Section: Microbiology

Original Research Article

PHENOTYPIC DETECTION OF CEFTAROLINE ACTIVITY AGAINST METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS IN A TERTIARY HEALTHCARE CENTRE

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Abstract

Background: Methicillin Resistant Staphylococcus aureus (MRSA) is one of the leading causes of hospital and community acquired infections worldwide. Drugs like vancomycin, teicoplanin and daptomycin are most commonly used to treat MRSA infections but the associated toxicity limits their use in critically ill patient. Hence the need for least toxic alternate drugs is in warrant to treat the MRSA infections. Ceftaroline, fifth generation cephalosporin has been introduced recently to treat MRSA infections. This study aims at determining the invitro susceptibility of Ceftaroline against MRSA isolates in our hospital. **Materials and Methods:** Fifty non duplicate MRSA isolates, which were identified by the standard phenotypic methods at Microbiology laboratory were included in this study. Susceptibility against ceftaroline was evaluated by MIC E-test method and results were interpreted as per CLSI. **Result:** Out of 50 MRSA isolates, majority samples were from skin and soft tissue infections (74%) and majority of samples were from Surgery department (38%). Antibiotic susceptibility testing showed, all the isolates were susceptible to vancomycin (100%) and Linezolid (100%) whereas Ciprofloxacin (36%) and erythromycin (44%) showed least resistance. MIC E test by Ceftaroline showed all the isolates were below MIC of 2µg/ml which indicates that all the isolates were susceptible to Ceftaroline (100%). **Conclusion:** From this study it was seen that Linezolid, Vancomycin and Ceftaroline showed no resistance to MRSA isolates, Ceftaroline can be used as a good alternate option to treat MRSA infection and to keep the Vancomycin as a reserve drug for future since the resistance to vancomycin was on surge in recent days.

INTRODUCTION

Staphylococcus aureus is a Gram-positive bacterium that cause a wide variety of clinical diseases. S. aureus is both a frequent commensal as well a leading cause of skin and soft tissue infections, osteomyelitis, endocarditis and bacteremia.[1] Frequency of Staphylococcus aureus colonization in carriers on various body sites accounts for Nose 100%, Hand 90%, Perineum 60%, Forearm and skin chest 45% and axilla 19%.

In 1940s Penicillin was introduced as the drug of choice for medical treatment of S.aureus infection . Later resistance to Penicillin was developed due to the production of Penicillinase enzyme. In 1959 Methicillin was introduced for Penicillinase resistant S.aureus and Methicillin-resistant S. aureus (MRSA) was observed within 1 year of their first clinical use. Since then, Vancomycin has become the drug of choice to treat MRSA.

Methicillin resistance Staphylococcus aureus is defined as an oxacillin minimum inhibitory concentration (MIC) greater than or equal to 4 micrograms per milliliter.[1] Methicillin-resistant Staphylococcus aureus (MRSA) is a significant bacterial pathogen that causes a variety of community-acquired and healthcare-associated illnesses.[2]

Methicillin resistance is mediated by mecA gene and acquired by horizontal transfer of a mobile genetic element designated Staphylococcal cassette chromosome mec (SCCmec). The gene mecA encodes penicillin-binding protein 2a (PBP2a), an enzyme responsible for crosslinking the peptidoglycans in the bacterial cell wall. PBP2a has

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a low affinity for β-lactams, resulting in resistance to this entire class of antibiotics.[3]

MRSA is a worldwide health concern, with an incidence of 25-50% in India.[4] MRSA is one of the main reasons for hospital- acquired infections, which is frequently linked to high rates of morbidity, death, length of stay and financial burden. MRSA infections can be categorized into Hospital-associated (HA-MRSA) and community- associated (CA-MRSA) infections. Their differences include differences in therapy and antibiotic susceptibility in addition to differences in clinical characteristics and molecular biology.[5] A serious worry is the rise in virulence of community-associated MRSA (CA-MRSA).[6] The One Health approach has also significantly informed MRSA epidemiology, with the recognition of CA-MRSA transmission between livestock and people.

