

## METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AMONG PEDIATRIC PATIENTS AT THE PHILIPPINE GENERAL HOSPITAL

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### ABSTRACT

**Objective:** This study aims to identify clinical risk factors associated with Methicillin-resistant *Staphylococcus aureus* (MRSA) infection among pediatric patients admitted at the Philippine General Hospital and their outcome.

**Study design:** Retrospective review of medical records

**Methodology:** All hospitalized pediatric patients with culture-proven *Staphylococcus aureus* (both methicillin-resistant and methicillin-sensitive) isolates from specimens such as blood, tissues, and body fluids reported by the Bacteriology Section of Central Laboratory of the Philippine General Hospital (PGH) from January 1999 to September 2001 were included. A systematic review of the medical records of these patients were done and the following data were recorded: 1) demographic profile, 2) clinical risk factors, and their 3) outcome. Risk factor data were analyzed using the relative risk at 95% confidence interval. Difference in proportion between groups [MRSA versus those with methicillin-sensitive *S. aureus* (MSSA)] was analyzed using chi-square test. A probability (p) value of <0.05 was considered statistically significant. Epi Info (1996) statistical software was used on all statistical tests.

**Results:** Out of 160 *S. aureus* infection cases reported, 60 were methicillin-resistant (prevalence rate of 37.5%). Out of these 160 cases, 69 charts (43% retrieval rate) were reviewed. Of these 69 charts, 31 patients had MRSA while 38 patients had MSSA infection. The demographics of the MRSA group were not significantly different from those with MSSA group. The following risk factors showed statistically significant correlation with MRSA infection: 1) presence of co-morbidities {RR=2.29 (1.27, 4.12) p-value <0.01}, 2) admission to intensive care or burn units {RR=3.27 (1.83, 5.82) p-value <0.01}, 3) previous antibiotic therapy {RR=4.24 (1.85, 9.74) p-value <0.01}, 4) previous hospitalization {RR=1.77 (1.09, 2.88) p-value <0.05}, 5) presence of surgical wound/burn wound {RR=2.77 (1.67, 4.60) p-value <0.01}, and 6) presence of 3 or more indwelling devices {RR=4.05 (1.90, 8.62) p-value <0.01}. Mortality rate was significantly higher in the MRSA group (13/31 or 42%) than the MSSA group (6/38 or 16%) {RR=1.90 (1.18, 3.07) p-value <0.05}.

**Conclusion:** Clinical risk factors found to be highly associated with MRSA infection were the following: 1) presence of co-morbid illnesses, 2) admission to intensive care or burn units, 3) previous antibiotic therapy, 4) previous hospitalization, 5) presence of surgical wound/burn wound, 6) presence of 3 or more indwelling devices. Mortality rate is high among patients with MRSA infection.

### INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is a exceedingly serious problem that is frequently unrecognized or overlooked. Only few investigators to date have tried to determine its true incidence and prevalence. The first of which was in 1968 at Boston City Hospital, USA where the first isolation of MRSA from 18 patients were recorded. The incidence of MRSA among all *Staphylococcus aureus* isolates at that institution was reported to be 1.4%. In a report by Panlilio, et al., in U.S. hospitals, MRSA infections increased in prevalence from 2.4% to 29% from 1975 to 1991.<sup>4</sup>

In the Philippines, information on MRSA was unreported until in 1987 when Navarro-Almarino, et al., did a review of antibiotic susceptibility pattern of *Staphylococcus aureus* at the Philippine General Hospital (PGH). In this study, 213 oxacillin disc-resistant isolates and minimum inhibitory concentration of 126 isolates showed that only 2.3% were truly resistant.<sup>2</sup>

Since then no subsequent studies were done until in 1997 when We and Pineda made a preliminary study on MRSA at the PGH where they reported a prevalence rate of 25% during the first quarter of 1996.<sup>3</sup>

Infections caused by MRSA can be community-acquired (CA) or nosocomially-acquired (NA). Community-acquired infections have been described less frequently and most of which involve adult patients.<sup>4</sup>

Many risk factors have been implicated. In children, known risk factors for MRSA infection include hospitalization in ICUs, severe underlying illness, prolonged hospital stays, invasive procedures, indwelling catheters, endotracheal tubes and prolonged or recurrent exposure to antibiotics.<sup>5</sup>

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Keywords: MRSA infection

It is also interesting to note that even with no known risk factors, Herold, et al., reported an increase in community-acquired MRSA infection in patients admitted at the University of Chicago Children's Hospital from 10 per 100,000 admissions in 1988 through 1990 to 259 per 100,000 admissions in 1993 through 1995.<sup>6</sup>

Most of the data regarding the epidemiology and clinical outcome of patients with MRSA infection were either limited or non-existent. This study was therefore conducted to describe the clinical profile, to identify clinical risk factors associated with MRSA infection, and to determine the clinical outcome of patients with MRSA infection among pediatric patients admitted at the Philippine General Hospital. Such information is deemed necessary to initiate proper methods for rapid and accurate diagnosis, to rapidly implement appropriate empiric and definitive treatment regimens, and for planning an effective infection control strategy to stop the spread of this potentially fatal disease.

