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Letter to the Editor

Comparative in-vitro activity of ceftaroline against *Staphylococcus aureus* isolates from India

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Dear Editor,

Staphylococcus aureus is a well established pathogen in hospital and community settings. Serious *S. aureus* infections including bacteremia and pneumonia are associated with high mortality and morbidity. The proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) is comparatively high in the clinical settings of endemic countries [1]. The prevalence of MRSA varies from 25% to 50% and is endemic across India [2]. The clinical guidelines recommend vancomycin as first line-drug in treating MRSA infection. The well recognized limitations with vancomycin are: i) slowly bactericidal, ii) poor penetration in tissues; iii) difficult to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets; iv) nephrotoxicity at higher dose; v) narrow therapeutic index, and vi) gradually increasing vancomycin minimum inhibitory concentration (MIC) [3]. Despite its low resistance rate, vancomycin associates with suboptimal therapeutic level in critically ill patients and leads to treatment failure. Many studies have reported poor outcomes in patients with high vancomycin MIC and decreased efficacy of vancomycin in microbiological eradication of MRSA [4].

Ceftaroline is a fifth generation parenteral cephalosporin with a wide spectrum of activity against Gram-positive and Gram-negative pathogens. Ceftaroline is a bactericidal agent which inhibits cell wall synthesis. Remarkably, ceftaroline was identified with potent anti-MRSA activity. It has high affinity for penicillin binding protein PBP2a, which associates with methicillin resistance in *S. aureus* [5]. It has been approved for community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSIs) by US Food and Drug Administration in 2010 [6]. Ceftaroline is used off-label to treat patients with MRSA bacteremia and endocarditis, particularly in patients who fail first line therapy [7].

Treating MRSA infection remains a great challenge for clinicians, because of limited treatment options. The Clinical and Laboratory Standards Institute (CLSI) guideline in 2013 has placed ceftaroline as a new member of cephalosporin with anti-MRSA activity. Currently, data supporting the spectrum of activity of ceftaroline is not available in India. This study was undertaken to evaluate the susceptibility of MRSA to ceftaroline, vancomycin, daptomycin, and linezolid and to determine MIC_{50} and MIC_{90} of MRSA isolates for the same antibiotics.

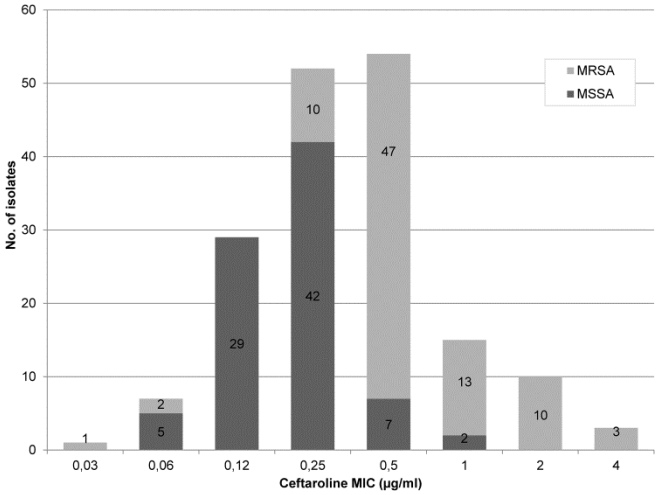
The study

A total of 171 non-duplicate *S. aureus* isolates (one per patient episode) were randomly selected from acute bacterial skin and skin structure infections (ABSSSI), lower respiratory tract infections (LRTI) and intra abdominal infections (IAI) between January

and December 2012. Isolates were collected from the following centers in India: Christian Medical college, Vellore, Tamil Nadu; Manipal hospital, Bangalore, Karnataka; Fortis hospital, Kolkata, West Bengal; the Calcutta Medical Research Institute, Kolkata, West Bengal; Choithram hospital, Indore, Madhya Pradesh; and Sanjay Gandhi postgraduate institute of medical science, Lucknow, Uttar Pradesh. Each center received institutional review board approval. The identification of *S. aureus* was carried out with standard microbiological methods [8]. Characterization of MRSA was done with cefoxitin disc diffusion method. Ceftaroline and various comparator agents (vancomycin, linezolid and daptomycin) were tested for susceptibility by reference broth microdilution method and interpretation were given as per CLSI guidelines 2015, MS100-S25. While testing with daptomycin, Mueller Hinton broth adjusted to the physiological level of calcium 50mg/liter was used. Concurrently, the *S. aureus* ATCC29213 quality control strain was tested and all the results were within established ranges.

