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Original article

IN VITRO ACTIVITY OF CEFTAROLINE AGAINST GRAM-POSITIVE BACTERIA AND ENTEROBACTERALES WITH EMPHASIS ON MRSA: A SINGLE-CENTER STUDY

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Abstract

Introduction: Antimicrobial resistance (AMR) among Gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), remains a major clinical challenge. Ceftaroline fosamil is a fifth-generation cephalosporin with activity against resistant Gram-positive bacteria, including MRSA.

Aim: To evaluate the *in vitro* activity of ceftaroline against Gram-positive bacteria and Enterobacterales isolated from clinical specimens.

Material and methods: A two-phase study was conducted at the Institute of Microbiology and Parasitology, Faculty of Medicine in Skopje. The pilot study (July–August 2022) included 144 isolates, while the six-month study (January–June 2023) included 330 isolates from wound and lower respiratory tract specimens. Susceptibility testing was performed using the disk diffusion method according to EUCAST breakpoints.

Results: All methicillin-susceptible *Staphylococcus aureus* (MSSA; n=133) and MRSA (n=76) isolates demonstrated 100% susceptibility to ceftaroline. Similar susceptibility was observed among coagulase-negative staphylococci and *Streptococcus* spp. (including *S. pyogenes* and *S. pneumoniae*). In contrast, all *Enterococcus* spp. isolates were resistant to ceftaroline. MRSA isolates were resistant to other tested cephalosporins. Among Enterobacterales, susceptibility varied. *Escherichia coli* isolates showed 86% susceptibility, while ESBL-producing strains were resistant. *Klebsiella pneumoniae* isolates demonstrated 60% susceptibility, with all ESBL-producing strains resistant. Susceptibility among *Enterobacter* spp. ranged from 46% to 63%, and among *Proteus mirabilis* from 65% to 75%.

Conclusion: Ceftaroline demonstrated excellent *in vitro* activity against MRSA and MSSA, supporting its role as a potential therapeutic option for resistant Gram-positive infections. However, its activity against Enterobacterales is limited and variable, emphasizing the need for susceptibility-guided use.

Keywords: ceftaroline, methicillin-resistant *Staphylococcus aureus*, antimicrobial susceptibility, Enterobacterales

Introduction

Antimicrobial resistance (AMR) is a major global health problem associated with increased morbidity, mortality, and healthcare costs worldwide[1,2]. It arises due to the misuse and overuse of antibiotics, which accelerates the emergence of resistant microorganisms[2,3]. Among Gram-positive pathogens, *Staphylococcus aureus* (particularly methicillin-resistant

strains, MRSA), *Enterococcus faecium* (including vancomycin-resistant enterococci, VRE), and *Streptococcus pneumoniae* are of particular concern due to their ability to develop multidrug resistance and cause severe infections[4-6].

Methicillin-resistant *Staphylococcus aureus* (MRSA), first isolated in the 1960s, became a prominent nosocomial pathogen over the past three decades. Today, MRSA is the leading cause of community-acquired skin and soft tissue infections (SSTI) and a cause of necrotizing pneumonia. The rapid global spread of MRSA, together with its natural resistance to many available antibiotics, has made it a major public health problem. Vancomycin (the standard intravenous antibiotic utilized in its management) is becoming less reliably effective against MRSA, due to gradual resistance, dosing limitations, and pharmacologic weaknesses. In addition, *S. aureus* strains with vancomycin-intermediate resistance (VISA), heteroresistance (hVISA), and vancomycin resistance (VRSA) have been described[7].

Fortunately, alternatives to vancomycin have been developed in the past decade for the treatment of multidrug resistant (MDR) Gram-positive bacterial infections including an oxazolidinone (linezolid), a lipopeptide (daptomycin), a streptogramin (quinupristin/ dalfopristin), and a glycylcycline (tigecycline) [8,9].