## OBJECTIVES

This study aims to describe the clinical profile, identify clinical risk factors and determine the clinical outcome of pediatric patients with MRSA infection admitted at the Philippine General Hospital.

## METHODOLOGY

This is a retrospective study of pediatric patients with culture-proven *Staphylococcus aureus* (both methicillin-resistant and methicillin-sensitive) isolates from specimens such as blood, tissues and body fluids reported by the Bacteriology Section of Central Laboratory of the Philippine General Hospital covering the period of January 1999 September 2001. The medical records of the corresponding patients were reviewed using a standardized collection form.

Each of the medical records were studied as were studied as to the patient's demographic profile which included the patient's age and sex. The presence of underlying disease/co-morbid illnesses such as malignancy, diabetes mellitus, renal disease, heart disease, liver disease, gastrointestinal disease, pulmonary disease, prematurity, glucocorticoid therapy, central nervous system disease, etc, were also reviewed.

Risk factors which were reported in various literature to be associated with MRSA infection were analyzed.

These included the following:<sup>5</sup> 1) admission to intensive care unit or burn unit, 2) previous antibiotic therapy (antibiotics taken within 60 days preceding the

infection), previous hospitalization (when there is a history of hospitalization one month prior to admission in PGH or prior to the onset of infection), 3) presence of 3 or more indwelling devices (vascular, urinary catheters, ventriculoperitoneal shunt devices, etc.), 4) presence of a surgical wound/burn wound. Patient outcome was also analyzed.

Data were analyzed using the relative risk ratio at 95% confidence interval. Difference in proportion between groups (those with MRSA versus those with MSSA) were analyzed using the chi-square test. A probability (p) value of <0.05 was considered statistically significant. Epi Info (1996) statistical software was used.

## RESULTS

During the period of January 1999 to September 2001, 160 cases of *Staphylococcus aureus* isolates from different specimens such as blood, CSF, tissues, and devices, were identified by the Bacteriology Section of Central Laboratory of the Philippine General Hospital. The prevalence rate of MRSA during this period is 37.5% (60 out of 160 isolates were MRSA). Sixty-nine medical records were reviewed (43% retrieval rate). The demographics, clinical risk factors and outcome of all included patients, and the corresponding data analysis were outlined in tables 1, 2, 3, 4, and 5 respectively.

Of the 69 medical records reviewed, 31 had MRSA infection while 38 had MSSA infection. The data on demographic information is seen in Table 1. Twenty-six out of 31 (84%) children with MRSA infection belong to the younger child age group (0-5 years old) while only 5 out of 31 (16%) were in the older child age group (>5 years old). Twenty-four out of 38 (63%) children with MSSA belong to the 0-5 age group while 14 out of 38 (37%) were in the more than 5 year age group. The age of the patients between the 2 groups was not statistically significant {RR= 1.98 95% confidence interval (0.89, 4.39) p-value of 0.55} (see Table 5).

When patient sex was reviewed (Table 1), 19 out of 31 (61%) MRSA patients were males while 12 out of 31 (39%) were females. Among MSSA patients, 26 out of 38 (68%) were males while 12 out of 38 patients were females (32%). There was no statistical difference between male and female sex in acquiring MRSA or MSSA infections {RR=0.84 (0.50, 1.43) p-value 0.54} (see Table5).

The presence of underlying diseases/co-morbid illnesses was analyzed. Table 2 shows that 21 out of 31 (68%) patients with MRSA infection were found to have co-morbid illnesses while 10 out of 31 (32%) did not have

an underlying disease. Highest occurrences of co-morbidities were as follows: prematurity ~ 9 cases (29%), CNS disease ~ 4 (13%), malignancy ~ 3 (10%). With regard to MSSA infection, only 12 out of 38 patients (32%) had co-morbid illnesses while 26 out of 38 (68%) did not have any underlying disease. The presence of underlying diseases/co-morbid illnesses has a significant association with the acquisition of MRSA infection {RR=2.29 (1.27, 4.12) p-value <0.01} (Table 5).

