinical success was evaluated in 18 studies (933 patients), 724 (77%) of these reached this positive outcome. Microbiological cure rates in the 5 studies with this endpoint were above 87%. Hospital length of stay (LOS) was analysed in 6 studies, with a mean LOS of 20 days. The mean time to eradication in the 6 studies reporting this parameter was 3 days.

Incidence of adverse events (AEs) was evaluated in 11 studies and 83 AEs (9% of patients) related to ceftaroline were reported.

Off-label ceftaroline use is discussed per indication below.

3.1. Bacteremia

Although vancomycin is the elective treatment for serious infections caused by MRSA, the prevalence of vancomycin-resistant *S. aureus* (VRSA; minimum inhibitory concentration [MIC] ≥ 16 µg/mL) and heterogeneous vancomycin intermediate-resistant *S. aureus* (hVISA)/VISA (MIC = 4-8 µg/mL) is increasing [3]. In

Table 2
Efficacy and safety results for the off-label use of ceftaroline by indication

Disease	Efficacy/Effectiveness	Mean time to eradication (days)	Concomitant antimicrobial therapy (no. of patients)	AEs (no. of events)	Treatment discontinuation because of AEs (no. of patients)	Reference (Year)
Bacteremia, pneumonia, bone and joint infection and other	Clinical success 88% (426/527); Hospital mortality 7.6% (40/527); 30-day readmission rate for same infection 9.1% (28/307); hosp. LOS median 12 days [IQR 7-21]	NR	29.2% (154/527) concomitant therapy; 42% metronidazole, 42% other anti-Staph agent	7.8% (41/527) Nausea, vomiting and diarrhea (9); rash (5); renal failure (6); CD-associated diarrhea (3)	NR	2014 [28]
Bacteremia and sepsis, bone and joint infection, pneumonia, endocarditis, meningitis, device infections	Hosp. mortality 5%; hosp. LOS median 5 [IQR 3-12]; 30-day hosp. readmission rate 33%	NR	NR	Rates of eosinophilia, leukopenia, leukocytosis, fibromyalgia, myalgia, myositis < 1%	NR	2017 [17]
Bacteremia	Clinical success 74.2% (23/31); microbiological cure at EOT[♦] 64.5% (20/31); mortality 6.5% (2/31)	(mean) 3.5 [1-8]	32.2% (10/31) concomitant therapy with additional anti-MRSA therapy (most frequently daptomycin)	9.7% (3/31) Peripheral eosinophilia (3), rash (1), antibiotic associated diarrhea (2)	Eosinophilic pneumonia (1); eosinophilia (1); nausea, diarrhea, rash (1)	2013 [6]
Bacteremia	Overall survival 96% (25/26)	(median) 2 [1-6]	100% (26/26) in combination with daptomycin	NR	NR	2014 [14]
Bacteremia	Clinical success 88% (14/16); microbiological cure 100% (16/16); hosp. LOS median 37 [IQR 21.8-76.3]	(median) 4 [IQR 3-75]	19% (3/16) one each with rifampicin, daptomycin, vancomycin	NR	NR	2014 [10]
Bacteremia	Clinical success 4/5 (80%)	NR	Vancomycin (5)	NR	NR	2016 [18]
Bacteremia	Clinical success 68.3% (86/126[α]) Microbiological cure at EOT 91.3% (115/126[α]); hosp. LOS median 12 [IQR 8-20]; hosp. mortality 22.2% (28/126[α])	(median) 3 [IQR 1-4]	21.8% (46/211)	7% (16/211) CD infection (6), rash (7), neutropenia (3)	Unknown	2017 [11]
Bacteremia	Microbiological cure at EOT 29/30 (97%); 30-day readmission 7% (2/30); 30-day mortality 14% (4/30)	NR	No	NR	NR	2017 [11]
Bacteremia	Clinical success 83% (5/6)	(mean) 2 [1-5]	No	NR	NR	2012 [15]
Bacteremia	Clinical success at 6 months 31% (9/20[β]) Microbiological success 90% (26/29);	(median) 3 [IQR 2-5]	In combination with trimethoprim-sulfamethoxazole 23/29, daptomycin 2/29	NR	Rash (1)	2014 [13]
Bacteremia	Clinical success 60% (6/10) Microbiological cure 70% (7/10)	NR	1/10 concomitant therapy with daptomycin	NR	NR	2014 [39]
Endocarditis	Clinical success 62% (5/8)	NR	rifampicin (1) daptomycin (2)	0	0	2014 [20]
Endocarditis	Clinical success 70.9% (39/55)	NR	monotherapy 23/55 (41.8%) daptomycin 19/55 (34.5%), vancomycin 9/55 (16.4%) rifampin 7/55 (12.7%)	2	2	2019 [21]

