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RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2025;30 • doi: 10.5578/flora.2025041464

In Vitro Activity of Ceftaroline Alone and in Dual Combinations Against Methicillin-Resistant *Staphylococcus aureus* Isolates

Seftarolinin Tek Başına ve İkili Kombinasyonlar Halinde Metisiline Dirençli *Staphylococcus aureus* İzolatlarına Karşı In Vitro Etkinliği

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Cite this article as: *Kara Altay G, Öksüz L. In vitro activity of ceftaroline alone and in dual combinations against methicillin-resistant Staphylococcus aureus isolates. FLORA 2025;30.*

**This study was presented as a poster (P1273) at the 34th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) held in Barcelona, Spain, on 27-30 April 2024.*

ABSTRACT

Introduction: *Methicillin-resistant Staphylococcus aureus (MRSA) remains a serious clinical concern with high morbidity and mortality rates. The emergence of MRSA isolates resistant to ceftaroline (CPT), which exhibits anti-MRSA activity, has necessitated the investigation of novel treatment options. Combinations of CPT-vancomycin (VAN) or CPT-daptomycin (DAP) are recommended for the treatment of serious MRSA infections. The study aimed to determine the effectiveness of CPT alone and in dual combinations against MRSA isolates.*

Material and Methods: *A total of 100 MRSA isolates obtained from clinical samples were included in the study. The disk diffusion method (DDM) was used to detect the susceptibility of routinely used antibiotics, while the broth microdilution (BMD) method was utilized for the detection of susceptibility against CPT, VAN and DAP. The evaluation of antibiotic susceptibility results was conducted in accordance with the established guidelines. The effectiveness of CPT-VAN and CPT-DAP combinations was investigated by the checkerboard method.*

Results: *The highest resistance rates in MRSA isolates were found for cotrimoxazole (77%), tetracycline (50%) and erythromycin (40%). Forty-one percent of all isolates had the iMLSb phenotype. Three isolates were resistant to CPT and two isolates were resistant to DAP. Resistance to CPT was found in 2.5% of blood stream infections (BSI) isolates, and 4.5% of skin and soft tissue infections isolates. The rate of "susceptible, increased exposure" to CPT was 56% using the BMD method and 2% using the DDM method. No VAN-intermediate- or VAN-resistant- S. aureus were detected. Both CPT-VAN and CPT-DAP combinations showed an indifference effect against CPT-resistant (CPT-R) isolates.*

Conclusion: *Despite the relatively low rate of CPT resistance detected in this study, concerns have been raised that the number of CPT-R isolates may increase over time. The indifferent effect of CPT in binary combinations highlights the necessity to test new synergistic antimicrobial combinations.*

Key Words: *Antibiotic resistance; Ceftaroline; Daptomycin; Vancomycin; Antibiotic combinations*

Received/Geliş Tarihi: 28/07/2025 - Accepted/Kabul Ediliş Tarihi: 20/10/2025

Available Online Date: 09.12.2025

ÖZ

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Giriş: *Metisiline dirençli Staphylococcus aureus (MRSA), yüksek morbidite ve mortalite oranlarıyla ciddi bir klinik sorun olmaya devam etmektedir. Anti-MRSA aktivitesi gösteren seftarolin (CPT)'e dirençli MRSA izolatlarının ortaya çıkması, yeni tedavi seçeneklerinin araştırılmasını gerektirmiştir. Ciddi MRSA infeksiyonlarının tedavisinde CPT-vankomisin (VAN) veya CPT-daptomisin (DAP) kombinasyonları önerilmektedir. Bu çalışmada, CPT'nin tek başına ve ikili kombinasyonlar halinde MRSA izolatlarına karşı etkinliğinin belirlenmesi amaçlanmıştır.*

Materyal ve Metod: *Klinik örneklerden elde edilen toplam 100 MRSA izolatı çalışmaya dahil edilmiştir. Rutin olarak kullanılan antibiyotiklerin duyarlılığının belirlenmesi için disk difüzyon yöntemi; CPT, VAN ve DAP'a karşı duyarlılığın belirlenmesi için ise sıvı mikrodilüsyon (BMD) yöntemi kullanılmıştır. Antibiyotik duyarlılık sonuçlarının değerlendirilmesi, European Committee Antimicrobial Susceptibility Testing rehberine uygun olarak gerçekleştirilmiştir. Seftarolin-VAN ve CPT-DAP kombinasyonlarının etkinliği dama tahtası yöntemiyle araştırılmıştır.*

Bulgular: *En yüksek direnç oranları kotrimoksazol (%77), tetrasiklin (%50) ve eritromisine (%40) karşı saptandı. Tüm izolatların %41'i iMLSb fenotipine sahipti. Üç izolat CPT'ye, iki izolat ise DAP'a dirençliydi. Kan dolaşımı infeksiyonları (BSI) izolatlarının %2.5'inde; cilt ve yumuşak doku infeksiyonları izolatlarının %4.5'inde CPT'ye direnç saptandı. Ayrıca CPT'ye "duyarlı, artan maruziyet (S-IE)" oranı BMD yöntemi ile %56, DDM yöntemi ile %2 olarak bulundu. VAN-orta duyarlı (VISA) veya VAN-dirençli S. aureus (VRSA) saptanmadı. Hem CPT-VAN hem de CPT-DAP kombinasyonları, CPT-R izolatlarına karşı indiferens etki gösterdi.*

Sonuç: *Bu çalışmada saptanan CPT direnci oranı nispeten düşük olmasına rağmen, CPT dirençli izolatların sayısının zamanla artabileceği endişesi bulunmaktadır. CPT'nin ikili kombinasyonlardaki etkisi, yeni sinerjik antimikrobiyal kombinasyonların test edilmesi gerekliliğini vurgulamaktadır.*

Anahtar Kelimeler: *Antibiyotik direnci; Seftarolin; Daptomisin; Vankomisin; Antibiyotik kombinasyonları*

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a gram-positive bacterium that can cause diseases such as bloodstream infections (BSI), skin and soft tissue infections (SSTI), and pneumonia. In the last two decades, the increase in numbers of MRSA isolates with reduced vancomycin susceptibility [vancomycin (VAN)-intermediate *S. aureus* (VISA), heterogeneous VAN-intermediate *S. aureus* (hVISA)] or daptomycin-resistant MRSA (DRSA) isolates has necessitated the search for alternative antibiotics [daptomycin (DAP), linezolid, quinupristin/dalfopristin, ceftaroline (CPT), ceftobiprole, etc.]. CPT has been preferred as rescue treatment in BSI caused by MRSA that do not respond to treatment with VAN and DAP. CPT is a fifth-generation cephalosporin effective against MRSA and has been approved in 2010 for SSTI and for community-acquired bacterial pneumonia[1,2]. However, in real-life practice it has been used for several off-label indications including BSI.

