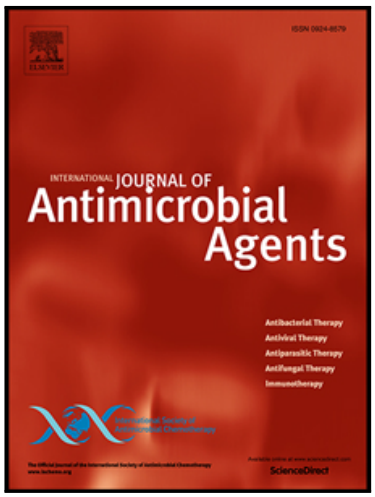

Off-label use of Ceftaroline Fosamil: a systematic review

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Highlights

- Ceftaroline fosamil is a fifth-generation cephalosporin with anti-MRSA activity, frequently prescribed off label in bacteremia, endocarditis, osteoarticular infections, hospital acquired pneumonia, meningitis
- All studies included in this review show efficacy of the off-label use of ceftaroline (77% of clinical success), few adverse events are reported (9%) but not all included studies reported adverse events
- Studies included in this review used different doses and dosing intervals, because of renal adjustment and because off-label use of higher doses which could reach higher pharmacodynamic targets in severe infections with better outcomes and a comparable safety profile
- Quality of included study is low because of the retrospective nature of studies, case series and small sample sizes
- Requirement of more structured evidences, RCT, PK/PD studies to assess real world efficacy and safety of ceftaroline in indications different from the approved

Off-label use of Ceftaroline Fosamil: a systematic review

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Abstract

Ceftaroline fosamil is a fifth-generation cephalosporin and the unique with anti-MRSA activity. It has been approved by EMA and FDA for the treatment of adults and children with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSI) However, given its broad spectrum of activity, safety and tolerability profile it is frequently used off-label.

The aim of this systematic review is to summarize evidence regarding off-label use of ceftaroline, with regard to safety and efficacy.

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

Overall, 21 studies were included for total of 1901 patients: 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 reason 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, of these 724 (77%) reached this positive outcome; incidence of adverse events was reported in 11 studies, in 83 (9%) cases there were adverse events (AEs) related to the use of ceftaroline; most common reported AEs were nausea, vomiting, diarrhea, rash and neutropenia.

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

Keywords

Ceftaroline fosamin; Teflaro; Zinforo; MRSA; bacteremia; endocarditis; osteoarticular infections; meningitis; off-label; dose; safety; efficacy

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

ABSSI 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

1. Introduction

Ceftaroline Fosamil is a fifth-generation cephalosporin with broad spectrum bactericidal activity. It has been initially 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 (ABSSI). In 2015 the FDA has approved a label expansion for the treatment of *Staphylococcus aureus* bacteremia associated with ABSSSI in adults. In 2016 it has been approved for pediatric use with the same indications.

Ceftaroline, like other β-lactams inhibits bacterial cell wall transpeptidation by binding penicillin binding protein (PBP) irreversibly, but in addition is the first and unique cephalosporine with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) because of its capability to bind PBP2a.

It is also active against other common bacteria, such as *S. pneumoniae*, *S. pyogenes*, *H. influenzae* and *M. catarrhalis* including resistant phenotypes. Furthermore, ceftaroline has activity against Gram-negative bacteria including *Klebsiella species* and *E. coli*. Of note, ceftaroline retained activity against heterogeneous vancomycin-intermediate *S. aureus* and it demonstrates activity against significant penicillin and cephalosporin-resistant *S. pneumoniae* strains [1][2].

Since its approval and because of its activity on MRSA, its broad spectrum of activity, the good tolerability and handling typical of a β-lactam, its pharmacokinetic profile, ceftaroline has been widely used off label both on the adult and pediatric patient.

The aim of this systematic review is to summarize available evidence regarding the efficacy and safety of off-label uses of ceftaroline.

2. Methods

2.1 Inclusion and exclusion criteria

We included 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. We have excluded reviews, case series with less than 5 patients, in vitro and studies on animals, abstracts and unpublished data.

