RISK FACTORS FOR METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION AT QUEEN SIRIKIT NATIONAL INSTITUTE OF CHILD HEALTH

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ABSTRACT

A retrospective study was conducted to determine risk factors, ratio and antibiogram pattern of MRSA and MSSA in pediatric patients admitted to or treated at Queen Sirikit National Institute of Child Health, during the period January 2002 to December 2003.

A total of 274 cases of *S. aureus*-infected patients were reviewed. Most of them (72%) were less than 2 years old. One hundred and fifty-four patients were male and 120 female. Most of the patients had MSSA (74.1%) and 71 (25.9%) had MRSA infections. One hundred and sixty-eight (61.3%) had community–acquired (CA) *S. aureus* infection, while 106 (38.7%) had hospital-acquired (HA) *S. aureus* infection.

Fifty-one percent of the patients had chronic and underlying diseases and 43.9% had received instrumentation. Chronic diseases not requiring immunosuppressive drugs were the most common (86%).

Most of the patients were admitted to the pediatric ward (54.4%) followed by the neonatal and surgical wards. The intensive care unit and the surgical ward had higher percentages of MRSA than the medical wards (62% vs. 14%).

Younger age (≤ 1 year), chronic and underlying disease, instrumentation and surgical intervention were found to be risk factors for MRSA infection.

All clinical isolates were susceptible to vancomycin while almost all (98%) of the isolates were resistant to penicillin G. Thirty percent of isolates were resistant to oxacillin. In addition to oxacillin, almost all MRSA were resistant to co-trimoxazole, erythromycin and gentamycin.

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KEY WORDS: *Staphylococcus aureus*, MRSA/MSSA/community-acquired/ hospital-acquired/children

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CONTENTS

LIST OF TABLES

LIST OF TABLES (CONT)

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation/symbols	Terms
ATB	Antibiotics
CA	Community acquired
CI	Confidence Interval
cm	centimeter
CoNS	Coagulase negative Staphylococcus
CSF	Cerebrospinal fluid
DD/MM/YY	Day/Month/Year
°C	Degree Celsius
e.g.	Example
ENT	Ear/Nose/throat
et al	An others
Gr.	grade
HA	Hospital acquired
ICU/NICU	Intensive care unit/ Neonatal intensive care unit
kg	kilogram
L	Liter
LTCFs	Long term care facilities
Mg	milligram
µg	microgram
MICs	Minimal inhibition concentrations
ml	milliliter
mm	millimeter
mo	month
mol	mole
MRSA	Methicillin resistant S*taphylococcus aureus*
MSSA	Methicillin sensitive *Staphylococcus aureus*

LIST OF ABBREVIATIONS (CONT)

Abbreviation/symbols	**Terms**
NaCl	Sodium Chloride
NCCLS	National Committee for Clinical Laboratory Standards
No.	number
OPD	Out patient department
p	probability
PBP 2a	Penicillin binding protein 2a
QSNICH	Queen Sirikit National Institute of Child Health
S. aureus	*Staphylococcus aureus*
SCC mec	Staphylococcal chromosome cassette *mec*
TSS	Toxic shock syndrome
U S	United States
USD	US Dollar
VISA	Vancomycin intermediate resistant *Staphylococcus aureus*
VRSA	Vancomycin resistant *Staphylococcus aureus*
W/v	Weight per volume
%	percent
β	Beta
<	Less than
>	More than
≥	More than and equal
≤	Less than and equal
χ^2	Chi-square

CHAPTER I
INTRODUCTION

Staphylococcus aureus (*S. aureus*) is an ubiquitous environmental organism, with a predilection to skin, particularly of the face, nose and hands, and routinely found in one third of adults as normal flora. Nasal carriage is mediated by teichoic acid and as many as 50% of population being intermittent carriers.

Since its description in 1880 and 1882 by Ogston, *S. aureus* has remained a versatile and dangerous pathogen in human. *S. aureus* is a significant cause of morbidity and mortality in children. It is one of the most commonly isolated pathogen in neonatal sepsis.

The frequencies of both community-acquired and hospital-acquired staphylococcal infections have increased steadily, with little change in overall mortality. Treatment of these infections has become more difficult because of the emergence of multi-drug resistant strains. *S. aureus* resistant to commonly used antibiotics, such as methicillin and oxacillin are called methicillin resistant *S. aureus* (MRSA). Strains of MRSA have become a major problem in neonatal intensive care unit (Haley et al., 1995). It is also a common cause of pneumonia, bacteremia, endocarditis, osteomyelitis, empyema, toxic shock syndrome, food poisoning, burn and wound infections (Locksley et al., 1982; Haddadin et al., 2002).

Like other strains of *S. aureus*, the body site most commonly colonized with MRSA is the anterior nares. Other body sites that may be colonized with MRSA include open wounds, the respiratory tract, perineum, upper extremities, umbilicus (in infants), urinary tract, and axilla. Some patients are colonized for only a few weeks and then become culture-negative without any specific therapy. However, patients with serious underlying diseases that require repeated hospitalization may be colonized for more than 3 years.

MRSA infections are usually mild, superficial infections of the skin that can be treated successfully with proper skin care and antibiotics. However, MRSA can be

difficult to treat and can progress to life-threatening blood or bone infections because there are fewer effective antibiotics available for treatment.

Since the first case report of MRSA infection in the United States in 1968 (Barret et al., 1968), MRSA has become an increasingly significant problem, now accounting for about 50% of nosocomial *S. aureus* infection isolates in the United States (Lowy , 1998).

Subsequently the view of MRSA as a nosocomial pathogen in patients with well-described risk factors has been challenged with recognition of community acquired MRSA (CA-MRSA).