MRSA isolates have acquired an additional PBP gene, *mec*A, encoding PBP2a, which is not inhibited by most beta-lactams. The ability of PBP2a to function in the presence of beta-lactams confers resistance to many beta-lactams. However, CPT is also capable of binding to PBP2a and has superior affinity to other beta-lactams. The MRSA activity of CPT is related to the addition of a 1,3-thiazole ring moiety to its structure[3,4]. CPT has strong *in vitro* activity against all s*taphylococci* including VISA, VAN-resistant *S. aureus* (VRSA) and DRSA isolates[5]. The 2010 AWARE study, which evaluated antimicrobial resistance, demonstrated that CPT exhibited high activity *in vitro* against MRSA isolates collected from various medical centers across the United States[6]. VAN and DAP were approved by the Food and Drug Administration (FDA) for monotherapy in MRSA bacteremia, but the poor bactericidal effects of glycopeptides against MRSA and the high mortality rates in MRSA-BSIs have led researchers to seek better antimicrobial

treatment strategies. To ensure appropriate antimicrobial management of sepsis, if there is no response to monotherapy, timely discontinuation of the current treatment and switching to targeted combination therapy is a critically important intervention[7-11]. Combination therapy for MRSA involves the administration of DAP in conjunction with beta-lactams, predominantly anti-staphylococcal penicillins or CPT[2]. The combination of CPT with antibiotics such as VAN or DAP has been recommended in CPT-resistant (CPT-R) BSIs[1]. Ceftaroline-VAN or CPT-DAP combinations have been recommended in treatment of infections caused by CPT-R isolates[1,12]. It has been reported that when DAP is used together with a beta lactam antibiotic, the binding affinity of DAP increases and the development of resistance to DAP is delayed[2,8,13]. CPT, a beta lactam antibiotic, increases the effectiveness of DAP by inhibiting the synthesis of the bacterial cell wall and allowing DAP to penetrate the cell membrane more easily[14]. When another alternative, beta lactam-VAN combination, is used, VAN reaches the target more easily due to the decrease in cell wall thickness in the presence of beta lactam, and provides a synergistic effect[8].

In the current study, resistance to CPT, DAP, and VAN was studied in MRSA isolates, followed by an investigation of the in vitro effectiveness of CPT in combination with VAN and DAP

MATERIALS and METHODS

Study Design

A total of 100 clinical MRSA isolates (from 78 BSI and 22 SSTI) collected retrospectively and prospectively were included in this study (Figure 1). Despite the fact that the study was originally conceived with the intention of examining solely MRSA isolates from BSIs, it was subsequently determined that the study would also encompass some surveillance isolates from previous years. This decision was made because the number of isolates obtained during the study period was insufficient to meet the study's objectives, and CPT had already received FDA approval for SSTIs.

The first isolate from each patient was included in the study. The study was approved by the İstanbul University İstanbul Faculty of Medicine, Clinical Research Ethics Committee (Ethical approval number (13.05.2022/09). The tests were repeated twice by two separate researchers and the repeatability of the data was verified.

Isolation and Identification of Bacterial Isolates

To isolate bacteria from BSIs, blood culture bottles were incubated in an automated blood culture system (BACTEC FX, Becton Dickinson, United States of America) for five days. For bottles with positive signals, then the samples were inoculated in 5% sheep blood agar and incubated at 37 °C for 18-24 hours. Bacterial identification was performed by conventional tests, and if necessary, the automated identification system (VITEK 2, bioMérieux, France) was used.

For isolating of the bacteria from SSTIs, skin and soft tissue samples sent from various clinics were inoculated into blood agar and incubated at 37 °C for 24-48 hours. Growing colonies at the end of the incubation period were evaluated for the presence of *S. aureus*. The isolated bacteria were identified using conventional methods (Gram morphology, catalase activity, plasma coagulase, DNAse, etc.), and by automated system (VITEK 2, bioMérieux, France), if necessary[15]. Cefoxitin screening test and commercial PBP2a kit (Oxoid, United Kingdom) were used to detect resistance to methicillin[15,16].

Antimicrobial Susceptibility Testing

The susceptibility of the bacterial isolates to routinely used antibiotics (penicillin G, erythromycin, clindamycin, co-trimoxazole, linezolid, tetracycline, rifampicin, levofloxacin, gentamicin) was determined by Kirby Bauer's disk diffusion method (DDM) and interpreted according to European Committee Antimicrobial Susceptibility Testing (EUCAST) recommendations[17,18]. For detection of sensitivity to VAN and DAP, the broth microdilution (BMD) method was used. Resistance to CPT was investigated by both DDM and BMD methods[15]. Isolates that demonstrated resistance to erythromycin, sensitivity to clindamycin, and the formation of a D-shaped inhibition zone around clindamycin that flattened towards the erythromycin disk were evaluated as having the

iMLSb (inducible macrolide-lincosamide-streptogramin B) phenotype. The evaluation of isolates revealed that those demonstrating resistance to both erythromycin and clindamycin exhibited the constitutive macrolide-lincosamide-streptogramin B (cMLSb) phenotype. Conversely, isolates exhibiting resistance to erythromycin, yet sensitivity to clindamycin, and the absence of a D-shaped inhibition zone, were designated as having the MSb (macrolide-streptogramin B) phenotype[19-21]. Resistance to VAN was performed by the VAN-agar screening method[15,16]. Furthermore, the presence of hVISA was investigated using the macro gradient test method in isolates with a VAN-minimum inhibitory concentration (MIC) value of 2 µg/mL. *S. aureus* ATCC 29213 strain was used as the standard strain in antibiotic susceptibility tests.