Despite these novel agents, resistance continues to evolve, and strains resistant to linezolid, quinupristin/dalfopristin and daptomycin have been described[10] Moreover, there are side-effects associated with these contemporary antibiotic classes. Finally, many of these unique agents (i.e., linezolid, daptomycin, and telavancin) are only active against Gram-positive bacteria[11]. Ceftaroline fosamil (brand name Zinforo) is a novel fifth-generation parenteral oxyimino- cephalosporin with bactericidal activity against MRSA. In contrast to most of the aforementioned MRSA antimicrobials, ceftaroline fosamil (hereafter, ceftaroline) exhibits broad-spectrum activity against common community-acquired Gram-positive and selected Gram-negative pathogens. Ceftaroline demonstrates potent activity against MRSA and some strains with reduced vancomycin susceptibility (VISA/hVISA), although activity against VRSA remains limited. It also has efficacy against respiratory bacterial pathogens such as *Streptococcus pneumoniae* (including multidrug-resistant strains), *Haemophilus influenzae*, and *Moraxella catarrhalis*. Mirroring other broad-spectrum cephalosporins, ceftaroline does not possess activity against extensively-resistant Gram-negative bacteria and exhibits limited activity against most non-fermentative Gram-negative bacilli (e.g., *Pseudomonas aeruginosa, Acinetobacter* spp.) and many anaerobic species[12,13].

Ceftaroline fosamil is a parenteral prodrug that is rapidly converted to its active metabolite, ceftaroline, following intravenous administration[14]. It is a bactericidal β-lactam antibiotic that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). Notably, ceftaroline demonstrates high affinity for PBP2a, the altered PBP responsible for methicillin resistance in MRSA, thereby restoring β-lactam activity against these strains[15,16].

In addition to PBP2a, ceftaroline binds with high affinity to PBPs such as PBP1a, PBP2b, PBP2x, and PBP3, enhancing its activity against *Streptococcus pneumoniae* and methicillin-sensitive *S. aureus* (MSSA) [17]. Compared to conventional β-lactams such as ceftriaxone and oxacillin, ceftaroline demonstrates enhanced binding affinity to these PBPs[15,16]. According to the European Medicines Agency (EMA) and product characteristics, ceftaroline fosamil is approved for the treatment of community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTI) in adults, adolescents, children, infants, and neonates. Guidelines from IDSA and ESCMID acknowledge ceftaroline as an alternative treatment for CAP and cSSTI when MRSA involvement is suspected or confirmed[18,19].

In North Macedonia, this antibiotic was registered in 2022 and introduced into hospital practice for the treatment of serious infections caused by resistant Gram-positive bacteria.

Considering that antibiotic prescribing is based on prior *in vitro* susceptibility testing, two studies were undertaken following the availability of ceftaroline discs[20].

The aim of these studies was to evaluate the antimicrobial activity of ceftaroline against locally isolated bacterial strains from respiratory tract and wound specimens, in accordance with the approved clinical indications, in order to support its inclusion in routine antibiogram panels for susceptibility testing of both Gram-positive and Gram-negative organisms and to compare the efficacy of ceftaroline to other cephalosporins from the routine antibiogram panels.

Study design

The study was divided into two parts. The first part was a pilot study conducted over a two-month period, while the second part was carried out six months later and covered a six-month period.

Two-month study (July-August 2022)

A two-month study was conducted at the Institute of Microbiology and Parasitology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, testing ceftaroline susceptibility in isolates from wound swabs and lower respiratory tract samples. A total of 157 bacterial isolates from 142 patients were analyzed.

Six-month study (January–June 2023)

A subsequent six-month surveillance study was conducted at the same center, analyzing 330 bacterial isolates.

Material and methods

To achieve the defined objective, all wound samples (swabs, aspirates, etc.) and respiratory tract samples (sputum, tracheal aspirates) obtained from patients hospitalized at the Clinics of the "Mother Teresa" Clinical Center were submitted to the Institute of Microbiology and Parasitology, Faculty of Medicine in Skopje, for microbiological analysis.