Many other investigators have identified and reported MRSA strains leading to serious clinical problems (Storch et al., 1986; Crossly et al., 1979), and that CA-MRSA is an increasingly common pathogen in pediatric population (Herold et al., 1998; Fergie, 2001; Sattler et al., 2002).

Whether MRSA is more virulent than methicillin susceptible *S. aureus* (MSSA) is a controversial issue. Some investigators have demonstrated higher mortality associated with MRSA bacteremia in analyses that controlled other factors (Romero-vivas et al., 1995; Conterno et al., 1998; Blot et al., 2002), while others have demonstrated that inappropriate antimicrobial therapy, co- morbid condition, and advanced patient age rather than MRSA accounted for increased mortality associated with MRSA bacteremia (; Harbarth et al., 1998; McClelland et al., 1999; Soriano et al., 2000).

One study (clinical update for Boyce 1998) showed that patients with serious MRSA infections stayed in the hospital for an average of 12 days longer, and had average hospital costs of USD 5,100 greater than comparable patients with MSSA infections. However, fatality rates among patients with MRSA infections are not significantly higher than those observed among patients with infection caused by MSSA.

In conclusion MRSA infection is important because of the following reasons:

1. MRSA is pathogenic, transmissible and is a common cause of hospital-acquired infections. MRSA outbreak can occur when one strain is transmitted to other patients.

2. Limited treatment options. Glycopeptides group (vancomycin) often is the only drug of choice for treatment of severe MRSA infections, although some strains remain susceptible to fluoroquinolones, trimethoprim/sulfamethoxazole, gentamicin or rifampin. Because of the rapid emergence of rifampin resistance, this drug should never be used as a single agent to treat MRSA infections.

3. These infections are associated with prolonged hospital stays and increased hospital costs, and few therapeutic options are available to treat affected patients.

According to the above-mentioned reasons, it is interesting to study the risk factors for MRSA infection in children and to compare the risk factors for MRSA and MSSA. The data from this study may be helpful for further control and proper management of infection caused by *S. aureus.*

CHAPTER II
OBJECTIVES

HYPOTHESIS

1. The risk factors for HA- MRSA and CA-MRSA are different.

OBJECTIVES OF THE STUDY:

General objectives

1. To evaluate the risk factors for MRSA and MSSA in pediatric patients.
2. To calculate the ratio of MRSA and MSSA in pediatric patient with *S. aureus* infection.

Specific Objectives

1. To study risk factors of hospital and community acquired *S.aureus* infection.
2. To study risk factors of MRSA comparing MSSA infection.
3. To describe the antibiogram pattern of MRSA comparing MSSA.

CHAPTER III
REVIEW OF LITERATURE

Microbiology and Genome

S. aureus is a member of the Family Micrococcaceae. On microscopical examination the organisms appear as gram-positive cocci in clusters. It is easily identified and distinguished from other staphylococcal species by their tendency to produce classical golden pigmented colonies, positive coagulase, mannitol fermentation, deoxyribonuclease tests and appearance of clustered, grape-like gram positive cocci on gram staining.

Other features of this organism are the production of a variety of biologically active components including enzymes, hemolysins, leukocidins, toxins and the cell surface proteins and cell wall components. These biological active components include enterotoxins A-E which are associated with food poisoning and toxic shock syndrome (TSS), the epidermolytic toxins A and B which are implicated in cases of scalded skin syndrome and TSS-1 which is associated with the most cases of TSS.

The staphylococcal genome consists of a circular chromosome with prophages, plasmids, and transposons. Genes governing virulence and resistance to antibiotics are found on the chromosome, as well as the extra chromosomal elements. These genes are transferred between staphylococcal strains, species, or other gram-positive bacterial species through the extra chromosomal elements.

In, resistance to methicillin and related β-lactam antibiotics is encoded by the *mec*A gene, which is carried on a mobile genetic element termed the staphylococcal chromosome cassette *mec* (SCCmec). The transfer of this element is mediated by two site-specific recombinases, *CcrA* and *CcrB*, which catalyse precise excision of SCCmec and its orientation in specific integration into the chromosome of recipient cells.

Staphylococcus resistance to oxacillin/methicillin occurs when an isolate carries an altered penicillin-binding protein 2a (PBP2a), which is encoded by the

*mec*A gene. This alteration does not allow the drug to bind well to the bacterial cell, causing resistance to β -lactam antimicrobial agents.

Mechanism of Resistance to Antimicrobial Agents

Penicillin is inactivated by β-lactamase, a serine protease that hydrolyzes the β-lactam ring. Methicillin is β-lactamase resistant penicillin. Resistance to methicillin confers resistance to all penicillin and cephalosporin. This high level of resistance requires the presence of the *mec* gene that encodes PBP2a (Chambers, 1997). Resistance to vancomycin has been reported in clinical isolates of *S. haemolyticus* (Schwalbe et al., 1987), a coagulase-negative species. It is expected that *S. aureus* may acquire this resistance property and vancomycin resistance strains are likely to pose a major therapeutic challenge in the future. Confirmation of sensitivity by the broth-dilution method is recommended to declare the antibiotic resistance (Tenover et al., 1998).

Pathogenesis

The pathogenesis of *S. aureus* infection depends on bacterial factors: virulence determinant factors of the bacteria, and host defense mechanism. Several factors contribute to the increased susceptibility to infection; these include the presence of foreign material, intravenous catheter, long-term indwelling catheter, and breach of skin and mucus membrane.

The cellular events leading to septic shock in staphylococcal infection are similar to infection with gram negative bacteria.

