Retrospective Analysis of Methicillin-Resistant Staphylococcus aureus Skin and Soft Tissue Infection among Patients Admitted at an Academic University Hospital From 2011 to 2015: a Five-Year Review

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ABSTRACT

Introduction The emergence of methicillin-resistant Staphylococcus aureus (MRSA) is a challenge in the management of skin and soft tissue infections (SSTIs).

Objective To describe the epidemiology of MRSA SSTIs among admitted patients at the University of Santo Tomas Hospital (USTH).

Methods This was a retrospective study of inpatients with MRSA SSTIs from 2011-2015. MRSA infections were classified as community-associated (CA-MRSA) and healthcare-associated (HA-MRSA). Demographic characteristics, clinical profile, comorbidities, complications, risk factors, antibiotic susceptibility and resistance, treatment used, and clinical outcome were determined.

Results Out of the 331 inpatients with Staphylococcus aureus SSTIs, 211 had MRSA with a prevalence of 63.7%, 80.1% of MRSA were CA-MRSA while 19.9% were HA-MRSA. The mean age was 41.58 years with male predominance. The majority presented with abscess (62.9%), on the legs (21.8%). The abscess was significantly associated with CA-MRSA while infected wounds, previous hospitalization, and surgery were correlated with HA-MRSA. Growing resistance to ciprofloxacin, tetracycline, macrolides, co-trimoxazole, and clindamycin was noted. A low percentage of resistance to vancomycin and linezolid was observed. Almost all cases improved with appropriate antibiotic therapy and 3.3% mortality.

Conclusion More than half of the patients with Staphylococcus aureus SSTIs had MRSA. and were mostly CA-MRSA and males. Abscess on the leg was the common presentation and significantly associated with CA-MRSA. Infected wounds, previous hospitalization, and surgery were associated with HA-MRSA. There was high resistance of MRSA to

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ciprofloxacin and tetracycline while low resistance to vancomycin and linezolid. Almost all improved with appropriate treatment.

Keywords Methicillin-resistant Staphylococcus aureus, MRSA, CA-MRSA, HA-MRSA, skin and soft tissue infection

INTRODUCTION

Staphylococcus aureus is the most commonly identified microorganism responsible for skin and soft tissue infections (SSTIs).[1] Treatment of early infections includes incision and drainage of the lesion, often accompanied by beta-lactam antimicrobial drugs.[1] Through the years, Staphylococcus aureus has developed resistance to methicillin and other beta-lactam antibiotics; hence, the term methicillin-resistant Staphylococcus aureus (MRSA).[2]

MRSA infections were recognized from the 1960s through the 1990s as a healthcare-associated (HA) disease. In the late 1990s, MRSA disease without established healthcare risk factors called community-associated (CA)-MRSA was increasingly reported. [1-3] A standardized definition of each was created by the US Centers for Disease Control and Prevention (CDC). According to CDC, the following criteria are needed for a diagnosis of CA-MRSA: (1) diagnosis of MRSA is made in the outpatient setting or by a culture positive for MRSA within 48 hours after admission to the hospital, (2) no medical history of MRSA infection or colonization, (3) no medical history in the past year of hospitalization, admission to a nursing home, skilled nursing facility or hospice, dialysis or surgery, or 4) no permanent indwelling catheters or medical devices that pass through the skin into the body. Patients with HA-MRSA, on the other hand, are those who do not meet the criteria for CA-MRSA.[4]

Since the emergence of MRSA, it's epidemic spread has led to a high burden of SSTIs.[2] Hence, its prevalence, clinical presentation, sites of predilection, comorbidities, complications, risk factors, antibiotic sensitivity, and resistance pattern and treatment outcome must be identified.

The aim of this study was to describe the epidemiology of MRSA skin and soft tissue infection among patients who were admitted to a tertiary hospital from 2011 to 2015. It specifically aimed to (1) determine the prevalence of MRSA SSTI in general and differentiate this into community-associated (CA-MRSA) and healthcare-associated (HA-MRSA) infection, (2) describe the demographic characteristics and clinical profile of patients with MRSA SSTI, (3) determine the comorbidities and risk factors associated with MRSA SSTI, (4) determine the antibiotic susceptibility and resistance pattern of MRSA, and (5) determine treatment outcome of patients with MRSA SSTI.

METHODOLOGY

This is a single-center, retrospective study of patients with SSTI due to MRSA admitted at the USTH from January 1, 2011 to December 31, 2015. This retrospective study was approved by the Institutional Review Board of the same hospital.

Included in this study were patients admitted at our institution with MRSA isolates from SSTIs. Excluded were those admitted patients whose SSTI were not proven by culture and whose charts were unavailable for review or inaccessible.

Data were obtained from culture results of SSTI patients which yielded Staphylococcus aureus isolates. The culture isolates were then further subdivided into methicillin sensitive Staphylococcus aureus (MSSA) and MRSA. Laboratory diagnosis of MRSA followed on the Clinical Laboratory Standards Institute with Performance Standards for Antimicrobial Susceptibility Testing. MRSA was diagnosed when the Staphylococcus aureus isolates were resistant to all penicillins, cephems (cephalosporins and cephamycins), imipenem and beta-lactam antibiotics. Available medical records of these patients were retrieved. Data were obtained from the culture results of SSTIs with MRSA culture isolates and from the medical records of patients who were available at our institution.

The variables of interest reviewed and analyzed include the following: patient's demographic data (age, sex), clinical presentation, sites of predilection, comorbidities, complications, risk factors, antibiotic sensitivity, and resistance pattern, treatment used and clinical outcome. In this study, the patients were further categorized based on age as follows: pediatric age group with age 0 to 17 years; adult group with age 18 to 65 years, and geriatric group with age greater than 65 years.

Descriptive statistics were utilized as measures of central tendencies for continuous variables while frequencies and percentages were used for categorical variables. Prevalence of MRSA was computed with

reference to the population exposed to culture isolation (number of MRSA patients divided by the total number of patients who had culture isolation from their SSTIs) and with reference to the population with Staphylococcus aureus isolates (number of MRSA patients divided by the total number of population with Staphylococcus aureus isolates). The odds ratio was determined by employing logistic regression wherein MRSA, either CA-MRSA or HA-MRSA, is the dependent variable and the demographic variables, clinical presentation, risk factors, and comorbidities are the explanatory variables. All conclusions of the hypothesis tests used a 0.05 level of significance. Statistical results were obtained using Stata MP 64 version 13.

RESULTS

From January 1, 2011 to December 31, 2015, a total of 1,616 patients admitted at our institution had skin and soft tissue culture isolates. Among these patients, 355 (22.0%) had Staphylococcus aureus isolates. The yearly percentage of SSTIs due to Staphylococcus aureus ranged from 19.8% to 23.9% and was highest in 2014.

The medical records of 331 (93.2%) admitted patients with Staphylococcus aureus isolates were available for review. Twenty-four medical charts of these patients were not retrievable and therefore were excluded in the data analysis.

The prevalence of MRSA SSTI was 13.3% (n=211) with reference to all skin and soft tissue isolates and was more than half (63.7%) with reference to Staphylococcus aureus isolates alone. Among the MRSA patients, 169 (80.1%) had community-associated MRSA (CA-MRSA) and 42 (19.9%) had healthcare-associated MRSA (HA-MRSA).

