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ORIGINAL ARTICLE

Epidemiology and Clinical Characteristics of Staphylococcal Bacteremia in Bahrain

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Abstract

Background and Objectives: *Staphylococcus aureus* bacteremia (SAB) is a significant health problem with high morbidity & mortality. The aim of this study was to evaluate the epidemiology of SAB in Bahrain along withs clinical characteristics and outcome.

Methods: This study was conducted at Salmaniya medical complex (SMC) microbiology laboratory including all patients with SAB for one year period (2019). Demographic, lab data & outcome were obtained from electronic record system of patients.

Results: A total of 164 episodes of SAB were identified during the study period. About 137 were encountered among inpatients, while 27 cases among outpatients attending hemodialysis unit. Bahraini nationality & male gender were predominant (141, 85.98% & 108, 65.85% respectively). Nosocomial SAB account for only 29.37%, while the majority of SAB cases were of community onset (116, 70.37%), but among such community onset cases; 83 (50.61% of total) were of health care associated category (56 had prior hospitalization and 27 were on regular dialysis). Among all patients with SAB, diabetes was the commonest risk factor encountered, followed by dialysis dependence and sickle cell diseases (SCD). Mortality rate was 25.6% (42 patients). Among the 122 survivors of the initial SAB episode, recurrence of bacteremia was documented among 26 cases (21.3%).

Conclusion: SAB was a significant health problem among the Bahraini. Diabetes Mellitus, SCD and dialysis dependence were found to be important risk factors. Recurrence of bacteremia was a common complication among the patient's dependant on hemodialysis.

Keywords: *Staphylococcus aureus*, Bacteremia, Nosocomial, Community onset, Hemodialysis

Introduction

Staphylococcus aureus is a Gram-positive pathogen that commonly exist as a commensal bacterium and colonizes the human body. It is also a crucial pathogen causing a wide range of clinical manifestations ranging from minor skin infection to life-threatening conditions such as *Staphylococcus aureus* Bacteremia (SAB).[1]

SAB is classified into three main categories based on the location and time of acquisition: hospital-onset (HO) (nosocomial), community onset-health care associated (CO-HA), community onset-community associated (CO-CA) infections.[2]

Community onset SAB refers to the infection acquired among outpatients or inpatients within the initial 48 hours of admission, this can be further stratified into community onset-health care associated, where the patient has a previous history of exposure to the health care system (like hospital admission, surgery, hemodialysis (HD) within the last 12 months), while community onset-community associated form is observed among patients who lack previous exposure.[3-4]The proportion of community onset-health care associated form constitutes the biggest proportion of SAB, as illustrated in a study of SAB, where 23 % nosocomial, 59 % community onset-health care associated, and 18 % cases were community acquired.[5]

S. aureus is considered as the principal cause of nosocomial bloodstream infection. In one study, among 24,000 nosocomial bloodstream infections, *S. aureus* accounted for about 20 % of cases and was the second commonest cause (after coagulase-negative staphylococci).[6-7]

Patients with community onset SAB are likely to present with complicated infections. In one study, more than 40 percent of patients had metastatic infection, including infective endocarditis (IE).[8] In a study of more than 500 patients with SAB, infective endocarditis was present in 21 percent of patients with community onset infection, a rate that was almost three times that seen among patients with nosocomial bacteremia.[9]

Incidence rates of SAB was found to vary by age and gender and was observed to be the highest at the two extremes of age and among male gender.[10-11]

Several risk factors were found to be associated with SAB such as, prosthetic device, intravascular catheter.[12-14] Surgical site infections, skin conditions such as chronic dermatitis & ulceration, comorbidities such as diabetes, cancer, dialysis dependence and injection drug use were also contributory to SAB.[15-18]

SAB mortality is high (20%–30%) and morbidity is significant due to the frequent occurrence of metastatic complications such as endocarditis, spondylitis, septic arthritis, and prosthetic joint infections.[8]

Methicillin Resistant *S. aureus* (MRSA) was found to have higher morbidity/morality, longer hospital stays and higher rates of treatment failure when compared with Methicillin Sensitive *S. aureus* (MSSA) bacteremia.[19]

The aim of this study was to assess the epidemiology of SAB in the main governmental health care facilities in Bahrain. Moreover, the study also assessed the risk factors among this population along with the outcome in terms of mortality and recurrence. This is a pioneer study to illustrate the epidemiology of SAB in Bahrain.

