ORIGINAL ARTICLE

ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF DAPTOMYCIN-SENSITIVE MRSA (METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*) FROM SKIN AND SOFT TISSUE INFECTIONS

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ABSTRACT

Background: *Staphylococcus aureus* is responsible for a significant number of skin and soft tissue infections (SSTIs) mostly abscesses and infected wounds. Treatment options for Methicillin-resistant *S. aureus* (MRSA) are limited specifically in Pakistan either because of unavailability, toxicity or due to lack of local susceptibility data. Hence, we evaluated the antimicrobial susceptibility pattern of DAP-sensitive MRSA isolates from skin and soft tissue infections.

Material & Methods: This cross-sectional study was conducted at the Clinical Microbiology Laboratory of the Aga Khan University Hospital. One hundred and five isolates of *S. aureus* characterized as Daptomycin-sensitive and Methicillin-resistant were collected via consecutive sampling from pus and tissue specimens representing SSTIs from 1st May to 31st October 2020. Antimicrobial susceptibility pattern of these isolates was determined using the VITEK®2 automated system (Biomerieux Inc) on the VITEK®2 Gram Positive Susceptibility card (AST-P580) and interpreted as sensitive, intermediate or resistant according to the Clinical and Laboratory Standards Institute's breakpoints.

Results: Majority of the patient population was male (63%) with 85.7% isolates from cutaneous and subcutaneous abscesses and 14.3% from necrotic and non-healing wounds. All isolates were susceptible to vancomycin and linezolid, 98% to rifampicin, 81.9% to clindamycin, 76.2% to fusidic acid, 74.3% to co-trimoxazole, 66.7% to tetracycline, 58.1% to gentamicin, 24.8% to levofloxacin and 31.4% to erythromycin.

Conclusion: In view of our study findings clindamycin, co-trimoxazole and tetracycline appear to be the best possible oral or parenteral antibiotics for empirical administration in patients for less severe cases whereas, vancomycin and linezolid are drugs of choice in serious cases of MRSA SSTIs.

Keywords: Daptomycin, Methicillin-resistant *Staphylococcus aureus* (MRSA), Skin and soft tissue infections (SSTIs)

BACKGROUND

Staphylococcus aureus (*S. aureus*) is one of the most virulent gram-positive pathogens and is responsible for a wide variety of infections ranging from skin and soft tissue infections to potentially life-threatening systemic infections including infective endocarditis. Through the integration of various environmental and host-derived signals, it expresses an array of virulence factors which allows it to invade, survive and adapt in the host environment.[1] Surveillance data from around the world has indicated a rise in multi-drug resistance in *S. aureus* with Methicillin-resistant *S. aureus* (MRSA) accounting for a significant number of reported infections in countries from all continents.[2]

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In Pakistan, an increase in the frequency of isolation of MRSA has been observed in the past couple of decades, with higher frequency as compared to some of the western regions namely Northern Europe.[3] Among the many infections caused by MRSA, skin and soft tissue infections (SSTIs), ranging in severity from mild to life threatening, appear to be the most common in the community and hospital settings.[4]

Owing to the colossal increase in multi-drug resistance, infections caused by *S. aureus* has been often difficult to treat with therapy limited to few drugs associated with adverse events further complicating patient survival and increasing health care burden. One such drug is vancomycin, which has been recommended by the Infectious Diseases Society of America (IDSA) as a parenteral drug of choice for the treatment of MRSA SSTIs.[5] However, there have been multiple factors related to its pharmacological characteristics and susceptibility profile that has limited its effectiveness as the drug of choice against these infections. In addition to the intravenous route requiring prolonged

duration of administration to reduce infusion-related reactions, vancomycin has seen a rise in minimum inhibitory concentrations (MICs) over the past couple of decades, often termed as 'MIC creep'.[6,7] Furthermore, adverse effects on renal function and anaphylactoid reactions has often led to treatment failures compounding patient outcomes.

In the back drop of this scenario, daptomycin (DAP) emerged as an alternative agent that has shown promising results in mitigating the risk of therapy associated morbidity, at the same time maintaining the same bactericidal capabilities and with more stable MICs over a long period of time.[8] In addition to requiring a single daily intravenous dose administered over a short duration of time, it has shown better outcomes in the treatment of SSTIs as compared to vancomycin.[8,9] However, DAP is unavailable in Pakistan, and it will require heavy expenses to import the drug for use in MRSA SSTIs on an individual case basis. Considering this fact, there has been a shift of focus to the use of more conventional drugs including clindamycin, fusidic acid and co-trimoxazole and for the treatment of MRSA SSTIs, which owing to their decreased usage remain susceptible in these infections.[10] Hence, the use of these drugs in place of vancomycin would not only reduce the burden on health care budgets but would also reduce the risk of increase in MICs associated with the ubiquitous use of vancomycin. The antimicrobial susceptibility pattern of MRSA may vary among geographical locations and the choice of appropriate antibiotics should be guided by the local antibiogram. Hence, we planned to evaluate the antimicrobial susceptibility pattern of DAP-sensitive MRSA isolates from skin and soft tissue infections.