Checkerboard Testing

The in vitro effectiveness of CPT-VAN and CPT-DAP combinations against CPT-R isolates (n= 3) was performed by the checkerboard method. The ΣFIC value obtained by adding the fractional inhibitory concentration (FIC) values of both antibiotics in the combination was evaluated as synergistic (≤0.5), indifferent-additive (0.5- ≤4) or antagonist (>4) effect according to guideline recommendations. (15).

RESULTS

Patients

Two-thirds (71%) of the patients from whom the studied MRSA strains were isolated were adult patients, and the rates of male patients (51%) and female patients (49%) were similar. The age range of all patients was 0-96 years; the median age was 8.5 years for pediatric patients and 48 years for adult patients. Clinical samples from which bacteria were isolated were mostly sent from internal medicine (34%), following pediatrics (16%) units. The distribution of MRSA isolates by the years is shown in Figure 1.

Antibiotic Resistance Results

Antibiotic resistance rates by DDM of isolates from BSI and SSTI samples are shown in Figure 2. The highest resistance rates in BSI isolates were detected against cotrimoxazole, erythromycin and tetracycline. In 2019, following the removal of the "intermediate" category from the EUCAST guidelines, the isolates with an MIC value of 2 µg/mL for CPT were included in the "susceptible, increased exposure (S-IE)" category[22]. In our study, no isolates resistant to CPT and linezolid were found, but the rate of isolates that S-IE to CPT was found to be 2% by DDM. The rate of S-IE to levofloxacin

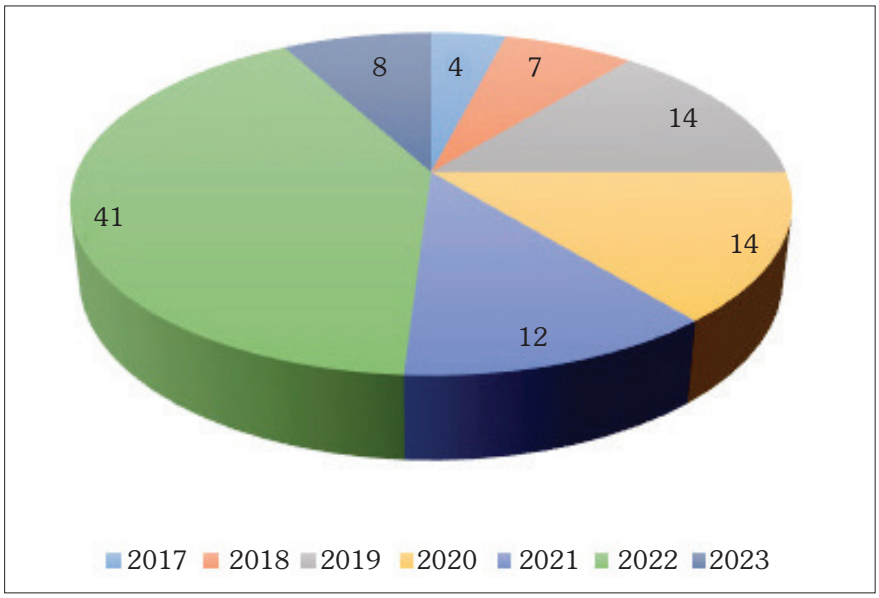

Figure 1. Numbers of MRSA isolates by years (n).

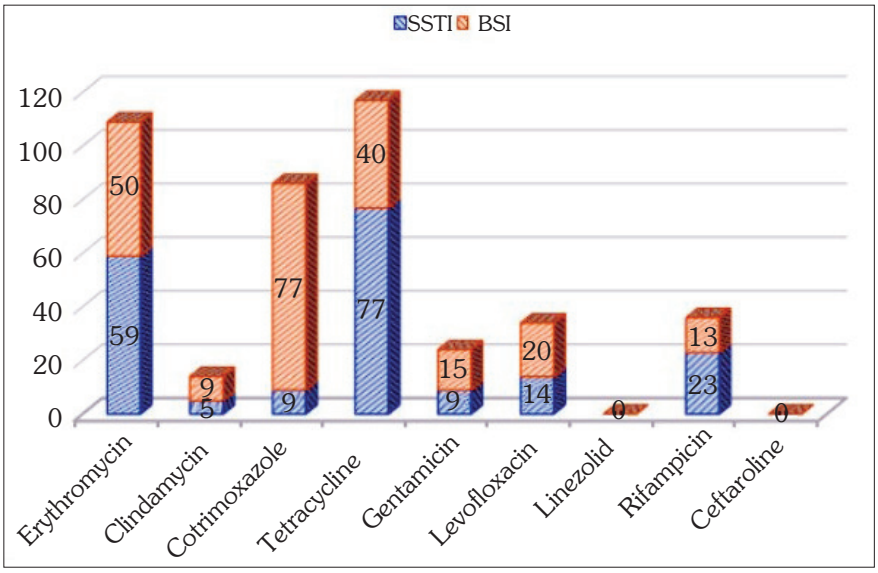

Figure 2. Resistance rates of disc diffusion test results by infection types (SSTI: Skin and soft tissue infection).

was 80% in BSI isolates (n= 78) and 86% in SSTI isolates (n= 22). Additionally, 5% (4/78) of the BSI isolates were found to be S-IE to co-trimoxazole. Among all isolates, the presence of $iMLS_b$ was detected in a total of 41 strains (Figure 3). Of the isolates showing the $iMLS_b$ phenotype, 32 were isolated from BSI and nine were isolated from SSTI samples.

