In Vitro Activity of Ceftaroline against Methicillin-Resistant *Staphylococcus Species*

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Abstract

Objectives

To determine the *in vitro* susceptibility of Ceftaroline against Methicillin-resistant *Staphylococcus species*.

Methodology

This observational study was conducted at the Department of Microbiology, Ziauddin University Hospital, Karachi, from July 2014 to March 2015. Consecutive clinical isolates of *Staphylococcus species* were collected and identified by conventional microbiological techniques. Antimicrobial susceptibility testing was carried out by Kirby-Bauer disc diffusion method. The results were interpreted by using Clinical Laboratory Standard Institute criteria. Methicillin resistance was detected by using Cefoxitin disk as a surrogate marker. Statistical analysis was performed by Statistical Package for the Social Sciences version-17.

Results

A total of 276 clinical isolates of Methicillin- Resistant *Staphylococci* were obtained during the study period. In these 276 isolates, 103 (37.3%) were Methicillin-Resistant *Staphylococcus aureus*, and 173 (62.7%) were Methicillin resistant Coagulase negative *Staphylococci*. All 276 (100%) isolates of Methicillin- Resistant *Staphylococci* were sensitive to Ceftaroline.

Conclusion

Ceftaroline exhibited potent antimicrobial activity against Methicillin- Resistant *Staphylococci* isolates including Methicillin-Resistant *Staphylococcus aureus*. Ceftaroline is equally effective as other options for treating Methicillin-Resistant *Staphylococci* isolates.

Keywords

In vitro susceptibility. Ceftaroline. Methicillin-resistant. Staphylococcus species.

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Introduction

Staphylococcus species are significant source of infections worldwide. They are also the major causes of hospital-acquired infections. *Staphylococcus aureus* (*S. aureus*) is among the most prevalent causes of clinical infections globally and has garnered substantial public attention due to increasing mortality associated with multi-drug resistance (MDR).[1] Other *Staphylococcus species* like strains of *Staphylococci epidermidis* (*S. epidermidis*) are resistant to various antimicrobials by forming biofilm and colonization. They can also serve as a reservoir for antibiotic resistant genes that can be transferred to other bacteria.[2] For the previous several years Methicillin-Resistant *Staphylococcus aureus* (MRSA) has become a common pathogen in hospital settings and characterize about 33% to 55% of all isolated *S. aureus* strains from hospital and 60% from critical care units.[3] The rate of MRSA in all community-associated *S. aureus* infections in Asian countries ranges from 2.5% to 39%.[4] In a study from Karachi, 38.6% of *S. aureus* isolates were found to be MRSA.[5] Many of the MRSA isolates are becoming MDR and they are susceptible only to the glycopeptide antibiotics such as Vancomycin (VA) which has considerable adverse effects. Linezolid (LZD) has been shown to achieve a higher clinical and microbiological response rate.[6] However, LZD is an expensive alternative with its own adverse side effects.[5]

Ceftaroline (CPT) is a novel, parenteral, bactericidal, anti-MRSA cephalosporin which exhibits a broad spectrum of activity against important community and hospital-acquired pathogens.[7] CPT has high affinity to bind Penicillin binding protein 2a making it effective against MRSA.[8] CANVAS-1 trail results for complicated skin or skin structure infections (cSSSI) proved a good safety profile for CPT and good clinical cure rates.[9]

CPT is an effective therapeutic option against MRSA as well as others Methicillin- Resistant *Staphylococcus species* (MRS) as the therapeutic options are narrowing. There is a strong need in developing countries to introduce new antibiotics to deal with these MDR bacteria in order to provide effective treatment which will decrease the cost of treatment, limit the stay in hospital, and decrease the selection pressure. Very limited data is published in Pakistan against usefulness of CPT against

MRS. Furthermore; local data is of prime importance. The objective of our study was to determine *in vitro* susceptibility of CPT against MRS. We also document the susceptibility pattern of other antimicrobials against *Staphylococcus species*.

Methodology

This observational study was conducted over a period of nine months from July 2014 to March, 2015 at the Department of Clinical Microbiology of Ziauddin University Hospital. Two hundred and seventy six consecutive clinical isolates of MRS including MRSA were collected from different clinical samples by convenient sampling. These isolates were included in the study. Sources were blood, respiratory secretions, wound swabs, central venous pressure (CVP) lines tips, and pus. All the duplicate isolates were excluded from the study. Written approval from the institutional ethical committee was obtained. Informed consent was taken from either the patient or any other patient's relative.

Clinical samples were received in a sterile container or in an Amies transport medium supplied from the Microbiology laboratory. These samples were processed and incubated at 37ºC ± 2ºC in ambient air for 24-48 hours, using standard microbiological techniques.[10] *Staphylococcus species* including *S. aureus* were identified using conventional techniques (colony morphology, gram staining, catalase test, coagulase test, mannitol salt agar, and DNase test).[10]

Antimicrobial susceptibility testing was performed on Mueller Hinton agar (MHA) medium (oxoid Ltd., England) using modified Kirby-Bauer disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) 2014 guidelines.[11] A 0.5 McFarland equivalent suspension of organism was prepared and inoculated onto a MHA plates. This is followed by the application of antimicrobials discs. CPT (30µg-Oxoid Ltd., England) disc was used. These plates were then incubated overnight at 37ºC in an ambient air incubator. The isolates were considered resistant to CPT if the zone of inhibition around the disc was ≤ 20 mm and susceptible if zone was ≥ 24 mm. *S. aureus* American Type Culture Collection (ATCC®) 25923 was used as control. Methicillin resistance was detected by using Cefoxitin (30µg-Oxoid Ltd., England) disk as a surrogate marker.[11]

A research proforma was used to document the essential data including age and gender. Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version-17. Frequencies and percentages were computed for presentation of all categorical variables like microorganisms, gender, sensitivity and resistance. Mean values and standard deviation was calculated for quantitative variables like age of patients.