MATERIAL AND METHODS

This was a cross-sectional study conducted at the Clinical Microbiology Laboratory of the Aga Khan University Hospital from 1st May to 31st October 2020. One hundred and five isolates of *S. aureus* characterized as Methicillin-resistant and DAP-sensitive were included in this study. Antimicrobial susceptibilities were determined for these isolates on the VITEK®2 automated system (Biomerieux Inc). Antimicrobials included in this study were gentamicin, clindamycin, erythromycin, fusidic acid, levofloxacin, co-trimoxazole, tetracycline, vancomycin, rifampicin and linezolid. The results were reported as sensitive, intermediate or resistant based on the Clinical and Laboratory Standards Institute (CLSI).[11]

Information regarding patient's age, gender and specimen source along with susceptibility data for different antibiotics was recorded on a standardized study proforma. Baseline data collected on hard copies of the study proformas was entered in the *MedCalc* Statistical *Software version* 20.027 (*MedCalc Software* bv, Ostend, Belgium). The entered data was twice matched for proper verification of transfer from the hard copies to the statistical software.

Statistical significance was analyzed for the association of susceptibilities for different antibiotics with the specimen source of the isolates using the Chi-square test. A p value of <0.05 was considered significant.

The study was exempted from ethical approval by the Institutional Review Board of Aga Khan University (Ref # 2020-5753-15344).

RESULTS

The median age of patient population in this study was 35 years (IQR: 51 - 18.5) of which majority were males (63.8%). The isolates predominantly represented cutaneous and subcutaneous abscesses (85.7%) with a small number from necrotic and non-healing wounds (14.3%). Information regarding patient demographics and source of isolates is shown in Table-1.

Table-1: Information regarding patient demographics and source of isolates.

Characteristic	Number of isolates n (%)
Age group	
≤ 16 years	n=24 (22.9%)
> 16 - ≤ 45 years	n=44 (41.9%)
> 45 years	n=37 (35.2%)
Gender	
Male	n=67 (63.8%)
Female	n=38 (36.2%)
Source of isolates	
Cutaneous & Subcutaneous Abscesses	n=90 (85.7%)
Necrotic & Non-healing Wounds	n=15 (14.3%)

All isolates were found susceptible to vancomycin and linezolid. Rest of the susceptibility was rifampicin 98.1%, clindamycin 81.9%, fusidic acid 76.2%, co-trimoxazole 74.3%, tetracycline 66.7%, gentamicin

58.1%, levofloxacin 24.8%, and erythromycin 31.4%. The antimicrobial susceptibility of the isolates is graphically represented in Figure-1.

The association of specimen source of the isolates with the antimicrobial susceptibility status didn't reach statistical significance for any of the antibiotics.

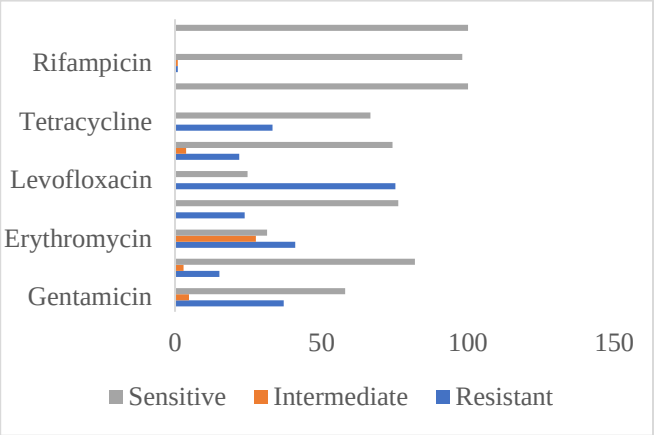

Figure-1: Graphical representation of antimicrobial susceptibility pattern of all DAP-sensitive MRSA isolates (*n*=105).