Three isolates (3%) were found to be resistant to CPT (MIC= 8 µg/mL each) by the BMD. The results obtained from all isolates studied with the BMD test are shown in Table 1, and the MIC distributions of all isolates studied are shown in Figure 4. The rate of S-IE to CPT was found to be 56% by the BMD test. The correlation between inhibition zone diameters and MIC values for CPT in all isolates tested is shown in Figure 5. In addition, the categorical agreement scheme for CPT was shown in Figure 6. In this study, one of the two isolates found to be

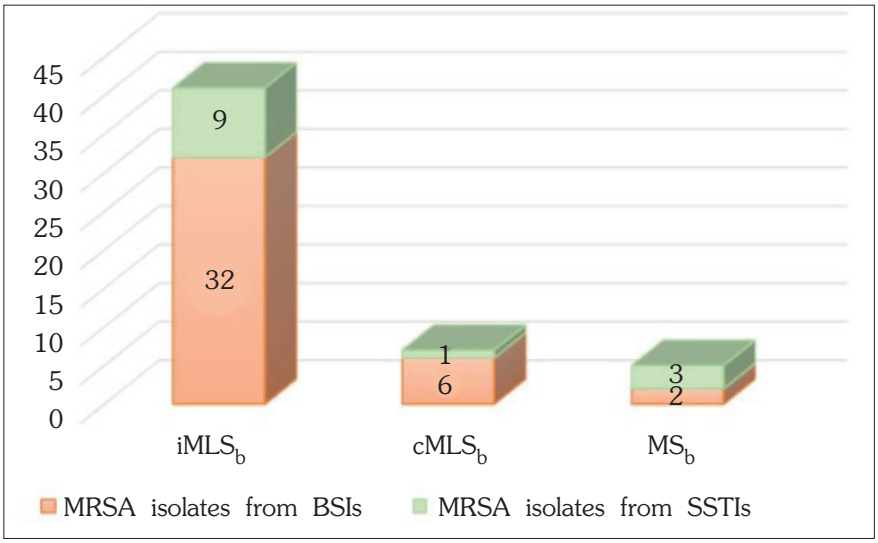

Figure 3. Numbers of $iMLS_b$, $cMLS_b$ and MS_b in total MRSA isolates (BSI: Bloodstream infections, SSTI: Skin and soft tissue infection).

Table 1. MIC ranges, MIC_{50} and MIC_{90} values for ceftaroline, daptomycin and vancomycin

MIC values (µg/mL)	Ceftaroline (CPT)	Daptomycin (DAP)	Vancomycin (VAN)
MIC ranges	0.125-8	0.125-2	0.5-2
MIC_{50}	2	0.25	2
MIC_{90}	2	0.5	2

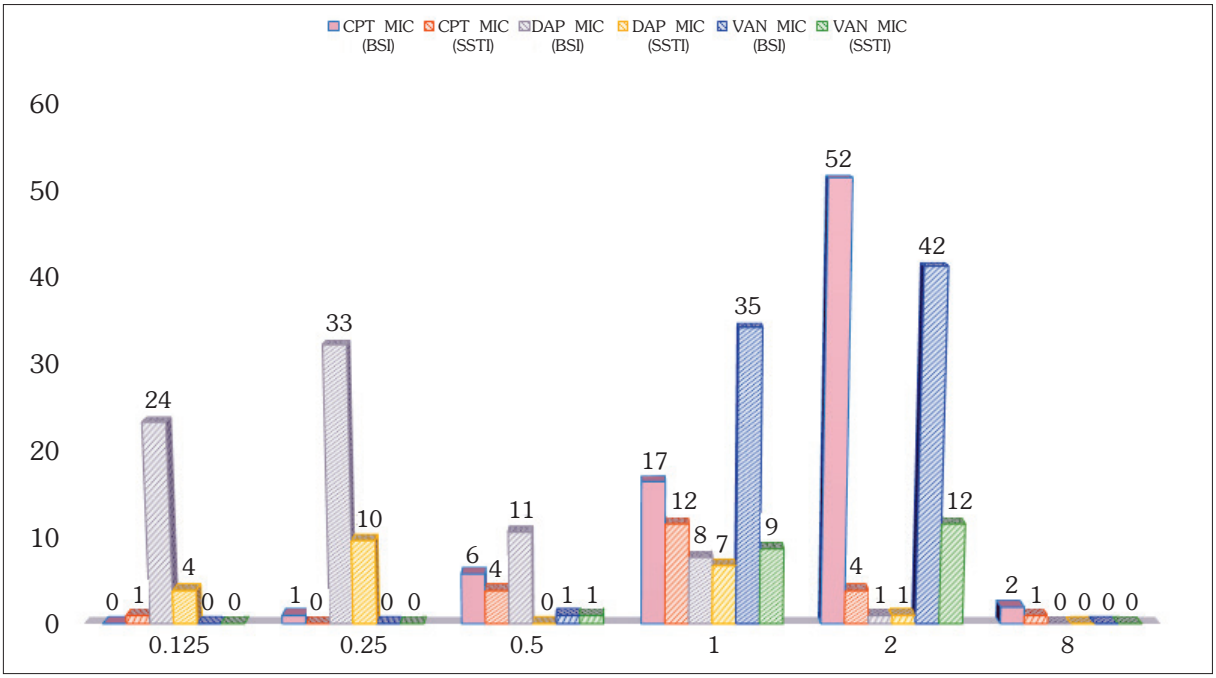

Figure 4. MIC distributions of total MRSA isolates (Breakpoint for DAP: 1 µg/mL; breakpoint for CPT and VAN: 2 µg/mL) (BSI: Bloodstream infections, SSTI: Skin and soft tissue infection).

resistant to DAP (both MIC= 2 µg/mL) was isolated from SSTI and the other from a BSI. The MIC_{50} and MIC_{90} values of both VAN and CPT were determined to be 2 µg/mL in total isolates tested.

No VAN-resistant (VRSA) strain was detected by the VAN-agar screening method, and no VISA or hVISA was detected by the macrogradient test method.

By the checkerboard method, CPT-VAN and CPT-DAP combinations showed an indifference effect against CPT-R isolates (n= 3) (Table 2). No synergistic or antagonistic interactions were observed.

DISCUSSION

Approximately 18.000-20.000 blood cultures/year are submitted to our laboratory from various units, with a positive rate of approximately 14-16%. MRSA isolates emerged as a nosocomial pathogen during the 1980s, subsequently becoming a significant concern due to its resistance to other commonly prescribed antibiotics in our country. As the MRSA isolates in question were found to be sensitive to vancomycin and teicoplanin, the use of glycopeptides began to increase. According to data from the National Antimicrobial Resistance Surveillance System collected in 2016, the prevalence of MRSA in our country has been reported as 23.6%. Projections by the European Centre for Disease Prevention and Control, as reported in their antimicrobial resistance surveillance reports, estimated a prevalence of 31.3% in 2019, 33.4% in 2020, and 31% in 2021 for Türkiye[23,24].

