THE CLINICAL AND EPIDEMIOLOGIC PROFILE OF COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION AMONG PEDIATRIC PATIENTS ADMITTED AT THE PHILIPPINE GENERAL HOSPITAL

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ABSTRACT
Background: Several studies have reported increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection among patients with no predisposing factors. This paper aims to determine the clinical and epidemiologic profile of community-associated MRSA (CA-MRSA) infection among children admitted at UP-PGH.
Methodology: A retrospective review of the medical records of patients 0-to-18 years old with *S. aureus* isolate admitted at University of the Philippines-Philippine General Hospital (UP PGH) from January 1, 2007 to December 31, 2008 was conducted. *S. aureus* isolates were classified as methicillin-susceptible *S. aureus* (MSSA), CA-MRSA or healthcare-associated MRSA (HA-MRSA). Risk factors for MRSA acquisition were identified. Demographic data, site of infection, outcome, and antibiotic susceptibility patterns were compared.
Results: *S. aureus* was isolated in 382 children. Medical records of 219 (57.33%) patients were available for review. Of the 219 patients, 40.64% had MSSA, 15.07% had CA-MRSA, and 44.3% had HA-MRSA isolates. The prevalence of CA-MRSA is seven per 1000 admissions. There was no statistical difference between the age, sex, outcome and the site of infection among the three groups. The most common source of isolates was exudates, followed by blood. There were statistically significant differences in the resistance patterns of S. *aureus* isolates, with MSSA and CA-MRSA having lower resistance rates (<10%) as compared to HA-MRSA (>40%) and non-beta lactam antibiotics such as tetracycline, clindamycin, cotrimoxazole, gentamicin and vancomycin.
Conclusion: This study showed that MRSA infection is no longer limited to patients with predisposing factors. The type of *S. aureus* infection cannot be predicted based on clinical and demographic profile of patients. Based on the susceptibility patterns in this study, CA-MRSA may be treated with tetracycline, clindamycin, cotrimoxazole, gentamicin and vancomycin.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a widely accepted nosocomial pathogen. It was initially thought to occur exclusively in the hospital environment. However, in the 1970s, reported cases of community-acquired MRSA infection among adults emerged. Studies showed that these infections, though acquired in the community, were healthcare associated. Patients tended to be chronically ill, and many have histories of nursing home residence, recent admission to acute or chronic health care facilities, previous intake of antibiotics and abuse of intravenous drugs. Hence, in such cases, infections were usually traceable to the hospital setting.

In the 1980s, cases of community-associated MRSA were reported in children without predisposing conditions. In the 1990s, these infections were noted to be higher in some areas of the world.

Several studies have reported increasing prevalence of CA-MRSA infection among patients with no predisposing factors. A study conducted by Herold, et al in the University of Chicago found that the prevalence of CA-MRSA in pediatric patients without risk factors increased from 10 per 100,000 admissions between 1988 to 1990 to 259 per 100,000 admissions between 1993-1995.[1] Another study conducted among children in Southern New England reported that the proportion of *S. aureus* cases attributable to MRSA has steadily increased over the five-year study period. Only thirty-five percent of patients with CA-MRSA had identifiable risk factors. Similar findings were reported by a study conducted in Taiwan where 35% of CA-MRSA was isolated from patients without predisposing risk factors.[2,3] Such reports of an increase in the prevalence of CA-MRSA infection among patients without risk factors were not reflected in all areas. In Singapore, CA-MRSA infection was found to be usually healthcare-associated.[4]

In our local setting, a study conducted in the Philippine General Hospital, which covers the period from January 1999 to September 2001, showed that MRSA comprised 37.5% of *S. aureus* cases. These infections were noted to be highly associated with predisposing risk factors such as previous antibiotic therapy, admission to intensive care unit and burn unit, presence of indwelling catheter and history of previous hospitalization.[5] A study on CA-MRSA in children conducted at the Philippine Children's Medical Center (PCMC) showed an increasing trend of *S. aureus* and MRSA infections over the ten-year study period (from 1991 to 2001).[6] Another study conducted at PCMC from 2004 to 2006 showed that among community acquired *S. aureus* infections, MRSA comprises about 57% of the staphylococcus isolates; No risk factor was found in 52.6% of these patients.[7]

