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RESEARCH ARTICLE

Prevalence and molecular epidemiology of ceftaroline non-susceptible methicillin-resistant *Staphylococcus aureus* isolates, first clinical report from Iran

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ABSTRACT

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the major pathogens in Iran with a high prevalence and a high level of antibiotic resistance. Ceftaroline is a fifth generation cephalosporin binding and inhibiting penicillin binding protein (PBP2a). *Methods:* In the present study, 228 clinical MRSA isolates were collected from four cities of Iran and their susceptibility to ceftaroline was evaluated by E-test and the disk diffusion method. *Results:* Our results showed a high susceptibility rate (97.3%) to ceftaroline in MRSA strains from Iran. Six isolates were found to be ceftaroline non-susceptible (CPT-NS) with Minimum inhibitory concentration (MIC) ≥2 μg/mL. All CPT-NS isolates were isolated from blood and tracheal aspirate and belonged to SCC*mec* type III as well as *agr* type I and were all susceptible to vancomycin. Out of six isolates, three, two and one belonged to *spa* type t030, t4864, and t969, respectively. Vancomycin, quinupristin/dalfopristin, linezolid, chloramphenicol, and tigecycline were the most active agents against CPT-NS isolates. *Conclusion:* Due to the broad-spectrum activity and low toxicity of ceftaroline as well as the increased rate of vancomycin resistance among MRSA strains in recent years, ceftaroline can be considered as a novel approach to treat MRSA-induced infections.

KEYWORDS

ceftaroline, Fifth-generation cephalosporin, MRSA, *Staphylococcus aureus*, Iran

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important bacterial pathogens worldwide, causing a number of community-acquired and health care-associated infections, including septicemia, skin and soft tissue infections, osteomyelitis, and endocarditis [1]. The mean prevalence of MRSA in Iran is between 57.2 and 93.3 percent [2]. Antibiotic misuse has led to high resistance levels in MRSA strains leading to an increased mortality rate, high costs of care and treatment, and longer hospitalization periods [3]. The mechanism of resistance in MRSA is attributed to the presence of the *mecA* gene and the subsequent expression of penicillin binding protein 2a (PBP2a) which confers low affinity to common β-lactam antibiotics and hence, mediates resistance. Owing to high resistance rates to different antibiotics, treatment of MRSA infections has become challenging, necessitating the development of novel therapeutics [4]. Ceftaroline is a member of the fifth generation

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cephalosporins approved by the US Food and Drug Administration (FDA) for the treatment of adults with community-acquired bacterial pneumonia (CABP) as well as acute bacterial skin and skin structure infections (ABSSSI). There are also reports on the efficacy of this antibiotic for the treatment of other infections, such as osteomyelitis and epidural abscesses [5–7]. Furthermore, previous studies have shown the efficiency of this antibiotic against methicillin-susceptible *S. aureus* (MSSA), MRSA, and *Streptococcus pneumoniae* [8, 9]. This antibiotic is probably also efficient against other pathogens including *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis* and non-extended-spectrum β-lactamase-producing *Enterobacteriales*. Ceftaroline is notably the first cephalosporin with a unique feature of high affinity to penicillin binding protein 2a (PBP2a) with 800- and 1,400-fold lower half-maximal inhibitory concentration for PBP2a compared to oxacillin and ceftriaxone, respectively, making it a suitable choice for the treatment of MRSA infections [10–13]. Therefore, due to the efficiency of ceftaroline in previous studies, its fewer side effects, and the increased prevalence of vancomycin-resistant *S. aureus* (VRSA) in recent years [14], the aim of this study was to determine the frequency of ceftaroline-resistance in MRSA strains collected from different cities of Iran.

MATERIALS AND METHODS

Bacterial isolates

A total of 228 MRSA isolates were used in this study isolated from blood (37.2%), tracheal aspirate (21.8%), wound (18.2%), nasal swabs (6.9%), hospital surfaces (6.2%), abscess (4.3%) skin lesion (1.7%), catheter (1.4%), and bone aspiration (1.3%) were collected from hospitals in four cities in Iran (including Tehran, Karaj, Yasuj, and Arak) between 2015 and 2018. The isolates were identified at the species level by biochemical tests and Polymerase chain reaction (PCR) amplification of the *S. aureus*-specific *nucA* gene was performed as the confirmatory test [2, 3, 15, 16].

