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Factors and Outcome in Cancer Patients with Bacteremia caused by Methicillin- susceptible (MSSA) and Methicillin-resistant *Staphylococcus aureus* (MRSA) at a Specialized Cancer Centre in Pakistan

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Abstract

Introduction
Methicillin resistant *Staphylococcus aureus* (MRSA) has become a serious public health problem worldwide being an important concern for hospital infection-control programs. Gram-positive organisms are also important causes of invasive infections among cancer patients.

Methodology
A cross sectional study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore in patients diagnosed to have cancer, who developed bacteremia caused by *Staphylococcus aureus (S. aureus)*, admitted between June 2006 to June 2016. We analyzed different demographic, clinical and laboratory factors such as age, comorbidities, the type of cancer and the absolute neutrophil count on outcome of these patients.

Results
A total of 187 patients with cancer and *S. aureus* bacteremia were included, of which MSSA was in 123 (65.8%) of the patients while 64 (34.2%) had MRSA bacteremia. More than half of total study patients 111 (59.4%) had hematological malignancies. On analysis of potential outcomes of bacteremia a greater proportion of those with MRSA bacteremia died but the difference did not reach statistical significance. Age, comorbidities, the type of cancer and the absolute neutrophil count on outcome of these patients did not have significant impact on outcome.

Conclusion
In patients with cancer and *S. aureus* bacteremia, demographic, clinical and laboratory factors did not impact outcome in those with methicillin sensitive versus methicillin resistant bacteremia. However, MRSA bacteremia may be associated with a higher likelihood of mortality.

Key words
Staphylococcus aureus bacteremia, MRSA, cancer

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Introduction
Infections with antibiotic-resistant organisms have resulted in higher morbidity and mortality compared to similar infections with antibiotic-susceptible strains.[1] However, the extent of this difference may vary according to the causative organism, the infectious site, and the patient's characteristics. In past two decades, the rates of bacterial infection caused by *S. aureus* have increased.[2]

Mortality ascribed to bacteremia due to *S. aureus* approaches rates of 15%–60%.[3-4] Resistance to methicillin among *S. aureus* isolates is a global problem and in one report, 52.3% of nosocomial infections in an intensive care unit (ICU) were due to methicillin-resistant *S. aureus* (MRSA), with a 37% increase in the incidence of MRSA infections from 1994 to 1998.[2]

Since its emergence in hospital environments[5] MRSA has become a serious public health problem worldwide being an important concern for hospital infection-control programs, especially in the ICU**,** where it can cause severe complications.[6-8]

Risk factors for MRSA infection have been analyzed, and invasive device exposure, hospital acquired infections, and previous antimicrobial treatment are well recognized as predisposing factors.[9] There has been great interest in the impact of initial appropriate therapy in sepsis and some recent studies have brought into question the protective effect of adequate, initial antimicrobial therapy, and its timely implementation in correct dosage after bacteremia onset.[10]

Gram-positive organisms are also important causes of invasive infections among cancer patients.[11]

The percentage of staphylococcus bacteremia has ranged from 1.2 to 14% among cancer population in various studies while the skin and soft tissue infection (26.7%) and pneumonia (25.4%) have been reported as the most common consequences of staphylococcal bacteremia.[12-13]

Low absolute neutrophil count (ANC), the presence of central venous catheter (CVC) and corticosteroids has shown to be associated with increased risk of infection and poor outcome

in patients with bacteremia with higher incidence of *S. aureus* bacteremia in patients with CVC.[15-17]

The main objective of this study is to look at the relative frequencies of MRSA and MSSA bacteremia in cancer population and to evaluate the impact of methicillin resistance upon outcome. A comprehensive study to look for the outcomes associated with both MSSA and MRSA bacteremia along with the associated risk factors has not been published among cancer population in Pakistan.

Methodology

A cross sectional study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Center Lahore, patients, including <18 years, diagnosed to have cancer, who developed bacteremia caused by *S. aureus*, admitted between June 2006 to June 2016 were included. After approval by the institutional review board (IRB), a questionnaire was designed and data was retrospectively collected from the hospital information system (HIS). All patients who had cancer and staphylococcus bacteremia were identified and classified into either methicillin sensitive (MSSA) or methicillin resistant (MRSA), based on the microbiology laboratory testing reports.

Variables for analysis included those relating to demographic and patient characteristics, risk factors and factors associated with potential outcomes such as use of corticosteroids, chronic kidney disease and diabetes mellitus etc.