A meta-analysis of the prevalence and risk factors of CA-MRSA was conducted by Salgado, et al, which covers the period from January 1966 to February 2002. The study included 27 retrospective studies and reported a pooled CA-MRSA prevalence of 30.2%; 86.1% of the patients have ≥1 healthcare-associated risk factor. The pooled CA-MRSA prevalence among 636 patients from five prospective studies was 37.3%; 86.9% of the patients have ≥1 healthcare-associated risk factor. This suggested that the prevalence of MRSA among persons without the typical risk factors remains relatively low (≤0.24%) and that most MRSA colonization and infection develops among those who have healthcare-associated risk factors or contact with other persons who have such risks.[8]

In PGH, suspected *S. aureus* infections are being treated empirically with semisynthetic penicillinase resistant penicillin. However, it is recommended that in areas where CA-MRSA has been isolated from children without identified risk factors, severe and life threatening infections suspected to be caused

by *S. aureus* should be treated empirically with nafcillin plus vancomycin.[9] If the observation that CA-MRSA infections in children without predisposing factors is increasing in some areas of the world is likewise documented in our local setting, then there is a need to re-evaluate empiric antibiotic therapy for patients suspected of having *S. aureus* infection in PGH. This paper aims to establish the prevalence of CA-MRSA infection in children admitted at PGH and to describe the clinical profile of patients with MRSA infections in order to give the clinician clues on the probability of MRSA infection and, thus, enable them to prescribe early institution of appropriate therapy.

MATERIALS AND METHODS

This study is a retrospective review of the medical records of patients at the Philippine General Hospital who are zero-to-18 years old and have *S. aureus* infection. Logbooks from the microbiology laboratory of the UP-PGH from January 1, 2007 to December 31, 2008 were reviewed and all culture results with *S. aureus* from any site were included. Laboratory identification of MRSA was based on the Performance Standards for Antimicrobial Susceptibility Testing of the Clinical and Laboratory Standards Institute.[10] MRSA are *S. aureus* isolates resistant to oxacillin and cefoxitin on disk diffusion method. Only *S. aureus* with borderline sensitivities were subjected to E-test to determine if these isolates are MRSA.

The medical records of all patients zero-to-18 years old with positive *S. aureus* isolates admitted at UP-PGH were retrieved from the Section of Medical Records for review. Only isolates whose charts were retrieved were included in the data analysis. Data extracted from the medical records included the following: age, sex, address, disposition (discharged/ mortality, culture site, antibiotic susceptibility, underlying chronic disorder/ underlying illness, and risk factors for MRSA infection (medical history in the past year of: Hospitalization, Dialysis, Surgery, Permanent indwelling catheters or medical devices that pass through the skin and into the body, MRSA infection or colonization and Antimicrobial therapy).

Patients were classified as having MSSA, CA-MRSA, or HA-MRSA infection. The definition of the Centers for Disease Control and Prevention of CA-MRSA and HA-MRSA will be used for the purpose of this study.[11]

Methicillin-susceptible *staphylococcus aureus* (MSSA) - *S. aureus* isolates susceptible to oxacillin and cefoxitin.

HA-MRSA - MRSA isolated with any of the following criteria:

1. Organism isolated >48 hours after admission to the hospital;
2. Medical history in the past year of: Hospitalization, Dialysis, Surgery, Permanent indwelling catheters or medical devices that pass through the skin into the body, MRSA infection or colonization, Antimicrobial therapy;

CA-MRSA - MRSA isolated within 48 hours after hospital admission for a patient lacking established HA-MRSA risk factors.

Statistical Analysis

Prevalence of CA-MRSA was computed from the total number of CA-MRSA cases per year over the total number of admission per year. Percentage of CA-MRSA is the total number of CA-MRSA over the total number of *S. aureus* cases per year. Percentage of HA-MRSA is the total number of HA-MRSA over the total number of *S. aureus* cases per year.