Materials and Methods

Setting & study population

This study was conducted at Salmaniya medical complex (SMC) microbiology laboratory, all patients with SAB for one year period (January 2019 to December 2019) were identified from microbiology database system in SMC lab, which is the main government microbiology lab that comprises all the Ministry of Health (MOH) facilities in Bahrain; both inpatients' facilities and the two main outpatient governmental hemodialysis units.

Demographic, epidemiological, clinical, and microbiological data was collected from electronic medical records for all included patients. All records were included in the analysis & there was no missing data.

Study Design

Retrospective observational analysis of all patients with SAB

Microbiological Identification: Isolates were identified by conventional phenotypic methods such as colony morphology, Gram's stain, Catalase test, Slide and Tube coagulase test, growth on mannitol salt agar, the Bruker MALDI Biotyper (Bruker Daltonics, Billerica, MA) matrix-assisted laser desorption ionization–time of flight mass

spectrometry (MALDI-TOF MS).

Identification of MRSA: All *Staphylococcus aureus* isolates were subjected to Cefoxitin disc diffusion testing using a 30 µg Cefoxitin disc. The results were interpreted according to Clinical and Laboratory Standards Institute guidelines with an inhibition zone diameter of ≤ 24 mm been reported as Methicillin resistant and ≥ 25 mm as Methicillin sensitive. [20]

Definitions:

a. SAB:

An episode of SAB was defined as the first positive blood culture specimen of *S. aureus* in a patient with signs consistent with infection.

b. Inpatients /outpatients:

Inpatients was defined as patients admitted to the health care facilities, while outpatients included patients attending the outpatient's hemodialysis unit and patients attending the emergency department in SMC but discharged without need of admission

c. Hospital Onset-MRSA (HO-MRSA) and Community Onset-MRSA (CO-MRSA):

1. Hospital onset-MRSA

A case was classified as hospital-onset (HO) for inpatients when the first *S. aureus* blood culture was obtained 48 hours or more after admission to the hospital.

2. Community Onset-MRSA

Community-onset infections (CO) were those who found to have the first positive blood culture obtained while they are outpatients or for inpatients when the first *S. aureus* blood culture was obtained within 48 h of admission to the hospital.

CO were further classified into healthcare-associated (CO-HA) and community-associated (CO-CA), the infection was classified as CO-HA if the patient had history of any of the following during the period of 12 months prior to the positive blood culture: surgery, hospitalization, dialysis, or residence in a long-term care facility, while infection was classified as CO- CA when lack of previous exposure history.

Outcome measures

Two outcomes were measured in the current study: mortality and recurrence among survivors. Mortality (all-cause mortality) for inpatients was determined based on the status of discharge (Survivors/ Deceased) from the concerned admission with SAB, for outpatients (including HD) the status of patient on day 30 (counted from the first day of positive culture) was defined as the outcome (Survivors/ Deceased)

Recurrence was monitored among the survivors of the first episode of SAB for 90 days (counted from the first day of positive blood culture). Recurrent episode of SAB in the same patient was identified if the bacteremia had initially cleared but subsequent blood culture performed more than 14 days after the initial positive culture and was reported positive.

Data Statistical analysis

Descriptive and analytical statistics were conducted. Continuous variables were presented as means and standard deviations while categorical variables were presented as numbers and percentages. Univariate relationships were examined, using two-sample t-tests for continuous variables and Chi-square or Fisher's exact test tests for categorical variables. P values of less than 0.05 were considered to indicate statistical significance. All calculations were performed with the use of SPSS software, version 22.0 SPSS.

Ethical approval

The study was approved by the Secondary Care Research Committee of Salmaniya Medical Complex, Ministry of Health, the Kingdom of Bahrain. All data were de-identified during analysis process and were used for research purposes only.

Results

Out of a total of 6,232 admissions to SMC and 500 outpatient visits to the government hemodialysis units during the study period, 164 cases of SAB were identified; 137 among inpatients were admitted to SMC, accounting to an incidence of 2.2 SAB episode /100 admissions. The remaining 27 SAB cases were among outpatients attending hemodialysis unit (Incidence rate of 5.4 SAB episode /100 hemodialysis patients).