Staphylococcal bacteremia may be complicated by endocarditis, metastatic infection, or septic syndrome. The typical pathological finding of staphylococcal disease is abscess formation. Leukocytes are the primary host defense against *S. aureus* infection (Verdrengh and Tarkowski, 1997).

Epidemiology

Human are a natural reservoir of *S. aureus*. About 20- 30% of healthy people carry *S.aureus* bacteria in their noses at various times without illness. Most of people begin to have staphylococcus growing harmlessly on their bodies before the age of one week. Their fingers can carry staphylococcus bacteria from one area of the body

to another to cause infections in wounds or broken skin. Both MSSA and MRSA isolates are persistent colonizers (Casewell and Hill, 1986; Sanford et al., 1994). Persons colonized with *S. aureus* are at increased risk for subsequent infections (Wenzel and Perl, 1995).

The prevalence of MRSA in hospitals varies considerably from one region to another and among hospitals in the same city and from country to country.

The main reservoir of MRSA in hospitals is patients colonized or infected with MRSA. Although colonized patients have no signs or symptoms of infection, they can still serve as a source from which transmission may occur. Colonized personnel and contaminated environmental surfaces can also serve as reservoirs, but are not as important as affected patients. Presumably, MRSA reservoirs in long-term care facilities (LTCFs) are similar to those in hospitals.

S. aureus including MRSA can be spread among people having close contact with infected people. MRSA is almost always spread by direct physical contact and not through the air. Spread may also occur through indirect contact by touching objects (e.g., towels, sheets, wound dressings, clothes, workout areas, or sport equipment's contaminated by the infected skin of a person with *S. aureus* or MRSA.

MRSA infections commonly occur among persons in hospitals and healthcare facilities. However, MRSA can cause illness in persons outside the hospitals and healthcare facilities as well. Cases of MRSA infection in the community have been associated with recent antibiotic use, sharing contaminated items, having recurrent skin diseases, and living in crowded settings.

The number of both community-acquired and hospital acquired staphylococcal infection have increased in the past twenty years. This trend either parallels increased use of intravascular device (Banerjee et al., 1991; Steinberg et al., 1996) or resulting in part from selective antibiotics pressure (Panlilio et al., 1992; Speller et al., 1997).

At the beginning these MRSA cases were restricted to the patients residing in LTCFs, intravenous drug users and those who were recently hospitalized or who underwent surgery, but in 1980, the first community acquired (CA) - MRSA infection in the US was reported. Several other investigators (Herold et al., 1998; Frank et al.,

1999; Hussain et al., 2000) found a high rate of community acquired MRSA among hospitalized children without risk factors.

Many investigators have studied the epidemiology of MRSA; some of them have reported increased prevalence of MRSA infection in nursery, community, and in children with or without risk factors; others have studied and compared risk factors for CA-MRSA and hospital acquired (HA) - MRSA, and tried to find out whether CA-MRSA is due to the spread of nosocomial infection into community or not.

Study in Queen Sirikit National Institute of Child Health (QSNICH) (Napaporn, 2003), has shown increased prevalence of MRSA, and that most of MRSA cases occurred in children less than one year of age. Similarly, Endo et al., (1996), reported increased prevalence of MRSA, and that MRSA has become the most frequent pathogen causing sepsis and/or meningitis in the nursery.

A review from five Canadian university hospitals, from 1990 to 1992 (Embil et al., 1994), has shown that 63% of MRSA isolates were identified within 72 hours of admission. This finding indicated increasing cases of CA-MRSA; also a study in the United States (US) hospital (Buckingham et al., 2004), reported that CA-MRSA has emerged as a potentially invasive pathogen among children in Memphis area, and that CA-MRSA strains were not nosocomially spread.

In the US, several other reports (Boyce and Causey, 1982; Herold et al., 1998) from their hospitals indicated that MRSA infection was no longer confined to hospital environment in patient with well-described risk factors, and found that MRSA infection occurred in children without identifiable risk factors.

Some investigators have traced the origin of CA-MRSA strain, their objective was to find out the proportion of nosocomial spread of CA-MRSA strains. A study in San Francisco (Charlebois et al., 2004), indicated that a large proportion of CA-MRSA are feral descendent of hospital endemic colonies, while the study in Memphis area, the US (Buckingham et al., 2004), found that CA-MRSA and HA-MRSA are completely independent strains.

Several other investigators have studied the risk factors for MRSA, CA-MRSA, and HA-MRSA. Some of them (Thompson et al., 1982; Locksley et al., 1982), reported risk factors for HA-MRSA infection included, prolonged or recurrent antibiotic exposure, prolonged hospitalization and hospitalization in intensive care

unit; while others (Levin et al., 1982; Saravolatz et al., 1982; Strausbaugh et al., 1991), found that outpatients with MRSA infection generally had been chronically ill, and many have history of nursing home residence, recent admission to acute or chronic health care facility, prior receipt of antibiotics or intravenous drug abuse and exposure to self administered prophylactic antibiotics.

By comparative studying of risk factors for CA-MRSA and CA-MSSA, a study (Sattler et al., 2002) found no significant difference in the exposure between the two groups.

Clinical Laboratory Diagnosis for MRSA

The National Committee for Clinical Laboratory Standards (NCCLS) has recommended "Screening Test for Oxacillin-resistant *S. aureus*" using an agar plate containing 6 μg/ml of oxacillin and Mueller-Hinton agar supplemented with NaCl (4% w/v; 0.68 mol/L).