(*continued on next page*)

Table 2 (*continued*)

Disease	Efficacy/Effectiveness	Mean time to eradication (days)	Concomitant antimicrobial therapy (no. of patients)	AEs (no. of events)	Treatment discontinuation because of AEs (no. of patients)	Reference (Year)
Hospital-acquired pneumonia	Clinical success 75% (30/40)	NR	18/40	NR	AE not recorded (1)	2015 [22]
Nosocomial pneumonia	Clinical success 60% (6/10)	NR	NR	NR	NR	2015 [23]
Nosocomial pneumonia	Clinical success 91% (32/35^); mean hosp. LOS 27.7 (24.4)	NR	No	0	0	2016 [1]
Nosocomial pneumonia	Clinical success 62% (19/25); hosp. LOS mean 25; 30-day readmission 9%; death 6%	NR	7/25 (23%)	0	0	2017 [27]
Osteoarticular infections	Clinical success 58% (7/12); hosp. LOS median 25.5 [7-75]	NR	No	4/12 (33%) Pancytopenia (2) AST/ALT increase (1), pruritic rash (1)	AST/ALT increase (1), pruritic rash (1)	2017 [29]
Osteoarticular infections	180 day all cause readmission 42% (21/50); IRR 22% (11/50); time-to-IRR median 49 [IQR 30-88]	NR	36% non-pseudomonal β-lactam, 10% metronidazole, 4% ciprofloxacin, 4% rifampicin	12/50 (24%) AKI (1), CD infection (2), nausea (3), rash (5)	(6)	2016 [28]
Osteoarticular infections	Clinical success 13/19 (68%) Clinical success at 6-month FU 7/19 (37%) (5 NR)	NR	17 (89.5%) rifampicin (7/19), trimetho-prim/sulfamethoxazole (3/19), fosfomycin (2/19), linezolid (2/19), vancomycin (1/19), daptomycin (1/19), metronidazole (2/19)	4/19 Neutropenia (2) Rash (2)	Neutropenia (2) Rash (2)	2017 [27]
Spinal infections	Clinical success 92% (34/37)	NR	0	3/37 eosinophilic pneumonia (1), drug fever (1), thrombocy-topenia (1)	Eosinophilic pneumonia (1), drug fever (1)	2018 [26]
Meningitis	Clinical success 83% (5/6)	NR	No	NR	NR	2015

AEs, adverse events; AKI, acute kidney injury; AST/ALT, aspartate transaminase/alanine transaminase; CD, *Clostridium difficile*; FU, follow up; IRR, infection related readmission; LOS, length of hospital stay; EOT, end of treatment; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported

♦ Not assessed in all patients

⊥ Composite failure outcome: 30-day mortality/42-day relapse/30-day readmission

^ 35 evaluable cases for the 14 days primary clinical outcome

◦ 14 evaluable cases for the 6-month FU

α 126 patients included in the efficacy analysis

β 9 patients lost to follow-up

addition, MRSA-reduced vancomycin susceptibility phenotype (MRSA-RSV phenotype) is a factor considered to be independently associated with higher vancomycin treatment failures rates [4]. Another concern regarding vancomycin use for serious MRSA infections is potentially lower effectiveness against pathogens with an MIC at the upper limit of susceptibility [5]. Furthermore, resistance to daptomycin and linezolid is emerging [6-8]. More weapons are needed against these serious infections and ceftaroline with its activity against MRSA could be one of these.

Eleven studies in the literature reported the successful use of ceftaroline in MRSA bacteremia [6,9–18]. Two studies were matched case-control, 5 were retrospective and 4 were case series studies, with a total of 595 patients enrolled. In most cases, the reason to use ceftaroline was persistent bacteremia or non-susceptibility of MRSA to vancomycin or daptomycin.

One of the two retrospective matched case-control studies, by Paladino et al., compared time to eradication and cure at the end of treatment in patients treated with other MRSA therapy and switched to ceftaroline or in patients directly treated with ceftaroline (case group) vs. patients treated with vancomycin (control group) [10]. In the case group, median time to eradication was 4 days (IQR, 3-7.5 days), 4 days less than the mean in the control group: 8 days (IQR, 5.8-19.5 days) (P=0.02).