Vancomycin is the recommended medication for treating serious MRSA infections. Unfortunately, a number of drawbacks have been linked to its use, including poor drug penetration into tissues, a narrow therapeutic index, a slow rate of bactericidal activity, challenges meeting pharmacokinetic and pharmacodynamic targets and possible adverse effects like nephrotoxicity and ototoxicity.[7] Additionally, there have been cases of vancomycin therapy failures in critically sick patients as a result of high MIC (Minimum Inhibitory Concentration) values or inappropriate therapeutic doses.[8] Alternative medications such as Teicoplanin, linezolid, and daptomycin are increasingly being utilized to treat MRSA infections.[9-12]

Ceftaroline fosamil is a fifth-generation cephalosporin that is effective against both methicillin- susceptible (MSSA) and MRSA. Ceftaroline acts by inhibiting cell wall formation by binding to Penicillin Binding Proteins (PBP) 1, 2, 3, and 2a in MRSA.[13] The FDA authorized it in October 2010 for the treatment of individuals with community-acquired bacterial pneumonia and acute bacterial/skin and skin structure infections (ABSSSI).[14] According to studies, the medicine is well tolerated by patients and is as effective as vancomycin, daptomycin, and linezolid in eliminating MRSA.[15,16] Although resistance to ceftaroline is unusual, multiple investigations have found that MRSA is less susceptible to ceftaroline in some cases. The mutation outside of the Penicillin-Binding Domain (nPBD) of the PBP 2a protein, specifically, may be the cause of the resistance.[17,18]

CLSI (Clinical Laboratory Standards Institute) breakpoints are used for susceptibility testing in clinical microbiology laboratories across the globe. CLSI also modified the Ceftaroline breakpoints in January 2019 and introduced the susceptible dose dependent (SDD) category for this agent, based on the European Medicines Agency's 2017 according to the recommendation-High dose regimen of 600 mg every 8 hours over 120 minutes. Despite the fact that this dosing regimen is not approved by the US Food and Drug Administration.[19] Research have been conducted in India to assess S. aureus's susceptibility to ceftaroline, and even less is known about the susceptibility pattern of S. aureus to ceftaroline.[20-22] Therefore, the purpose of this study is to determine the in vitro susceptibility of MRSA isolates to ceftaroline by E strip method in our healthcare facility .

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Microbiology, Stanley medical college and Hospitals in North Chennai for a period of 6 months (June to November 2023). Institutional Ethics Committee clearance was obtained to conduct the study.

Sample collection and processing:

1. Identification of staphylococcus aureus:

During the study period, the received samples are processed by standard laboratory techniques. Staphylococcus aureus was identified phenotypically by growth on 5% Sheep blood Agar Plate which showed white opaque colonies with a narrow Zone of β-hemolysis, Small golden yellow non diffusible pigment producing colonies on Nutrient Agar plate, Small Lactose Fermenting opaque colonies on MacConkey agar plate and yellow colonies on Mannitol Salt agar. Gram staining done from the colony showed Gram positive cocci in clusters.

Further Biochemical identification test like Catalase test, coagulase test, urease test, Hugh-Leifson's Oxidation Fermentation test was performed and Staphylococcus aureus was identified.

2. Antimicrobial susceptibility testing and MRSA detection:

As per CLSI M100 2023 guidelines, Antimicrobial susceptibility testing for the isolated Staphylococcus aureus species was done along with the detection for MRSA by Kirby bauer disk diffusion method using a Cefoxitin disk (30 µg).