Accurate detection of oxacillin/methicillin resistance can be difficult due to the presence of two subpopulations (one susceptible and the other resistant) that may coexist within a culture (Kloos and Bannerman, 1999). All cells in a culture may carry the genetic information for resistance but only a small number can express the resistance in vitro. This phenomenon is termed heteroresistance and occurs in staphylococci resistant to penicillinase-stable penicillins, such as oxacillin.

Heteroresistance is a problem for clinical laboratory personnel because cells expressing resistance may grow slower than the susceptible population. This is why NCCLS recommends incubating isolates being tested against oxacillin, methicillin, or nafcillin at 35 º C for a full 24 hours before reading (NCCLS, 1999).

Treatment of *S. aureus* Infection

Penicillin remains the drug of choice if the isolate is sensitive to it. Semisynthetic penicillin (nafcillin or oxacillin) is indicated for β-lactamase-producing strains. In patients, allergic to penicillin, a cephalosporin such as cefazolin or cephalotin is an acceptable alternative.

Glycopeptides (vancomycin) is the drug of choice for methicillin-resistant isolates. Patients unable to tolerate vancomycin can be treated with fluoroquinolones,

trimethoprim-sulfamethoxazole, clindamycin, or minocycline. However they are not as effective as vancomycin.

CHAPTER IV
MATERIALS AND METHODS

Study Design

A retrospective study was performed during a 9-week data collection period from 8 November 2004 to 7 January 2005.

Study Site

This study was carried out at Queen Sirikit National Institute of Child Health (QSNICH), Ministry of Public Health, Bangkok, Thailand.

Subjects

Data was collected from pediatric patients who had culture proven *S. aureus* infection, were admitted or treated as out patients at QSNICH during January 1, 2002 to December 31, 2003.

Sample Size

The sample size was calculated by using the following formula:

$$N = \frac{Z^2\ \alpha/2\ (p)\ (q)}{\delta^2}$$

Where N= number of sample. q = 1-p

Z α/2 =the standard normal number deviate for two sided α Where (1-α) is the confidence level (since α=0.05 for a 95% confidence level, Z α/2 = 1.96)

p= prevalence of MRSA from the previous study, p=0.2(data from QSNICH).

δ= the effect size, is the difference of estimate that we wish to detect

$$N = \frac{(1.96)^2 * (0.2)*(0.8)}{(0.05)^2}$$

= 246 patients

Operational Definition

1. Immunosuppression

- Patient was considered immunosuppressive if he or she received a dose of 2mg/kg/day of steroids for more than 2 weeks.
- The immunosuppressive effect was considered if the patient was receiving or received a dose of 2mg/kg/day of steroids within two weeks prior to the onset of studying illness caused by *S. aurues*.

2. Staphylococcal Resistant Pattern

In this retrospective study, we identified children from whom *S.aureus* was isolated from any body site by QSNICH microbiology laboratory. The identified *S.aureus* infections were stratified into MRSA and MSSA on the basis of the property of methicillin resistance or methicillin sensitive, respectively.

The 1999 NCCLS breakpoints for *S. aureus* were taken as reference for definition of MRSA, MSSA. The minimal inhibitory concentration and the zone size used for differentiation are shown in the following table. The criteria are different from those for coagulase-negative Staphylococci *(*CoNS).

Minimal Inhibitory Concentration (MICs)	Oxacillin Susceptible	Oxacillin Intermediate	Oxacillin Resistant
S. aureus	$\leq$ 2 μg/ml	no intermediate MIC	$\geq$ 4 μg/ml
CoNS	$\leq$ 0.25 μg/ml	no intermediate MIC	$\geq$ 0.5 μg/ml

Zone Sizes	Susceptible	Oxacillin Intermediate	Oxacillin Resistant
S. aureus	$\geq$13 mm	11-12 mm	$\leq$10 mm
CoNS	$\geq$18 mm	no intermediate zone	$\leq$17 mm

Oxacillin is tested instead of methicillin and isolates are called MRSA instead of ORSA, this is because:

1. Oxacillin is more resistant to degradation in storage and is more likely to detect most heteroresistant strains. In addition, methicillin is no longer commercially available in the United States. Antimicrobials like oxacillin and nafcillin now are used for treatment of *S. aureus* infections.

2. When resistance was first described in 1968, methicillin was used to test and treat infections caused by *S. aureus*. Now, methicillin is no longer the agent of choice for testing or treatment of susceptible staphylococcal infections. However, the acronym MRSA is still used by many to describe these isolates because of its historic role.

On the basis of above information MRSA and MSSA were defined according to NCCLS MICs breakpoints of ≥ 4 μg/ml and ≤ 2 μg/ml, respectively.

Additionally, MRSA and MSSA were defined if a clear zone of inhibition is $\leq$10 mm and $\geq$13 mm, respectively.

3. Hospital Acquired (HA)-*Staphylococcus aureus* Infection Definition:

1. Any isolate of *S. aureus* infection occurred > 48 hours after hospitalization.

2. Any new infection or super infection occurred > 48 hours after hospitalization.

4. Community Acquired (CA)-*Staphylococcus aureus* Infection Definition:

1. Any isolate from outpatients.
2. Any isolation within 48 hours of hospitalization for in-patients.
3. Any isolate from patients with abscess or cellulities on admission regardless the isolation time after hospitalization.

Inclusion Criteria:

1. Age less than or equal 15 years infected with *S. aureus* confirmed by culture and had the susceptibility result according NCCLS recommendation.
2. The patient medical record was available for reviewing.

Exclusion Criteria:

The infection was assumed as contamination.

In addition to laboratory data, demographic, hospitalization and outcome details were extracted from the medical record of the patients.

The *S. aureus* infections were classified as superficial, which include skin and subcutaneous tissue infection, and deep seated, i.e. osteomyelitis or bacteremia.