In the five-year span of the study, community-acquired MRSA increased with an 18.2% difference between the years 2011 and 2012. After 2012, the increase continued but was minimal – with the percentages between years 2012 and 2013 having the least difference of 1%. Since 2011, the prevalence of CA MRSA increased from 61.8% to 88.4% in 2015. In contrast, the prevalence of HA-MRSA decreased yearly from 38.2% to 11.6% (Figure 1).

Demographic Data

The age of patients with MRSA ranged from 1 month to 88 years old with a mean age of 41.58 (± 24.83) years. Figure 2 shows that more than half of the MRSA patients (58.0%) belonged to the adult group while 22.0% belonged to the pediatric group and 20.0% to the geriatric group.

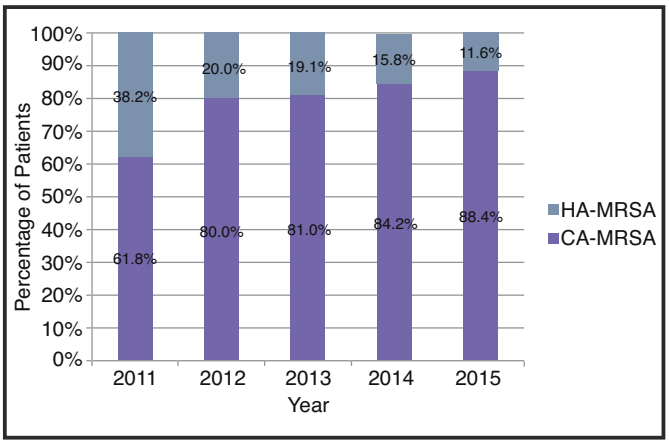

Figure 1. Percentage distribution of the types of MRSA (year 2011 to 2015)

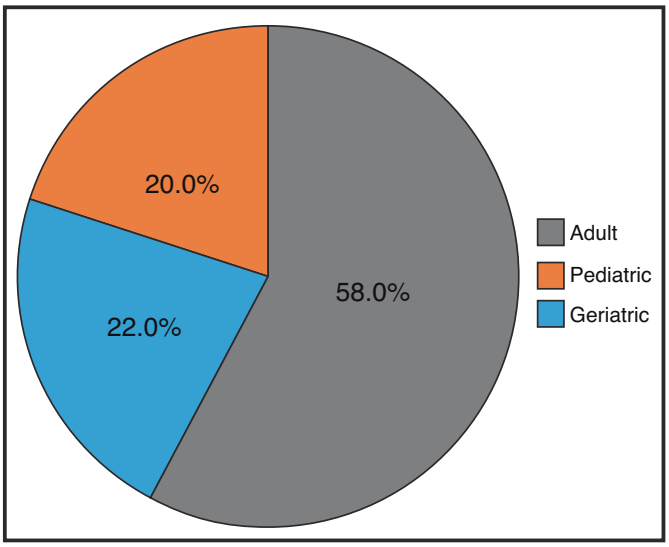

Figure 2. Age distribution of patients with MRSA SSTI isolates

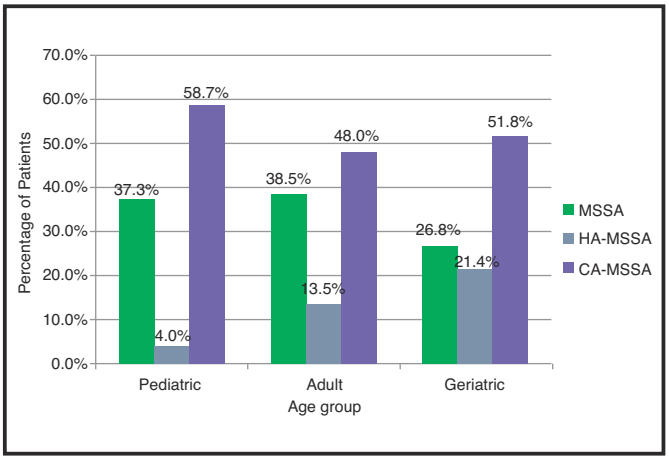

Figure 3. Percentage distribution of *Staphylococcus aureus* SSTI isolates for each age group

Table 1. Count and proportion of the clinical presentation of skin and soft tissue infection with MRSA isolates.

Clinical Presentation*	MRSA n (%)	CA-MRSA n (%)	HA-MRSA n (%)
Abscess	**132 (62.9)**	**111 (66.5)**	**21 (48.8)**
Abscess only	112 (53.3)	96 (57.5)	16 (37.2)
Abscess with cellulitis	20 (9.5)	15 (9)	5 (11.6)
Cellulitis only	7 (3.3)	4 (2.4)	3 (7)
Bullous cellulitis	4 (1.9)	4 (2.4)	0 (0)
Infected wounds	32 (15.2)	17 (10.2)	15 (34.9)
Infected wounds only	27 (12.9)	12 (7.2)	15 (34.9)
Infected wounds with cellulitis	5 (2.4)	5 (3)	0 (0)
Furunculosis	17 (8.1)	15 (9)	2 (4.7)
Furunculosis only	11 (5.2)	10 (6)	1 (2.3)
Furunculosis with cellulitis	6 (2.9)	5 (3)	1 (2.3)
Furuncle	5 (2.4)	4 (2.4)	1 (2.3)
Furuncle only	2 (1)	2 (1.2)	0 (0)
Furuncle with cellulitis	3 (1.4)	2 (1.2)	1 (2.3)
Carbuncle	6 (2.9)	6 (3.6)	0 (0)
Carbuncle only	6 (2.9)	6 (3.6)	0 (0)
Carbuncle with cellulitis	0 (0)	0 (0)	0 (0)
Impetigo contagiosa	4 (1.9)	4 (2.4)	0 (0)
Decubitus Ulcer	5 (2.4)	2 (1.2)	3 (7)
Stasis ulcer	0 (0)	0 (0)	0 (0)
Folliculitis	1 (0.5)	1 (0.6)	0 (0)
Fournier's gangrene	1 (0.5)	1 (0.6)	0 (0)

* Some patients presented with more than one clinical presentation

Table 2. Percentage of clinical presentation of SSTI among MRSA patients according to age groups.

Clinical Presentation	CA-MRSA			HA-MRSA			MRSA		
	Pediatric	Adult	Geriatric	Pediatric	Adult	Geriatric	Pediatric	Adult	Geriatric
Abscess	**63.6**	**70.8**	**51.7**	**66.7**	**55.6**	33.3	63.8	67.5	46.3
Cellulitis	20.5	17.7	34.5	0	22.2	16.7	19.2	18.7	29.3
Bullous cellulitis	2.3	3.1	3.5	0	0	0	2.1	2.4	2.4
Infected wound	2.3	9.4	24.1	33.3	29.6	**58.3**	4.3	13.8	34.2
Furunculosis	9.1	10.4	0	0	0	0	8.5	8.1	0
Furuncle	4.6	2.1	0	0	0	8.3	4.3	1.6	2.4
Carbuncle	4.6	3.1	3.5	0	0	0	4.3	2.4	2.4
Impetigo contagiosa	9.1	0	0	0	0	0	8.5	0	0
Decubitus ulcer	2.3	0	3.5	0	7.4	8.3	2.1	1.6	4.9
Stasis ulcer	0	0	0	0	0	0	0	0	0
Folliculitis	0	1.0	0	0	0	0	0	0.8	0
Fournier's gangrene	0	0	3.5	0	0	0	0	0	2.4

Table 3. Distribution of the site of skin and soft tissue infection of the MRSA patients.