Drug	Disc Content	Zone diameter		
		Susceptible	Intermediate	Resistant
Cefoxitin	30µg	≥22mm	-	≤21mm
Erythromycin	15µg	≥23mm	14-22	≤13mm
Clindamycin	2µg	≥21mm	15-20	≤14mm
Doxycycline	30µg	≥16mm	13-15	≤12mm
Cotrimoxazole	1.25/23.75µg	≥16mm	11-15	≤10mm
Penicillin	10 units	≥29mm		≤28mm
Linezolid	30µg	≥23mm	21-22	≤20mm
Ciprofloxacin	5µg	≥21mm	16-20	≤15mm

Vancomycin agar screen for MRSA isolates:

- By agar dilution method BHI agar with 6 µg/ml vancomycin (HIMEDIA) is added and distributed in petri Plates. Colony suspension of 0.5 Mcfarland standard was prepared .
- Spot inoculation of 10mm was done using swab. Then the plate was incubated at 37°c for 24 hours.

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The plate was examined carefully with transmitted light.

Interpretation: >1 colony or light film of growth indicate reduced susceptibility to Vancomycin.

Vancomycin MIC detection by Epsilometer test:

- The Susceptibility of the isolates to Vancomycin was carried out by MIC using E-strips (Himedia) containing a concentration gradient range of VAN (0.016-256 µg/ml).
- Interpretation was carried out according to CLSI M100 2023 guidelines.

Drug	Disc Content	Zone diameter		
		Susceptible	SDD	Resistant
Vancomycin (E-strip)	0.016-256 µg/ml	≤ 2 µg/ml	4-8 µg/ml	≥ 16 µg/ml

Susceptibility of the isolates to Ceftaroline was carried out by MIC E-strips (Himedia) containing a concentration gradient range of CPT (0.002-32 µg/ml).

Drug	Disc Content	Zone diameter		
		Susceptible	SDD	Resistant
Ceftaroline (E-strip)	0.0002-32 µg/ml	≤ 1 µg/ml	2-4 µg/ml	≥ 8 µg/ml

SDD-Susceptible Dose Dependent

RESULTS

This prospective cross-sectional study was conducted in the Department of Microbiology at Government Stanley Medical College and Hospital for the period of 6 months from June 2023 to November 2023.As per inclusion criteria a total of 50 consecutive non duplicate MRSA isolates were included in the study. MRSA isolate was identified based on the standard phenotypic identification methods.

The study results were discussed as follows:

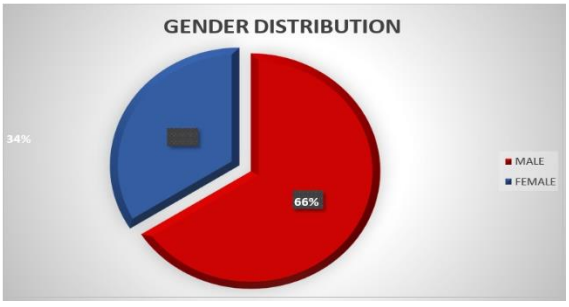

Chart 1: Gender distribution of clinical samples of MRSA isolates

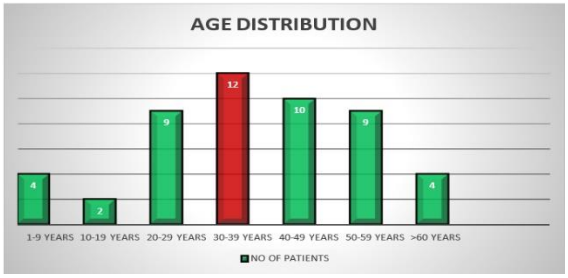

Chart 2: Age distribution of clinical samples of MRSA isolates

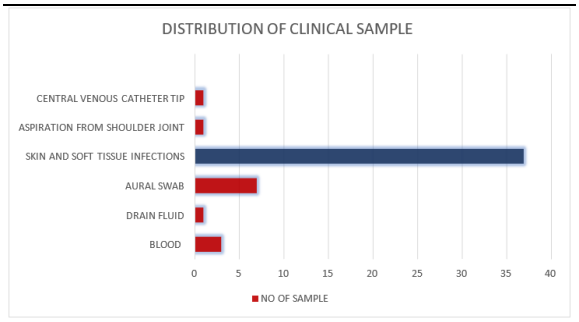

Chart 3: Distribution of types of clinical sample received

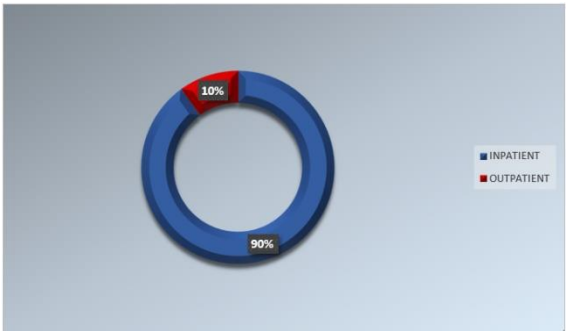

Chart 4: Distribution of MRSA samples among inpatient and outpatient

Chart 5: Ward wise distribution of MRSA samples

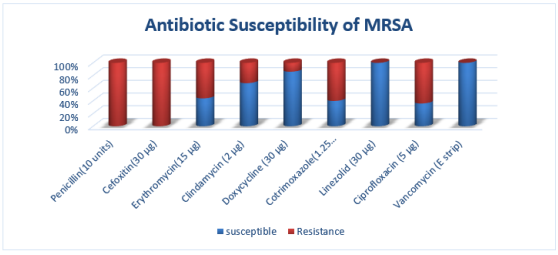

Chart 6: Antimicrobial susceptibility pattern of MRSA isolates

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Chart 7: Ceftaroline susceptibility pattern of MRSA isolates (E strip) with MIC.

Table 1: Gender distribution of clinical isolates

Gender	No of patients(n=50)	Percentage (%)
Male	33	66%
Female	17	34%
Total	50	100%

Table 2: Age distribution of clinical samples of MRSA isolates

Age	No of patients (n=50)	Percentage (%)
1-9 years	4	8%
10-19 years	2	4%
20-29 years	9	18%
30-39 years	12	24%
40-49 years	10	20%
50-59 years	9	18%
>60 years	4	8%
Total	50	100%

Table 3: Distribution of types of clinical sample received

Sample type	No of samples (n=50)	Percentage (%)
Skin and soft tissue infections	37	74
Aural swab	7	14
Blood	3	6
Drain fluid	1	2
Aspiration from shoulder joint	1	2
Central venous catheter tip	1	2
Total	50	100%

Table 4: Distribution of MRSA samples among inpatient and outpatient

In/out patient	Total samples(n=50)	Percentage
Inpatient	45	90%
Outpatient	5	10%
Total	50	100%

Table 5: Ward wise Distribution of MRSA Samples

Ward	No of sample	Percentage
General surgery	19	38%
Orthopedics	8	16%
Ent	8	16%
General medicine	5	10%
Plastic surgery	3	6%
Paediatrics	2	4%
O&G	2	4%
Others(Derm/TAEI/Neuro)	3	6%
Total	50	100%

Table 6: Antimicrobial susceptibility pattern of MRSA isolates

Drug with disc content	Susceptibility of MRSA isolates (n=50)	Percentage (%)	Resistance of MRSA Isolates (n=50)	Percentage (%)
Penicillin(10 units)	0	0	50	100%
Cefoxitin(30 µg)	0	0	50	100%
Erythromycin(15 µg)	22	44%	28	56%
Clindamycin (2 µg)	34	68%	16	32%
Doxycycline (30 µg)	43	86%	7	14%
Cotrimoxazole(1.25/23.75µg)	20	40%	30	60%
Linezolid (30 µg)	50	100%	0	0
Ciprofloxacin (5 µg)	18	36%	32	64%
Vancomycin (E strip)	50	100%	0	0

Table 7: Growth on vancomycin agar screen (6 µg/ml)