2.2 Literature search

We performed a literature search of MEDLINE, EMBASE and CENTRAL databases (2010-2018). We used as keywords "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", "hospital acquired pneumonia".

2.3 Study selection and data extraction

Study selection and data extraction have been performed by two independent reviewers (A.P. and V.F.). We screened the articles produced by the literature search for off label uses of ceftaroline and we selected those potentially relevant. We assessed full text of selected articles and considered eligible all those who respected inclusion and exclusion criteria previously described. Selection process flowchart is shown in **Figure 1**. The characteristics of included studies are listed in **table 1.**

For each study we reported: Disease indication, Study design, Reason for off-label use, Days of ceftaroline therapy, Age of patients, Dose of Ceftaroline, Charslon comorbidity index (CCI), and Year of publication.

3. Results

Table 1. reports study characteristics of 22 included studies. Overall, 10 were retrospective, 3 were case-control studies, 9 case series with more than 5 patients. Indication for off-label use for bacteremia has been investigated in 12 studies, endocarditis in 12, osteoarticular infections in 12, hospital acquired pneumonia in 4 and meningitis in 2.

Efficacy and safety results have been reported in **table 2.** Studies included in this review reported different endpoints for measurement of ceftaroline efficacy: clinical success has been evaluated in 18 studies and authors have globally reported this positive outcome in 77% of evaluated patients while reported microbiological cure rate were above 87% in the 5 studied which took account of this endpoint. Also, hospital length of stay has been frequently analyzed (6 studies), with a mean LOS of 20 days. The mean time to eradication in the six studies reporting this parameter was 3 days.

Incidence of adverse events (AEs) has been evaluated in 11 studies, globally, 83 AEs related to ceftaroline have been reported (9%).

Below we will discuss ceftaroline use per off-label indication.

3.1 Bacteremia

Although Vancomycin is the elective treatment for serious infections caused by MRSA, the prevalence of VRSA (MIC ≥ 16 μg/mL) and hVISA/VISA (MIC = 4-8 μg/mL) is increasing [3] and MRSA-RSV phenotype is considered a factor independently associated with higher vancomycin treatment failures rates [4]. Another raising concern regarding vancomycin use for MRSA serious infections is the possibility of a lower effectiveness against pathogens with a MIC at the upper limit of susceptibility [5]. Furthermore, resistances to daptomycin and linezolid are emerging [6][7][8]. For these reasons we need more weapons against these serious infections and ceftaroline with its activity against MRSA could be one of these.

Eleven published studies [6], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18] were found in the literature reporting the successful use of ceftaroline in MRSA bacteremia. 2 matched case-control, 5

retrospective and 4 case series studies for a total number of 595 patients enrolled. In most cases the reason to use cefaroline was persistent bacteremia or non-susceptibility of MRSA to vancomycin or daptomycin.

One of the two retrospective matched case-control study, Paladino et al. [10] 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). 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: 4 days (IQR, 5.8-19.5 days) (P=0.02). The rate of clinical success at the EOT vas higher in the case group with respect to the control group, but the difference was not statistically significative (81% vs. 44% respectively: P=0.06). Thirteen on sixteen patients received ceftaroline recommended dose (600 mg every 12 hours), three patients received 600 mg every 8 hours for the treatment of ABSSI (2 patients) and osteomyelitis (1 patient).

Another retrospective matched cohort study evaluated the overall 30-day mortality rate of 30 consecutive patients diagnosed with MRSA bacteremia and treated with ceftaroline. Ceftaroline group patients were matched with 56 MRSA bacteremia cases treated with vancomycin and 46 treated with daptomycin. 30-day mortality rate was 13% (n=4) in the ceftaroline group versus 24% (n=11) in the daptomycin group and 11% (n=6) in the vancomycin.