The rate of clinical success at the end of therapy (EOT) was higher in the case group than in the control group, but the difference was not statistically significant (81% vs. 44%, respectively: P=0.06). Thirteen of 16 patients received ceftaroline at the recommended dose (600 mg every 12 h), and the remaining 3 patients received 600 mg every 8 h for the treatment of ABSSSI (2 patients) and osteomyelitis (1 patient).

The second retrospective matched cohort study evaluated overall 30-day mortality rate of 30 consecutive patients diagnosed with MRSA bacteremia and treated with ceftaroline [1]. Ceftaroline group patients were matched with 56 MRSA bacteremia cases

treated with vancomycin and 46 treated with daptomycin. The 30-day mortality rate was 13% (n=4) in the ceftaroline group vs. 24% (n=11) in the daptomycin group and 11% (n=6) in the vancomycin group.

In the case series by Polenakovik et al., 31 patients treated with ceftaroline for persistent or recurrent MRSA bacteremia (MRSAB) after treatment with vancomycin or daptomycin or because of infection with VRSA (MIC ≥ 2 μg/mL) or VISA (MIC of 4-8 μg/mL) or daptomycin non-susceptible (MIC > 1 μg/mL) *S. aureus* were selected [6]. Clinical success was observed in 23 patients (74.2%) and microbiological cure at EOT was reached in 20 patients (64.5%), although not all patients had a microbiological cure assessment.

Casapao et al. performed a large retrospective analysis on 527 patients treated with ceftaroline for different reasons, with 133 patients having bacteremia due to *S. Aureus* [12]. In the subpopulation of patients with *S. aureus* bacteremia, median duration of therapy was 9 days (IQR, 4-16 days), success rate was 78.3% and microbiological success rate was 90.8%.

Another multicenter observational study of 211 patients with MRSAB treated with ceftaroline showed a clinical success rate of 68.3%; 69.7% when ceftaroline was used as monotherapy and 64.9% when used in combination [9]. Median time to eradication was 2 days (IQR, 1-4 days). A bivariate comparison between success and failure groups showed no difference in ceftaroline MICs. APACHE II score and malignancy were identified as independent predictors of treatment failure as result of a multivariate logistic regression.

A lower clinical success rate (31%) was observed by Fabre et al. in their retrospective study in 29 patients with MRSA bacteremia who had been treated with ceftaroline in combination with trimethoprim-sulfamethoxazole [13]. Despite the lower clinical success rate, they reported a microbiological success rate in line with the other studies. Another case series of 26 patients reported success of ceftaroline in combination, this time with daptomycin [14], indicating a synergistic effect of these two antimicrobials. Lin et al. [16] and Ho et al. [15] with their case series on 10 and 6 patients, respectively, confirmed the previously reported rates of ceftaroline efficacy.

Britt el al. performed a retrospective population-based evaluation in the United States Veterans Health Care System including 764 patients treated with ceftaroline for different indications [17]. Of the 764 enrolled patients, 87 received ceftaroline for bacteremia, with a reported hospital mortality of 6% and a median hospital LOS of 8 days (IQR, 3-18) and a 30-day hospital readmission rate of 48% due to unknown causes.

3.2. Endocarditis

β-Lactams are the backbone of first-line endocarditis therapy because of their safety profile and bactericidal activity [19]. Ceftaroline activity against MRSA also makes it an interesting alternative for complicated endocarditis.

Many ceftaroline studies in the literature included patients with endocarditis; however, the results for this indication were not discussed separately [6,9,10–16,18].

Tattevin and collaborators reported a case series of 8 patients treated with ceftaroline for endocarditis. Results showed a positive outcome for 5 patients and immediate clearance of blood cultures after ceftaroline initiation in 7 of 8 patients [20].

The study by Britt et al. reported separate results for the endocarditis group (46/764 patients), with hospital mortality of 11% and 30-day hospital readmission rate of 28% [17].

Also, a recent analysis of the CAPTURE retrospective study involving 55 patients with Gram-positive endocarditis treated with ceftaroline reported an overall clinical success rate of 70.9% [21]. Notably, patients treated with ceftaroline as first-line therapy had a high success rate (75.0%), as did patients who had right-sided endocarditis (80.8%) and patients with MRSA infection (77.3%).