If the primary infection site was superficial, but *S. aureus* was isolated from the blood stream, the infection will classified as deep seated.

Study Method

All clinical samples from pediatric patients whose culture were done during 2002 to 2003 at QSNICH were reviewed. *S. aureus* culture positive patients were identified.

The medical record of these patients were traced and identified. Demographic and clinical data and laboratory finding were collected according to the case record form (Appendix-1).

Data Analysis:

Descriptive statistics were used to describe the demographic characteristics, clinical symptoms and signs and laboratory tests of subjects.

Possible risk factors were compared between MRSA and MSSA in one hand and between community and hospital acquired *S. aureus* infection in another hand.

The categorical variables were analysed by chi-squire test with a preset 95 % Confidence Interval (CI) ($p < 0.05$). The statistical software package of SPSS and Epi. Info.6.1 was used.

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The Faculty of Tropical Medicine, Mahidol University, Thailand, supported this study.

CHAPTER V
RESULTS

There were 274 clinical specimens positive for *S. aureus* and met the study criteria, during January 2002 to December 2003.

For understanding and simplicity, the result will be classified into three parts: General characteristics, relationship of various variables and risk factors.

PART I

General Characteristics

Among 274 pediatric patients who were enrolled in the study, one hundred and fifty four patients (56.2%) were male and 120 patients (43.8%) were female. The age distribution of the patients is shown in table 1 and figure 1. Most of them aged ≤ 2 mo (43%), followed by 2months to 24 months (29%), over 60 mo (16%), and 24 mo to 60 mo (12%). About 72% of all patients were less than 2 years of age.

Most of the isolated *S. aureus* were MSSA (74%) and only 71 patients (26%) had MRSA infection. One hundred and sixty eight patients (61.3%) acquired infection from the community, while 106 patients (38.7%) acquired infection from the hospital (Table. 2).

Most of the isolated *S. aureus* were from skin and soft tissue (36.5%) followed by blood (30.3%), tracheal suction (12.0%), eye discharge (8.8%), urine (2.6%), sputum (2.2%), ear discharge (1.8%) and others (5.8%) as shown in Table 3 and Figure 2.

Regarding the site of *S. aureus* infection, skin and soft tissue were the most common site (32.5%), followed by systemic (>1 organs) (28.8%), respiratory tract (16.7%), eye (8.3%), musculoskeleton (2.9%), genitourinary tract (2.5%), ENT (2.5%), gastrointestinal (2.5%), and others (2.9%) as shown in Table 4 and Figure 3.

The characteristics of studied patients were shown in Table 5. Fifty one percent of patients were having chronic or underlying diseases, while 36% and 44%

of the patients had surgical intervention and instrumentation procedure, respectively. Few patients in this study received immunosuppressive drugs (4%) and only 2% had prior cutaneous infection (Table 5).

PART II

Relationship between Source of Organism Acquired, Methicillin Susceptibility Pattern and Other Factors

As shown in Table 2, it is found that hospital acquired *S. aureus* infection occurred more commonly in infant ≤ 2 months of age with the ratio of HA: CA about 1.3:1 while the ratio in other age group was 1:3. The ratio of MRSA: MSSA is higher in HA infection (1:1) than in CA infection (0.1:1).

We reviewed and compared the different source of organism (HA and CA) among different site of *S. aureus* infection and found that CA were more common than HA (84.3% vs. 15.7%) in the skin and soft tissue infection, while HA were more common than CA (63.3% vs. 36.7%) in systemic infection (>1 organs) (Table 6 & 7).

In community acquired *S. aureus* infection, those who had respiratory tract or systemic (>1 organs) infection had 2.8 and 4 times respectively, chance of MRSA infection (Table 6).

Comparing to the total ratio, MRSA infection was more common in gastrointestinal infection ($p < 0.001$), while MSSA infection was more common in skin, soft tissue ($p < 0.001$), systemic infection (1>organs) ($p < 0.001$), respiratory tract infection ($p = 0.03$), and ENT infection ($p<0.001$) (Table 8).

Most of the patients were in pediatric ward (54.4%) followed by neonatal nursery (20.4%), surgical ward (10.6%) and intensive care unit (PICU + NICU) (10.5%). Only few patients were in Eye and ENT wards (Table 9).

Regarding relationship between attending department of the patients and methicillin susceptibility pattern, 62% of *S. aureus* infection in the patients from intensive care unit (PICU +NICU) and surgical ward had MRSA, while 87% of *S. aureus* infection in the patients from pediatric ward had MSSA (Table 9, figure 4). Among, hospital acquired *S. aureus* infection, 49% of them were MRSA while MRSA occurred in only 11% of CA infection. HA-MRSA infection was more

common in both intensive care units (PICU+NICU) and surgical ward than other departments (Table 10).

Regarding the antibiotic susceptibility pattern, about one-fourth of clinical isolates were resistant to co-trimoxazole, erythromycin, gentamicin and oxacillin but almost all (98%) of the isolates were resistant to penicillin G. All the isolates were sensitive to vancomycin (Table 11). HA-MRSA and CA-MRSA had comparable susceptibility pattern, as it is found that almost all of them were resistant to co-trimoxazole, erythromycin, gentamicin and penicillin G, while HA-MSSA and CA-MSSA had similar susceptibility pattern but different from MRSA (Table 12). More than 95% of all MRSA isolates were resistant to co-trimoxazole, gentamicin and erythromycin (Table 13).