In the case series of Polenakovik et al [6] 31 patients have been selected if treated with ceftaroline for persistent or recurrent MRSAB after treatment with vancomycin or daptomycin or because of infection with VRSA (MIC $\geq$ 2 μg/ml) or VISA (MIC of 4-8 μg/ml) or daptomycin non susceptible (MIC>1 μg/ml) *Staphylococcus aureus*. Clinical success has been 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.[12], performed a large retrospective analysis on 527 patients treated with ceftaroline for different reasons, of which 133 with bacteremia due to *S. aureus*. Among *S. aureus* bacteriemic patient's subpopulation, the median therapy duration was 9 days (IQR, 4 -16 days), the success rate was 78.3% and the microbiological success was 90.8%.

Another multicenter observational study [9] evaluated 211 patients with MRSAB treated with ceftaroline and showed a clinical success rate of 68.3%; 69.7% when ceftaroline was used as monotherapy and 64.9% when used in combination. The median time to eradication in this case was of 2 days (IQR 1-4 days). A bivariate comparison between success and failure group was performed and no differences were founded 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%) has been observed only by Fabre et al. [13] who performed a retrospective study in 29 patients with MRSA bacteremia which have been treated with ceftaroline in combination with trimethoprim-sulfametoxazole. Despite the lower clinical success rate, they reported a microbiologic 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], suggesting also a synergistic effect of these two antimicrobials. Lin et al. [16] and Ho et al. [15] with their case series on respectively 10 and 6 patients confirmed the previously reported rates of ceftaroline efficacy.

Britt el al. [17] performed a population-based evaluation in the United States Veterans Health Care System, enrolling retrospectively 764 patients treated with ceftaroline for different indications. 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), with a 30-day hospital readmission rate of 48% due to unknown causes.

3.2 Endocarditis

Because of their safety profile and bactericidal activity, beta lactams are the backbone of first line endocarditis therapy [19]. Ceftaroline activity against MRSA makes it an interesting alternative also for complicated endocarditis.

Many of the previously reported studies [15], [6], [16], [13], [12], [9], [10], [14], [11], [18] included patients treated with ceftaroline with endocarditis, but results are not discussed separately.

Tattevin and collaborators [20] 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 out of 8 patients.

The already cited study performed by Britt et al. [17], reported separated results for endocarditis group (46/764 patients) and showed an hospital mortality for this group of 11% and a 30-day hospital readmission rate of 28%.

Also a very recent analysis of the CAPTURE retrospective study [21] involving 55 patients with gram positive endocarditis treated with ceftaroline, reported an overall clinical success of 70.9%. Of note, patients treated with ceftaroline as a first-line therapy had a higher success rate 75.0% as well those with right-sided endocarditis (80.8%) and patients with MRSA infection (77.3%).

3.3 Hospital-acquired pneumonia and health-care associated pneumonia

Ceftaroline fosamil has been approved for the treatment of CABP, but Ceftaroline spectrum of activity extends to pathogens associated with nosocomial pneumonia (NP): hospital-acquired pneumonia (HAP), health-care associated pneumonia (HCAP) included ventilator-associated pneumonia (VAP). Ceftaroline is active against non MDR enterobacteriaceae and non-fermenter gram negative bacilli that may cause HAP or HCAP so that it can be used for targeted therapy of these infection. Furthermore, with its activity against MRSA, it may be used also when this pathogen is isolated in NP.

We have selected from the literature 1 case series study and 3 retrospective clinical trial, reporting globally the outcome of 115 patients treated with ceftaroline for NP with an MRSA infection in most

cases.

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

Pasquale et al. [23] reported a case series of 10 patients treated with ceftaroline for treatment of MRSA nosocomial pneumonia (HAP, HCAP and VAP infections) because of a high vancomycin MIC of MRSA isolates ($\geq$ 1.5 μg/ml). 6 patient reached clinical cure or clinical improvement, 3 patients expired probably for the concomitance of multiple diseases and advanced age and 1 patient relapsed clinically and microbiologically.