Characteristics of patients with MRSA and MSSA infections were determined (Table 3). Twenty-six out of 31 (84%) patients with MRSA infection had a history of antibiotic intake prior to the onset of infection while 5 out of 31 (16%) did not have a previous antibiotic therapy. As for MSSA infection, 12 out of 38 patients (32%) had a history of prior antibiotic therapy while 26 out of 38 (68%) had taken antibiotics prior to the onset of infection. Previous antibiotic therapy was found to have a highly significant correlation with acquiring MRSA infection {RR=4.24 (1.85, 9.74) p-value <0.01} (Table 5).

Admission to intensive care unit, burn unit, and wards was reviewed (Table 3). Twenty-one out of 31 (68%) patients with MRSA infection were found to have been admitted to the intensive care (Pediatric ICU, Neonatology ICU) and burn units while 10 out of 31 (32%) MSSA patients had been admitted to regular pediatric wards. Only 6 out of 38 (16%) patients with MSSA had been admitted to the PICU, NICU, and burn units while 32 out of 38 (84%) had been admitted to the regular pediatric wards. Admission to intensive care or burn units had a highly significant correlation with MRSA infection {RR=3.27 (1.83, 5.82) p-value <0.01} (Table 5).

The presence of 3 or more indwelling devices was included. Twenty-five out of 31 (81%) MRSA patients had at least 3 indwelling devices while 6 of the 31 patients (19%) did not have 3 or more indwelling devices. Among MSSA patients, only 10 out of 38 (26%) had at least 3 indwelling devices while 28 out of 38 (74%) did not have 3 indwelling devices. The presence of 3 or more indwelling devices significantly correlates with the acquisition of MRSA {RR=4.05 (1.90, 8.62) p-value <0.01}.

History of previous hospitalization was also determined (Table 3). Among MRSA patients, 13 out of 31 (42%) were hospitalized prior to the onset of infection while 18 out of 31 (58%) did not have a history of previous hospitalization. Among MSSA patients, only 7 out of 38 (18%) had a history of previous hospitalization while 31 out of 38 (82%) had none. The risk of having MRSA is significantly high among those who had a history of

previous hospitalization {RR=1.77 (1.09, 2.88) p-value <0.05} (Table 5).

The presence of a surgical wound/burn wound was analyzed. Eighteen out of 31 (58%) MRSA patients had a surgical wound/burn wound while 13 out of 31 (42%) had none. Among MSSA patients, only 5 out of 38 (13%) had a surgical wound/burn wound while 33 out of 38 (87%) had none. The presence of a surgical wound/burn wound was significantly correlated with MRSA acquisition. {RR=2.77 (1.67, 4.60) p-value <0.01} (Table 5).

The clinical outcome of patients in the two groups (MRSA and MSSA) were compared (Table 4). Thirteen out of 31 (42%) MRSA patients died while 18 out of 31 (58%) were discharged alive. Among MSSA patients, 6 out of 38 (16%) died while 32 out of 38 (84%) were discharged alive. The number of deaths was significantly higher among patients with MRSA infection as compared with MSSA patients.

**Table 1. Demographic information of the subject population**

VARIABLES	MRSA(N=31)	MSSA(N=38)
<b>Age</b>		
0-5 years old	26 (84%)	24 (63%)
> 5 years old	5 (16%)	14 (37%)
<b>Sex</b>		
Male	19 (61%)	26 (68%)
Female	12 (39%)	12 (32%)

**Table 2. Underlying diseases/ Co-morbid illnesses in MRSA patients**

DISEASES	MRSA (N=31)	MSSA (N=38)
Malignancy	3 (10%)	7 (18%)
Renal disease	0	1 (3%)
Heart disease	1 (3%)	1 (3%)
Gastrointestinal disease	1 (3%)	1 (3%)
Pulmonary disease	3 (10%)	1 (3%)
Prematurity	9 (29%)	0
Glucocorticoid therapy	0	1 (3%)
CNS disease	4 (13%)	0
No underlying disease	10 (32%)	26 (68%)

**Table 3. Clinical characteristics of the subject population**

FACTORS	MRSA (N=31)	MSSA (N=38)
Previous antibiotic therapy		
Yes	26 (84%)	12 (32%)
No	5 (16%)	26 (68%)
Admission to ICU/Burn unit		
ICU/Burn unit	21 (68%)	6 (16%)
Regular wards	10 (32%)	32 (84%)
Previous hospitalization		
Yes	13 (42%)	7 (18%)
No	18 (58%)	31 (82%)
Presence of surgical wound/ burn wound		
With	18 (58%)	5 (13%)
Without	13 (42%)	33 (87%)
Presence of 3 or more indwelling catheters		
With	25 (81%)	10 (26%)
Without	6 (19%)	28 (74%)