Bahraini nationality and male gender were predominant,141,(85.98%) and 108, (65.85%) respectively. The mean age of SAB cases was 48.5 years ± 23.05 (95% confidence interval (CI): 44.9-52.0) with a wide age range, (ranging from 3 days to 94 years, 12 cases (7.3%, 95% CI: 3.7-11.6) were encountered among neonates (less than 28 days) , small number of cases were among pediatrics aged 28 days -12 years old (3 cases, 1.83%) & adolescents aged 13-18 years (4 cases , 2.44%), while the main bulk of cases were among adult & middle age population which include adults (33.5%, 95% CI: 26.2-40.8) and middle aged participants (30.5%, 95% CI: 23.2-37.8). Additionally, 40 of the participants were in the elderly age group (24.4%, 95% CI: 17.7-31.7).

Among all patients with SAB, diabetes mellitus (DM) was the commonest associated comorbidity but stratifying the patients by age groups revealed that different age groups have variable associated comorbidities (Tables 1 and 2).

HO-SAB (nosocomial) accounts for only 29.27% (95% CI:22.62-36.64), while the majority of SAB cases were of community onset (116, 70.73%; CI: 63.41-77.41), but among such community onset cases; 83 (50.61% of total) were of healthcare associated category (56 had prior hospitalization and 27 were on regular dialysis); only 33 cases (20.12%) were community associated with no documented prior exposure to the health care facility.

MSSA contribute to 54.88 % (95 CI=47.63-62.23; 90 cases) of all SAB patients, while the remaining isolates (74 cases; 45.12%, 95% CI 37.82-52.42%) were MRSA.

Table 1: Baseline descriptive characteristics of the SAB patients

Variables		**Total number = 164 n (%)**
Age, mean ± Standard Deviation (SD)		48.48±23.05
Age groups	Neonates (< 28 days of age),	12 (7.32%)
	Paediatrics (28 days- 12 years)	3 (1.83%)
	Adolescents (13-18 years)	4 (2.44%)
	Adults (19-49 years)	55 (33.54%)
	Middle age (50-65years)	50 (30.49%)
	Elderly (> 65 years)	40 (24.39%)
Sex, males		108 (65.85%)
Nationality, Bahraini		141 (85.98%)
Comorbidities	Diabetes Mellitus	72 (43.90%)
	End Stage Renal Disease	57 (34.76%)
	Hypertension	49 (29.88%)
	Ischemic Heart Disease	41 (25.00%)
	Sickle Cell Disease	23 (14.02%)
	Malignancy	9 (5.49%)
	Prematurity	6 (3.66%)
	Dermatological Diseases	6 (3.66%)
	Chronic Obstructive Pulmonary Disease	4 (2.44%)
	No comorbidities	18 (10.98%)
Community onset (CO) vs hospital onset infection (HO)	Hospital Onset infections (HO)	48 (29.27%)
	Community Onset infections (CO)	116 (70.73%)
	Community-associated (CO- CA)	83 (50.61%)
MRSA vs MSSA infection	Methicillin-Susceptible Staphylococcus Aureus (MSSA)	90 (54.88%)
	Methicillin-Resistant Staphylococcus Aureus (MRSA)	74 (45.12%)

Among neonates (less than 28 days), the only risk factor was prematurity (defined as gestational age less than 34 weeks / low birth weight less than 2.5kg) which was present among half the cases. Among pediatrics patients (aged 28 days -12 years); end stage renal disease (33.3%) and malignancy (33.3%) were encountered. While among adolescent (13 -18 year sold) ; comorbidities include end stage renal disease (25%), DM (25%) & sickle cell disease (25%).

Among adults, the most common comorbidities were end stage renal disease (36.36%), followed by sickle cell disease (29.09%), while among middle age & elderly; presence of diabetes, hypertension & ischemic heart disease were commonly encountered comorbidities in addition to end stage renal disease.