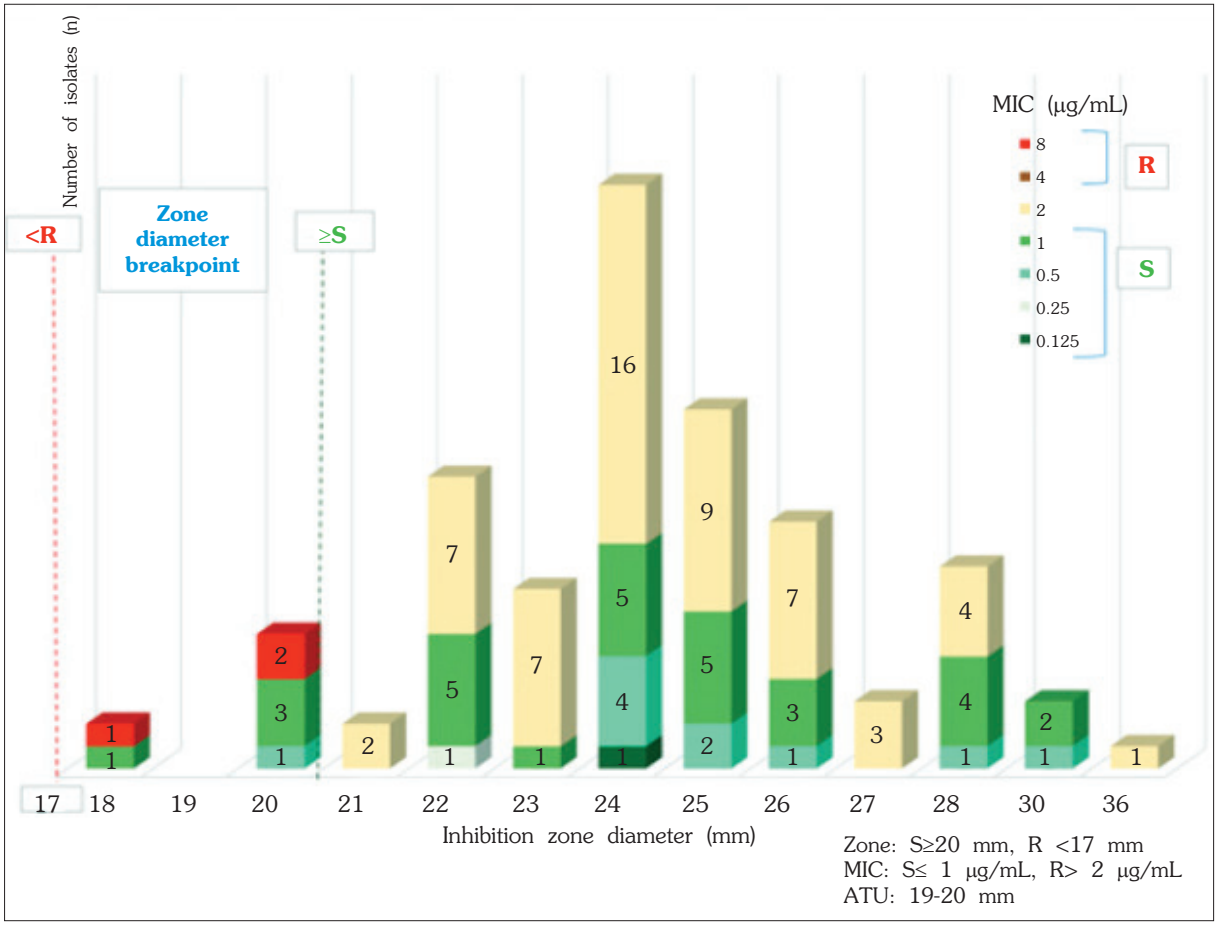

Figure 5. Correlation between inhibition zone diameters and MIC values of ceftaroline for MRSA isolates

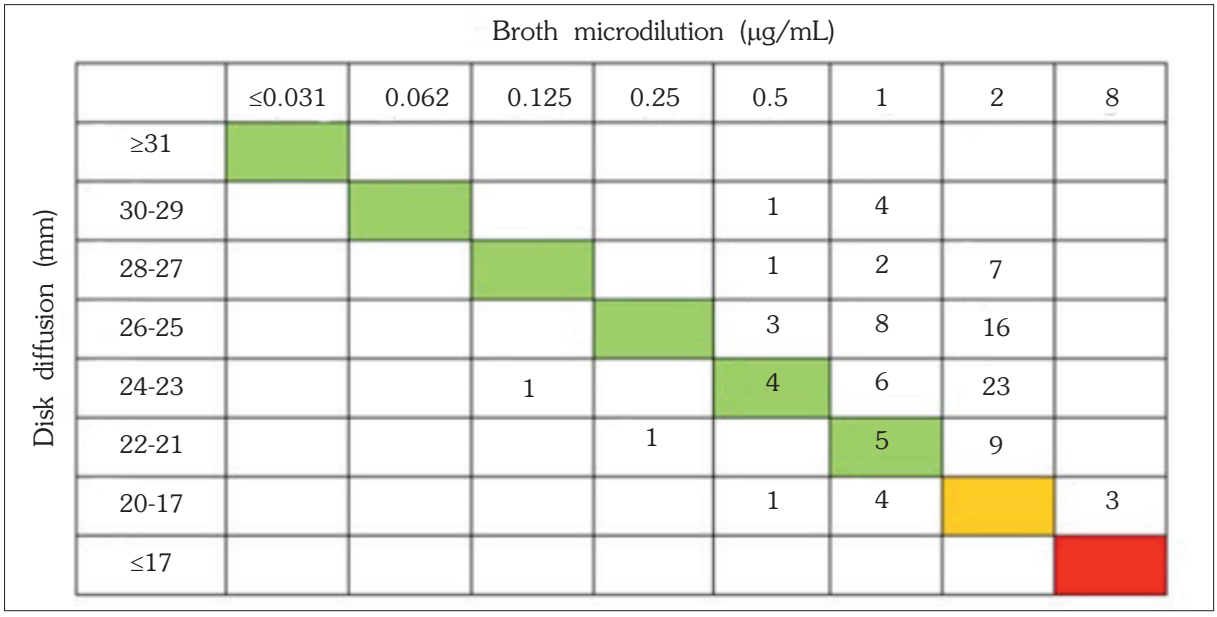

Figure 6. Categorical agreement scheme for ceftaroline.