Results

A total of 276 clinical isolates of MRS were obtained during the study period. Distribution of isolates of MRS from different clinical samples is shown in Figure 1. In these 276 isolates, 103 (37.3%) were MRSA, and 173 (62.7%) were Methicillin resistant Coagulase negative *Staphylococci* (MRCoNS). Predominantly, the isolates were from female patients 156/276 (56.5%), while isolates from male patients were 120/276 (43.5%). Female to male ratio was 1.3:1. The mean age of patients with MRS isolates was 36.1 ± 27.7 years. All 276 (100%) isolates of MRS were sensitive to CPT, Linezolid, and Teicoplanin. Overall, 241/276 (87.3%) were sensitive to Amikacin, 84/276 (30.4%) were sensitive to Ciprofloxacin, 162/276 (58.6%) were sensitive to Clindamycin, 122/276 (44.2%) were sensitive to Co-trimoxazole, 52/276 (18.8%) were sensitive to Erythromycin, and 22/276 (8%) were sensitive to Penicillin. Sensitivity pattern of antimicrobials tested against MRSA and MRCoNS is shown in Figure 2.

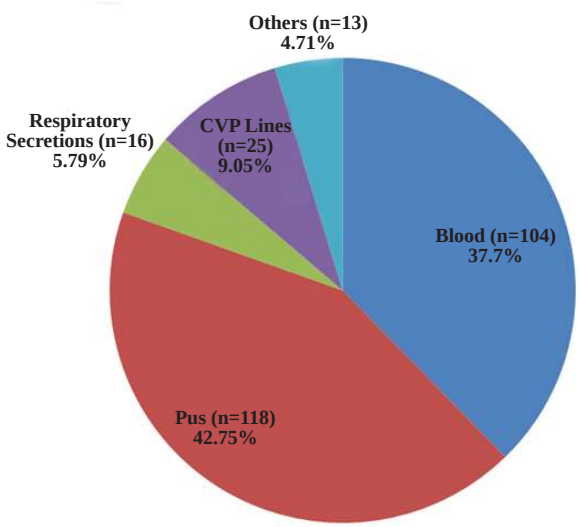

Fig 1. Distribution of isolates of MRS from different clinical samples.

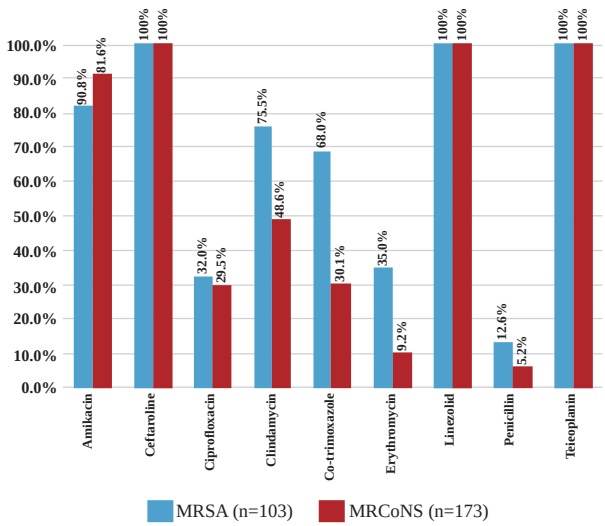

Fig 2. Sensitivity pattern of antimicrobials tested against MRSA and MRCoNS.

Discussion

Antimicrobial resistance is rising during the past years. There is a need to foster new antimicrobials especially for treating Gram-positive organisms. MRSA and MRCoNS are foremost origins of both health-care and community-associated infections.[12-14] Gu *et al*. reported emerging LZD resistance among *Staphylococcus species*.[15] Taj *et al*. reported emergence of VA resistant and VA-intermediate *S. aureus*.[5] Both LZD and VA are considered the last options for treating MRS. CPT is a new effective option for treating cSSSI and community-acquired bacterial pneumonia due to MRS and is approved by FDA. Iizawa *et al*. reported that infections caused by MRSA like osteomyelitis and endocarditis can be treated by CPT.[16] In our study, MRS isolates were 100% sensitive to CPT, LZD, and Teicoplanin (glycopeptide). These three antimicrobials are highly effective and favorable treatment choice. From different parts of the world, slightly different results representing the demographic variation. Sader *et al*. reported 97.5% sensitivity to CPT while Yigong *et al*. showed 98% sensitivity to CPT against the isolates of MRSA from USA and Europe.[17,18] A study conducted in Islamabad, Hafeez *et al*. reported 96% sensitivity to CPT against MRSA.[19] Moreover, in an international study CPT demonstrated 100% sensitivity against the isolates of MRCoNS.[7]

Conclusion

CPT exhibited potent antimicrobial activity against MRS isolates including MRSA. CPT might be effective on the basis of *in vitro* data like other options for treating MRS isolates. CPT should be use judiciously especially against Gram positive organisms on the basis of culture and sensitivity. CPT might reduce selection pressure on other antimicrobials for treating MRS related infections. This will curtail antimicrobial resistance against MRS isolates. Further studies are needed for the effectiveness of CPT especially on bacteremic isolates.

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