Table 2: Comorbidities of SAB among different age groups

Comorbidities	Neonates* TN**= 12 n (%)	Pediatrics* TN**=3 n (%)	Adolescents* TN**=4 n (%)	Adults* TN**=55 n (%)	Middle aged* TN**=50 n (%)	Elderly* TN**=40 n (%)
Diabetes Mellitus	0 (0%)	0 (0%)	1 (25%)	7 (12.73%)	37 (74%)	27 (67.50%)
End Stage Renal Disease	0 (0%)	1 (33.33%)	1 (25%)	20 (36.36%)	24 (48%)	11 (27.50%)
Hypertension	0 (0%)	0 (0%)	0 (0%)	1 (1.82%)	25 (50%)	23 (57.50%)
Ischemic Heart Disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (38%)	22 (55%)
Sickle Cell Disease	0 (0%)	0 (0%)	1 (25%)	16 (29.09%)	5 (10%)	1 (2.50 %)
Malignancy	0 (0%)	1 (33.33%)	0 (0%)	1 (1.82%)	3 (6%)	4 (10%)
Prematurity	6 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dermatological disease	0 (0%)	0 (0%)	0 (0%)	4 (7.27%)	2 (4%)	0 (0%)
COPD***	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	3 (7.50%)

**Neonates group: less than 28 days, Pediatrics group: 28 days to 12 years, Adolescent: 12-18 years, Adult:19-49 years, Middle age: 50-65 years, Elderly > 65 years*

*** Total Number *** Chronic Obstructive Pulmonary Disease (COPD)*

Different proportions were encountered among variable groups, among the 23 SCD patients with SAB; there was no single case of community associated acquisition; the proportion of nosocomial cases was higher (13 patient, 56%) and the remaining 10 patients (44 %) were all of CO-HA as all patients had repeated admission to the hospital in the previous months prior to the development of SAB. While among the 18 patients with no known risk factors; proportion of CO-CA SAB were significantly higher (15/18, 83.33%), P <0.001, Table 3.

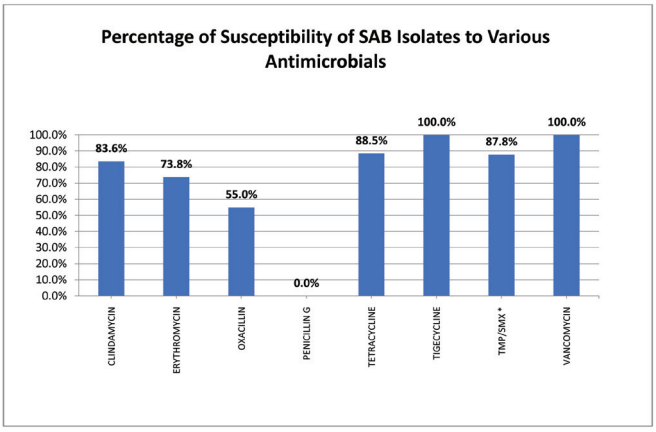
Table 3: Comorbidities among different SAB categories

Subgroup		Hospital-Onset SAB ◊ TN=48 n (%)	Community-Onset (CO) SAB		
			All CO TN=116	**CO-HA ◊◊ TN= 83**	**CO-CA ◊◊◊ TN= 33**
Comorbidities	Diabetes Mellitus (n=72)	14 (29.17%)	58 (50%)	48 (57.83%)	10 (30.30%)
	End Stage Renal Disease (n=57)	10 (20.83%)	47 (40.52%)	46 (55.42%)	1 (3.03%)
	Hypertension (n=49)	14 (29.17%)	35 (30.17%)	28 (33.73%)	7 (21.21%)
	Ischemic Heart Disease (n=41)	9 (18.75%)	32 (27.59%)	29 (34.94$)	3 (9.09%)
	Sickle Cell Disease (n=23)	13 (27.08%)	10 (8.62%)	10 (12.05%)	0 (0%)
	Malignancy (n=9)	2 (4.17%)	7 (6.03%)	6 (7.23%)	1 (3.03%)
	Prematurity (n=6)	6 (12.50%)	0 (0%)	0 (0%)	0 (0%)
	Dermatological Diseases (n=6)	3 (6.25%%)	3 (2.59%)	1 (1.20%)	2 (6.06%)
	COPD* (n=4)	1 (2.08%)	3 (2.59%)	1 (1.20%)	2 (6.06%)
	No comorbidities (n=18)	2 (4.17%)	16 (13.79%)	1 (1.20%)	15 (45.45%)
MSSA vs MRSA infection	MSSA** (n=90)	26 (54.17%)	64 (55.17%)	46 (55.42%)	18 (54.55%)
	MRSA*** (n=74)	22 (45.83%)	52 (44.83%)	37 (44.58%)	15 (45.45%)

◊Staphylococcus Aureus Bacteremia (SAB), ◊◊Community Onset-Health care associated (CO-HA) infections, ◊◊◊Community Onset-Community associated (CO-CA) infections, *Chronic Obstructive Pulmonary Disease, **Methicillin-Susceptible Staphylococcus Aureus (MSSA), ***Methicillin-Resistant Staphylococcus Aureus (MRSA)

Antimicrobial sensitivity profile of S. aureus

SAB strains showed low levels of resistance among most tested antibiotics. The percentage of susceptibility of *S. aureus* against various antibiotics during the study period are illustrated in Figure 1.