Site of SSTI*	CA-MRSA n (%)	HA-MRSA n (%)	MRSA Overall n (%)
Leg	36 (21.3)	10 (23.8)	**46 (21.8)**
Head	33 (19.5)	9 (21.4)	**42 (19.9)**
Trunk	34 (20.12)	7 (16.7)	**41 (19.4)**
Genital region	18 (10.7)	6 (14.3)	24 (11.4)
Foot	18 (10.7)	4 (9.5)	22 (10.4)
Gluteal region	11 (6.5)	2 (4.8)	13 (6.2)
Hand	11 (6.5)	2 (4.8)	13 (6.2)
Arm	7 (4.1)	3 (7.1)	10 (4.7)
Neck	7 (4.1)	2 (4.8)	9 (4.3)

*Some patients presented with more than one site of SSTI

Table 4. Distribution of the site of skin and soft tissue infection of the MRSA according to age group.

Site of SSTI*	CA-MRSA			HA-MRSA			MRSA		
	Pediatric	Adult	Geriatric	Pediatric	Adult	Geriatric	Pediatric	Adult	Geriatric
Leg	3 (6.8)	**21 (21.9)**	**12 (41.4)**	**1 (33.3)**	**6 (22.2)**	**3 (25)**	4 (8.5)	27 (22)	15 (36.6)
Head	**21 (47.7)**	10 (10.4)	2 (6.9)	0 (0)	6 (22.2)	3 (25)	21 (44.7)	16 (13)	5 (12.2)
Trunk	8 (18.2)	21 (21.9)	5 (17.2)	**1 (33.3)**	4 (14.8)	2 (16.7)	9 (19.2)	25 (20.3)	7 (17.1)
Genital region	3 (6.8)	12 (12.5)	3 (10.3)	0 (0)	5 (18.5)	1 (8.3)	3 (6.4)	17 (13.8)	4 (9.8)
Foot	5 (11.4)	9 (9.4)	4 (13.8)	0 (0)	2 (7.4)	2 (16.7)	5 (10.6)	11 (8.9)	6 (14.6)
Gluteal region	1 (2.3)	8 (8.3)	2 (6.9)	**1 (33.3)**	0 (0)	1 (8.3)	2 (4.3)	8 (6.5)	3 (7.3)
Hand	3 (6.8)	8 (8.3)	0 (0)	0 (0)	2 (7.4)	0 (0)	3 (6.4)	10 (8.1)	0 (0)
Arm	2 (4.6)	4 (4.2)	1 (3.5)	0 (0)	2 (7.4)	1 (8.3)	2 (4.3)	6 (4.9)	2 (4.9)
Neck	1 (2.3)	5 (5.2)	1 (3.5)	0 (0)	2 (7.4)	0 (0)	1 (2.1)	7 (5.7)	1 (2.4)

*Some patients presented with more than one site of SSTI

Figure 3 shows that across all age groups, CA-MRSA was the most dominant Staphylococcus aureus isolate, being most prevalent in the pediatric group (58.7%) and least prevalent in the adult group (48.0%). The occurrence of HA-MRSA increased with the age group. Generally, MRSA cases outnumbered MSSA cases. The pediatric and adult age groups had almost the same prevalence of MSSA (37.3%, 38.5%), while the geriatric age group had a lower prevalence of MSSA (26.8%).

More than half of the patients with MSSA SSTIs were males (55.2%). The predominance of male patients was a consistent finding each year from 2011 to 2015.

Clinical Presentation

The most dominant clinical presentation of SSTI among MRSA was abscess (n=132, 62.9%). It was also the most dominant for both CA-MRSA (n=111, 66.5%) and HA-MRSA (n=21, 48.8%). Other SSTIs with MRSA included cellulitis, infected wounds, furunculosis, carbuncle, impetigo contagiosa, decubitus ulcer, stasis ulcer, folliculitis, and Fournier's gangrene (Table 1).

Based on different age groups, the predominant presentation of CA-MRSA was abscess for all age groups. The same finding was noted in pediatric and adult patients with HA-MRSA except for geriatric patients with HA-MRSA who commonly presented with an infected wound (Table 2).

Sites of Predilection

Table 3 shows that the common site of MRSA SSTIs was the legs (21.8%), followed by the head (19.9%) and trunk (19.4%). Other sites were genital region, feet, gluteal area, hand, arms, and neck.

Based on the different age groups, the head (47.7%) was the most common site among pediatric patients with CA-MRSA, but the leg, trunk, and gluteal region were the common sites among pediatric patients with HA-MRSA. The leg was the most common site for both adult and geriatric patients with CA-MRSA and HA-MRSA (Table 4).

Comorbidities

Among patients with MRSA, diabetes mellitus and cardiovascular disease were the most common comorbidities. Most of the pediatric patients with MRSA (63.8%) presented with no accompanying comorbidity. The comorbidity noted was only among the pediatric patients with CA-MRSA who had a respiratory disorder (23.3%), specifically asthma. For adult patients with CA-MRSA, diabetes mellitus (44.8%) was the most common followed by cardiovascular disease (29.2%), while the geriatrics group with CA-MRSA presented mostly with cardiovascular disease (82.1%). For patients with HA-MRSA, cardiovascular disease was the most common morbidity followed by diabetes mellitus for both the adult and geriatrics group (Table 5).

Complications

Out of the 31 patients with Staphylococcus aureus infection who had complications, 24 (77.4%) had MRSA. The top two complications were osteomyelitis followed by MRSA bacteremia. The complete list is shown in Table 6.

Risk Factors

Based on the literature, this study listed seven potential risk factors for MRSA. Among the 211 patients with MRSA SSTIs, 89 (42.2%) did not possess any of the risk factors. The tabulation of risk factors and their occurrence is presented in Table 7. The most commonly identified risk factor among patients with MRSA isolates was previous antibiotic (50.2%) followed by surgical site/medical device infection (7.1%). No patient had a permanent indwelling catheter. The least prevalent risk factors were dialysis and a history of medical devices that passed through the skin (0.5%). In CA-MRSA isolates, previous antibiotic therapy was the common risk factor while surgical site/medical device was predominant in HA-MRSA isolates.

The potential risk factors and their association with MRSA and specifically CA-MRSA and HA-MRSA are shown in Table 8. The measure of association is presented as an odds ratio. Sex and age group were not significantly associated with MRSA. Among the clinical presentations of SSTI, an abscess was associated with CA-MRSA (p-value = 0.0002). Patients with abscess as clinical presentation of SSTI were 2.3 times more likely to be CA-MRSA as compared to patients whose clinical presentation of SSTI was not abscess. On the other hand, a clinical presentation of an infected wound increased the odds of patients with Staphylococcus aureus SSTI to be HA-MRSA by 2.9 times. The presence of previous hospitalization and previous surgery increased the odds of patients with Staphylococcus aureus SSTI to be HA-MRSA by 3.6 and 3.2 times, respectively.

The presence of any complication such as osteomyelitis, MRSA bacteremia, compartment syndrome, pyomyositis, sepsis, Fournier's gangrene, or septic shock; a medical device that passes through the skin; previous MRSA infection; previous or concomitant skin infection and previous antibiotic therapy were not significantly associated with MRSA. Furthermore, the presence of any comorbidity did not also yield a significant association with MRSA. Each type of comorbidity was tested for association with MRSA and all results were not significant.

