ORIGINAL ARTICLE

CLINICAL FEATURES AND OUTCOME OF *STAPHYLOCOCCUS AUREUS* BACTEREMIA FROM A TERTIARY CARE HOSPITAL IN PAKISTAN

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ABSTRACT

Background: *Staphylococcus aureus* bacteremia (SAB) is known to be an independent risk factor for mortality and metastatic complications. It also carries high morbidity and mortality. There is limited clinical data on SAB from Pakistan. This study aimed to describe the clinical presentation and outcome of SAB from a tertiary care hospital.

Material and Methods: A prospective cohort study done at Sindh Institute of Urology and Transplantation (SIUT) Karachi. All patients aged > 18 years with documented SAB were included. Demographics, clinical features and treatment were noted. Patients were followed at day 3 and 14 for complications and outcome. Outcome was recorded as microbiological cure and mortality.

Results: Out of 92, 81(88%) were Methicillin resistant *S. aureus* (MRSA) and 11(12%) Methicillin sensitive *S. aureus* (MSSA). Overall, being on hemodialysis 72 (78%) and central line 68(73.9%) were the major risk factors of *S. aureus* bacteremia. In 66 (71.7%) patients, the source of SAB was dialysis lines. Significantly more patients with MSSA did not have source identified (p=0.009). Fever 75(81.5%) and hypotension 19 (20.7%) were the presenting symptoms. Significantly more patients with MSSA presented with severe disease such as altered level of consciousness, cardiac arrest and mechanical ventilation. Around, 22(24%) developed complications, MRSA had more complications than MSSA however, endophthalmitis (27%) was noted only in MSSA. Overall, 17(18%) died. Non survivors were more associated with acute renal failure, being on hemodialysis and no identifiable source, however not statistically significant.

Conclusion: *S. aureus* bacteremia carries high mortality and major source was dialysis catheters in our cohort. Around one fourth of patients developed complications. MSSA bacteremia presented with significantly more severe disease while MRSA with complication however not statistically significant. Non survivors were more associated with hemodialysis, acute renal failure, unidentifiable source and complications. High staff to patient ratio with strict infection control measures needed to prevent SAB in dialysis patients.

Keywords: *Staphylococcus aureus*, Bacteremia, MRSA, MSSA, Haemodialysis

BACKGROUND

Staphylococcus aureus (*S.aureus*) is a gram-positive bacterium that cause a wide variety of community and hospital acquired infections. Infections in hospital care settings has become a serious problem with high mortality.[1]In United States the incidence of invasive *S. aureus* infection is 31.8 per 100,000 out of which 75% cases were blood stream infections.[2]Data from the European Antimicrobial Resistance Surveillance System reported the prevalence of hospital acquired methicillin resistant *S.aureus* (MRSA) in acute care and long-term settings ranged between 1% and 24% with considerable intra-country and intercountry variation.[3] Methicillin resistance in *S. aureus* usually acquire through horizontal transfer of mecA gene that codes penicillin binding protein (PBPs) results in poor affinity for beta lactam antibiotics.[4] According to World Health organization (WHO),53% of invasive isolates reported from Eastern Mediterranean Region are MRSA.[5] In Pakistan a multicenter study showed the prevalence of *S.aureus* in all clinical isolates as 42%.[6]Another study from Rawalpindi reported the frequency of *S.aureus* bacteremia among chronic kidney diseases and hemodialysis patients to be 13%.[7]

MRSA bacteremia is known to be an independent risk factor for increased mortality. It has been observed that MRSA as compared to MSSA possess great challenge due to resistance of first line beta lactam antibiotics for *S.aureus* infection results in poor clinical outcome. Due to resistance to all major antibiotics and limited option of treatment for MRSA, it has a poor clinical

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outcome as compared to Methicillin sensitive *S.aureus* (MSSA) bacteremia.[8] SAB is characterized by metastatic complications. There are several structural and virulent factors and the most important is microbial surface components recognizing adhesive matrix molecules" (MSCRAMMs) and it results adhesion of bacterium to the host cells.[9] *S. aureus* is a pyogenic bacterium and known to cause disseminated and remote abscess formation like endocarditis, septic arthritis, empyema thoracic etc.[10]

Sindh Institute of Urology and Transplantation (SIUT) is mainly a renal disease center with a large dialysis unit. Around 1100 dialysis per day take place in this institute. There are a lot of patients awaiting for renal transplant need access for dialysis usually through fistula which takes at least few weeks to mature and during this period dialysis done via central venous lines. These patients are on high risk of developing central line associated blood stream infection especially SAB.[7] A study from SIUT showed one fourth of the blood culture isolates were MRSA.[11]There are limited reports on clinical features and outcome of SAB from Pakistan. This study aimed to describe the clinical presentation and outcome of SAB among adult patients from SIUT.