3.3. Hospital-acquired pneumonia and health-care associated pneumonia

Ceftaroline fosamil is approved for the treatment of CABP; however, the ceftaroline spectrum of activity extends to pathogens associated with nosocomial pneumonia (NP), including hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). Ceftaroline is active against non-multidrug-resistant (non-MDR) Enterobacteriaceae and non-fermenter Gram-negative bacilli that may cause HAP or HCAP; therefore, it can be used for targeted therapy of these infections. Furthermore, as ceftaroline has activity against MRSA, it may also be used when this pathogen is isolated in NP.

One case series study and 3 retrospective clinical studies with a total of 115 patients treated with ceftaroline for NP with an MRSA infection in most cases were selected from the literature.

The CAPTURE study is a multicenter, retrospective cohort study on clinical use of ceftaroline [22]. Data from a sub-analysis of the CAPTURE registry on patients with HAP and VAP reported an overall clinical success rate of 75% (82% in patients with HAP and 62% in patients with VAP) [22]. The clinical success rate was 100% for patients treated in general hospital wards and 63% for patients treated in the ICU. Karki and collaborators reported an overall clinical success rate of 62% in their population of 25 patients treated with ceftaroline for MRSA HAP, HCAP or VAP [39].

Pasquale et al. reported a case series of 10 patients treated with ceftaroline for treatment of MRSA NP (HAP, HCAP and VAP infections) because of a high vancomycin MIC of MRSA isolates (≥ 1.5 μg/mL) [23]. Six patients achieved clinical cure or clinical improvement, 3 patients expired (probably because of multiple concomitant diseases and advanced age) and 1 patient relapsed clinically and microbiologically.

The retrospective, matched case-control study by Arshad et al. compared the effectiveness of ceftaroline with that of vancomycin, linezolid and/or cefepime and showed a clinical success rate of 91% of patients treated with ceftaroline vs. 75% for other comparators and a 28-day mortality rate of 10% vs. 14.7%, respectively, but there was no statistical significance (P=0.592) [1]. Multivariate regression and logistic regression analyses showed an association between ceftaroline and lower 28-day mortality (odds ratio [OR] <1) and between ceftaroline and decreased risk of clinical failure (adjusted odds ratio [AOR] 0.207, 95% confidence interval [CI] 0.034-1.245), but many limitations were reported for this study.

3.4. Osteoarticular infections

Staphylococcus aureus is the most common pathogen implicated in osteoarticular infections (OAIs) and vancomycin is the most utilized antibiotic for both empirical and definitive therapy. Despite this, treatment failure rates with vancomycin in OAIs have been reported to be 35-46% [24]. In a rabbit experimental osteomyelitis model, ceftaroline demonstrated significantly better activity against MRSA and glycopeptide-intermediate *S. aureus* (GISA) strains than vancomycin [25].

Many of the previously cited studies evaluating ceftaroline use in patients with bacteremia reported OAIs as the source of bacteremia, but apart from the paper by Britt and colleagues, results were not discussed separately [6,9–12,14,16–18].

There are four other studies in the literature that specifically evaluate ceftaroline in OAIs: three retrospective observational studies [26–28] and one case series [29]. A total of 368 patients with OAIs have been evaluated for off-label use of ceftaroline.

Table 3
Infections associated with bacteremia

Reference	Endocarditis	Bone/joint	Skin/wound	CVC
Arshad 2017	7/30 (23%)	8/30 (27%)	9/30 (30%)	Unknown
Paladino 2014	8/16 (50%)	6/16 (37%)	10/16 (62%)	Unknown
Fabre 2014	15/29 (51%)	9/29 (31%)		Unknown
Polenakovik 2013	9/31 (29%)	1/31 (3.2%)	6/31 (19.3%)	7/31 (22.5%)
Sakoulas 2014	14/26 (54%)	13/26 (50%)	4/26 (15%)	Unknown
Gritsenko 2016	2/5 (40%)	3/5 (60%)	0/5	0/5
Casapao 2014	31/133 (23.3%)	30/133 (22.6%)	10/133 (7.5%)	10/133 (7.5%)
Zasowski 2017	31/126 (24.6%)	26/126 (20.6%)	11/126 (8.7%)	20 (15.9%)

CVC, central venous catheter

In a retrospective, matched cohort study evaluating 50 patients treated with ceftaroline for OAI (osteomyelitis 90%, septic arthritis 4%, prosthetic joint infection 6%) vs. the same number of patients treated with vancomycin, the infection-related readmission (IRR) incidence was 22% for ceftaroline, compared with 30% for vancomycin (OR=0.66 [95% CI=0.27-1.62; P=0.362]) and no significant differences were found between the two groups in all cause readmission [28]. Furthermore, as well as having comparable effectiveness, ceftaroline had similar or even better tolerability.