Vancomycin agar screen	No of isolates(n=50)	Percentage (%)
Growth	0	0
No growth	50	100%
Total	50	100%

Table 8: Ceftaroline susceptibility pattern of MRSA isolates by MIC (CPT E Strip)

MIC ZONE- CPT (0.002-32 µg/ml)	No of MRSA isolates	Percentage	Interpretation
0.38 µg/ml	1	2%	Susceptible
0.5 µg/ml	12	24%	Susceptible
0.75 µg/ml	19	38%	Susceptible

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1 µg/ml	18	36%	Susceptible
Total	50	100%	Susceptible

Figure 1: MRSA on Mannitol salt agar

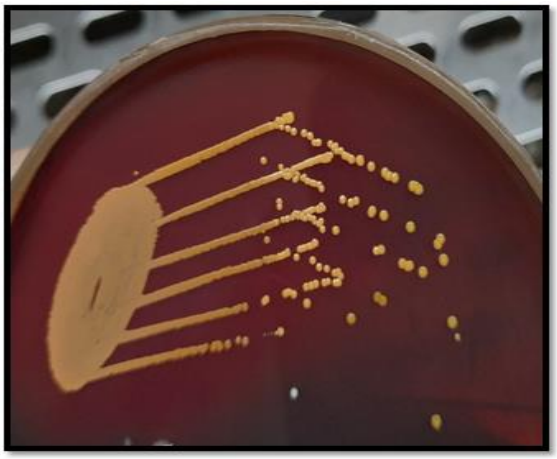

Figure 2: Golden yellow pigmented colony on 5% Blood agar plate

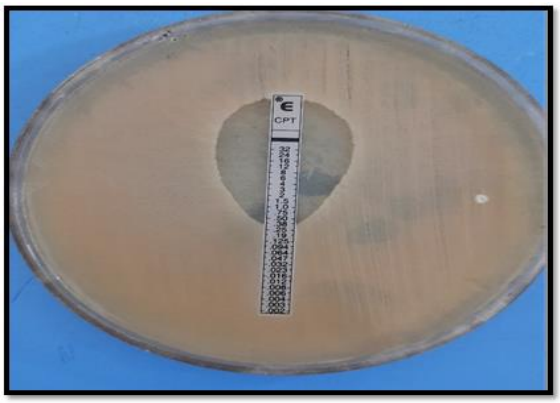

Figure 3: Ceftaroline E strip MIC=0.38µg/ml

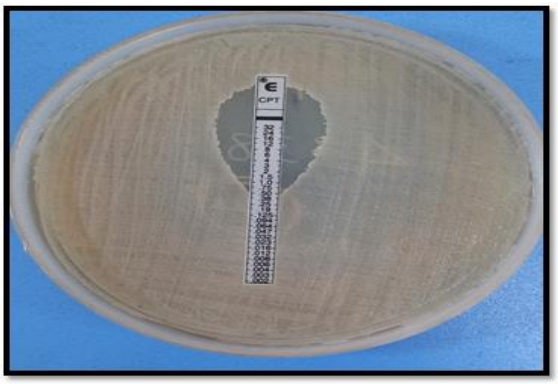

Figure 4: Ceftaroline E strip MIC=0.50µg/ml

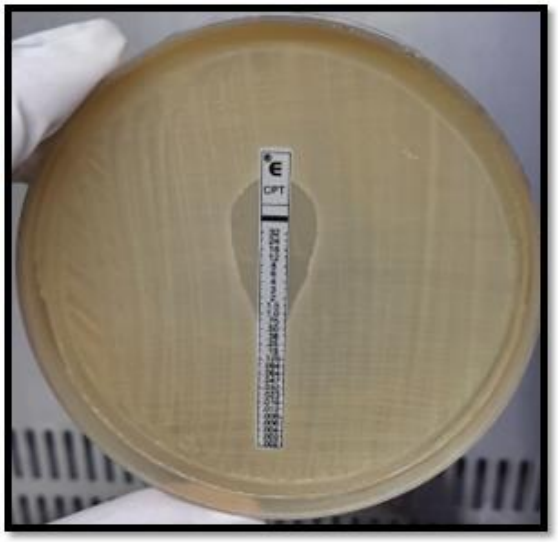

Figure 5: Ceftaroline E strip MIC=0.75µg/ml

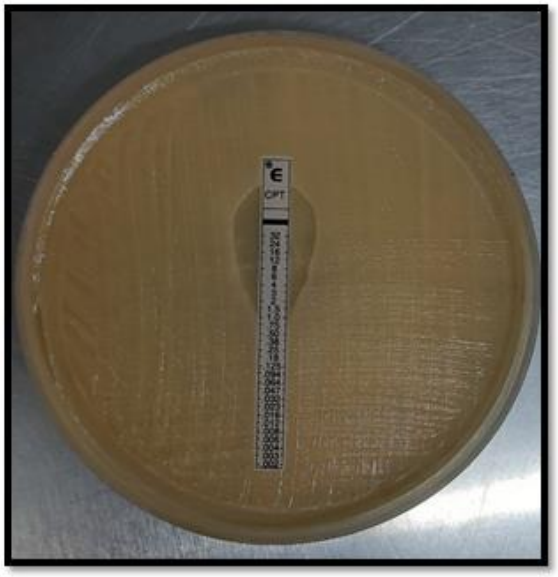

Figure 6: Ceftaroline E strip MIC=1.0µg/ml

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Figure 7: Vancomycin E strip MIC=1.5µg/ml

DISCUSSION

Antibiotic resistance is a major health concern worldwide especially in developing countries like India. The prevalence of methicillin-resistant S. aureus, particularly community-associated MRSA, has alarmingly increased in India in recent years. MRSA is now endemic throughout India, with varying incidence rates. The study presents the current comprehensive data about the Antibiotic susceptibility pattern of MRSA along with its susceptibility to the drug Ceftaroline.

A total of 50 consecutive, non-duplicate Methicillin Resistant Staphylococci aureus (MRSA) isolates were included in the study from various department from our hospital.

Among the 50 MRSA, majority of the sample were from male patients (66%) and female patients accounts for 34%. This shows the male preponderance. The age range of the patients from whom the isolates were obtained ranged from neonate to 70-year- old. Major isolates were between the age group of 30-39 years.