MATERIAL AND METHODS

A prospective cohort study was done at Sindh Institute of Urology and Transplantation (SIUT) Karachi Pakistan from March 2019 till December 2020.All patients aged > 18 years who had documented SAB were included. Patients <18 years and renal transplant recipients were excluded.

Patients were identified from blood cultures with *S aureus* growth in the microbiology laboratory. The patients were then located in the wards and a structured questionnaire was filled after taking an informed consent from the patient or surrogate. Demographics, clinical features, and treatment received at the time of presentation were documented. Patient were then followed on day 3, when a repeat blood culture was taken to document bacterial clearance. Fever, complete blood count and any complications were also documented.

Complications were defined as any of the following: endocarditis, empyema, septic arthritis, septic thrombophlebitis, brain abscess, infected fistula, septic emboli in lungs, endophthalmitis, or skin and soft tissue infections. The diagnosis of complications was made as per clinical and radiological evidence after discussion with the primary physicians. We define severe disease as those who presented with septic shock, cardiac arrest, or on mechanical ventilation.

Outcome was recorded as microbiological cure and mortality. Microbiological cure was defined as clearance of bacteremia on repeat blood culture at day 3. Patients were followed again at day 14 for all-cause mortality and if discharged patients were followed for mortality on telephone. SPSS, version 19.0, will be used for data entry and analysis. Frequencies are reported for categorical variables and mean and standard deviation for continuous variables. For all tests, P value <0.05 was considered significant at univariate level. All variables found significant at univariate level were entered in the multivariable model using the stepwise approach. Crude and adjusted odds ratio and 95% CI are reported.

RESULTS

A total of 92 cases with *S. aureus* bacteremia were included. The mean age was 40±17 years with 63% males. Hemodialysis 72(78%) and central line 68(73.9) were the major risk factors found. In 66 (71%) patients the source of SAB was central line. Out of whom the infected line was not removed in 11 (16.6%) patients. A total of 75(81.5%) patients had fever and 19(20.7%) were hypotensive at presentation. Out of 92 SAB, 81(88%) had MRSA and 11(12%) MSSA. Around 88(95.7%) patients had only staphylococcus in their blood culture while 4(4.3%) had staphylococcus plus gram negative rods. The median time of appropriate antibiotics received from blood culture positivity was 1 day (IQR: 1-2 days).We were able to check Vancomycin levels in 74 out of 81 patients (91%) with MRSA SAB. The first vancomycin level was sent at the mean of 3 days with a mean level was 16.6µg/ml. and the second was sent at the mean of 8 Days with mean level of 20µg/ml. All MSSA patients received cefazolin. Around 22(24%) developed complication, endocarditis was the most common. Out of 79 patients in whom we were able to send repeat blood cultures, 77(97%) had documented bacterial clearance. A total of 17(18.4%) patients expired, with 6(6.5%) died within 24 hours.

Comparison between MRSA and MSSA bacteremia showed that there were more male patients with MSSA

bacteremia as compared with MRSA. (Table 2)Significantly more patients with MSSA presented with altered level of consciousness [12% vs 45.6%p= 0.005, 95% CI (0.073-0.60)], cardiac arrest [3.7% vs 27% p= 0.003, 95%CI (0.048-0.52)]and were on mechanical ventilation [8(9.9%)vs 4(36.4%)p= 0.014, 95%CI (0.036-0.55).When we compared the source of bacteremia between MSSA and MRSA, significantly more patients with MSSA bacteremia did not have source identified [4.9%vs 27% p=0.00 95% CI(0.03-0.51)]. MRSA was found to have more complications than MSSA. Out of 23 patients with complications 20 had MRSA bacteremia. However, all 3 cases of endophthalmitis had MSSA bacteremia. There is no difference between microbiological clearance and all-cause mortality between MSSA and MRSA.

When we compared survivors and non-survivors, acute renal failure, those on hemodialysis, patients with unidentifiable source and SAB complications were more associated with death but not statistically significant.