Antibiotic Susceptibility and Resistance

The yearly variation in the susceptibility of MRSA to different drugs is shown in Figure 4. MRSA isolates were only noted to have 100% susceptibility to vancomycin in the years 2013 and 2015 and to linezolid in the years 2011, 2012, and 2015, respectively. MRSA isolates were also noted to be 100% susceptible to other antibiotics such as chloramphenicol (year 2012, 2013), gentamicin (year 2012, 2013, 2015) and co-trimoxazole (year 2011). The lowest susceptibility of MRSA to an antibiotic was noted in 2013 where only 61.9% of MRSA were susceptible to ciprofloxacin.

Considering the cumulative percentage susceptibility of MRSA for 5 years, 90% or more showed susceptibility to the following antibiotics: vancomycin, linezolid, gentamicin, chloramphenicol, co-trimoxazole, clindamycin, erythromycin, and azithromycin. Only 81.9% and 75.7% of the MRSA isolates showed susceptibility to tetracycline and ciprofloxacin, respectively (Figure 5).

Table 5. Prevalence of co-morbidities among SSTI patients with MRSA isolates.

Comorbidity	MRSA			CA-MRSA			HA-MRSA		
	Pediatric n (%)	Adult n (%)	Geriatric n (%)	Pediatric n (%)	Adult n (%)	Geriatric n (%)	Pediatric n (%)	Adult n (%)	Geriatric n (%)
Diabetes mellitus (DM)	2 (4.3)	51 (41.5)	25 (62.5)	1 (2.3)	**43 (44.8)**	20 (71.4)	1 (25)	**8 (29.6)**	**5 (41.7)**
Cardiovascular disease (CVD)	0 (0)	38 (30.9)	33 (82.5)	0 (0)	**28 (29.2)**	**23 (82.1)**	0 (0)	**10 (37)**	**10 (83.3)**
Autoimmune disorder	2 (4.3)	2 (1.6)	2 (5.0)	1 (2.3)	0 (0)	0 (0)	1 (25)	2 (7.4)	2 (16.7)
Respiratory disorder	10 (21.3)	7 (5.7)	4 (10.0)	**10 (23.3)**	5 (5.2)	1 (3.6)	0 (0)	2 (7.4)	2 (25.0)
Renal/liver disorder	0 (0)	10 (8.1)	10 (25.0)	0 (0)	9 (9.4)	5 (17.9)	0 (0)	1 (3.7)	5 (41.7)
Previous/ concomitant skin infection	3 (6.4)	4 (3.3)	1 (2.5)	3 (7.0)	3 (3.1)	1 (3.6)	0 (0)	1 (3.7)	0 (0)
Endocrine disorder	0 (0)	1 (0.8)	3 (7.5)	0 (0)	0 (0)	1 (3.6)	0 (0)	1 (3.7)	2 (16.7)
Neurological disorder	0 (0)	4 (3.3)	3 (7.5)	0 (0)	1 (1)	2 (7.1)	0 (0)	3 (11.1)	1 (8.3)
Hematologic disorder	0 (0)	3 (2.4)	1 (2.5)	0 (0)	3 (3.1)	0 (0)	0 (0)	0 (0)	1 (8.3)
Gastrointestinal disorder	2 (4.3)	4 (3.3)	1 (2.5)	2 (4.7)	4 (4.2)	1 (3.6)	0 (0)	0 (0)	0 (0)
Inflammatory disorder	1 (2.1)	2 (1.6)	0 (0)	1 (2.3)	1 (1)	0 (0)	0 (0)	1 (3.7)	0 (0)
Others: AOM	2 (4.3)	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)
Thermal injury	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
At least 2 of the above	6 (12.8)	41 (33.3)	30 (75.0)	5 (11.6)	30 (31.1)	19 (67.9)	1 (25)	11 (40.7)	11 (91.7)
Cancer	1 (2.1)	6 (4.9)	3 (7.5)	1 (2.3)	3 (3.1)	1 (3.6)	0 (0)	3 (11.1)	2 (16.7)
None	30 (63.8)	42 (34.1)	1 (2.5)	28 (65.1)	34 (35.4)	0 (0)	2 (50)	8 (29.6)	1 (8.3)

Table 6. Distribution of the complications among patients with Staphylococcus aureus SSTI.

Complication	CA-MRSA	HA-MRSA	MRSA	Staphylococcus aureus
	n (%)	n (%)	n (%)	n (%)
Osteomyelitis	**6 (3.6)**	**3 (7.1)**	**9 (4.3)**	13 (3.9)
MRSA bacteremia	**7 (4.1)**	**2 (4.8)**	**9 (4.3)**	10 (3)
Compartment syndrome	1 (0.6)	1 (2.4)	2 (1)	2 (0.6)
Pyomyositis	0 (0)	1 (2.4)	1 (0.5)	2 (0.6)
Sepsis	1 (0.6)	0 (0)	1 (0.5)	2 (0.6)
Fournier's gangrene	1 (0.6)	0 (0)	1 (0.5)	1 (0.3)
Septic shock	1(0.6)	0 (0)	1 (0.5)	1 (0.3)

Table 7. Prevalence of potential risk factors for MRSA among SSTI isolates.

Risk Factor*	MRSA	CA-MRSA	HA-MRSA
	n (%)	n (%)	n (%)
Previous hospitalization	9 (4.3)	5 (3.0)	4 (9.5)
Dialysis	**1 (0.5)**	0 (0)	1 (2.4)
Permanent indwelling catheter	**0 (0)**	0 (0)	0 (0)
Medical device that passes through the skin	**1 (0.5)**	0 (0)	1 (2.4)
Previous MRSA infection	6 (2.8)	6 (3.6)	0 (0)
Previous antibiotic therapy	**106 (50.2)**	**98 (58.0)**	8 (19.1)
Surgical site/medical device infection	**15 (7.1)**	0 (0)	**15 (35.7)**
None	**89 (42.2)**	69 (40.8)	20 (47.6)

*Some patients had more than one potential risk factors

The resistance pattern of MRSA during the five-year study is shown in Figure 6. Among the antibiotics, resistance to azithromycin, ciprofloxacin, and erythromycin was noted yearly for the five-year period while resistance to clindamycin, co-trimoxazole, and tetracycline was noted yearly starting 2012. Among the antibiotics, ciprofloxacin yielded the highest MRSA resistance, especially in the year 2013 (38.1%). Vancomycin resistance was noted in the years 2011 (2.9%), 2012 (2.9%), and 2014 (1.4%) while linezolid resistance was noted in the years 2013 (2.4%) and 2014 (3.6%).

The cumulative percentage resistance of MRSA to ciprofloxacin during the five-year study was 18.1% while MRSA resistance to tetracycline was noted to be at 12.4%. MRSA yielded less than 10% resistance to antibiotics such as azithromycin (9.5%), erythromycin (8.6%), clindamycin (6.7%), co-trimoxazole (5.7%), chloramphenicol (2.4%), and gentamicin (1.0%). MRSA resistance was at 1.4% for both vancomycin and linezolid (Figure 7).

Comparing the antibiotic susceptibility between CA-MRSA and HA-MRSA, the only significantly different susceptibility rates of the specific MRSA types were seen with azithromycin and erythromycin. The susceptibility of CA-MRSA to erythromycin and azithromycin was higher at 93.4% and 92.2%, respectively as compared to the susceptibility of HA-MRSA to both erythromycin and azithromycin which only yielded 83.7% (Figure 8).

Table 8. Association of MRSA with potential risk factors among MRSA SSTI patients.