DISCUSSION

S. aureus is responsible for a significant number of SSTIs ranging from uncomplicated infections such as impetigo and abscesses to the more complicated necrotizing fasciitis. IDSA recommends incision and drainage of pus along with an effective anti-*staphylococcal* antibiotic. The recommended empiric oral antibiotic of choice for outpatients having SSTIs with community-acquired MRSA include clindamycin, trimethoprim sulfamethoxazole, linezolid or a tetracycline.[5]

In this study, all DAP-sensitive MRSA isolates were found susceptible to vancomycin and linezolid, 81.9% to clindamycin, 76.2% to fusidic acid, 74.3% co-trimoxazole and 66.7% tetracycline was around 75%. This is encouraging, as one can use empirical oral antimicrobials in outpatient setting as per IDSA recommendation. Similar data has been reported from studies conducted in this region and from around the world.[3,12,13] A similar multicenter study was conducted in India on MRSA isolated in 2,972 pus samples. In that study, around 50% isolates were found susceptible to clindamycin (53.4%) and 100% to linezolid whereas, lower susceptibilities to gentamicin (41.7%) and erythromycin (29.2%)(12). Likewise, another study from USA documented antimicrobial susceptibilities of *S. aureus* strains, both methicillin sensitive and resistant, in dermatology outpatients with SSTIs. The antibiotics found most effective were co-trimoxazole (95%), clindamycin (86%), tetracycline (94%), erythromycin (65%), gentamicin (100%), linezolid (100%) and rifampicin (100%).[13] In comparison local gentamicin and erythromycin data showed more resistance with 61% and 33% susceptible isolates respectively.

Co-trimoxazole available in oral formulation, is rapidly absorbed following ingestion, achieving peak plasma levels within 1 to 4 hours with a mean plasma half-life of 8 to 10 hours. However, it is contraindicated in children ≤2 months of age and caution should be exercised while administrating in patients >65 years of age or with impaired renal and hepatic function(14). In light of our findings which showed good in-vitro results for co-trimoxazole with 78% susceptibility in our isolates and owing to its bactericidal effect seems to be a good option for MRSA SSTIs in the pediatric (except ≤2 months of age), young and middle-aged outpatients.

Clindamycin, a protein synthesis inhibitor, is widely used for the treatment of serious infections due to *S. aureus* and MRSA SSTIs. A single oral dose is followed by rapid absorption and wide distribution in the body fluid, tissue and bone, achieving peak plasma concentrations within 45 minutes. Nonetheless, serious adverse events such as severe skin reactions and *Clostridium difficile* associated diarrhea have been reported with use of clindamycin(15). Keeping in view local susceptibility data and the IDSA recommendation for empirical use in MRSA SSTIs, it is generally a safe option if inquiries into previous drug sensitivities and proper antibiotic stewardship is employed.

Fusidic acid has potent anti-staphylococcal activity and is available for oral and topical administration.[16] It is well absorbed after oral administration with more than >90% bioavailability.[17] The main adverse effects are usually minor and include gastrointestinal discomfort, diarrhea and headache.[18] Our isolates showed a high susceptibility (80%) to fusidic acid with its protein synthesis inhibiting action and easy to use formulations appears to be a sound option for monotherapy. It is important to note that use of fusidic acid as a sole agent is not recommended due to emergence of antimicrobial resistance.

Tetracycline, another potent protein synthesis inhibitor, though traditionally not used for treating MRSA SSTIs as a primary agent, has shown promising results as an alternative therapy in complicated SSTIs[19]. Available in oral and intravenous formulations, it achieves high concentrations in biologically active forms for long duration. Chief concerns limiting its usage as primary agent include severe anaphylactic reactions and contraindication in pregnancy, infancy and children up to 8 years of age[20]. However, our data suggests its higher susceptibility (70%) and therefore, it could be a reasonable option for treatment in cases of resistance to first line agents.

Ninety eight percent isolates were found susceptible to rifampicin however, due to its use in the treatment of tuberculosis and the rapid development of resistance discourages its use in staphylococcal infections. Linezolid is a good option to treat SSTIs in situations where resistance is an issue however, due to concerns of hematologic toxicity, peripheral and optic neuropathy and lactic acidosis it should be saved for selected cases.[5,13]

There are a few limitations to our study. Firstly, this was a single center study conducted in Karachi and was not representative of the wider Pakistani population, though this lab receives clinical specimens through a wide network of collection points distributed throughout Pakistan. Another important limitation was the unavailability of clinical data regarding severity of infection and patient outcome as this was a lab-based study. A future collaborative study including major centers from all over Pakistan analyzing directed antibiotic therapy in accordance with severity of infection and assessing its outcomes in SSTIs would be relevant in this regard.

CONCLUSION

In view of our study findings clindamycin, co-trimoxazole and tetracycline appear to be the best possible oral or parenteral antibiotics for empirical administration in patients for less severe cases whereas, vancomycin and linezolid are drugs of choice in serious cases of MRSA SSTIs. We believe our findings would be of benefit in guiding clinicians for appropriate treatment options at the same time providing a stepping stone for future studies aiming at improving patient outcomes.

AUTHOR CONTRIBUTION

Moiz Ahmed Khan: The acquisition, data collection, analysis, interpretation of data and manuscript writing

Seema Irfan: Conception and revised critically for important intellectual content

Mohammad Zeeshan: Conception and revised critically for important intellectual content. Imran Ahmed: Conception and revised critically for important intellectual content

Afia Zafar: The acquisition and revised critically for important intellectual content

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