A study conducted by Tasneem et al., at Lucknow showed the similar age group and Gender prevalence of 36.5 years of median age and male: female ratio of 1.3:1.[23]

Sahai et al., who conducted study at Tertiary care hospital at North India showed the highest prevalence of MRSA between the age group of 31-40 years and Male outnumbered the female with the ratio of 1.1:1.[24]

During this study period, the positive MRSA isolate was received from Inpatient wards and ICU accounting for 90% and 10% were from Out patient department. The major samples were from General surgery department 38% followed by Orthopedics and ENT 16% each and the remaining 30% were from other departments.

From the various clinical samples, MRSA was isolated majority from the skin and soft tissue infection accounting for 74% followed by aural swab 14%, Blood 4% and Drain fluid, aspiration from shoulder joint and Central venous catheter tip constitutes 2% each.

A study conducted by FazilBari et al., at Lady Reading hospital during the year 2015, Pakistan has showed the similar distribution of samples from Surgery department 51%, and the skin and soft tissue specimen accounts for 45% and Blood accounts for 13%.[25]

Shoiab mohammed kahn et al., who conducted study at Government medical college, Srinagar (2019) has showed the maximum MRSA isolate from pus specimen 44%, aural swab 29% and Blood 8%.[26]

Out of 50 MRSA isolates, all the isolates were susceptible to Vancomycin (MIC by Estrip)-100% and Linezolid(100%), followed by Doxycycline 86%, Clindamycin 68%, erythromycin 44%, Cotrimoxazole 40% and Ciprofloxacin 36%. Highest resistance was noted to penicillin (100%), Ciprofloxacin (64%), co-trimoxazole (60%), erythromycin (56%) and Clindamycin (32%).