Table 2. Effect of antibiotic combinations on ceftaroline-resistant isolates

Isolate No.	CPT*-DAP[Ý] combination	CPT-VAN[ý] combination	CPT MIC[§] (µg/mL)	DAP MIC (µg/mL)	VAN MIC (µg/mL)
43	Indifference	Indifference	8-R[‖]	0.25-S[¶]	2-S
55	Indifference	Indifference	8-R	0.5-S	2-S
69	Indifference	Indifference	8-R	0.125-S	1-S

*Ceftaroline, Ý: Daptomycin, ý: Vancomycin, §: Minimum inhibitory concentration, ||: Resistant, ¶: Susceptible.

The highest resistance rates in BSI isolates were detected against cotrimoxazole, tetracycline and erythromycin by DDM. These findings confirm the multidrug resistance profile of MRSA isolates in Türkiye and serve as an important warning for clinicians. Despite the relatively low resistance rate to levofloxacin, the significant S-IE rate of 80% and 86% in BSI and SSTI isolates, respectively, is of considerable concern, as it suggests the potential for increased resistance in the near future. No strains resistant to CPT were detected with the DDM, and it is encouraging that the S-IE rate was also relatively low. In the present study, the $iMLS_b$ phenotype was found to be higher than the $cMLS_b$ phenotype. A study conducted in the same hospital in 2013 reported that 18% of MRSA isolates from various clinical samples exhibited iMLSb resistance[25]. A comparison of this data with the findings of the current study reveals a noteworthy increase in iMLSb resistance, which escalated by 23% over a 10-year period. Pardo et al. reported that 5% of MRSA isolates from various clinical samples between 2012 and 2013 showed $iMLS_b$ phenotype and 21% showed $cMLS_b$ phenotype[26]. A comparison of the results of Pardo's study with those of our own reveals that a relatively higher (41%) iMLSb and lower (7%) cMLSb phenotype were detected. In a study conducted by Goudarzi et al. from Iran in 2020, it was reported that 30.2% $cMLS_b$ and 33.8% $iMLS_b$ were found in MRSA isolates from various clinical samples[27]. Contrary to the findings of Goudarzi's study, this investigation has identified a comparatively elevated prevalence of iMLSb, accompanied by a comparatively diminished prevalence of cMLSb.

The high affinity of CPT for PBP2a is the key factor that led to its identification as the first beta-lactam to show activity against MRSA. Data from international epidemiological reports have shown that resistance in MRSA is rare and around 5-10%, but in some cases it can increase up to 25%[2]. In specific circumstances, this figure has been known to increase to as high as 67%, with variations depending on the breakpoint ranges specified in the guideline employed and the year of the study[28-33]. In the present study, two of the strains found to be resistant to CPT by the BMD method were isolated from breast cancer patients and one from SSTI patients. The use of beta-lactam antibiotics in previous treatments, in addition to the presence of concomitant diseases in these patients, may have contributed to the development of CPT resistance. The rate of isolates that S-IE (MIC= 2 µg/mL) to CPT by BMD method was 56% (52 from BSI samples, four from SSTI) among total isolates (Figure 4). Given that the ECOFF value is 1 mg/L, it can be deduced that 56% of the strains in the present study appear to be non-wild-type. If similar MIC values are reported in relevant studies, it may be considered that the 2 mg/L concentration can be included in the wild-type population in the future. The rate of isolates that S-IE was determined as 2% with DDM, indicating a low level of categorical agreement between the DDM and BMD methods. EUCAST recommends implementing an alternative testing method for breakpoints that fall within the "area of technical uncertainty" (ATU) zone. In 2019, EUCAST warned that there was an ATU zone in DDM of CPT against *S. aureus* isolates, stating the ATU for *S. aureus* isolates (indications other than pneumonia) at 19-20 mm. In our study, three (3%) strains with an inhibition zone diameter of 18-20 mm (S-IE) were found to be resistant to CPT by BMD method (Figure 5, 6). This ratio is in agreement with the 3–4%

mentioned by EUCAST[22,34]. Furthermore, it is imperative to note that 52 (93%) of those strains were isolated from BSIs, as this may result in challenges when interpreting the susceptibility category and may affect treatment options. This situation underlines the need for caution in interpreting CPT susceptibility tests. In a thesis study conducted in our country in 2017, 1.4% ceftaroline resistance and 31% S-IE isolates were detected in 143 MRSA isolates from various clinical samples[33]. In a study conducted by Andrey et al. from the University of Geneva, it was found that resistance to CPT (MIC> 1 µg/mL) was 7.2% in BSIs and 17% in SSTI samples in 96 MRSA isolates (22 blood, 74 SSTI samples). Furthermore the inhibition zone diameters of CPT-R strains by DDM varied between 10 and 20 mm[28]. In contrast, the present study revealed that resistance to CPT was found to be lower in isolates from BSIs and SSTI samples (2.5% and 4.5%, respectively). The rationale behind this discrepancy can be attributed to the modification of the "intermediate" category within the EUCAST guide. Specifically, strains exhibiting a MIC of 2 µg/mL were reclassified under the S-IE category. In the present study, the inhibition zone diameters of CPT-R isolates were found to be between 18-20 mm, which is not in accordance with the results obtained by Andrey.