The comparative retrospective matched case-control study performed by Arshad et al. [1] with the aim to evaluate the effectiveness of ceftaroline in comparison with vancomycin, linezolid and/or cefepime showed a clinical success rate of 91% of patients treated with ceftaroline vs 75% for other comparators and a 28-days mortality rate of 10% vs 14.7% respectively, but there was no statistical significance (p=0.592). However, a multivariate regression and a logistic regression analysis showed an association between ceftaroline and lower 28-day mortality (OR <1) and ceftaroline and decreased risk of clinical failure (AOR 0.207, 95%CI 0.034-1.245), but the authors themselves reported many limitations of 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, OAIs vancomycin failure treatment rates have been described to be around 35-46% [24]. In a rabbit experimental osteomyelitis model, ceftaroline demonstrated significantly better activity against methicillin-resistant *Staphylococcus aureus* (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 osteoarticular infections as source of bacteremia, but except in the case of Britt and colleagues, results are not discussed separately [6], [9]–[12], [14], [16]–[18].

We have found in literature other four works evaluating specifically ceftaroline in osteoarticular infections: three retrospective observational studies [26]–[28] and one case series [29]. In total, 368 patients with osteoarticular infection, have been evaluated for the off-label use of ceftaroline.

In a retrospective matched cohort study evaluating 50 patient 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 incidence (IRR) was 22% for ceftaroline,

compared to the 30% of vancomycin patients, OR=0.66 (95% CI=0.27-1.62; p=0.362) and no significant differences were found in all cause readmission between two groups [28]. Furthermore, aside from having comparable effectiveness, ceftaroline demonstrated to have also similar or even better tolerability.

In the case series of 12 patients treated with ceftaroline for osteomyelitis caused by MRSA [29], Lalikian et al. reported a clinical success rate of 58% with a leght of hospital stay of 25.5. (7 to 50) days. A recent retrospective multicenter study [26] performed 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, doxacicline).

At a multivariate analysis the odds ratio of clinical success was higher in the group of patients treated with ceftaroline after controlling for CKD, immunosuppression and brain emboli, but the difference was not statistically significative (adjusted odds ratio AOR 1.49; p=0.711).

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

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

3.5 Meningitis

The potential of ceftaroline for the treatment of bacterial meningitis has been explored in some animal models with apparently promising results. In the study performed by Stucki et al. [30], authors have 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 versus time curves (AUCs). Ceftaroline i.v., at the dose of 40 mg/k, has shown a penetration of CSF that was approximately 15% in inflamed meninges, while in uninflamed meninges penetration was around 3%. Furthermore ceftaroline has demonstrated higher efficacy compared with that of cefepime against in *Klebsiella pneumoniae* and an *Escherichia coli* strain in experimental meningitis: ΔKilling/8h 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 of the same group [31], Ceftaroline has also shown higher efficacy compared to ceftriaxone plus vancomycin against penicillin-resistant *Streptococcus pneumoniae* in a rabbit meningitis model, with ΔKilling/8h of -5.54±0.61 log10 (Δlog10 CFU/ml/8 h) vs -4.65±1 log10 (Δlog10 CFU/ml/8 h) P<0.03.

Unfortunately, just few evidences about of the use of ceftaroline for meningitis, are reported in literature [32] [17], one of them is a case series reported by Saukolas et. al regarding 5 patients treated with cefatroline for bacterial meningitis (1 caused by *Staphylococcus aureus* and 4 caused by *Streptococcus pneumoniae*). They reported a positive outcome in 4 out of 5 patients.

The second study examinating ceftaroline efficacy in patients with meningitis is the phase 4 population-based study already discussed [17]. Britt et all. enrolled 18 patients with meningitis treated with ceftaroline who had a mean hospital LOS of 9 days (IQR 4-34 days) and an intrahospital mortality of 6%.

4. Off label dose

Ceftaroline is approved for the dose of 600 mg every 12 hours in adults and adolescents (aged from 12 to < 18 years with bodyweight ≥ 33 kg) with 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 hours using 2-hour infusions. Furthermore, an adjustment is indicated in ceftaroline dose if creatinine clearance (CrCL) is ≤ 50 mL/min. [33]

As reported in table 1. twelve of the selected studies reported the utilization of the 600 mg q8 dose [12], [10], [14], [15], [18], [26], [27], [29], [31], [13] and three of the 800 mg q12 dose [16], [20], [26].