The presence or absence of a predisposing factor was determined. Analysis of variance (ANOVA) was used to compare quantitative variables. Chi square test was used to compare proportions of the attributes of interest among the groups. Fischer's exact test was used if sample size is too small for chi square test.

The protocol was approved by the Departmental Technical Reviewer for ethical

clearance and the Ethical review board of the Philippine General Hospital.

RESULTS

From January 1, 2007 to December 31, 2008, there were a total of 382 patients with *S. aureus* isolates among children admitted at UP-PGH. Of these isolates, 155 (40.60%) were MSSA and 227 (59.40%) were MRSA.

Medical records of 219 (57.33%) patients were available for review. Of the 219 patients with *S. aureus* isolates, 89 (40.64%) patients had MSSA, 33 patients (15.07%) had CA-MRSA and 97 (44.3%) had HA-MRSA isolates.

The total number of *S. aureus* infection remained relatively constant over the two-year study period (Figure 1).

The Department of Pediatrics of PGH had a total admission of 2,307 patients and 2167 patients for years 2007 and 2008, respectively. For the two-year study period, the prevalence of CA-MRSA was 7 per 1000 admissions.

There was no statistical difference between the ages, sex, location of residence and outcome of patients infected with MSSA, CA-MRSA or HA-MRSA. Patients with CA-MRSA infection had a significantly lower incidence of an underlying medical condition as compared to patients with MSSA and HA-MRSA (Table 1). *S. aureus* infection was most commonly seen in patients less than one year old (Table 2).

Majority of patients with MSSA (27%) and CA-MRSA (54.5%) where isolated from patients admitted at the emergency department of PGH. Patients with HA-MRSA are most commonly seen at the burn unit (Table 3).

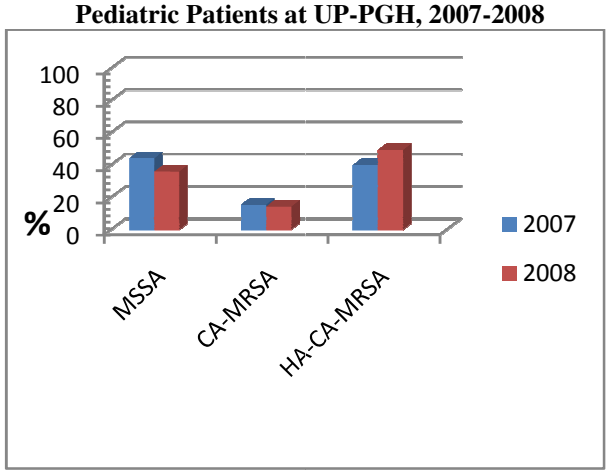
The presence of risk factors was identified in 35.96% of patients with MSSA and 47.42% of those with HA-MRSA. The most common risk factors identified among patients with *S. aureus isolates* (MSSA and HA-MRSA) infection were a history of previous hospitalization, followed by antibiotic intake (Table 4).

Table 1. Demographic and Clinical Profile of Pediatric Patients with MSSA, CA-MRSA and HA-MRSA infection.

	MSSA n=89	CA-MRSA n=33	HA-MRSA n=97	p-value
Age (yrs) Mean SD Range	 6.19 6.17 0.003 – 18	 5.98 5.55 0.011 - 17	 5.45 6.12 0.003 –18	0.694
Sex (Male, %)	49(55%)	24 (73%)	57(59%)	0.218
Location of Residence NCR*	48%	45.55%	48%	0.966
Disposition Discharged Mortality LAMA**	 72(81%) 11(12%) 6 (7%)	 24 (72%) 7 (21%) 2 (6%)	 83 (86%) 12 (12%) 2 (2%)	0.287
Underlying chronic illness	26(29%)	3 (9%)	41 (42%)	0.001

*NCR- National Capital Region
** LAMA- Left against medical advice

Figure 1: Proportion of *S. Aureus* isolates among Pediatric Patients at UP-PGH, 2007-2008



***S. aureus* isolates**

Table 2. Distribution of Patients according to Age Groups.