Antimicrobial susceptibility testing

The Liofilchem E-test strips (Roseto degli Abruzzi, Italy) as well as the Mast (Liverpool, UK) and BD (New Jersey, USA) antibiotic susceptibility discs were used for the determination of susceptibility profiles. Susceptibility to ceftaroline was tested by a ceftaroline disc (30 µg) using the disk diffusion method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines [15]. Susceptibility to ceftaroline was confirmed by gradient diffusion test (E-test) and the results were interpreted according to the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [10, 17, 18]. Additional antibiotic susceptibility testing for ceftaroline non-susceptible (CPT-NS) strains was performed for the following antibiotics: nitrofurantoin (300 µg), gentamicin (10 µg), rifampicin (5 µg), norfloxacin (10 µg), tigecycline (15 µg), trimethoprim/sulfamethoxazole (25 µg), chloramphenicol (30 µg), cefixime (5 µg), erythromycin (15 µg), clindamycin (2 µg), tetracycline (30 µg), penicillin G (10 U), linezolid (30 µg), cefepime (30 µg), quinupristin/dalfopristin (15 µg) ciprofloxacin (5 µg), and imipenem (10 µg) [19]. E-test gradient diffusion test was also performed for the determination of vancomycin resistance.

DNA extraction and molecular typing of MRSA strains

DNA extraction was performed by the boiling method using TE buffer (10 mMTris, 1 mM EDTA [pH 8.0]) as previously described [20]. Identification of MRSA strains was performed by the detection of *mecA* using PCR.

spa typing

The *spa* gene was amplified using the method described by Harmsen et al. [21]. Amplicons were sent to Bioneer Co. (Seoul, South Korea) for DNA sequencing. Data were analyzed using the Ridom SpaServer database to determine the Spa type of each isolate (http://www.spaserver.ridom.de) [15, 16].

SCC*mec* typing

To determine the SCC*mec* types, a multiplex-PCR with four pairs of primers was performed according to the method described by Boye et al. [22, 23]. Each reaction contained 0.5µM of each primer and the final volume was 25 µL. Finally, the PCR products were visualized by electrophoresis on 1% agarose gels containing safe stain (Kawsar Biotech Company, Iran) [15].

agr typing

To determine the agr types, PCR was performed as described by Shopsin et al. [24]. In brief, agr types (I–IV) were determined by multiplex PCR using the agr-specific primers. Each agr type was analyzed in each strain after visualization on 1% agarose gels containing safe stain [15].

RESULTS

Two hundred out of 228 strains [Tehran (95%), Yasuj (94%), Karaj (75%) and Arak (77%)] were ceftaroline susceptible upon disk diffusion. The Ceftaroline E-test strip was used to determine the MIC values on 28 strains were non-susceptible upon disk diffusion and according to the results, six isolates showed an MIC of 2 µg/mL, including five isolates from Arak and one from Tehran (Fig. 1). These six isolates showed additional resistance to penicillin G, norfloxacin, gentamicin, erythromycin, cefepime, cefixime, ciprofloxacin, tetracycline, and imipenem and high resistance to clindamycin (83.33, $n = 5$) and rifampicin (83.33, $n = 5$) (Table 1). On the other hand, all CPT-NS isolates were susceptible to vancomycin, quinupristin/dalfopristin, linezolid, chloramphenicol, and tigecycline. The most frequent *spa* type was t030 (50%, $n = 3$), followed by t4864 (33.3%, *n*