Table-1:Clinical characteristics, source of bacteremia and risk factors in patients with *Staphylococcus aureus* bacteremia. N=92

Characteristics	**N(%)**
Age (years) mean±SD	**40±17.3**
Gender (Males)	**58 (63)**
Clinical features	
Fever	**75(81.5)**
Hypotension	**19(20.7)**
Altered consciousness	**15(16)**
On Mechanical ventilation	**12 (13)**
Cardiac arrest	**6(6.5)**
Risk Factors	
Diabetes	**22(23.9)**
Acute Renal Failure	**14(15)**
Chronic Renal Failure	**65(70.7)**
Hemodialysis	**72(78)**
Central line	**68(73.9)**
ICU stay>48hours	**28(30)**
Recent antibiotics within 3 months	**31(33.7)**
Immunosuppressive medications	**7(7.6)**
Malignancy	**4(4.3)**
Source	
Central line	**66(71.7)**
Phlebitis	**6(6.5)**
Urine	**3(3.3)**
Pneumonia	**3 (3.3)**
Skin and soft tissues	**3(3.3)**
Infected fistula	**4(4.3)**
No source identified	**7(7.6)**
Complications	**22 (23.9)**
Endocarditis	7(7.6)
Septic thrombophlebitis	1 (1.1)
Brain abscess	1 (1.1)
Septic emboli lungs	5(5.4)
Empyema	3(3.3)
Septic arthritis	4(4.3)
Skin abscess	1(1.1)
Endophthalmitis	3 (3.3)
Outcome	
Microbiological clearance	77/79 (97.5)
Death	17/92(18.5)
Death within 24 hour	6/92(6.5)

Table-2: Comparison between MRSA and MSSA bacteremia. N=92

Characteristics	MRSA N=81	MSSA N=11	P value (95% CI)
Age (years) mean	40±17.3	41±17.7	0.81
Males	48(59.3)	10(90.9)	0.041 (0.01-0.44)
Clinical features			
Fever			
Hypotension	67 (82.7)	8(72.7)	0.42
Altered level of consciousness	17 (21)	2 (18)	0.82
Mechanical ventilation	10(12)	5(45.6)	0.005(0.073-0.60)
Cardiac arrest	8(9.9)	4(36.4)	0.014(0.036-0.55)
	3(3.7)	3(27)	0.003(0.048-0.52)
Risk factors			
Diabetes	19(23.5)	3(27)	0.78
ARF	14(17.3)	0	0.13
CRF	55 (67.9)	10(90.9)	0.11
On Hemodialysis	61(75.3)	11(100)	0.062
Central line	58(71.6)	8(72.7)	0.93
ICU stay	24(29.6)	4(36.4)	0.64
Recent antibiotics	28(34.6)	3(27)	0.63
Immunosuppression	7(8.6)	0	0.31
Malignancy	4(4.9)	0	0.45
Source			
Central line	58(71.6)	8(72.7)	0.93
Phlebitis	6(7.4)	0	0.35
Urine	3(3.7)	0	0.51
Pneumonia	3(3.7)	0	0.51
SSTI	3(3.7)	0	0.51
Fistula	4(4.9)	0	0.45
No source identified	4(4.9)	3(27)	0.009
Complications	20(24.7)	3(27.3)	0.85
Endocarditis	7	0	
Septic thrombophlebitis	1	0	
Brain abscess	1	0	
Septic emboli lungs	5	0	
Empyema	3	0	
Septic arthritis	4	0	
Skin abscess	1	0	
Endophthalmitis	3	3(27)	
Outcome			
Microbiological clearance	70/72(97)	7/7 (100)	0.65
Death	13(16)	4(36.4)	0.10
Within 24 hours n=6	4(4.9)	2(18)	0.15

Table 3: Comparison between survivors and non-survivors: n=92

Characteristics	Non-survivors 17(18.5%)	Survivors 75(81.5%)	p
Organisms			
MSSA	4(23.5%)	7(9.3%)	0.11
MRSA	13(76.5%)	68(90.7%)	
No source identified	3(17.6%)	4(5.3%)	0.08
Infected line not removed n=68	4/13	7/55	0.11
Risk factors			
Diabetes Mellitus	18(25%)	4(23.5%)	0.96
Acute Renal Failure	5(29.4%)	9(12%)	0.07
Hemodialysis	16(94%)	56(74.7%)	0.07
Recent antibiotics	4(23.5)	27(36%)	0.32
Complications	7(41.2)	16(21.3)	0.08

DISCUSSION

To the best of our knowledge, this is first study on clinical characteristics and outcome of SAB has rarely been studied in Pakistan population. This is the first study on clinical features, complications and outcome of SAB from Pakistan.

The median age of patients in our study population is 40 years which is in contrast to previous studies.[12-14] SIUT is a public sector hospital mainly caters to renal diseases, we have a large number of dialysis dependent patients in our study. The median age of Pakistan population is 22.8 years.[15] Sakhuja *et al* also reported the median age of patients with end stage renal disease in Pakistan as 44 years.[16] Given the above facts, we saw the same trend in our study population with a much younger group with SAB than reported in literature.