In the case series of bacterial meningitis reported by Saukolas and colleagues [32] the only case with unfavorable outcome received a dose of 600 mg q 12 hrs (the dose approved for ABSSS and CABP) while the other 4 successful patients received 600 mg q 8 hrs, suggesting a better penetration of CSF at the TID dose. At the same time, in the case series reported by Tattevin [20] where ceftaroline has been used as a salvage treatment for MRSA endocarditis all patients, except those with renal failure, received an off label dose: 2 patients received 800 mg q 8 hrs and 4 patients 600 mg q 8 hrs, with very fast negativization of blood cultures, positive outcome in 4 cases and no reported adverse effects.

Polenakovic [6] reported 6 AEs, of this one case of periferic eosinophilia in 1 patients receiving a total daily dose (TDD) of ceftaroline 1200-1800 mg and one case of eosinophilic pneumonia in 1 patient receiving 1800 ceftaroline TDD. Also, Lalikian [29] reported 6 AEs, of these the 4,5-fold increase in AST and 13,7-fold increase in ALT levels in the only patient receiving ceftaroline TDD of 1800 mg after 19 days of therapy. Malandain [27] instead, reported the incidence of neutropenia requiring ceftaroline discontinuation in 2 patients, in one patient receiving the TDD of 1800 mg plus trimethoprim/sulfametoxazole, but also in one patient receiving the standard dose. In his work, Casapao [12] reported 13 AEs associated with off label dose (out of a total number of 41 reported AEs): diarrhea, constipation, hypokalemia, thrombocytopenia, chest pain, leukopenia reported in one patient each, rash and renal failure in three patients each.

5. Discussion

In the large retrospective evaluation performed by Casapao el al. [12] of 527 patients treated with ceftaroline, 66.8% of prescriptions was off-label. The most common indication was 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 and CNS. Casapao reported a low overall hospital mortality of 7.5%, similar to the one (5%) reported in another big evaluation performed by Britt et al. on 764 patients [17] describing real world use of ceftaroline in Veterans Health Care Systems.

Should be noticed that in both cases ceftaroline was used relatively in early phases of infection and not as a salvage therapy. Casapao et al. reported an overall clinical success rate of 88% and a median hospital LOS of 12 days, while Britt et al. reported a shorter hospital LOS of 5 days. Rates of readmission at 30 days also are different in these studies, with a 9% reported by Casapao and a much higher 33% reported by Britt. Authors of the study performed in VHA population highlighted how hospital readmission rate varied greatly according infection type, with the highest rate for bacteremia (48%) and meningitis (44%). Unfortunately, reasons for readmissions have not been collected, so there is the possibility that readmission could be probably correlated with other comorbidities, in fact, comparing Charlson Comorbidity index of Casapao's study with Britt's we can notice an appreciable difference (median 2 vs 6).

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

Ceftaroline could be a valid option also 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. [18] reported a positive outcome in 4 out of 5 patients treated with the combination of ceftaroline plus vancomycin for MRSA bacteremia. Furthermore, ceftaroline demonstrated a synergistic effect also in combination with daptomycin against daptomycin non-susceptible *Staphylococcus aureus* enhancing bacterial killing and restoring daptomycin sensibility.

The ceftaroline dose and dose-frequency issue is still debate: as previously reported, in this review we included studies using doses ranging from 200 mg q12 (renal adjusted) to 800 mg q8. In vitro evidences showed that shorter dosage interval and higher doses could increase ceftaroline percentage of time of free drug concentration above the MIC (%fT_{MIC}) [36], suggesting potential benefits in treating more severe and deep seated MRSA infections through the increase of its pharmacodynamic effects and also reducing the resistance emergence [37], [38]. Unfortunately, many of the included works do not report dose-response correlations but where reported, there are good evidences in favor of the use of ceftaroline at higher doses, especially for deeper and more serious infections such as MRSA endocarditis and meningitis, while maintaining a good tolerability profile.