A study was conducted by BMD and DDM to examine the effectiveness of CPT on 60 hospital-acquired MRSA (HA-MRSA) strains[31]. These strains were classified as intermediate to glycopeptides (GISA) and isolated from BSIs between 1994 and 2003, prior to the implementation of CPT in clinical practice[31]. According to the finding of Kelly's study, the rate of resistance to CPT (MIC >1 µg/mL) was reported as 67%. Thirty-seven of the strains showed an MIC of 2 µg/mL, while only three showed an MIC of 4 µg/mL. In relation to this elevated rate, the authors hypothesized that the unexpected resistance may be attributable to a subset of strains isolated in subsequent years, following an epidemic at the same hospital in 1998 during which an aggressive HA-MRSA strain predominated. If the breakpoint value for CPT in the aforementioned study been greater than 2 µg/mL, as stated in EUCAST, the resistance rate would have been lower (5%) and closer to our results. Furthermore, it is important to note that the isolates employed in Kelly's study were GISA isolates. The inhibition zone diameters of CPT-R strains by the DDM were reported to be between 18-21 mm. In the present study, the resistance rate to CPT was found to be comparatively low. Furthermore, the inhibition zone diameters (18-20 mm) of CPT-R isolates were found to be similar.

In a study conducted by Siddiqui et al, sensitivity to CPT was investigated by the gradient-test method in 19 MRSA isolated from various clinical samples in 2020, and 89.5% of MRSA isolates were found to be susceptible to CPT[32]. Despite the 10.5% resistance rate documented in this study being higher than the rates reported in our own research, it is important to note that this may not be a precise reflection of the actual rates, given the limited number of strains analyzed. Within the scope of the Antimicrobial Test Leadership and Surveillance program (ATLAS), the antimicrobial activity of CPT against SSTI isolates was evaluated in Latin America between 2016 and 2020. Susceptibility to CPT was reported as 92.5%, which is higher than in the current study, and the MIC_{90} was determined to be 1 mg/L according to EUCAST guidelines[35]. Thirty MRSA isolates from various clinical specimens were evaluated by gradient testing over a two-month period in Southern India in 2023 to assess the susceptibility of clinical MRSA isolates to CPT. Of the thirty isolates tested according to CLSI guidelines, 28 (93%) were found to be susceptible to CPT, and two were found to be susceptible dose-dependent (SDD). Although this percentage is considered higher than the resistance rates in the present study, the diverse clinical specimens collected and the small number of isolates do not allow for full comparison of the data[36]. In a study conducted in Egypt between 2022 and 2023, no CPT-resistant strains were found in 412 clinical MRSA (mostly SSTI) isolates, 98.7% were found susceptible, and 1.3% showed a SDD profile with MIC values of 2-4 µg/mL[37].

Abdizadeh et al. investigated the susceptibility to CPT investigated by the gradient-test method in a total of 91 MRSA isolates from BSIs between 2018-2019, utilizing the gradient-test method. The authors stated that according to the Clinical Laboratory Standards Institute (CLSI) criteria in effect at that time, the breakpoint values were as follows: susceptible (S) ≤1 µg/mL, susceptible-increased exposure (S-IE) 2-4 µg/mL, and resistant (R) ≥8 µg/mL. The study found that 84 (92%) isolates were sensitive and seven (8%) MRSA isolates were S-IE with an MIC value of 2 µg/mL[30]. In contrast to the findings reported by Abdizadeh, our study revealed a higher prevalence of S-IE and 3% CPT resistance (MIC= 8 µg/mL) were detected. Nevertheless, in accordance with the present study, resistance to levofloxacin was detected by DDM in all strains resistant to CPT.

Daptomycin is FDA-approved for adults with *S. aureus* bacteremia, right-sided infective endocarditis, and cSSTI. Nonsusceptible isolates have emerged during therapy in association with treatment failure. For adults with uncomplicated bacteremia, vancomycin or daptomycin 6 mg/kg/dose IV once daily is recommended for at least two weeks. For complicated bacteremia, 4–6 weeks of therapy is advised, depending on the extent of the infection. Some experts recommend higher doses of daptomycin at 8–10 mg/kg/dose IV once daily[38]. Daptomycin, even when administered at doses higher than the FDA-approved level, has been associated with clinical failure rates approaching 30% and the emergence of DAP-nonsusceptible strains[13,39]. According to data from the Centers for Disease Control and Prevention (CDC), the global prevalence of DAP-resistant *S. aureus* was 0.4% in 2021[40]. In the present study, 2% resistance to DAP was found among all isolates by the BMD method. Öksüz et al. did not detect resistance to DAP in the same hospital ten years ago[25]. However, the 2% resistance rate in the current study suggests that attention should be paid to the use of this antibiotic, even though development of resistance is slow.

Vancomycin has been the mainstay of parenteral therapy for MRSA infections. However, its effectiveness has been questioned due to its slow bactericidal activity, the emergence of resistant strains, and concerns about a possible "MIC shift" among susceptible strains[38]. The occurrence of vancomycin resistance in *S. aureus* isolates is an exceptionally rare phenomenon. However, in cases of persistent bacteremia, the failure of vancomycin therapy is a frequent occurrence. With regard to the data from the CDC, the global rate of VRSA in 2021 was 0.1%[41]. In a 2020 study on the global prevalence of VRSA, Shariati et al. reported that the prevalence of VRSA was 1.2% in Asia, 1.1% in Europe, 3.6% in America, and 2.5% in Africa. The study also found that the prevalence of VISA strains was higher on the Asian continent. The highest number of VRSA strains (n= 70) were also reported from Asia[42]. In the present study, no VISA, hVISA or VRSA isolates were found in the isolates from BSI and SSTI samples. In a surveillance study conducted in Latin America, susceptibility to VAN was investigated in a total of 1189 MRSA isolates. These isolates were obtained from different clinical samples between 2006 and 2008 and from BSIs only between 2011 and 2014. No VRSA was detected by the agar screening method during the 2006-2008 period; however, nine isolates (1.4%) were identified as hVISA using the gradient test method. Between 2011 and 2014, it was reported that 70% of the patients from whom the strains were isolated had received glycopeptide treatment, and 30 hVISA (5.6%) isolates were detected using the gradient test method[43].