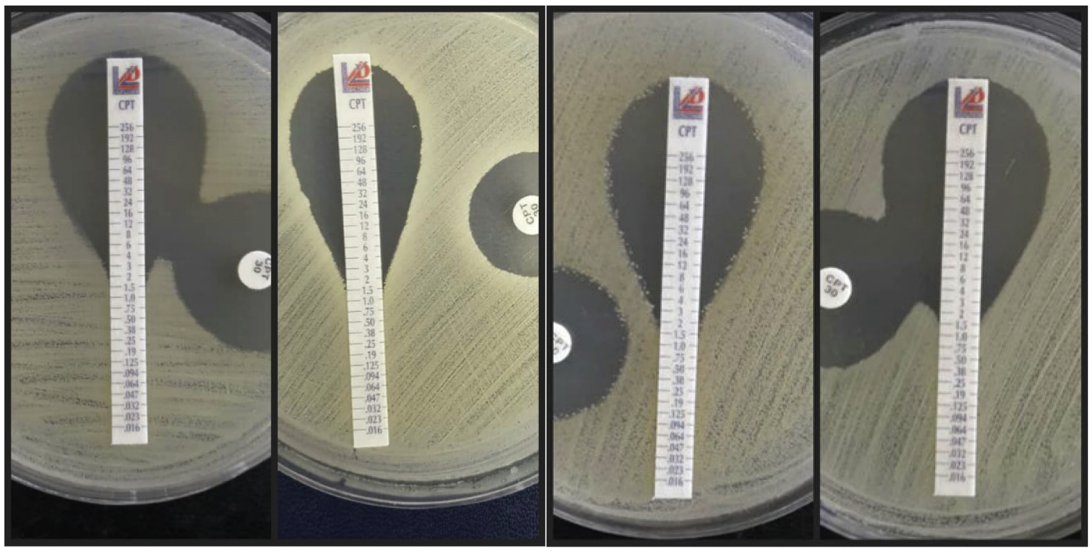

Fig. 1. Results of Ceftaroline susceptibility testing by gradient diffusion test among MRSA isolates

Table 1. Antibiotic susceptibility pattern of the ceftaroline-nonsusceptible MRSA isolates by disk diffusion method

Antibiotics	Isolates N		
	Susceptible	Intermediate	Resistant
Cefepime	0 (0%)	0 (0%)	6 (100%)
Cefixime	0 (0%)	0 (0%)	6 (100%)
Chloramphenicol	6 (100%)	0 (0%)	0 (0%)
Ciprofloxacin	0 (0%)	0 (0%)	6 (100%)
Clindamycin	1 (16.7%)	0 (0%)	5 (83.3%)
Erythromycin	0 (0%)	0 (0%)	6 (100%)
Gentamicin	0 (0%)	0 (0%)	6 (100%)
Imipenem	0 (0%)	0 (0%)	6 (100%)
Linezolid	6 (100%)	0 (0%)	0 (0%)
Nitrofurantoin	1 (16.7%)	5 (83.3%)	0 (0%)
Norfloxacin	0 (0%)	0 (0%)	6 (100%)
Penicillin G	0 (0%)	0 (0%)	6 (100%)
Quinupristin/ Dalfopristin	6 (100%)	0 (0%)	0 (0%)
Rifampicin	1 (16.7%)	0 (0%)	5 (83.3%)
Tetracycline	0 (0%)	0 (0%)	6 (100%)
Tigecycline	6 (100%)	0 (0%)	0 (0%)
Trimethoprim/ Sulfamethoxazole	5 (83.3%)	0 (0%)	1 (16.7%)

= 2), and t969 (16.6%, n = 1). Moreover, all six isolates belonged to *agr* type I (100%, n = 6) and SCC*mec* type III (100%, n = 6) (Table 2).

DISCUSSION

S.aureus infections are one of the major problems around the world. In Iran, vancomycin has been frequently used to treat complex infections caused by *S. aureus*, but in recent years, resistance to this antibiotic has been reported, necessitating novel therapeutic antibiotics [25–27]. We collected 228 MRSA from four different Iranian cities to evaluate the performance of ceftaroline against this pathogen. In a study by Dehkordi et al. on antibiotic resistance pattern of the MRSA isolated from hospital food, among 485 isolates, all of them were resistant to ceftaroline [28]. In addition, in another study on phenotypic and genotypic characterization of antibiotic resistance in the MRSA strains isolated from hospital cockroaches, all isolates recovered from external washing samples and gut content samples were resistance to ceftaroline [29]. Despite two previous studies from Iran in non-clinical samples, according to our research, this is the first report from Iran to evaluate the sensitivity of clinical MRSA isolates to ceftaroline. The results of the present study showed that 97.3% (222/228) of the MRSA isolates showed susceptibility to ceftaroline, while six isolates were non-susceptible. According to CLSI guideline, the susceptible dose dependent (SDD) range of ceftaroline is between 2 and 4 µg/mL, meanwhile EUCAST consider 2 µg/mL as resistance [17, 18]. In this study, ceftaroline MIC 2 µg/mL considered as non-susceptible. All six isolates were highly resistant to other beta-lactams, gentamicin, erythromycin, ciprofloxacin, norfloxacin, and tetracycline. on the other hand, they were completely inhibited by linezolid, vancomycin, quinupristin/dalfopristin, and tigecycline which is similar to other studies from Iran [2, 30]. In a study performed on 8037 *S. aureus*, four isolates were reported as CPT-NS strains which were susceptible to linezolid and vancomycin, and belonged to SCC*mec* types III [31]. In a study from Switzerland, 24% (23/96) of MRSA collected from deep infections, blood cultures, and superficial infections with MIC≥ 2 mg/L were reported as CPT-NS [32]. In the Atlas program, in which the ceftaroline susceptibility of *S. aureus* isolates from different countries was tested, 93.7% of the isolates were susceptible to this antibiotic, 5.9% were susceptible-dose dependent (SDD) and only 0.4% (263/61,045) were found to be resistant. Among