Off course, there are many limitations in presented evidences, all studies included in this review are retrospective and case series and many of the reported observational studies are based on small sample sizes. We should also highlight that only nine studies reported AEs, making less complete the overall evaluation of the safeness in the off-label use of ceftaroline.

6. Conclusions

Ceftaroline has incontrovertibly shown to be an interesting resource, in particular against MRSA

infections, with a safety and tolerability profile typical of a beta-lactam and we increasingly need more antibiotic options in these infections, especially for patient who fails the first line.

Unfortunately evidences at our disposal are insufficient, we need to perform large prospective randomized controlled trials to assess efficacy and safety of ceftaroline to treat bacteremia, endocarditis, osteoarticular infections and CNS infections and more pharmacokinetics/pharmacodynamic studies to evaluate %fTMIC, to establish the right frequency of dose and assess safeness of long course treatments.

Declarations

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Ethical Approval: Ethical Approval was not required

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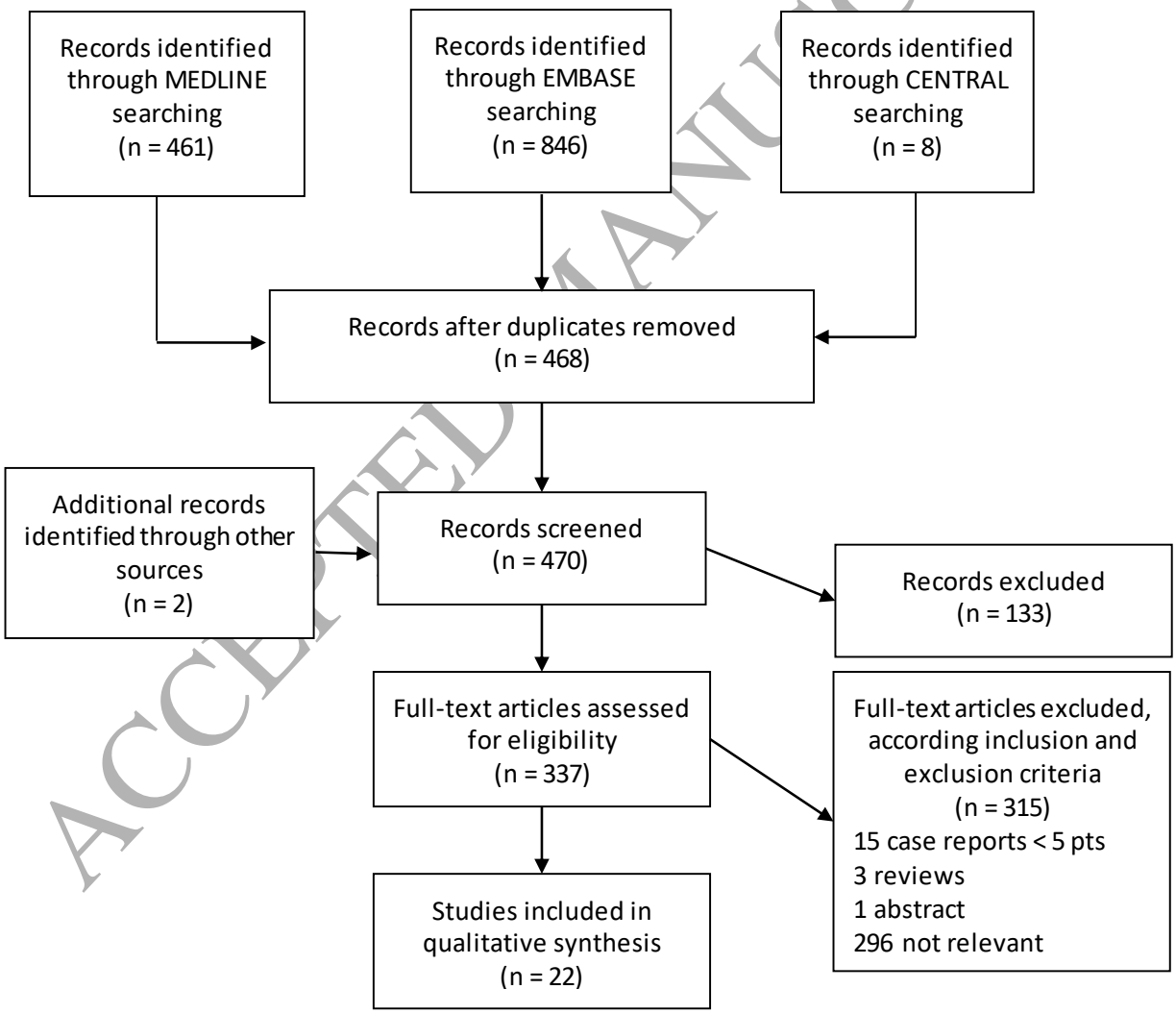