Regarding the disease outcome, thirty-two patients died (12%); children aged 2months or younger were more likely to die than elder children. Sixty five percent of those who died had age ≤ 2months and 78% of those who died had MRSA infection. However, the causes of death were not exclusively due to *S. aureus* infection, there were other underlying or condition associated, such as congenital diseases, malignancy and malformations (Table 14 and 15).

Among the patients with chronic and underlying disease, MRSA was more common those with chronic disease not required immunosuppressive drugs than those with chronic disease required immunosuppressive drugs (93% vs.7%). Among patients with history of previous hospitalization, MRSA was more common in those who required surgical intervention than those who did not required surgical intervention (50% vs. 6 and 30%). Eighty six percent of those with disease required surgical intervention had HA-MRSA while 29% of them had CA-MRSA (Table.16).

PART III

1. Risk Factors for MRSA and MSSA Infection

By using univariate analysis, it is found that the significant risk factors for MRSA infection include:

1.1 Age:

Sixty-one percent of patients were ≤ 1 year of age. This age group had 4 times chance of MRSA infection comparing to other age group (OR=4.3; p =0.001) (Table 17).

1.2 Chronic and underlying disease:

Nearly half of the patients were having chronic or underlying diseases, it is found that chronic and underlying disease were significantly associated with MRSA infection (OR=7.7, p = 0.001) (Table 17).

1.3 Other condition:

Comparing the association between instrumentation procedure, surgical intervention and methicillin susceptibility, it was found that surgical intervention and instrumentation procedure have increased the risk of MRSA infection (OR=3.4 and OR=10.9) and the association was statistically significant (p = 0.00) (Table 17).

School attendance seemed to be have protective effect on MRSA infection (OR = 0.2, P = 0.024), this may be due to the small number of children who attended school (11%).

Other factors such as previous hospitalization, taking immunosuppressive drug and prior cutaneous infection had no significant association with MRSA infection.

By multivariate analyses, it is found that younger ≤ 1 year of age, chronic or underlying diseases, surgical intervention and instrumentation procedure were significant risk factor for MRSA, but school attendance was not (Table 20).

2. Risk Factors for CA – MRSA and HA – MRSA Infection

By using univariate analysis, it is found that the significant risk factors for CA – MRSA and HA - MRSA infections include:

1. In the community, when we compared risk factors for CA - MRSA and CA- MSSA infection, we found that age ≤ 1 year (OR= 6, p =0.003) and chronic or underlying diseases (OR = 6.6, $p < 0.001$) were significantly associated with CA – MRSA infection, Table 18. By multivariate analyses, it is found that only chronic or underlying diseases were significantly risk factor for CA-MRSA ($p = 0.001$) (Table 21).

2. In hospital, when we compared risk factors for HA – MRSA and HA – MSSA infections we found that surgical intervention (OR = 5, $p < 0.01$), instrumentation procedure (OR = 9.5, $p <0.01$) and chronic or underlying diseases were associated with HA – MRSA infection. Table19. By multivariate analyses, it is found that instrumentation procedures ($p = 0.003$) and surgical intervention ($p = 0.003$) were significant risk factors for HA – MRSA (Table 22).

Table 1. **The age and gender distribution of *S. aureus* infected patients**

Age group	Gender		Total (%)
	Male (%)	Female (%)	
≤ 2mo	60 (38.4)	58 (48.3)	118 (43.1)
> 2mo – 24mo	54 (35.1)	26 (21.8)	80 (29.2)
> 24mo – 60 mo	20 (13.2)	12 (10.3)	32 (11.7)
> 60mo	20 (13.2)	24 (20.5)	44 (16.1)
Total	154 (100)	120 (100)	274(100)

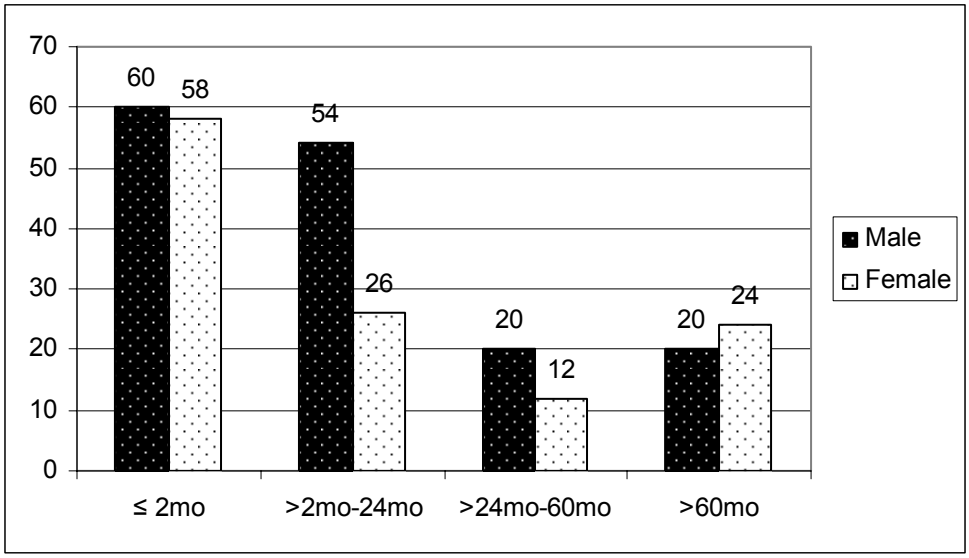

Figure1. The age and gender distribution of *S. aureus* infected patients

Table 2. Source of *S. aureus* acquired and methicillin susceptibility in patients with different age group

