Risk Factors and Outcome Differences in Methicillin Resistant and Methicillin Sensitive *Staphylococcus Aureus* Septic Arthritis

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Abstract

Background
Septic arthritis caused by *Staphylococcus* is very common and causes high mortality and economic burden. In addition, rising cases of its resistant strains (Methicillin resistant *Staphylococcus Aureus*) is alarming. Conflicting results in literature mandates a comparison between resistant and sensitive strains in terms of risk factors, mortality and morbidity which becomes crucial in this regard to delineate any differences in our population.

Results
We gathered 66 patients with septic arthritis, out of which 46 were men, with mean age (SD) of 51.4(18.9) years. 30 patients had MRSA and 36 had MSSA. Most patients (n=61) had one joint involved, the most common joint was the knee joint (n=31), followed by hip (n=21), ankle (n=11), shoulder (n=4) and elbow (n=2). Most patients(49) had native joints involved. The inflammatory markers were not significantly different across the two groups. Hospital stay in both groups was almost similar(9.6 days for MRSA and 10.3 days for MSSA). Mortality3(10.0) was higher in MRSA group.

Conclusion
No differences were found in the inflammatory markers as well as synovial fluid and blood white cell count between patients infected with Methicillin resistant and sensitive *Staphylococcus aureus* these should not be used as a differentiating factor between the two.

Keywords
MRSA, MSSA, Septic arthritis, risk factors.

Background
Septic arthritis is a fulminant infection of joints which impacts 2 to 10 per 10,000 patients on a yearly basis and impairs joint function in 25 to 50% cases.[1] it causes significant debilitating morbidity and mortality if not treated timely and leads to excessive financial burden.[2,3,4,5] The commonest pathogen involved in septic arthritis is *Staphylococcus aureus*[3,6,7] which is a virulent organism causing a cataclysmic mortality of 15% if not treated emergently with appropriate medical and surgical management.[6,7,8,9] Staphylococcal infections have been known to cause immense economic burden with methicillin resistance causing steep health costs.[3,10,11]

Methicillin resistant *Staphylococcus aureus* (MRSA) has emerged as an established nosocomial pathogen all over the world.[6,12] There have been several western and a couple Asian studies highlighting the importance of methicillin resistant *Staphylococcus aureus* (MRSA) septic arthritis in terms of escalating virulence, relationship with underlying comorbidities and risk factors and the age group affected in comparison to methicillin sensitive strains (MSSA).[8,9,13] However there have also been conflicting studies indicating Methicillin sensitive *Staphylococcus aureus* (MSSA) to have an equal pathogenicity.[14] Data from the subcontinent is however lacking in this regard. A comparison between MSSA and MRSA septic arthritis in terms of mortality, risk factors and their association with length of hospital stay becomes crucial in our population as MRSA is deemed a difficult to treat infection on account of resistance to a major class of antibiotics and limited options of antibacterials available.[15]

Initially thought of as a hospital acquired pathogen research has revealed an upscale surge in MRSA acquired from community settings called community acquired MRSA which is another reason to study this in patients coming with septic arthritis.[16]

Inequalities in health conditions are well established in different populations of the world in terms of social income, ethnic, genetic and demographic differences. Pakistan being a low income country with all the aforementioned differences in its population as compared to the west is more prone to long standing ailments and comorbidities and these figures are on the rise as stated by a report. Pakistani population are more prone to Cardiovascular diseases and diabetes mellitus almost thrice as compared to the west.[17] Also low income countries have increased risk of infections with infections being a major

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cause of death as compared to high income countries.[18] On account of these differences, it is of unrelenting importance that we study the difference in outcomes as well as risk factors and prevalence in our patients and our population and do risk profiling between MSSA and MRSA.

There have been studies indicating that MRSA bacteremia and arthritis is associated more with risk factors like hemodialysis, malignancy, intravenous line usage, increased hospital stay, old age, as compared to MSSA arthritis,[19,20] but there have not been any studies in our population setting which is entirely different than the western and Asian population. The objectives of conducting this study were to determine the difference in risk factors, mortality and length of hospital stay between MRSA and MSSA septic arthritis.

Materials and Methods

A retrospective cross-sectional study was conducted. Patients with either MRSA or MSSA positive identified in pus culture from the joint or blood (with joint involvement) presenting to AKUH during 2000 to 2015 were identified from the medical records and their files were reviewed.