A study evaluating the efficacy of fifth-generation cephalosporins for the treatment of MRSA-BSI infections reported that CPT and ceftobiprole demonstrated significant efficacy in this patient group. These agents may be considered more effective than VAN or DAP and could serve as the basis for treatment, either as monotherapy or in combination[44]. However, in present study, both the CPT-VAN and CPT-DAP combinations exhibited indifference effects against CPT-R isolates. This finding reinforces the need to explore new synergistic combinations, which is the main thesis of the study. The absence of synergy between CPT-VAN and CPT-DAP combinations against resistant isolates serves as a reminder for

clinicians to exercise caution when considering combination therapy in the treatment of MRSA. These data are consistent with some findings from previous studies. In a study conducted by Romero et al, the in vitro effectiveness of CPT in combination with DAP, linezolid, and VAN against a total of 70 *Staphylococcus* species, 16 of which were MRSA, was evaluated using the gradient test method. The findings of the present study align with those reported in the literature, particularly the CPT-DAP combination, which exhibited an additive effect in 81% of cases, with no synergistic or antagonistic outcomes. However, in contrast to our findings, the CPT-VAN combination demonstrated a synergistic effect in 87% of the isolates. It is imperative to note the relatively small number of MRSA isolates used in Romero's study[45].

Similarly, in a 2016 study conducted by García et al. from Spain, the activities of CPT, VAN, and DAP -both alone and in combination- were assessed using the gradient test method, as in the present study. The analysis was conducted on 53 MRSA isolates stored from a hospital outbreak that occurred seven years prior. All tested isolates were susceptible to CPT at concentrations ranging from 0.38 µg/mL to 1 µg/mL, to DAP at concentrations ranging from 0.125 µg/mL to 1 µg/mL, and to VAN at concentrations ranging from 0.75 µg/mL to 2 µg/mL. The CPT-DAP combination resulted in indifference in 18 isolates (34%), additive effects in 31 (58.5%), and synergism in four isolates (7.5%). These findings differ from our data, which showed no synergism. In the CPT-VAN combination, 41 isolates (77%) showed indifference, while 12 (23%) exhibited additive effects. In contrast to García et al.'s study, three strains in our dataset were resistant to CPT (MIC range= 0.125–8 µg/mL), showed increased MIC values for DAP (0.125–2 µg/mL), and both CPT-DAP and CPT-VAN combinations demonstrated indifferent effects against these CPT-R strains.

In light of in vitro investigations, a study conducted by Tsai et al. evaluated the efficacy of DAP), VAN, and CPT, both individually and in combination, against 10 MRSA isolates obtained from BSIs in Taiwan between 2014 and 2018. The study found that all MRSA isolates were susceptible to CPT and VAN monotherapy. However, two MRSA isolates demonstrated resistance to DAP, with MICs of 2 µg/mL and 4 µg/mL, respectively. The checkerboard method revealed a 30% synergistic effect for the CPT-DAP combination and a 10% synergistic effect for the CPT-VAN combination[46].

In a more recent study, the interaction of CPT or VAN with carbapenems-despite their lack of indication for MRSA-was explored, and both in vitro and in vivo synergy was observed between these combinations[47].

It should be noted that the number of isolates in Tsai et al.'s study was small (n= 10), which may limit the generalizability of the findings. In contrast, the present study did not observe any synergistic effect with either combination. This discrepancy may be attributed to the temporal overlap of our study period with the onset of the global coronavirus diseases-2019 pandemic, which may have contributed to the emergence of more resilient MRSA strains. Additionally, the presence of comorbidities and prior antibiotic use in the patient population may have been contributing factors.

The clinical outcomes of combination therapies involving CPT are of considerable importance. A multicenter retrospective study from Spain compared the outcomes of CPT treatment with those of standard therapy (VAN or DAP) in 429 adult patients with MRSA BSIs. Patients in the CPT group more frequently received combination therapy due to higher Sequential Organ Failure Assessment scores (>2), complicated BSI, and infective endocarditis. Although no statistically significant difference in 30-day mortality was observed between the groups, the incidence of adverse events in the CPT group was 12.0%—approximately three times higher than in the standard therapy group. Notably, most adverse events occurred when CPT was administered in combination[48]. These findings underscore the need for caution when using CPT-based combination therapies in clinical settings.

Despite these clinically relevant insights, the present study has certain limitations. It could not be conducted on consecutive isolates, and its

retrospective design may limit the representativeness of the sample. However, the low number of MRSA isolates, due to effective infection control practices at our hospital, necessitated this study design. Another limitation is that checkerboard synergy testing was performed only on CPT-R isolates (n= 3) due to budgetary constraints. The study focused exclusively on evaluating antibiotic combination efficacy in CPT-R strains, as CPT-susceptible strains are already being utilized in current treatment regimens. This may restrict the generalizability of the results.

Nevertheless, the observed indifference between CPT-VAN and CPT-DAP combinations in CPT-R isolates is a noteworthy and thought-provoking finding, especially in light of the expected synergistic effects. Additionally, population analysis profiling was not employed for the detection of hVISA, as this was beyond the scope of the present study.

CONCLUSION

We believe that the current study provides important findings regarding the in vitro efficacy of CPT. Although the rate of CPT resistance detected was relatively low, concerns remain that the number of CPT-R isolates may increase over time. The use of β-lactam antibiotics by patients from whom CPT-R strains were isolated, along with the presence of comorbid conditions, may have contributed to the development of resistance against CPT. The observed indifferent effects of CPT in binary combinations underscore the need to explore novel synergistic antimicrobial combinations. Future studies are planned to evaluate the efficacy of CPT in combination with meropenem and linezolid. Clinical studies will be essential to validate and substantiate the outcomes observed in this in vitro investigation.

ETHICS COMMITTEE APPROVAL

This study was approved by the İstanbul University İstanbul Faculty of Medicine, Clinical Research Ethics Committee (Decision no: 09, Date: 13.05.2022).

FINANCIAL DISCLOSURE

This study was funded by Scientific Research Projects Coordination Unit of İstanbul University İstanbul Faculty of Medicine Project No: 39557.

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: LÖ

Analysis/Interpretation: LÖ, GKA

Data Collection or Processing: GKA, LÖ

Writing: GKA, LÖ

Review and Correction: LÖ, GKA

Final Approval: GKA, LÖ

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