Age group	MSSA	CA-MRSA	HA-MRSA	Total
0-1	39.33%	36.36%	48.45%	42.92%
1-5	14.61%	15.15%	13.4%	14.16%
5-12	24.72%	33.33%	19.59%	23.74%
>12	21.35%	15.15%	18.56%	19.18%

Table 3. Distribution of Patients According to Area Admitted.

Area	MSSA	CA-MRSA	HA-MRSA
Pediatrics Ward 9	14 (16%)	0	14 (14%)
Pediatrics Ward 11	21 (24%)	9 (27%)	19 (20%)
Orthopedics Ward	11 (12%)	3 (9%)	12 (12%)
Trauma ward	1 (1%)	0	3 (3%)
PICU	3 (3%)	3 (9%)	1 (1%)
NICU	8 (9%)	0	6 (6%)
ER	24 (27%)	18 (54%)	13 (13%)
Burn Unit	4 (4%)	0	26 (27%)
Surgery Ward	3(3%)	0	3 (3%)

Table 4. Distribution of Risk Factors.

Risk Factors	MSSA	HA-MRSA
Hospitalization	28 (31%)	42 (43%)
Dialysis	3 (3%)	1(1%)
Surgery	2 (2%)	12 (12%)
Permanent indwelling catheters / device	8 (9%)	4 (4%)
MRSA infection or colonization	0	1 (1%)
Antimicrobial therapy	19 (21%)	36 (37%)

Table 5. Distribution of risk factors among patients with HA-MRSA isolated less than 48 hours and those isolated within 48 hours of admission.

Risk factors	HA-MRSA (>48 hrs) N=72	HA-MRSA (≤48 hrs) n=25
Hospitalization	18 (25%)	24 (96%)
Dialysis	0	1 (4%)
Surgery	3 (4.17%)	9 (36%)
Indwelling catheters/ device	3 (4.17%)	1 (4%)
MRSA infect. or colonization	0	1 (4%)
Antimicrobial therapy	16 (22.22%)	20 (80%)

Table 6. Sources of MSSA, CA-MRSA and HA-MRSA Isolates.

Culture Site	**MSSA**	**CA-MRSA**	**HA-MRSA**
Blood	35 (39%)	12 (36%)	32 (33%)
Wound (Exudates)	40 (45%)	19 (58%)	36 (37%)
Pleural Fluid	1 (1%)	2 (6%)	1 (1%)
Peritoneal fluid	1(1%)	0	3 (3%)
Tissue	10 (11%)	0	22 (23%)
Bone	2 (2%)	0	2 (2%)
CSF	0	0	1(1%)

Table 7: Percent Resistance of *S. aureus* isolates

Antibiotics	N	MSSA	CA-MRSA	HA-MRSA	P value
Pen G	216	94	100	100	0.024
Oxacillin	217	6	100	100	<0.001
Erythromycin	211	6	3	53	<0.001
Tetracycline	153	3	0	41	<0.001
Clindamycin	208	5	0	48	<0.001
Chloramphenicol	149	0	0	13	0.003
Vancomycin	204	0	0	0	NT
Cotrimoxazole	182	0	7	49	<0.001
Gentamicin	187	3	0	47	<0.001
Moxifloxacin	75	3	0	25	0.005
Tigecycline	18	0	0	0	NT
Linezolid	3	0	NT	0	NT
Ciprofloxacin	8	0	0	40	0.345
Ertapenem	15	0	33	25	0.543
Clarithromycin	1	NT	100	NT	NT

NT – not tested

Table 5 shows the distribution of risk factors for HA-MRSA isolated ≤48 hrs and those isolated > 48 hrs.

The distribution of patients by site of infection is similar among the three groups. Exudates were the most common source of isolates followed by blood (Table 6).

There were statistically significant differences in the resistance rates between MSSA, CA-MRSA and HA-MRSA isolates. Except for penicillin and oxacillin, both MSSA and CA-MRSA were associated with lower resistance rates to different antibiotics (<10%) while HA-MRSA was associated with high resistance rate

of >40% to erythromycin, tetracycline, clindamycin, cotrimoxazole and gentamicin (Table 7).