All cases of MRSA and MSSA septic arthritis were screened for the selection criteria that is adults aged 18 to 85 years diagnosed with septic arthritis as per radiological or clinical signs of septic arthritis with pus cultures or blood cultures growing *staphylococcus aureus*. Patients with mixed growth that is *Staphylococcus Aureus* and other organisms were not included.

Statistical analysis was conducted using statistical package for social sciences (SPSS, version 19.0). Mean with standard deviation were reported for all quantitative variables such as age, duration of hospitalization, number of joints, WBC count, clearance days, ESR, CRP etc. Frequencies with percentages were reported for all categorical variables such as gender, comorbid conditions, type of malignancies, type of joints, use of antibiotics and outcomes. Independent sample T-test was used to compare quantitative variables across the categories of MSSA and MRSA arthritis and Chi square test was done to compare categorical variables. P-values of <0.05 was considered to be significant.

Results

During the study period, 66 cases of *Staphylococcus Aureus* were identified from the records with mean age (SD) of 51.4 (18.9) years, half of the patients (50%) were aged 55 and above. Majority patients were men (n=46, 69.7%). Clinical characteristics of study patients are given in table 1. Most common comorbid condition was hypertension (30.3%) followed by Diabetes (22.7%) and osteoarthritis (16.7%).About 9 patients had chronic kidney disease,8 had a history of trauma, 6 were on steroids, 5 had chronic liver disease, 5 were dialysis dependent and 4 patients had malignancy, one each of Giant cell tumor, B cell lymphoma, Spindle cell tumor and T cell lymphoma. In addition, 3 had pulmonary Tuberculosis and 1 had Asthma. Most patients had single joint involved (n=61, 92.4%), followed by two (n=4, 6.1%) and three joints (n=1, 1.5%). About 49 patients had Native joint and 16 had prosthetic joint involvement. Knee was the commonest joint involved (n=31, 46.9%), followed by hip (n=21,31.8%), ankle (n=11,16.6%), shoulder (n=4, 6.0%) and elbow (n=2,3.0%).

Table 1 also shows comparison between patients with MRSA and those with MSSA. Patients with MRSA were older (53.5 vs. 49.6) as compared to MSSA. Immunosuppressive drugs, transplant, trauma, hemodialysis and Chronic kidney disease (CKD) were found to be more common with MRSA (p value =0.28), however, Chronic liver disease (CLD), Diabetes Mellitus (DM), Hypertension and central line placement showed no difference amongst both the groups. The inflammatory markers and WBC were not different across the two categories. However, synovial fluid WBC were higher for MRSA group. There was no difference in hospital stay in both groups (9.6 days MRSA 10.3 days MSSA). The duration between discharge and readmission was shorter for MRSA as compared to MSSA (3.47 ± 7.8 vs. 7.5 ± 21.5). Comparison of joints involved across both the infections are presented in figure 1.

Three of the patients with MRSA died and 1 was lost to follow-up. In contrast, there were no deaths in MSSA group. Statistically significant differences were seen across the categories of blood and pus fluid cultures. MSSA was isolated more in pus cultures (34 vs. 22) whereas isolation in blood was higher for MRSA (15 in MRSA and 11 MSSA). Clearance from blood took significantly more time in MRSA (68.5 days) as compared to MSSA (14.0 days).

Discussion

Extensive literature search shows results slightly similar to our study. A retrospective 13 year study from West Texas Shows 22.6 % of septic arthritis to be MRSA with a mortality of 5.5% with a length of hospital stay of around a fortnight to a month. The elderly, MRSA infection and prosthetic joint infections were associated with worse outcomes.[21] A study found MRSA to be more than half of MSSA cases and more prevalent in IV drug abusers (IVDU).[22] Contrastingly, Al-Nammari states that MSSA is seen more in IV Drug users which co relates with our study results of finding more MSSA in central line users, also knee involvement was more seen with MSSA.[8] Another study with 93 Staphylococcus septic arthritis cases found 38 (40.9%) patients with MRSA out of which around 90% were deemed community-acquired. Also they found MRSA to be more associated with Diabetes mellitus (44.1%), chronic kidney disease and liver cirrhosis. 5.4% was the mortality rate, this contrasts with our results.[23] A study looking at the knee joint only found *Staphylococcus* to be the dominant bacteria with 72.1% and mostly isolated from synovial fluid cultures with isolation on gram stain in around half of the cases.[24] A 5 year