For cultivation and biochemical identification of the microorganisms, standard media and biochemical reactions were used. Susceptibility testing was performed exclusively using the disk diffusion method according to EUCAST guidelines. The following cephalosporin discs were used for testing *Staphylococcus*: cefoxitin (30 μg), ceftriaxone (30 μg), and cefotaxime (30 μg). For testing Enterobacterales the following cephalosporin discs were used: cefuroxime (30 μg), ceftazidime (10 μg), ceftriaxone (30 μg), and cefepime (30 μg). In both types of studies, a ceftaroline (5 μg) disc was also included. A comparative analysis with other cephalosporins was performed only for *Staphylococcus* spp., as no clinically meaningful differences in susceptibility patterns were observed among Enterobacterales when compared to the tested cephalosporins.

Statistical comparisons of susceptibility proportions were performed using Fisher's exact test for comparisons between independent groups. For the comparison of ceftaroline with other cephalosporins among MRSA isolates, McNemar's exact test was used, as the same isolates were tested against both antibiotic groups. A p-value < 0.05 was considered statistically significant.

Results

During the study period, ceftaroline was added to the antibiograms for bacteria isolated from wound and lower respiratory tract samples (Table 1).

Table 1. Distribution of clinical samples included in the study

Sample type	Pilot study		Six-month study	
	Number of processed samples	% of total	Number of processed samples	% of total
Wound swab	110	76.4	255	77
Punctate	13	9	25	7.6
Sputum	10	6.9	34	10.3
Tracheal aspirate	11	7.6	16	4.8
Total	144	100	330	100

The distribution of samples for both the pilot (July–August 2022) and the six-month (January-June 2023) study periods is presented in Table 1. Percentages indicate the proportion of each sample type relative to the total number of processed samples.

Table 2 summarizes the distribution of bacterial isolates tested for ceftaroline susceptibility during the pilot and six-month study periods. A total of 144 isolates were collected during the pilot study, increasing to 330 isolates during the six-month study. Among Gram-positive bacteria, methicillin-susceptible *Staphylococcus aureus* (MSSA) was the most frequently isolated organism in both periods, followed by methicillin-resistant *S. aureus* (MRSA). Among Gram-negative bacteria, *Escherichia coli*, *Enterobacter* spp., and *Proteus mirabilis* were commonly recovered.

Table 2. Distribution of bacterial isolates tested for ceftaroline susceptibility during the pilot and six-month study periods

Bacteria	Pilot study Number of isolates	Six-month study Number of isolates
Gram-positive bacteria		
MSSA	34	99
MRSA	21	55
CoNS	5	8
Enterococcus	8	10
Streptococcus pyogenes	6	7
Streptococcus pneumoniae	0	5
Gram-negative bacteria		
E. coli	22	36
E. coli ESBL+	10	24
Klebsiella pneumoniae	12	20
K. pneumoniae ESBL+	2	4
Enterobacter spp.	13	32
Enterobacter ESBL+	3	4
Proteus mirabilis	8	26
Total	144	330

MSSA - methicillin sensitive *Staphylococcus aureus,* MRSA - methicillin resistant *Staphylococcus aureus,* CoNS - coagulase negative *Staphylococcus*

Table 3. Susceptibility of MSSA and MRSA isolates to ceftaroline compared to other cephalosporins

Isolate group	Ceftaroline susceptible N%	Other cephalosporins susceptible N%
MSSA (pilot study)	34 (100%)	34 (100%)
MSSA (6-month study)	99 (100%)	99 (100%)
MRSA (pilot study)	21 (100%)	0 (0%)
MRSA (6-month study)	55 (100%)	0 (0%)

Ceftaroline demonstrated significantly higher activity against MRSA compared to other tested cephalosporins (76/76 *vs*. 0/76; McNemar's exact test, $p<0.0001$).