The presence of male predominance in our study is in consistence with other studies.[17] Increase body hair and oil content of the skin in males may lead to colonization of skin with *S.aureus* that can cause increase infection when the skin is breached.[18]

Hemodialysis is a major risk factor for SAB. A nationwide study from Denmark showed 4-fold increase in incidence of SAB in patient on hemodialysis as compared to those on peritoneal dialysis. The study also emphasized the increased risk with dialysis lines than with fistulas.[19]We also found 71% of our patients had central line and only 4 percent had fistulas as a source. Colonization with *S.aureus*, impaired host defense due to uremia, iron overload and co-morbid are reported risk factors for SAB in dialysis dependent patients.[12]

Diabetes is also a risk factor for SAB.[18] A large population-based study showed increase risk of community acquired *S.aureus* bacteremia with diabetes.[19] We found one fourth of our patients were diabetic. This may be due to the fact that majority of our patients had renal failure which is a complication of diabetes. Prolonged ICU stay and treatment with antibiotics is also a known risk factor for SAB.[20]

In our study the major source of SAB was central line, commonly dialysis lines. SAB is very commonly associated with device associated infections, particularly the dialysis catheters. Tong *et al* in a review article reported 25% of SAB due to line infection.[14] A study from Pakistan reported source of SAB was dialysis lines in 100% of cases and central lines in 61% of cases.[20] SIUT has a large dialysis unit with more than 1000 dialysis taking place daily. Huge patient burden and busy schedules lead to breach in good infection control practices. This is reflected in our study with a large burden of central line related *S. aureus* infection. Increase in staff to patient ratio and stringent infection control measures can prevent the risk of SAB.[16] Furthermore early diagnosis of chronic kidney disease with prompt fistula formation has been shown to be associated with decrease infection with *S. aureus.*

Regarding clinical features, we found majority had fever and 20% presented with hypotension at the time presentation. *S.aureus* is a major pathogen to produce gram positive septic shock. It induces the release of bradykinins which cause increase in vascular permeability and hence causes hypotension.[22]

Around one fourth of our patients developed complications such as endocarditis, septic emboli, endophthalmitis etc. A study from United States found similar frequency, around 24% among patients with access related *S.aureus* bacteremia.[23] Endocarditis is the most common complication found in our patients. Rasmussen *et al* also reported a high risk of endocarditis with SAB with high mortality and morbidity.[24]

The mortality rate in SAB was found 18.5%. Studies around the world reported case fatality rate between 15 to 50%.[14] Hospital acquired SAB is known to have high mortality. In our patient cohort underlying comorbidities like renal failure and being on hemodialysis is found to be associated with mortality. This has also been reported in the literature with renal failure as a major risk factor for mortality in SAB.[13,25]

Within SAB, we found 88% had MRSA. Such a high frequency of MRSA infection is also reported by Aslam *et al* where 66% of patients had MRSA bacteremia.[20]Pakistan has a high prevalence (42%-51%) of *S aureus* infection.[6,26] This reflects in our study too. Another reason for high MRSA infection is that majority of our patient cohort are dialysis dependent and they need to come to health care facilities for dialysis. Frequent hospital stays and central lines with compromised infection control practices are the major factors leading to high frequency of MRSA bactermia.[20,27]

In our study, significantly more patients with MSSA had severe disease on presentation, however there is no difference in mortality. We defined severe disease as

those who presented with SAB and altered level of consciousness, cardiac arrest or respiratory failure required mechanical ventilation. This is unusual as MRSA is reported to be more virulent in terms of clinical features as compared to MSSA.[9,28] In our patient population MSSA was associated with unidentified source. Also, we found higher mortality among those patients in whom we were unable to find any identifiable source. Kaasch *et al* also reported a strong association of mortality with unidentifiable infective focus.[12] The reason for MSSA having no source identified and severe disease need to be studied further.

We found that although MRSA has more metastatic infections, endophthalmitis was found to be more in patients with MSSA. Endophthalmitis due to SAB is a known complication, however MSSA causing endophthalmitis more than MRSA has never been reported in the literature.

CONCLUSION

In conclusion SAB was a major infectious agent among patients with central lines, particularly dialysis lines. There was high morbidity with one fourth of our patients develop complications. MSSA seems to be more virulent than MRSA in terms of clinical parameters. Hemodialysis, acute renal failure, unidentifiable source and complications were more associated with mortality. We need high staff to patient ratio with strict infection control measures to prevent SAB among our patient population.

AUTHOR CONTRIBUTION

Shahnila Javaid: Conception, the acquisition, data collection, interpretation of data and manuscript writing

Asma Nasim: Data analysis, conception

Sunil Kumar Dodani: Acquisition, reviewed critically for important intellectual content

Zaheer Uddin Babar: Conception, data analysis

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