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ORIGINAL RESEARCH

Evaluation of antibacterial activity of Ceftaroline against clinical isolates of Methicillin Resistant Staphylococcus aureus in a tertiary care centre, South India

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ABSTRACT

Background: *Staphylococcus aureus (S.aureus)* is one of the most common causes of community acquired and hospital acquired infections. The treatment of infections caused by *S.aureus*remains challenging mainly due to the emergence of drug resistant isolates especially MRSA (Methicillin-Resistant *Staphylococcus aureus*). Multi drug resistance is one of the most common problem encountered in MRSA and this limits the treatment options.Ceftaroline, a fifth-generation broad-spectrum cephalosporin has been approved by United States Food and Drug Administration (US FDA) for treating acute bacterial SSI caused by susceptible micro-organisms including MRSA, Community acquired respiratory tract infection, MRSA bacteremia etc. **Aim:** To assess the susceptibility of clinical isolates of *S. aureus* to ceftaroline, in a Tertiary Care Hospital, South India. **Materials and Methods:** This cross sectional study was conducted in the Department of Microbiology of a Tertiary Care Hospital, South India, over a period of two months from May to July 2023. Thirty non duplicate S.*aureus*isolates from various clinical samples were screened for methicillin resistance by disc diffusion method using cefoxitin disc, Hi-Media (30 µg) and ceftaroline susceptibility of these isolates was assessed by E-strip method (Biomerieux). The isolates were classified as ceftaroline susceptible (≤1 µg/ml), Susceptibility Dose Dependent (SDD) (2-4 µg/ml) and ceftaroline resistant (≥ 4 µg/ml) respectively as per CLSI guidelines. A descriptive analysis of the data was done and the results were presented as frequencies and percentages.**Results:** Out of the thirty isolates tested, 28 (93%) of*S.aureus*isolates were found to be susceptible to ceftaroline, with MIC's ranging from 0.125 to 1 µg/mL.and two were Susceptible Dose Dependent (SDD). For Eight isolates the MIC value was 0.25 µg/mL.**Conclusion:** Ceftaroline can be considered as an effective alternative for treatment of infections caused by MRSA as it is showing good in vitro activity.

Keywords: Ceftaroline, *Staphylococcus aureus*, Methicillin resistance, Minimum inhibitory concentration

INTRODUCTION

Staphylococcus aureus (*S.aureus)* is one of the most important pathogens commonly encountered in hospital and community settings[1]. Due to the increased drug resistance trends, infection caused by *S.aureus*are difficult to treat[2]. Though, humans are colonised with *S.aureus*on the external skin surfaces and respiratory tract., *S.aureus*being an opportunistic pathogen can lead to serious infections when right opportunity comes [3]. There are a number of antibiotics available to treat *S.aureus*butdrug resistance is one of the major problems faced in the treatment of *S.aureus*especially methicillin resistant *S.aureus*(MRSA). Infections with MRSA is now one of the global health problems and the prevalence rate of MRSA in India ranges from 25–50%[4]. For the treatment of MRSA, glycopeptides like Vancomycin and teicoplanin was considered the therapeutic options.Even though vancomycin is the first line treatment option available for MRSA, along with the emergence of drug resistance there are other concerns like clinical failures, poor tolerance and elevated minimum inhibitory concentrations (MICs). Therefore, daptomycin and other fifth generation cephalosporins likeceftaroline andceftobiprole are now increasingly used [5].

Even though variousnewer drugsare available for use against MRSA, the one which is found effectiveand with wide spectrum activity, is the CeftarolineFosamil (prodrug of ceftaroline), a fifth generation, parenteral

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cephalosporin[6].The US Food and Drug Administration (US-FDA)has approved, Ceftaroline for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP)including MRSA infections[6]. Studies have proved that Ceftaoline is very well tolerated by patients who are onalready on vancomycin, daptomycin and linezolid which is used in eradicating MRSA [7]. Ceftaroline acts by inhibiting cell wall synthesis by binding to Penicillin Binding Proteins (PBP) 1, 2, 3 and PBP 2a for MRSA[8]. Minimal literature is available on resistance to ceftaroline but there are sporadic reports of decreased susceptibility of MRSA[8].There is very little data available about the susceptibility pattern of *S.aureus* to ceftaroline[1,9] in India , therefore the present study is undertaken to know the susceptibility patterns of MRSA against this agent.