Age group	Source of infection					
	Community acquired			Hospital acquired		
	MRSA (%)	MSSA (%)	Total (%)	MRSA (%)	MSSA (%)	Total (%)
≤ 2mo	8 (42.1)	43 (28.9)	51 (43)	37 (71.2)	30 (55.6)	67 (57)
>2mo – 24mo	9 (47.4)	51(34.2)	60(75)	7 (13.5)	13 (24.1)	20 (25)
> 24mo – 60 mo	0	24 (16.1)	24 (75)	5 (9.6)	3 (5.6)	8 (25)
> 60 mo	2 (10.5)	31 (20.8)	33 (75)	3 (5.8)	8 (14.8)	11 (25)
Total	19 (100)	149 (100)	**168 (61.3)**	52(100)	54 (100)	**106 (38.7)**

Table 3. Source of specimen that *S. aureus* were isolated

Source of specimen	Frequency	Percentage
Skin and soft tissue	100	36.5
Blood	83	30.3
Tracheal suction	33	12.0
Eye discharge	24	8.8
Urine	7	2.6
Sputum	6	2.2
Ear discharge	5	1.8
Others	16	5.8
Total	274	100.0

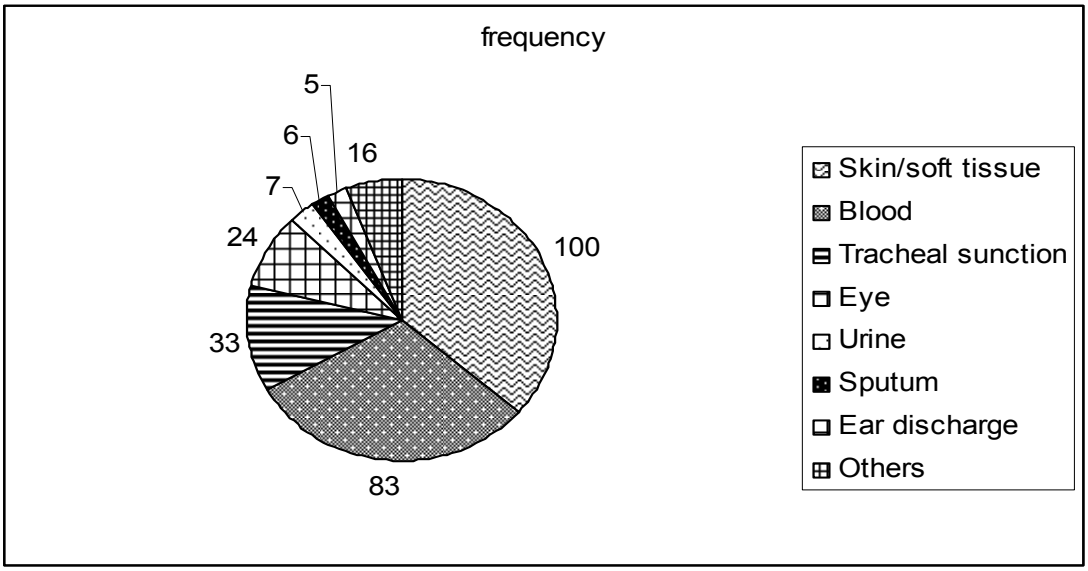

Figure 2. Distribution of the specimen that *S. aureus* were isolated

Table 4. Distribution of *S. aureus* infection by organ system

Site of organ system	Number (%)
Skin and soft tissue	89(32.5)
Systemic (>1 organs)	79(28.8)
Respiratory tract	46(16.7)
Eye	23 (8.3)
Musculoskeleton	8(2.9)
Genitourinary tract system	7 (2.5)
ENT	7 (2.5)
Gastrointestinal system	7(2.5)
Others	8(2.9)
Total	274(100)