Risk Factor	CA-MRSA			HA-MRSA		
	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Sex	0.852	0.552 to 1.315	0.4694 ns	0.933	0.491 to 1.774	0.8325 ns
Adult (reference = Pediatric)	0.8718	0.51 to 1.49	0.6165 ns	1.6686	0.66 to 4.23	0.2813 ns
Geriatric (reference = Pediatric)	0.7593	0.38 to 1.52	0.4349 ns	2.6135	0.90 to 7.56	0.0763
Abscess	2.307	1.478 to 3.599	0.0002**	0.692	0.364 to 1.314	0.2604 ns
Cellulitis	0.315	0.099 to 0.997	0.0494 ns	1.587	0.433 to 5.813	0.4860 ns
Infected wound	0.190	0.096 to 0.374	0.0001 ns	2.893	1.432 to 5.844	0.0031**
Furunculosis	1.447	0.537 to 3.897	0.465 ns	0.405	0.052 to 3.133	0.3863 ns
Presence of complication	1.247	0.580 to 2.682	0.5719 ns	1.079	0.356 to 3.267	0.8930 ns
Previous hospitalization	0.701	0.218 to 2.255	0.5512 ns	3.560	1.033 to 12.481	0.0444**
Medical device that passes through the skin	0.161	0.019 to 1.349	0.0921 ns	1.119	0.131 to 9.528	0.9180 ns
Previous MRSA skin infection	-	-	0.9979 ns	-	-	0.9983 ns
Previous skin infections or concomitant skin infections	1.230	0.496 to 3.052	0.655 ns	0.731	0.164 to 3.271	0.6826 ns
Close contact with SSTI patients	0.994	0.138 to 7.141	0.9952 ns	6.976	0.956 to 50.885	0.0554
Previous surgery	0.368	0.189 to 0.718	0.0034 ns	3.234	1.540 to 6.804	0.0019**
Previous antibiotic therapy	1.423	0.923 to 2.195	0.1103 ns	0.618	0.319 to 1.196	0.1528 ns
With comorbidity	0.857	0.542 to 1.355	0.5085 ns	0.818	0.420 to 1.591	0.5533 ns
With diabetes	0.625	0.400 to 0.975	0.0385 ns	1.043	0.541 to 2.009	0.9007 ns
With kidney disease	1.151	0.542 to 2.441	0.7149 ns	1.784	0.684 to 4.652	0.2366 ns
With hypertension	0.936	0.584 to 1.500	0.7822 ns	1.671	0.861 to 3.243	0.1292 ns

** Significant at 5% level of significance
ns not significant

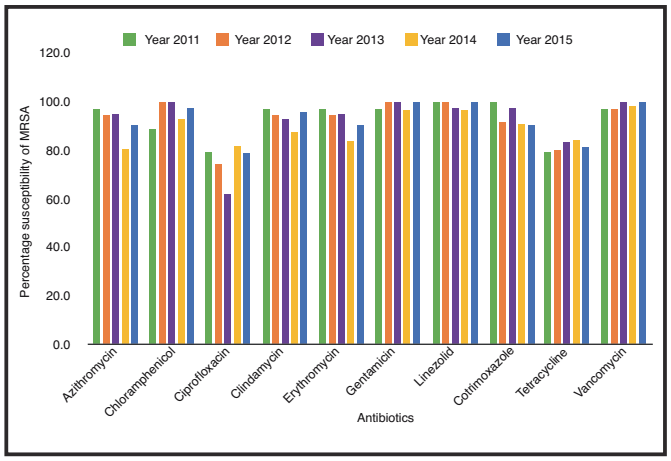

Figure 4. Yearly susceptibility of MRSA to different antibiotics

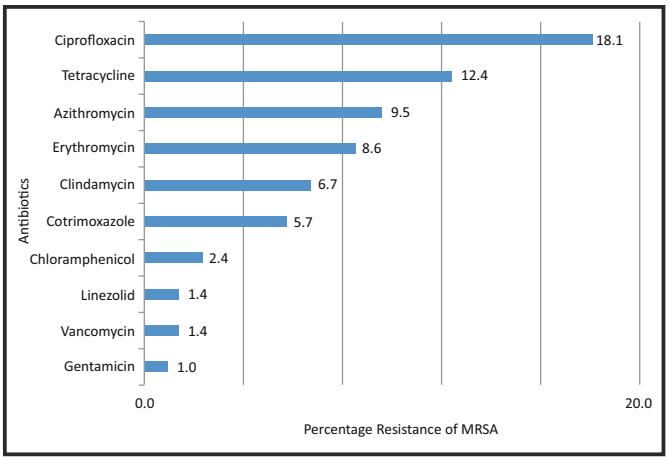

Figure 7. Cumulative percentage resistance of MRSA from year 2011 to 2015

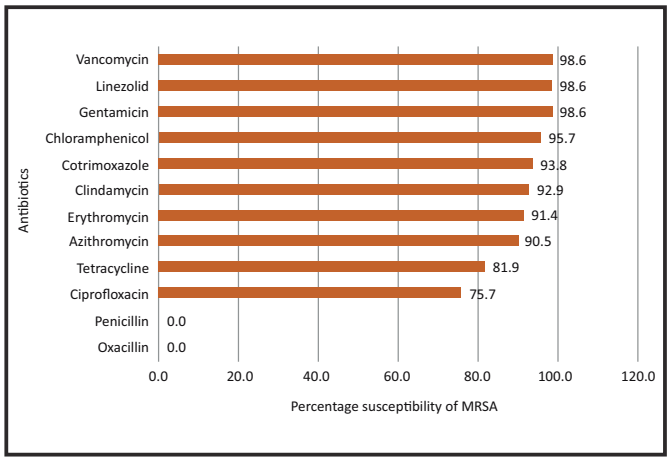

Figure 5. Cumulative Percentage susceptibility of MRSA from year 2011 to 2015

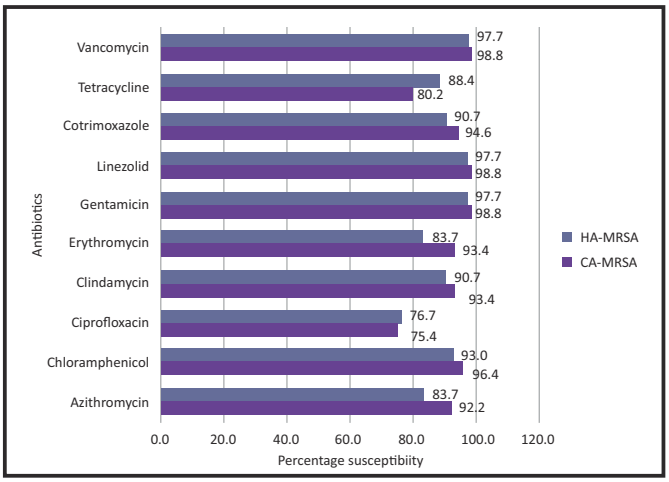

Figure 8. Comparison of the percentage susceptibility pattern between CA-MRSA and HA-MRSA