MATERIALS AND METHODS

This cross sectional study was conducted in the Department of Microbiology of a Tertiary Care Hospital, South India, over a period of two months from May to July 2023.Thirty nonduplicate *S.aureus* isolates from various clinical samples which were screened for methicillin resistance by disc diffusion method using cefoxitin disc, Hi-Media (30 µg) and found resistant were included in the study.A zone size of ≥22 mm was interpreted as methicillin sensitive and ≤21 mm was interpreted as methicillin resistant as per Clinical and Laboratory Standards Institute (CLSI) guidelines[10]. *S. aureus* American Type Culture Collection (ATCC) strain 25923 were used as susceptibility controls. Screening for methicillin resistance was done by modified Kirby Bauer disc diffusion method using cefoxitin (30 µg) discs. A zone size of ≥22 mm was interpreted as methicillin sensitive and ≤21 mm was interpreted as methicillin resistant as per Clinical and Laboratory Standards Institute (CLSI) guidelines.*S. aureus* American Type Culture Collection (ATCC) strain 25923 were used as susceptibility controls respectively. Isolates which were Methicillin sensitive were excluded from the study.

Among the thirty isolates, ten were randomly selected and were tested for ceftaroline(CPT) susceptibility by E-strip method (Biomerieux) with a concentration gradient range of CPT (0.002-32 µg/ml). The E- test strips were placed on the lawn culture of the organism and the plates were incubated at 37°C for 18–24 hours. MIC's were read where the ellipse intersects the MIC (Minimum Inhibitory Concentration) scale. Since E-test strip has continuous gradient, MIC values "in-between" two-fold dilutions were obtained. These values were rounded up to next two-fold dilution before categorisation. MICs were interpreted according to CLSI 2023. The isolates were classified as ceftaroline susceptible (≤1 µg/ml), Susceptibility Dose Dependent (SDD) (2-4 µg/ml) and ceftaroline resistant (≥ 4 µg/ml) respectively as per CLSI guidelines. A descriptive analysis of the data was done and the results were presented as frequencies and percentages.

RESULTS

A total of 30 MRSA isolates were included in the study. Among the 30 isolates, 12 isolates (40%) were obtained from the patients of Out-Patient Department (OPD) and 18 isolates (60%) were from the patients of In-Patient Department (IPD). Most of the patients had clinical histories of wounds, abscesses and ulcers. Maximum isolates were from age group of 41-60 years and were males (Table 1).

Table 1: Distribution of patients according to their age and sex

AGE GROUP (in years)	MALES	FEMALES
0 - 20	2	1
21 - 40	3	4
41 - 60	10	3
61 - 80	2	3
81 and above	-	2

Maximum number of isolates were obtained from pus samples (67%)) followed by nasal swab (3%) and sputum (3%) (Table 2).

Table 2: Distribution of MRSA isolates in different clinical samples

Type of sample	Number of isolates (%) (n = 30)
Pus	20 (67%)
Blood	2 (6.7%)
Urine	1 (3.3%)
Nasal swab	3 (10%)
Sputum	3 (10%)
Throat swab	1 (3.3%)

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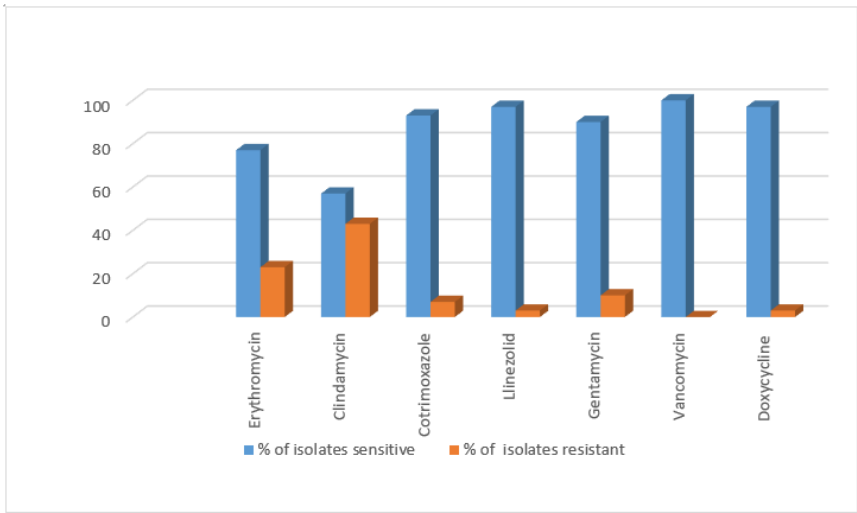

Figure 1: Antimicrobial susceptibility pattern of MRSA isolates n=30

The isolates showed maximum susceptibility to Vancomycin (100%) followed by Linezolid (97%) and Doxycycline (97%). The isolates showed maximum resistance to Clindamycin (57%).