The presence of co-morbidities was included in the data analysis as a dichotomous variable by reviewing physician notes. The ANC was stratified into two groups; (less than 500cells/µl and above 500cells/µl).[18] Patients were deemed to have 'skin and soft tissue infection' if they had evidence of the following; cellulitis, folliculitis or subcutaneous abscesses. The presence of central venous catheters was stratified into three categories (none, tunneled and non-tunneled).[19]

The antibiotic start time was stratified into three categories and duration of antibiotic was recorded according to IDSA guidelines.[20] In this work the following potential complications were included for analysis: metastatic infection, meningitis, osteomyelitis, septic arthritis, infective endocarditis, systematic inflammatory response syndrome (SIRS), septic shock[21] and death. Metastatic infections were further segregated into pneumonia, septic thrombophlebitis and multiple abscesses, based on the clinical notes. Infective endocarditis was categorized into three categories based upon the presence of vegetation on echocardiography (no findings, the presence of findings and not performed). The clinical recovery and clearance of bacteremia was documented by reviewing physician's notes and patient's reports.

Statistical analysis was carried out using the SPSS software (version 20.0; SPSS, Chicago, IL, USA). Continuous variables were stated as mean ± standard deviation and categorical variables were computed as frequencies and percentages. Categorical variables were compared using chi square test or fisher's exact test (where necessary). Statistical significance was defined as a two-tailed p-value 0.05.

Results

A total of 187 patients with cancer and *S. aureus* bacteremia were included in the study, of which MSSA was seen in 123 (65.8%) patients while 64 (34.2%) had MRSA bacteremia. The majority of patients were adults 101 (54.0%), with a mean age and standard deviation of 25.05 ± 19.75 years. Males represented 61.5% of the study population. More than half of total study population 111 (59.4%) had hematological malignancies as shown in Table 1, and most patients (76.5%) had received chemotherapy within the prior three months. However only (12.8%) had comorbidities, among these (7.5%) had diabetes mellitus, (6.4%) had chronic kidney disease and (11.2%) used corticosteroids. Moreover, the source of bacteremia was identified more than half (55.1%) patients.

Antibiotics were administered within 24 hours in more than half the patients and the majority (79.2%) of patients were treated for two weeks. MSSA bacteremia was mostly treated with cloxacillin (28.5%), cefazolin (16.3%), teicoplanin (22%) and vancomycin (16.3%) while those with MRSA bacteremia were treated with vancomycin (59.4%) or teicoplanin (28.1%).

Furthermore, there was statistical significant association between age and *S. aureus* bacteremia p-value (0.03), cancer type and *S. aureus* bacteremia p-value (0.03) and co-morbidity and *S. aureus* bacteremia p-value (0.03). Additionally, there was

Table 1. Description of study population.

Variables	Characteristics	Frequency N (%)
Age (years)	Pediatrics	86 (46.0%)
	Adults	101 (54.0%)
Gender	Females	72 (38.5%)
	Males	115 (61.5%)
Comorbidity	Absent	163 (87.2%)
	Present	24 (12.8%)
Cancer type	Hematological	111 (59.4%)
	Genitourinary	16 (8.6%)
	Gastrointestinal	18 (9.6%)
	Miscellaneous	42 (22.5%)
Bacteremia type	MSSA	123 (65.8%)
	MRSA	64 (34.2%)

marginally statistical significant association between *S. aureus* bacteremia and mortality p-value (0.07). Important predisposition (Table 2) and outcome (Table 3) variables were analyzed and mortality was seen to be higher in MRSA group (31.2%) as compared to MSSA group (19.5%).

Discussion

In 2015, 90.5 million people were diagnosed to have cancer in the world.[22] Developments in the management of cancer have resulted in early detection and treatment and consequent improvement in prognosis but patients undergoing chemotherapy remain highly susceptible to a number of infections caused by bacteria and fungi as it has effects on both cellular and humoral immunity.[23] Infections caused by MRSA are an important problem; moreover it is an important nosocomial pathogen.

Table 2. Potential predispositions a comparison of relative proportions amongst MSSA and MRSA bacteremia patients

Variables	MSSA n=123	MRSA n=64	p-value
Age in years			0.02
Pediatrics	64 (52.0%)	22 (34.4%)	
Adults	59 (48%)	42 (65.6%)	
Sex			0.67
Female	46 (37.4%)	26 (40.6%)	
Male	77 (62.6%)	38 (59.4%)	
Cancer Type			0.03
Hematological	73 (59.3%)	38 (59.7%)	
Genitourinary	10 (8.1%)	6 (9.3%)	
Gastrointestinal	7 (5.8%)	11 (17.0%)	
Miscellaneous	33 (26.8%)	9 (14.0%)	
Chemotherapy (within prior 3 months)			0.15
No	25 (20.3%)	19 (29.7%)	
Yes	98 (79.7%)	45 (70.3%)	
Comorbidities			0.03
None	112 (91.0%)	51 (79.7%)	
Present	11 (9.0%)	13 (20.3%)	
Absolute neutrophils counts (ANC)			0.02
< 500 cells / µl*	61 (49.6%)	20 (31.3%)	
> 500 cells / µl*	62 (50.4%)	44 (68.7%)	
Source			0.14
Not identified	60 (48.8%)	24 (37.5%)	
Identified	63 (51.2%)	40 (62.5%)	
Central venous catheter			0.27
Not present	82 (66.7%)	35 (54.6%)	
Present (tunneled)	19 (15.4%)	14 (22.0%)	
Present (non-tunneled)	22 (17.9%)	15 (23.4%)	