As shown in Table 3 and Figure 1, ceftaroline demonstrated 100% activity against MSSA and MRSA, while other cephalosporins showed no activity against MRSA. Similar susceptibility rates were observed among isolates of coagulase-negative *Staphylococcus*, as

well as among isolates of *Streptococcus pyogenes* and *Streptococcus pneumoniae*. All tested isolates showed susceptibility to ceftaroline. In contrast to other Gram-positive bacteria, none of the *Enterococcus* isolates demonstrated susceptibility to ceftaroline.

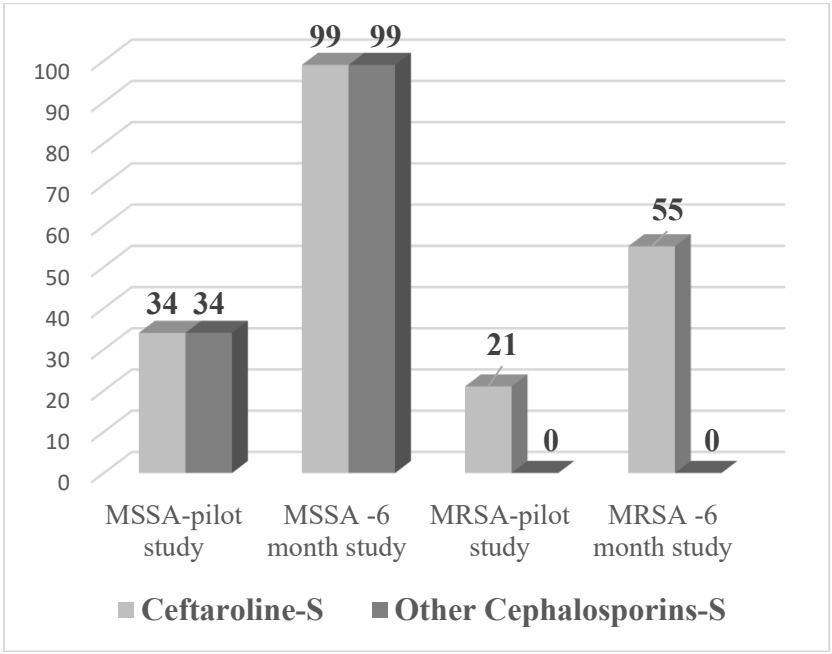

Fig. 1. Susceptibility of MSSA and MRSA isolates to ceftaroline, compared to other cephalosporins

Among Gram-negative bacteria, ceftaroline demonstrated variable activity, with reduced susceptibility observed among Enterobacterales (Figure 2).