Table 8. Percent Resistance of HA-MRSA isolated <48 hrs and >48 hour from admission

Antibiotics	N	HA-MRSA (> 48 hrs)	HA–MRSA (≤48 hrs)
Pen G	97	100	100
Oxacillin	97	100	100
Erythromycin	94	61.43	29.17
Tetracycline	69	48.15	13.33
Clindamycin	92	55.88	25
Chloramphenicol	63	14.89	6.25
Vancomycin	94	0	0
Cotrimoxazole	82	60	5.88
Gentamicin	80	59.65	17.39
Moxifloxacin	28	30	12.50
Tigecycline	10	0	0
Linezolid	1	0	NT
Ciprofloxacin	5	50	0
Ertapenem	8	33.33	0

NT – Not tested

The resistance pattern of HA-MRSA distributed according to time of isolation from admission showed that HA-MRSA isolated within 48 hours of admission had a lower resistance pattern as compared to HA-MRSA isolated more than 48 hours after admission (Table 8).

DISCUSSION

Several studies were already done on CA-MRSA infections in different areas of the world. However, there are few local studies done in our setting. One difficulty encountered in interpreting the results of these studies was the different definitions for CA-MRSA that were used. In this study, in using the CDC definition to define CA-MRSA infection, we found CA-MRSA to comprise 15% of all *S. aureus* isolates. This proportion only includes MRSA isolated in patient without any of the risk factors traditionally associated with MRSA acquisition. Data is lacking as to what specific MRSA prevalence rate can be considered significant to indicate that a problem of CA-MRSA exist in a community and may warrant a change in the empiric therapy for suspected *S. aureus* infection. A prevalence of >10% to 15% of CA-MRSA in the community has been suggested by some reports.[12, 13]

The MRSA proportion of 59% in this study was higher than the 37.5% reported by Mamauag-Estrada, et al for the year 1999 to 2001 in PGH.[5] The prevalence of 7 per 1,000 admitted patients for CA-MRSA in this study is also considerably higher than the reported prevalence of 259 per 100,000 admission by Herold, et al in 1998.[1] In this study, due to the lack of data on the exact number of pediatric patients admitted at the other wards outside of the pediatric wards, the computation of prevalence was based only on admissions to the pediatric wards. This may be a factor which could have contributed to the higher prevalence.

The demographic profile of patients infected with MSSA, CA-MRSA and HA-MRSA in terms of age, sex, location of residence and outcome is similar in the three groups. In the study done in PGH in 2001, age and sex also did not differ among patient infected with MSSA and MRSA but mortality was significantly higher among patients with MRSA infection as compared with MSSA.[5] *S .aureus* infections (MSSA, CA-MRSA, and HA-MRSA) were most commonly seen among patients less than one year old which is consistent with the observation in the study by Manahan-Soriano, et al conducted at PCMC.[6] Proper care in the handling of these infants should be done as they can be considered high risk for the acquisition of *S. aureus* infection.

The different risk factors associated with acquisition of HA-MRSA infection are also present among patients with MSSA infection. The clinical syndromes caused by MSSA, CA-MRSA and HA-MRSA are likewise similar with abscess and blood, which are the predominant sources of the isolates. This information highlights the important fact that the *S. aureus*

infection cannot be predicted based on the clinical and demographic profile of patients.

The optimal strategies for the management of CA-MRSA infections have not been established. Approach to the management of these infections varies and is based on local epidemiologic and susceptibility data. The patterns of antibiotic susceptibilities/resistance of these organisms are important in the selection of antimicrobial agents for the proper management of these patients. This varies in different areas and location of isolation. For non-life threatening infections suspected to be due to *S. aureus*, antistaphylococcal penicillins and cephalosporins are the empirical agents of choice in areas where rates of methicillin resistance are low. In populations where more than 10% to 15% of community isolates of *S. aureus* are methicillin-resistant, adding a non-beta-lactam antistaphylococcal antibiotic pending culture results may be considered.[12,13]

In this study, the proportion of CA-MRSA isolates in the two-year study period ranges from 14.5% to 15.5%. Therefore, clinicians should have a high index of suspicion for the occurrence of CA-MRSA as a possible etiologic agent when *S. aureus* infection is suspected. Depending on the clinical condition of the patient, addition of an antibiotic with coverage for MRSA to the initial empiric treatment may be warranted.