In the case series of 12 patients treated with ceftaroline for osteomyelitis caused by MRSA, Lalikian et al. reported a clinical success rate of 58% with hospital LOS of 25.5. (7 to 50) days [29]. A retrospective, multicenter study in patients with infection of the spine compared 37 patients (epidural abscess 57%, vertebral osteomyelitis 59%, discitis 70%) treated with ceftaroline with a control group treated with the standard of care (vancomycin, daptomycin, linezolid, doxycycline) [26]. Multivariate analysis showed the OR of clinical success was higher in the group of patients treated with ceftaroline after controlling for chronic kidney disease (CKD), immunosuppression and brain emboli, but the difference was not statistically significative (AOR 1.49; P=0.711).

In the retrospective study by Malandain et al. using ceftaroline as salvage therapy for complex bone and joint infections, 16 of 19 enrolled patients had a polymicrobial infection, and in 17 cases ceftaroline was co-administered with another antibiotic [27]. Researchers reported a positive outcome at EOT in 68% of patients and at 6 months' follow-up in 37% of patients (6 months' follow-up outcome was not reported in 5/19 patients).

For OAIs, Britt et al. reported a median hospital LOS of 5 (IQR, 3-15) days, with 3% hospital mortality and 30-day readmission rate of 35% [17].

3.5. Meningitis

The potential of ceftaroline for treatment of bacterial meningitis has been explored in animal models with promising results. Stucki et al. compared levels of ceftaroline and cefepime in rabbit models with inflamed meninges and in healthy subjects, measuring cerebrospinal fluid (CSF) and areas under the concentration vs. time curves (AUCs) [30]. Penetration of intravenous (iv) ceftaroline at 40 mg/kg into the CSF was approximately 15% in inflamed meninges, and around 3% in uninflamed meninges. Furthermore, ceftaroline was more efficacious than cefepime against *K. pneumoniae* and an *E. coli* strain in experimental meningitis: ΔKilling/8 h was -5.61±1.08 log10 (Δlog10 CFU/mL/8 h) for ceftaroline vs. -3.54±0.94 log10 (Δlog10 CFU/ml/8 h), P<0.0007, and -5.65±1.31 log10 (Δlog10 CFU/mL/8 h) vs -3.67±1.08 log10 (Δlog10 CFU/ml/8 h), P<0.0016, respectively. In another study from the same group, ceftaroline showed greater efficacy than ceftriaxone plus vancomycin against penicillin-resistant *S. pneumoniae* in a rabbit meningitis model, with ΔKilling/8 h of -5.54±0.61 log10 (Δlog10 CFU/mL/8 h) vs. -4.65±1 log10 (Δlog10 CFU/mL/8 h), P<0.03 [31].

There is little evidence in the literature about the use of ceftaroline for meningitis [17,32]. Sakoulas et al. conducted a case series study of 5 patients treated with ceftaroline for bacterial meningitis (1 caused by *S. aureus* and 4 caused by *S. pneumoniae*) [32]. They reported a positive outcome in 4 of 5 patients.

The phase 4 population-based study by Britt et al. examined ceftaroline efficacy in 18 patients with meningitis and showed a mean hospital LOS of 9 days (IQR, 4-34 days) and a hospital mortality of 6% [17].

4. Off-label dose

Ceftaroline is approved for the dose of 600 mg every 12 h in adults and adolescents (aged from 12 to <18 years with bodyweight ≥ 33 kg) with creatinine clearance (CrCL) > 50 mL/min, and the recommended dose regimen for treatment of cSSTI due to *S. aureus* for which the ceftaroline MIC is 2 or 4 mg/L is 600 mg every 8 h using 2-h infusions. Ceftaroline dose adjustment is indicated for CrCL ≤ 50 mL/min [33].

As reported in Table 1, 12 of the selected studies utilized the 600 mg q8 dose [10,12–16,18,20,26,27,29,31] and three the 800 mg q12 dose [16,20,26] (Table 3).

In the case series of bacterial meningitis reported by Sakoulas and colleagues, the only case with unfavorable outcome received a dose of 600 mg q 12 h (the dose approved for ABSSS and CABP) whereas the 4 successful cases received 600 mg q 8 h, indicating a better penetration of CSF at the three times a day (TID) dose [32]. In the case series by Tattevin, ceftaroline was used as salvage treatment for MRSA endocarditis and all patients, except those with renal failure, received an off-label dose: 2 patients received 800 mg q 8 h and 4 patients received 600 mg q 8 h; blood cultures quickly became negative, there was a positive outcome in 4 cases and no adverse effects were reported [20].