Table 2. Resistance patterns

Isolate	Source	Specimen	*spa*	SCC*mec*	*agr*	Vancomycin MIC	Resistance Pattern
B123	Tehran	Blood	t4864	III	I	1	NOR, IMI, T, GM, CIP, CFM, FEP, E, TS, PG
Ar33	Arak	Blood	t030	III	I	0.75	NOR, RIF, CD, IMI, T, GM, CIP, CFM, FEP, E, PG
Ar44	Arak	Blood	t4864	III	I	0.75	NOR, RIF, CD, IMI, T, GM, CIP, CFM, FEP, E, PG
Ar59	Arak	Tracheal aspirate	t030	III	I	1	NOR, RIF, CD, IMI, T, GM, CIP, CFM, FEP, E, PG
Ar61	Arak	Blood	t030	III	I	0.75	NOR, RIF, CD, IMI, T, GM, CIP, CFM, FEP, E, PG
Ar72	Arak	Tracheal aspirate	t969	III	I	0.75	NOR, RIF, CD, IMI, T, GM, CIP, CFM, FEP, E, PG

NOR: Norfloxacin. IMI: Imipenem. T: Tetracycline. GM: Gentamicin. CIP: Ciprofloxacin. CFM: Cefixime. FEP: Cefepime. E: Erythromycin. TS: Trimethoprim/Sulfamethoxazole. PG: Penicillin G. RIF: Rifampicin. CD: Clindamycin.

the resistant strains, 92% (242/263) were from Asia and similar to our results, all bacterial isolates were susceptible to vancomycin and linezolid and the highest resistance rate was reported to clindamycin, erythromycin, and gentamicin. Apparently, the rate of resistance to ceftaroline, gentamicin, clindamycin, and minocycline among MRSA isolates was much higher in the Asia-Pacific region compared to other parts of the world [33]. According to a study performed by Pfaller et al. including 1732 community-acquired MRSA isolates from the United States, only 3.1% were CPT-NS and all these isolates were susceptible to vancomycin, linezolid, and tigecycline [1]. Moreover, the results of another study showed that 100% non-duplicate MRSA isolated from different samples of hospitalized patients, were susceptible to ceftaroline, while 63% were resistant to gentamicin, erythromycin, clindamycin, and ciprofloxacin and 15% were resistant to vancomycin [34]. Finally, Sader et al. reported that all 523 studied *S. aureus* were susceptible to ceftaroline, and this antibiotic could be used as surgical prophylaxis that would cover all MRSA infections [35].

Our CPT-NS strains had *agr* types I and SCC*mec* types III which has been related to hospital-acquired infection and has been reported as the main SCC*mec* type in Iran with a prevalence between 45% and 76% [2]. Half of these non-susceptible isolates were obtained from Arak city and characterized with *spa* type t030 which is one of the most common *spa* types in Iran and seemingly most of them reported to be member of ST239-CC8. To date, this clone is spreading in several countries across Asia [2, 36]. Moreover, in study on susceptibility to ceftaroline and molecular epidemiology of MRSA isolates in China, results revealed that the 95.2% of CPT-NS isolates were belong to CC8. Additionally, the CPT-NS CC8 isolates were largely ST239-III-t030 and ST239-III-t037 [37]. The results of a systematic review which evaluated the clinical outcomes and side effects of ceftaroline showed that this antibiotic improves the treatment of severe MRSA infections [38]. In addition, drug toxicity was infrequent and was only observed in case of long-term use, and evaluation of blood parameters is recommended [38]. Therefore, due to high efficacy and low toxicity of ceftaroline, recently increased vancomycin resistance, high cost of linezolid and unavailability of daptomycin in Iran, ceftaroline may be considered as a suitable alternative to treat MRSA-induced infections. However, given the varying degrees of resistance in different areas, it is suggested to perform more comprehensive studies to fully investigate the mechanism and frequency of ceftaroline nonsusceptibility in MRSA strains.

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Author contribution: AKH, ASH, and DDS conceived and designed the study. EGHR and DDS contributed in comprehensive research. AKH, ASH and DDS wrote the paper. DDS and AvB participated in manuscript editing.

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