* TRIMETHOPRIM/SULPHAMETHOXAZOLE

Figure 1: Percentage of susceptibility of SAB isolates to various antibiotics

Outcome (Recurrence & Mortality)

Death as an outcome was observed in 42 patients (25.6%). Mortality rate showed variability among different age groups (Figure 2), neonates (less than 28 days) had the highest mortality of 41.67% , while there was no mortality among pediatrics aged 28 days -12 years old & adolescents (13-18 years old), after that there was incremental increase of the mortality by increasing the age , with mortality rate of 18.18%, 28 %, 32.5 % among adults, middle age & elderly population respectively .

Among the comorbidities, malignancy & prematurity were the two important predictors of mortality among our population (Table 4)

Mortality encountered among MRSA bacteremia (28.4 %) was higher than MSSA bacteremia (23.3%), but the difference was not statistically significant (P value: 0.461). Similarly, a higher mortality rate was observed among the hospital onset SAB in comparison to the community onset cases and the results were not statistically significant (35.42% Vs. 21.55% respectively, P value: 0.064),

Table 4: Comparison of variables in relation to mortality outcomes among patients with *Staphylococcus aureus* Bacteremia (SAB)

Subgroup		Total cohort n	Mortality group n (%)	P value
Comorbidities	Diabetes Mellitus	72	17 (23.61%)	0.604
	End Stage Renal Disease	57	11 (19.30%)	0.177
	Hypertension	49	14 (28.57%)	0.571
	Ischemic Heart Disease	41	11 (26.83%)	0.836
	Sickle Cell Disease	23	2 (8.70%)	0.068
	Malignancy	9	5 (55.56%)	**0.049**
	Prematurity	6	5 (83.33%)	**0.004**
	Dermatological Diseases	6	1 (16.67%)	0.693
	Chronic Obstructive Pulmonary Disease	4	1 (25%)	0.729
	No comorbidities	18	4 (22.22%)	0.490
Hospital vs Community onset infection	Hospital Onset infections (HO)	48	17 (35.42%)	0.064
	Community Onset infections(CO)	116	25 (21.55%)	
CO-HA vs CO-CA Infection	Healthcare-associated(CO- HA)	83	17 (20.48%)	0.165
	Community-associated (CO- CA)	33	8 (24.24%)	
MSSA vs MRSA infection	Methicillin-Susceptible Staphylococcus Aureus (MSSA)	90	21 (23.33%)	0.461
	Methicillin-Resistant Staphylococcus Aureus (MRSA)	74	21 (28.38%)	

Among the 122 survivors of the initial SAB episode, recurrence of bacteremia was documented during the following 90 days among 26 cases (21.3%). Table 5 showed the variable risk factors studied on the risk of recurrence. The only two predictors of recurrence were the presence of end stage renal dialysis & health care acquisition of SAB.

Table 5: Comparison of variables in relation to recurrence of the infection at 90 days among patients with Staphylococcus Aureus Bacteremia (SAB)

Subgroup		Total Cohort	Recurrence n (%)	P value
Age groups	Neonates	12	0 (0%)	
	Paediatrics	3	0 (0%)	
	Adolescents	4	1 (25%)	
	Adults	55	9 (16.36%)	
	Middle age	50	9 (18.00%)	
	Elderly	40	7 (17.50%)	
Comorbidities	Diabetes Mellitus	72	15 (20.83%)	0.122
	End Stage Renal Disease	57	18 (31.58%)	**<0.001**
	Hypertension	49	10 (20.41%)	0.297
	Ischemic Heart Disease	41	9 (21.95%)	0.217
	Sickle Cell Disease (SCD)	23	3 (13.04%)	0.691
	Malignancy	9	0 (0%)	0.357
	Prematurity	6	0 (0%)	0.591
	Dermatological Diseases	6	1 (16.67%)	0.651
	Chronic Obstructive Pulmonary Disease	4	0 (0%)	0.616
	No comorbidities	18	1 (5.56%)	0.312