Polenakovic reported 6 AEs, including peripheral eosinophilia in 1 patient receiving a total daily dose (TDD) of ceftaroline 1200-1800 mg and eosinophilic pneumonia in 1 patient receiving 1800 mg ceftaroline TDD [6]. Lalikian also reported 6 AEs, including a 4.5-fold increase in aspartate transaminase (AST) and 13.7-fold increase in alanine transaminase (ALT) levels in the only patient receiving ceftaroline 1800 mg TDD after 19 days of therapy [29]. Malandain reported neutropenia requiring ceftaroline discontinuation in two patients, one received 1800 mg TDD plus trimethoprim/sulfamethoxazole and one received the standard dose [27]. Casapao reported 13 AEs associated with off-label dose (of a total of 41 reported AEs): diarrhea, constipation, hypokalemia, thrombocytopenia, chest pain, leukopenia reported in one patient each, rash and renal failure reported in three patients each [12].

5. Discussion

In the large, retrospective evaluation by Casapao el al. of 527 patients treated with ceftaroline, 66.8% of prescriptions were off-label [12]. The indications were bacteremia (42%), bone and joint

infections (23%), nosocomial and/or MRSA pneumonia (19.3%) and other indications (15.6%), including diabetic foot infections, intra-abdominal infections and central nervous system (CNS) infections. Casapao reported a low overall hospital mortality of 7.5%, which is similar to the 5% reported in the evaluation by Britt et al. on 764 patients describing real world use of ceftaroline in the Veterans Health Care Systems [17]. In both cases, ceftaroline was used in early phases of infection and not as salvage therapy. Casapao et al. reported an overall clinical success rate of 88% and a median hospital LOS of 12 days, whereas Britt et al. reported a shorter hospital LOS of 5 days. Rates of readmission at 30 days were also different in these studies, with 9% reported by Casapao and a much higher 33% reported by Britt. Hospital readmission rate varied greatly according to infection type, with the highest rate for bacteremia (48%) and meningitis (44%). Unfortunately, reasons for readmission were not collected, so readmission could be correlated with other comorbidities; in fact, comparing the Charlson Comorbidity index (CCI) of Casapao's study with Britt's reveals an appreciable difference (median 2 vs. 6).

Furthermore, ceftaroline was shown to be safe and effective with clinical success rates over 60% in all included studies and over 70% in most cases, and with even higher microbiological success rates. When reported, clearance of blood cultures was very rapid, from 2 to 4 days, even if it could be biased by the prior use of other antimicrobials.

Ceftaroline could also be a valid option for combination therapies. In vitro studies have demonstrated the synergy between ceftaroline and vancomycin against VISA and hVISA [34,35]. Unfortunately, there are few experiences of the use of ceftaroline in combination in clinical practice. Gritsenko et al. reported a positive outcome in 4 of 5 patients treated with ceftaroline plus vancomycin for MRSA bacteremia [18]. Furthermore, ceftaroline demonstrated a synergistic effect in combination with daptomycin against daptomycin non-susceptible *S. aureus*, enhancing bacterial killing and restoring daptomycin susceptibility.

The ceftaroline dose and dose-frequency issue is still debated. This review includes studies using doses ranging from 200 mg q12 (renal adjustment) to 800 mg q8. In vitro studies show that a shorter dosage interval and higher doses of ceftaroline could increase the time the free drug concentration is above the MIC ($\%fT_{MIC}$) [36], which indicates potential benefits in treating more severe and deep-seated MRSA infections through increased pharmacodynamic effects while reducing the emergence of resistance [37,38]. Unfortunately, many of the included works do not report dose-response correlations; however, where reported, there is good evidence in favor of the use of ceftaroline at higher doses, particularly for deeper and more serious infections, such as MRSA endocarditis and meningitis, while maintaining a good tolerability profile.

There are many limitations to this review: all studies included in this review were retrospective and case series and many of the reported observational studies were based on small sample sizes. In addition, only nine studies reported AEs, thus limiting the overall evaluation of safety of off-label use of ceftaroline.

6. Conclusions

Ceftaroline is an interesting resource, particularly against MRSA infections, with a safety and tolerability profile typical of a β-lactam. There is an increasing need for more antibiotic options in MRSA infections, particularly for patients who fail first-line treatment.