**Table 4. Clinical outcome of MRSA patients**

Outcome	MRSA(N=31)	MSSA(N=38)
Died	13 (42%)	6 (16%)
Discharged alive	18 (58%)	32 (84%)

**Table 5. Analysis of data**

Variables	MRSA/MSSA Relative risk at 95% confidence interval/ p-value
Age	
0-5 years old	RR= 1.98 (0.89, 4.39)/0.055
>5years old	
Sex	
Male	RR= 0.84 ( 0.50, 1.43)/ 0.54
Female	
Presence of underlying diseases or co-morbid illnesses	RR=2.29 (1.27, 4.12)/<0.01
Presence of 3 or more indwelling devices	RR=4.05(1.9, 8.62)/<0.01
Previous antibiotic therapy	RR=4.24(1.85, 9.74)/ <0.01
Admission to ICU/ Burn Unit	RR=3.27(1.83, 5.82)/ <0.01
Previous hospitalization	RR=1.77(1.09, 2.88)/ <0.05
Presence of surgical wound/burnwound	RR=2.77(1.67, 4.60)/ <0.01
Outcome	RR=1.90(1.18, 3.07)/ <0.05

## DISCUSSION

During the past few years, several studies have already been made regarding the risk factors in the acquisition of MRSA infections in children, however no other study has been done in the Philippines aside from that of We and Pineda.<sup>3</sup> In the Philippine General Hospital (PGH), the prevalence rate of MRSA (adult and pediatric patients) during the first quarter of 1996 was 25% (We and Pineda).<sup>3</sup> The present study showed that the prevalence rate of MRSA among pediatric patients of PGH covering the period of January 1999 to September 2001 was 37.5%. This increase in prevalence rate was similar to the study made by Panlilio, et al. that in US hospitals, MRSA increased in prevalence from 2.4% to 29% from 1975 to 1991.<sup>4</sup> This was also consistent with the finding of Morgan, et al. that MRSA prevalence rate has risen steadily. The rise in prevalence of MRSA could be attributed to the emergence of several possible risk factors included in this study such as prior antibiotic therapy, admission to ICU/Burn Unit, previous hospitalization, presence of surgical/burn wound, and presence of 3 or more indwelling catheters. In adults, risk factors identified for MRSA infection include chronic liver, lung or vascular disease, dialysis, malignancy, or prolonged exposure to antimicrobial agents. Despite fewer descriptive data, predisposing risk factors for MRSA infections documented in pediatric populations include presence of invasive or surgical procedures, indwelling catheters, and prior exposure to antibiotics.<sup>8</sup> This was in agreement with the findings of the present study.

Patient age (older or younger age group) was not associated with an increased risk of MRSA infection (Tables 1&5). This was in contrast with the study of Herold, et al. which revealed that MRSA was highest among toddlers (3-36 months).<sup>6</sup> Likewise, Sadoyama<sup>11</sup> and Filho reported that age was one of several factors associated with an increased risk of MRSA infections. Increased MRSA acquisition during the younger age group could plausibly be due to an immunologic mechanism strengthening the fact that the nadir of immune resistance against infections in children was during infancy, particularly 4-6 months of age. However, this study was not able to demonstrate an association of increased MRSA infection with younger age group because of a limited study population.

Methicillin-resistant *S. aureus* was not significantly associated with either male or female sex (Tables 1&5). This result parallels the finding of Herold, et al. that the risk of acquiring MRSA or MSSA infections did not differ significantly with respect to sex.<sup>6</sup>

Infection with MRSA was found to be significantly higher among those with underlying diseases or co-morbid illnesses (Tables 2&5) such as prematurity, pulmonary disease, malignancy, CNS, renal, heart, and gastrointestinal diseases. This observation was consistent with the study of Sanford, et al., wherein 84% of MRSA patients in hospitalized children were found to have one or more underlying diseases/co-morbid illnesses. Maranan, et al. had an identical finding of increased MRSA infections among adult patients with underlying diseases. Although with no clear evidence at hand, it was possible that because of their co-morbid illnesses, these individuals required prolonged hospitalization/multiple drug therapy and thus, they were more susceptible to nosocomial infections such as MRSA. Consistent with the study of Madani, et al., the patients who received previous antibiotic therapy had a significantly increased risk of acquiring MRSA infections (Tables 3&5). Herold, et al. had a similar finding. Sadoyama, et al., reported that the previous use of 3 or more antimicrobials was one of the several factors associated with an increased risk of MRSA infection. These observations validate the fact that prior use of antibiotics, especially if multiple, will lead to the emergence of resistant microbial strains, an example of which is MRSA.