There are limited studies done on the treatment of MRSA infection in pediatric patients. Various agents, including clindamycin, cotrimoxazole, vancomycin, linezolid, tetracyclines (doxycycline and minocycline), and tigecycline are antibiotics that have been recommended by several authors for the treatment of MRSA infection.[13-16] The recommended empiric treatment for severe, life threatening infections suspected to be caused by *S. aureus* in areas where CA-MRSA has been isolated from children without identified risk factors is nafcillin plus vancomycin. The addition of gentamicin may be considered for synergistic purpose. For mild to moderate infections caused by MRSA, empirical treatment may include antibiotics such as clindamycin or cotrimoxazole. Doxycycline and minocycline are alternative agents for children older than eight years old.[9, 13]

Based on this study, CA-MRSA isolates among pediatric patients at UP-PGH are susceptible to antibiotics such as clindamycin, gentamicin, cotrimoxazole, tetracycline and vancomycin. Among those with HA-MRSA, it is also interesting to note that the proportion of patients with MRSA isolated within 48 hours of admission had lower resistance rates to these antibiotics than those isolated more than 48 hours after admission. This would imply that for patients suspected of having MRSA within 48 hours of admission, the isolates may be susceptible to antibiotics such as tetracycline (Doxycycline and minocycline), clindamycin, cotrimoxazole, gentamicin and vancomycin. However, it is important to note that the tetracyclines (Doxycycline and minocycline) can only be used for children eight years old and above. For suspected HA-MRSA infection after 48 hours of admission, vancomycin is the recommended treatment because of the high resistance rates exhibited by these isolates to other antimicrobial agents.

Limitation of the Study

This study has the inherent limitations of a retrospective study design. There was only 53% chart retrieval rate. Only isolates whose charts were retrieved were included in the data analysis. Hence, data in this study are, at best, estimates of the true values of the data of interest. Furthermore, it would be difficult to determine whether the isolates were clinically significant pathogens and whether proper aseptic technique was used in the collection of specimens. To establish the optimal regimen in the management of MRSA infection, data are needed from clinical and efficacy trials.

CONCLUSIONS

Physicians at PGH handling pediatric patients should have a high index of suspicion for the

presence of MRSA infection in patients suspected to have *S .aureus* infection. This study showed that MRSA infection is no longer limited to patients with the risk factors traditionally associated with MRSA acquisition. The clinical spectrum of patients with MRSA is similar to that of MSSA. Furthermore, MRSA infection cannot be predicted based on clinical and epidemiologic characteristics.

For mild infections, unresponsiveness to antistaphylococcal penicillins and cephalosporins should prompt shifting to antibiotics with MRSA coverage. For moderate to severe infections, coverage for both MSSA and MRSA should be included in the empiric treatment. Based on the susceptibility pattern seen in this study, clindamycin, cotrimoxazole, gentamicin, vancomycin, and the tetracyclines; doxycycline and minocycline are agents which may be used in the empirical treatment of patients suspected to have CA-MRSA. With the exception of vancomycin, patients with HA-MRSA isolated after 48 hours of admission showed a high resistance rates to these antimicrobials. Once an organism is isolated, therapy should be modified based on the susceptibility patterns of the isolate.

RECOMMENDATIONS

Based on the result of the current study, physicians caring for pediatric patients are encouraged to collect specimens for culture when *S. aureus* infection is suspected. Because of the high rate of MRSA among pediatric patients in PGH, it would be useful to develop practice guidelines for the management of patients suspected to have *S. aureus* infection. It is recommended that initial empiric treatment of patient suspected of having *S. aureus* infection be re-evaluated after 48 hours of therapy. A poor response should prompt the physician to give treatment which will include coverage of MRSA. It is also recommended that clinical trials be conducted to determine appropriate treatment regimen for MRSA infection. Finally, it is recommended that a prospective study be conducted in PGH to determine changes in the prevalence and antibiotic susceptibility of MRSA. A prospective multicenter study would further establish the magnitude the problem of MRSA infection in the Philippines.

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