Table1: Comparison of characteristics between patients with MRSA versus MSSA

Characteristics	Overall	MRSA n=30 n(%)	MSSA n=36 n(%)	P-Values
Age, mean(SD), range: 17-87	51.4(18.9)	53.5(19.6)	49.6(18.4)	0.40
Gender				
Male	46(69.7)	21(70.0)	25(69.4)	0.96
Female	20(30.3)	9(30.0)	11(30.6)	
Previous hospitalization, mean(SD), range: 0-120 days back n=13	5.67 (16.7)	3.47(7.8)	7.5(21.5)	0.33
Duration of hospitalization, mean(SD), range: 3 to 27 days	10.05(6.05)	9.6(5.3)	10.3(6.6)	0.64
Number of joints, mean(SD)	1.09(0.33)	1.07(0.25)	1.11(0.39)	0.58
Type of Joint				
Native	49(74.2)	16(24.2)	1(1.5)	0.61
Prosthetic	22(73.3)	8(26.7)	0(0)	
both	27(75.0)	8(22.2)	1(2.8)	
Culture and Sensitivity Blood	26(39.3)	15(50)	11(30.5)	<0.001
Culture and Sensitivity Pus Fluid	56(84.8)	22(73.3)	34(94.4)	<0.001
Clearance Days, mean(SD), range: 2-304 n=19	42.6(92.0)	68.5(123.4)	14.0(13.2)	0.20
ESR, mean(SD), range: 10-134 n=46	79.07(33.6)	84.6(32.1)	75.1(34.7)	0.34
CRP, mean(SD) range: 0.1-40.9 n=52	14.2(10.7)	11.1(7.0)	16.8(12.6)	0.05
WBC, mean(SD), range: 1.7-47.5	13.8(8.6)	14.5(10.7)	13.2(6.4)	0.57
Fluid WBC, mean(SD), range: 4000 to 143,800	39151.67	39460(47714.3)	38931(47895.2)	0.98
Outcomes				
Alive	62(93.9)	3(4.5)	1(1.5)	0.07
Dead	26(86.7)	3(10.0)	1(3.3)	
Lost to follow	36(100)	0	0	

SD, Standard deviation; ESR, Erythrocyte sedimentation rate; WBC, white blood cell; CRP, C-reactive protein

spanning retrospective study published in 2007 found 58 cases of staphylococcus septic arthritis involving only 15 MRSA and 43 MSSA with MRSA infecting the 70 plus population mostly. Ross *et al* found a significant association between prior hospitalization and MRSA (80% cases compared with 34% in MSSA) which our study failed to identify, also the mean number of comorbidities were higher in MRSA in their study and specifically involving the elderly. No significant difference was

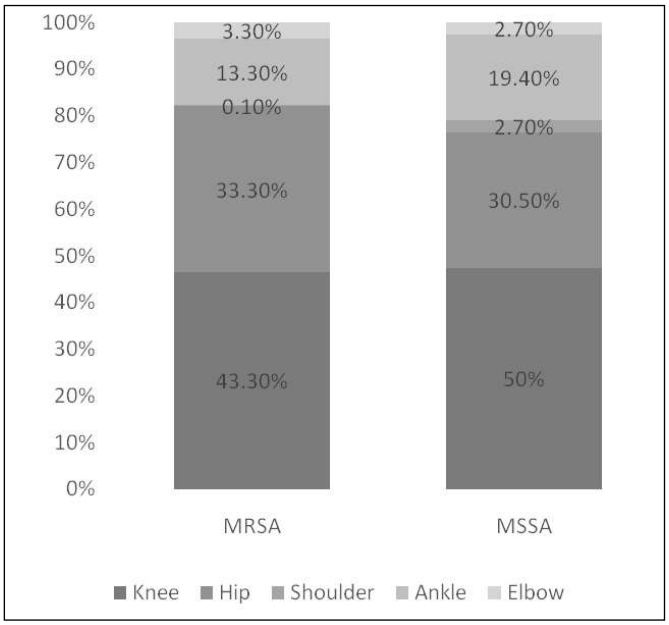

Fig 1. Comparison of joints involved in MRSA versus MSSA Septic arthritis

found in the type of joint involved however, except that shoulder involvement was more common in MRSA (40% vs.14%).[19]

Conclusion

MRSA is more prevalent in patients on immunosuppressive, Dialysis dependent and kidney failure with higher mortality rates in MRSA, therefore this should be kept in mind and Vancomycin containing regimens must be chosen empirically till cultures finalized. Also no difference was found in the inflammatory markers and total leukocyte count in blood among the two groups so these should not be used as a differentiating parameter.

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