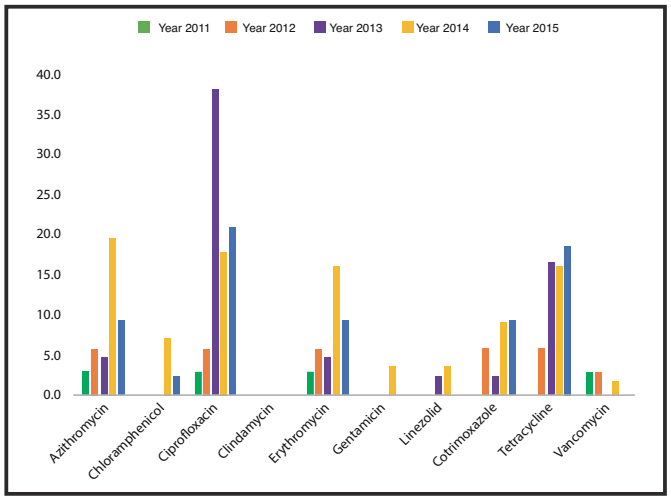

Figure 6. Yearly resistance of MRSA to the different antibiotics

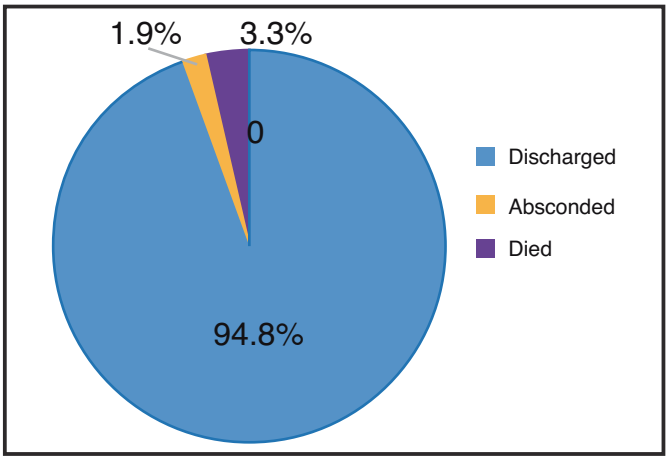

Figure 9. Clinical outcome distribution of patients with MRSA SSTI

Treatment Used

Different antibiotics were utilized as empiric treatment for SSTIs. Among the pediatric age group, oxacillin was the most commonly used (39.2%) followed by clindamycin (33.8%). In the adult group, clindamycin (38%) was predominantly used followed by ampicillin-sulbactam (19.5%), while patients in the geriatric age group were given clindamycin (49.1%) and ciprofloxacin (28.1%). After the result of culture isolates, the treatment shift to clindamycin (27.0%) was noted in the pediatric group. In the adult group, a treatment shift to clindamycin (26.0%) and vancomycin (10.0%) was observed while in the geriatric group, there were treatment shifts to clindamycin (24.6%), ciprofloxacin (17.5%), and vancomycin (10.5%).

Based on the type of MRSA, the most common drugs utilized for empiric treatment among patients with CA-MRSA include the following: clindamycin (31.7%), ciprofloxacin (11.2%), and ampicillin-sulbactam (10.0%). While HA-MRSA patients were empirically given mostly ampicillin-sulbactam (20.7%), ciprofloxacin (8.6%) and co-amoxiclav (8.6%). Patients with CA-MRSA had treatment shifts to clindamycin (17.3%) and vancomycin (5.6%) while those with HA-MRSA also had treatment shifts to clindamycin (15.5%) and vancomycin (15.5%).

In this study, 104 (49.3%) patients with MRSA SSTIs shifted to another treatment after the result of the culture isolates. Among the patients who shifted treatment, 72 (69.2%) had CA-MRSA while 32 (30.8%) had HA-MRSA.

Clinical Outcome

Figure 9 shows the clinical outcome of patients with MRSA SSTI. The majority of them were discharged improved (94.8%). Eight patients died (3.3%). Among those who died, six were HA-MRSA while two were CA-MRSA. Five patients had surgical site infection status such as post mastectomy, craniotomy, and ventriculoatrial shunt. One patient with abscess on the lower leg had multiple comorbidities such as immunocompromised state (SLE), DM, chronic kidney disease on hemodialysis, hypertension, and chronic obstructive pulmonary disease; one patient with furunculosis on the scalp had biliary liver disease; and one patient with Fournier's gangrene in the vulvar area had DM.

DISCUSSION

The findings from this study indicate that MRSA SSTI is rapidly emerging and increasing in number. The number of MRSA cases was 1.76 times the number of MSSA among the admitted patients with Staphylococcus aureus SSTI isolates. Over the five-year study period, there was also a yearly increase in the number of patients with MRSA. This trend is consistent with the findings from a study done in Cebu City where the prevalence of MRSA among patients increased from 16.9% in 2008 to 49.8% in 2010 with most of the culture isolates taken from SSTIs.[5] These data indicate that the number of MRSA SSTI is substantial and that its emergence may affect healthcare situations. Healthcare providers should be aware of this fact which can affect the formulation of proper diagnosis, management, and prevention plans.

The percentage of patients with CA-MRSA in this study was higher compared to the percentage of those with HA-MRSA, indicating that CA-MRSA is becoming a dominant pathogen even among hospitalized patients with SSTIs. This is similar to several studies which reported that a majority of MRSA SSTIs were due to community-associated MRSA. [4,6,7]. There were reports of CA-MRSA infections causing outbreaks in the hospital setting and findings of CA-MRSA in persons with healthcare-associated risk factors which further substantiate the changing pattern of this infection.[8] Although CA-MRSA and HA-MRSA may have a similar clinical presentation, they differ in genotypic, epidemiologic, and microbiologic characteristics.[9] The methicillin resistance of MRSA strains is mediated by PBP2a, an altered penicillin-binding protein.[10,11] PBP2a strengthens the cell wall and increases resistance to beta-lactam antibiotics by blocking the beta-lactam binding site. It is encoded by the mecA gene that permits the organism to grow and divide in the presence of methicillin and other beta-lactam antibiotics.[12] The mecA gene is located on a mobile genetic element called Staphylococcus chromosome cassette (SCCmec).[10] SCCmec elements type IV and V have been commonly identified among CA-MRSA strains. These account for the fact that CA-MRSA strains tend to be more resistant to antibiotics.[13] It also expresses a cytotoxic virulence factor, Panton-Valentine leukocidin, which is responsible for

increased severity and necrosis of skin infections. [13] These features can account for epidemic outbreaks that have been reported. CA-MRSA as an emerging dominant etiologic agent of SSTIs among hospitalized patients [14,15] should make clinicians be more cautious when dealing with SSTIs to avoid the spread of infection in a hospital setting to an epidemic proportion.

Demographic data in this study showed that MRSA affects all age groups indicating that MRSA is a formidable bacterium to be faced with by clinicians. This study also showed that the majority of patients with MRSA were adults. Adults and geriatric patients, in general, suffer from certain comorbidities such as diabetes mellitus and cardiovascular diseases, which can alter immune function and decrease tissue perfusion that subsequently favors the entry and proliferation of bacteria in the skin. Various studies [4,13,16] support this. In this study, male gender constantly accounted for the majority of admitted patients with MRSA SSTIs. A common finding of male predominance was seen in several studies.[4,17] On the other hand, a retrospective study done in the United States showed female predominance among patients with MRSA skin and soft tissue isolates.[16] The measures of association in this study indicated that gender and sex were not significant predisposing risk factors for MRSA infection.

Clinically, CA-MRSA and HA-MRSA are indistinguishable. This study showed that the abscess is the predominant clinical presentation for CA-MRSA and HA-MRSA. An abscess caused by Staphylococcus aureus commonly occurs in folliculocentric infections.[18] It can also occur at sites of trauma, foreign bodies, burns, or sites of insertion of intravenous catheters. From an erythematous nodule, it can evolve into a pus-filled cavity if left untreated.[18] It is wider in scope and a more general term used by many clinicians to diagnose conditions that contain purulent discharge. In the study by Cuaresma et al. in 2008, abscess was also reported to be the most common clinical presentation of CA-MRSA SSTIs.[4] Statistical analysis in this study showed that abscess was determined to be associated with CA-MRSA while having an infected wound was associated with HA-MRSA.