Figure 1 Flowchart summarizing the selection process of included studies

Table 1. Characteristics of included articles

Disease	Study design	Reason for off-label use	Lenght of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCI Mean/ 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 empiric 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 epidemiologic	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	(median) 30.4 [7-60]	31	(median) 49 [22-86]	NR	NR	2013 [6]

Disease	Study design	Reason for off-label use	Lenght of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCI Mean/ median (SD) [range]	Year of publication
		vancomycin and daptomycin						
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 empiric 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]

Disease	Study design	Reason for off-label use	Lenght of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCI Mean/ median (SD) [range]	Year of publication
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]
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	(mean) 13.4 (9.7)	55	52.3 (16.6)	600 mg q12 (15/55) 600 mg q8	NR	2019 [21]

Disease	Study design	Reason for off-label use	Lenght of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCI Mean/ median (SD) [range]	Year of publication
		after previous therapies				(14/55) 400 mg q12 (10/55) 400 mg q8 (6/55) 300 mg q12 (7/55) 300 mg q8 (4/55)		
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,	Toxicity of prior therapy, anticipated	(median) 39 [IQR 31-45]	50	(mean) 56.6 (15.9)	600 mg q12 (82%)	(mean) 2.4 (2.1)	2016 [28]

Disease	Study design	Reason for off-label use	Lenght of ceftaroline therapy, mean/median (SD) [range], days	No. of patients	Age of patients, mean/median (SD) [range], y	Dose	CCI Mean/ median (SD) [range]	Year of publication
	multicenter study	toxicity risk of vancomycin, empirical therapy				400 mg q12 (8%) 300 mg q12 (3%)		
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, empiric, 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

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	(median) 4 [IQR 3-	19% (3/16) one each with	NR	NR	2014 [10]

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)
	cure 100% (16/16); hosp. LOS median 37 [IQR 21.8-76.3]	75]	rifampicin, daptomycin, vancomycin			
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]

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)
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]
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	Clinical success 13/19 (68%)	NR	17 (89.5%)	4/19	Neutrope	2017 [27]

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)
infections	Clinical success at 6-month FU 7/19 (37%) (5 NR)°		rifampicin (7/19), trimethoprim/sulfamethoxazole (3/19), fosfomycin (2/19), linezolid (2/19), vancomycin (1/19), daptomycin (1/19), metronidazole (2/19)	Neutropenia (2) Rash (2)	nia (2) Rash (2)	
Spinal infections	Clinical success 92% (34/37)	NR	0	3/37 eosinophilic pneumonia (1), drug fever (1), thrombocytopenia (1)	Eosinophilic pneumonia (1), drug fever (1)	2018 [26]
Meningitis	Clinical success 83% (5/6)	NR	NO	NR	NR	2015

Table 2. AEs adverse events; IRR infection related readmission; AKI acute kidney injury; LOT length of hospital stay; EOT end of treatment; 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

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%)
Saukolas 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%)