The ceftaroline susceptibility of these isolates was assessed by E-strip method (Biomerieux) (Table 3).

Table 3: In vitro activity of Ceftaroline tested against MRSA

Ceftaroline MIC µg/mL	No of MRSA isolates
0.125	4
0.19	3
0.25	8
0.38	4
0.5	4
0.75	3
1	2
2	2

MIC-Minimum inhibitory concentration, MRSA-Methicillin resistant*Staphylococcus aureus*

Out of the thirty isolates tested, 28 (93%) of*S.aureus* isolates were found to be susceptible to ceftaroline, with MIC's ranging from 0.125 to 1 µg/mL.and two were Susceptible Dose Dependent (SDD). For Eight isolates the MIC value was 0.25 µg/mL.

DISCUSSION

S.aureus is one of the leading causes of both nosocomial as well as community acquired infections worldwide[11]. The emergence ofresistance to the antibiotics used in treatment of*S,aureus* is increasing along with multi drug resistant MRSA has complicated the issueof managing the infection[11]. Due to this, the need for newer antibiotics as a treatment options is the need of the hour. Ceftarolinefosamil, is a fifth-generation cephalosporin with broad-spectrum activity against many Gram-positive and Gram-negative organisms and has been approved as a treatment option for severe MRSA infection[8]. Not much information is available regarding the susceptibility of MRSA towards Ceftaroline in Indian sceranio and especially in the Southern states, hence this study was undertaken to found out the invitro susceptibility of MRSA isolates to Ceftaroline.

Among the thirty isolates tested, maximum isolates were obtained from pus specimen, ie about 67%. This increasing trend may be because of the colonisation of the skin by MRSA and the increased chances of invasion during invasive procedures[12]. Lohan *et al.* (2021), DalelaG *et al.*(2012), Anupurba S *et al.* (2003) etc have shown similar trends across various parts of India.[12-14]

During the present study, all the thirty MRSA isolates were sensitive to Vancomycin (100%) followed by Linezolid and Doxycycline (97%) each. Vancomycin was considered as the last resort antibiotic to treat MRSA patients but now owing to the overuse, resistance is slowly emerging. Studies from India and various parts of the world have reported resistance to Vancomycin either completely or reduced susceptibility[15,16]. But in our study Vancomycin susceptibility is 100%. This may be because of the cautious use of Vancomycin in the clinical settings.

From testing the MIC of MRSA isolates towards Ceftaroline, it was found that the MIC ranged from 0.125- 2 µg/mL.In our study, none of the isolates were found completely resistant to ceftaroline, which may be due to the limited use of the drug in India This is similar to the study conductedby Gaikwad *et al.*[17]. Eight isolates showed an MIC value of 0.125µg/mLTwenty six isolates showed an MIC value below 1 µg/mL.This is similar to the studies

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conducted by Basireddy*et al.* andMushtaq S, *et al.* (2021), where the MIC values in their study ranged from 0.125 to 1.5µg/mL.[18,19] But two isolates showed an MIC value of 2 µg/mL which according to CLSI guidelines is SDD. Sreedharan H (2021) fromSouth India has reported similar findings.[20]The low MIC values obtained in the study points out the fact that Ceftaroline can be an effective drug to treat patients with MRSA infection.Ceftaroline is a drug which is new to Indian scenarios and is hardly been used, and therefore resistance patterns too are not documented.

The limited sample size and less duration of study are the major limitations of this study. A study with a larger sample size and more time period will through an insight of the importance of this novel drug in combating MRSA infections.

CONCLUSION

Ceftaroline is found to be an important drug which can be used for both community acquired as well as hospital acquired infections. But the drug needs to be given under strict surveillance to avoid future emergence of drug resistant strains.

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