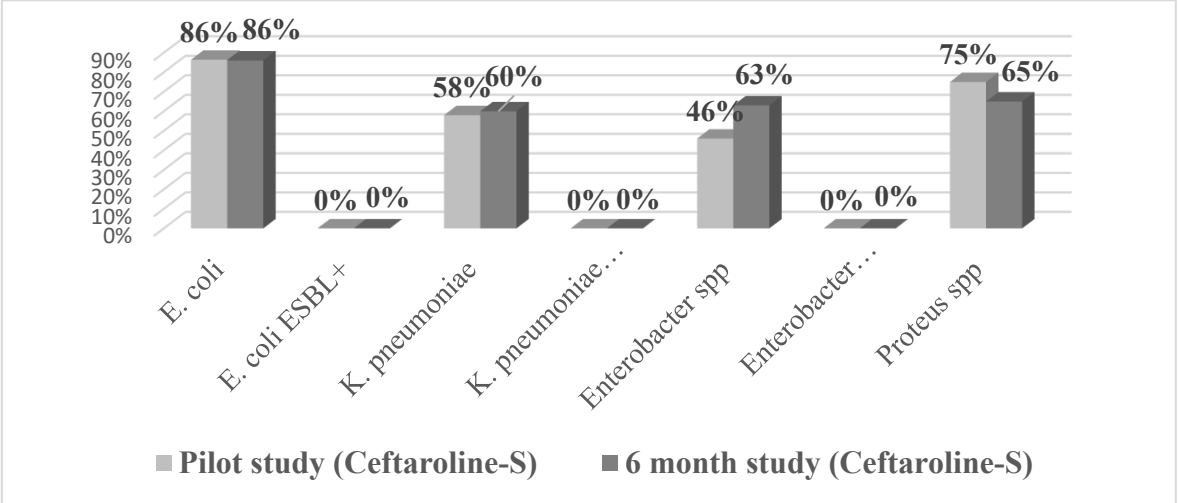

Fig. 2. *In vitro* susceptibility of selected Enterobacterales to ceftaroline during the pilot and six-month study periods. Percentages indicate isolates categorized as susceptible according to EUCAST

During both study periods, an identical percentage of *Escherichia coli* isolates (86%) were susceptible to ceftaroline (19/22 in the pilot study and 31/36 in the 6-month study). ESBL-producing *E. coli* isolates were resistant to ceftaroline. Regarding *Klebsiella pneumoniae* isolates, the percentage of susceptible isolates was almost identical in both studies (58.3% *vs*. 60%) (7/12 in the pilot study and 12/20 in the 6-month- study), while ESBL-producing *K.*

pneumoniae strains were resistant to ceftaroline. Statistically significant differences in ceftaroline susceptibility were observed between ESBL-producing and non-ESBL-producing isolates of both *Escherichia coli* ($p<0.0001$) and *Klebsiella pneumoniae* ($p=0.0197$).

With respect to *Enterobacter* spp., ESBL-positive strains were resistant to ceftaroline. In contrast, among ESBL-negative *Enterobacter* isolates, a difference in the percentage of susceptible strains was observed between the two studies (46% *vs*. 63%). A difference in susceptibility was also observed among *Proteus* spp. isolates between the two studies (75% *vs*. 65%) (Table 4).

Table 4. Comparison of the results of two studies involving bacteria with larger observed differences

Bacteria	Type of study	Number of isolates	Susceptibility (S) to ceftaroline N%
Enterobacter spp.	Pilot study	13	6 (46%)
	6-month study	32	20 (63%)
Proteus mirabilis	Pilot study	8	6 (75%)
	6-month study	26	17 (65%)

No statistically significant differences were observed in ceftaroline susceptibility for *Enterobacter* spp. and *Proteus mirabilis* isolates from the pilot and six-month study periods (46% *vs*. 63%, Fisher's exact test, $p = 0.34$) and (75% *vs*. 65%, Fisher's exact test, $p = 0.69$), respectively.

Discussion

The present study demonstrates that ceftaroline exhibits excellent *in vitro* activity against Gram-positive bacterial isolates, particularly *Staphylococcus aureus* (including methicillin-resistant *S. aureus* - MRSA) and *Streptococcus pyogenes*. All tested MSSA and MRSA isolates were susceptible to ceftaroline, confirming its potent activity against methicillin-resistant strains. These findings are consistent with previously published studies reporting high MRSA susceptibility rates, attributed to the strong affinity of ceftaroline for penicillin-binding protein 2a (PBP2a), the key mediator of methicillin resistance. Data from the AWARE surveillance study, which included more than 12,000 MRSA isolates, demonstrated that 97.6% were susceptible to ceftaroline[21]. Similarly, global surveillance studies of bloodstream infections have reported susceptibility rates exceeding 95% among *S. aureus* isolates, highlighting the consistent efficacy of ceftaroline across diverse clinical settings[22].

The complete susceptibility of MRSA isolates observed in this study is of particular clinical importance, given the increasing prevalence of MRSA infections and the limitations associated with traditional agents such as vancomycin, including reduced susceptibility and potential toxicity. This observation was further supported by statistical analysis, which showed a highly significant difference compared to other tested cephalosporins (McNemar's exact test, $p < 0.0001$). This finding highlights the unique ability of ceftaroline to overcome methicillin resistance through effective binding to PBP2a, in contrast to other cephalosporins that lack this capability. Although alternative agents such as linezolid, daptomycin, quinupristin/dalfopristin, and tigecycline are available for the treatment of infections caused by multidrug-resistant Gram-positive bacteria, their use may be limited by emerging resistance, adverse effects, pharmacokinetic constraints, or a restricted antimicrobial spectrum[23,24].