Data on ceftaroline are scarce. Large, prospective, randomized controlled trials are needed to assess the efficacy and safety of ceftaroline to treat bacteremia, endocarditis, OAIs and CNS infections, and more pharmacokinetic/pharmacodynamic studies are required to evaluate %fTMIC to establish the correct frequency of dose and assess safety of long course treatments.

Declarations

Funding: No funding has been received for the conduct of this study and/or preparation of this manuscript

Competing interests: Professor Francesco Scaglione declares to have received speaking fees from GSK, Pfizer and MSD in the past three years. All other authors declare no conflict of interest.

Ethical Approval: Ethical Approval was not required

References

[1] Arshad S, Hartman P, Perri MB, Moreno D, Zervos MJ. Ceftaroline fosamil for treatment of methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia and health care–associated pneumonia. Infect Dis Clin Pract 2016;24:87–91.
[2] Saravolatz LD, Stein GE, Johnson LB. Ceftaroline: A novel cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 2011;52:1156–63.
[3] McGuinness WA, Malachowa N, DeLeo FR. Vancomycin resistance in *Staphylococcus aureus*. Yale J Biol Med 2017;90:269–81.
[4] Yang CC, SY CL, Huang YC, Shie SS, Shu JC, Hseih PH, et al. Risk factors of treatment failure and 30-day mortality in patients with bacteremia due to MRSA with reduced vancomycin susceptibility. Sci Rep 2018;8:7868.
[5] van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis 2012;54:755–71.
[6] Polenakovik HM, Pleiman CM. Ceftaroline for methicillin-resistant *Staphylococcus aureus* bacteraemia: Case series and review of the literature. Int J Antimicrob Agents 2013;42:450–5.
[7] Azhar A, Rasool S, Haque A, Shan S, Saeed M, Ehsan B, et al. Detection of high levels of resistance to linezolid and vancomycin in *Staphylococcus aureus*. J Med Microbiol 2017;66:1328–31.
[8] Kelley PG, Gao W, Ward PB, Howden BP. Daptomycin non-susceptibility in vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous-VISA (hVISA): implications for therapy after vancomycin treatment failure. J Antimicrob Chemother 2011;66:1057–60.
[9] Arshad S, Huang V, Hartman P, Perri MB, Moreno D, Zervos MJ. Ceftaroline fosamil monotherapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a comparative clinical outcomes study. Int J Infect Dis 2017;57:27–31.
[10] Paladino JA, Jacobs DM, Shields RK, Taylor J, Bader J, Adelman MH, et al. Use of ceftaroline after glycopeptide failure to eradicate meticillin-resistant *Staphylococcus aureus* bacteraemia with elevated vancomycin minimum inhibitory concentrations. Int J Antimicrob Agents 2014;44:557–63.
[11] Zasowski EJ, Trinh TD, Claeys KC, Casapao AM, Sabagha N, Lagnf AM, et al. Multicenter observational study of ceftaroline fosamil for methicillin-resistant *Staphylococcus aureus* bloodstream infections. Antimicrob. Agents Chemother 2017;61:e02015–16.
[12] Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother 2014;58:2541–6.
[13] Fabre V, Ferrada M, Buckel WR, Avdic E, Cosgrove SE. Ceftaroline in combination with trimethoprim-sulfamethoxazole for salvage therapy of methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis. Open Forum Infect Dis 2014;1:ofu046.
[14] Sakoulas G, Moise PA, Casapao AM, Nonejuie P, Olson J, Okumura CY, et al. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. Clin Ther 2014;36:1317–33.
[15] Ho TT, Cadena J, Childs LM, Gonzalez-Velez M, Lewis JS. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother 2012;67:1267–70.
[16] Lin JC, Aung G, Thomas A, Jahng M, Johns S, Fierer J. The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. J Infect Chemother 2013;19:42–9.
[17] Britt RS, Evoy KE, Lee GC, Reveles KR, Sorensen KM, Jones X, et al. Early use of ceftaroline fosamil in the United States Veterans Health Care System. Drugs 2017;77:1345–51.
[18] Gritsenko D, Fedorenko M, Ruhe JJ, Altshuler J. Combination therapy with vancomycin and ceftaroline for refractory methicillin-resistant *Staphylococcus aureus* bacteremia: a case series. Clin Ther 2017;39:212–18.
[19] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36:3075–128.
[20] Tattevin P, Boutoille D, Vitrat V, Van Grunderbeeck N, Revest M, Dupont M, et al. Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study. J Antimicrob Chemother 2014;69:2010–13.