Admission to intensive care and burn units was significantly correlated with acquiring MRSA infections (Tables 3&5). This was in congruence with the observation of Madani, et al. that MRSA prevalence was highest among patients admitted in the intensive care units.<sup>10</sup> It can be surmised that the presence of life-saving devices such as endotracheal tubes, mechanical ventilator, several other tubes/indwelling devices in the ICU was a good environment for MRSA organisms to thrive and one possible reason for spread of infection was via direct contact through the hands of nurses, doctors, watchers, medical personnel who make frequent monitoring and visits to the patients.

Previous hospitalization was reported by Maranan et al to be one of the risk factors for acquiring MRSA infections.<sup>10</sup> According to various studies made by Dunkle et al, Kline et al, and Ribner et al, one of the predisposing risk factors for MRSA infections in pediatric populations include previous/prolonged hospitalization.<sup>12,13,14</sup> In this study, previous hospitalization proved to be significantly correlated with MRSA (Tables 3&5). Although several reports on the emergence of community-acquired MRSA infections are increasing, this study confirms the importance of MRSA as a major nosocomially-acquired pathogen.

The presence of a surgical/burn wounds was shown to be significantly high in patients with MRSA (Tables 3&5). This was in agreement with the report made by Herold et al that invasive or surgical procedures was one of the risk factors for MRSA infections.<sup>6</sup> Madani et al revealed that one of the most common sites of infection in MRSA was from surgical wounds.<sup>10</sup> Likewise, Sadoyama et al had a similar finding.<sup>11</sup> Patients at risk for MRSA infections include those with burns as mentioned in Nelson's Textbook of Pediatrics. This could be explained by the pathogenesis of *S.aureus* organisms in general. The intact skin and mucous membranes serve as barriers to invasion by *S.aureus*, and any defect in the mucocutaneous barriers produced by trauma, surgery and burns increase the risk of infection *S. aureus* in general.

It was also shown that the presence of 3 or more indwelling catheters was significantly associated with MRSA infection (Tables 3&5). In a study by Sadoyama et al, the result similarly showed that the presence of 3 or more indwelling devices was one of the several factors associated with an increased risk of MRSA infection.<sup>11</sup> Herold et al<sup>6</sup> and Madani et al<sup>10</sup> found that indwelling catheters, endotracheal tubes, and central venous catheters were predisposing risk factors for MRSA infections. This could be explained by the aforementioned pathogenesis of MRSA.

When clinical outcome of MRSA patients in this study was analyzed, it was found that mortality was significantly high (42%) among patients with MRSA (Tables 4&5). This was comparable with the study of Madani et al<sup>10</sup> which revealed that mortality of patients with MRSA was 53.7%. Untreated staphylococcal septicemia was said to be associated with a mortality rate of 80% or greater<sup>15</sup>. The high mortality rate seen among patients with MRSA could be on account of the virulence of the organism and the immunocompromised state of most patients with MRSA, e.g seriously ill patients (those with burns, surgical wounds, co-morbid illnesses).

## CONCLUSION

This study confirms the high mortality rate of MRSA infection among pediatric patients admitted to PGH. It was also shown that MRSA infection was significantly higher among patients with presence of co-morbid/underlying illness, presence of 3 or more indwelling devices, previous antibiotic therapy, admission to ICU/Burn Unit, previous hospitalization and presence of surgical or burn wound. Age and sex were not found to be significant factors for infection.

## RECOMMENDATION

Generally, once MRSA infection appears in an institution, it becomes established as a persistent cause of nosocomial infection.<sup>7</sup> The need for widespread control measures was supported by the high morbidity and mortality associated with MRSA infection that was shown in this study, hence should be heavily emphasized.

It is therefore recommended that control efforts within the hospital should focus on the identification of

the MRSA reservoir (carriers and infected patients), with the subsequent implementation of isolation procedures. In addition, the proper use of gloves and handwashing technique should always be implemented to decrease, if not totally prevent bacterial transmission. Lastly, prospective studies should be done to determine other risk factors which may contribute to the transmission and subsequent infection with MRSA.

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