Table 3. Outcomes comparison of relative proportions with amongst MSSA and MRSA bacteremia patients

Variables	MSSA n=123	MRSA n=64	p-value
Clearance of bacteremia at 48 hours			0.49
Positive cultures at 48 hours	15 (12.2%)	10 (15.6%)	
Negative cultures at 48 hours	84 (68.3%)	38 (59.4%)	
Not repeated	24 (19.5%)	16 (25.0%)	
Clinical Improvement			0.19
Not improved	12 (9.8%)	11 (17.2%)	
Improved within 72 hours	55 (44.7%)	31 (48.4%)	
Improved after more than 72 hours	56 (45.5%)	22 (34.4%)	
Infection at other sites			0.36
Not seen	68 (55.3%)	37 (57.8%)	
Pneumonia	39 (31.6%)	24 (37.5%)	
Multiple abscesses	4 (3.3%)	1 (1.6%)	
Thrombophlebitis	12 (9.8%)	2 (3.1%)	
Infective endocarditis			
No echocardiographic findings	76 (61.8%)	39 (60.9%)	
Echocardiographic findings seen	4 (3.2%)	5 (7.8%)	
Echocardiography not performed	43 (35.0%)	20 (31.3%)	
Sepsis			0.68
No	73 (59.3%)	36 (56.3%)	
SIRS*	50 (40.7%)	28 (43.8%)	
Septic shock			0.23
No	98 (79.7%)	46 (71.9%)	
Yes	25 (20.3%)	18 (28.1%)	
Intensive care unit Admission			0.52
No	90 (73.2%)	44 (68.8%)	
Yes	33 (26.8%)	20 (31.2%)	
Mortality			0.07
Alive	99 (80.5%)	44 (68.8%)	
Died	24 (19.5%)	20 (31.2%)	

*Systematic inflammatory response syndrome

In our analysis of the two groups with MSSA bacteremia was in two third patients. Our study included analysis which includes children as well as inclusion of the analysis and impact of the absolute neutrophil count, something which has not been commonly reported in the past other than Srinivasan A *et.al*, who reported the effects of methicillin resistance on outcomes in pediatric cancer population[16] and Kang *et al*. who studied this in non-neutropenic cancer patients.[13]

In terms of factors that may influence the development methicillin sensitive versus methicillin resistant disease, we found that age, cancer type, presence of comorbidities and the ANC had significantly different proportionate representations in each group. The MRSA group had more adults in it, probably reflecting greater exposure and colonization likelihood with time. Similarly, there was a significantly larger representation of gastrointestinal malignancies and comorbidities in the MRSA group, similar to published reports[6]. On the other hand, the MRSA group had fewer people with a low absolute neutrophil count, a somewhat counterintuitive finding.

When potential outcomes of bacteremia are analyzed, we found that while a greater proportion of those with MRSA bacteremia died, this difference did not reach statistical significance. Other potential consequences of staphylococcal bacteremia – clearance of bacteremia, distant seeding, need for ICU, sepsis and septic shock - were similarly represented in both groups and any differences noted were not statistically significant.

The published literature has mixed results – some studies suggest more intensive care unit admissions, development of pneumonia and higher mortality rates in the MRSA bacteremia as compared to MSSA bacteremia[6, 16] on the other hand Gopal et al found methicillin-resistance to not be associated with an adverse outcome.[24]Another study has reported no significant difference in mortality and hospital stay between MRSA and MSSA bacteremia among cancer population, but there were more ICU admissions and surgical episode in MRSA group (P <0.03 and 0.06 respectively) but only 21 patients were included.[14]

In our patients thrombophlebitis was seen more commonly amongst MSSA, possibly due to lower utilization of central catheters compared to those with MRSA (Table 2).ÊFlynn *et al*. reported no difference in short-term eradication of bacteremia among catheter types.[25]

Conclusion

In patients with cancer and *S. aureus* bacteremia, age, comorbidities, the type of cancer and the absolute neutrophil count may have an impact on the development of methicillin sensitive versus methicillin resistant bacteremia. The presence of methicillin resistance may be associated with a higher likelihood of mortality but a larger analysis is warranted to definitively demonstrative this and to factor in the effect of confounding co-variables.

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