Of the 171 tested *S. aureus*, 50% (n = 88), 27% (n = 47) and 21% (n = 36) were isolated from the clinical infections ABSSSI, IAI and LRTI respectively. Among 171 tested, 50% (n = 86) were MRSA. All *S. aureus* isolates, including MRSA, were susceptible to vancomycin daptomycin, and linezolid. Ceftaroline showed potent *in vitro* activity; 92% of *S. aureus* were susceptible (Table 1 and Figure 1). The highest MIC observed for antibiotics were as follows: vancomycin (1µg/ml), linezolid (4µg/ml) and ceftaroline (4µg/ml). To accurately determine MIC50 and MIC90, at least 100 isolates should be tested. Since the number of methicillin-susceptible *Staphylococcus aureus* (MSSA) (n=85) and MRSA (n=86) isolates included in this study were less than 100, establishment of $MIC_{50/90}$ was practically not informative. Therefore, $MIC_{50/90}$ was calculated from overall tested *S. aureus* population irrespective of MSSA and MRSA. The MIC_{50} and MIC_{90} of ceftaroline were 0.25 µg/ml and 1 µg/ml. Vancomycin ($MIC_{50/90}$, 0.5/1 µg/ml), daptomycin ($MIC_{50/90}$, 0.5/1 µg/ml), linezolid ($MIC_{50/90}$, 1/4 µg/ml) were all active against *S. aureus*. Ceftaroline was equally effective as vancomycin and daptomycin on comparison of MIC_{50} and MIC_{90}. Remarkably, ceftaroline ($MIC_{90,}$ 1 µg/ml)wasfour-fold more potent than linezolid (MIC_{90}, 4 µg/ml).

Figure 1. Ceftaroline activity against S. aureus. CLSI breakpoints for ceftaroline ≤1µg/ml (Susceptible), 2 µg/ml (Intermediate), ≥ 4 µg/ml (Resistant).



Mengeloglu *et al*. conducted a multicentric study across seven provinces in Turkey and reported that 94.3% of tested MRSA isolates were susceptible to ceftaroline (MIC ≤ 1 µg/ml) [9]. Another multicenter study from Spain, reported that all the tested *S. aureus* isolates were susceptible to ceftaroline with an MIC of ≤ 1 µg/ml [10]. Similarly, in the present study, 92% of tested *S. aureus* were susceptible to ceftaroline.

Yet another multicenter study from China investigated ceftaroline susceptibility of MRSA causing infections of the skin and its structure. The study revealed 33.5% of isolates to be non-susceptible to ceftaroline (MICs of 2 µg/ml). However there were no isolates with an MIC of > 2 µg/ml [11]. The present study showed that 6% (n = 10) and 2% (n = 3) of tested *S. aureus* were non-susceptible to ceftaroline with an MIC of2 µg/ml and 4 µg/ml, respectively (Figure 1).

Table 1. Ceftaroline MIC distribution in *S. aureus* and its respectiveMIC_{50} and MIC_{90}

Organism (No. of isolates tested)	No. of isolate (%) inhibited at ceftaroline MIC (µg/ml)									MIC (µg/ml)	
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	MIC_{50}	MIC_{90}
S. aureus (n=171)	0	1	7	29	52	54	15	10	3	0.25	1
MSSA (n=85)	0	0	5	29	42	7	2	0	0	*< 100 isolates	
MRSA (n=86)	0	1	2	0	10	47	13	10	3	*< 100 isolates	

* At least 100 isolates are necessary for calculation of MIC_{50} and MIC_{90}

As a part of the ceftaroline surveillance programme in 2010, a total of 2,351 isolates (gram-positive and gram-negative) were investigated for *in vitro* activity of ceftaroline. Of the tested *S. aureus*, 93.4 % were susceptible with the $MIC_{50/90}$ of 0.25/1 µg/ml. Likewise, in the present study susceptibility to ceftaroline of 92% of the isolates was seen with the $MIC_{50/90}$ of0.25/1 µg/ml among tested *S. aureus* isolates [12]. Interestingly, Sader *et al*. demonstrated that daptomycin and linezolid non-susceptible *S.aureus* isolates were susceptible to ceftaroline [13]. However, in this present study none of the isolates were resistant to either daptomycin or linezolid. From the aforementioned studies, it could be derived that ceftaroline has a potent *in vitro* activity against MRSA, and daptomycin and linezolid non-susceptible *S. aureus* as well.

Treatment of *S. aureus* infection is of great concern to the clinician. High vancomycin MIC (>1µg/ml) is associated with treatment failure and poor outcome in patients with MRSA infection. Extensive use of vancomycin for over 40 years led to the declining efficacy of vancomycin in treatment. Cross-resistance of daptomycinin vancomycin non-susceptible *S. aureus* has been reported [14]. Interestingly, though resistance tovancomycin, daptomycin and linezolid were rarely seen, effective monitoring of therapeutic option in treating MRSA is essential. Ceftaroline may be a useful alternative option for MRSA with reduced vancomycin susceptibility or resistant to daptomycin or linezolid. The advantage is that on administration, the prodrug ceftaroline fosamil is rapidly converted into active ceftaroline and achieves the maximum serum concentration of 20 mg/L [15].

Conclusion

In the present study, *in-vitro* evaluation of ceftaroline was found to be equally effective as vancomycin, daptomycin and better than linezolid. In summary, ceftaroline was non-inferior to vancomycin, daptomycin and linezolid against tested *S. aureus* isolates. Ceftaroline is a valuable option for treating life threatening MRSA infections with rapid target attainment and safety profile.

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