[21] Destache CJ, Guervil DJ, Kaye KS. Ceftaroline fosamil for the treatment of Gram-positive endocarditis: CAPTURE study experience. Int J Antimicrob Agents 2019;53:644–9.
[22] Kaye KS, Udeani G, Cole P, Friedland HD. Ceftaroline fosamil for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. Hosp Pract 2015;43:144–9.
[23] Pasquale TR, Tan MJ, Trienski TL, File TM. Methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. J Chemother 2015;27:29–34.
[24] Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax–Rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2018;378:1107–20.
[25] Jacqueline C, Amador G, Caillon J, Le Mabecque V, Batard E, Miègeville AF, et al. Efficacy of the new cephalosporin ceftaroline in the treatment of experimental methicillin-resistant *Staphylococcus aureus* acute osteomyelitis. J Antimicrob Chemother 2010;65:1749–52.
[26] Watkins RR, Yenedewa G, Burdette SD, Horattas S, Haller NA, Mangira C, et al. DISC: Describing Infections of the Spine treated with Ceftaroline. J Glob Antimicrob Resist 2018;13:146–51.
[27] Malandain D, Dinh A, Ferry T, Touchais S, Lustig S, Laurent F, et al. Salvage therapy for complex bone and joint infections with ceftaroline: a multicentre, observational study. Int J Antimicrob Agents 2017;50:277–80.
[28] Athans V, Kenney RM, Wong J, Davis SL. Outpatient use of ceftaroline fosamil versus vancomycin for osteoarticular infection: a matched cohort study. J Antimicrob Chemother 2016;71:3568–74.
[29] Lalikian K, Parsiani R, Won R, Chang E, Turner RB. Ceftaroline for the treatment of osteomyelitis caused by methicillin-resistant *Staphylococcus aureus*: a case series. J Chemother 2018;30:124–8.
[30] Stucki A, Acosta F, Cottagnoud M, Cottagnoud P. Efficacy of ceftaroline fosamil against *Escherichia coli* and *Klebsiella pneumoniae* strains in a rabbit meningitis model. Antimicrob Agents Chemother 2013;57:5808–10.
[31] Cottagnoud P, Cottagnoud M, Acosta F, Stucki A. Efficacy of ceftaroline fosamil against penicillin-sensitive and -resistant *Streptococcus pneumoniae* in an experimental rabbit meningitis model. Antimicrob Agents Chemother 2013;57:4653–5.
[32] Sakoulas G, Nonejuie P, Kullar R, Pogliano J, Rybak MJ, Nizet V. Examining the use of ceftaroline in the treatment of *Streptococcus pneumoniae* meningitis with reference to human cathelicidin LL-37. Antimicrob Agents Chemother 2015;59:2428–31.
[33] CHMP, ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS.
[34] Barber KE, Rybak MJ, Sakoulas G. Vancomycin plus ceftaroline shows potent in vitro synergy and was successfully utilized to clear persistent daptomycin-non-susceptible MRSA bacteraemia. J Antimicrob Chemother 2015;70:311–13.
[35] McConeghy KW, Bleasdale SC, Rodvold KA. The empirical combination of vancomycin and a β-lactam for Staphylococcal bacteremia. Clin Infect Dis 2013;57:1760–5.
[36] Vidaillac C, Leonard SN, Rybak MJ. In vitro activity of ceftaroline against methicillin-resistant *Staphylococcus aureus* and heterogeneous vancomycin-intermediate *S. aureus* in a hollow fiber model. Antimicrob Agents Chemother 2009;53:4712–17.
[37] MacGowan AP, Noel AR, Tomaselli S, Bowker KE. Pharmacodynamics of ceftaroline against *Staphylococcus aureus* studied in an in vitro pharmacokinetic model of infection. Antimicrob Agents Chemother 2013;57:2451–6.
[38] Stryjewski ME, Jones RN, Corey GR. Ceftaroline: clinical and microbiology experience with focus on methicillin-resistant *Staphylococcus aureus* after regulatory approval in the USA. Diagn Microbiol Infect Dis 2015;81:183–8.
[39] Karki A, Thurm C, Cervellione K. Experience with ceftaroline for treatment of methicillin-resistant *Staphylococcus aureus* pneumonia in a community hospital. J Community Hosp Intern Med Perspect 2017;7:300–2.