A study conducted by Abarna velayudhum et al., showed almost similar prevalence of resistance pattern of Cotrimoxazole (78%), Erythromycin (72%), Ciprofloxacin (60%), Gentamicin (48%).[27]

Another study by Bhavana et al., on Community and Hospital acquired MRSA, showed the resistant pattern of Gentamicin (79%), Cotrimoxazole (74%), Ciprofloxacin (74%), Erythromycin (60%).[28]

In our study it was observed that there is no growth observed in Vancomycin agar screen and susceptibility of Vancomycin by MIC Etest has showed that all the isolates were ≤ 2µg/ml. No vancomycin resistance was noted by the above two methods. In our study Vancomycin agar screen sensitivity was 100% in comparing with MIC hence it can be used for routine screening method at hospital setup where the MRSA prevalence was quite high.

Aref shariati et al., has conducted Meta analysis study on Global prevalence and distribution of VRSA/VISA/hVISA has showed the global prevalence of VRSA, VISA and hVISA isolates was 1.5%, 1.7%, and 4.6%, respectively. Compared to other continents, Asia has a greater VISA prevalence. It should be mentioned that Iran and India accounted for 67% (327/485) of the strains that were resistant to vancomycin. The greater frequency of VISA and VRSA in Asia compared to Europe and the Americas can be attributed to a factor like majority of Asian nations are developing nations with differing views on antimicrobial treatments and increased microbial transmission caused by high population density can result in an increase in MRSA infections.[29]

Of all the 50 MRSA isolates tested, all were sensitive to ceftaroline by E test.19 isolates showed MIC of 0.75 µg/ml, 18 isolates showed MIC range of 1 µg/ml, 12 isolates showed 0.5 µg/ml MIC and 1 isolate showed 0.38 µg/ml.

A prospective cross sectional study conducted at 2023 by Ankita roy et al., from 198 MRSA isolates, has showed no resistance to the drug Ceftaroline.[30]

The other study by Sreedharan et al,[31] has showed the similar results. There are few studies in India which showed higher MIC of Ceftaroline against MRSA isolate.

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A study conducted by Arun sachu at Kerala has showed the highest resistant of 30% of MRSA against ceftaroline.[32]

The other study conducted by Gaikwad et al., has showed 28/30 isolates were susceptible to Ceftaroline accounts for 7% resistant.[22]

Despite the fact that ceftaroline was just introduced a few years ago, ceftaroline- resistant bacteria have been found in an increasing number. Furthermore, it was demonstrated that resistant strains have existed for at least a dozen years prior to the introduction of ceftaroline. The resistant was due to the alteration in PBP2a, PBP3, PBP4.

CONCLUSION

Ceftaroline has showed potent invitro activity against MRSA which could be considered as a better alternative for the treatment of MRSA. Though, Vancomycin and Ceftaroline has showed 100% susceptibility against MRSA isolates in our study, Unlike Vancomycin, Ceftaroline has established good clinical safety and efficacy, good tolerability by patient, cost effective and broad-spectrum antibacterial activity.

However Ceftaroline like other drug will loses its efficacy soon if misused or overused in the community. Continuous surveillance and strict antimicrobial policies are needed to be monitored as the clinical usage of the drug increases. To prevent the spread of MRSA infection among Health care facility, Standard precautions like Hand hygiene, regular screening and decolonization of MRSA carriers among Health care workers through Mupirocin oinment application locally, isolation of MRSA cases in wards should be followed. Health care with increasing resistance to the available antibiotics and limited newer antibiotics in the pipeline, necessitates the need to stop misusing the antibiotics in order to combat the further development of resistance and prevent going to pre-antibiotic era.

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