Hospital vs Community onset infection	Hospital Onset infections (HO)	48	4 (8.33%)	0.104
	Community Onset infections (CO)	116	22 (18.97%)	
CO-HA vs CO-CA Infection	Healthcare-associated (CO- HA)	83	20 (24.10%)	**0.016**
	Community-associated (CO- CA)	33	2 (6.06%)	
MSSA vs MRSA infection	Methicillin-Susceptible Staphylococcus Aureus (MSSA)	90	12 (13.33%)	0.330
	Methicillin-Resistant Staphylococcus Aureus (MRSA)	74	14 (18.92%)	

Discussion

This study consisted of 164 episodes of SAB. In agreement with other published studies, the majority were of community onset – health care associated, with a predominance of male gender. [10-11]

Among the adults, common comorbidities associated with SAB were similar to other previously published data such as dialysis dependence, ischemic heart disease, diabetes, hypertension, and chronic dermatitis.[12-15] In addition to previously documented comorbidities ; we found in our study that the presence of SCD is associated with SAB among adult population aged 19-49 years and all SAB cases were hospital associated or nosocomial which explain that their acquisition of bacteremia is mostly related to their repeated admission and long stay in the hospital. The association of SAB bacteremia among SCD patients to the presence of intravenous lines (central/peripheral) was not addressed in our study, this could provide directions to future studies, where the risk factors of SAB among SCD patients can be defined to plan effective preventive strategies.

Among pediatric patients aged between 28 days and 12 years; end stage renal disease (33.3%) and malignancy (33.3%) were observed. While among adolescents aged between 13 and 18 years old ; comorbidities included end stage renal disease (25%), DM (25%) & sickle cell disease (25%). Caution must be exercised while interpreting such results as the number of SAB among pediatrics & adolescent age groups were very small (3 & 4 patients respectively).

Mortality among our study cohort of SAB was 25.6%, which was similar to a few studies, but in contradiction to other studies. [21-23] The authors did not find MRSA bacteremia or acquisition in the health care system as a significant predictor of mortality in comparison to MSSA bacteremia or community associated bacteremia; while most other previous studies documented MRSA and health care acquisition as an important risk factor for death among SAB.[24-25] This might be explained by the presence of other confounders that affect the mortality, which were not assessed in our study (such as source of SAB & the treatment regimen used) as these details were unavailable in the electronic health record system.

The main significant risk factors for mortality among our population was prematurity which was reported among the neonates who had SAB, and the presence of malignancy among middle aged population, similar finding was also obtained in previous studies.[26]

Recurrence rate among survivors was 21.3%, with the highest risk among patients on regular hemodialysis and health care associated SAB, this should initiate more vigilance measures among patients on hemodialysis to raise the level of clinical suspicion with prompt initiation of empirical antibiotics among patient who recovered from an episode of SAB. This is crucial, keeping in mind that hemodialysis patients have a significantly increased risk for morbidity and mortality from infectious diseases; where infections account for 12 to 36% of the mortality in patients with ESRD and is second only to cardiovascular disease as a cause of death.[27]

The main strength of our study is that it includes a big population of patients on regular hemodialysis (a total of 500 patients attending the two main government hemodialysis centers in Bahrain). This study has thus established the baseline data, which is vital to study the present trends & outcomes of SAB among dialysis dependent patients as a quality indicator of dialysis events in any hemodialysis center.[28]

On the other hand; as our study was a retrospective, some limitations were inherent to its design, information was dependent on the available information from the electronic medical records of patients, which lack the source of SAB and the treatment details among patients, which both definitely had a crucial impact on the outcome of the patients.

Conclusion

SAB is significant health problem with high mortality. Among our population, DM, SCD and dialysis dependence were important risk factors for the development of bacteremia, recurrence of bacteremia is a common complication among patients on regular hemodialysis.

Future prospective studies are suggested to follow the trend of SAB among hospitalized patients & patients on regular hemodialysis along with monitoring its outcomes. More targeted studies of SAB among special population like SCD would be also of importance to define their special risk factors & plan appropriate preventive strategy.

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