MRSA SSTIs can occur in different sites of the body. The reported predominant body site differs from one study to another. In this study, the most common site of involvement is the lower extremity, particularly the leg, followed by the head and the trunk. In a study by Cuaresma et al. infections were located most commonly in the lower extremities followed by the upper extremities, head and neck, and perineum.[4] This finding may be explained by the fact that the lower extremities are anatomically a body site more exposed and constantly subjected to trauma. A break into the protective barrier of the skin serves as a nidus for microbial invasion of the skin and soft tissue, thereby facilitating proliferation of infection.

Several factors have been found to be associated with a higher risk for acquisition of MRSA such as the presence of comorbidities. In this study, the most common comorbidities include diabetes mellitus (DM) and cardiovascular diseases. This is similar to a study by Cuaresma et al., which identified that among the comorbidities of patients with CA-MRSA, DM was the most common.[4] In a study by Dryden et al., it was revealed that complicated SSTIs were of particular concern in advanced DM and peripheral vascular disease because skin breakdown leading to ulceration in these patients provided a portal of entry for bacteria.[19] The altered immune function in patients with DM also leads to increased risk of SSTIs due to decreased response to the pathogens. Inadequate tissue perfusion leading to poor antibiotic penetration and again underlying immune defects contributed to the poor outcome of SSTI due to MRSA.[19] The development of MRSA may also be related to the severity or how advanced the DM is.[20] In patients with HA-MRSA, the predominant comorbidity was cardiovascular disease, probably because the geriatric patients had frequent hospitalization that could predispose them to be affected by HA-MRSA.

The presence of systemic involvement and complications of SSTIs such as osteomyelitis, MRSA bacteremia, compartment syndrome, pyomyositis, sepsis, Fournier's gangrene, and septic shock were noted among patients with MRSA. Complications are more commonly seen in CA-MRSA cases due to the virulence factor such as the Panton-Valentine leukocidin (PVL).[21] In a study by Tong, et al., PVL-positive MRSA strains were found to exert toxic effects on keratinocytes. After being taken up by the host cells, the PVL-positive strains are able to escape and induce keratinocyte apoptosis, facilitating local spread and inflammation. The presence of alpha-hemolysin has

also been associated with more severe cutaneous lesions because it appears to contribute to the penetration of keratinocytes in skin infection.[22]

Risk factors were identified to determine the probability of acquiring an MRSA infection. In this study, previous hospitalization and surgical procedures were associated with HA-MRSA based on the odds ratio of 3.6 and 3.2, respectively. However, previous antibiotic therapy was not a risk factor among patients with MRSA SSTIs in this study. A similar finding was noted in a study by Turabelidze, et al.[23] who stated that no significant risk factor in developing MRSA was noted in patients who had intake of antimicrobial drugs within three months. This is contrary to various studies that stated that prior antibiotic use is a risk factor for development of MRSA. [4,24,25,26] Other risk factors such as the medical device that passes through the skin and dialysis were least identified to be present among MRSA patients involved in the study. This is in contrast to the findings of CDC in 2005, wherein 5287 cases of invasive MRSA infection were reviewed and identified that 15.0% occurred in dialysis patients. [27] In another study done in the United States from 2005-2011, it was shown that there was a significant decrease in the incidence of invasive MRSA among dialysis patients.[28] This finding is similarly observed in the present study.

This study also showed the variation and constant changes in the antibiotic susceptibility and resistance pattern of MRSA. During the 5-year study period, a statistically significant change in susceptibility pattern was noted with the macrolides such as azithromycin and erythromycin; chloramphenicol and ciprofloxacin. The majority of the MRSA isolates were sensitive to the following antimicrobials namely, vancomycin, linezolid, gentamicin, chloramphenicol, co-trimoxazole, clindamycin, erythromycin, and azithromycin. However, there was a growing resistance noted to azithromycin, erythromycin, co-trimoxazole, ciprofloxacin, tetracycline, and even clindamycin. The highest resistance was observed with ciprofloxacin followed by tetracycline. In a study by Daum, it was stated that the use of certain antibiotics as empiric therapy should be avoided when MRSA resistance rates to them exceed 10.0% to 15.0%.[29] In view of the cumulative resistance rates of ciprofloxacin and tetracycline of 18.1% and 12.4%, respectively, it is prudent to avoid their use as empiric therapy when MRSA SSTI is being considered, but continuous monitoring of the possible change in MRSA susceptibility and resistance pattern to these drugs should be done. The finding of MRSA resistance, although of low percentage, observed with the use of vancomycin and linezolid is important because these are antibiotics that are being used currently as empiric treatment for patients at risk of MRSA infections. In the Philippines, a good guide for the susceptibility and resistance pattern to antibiotics is the 2015 Data Summary Report of the Department of Health Antibiotics Resistance Surveillance Program. [30] This data summary report showed a similar pattern as the present study although with a different degree in MRSA susceptibility and resistance. Higher resistance of MRSA to both ciprofloxacin and tetracycline and lower resistance to co-trimoxazole, erythromycin, clindamycin, linezolid, and vancomycin were observed in this study compared to the summary report in 2015.[30] In order to properly manage SSTIs, clinicians, therefore, should constantly keep track of the pattern of MRSA resistance and susceptibility in their own locality, especially to the antibiotics commonly used as empiric therapy. Proper selection of antibiotics to use or antibiotic stewardship will certainly prevent the emergence of resistant organisms.

The majority of patients in this study were discharged improved while a few cases led to death. Mortality happened in patients with surgical site infection, multiple comorbidities, immunocompromised state, and involvement of body sites such as the head and vulvar area, which were associated with moderate and severe SSTIs. In a study done by Tiwari and Lal, it was revealed that involvement of the head, genital areas, and hand, and the presence of gangrene were associated with increased morbidity and mortality.[20]

The information from this study is significant because when dealing with SSTIs, it is imperative that there is a prompt diagnosis based on the patient's clinical presentation and associated risk factors. Together with this, the correct choice of antibiotics as empiric and definitive therapy will lead to competent management of SSTIs, which will truly benefit the patients.

CONCLUSION

This study showed that the prevalence of MRSA SSTIs was increasing. Cases of MRSA were predominantly CA-MRSA affecting commonly males.

Across all age groups, those with MRSA SSTIs belonged mostly to the adult group. CA-MRSA cases were the most prevalent in the pediatric group while the occurrence of HA-MRSA increased with age.
The abscess was the most dominant clinical presentation of MRSA SSTIs and was significantly associated with all cases of CA-MRSA. It is also commonly seen among all age groups with HA-MRSA except for geriatric patients wherein the infected wound was a common presentation.

Overall, the leg was the most common site of MRSA SSTIs followed by the head and trunk. However, in pediatric patients with CA-MRSA, the head was the most common site.

DM and cardiovascular disease were the most common comorbidities. While in pediatric patients, the most common comorbidity among CA-MRSA was respiratory disorder.

Among patients with MRSA SSTIs, the most common complications were osteomyelitis and MRSA bacteremia.

Previous antibiotic therapy was the most common risk factor for MRSA followed by surgery/medical device infection. The presence of previous hospitalization and previous surgery increased the odds of patients with Staphylococcus aureus SSTI to be HA-MRSA by 3.6 and 3.2 times, respectively.

Based on the culture results, growing resistance to ciprofloxacin, tetracycline, macrolides, co-trimoxazole, and clindamycin was noted. Low rates of resistance were observed with vancomycin and linezolid.