As expected, enterococci demonstrated resistance to ceftaroline, reflecting their intrinsic resistance to most cephalosporins. This resistance is primarily associated with the presence of low-affinity penicillin-binding protein PBP5, which reduces β-lactam activity. The

findings of the present study are therefore consistent with previously reported data indicating that ceftaroline is not effective against *Enterococcus faecalis* or *Enterococcus faecium*[25].

In contrast to Gram-positive bacteria, Enterobacterales exhibited lower and more variable susceptibility to ceftaroline. Previous surveillance studies have reported susceptibility rates of approximately 70–90% among non-ESBL-producing *Escherichia coli*, with significantly lower rates observed in ESBL-producing isolates, supporting the variability identified in this study[27,28]. Reduced susceptibility among Enterobacterales is primarily associated with β-lactamase production, particularly extended-spectrum β-lactamases (ESBLs) and AmpC enzymes, which compromise the activity of cephalosporins.

In the present study, all ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates were resistant to ceftaroline, with statistically significant differences observed between ESBL-producing and non-ESBL-producing isolates. Among non-ESBL-producing isolates, susceptibility rates were 80% for *E. coli*, 60% for *K. pneumoniae*, 46–63% for *Enterobacter* spp., and 65-75% for *Proteus* spp. Although a higher proportion of susceptible *Enterobacter* spp. isolates was observed in the six-month study compared to the pilot phase, this difference was not statistically significant and likely reflects differences in sample size, isolate distribution, or temporal variation in local resistance patterns. Similarly, no statistically significant difference in ceftaroline susceptibility was observed between *Proteus mirabilis* isolates from the pilot and six-month study periods (75% *vs*. 65%, Fisher's exact test, p=0.69). Although a numerical difference was noted, it was not statistically significant and may reflect natural fluctuations in local antimicrobial resistance patterns. Similar fluctuations have been reported in longitudinal surveillance studies and are commonly attributed to changes in sample composition, local epidemiology, and temporal trends in resistance[29]. These findings highlight the importance of continuous antimicrobial resistance surveillance, particularly for Gram-negative bacteria, in which resistance mechanisms are diverse and rapidly evolving.

The results of this study support the inclusion of ceftaroline in routine antibiogram panels, particularly for Gram-positive pathogens. Its demonstrated activity against MRSA suggests that it may represent an effective alternative to established anti-MRSA agents in selected clinical settings. However, the limited and variable activity observed among Enterobacterales indicates that ceftaroline should not be considered a first-line agent for suspected Gram-negative infections without prior susceptibility testing.

This study has several limitations. First, antimicrobial susceptibility testing was performed exclusively using the disk diffusion method according to EUCAST guidelines, without determination of minimum inhibitory concentrations (MICs); therefore, the results reflect categorical interpretations rather than quantitative measurements. Second, comparative analysis with other cephalosporins was performed only for *Staphylococcus* spp., as no clinically meaningful differences were observed among Enterobacterales. Finally, the study was conducted at a single center, which may limit the generalizability of the findings.

Despite these limitations, the present study provides valuable local data on ceftaroline susceptibility, supporting its role in the treatment of infections caused by resistant Gram-positive bacteria. Continued surveillance and periodic reassessment of antimicrobial susceptibility patterns are essential to monitor emerging resistance trends.

In conclusion, ceftaroline demonstrated excellent *in vitro* activity against Gram-positive bacteria, including MRSA, while showing limited and variable activity against Enterobacterales. These findings support its inclusion in routine susceptibility testing panels and its consideration as a therapeutic option for infections caused by resistant Gram-positive pathogens, particularly when MRSA involvement is suspected or confirmed.

Conflict of interest statement. None declared.

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