Almost all of the cases improved with appropriate antibiotic therapy. Mortality cases were due to moderate to severe MRSA SSTIs.

Limitations of the Study

This is a retrospective study where the information is only limited to the data written in the records of the patients. The admitted patients who did not have a culture-proven SSTI and whose charts were unavailable for review or inaccessible were excluded. Hence, it is possible that the actual number of patients who presented with MRSA SSTIs may be higher than those reported in this study.

RECOMMENDATION

It would be ideal if a prospective study can be done which will be able to document the needed data more accurately and comprehensively. A more detailed history taking is necessary to identify all the possible risk factors and comorbidities associated with MRSA skin and soft tissue infection.

DISCLOSURE AND CONFLICT OF INTEREST

This study is investigator-initiated and not industry-funded or company-sponsored. There is no potential conflict of interest.

REFERENCES

1. McCaig LF, McDonald LC, Mandal S, Jernigan DB. Staphylococcus aureus–associated skin and soft tissue infections in ambulatory care. Emerging Infectious Diseases. 2006 Nov;12(11):1715.
2. Tattevin P, Schwartz BS, Graber CJ, Volinski J, Bhukhen A, Bhukhen A, et al. Concurrent epidemics of skin and soft tissue infection and bloodstream infection due to community-associated methicillin-resistant Staphylococcus aureus. Clinical Infectious Diseases. 2012 Jun 5;55(6):781-8.
3. Tinelli M, Monaco M, Vimercati M, Ceraminiello A, Pantosti A. Methicillin-susceptible Staphylococcus aureus in skin and soft tissue infections, Northern Italy. Emerging Infectious Diseases. 2009 Feb;15(2):250.
4. Cuaresma AL, FPCP MM, FPCP F. Socio-demographic Profile and Clinical Presentation of Inpatients with Community Acquired-Methicillin Resistant Staphylococcus aureus (CA-MRSA) Skin and Soft Tissue Infection at the University of Santo Tomas Hospital. Philippine Journal of Microbiology and Infectious Diseases. 2008 Jan;37(1).
5. Kho EH, Lim J. A retrospective study of the prevalence and sensitivity pattern of methicillin-resistant staphylococcus aureus in a Chong Hua Hospital, Cebu City, 2007-2010. Pediatric Infectious Disease Society of the Philippines Journal. 2013 Dec 1;14(2):85-93.
6. Frazee BW, Lynn J, Charlebois ED, Lambert L, Lowery D, Perdreau-Remington F. High prevalence of methicillin-resistant Staphylococcus aureus in emergency department skin and soft tissue infections. Annals of Emergency Medicine. 2005 Mar 1;45(3):311-20.
7. Song JH, Hsueh PR, Chung DR, Ko KS, Kang CI, Peck KR, et al. Spread of methicillin-resistant Staphylococcus aureus between the community and the hospitals in Asian countries: an ANSORP study. Journal of Antimicrobial Chemotherapy. 2011 Feb 20;66(5):1061-9.
8. Otter JA, French GL. Nosocomial transmission of community-associated methicillin-resistant Staphylococcus aureus: an emerging threat. The Lancet Infectious Diseases. 2006 Dec 1;6(12):753-5.
9. Johnson JK, Khoie T, Shurland S, Kreisel K, Stine OC, Roghmann MC. Skin and soft tissue infections caused by methicillin-resistant Staphylococcus aureus USA300 clone. Emerging Infectious Diseases. 2007 Aug;13(8):1195.
10. Peacock SJ, Paterson GK. Mechanisms of methicillin resistance in Staphylococcus aureus. Annual Review of Biochemistry. 2015 Jun 2;84.
11. Ontengco DC, Matias RR, Md CA, Tuazon EO. 1 Methicillin-resistant Staphylococcus aureus isolates from Filipino patients (1999-2003).
12. Farley JE. Epidemiology, clinical manifestations, and treatment options for skin and soft tissue infection caused by community-acquired methicillin-resistant Staphylococcus aureus. Journal of the American Academy of Nurse Practitioners. 2008 Feb;20(2):85-92.
13. Ho PL, Chuang SK, Choi YF, Lee RA, Lit AC, Ng TK, et al. Community-associated methicillin-resistant and methicillin-sensitive Staphylococcus aureus: skin and soft tissue infections in Hong Kong. Diagnostic microbiology and infectious disease. 2008 Jul 1;61(3):245-50.
14. Huang SS, Platt R. Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization. Clinical Infectious Diseases. 2003 Feb 1;36(3):281-5.
15. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant Staphylococcus aureus: a meta-analysis of prevalence and risk factors. Clinical Infectious Diseases. 2003 Jan 15;36(2):131-9.
16. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a US population: a retrospective population-based study. BMC Infectious Diseases. 2013 Dec;13(1):252.
17. Uy AM, Liza GM, Anna OL. The clinical and epidemiologic profile of community-associated methicillin-resistant Staphylococcus aureus infection among pediatric patients admitted at the Philippine General Hospital. Pediatric Infectious Disease Society of the Philippines Journal. 2011 Jan 1;12(1):2-10.
18. Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ. Fitzpatrick's Dermatology in General Medicine, 2 volumes. Transplantation. 2008;85(654).
19. Dryden M, Baguneid M, Eckmann C, Corman S, Stephens J, Solem C, et al. Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections. Clinical Microbiology and Infection. 2015 Sep 1;21:S27-32.
20. Tiwari AK, Lal R. Study to evaluate the role of severity stratification of skin and soft tissue infections (SSTIs) in formulating treatment strategies and predicting poor prognostic factors. International Journal of Surgery. 2014 Feb 1;12(2):125-33.
21. Skov R, Christiansen K, Dancer SJ, Daum RS, Dryden M, Huang YC, et al. Update on the prevention and control of community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA). International Journal of Antimicrobial Agents. 2012 Mar 1;39(3):193-200.
22. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clinical Microbiology Reviews. 2015 Jul 1;28(3):603-61.
23. Turabelidze G, Lin M, Wolkoff B, Dodson D, Gladbach S, Zhu BP. Personal hygiene and methicillin-resistant Staphylococcus aureus infection. Emerging Infectious Diseases. 2006 Mar;12(3):422.
24. Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG. The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA). Proceedings of the National Academy of Sciences. 2002 May 28;99(11):7687-92.
25. Boyce JM. Methicillin-resistant Staphylococcus aureus in hospitals and long-term care facilities: microbiology, epidemiology, and preventive measures. Infection Control & Hospital Epidemiology. 1992 Dec;13(12):725-37.
26. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community-and health care–associated methicillin-resistant Staphylococcus aureus infection. Jama. 2003 Dec 10;290(22):2976-84.
27. Centers for Disease Control and Prevention (CDC. Invasive methicillin-resistant Staphylococcus aureus infections among dialysis patients–United States, 2005. MMWR. Morbidity and Mortality Weekly Report. 2007 Mar 9;56(9):197.
28. Nguyen DB, Lessa FC, Belflower R, Mu Y, Wise M, Nadle J, et al. Invasive methicillin-resistant Staphylococcus aureus infections among patients on chronic dialysis in the United States, 2005–2011. Clinical Infectious Diseases. 2013 Aug 19;57(10):1393-400.
29. Daum RS. Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus. New England Journal of Medicine. 2007 Jul 26;357(4):380-90.

30. Research Institute for Tropical Medicine. Department of Health, Philippines. Antimicrobial Resistance Surveillance Program: 2015 Data Summary Report. 2015;84.