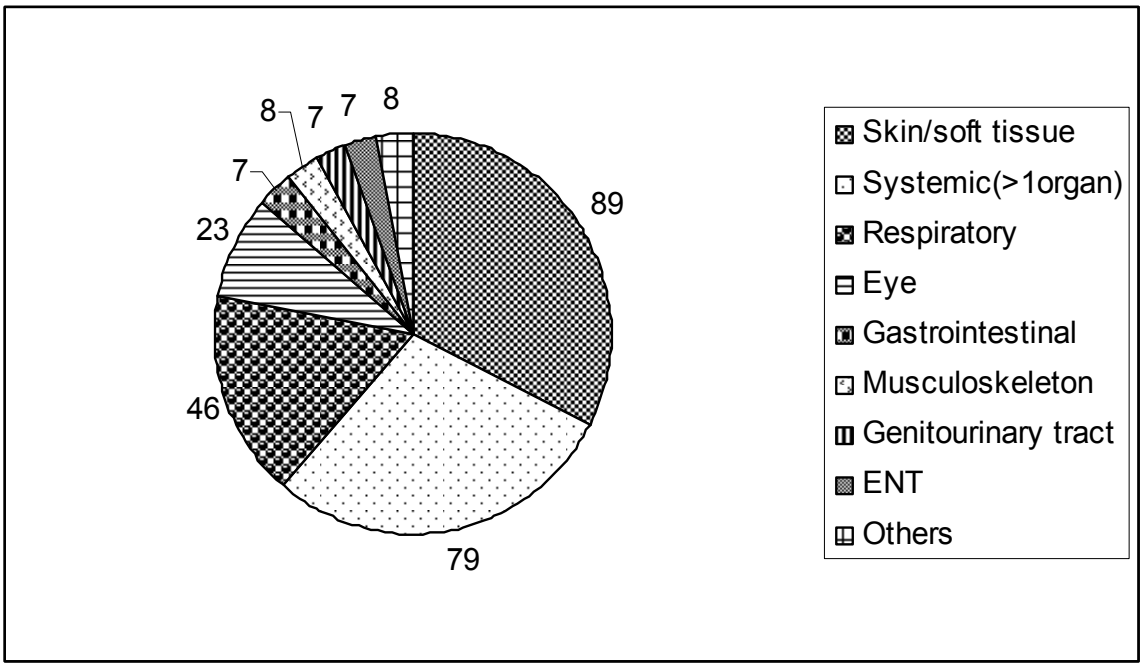

Figure 3. Distribution of *S. aureus* infection by organ system

Table 5. Characteristics of the studied patients

Variable	
Mean (SD) age in months (N=274)	25.3(40)
Mean (SD) weight in kg (N=268)	9 (8.5)
Mean (SD) height in cm (N=120)	75.6 (24.7)
Number (%) who had school attendance (N=255)	28 (11)
Number (%) who had previous hospitalization (N=236)	44 (18.6)
Number (%) who had concomitant chronic or underlying disease (N=268)	136 (50.7)
Number (%) taking immunosuppressive drugs (N=262)	11 (4.2)
Number (%) who had prior cutaneous infection (N=246)	6 (2.4)
Number (%) person with household*	78 (28.5)
Source of organism (N=274)	
CA	168 (61.3)
HA	106 (38.7)
Methicillin resistance pattern (N=274)	
MRSA	71 (25.9)
MSSA	203 (74.1)
Number (%) who had Surgical intervention (N=270)	96 (35.6)
Number (%) who had Instrumentation procedure (N=267)	117 (43.9)

***Household data of 196 persons is missing.**

Table 6. Methicillin susceptibility of *S. aureus* in different site of infection in community acquired infection

Site of infection	Community acquired		Total	Odd ratio (95% CI)	*p*-value
	MRSA (%)	MSSA (%)			
Skin and soft tissue infection	3 (4)	72 (96)	75	0.2 (0.04 -0.77)	0.01**
Genitourinary tract infection	1 (25)	3 (75)	4	2.7 (Invalid)	0.38**
Musculoskeleton	0	7 (100)	7	0.0 (0.0-6.44)	1.00**
Gastrointestinal tract	2 (50)	2 (50)	4	8.6 (0.8 –93.89)	0.06**
Systemic (>1 organs)	8 (27.6)	21(72.4)	29	4.03 (1.32 –12.28)	0.008*
Respiratory tract	5 (22.7)	17 (77.3)	22	2.8 (0.76-9.71)	< 0.01**
Eye	0	15(100)	15	-	-
ENT	0	6(100)	6	-	-
Others	0	6(100)	6	-	-

***Chi – square test. ** Fisher Exact Test**

Table 7. Methicillin susceptibility of *S. aureus* different site of infection in hospital acquired infection

Site of infection	Hospital acquired		Total	Odd ratio (95% CI)	*p*-value
	MRSA (%)	MSSA (%)			
Skin and soft tissue infection	4 (28.6)	10 (71.4)	14	0.3 7 (0.09-1.40)	0.2*
Genitourinary tract infection	1 (33.3)	2 (66.7)	3	0.51 (0.02-7.50)	1.0**
Musculoskeleton	1(100)	0	1	Undefined	0.5**
Gastrointestinal tract	3(100)	0	3	Undefined	0.11*
Systemic (>1 organs)	30 (60)	20 (40)	50	2.32 (0.99-5.46)	0.05*
Respiratory tract	12 (50	12(50	24	1.05 (0.39-2.86)	0.9*
Eye	0	8 (100)	8	-	-
ENT	0	1 (100)	1	-	-
Others	1(5)	1 (50)	2	-	-

***Chi – square. ** Fisher Exact Test**

Table 8. Methicillin susceptibility of *S. aureus* in different site of infection

Site of infection	Methicllin susceptibility		Total	Odd ratio (95% CI)	*p* -value
	MRSA (%)	MSSA (%)			
Skin and soft tissue infection	7 (7.8)	82 (92.1)	89	0.2 (0.06-0.39)	< 0.001*
Genitourinary tract infection	2 (28.6)	5 (71.4)	7	1.15 (0.15-6.87)	0.87**
Musculoskeleton	1(12.5)	7 (87.5)	8	0.4 (0.02-3.32)	0.68**
Gastrointestinal tract	5 (71.4)	2 (28.6)	7	7.61 (1.27-58.15)	<0.01**
Systemic (>1 organs)	38 (48.1)	41 (51.9)	79	4.55 (2.45-8.47)	< 0.001*
Respiratory tract	17 (37.0)	29 (63.0)	46	2.12 (1.03-4.35)	0.03*
Eye	0	23	23	-	-
ENT	0	7	7	-	-
Others	1 (43.8)	7(56.3)	8	-	-
Total	71 (25.9)	203 (74.1)	274		

*** Chi- square test ** Fisher Exact Test**

Table 9. Relationship between methicillin susceptibility of *S. aureus* and attending department of the patients

Admitted ward / OPD	Methicillin susceptibility		Total (%)
	MRSA (%)	MSSA (%)	
Pediatric Medical ward	20 (13.4)	129 (86.6)	149 (54.4)
PICU + NICU	18 (62)	11 (38)	29 (10.5)
Pediatric OPD	0	5 (100)	5 (1.8)
Neonatal ward	13 (23.2)	43 (76.8)	56 (20.4)
Surgical ward	18 (62)	11 (38)	29 (10.5)
Surgical OPD	1 (50)	1(50)	2 (0.7)
ENT or Eye ward	1 (50)	1 (50)	2 (0.7)
ENT or Eye OPD	0	2 (100)	2 (0.7)
Total	71	203	274 (100)

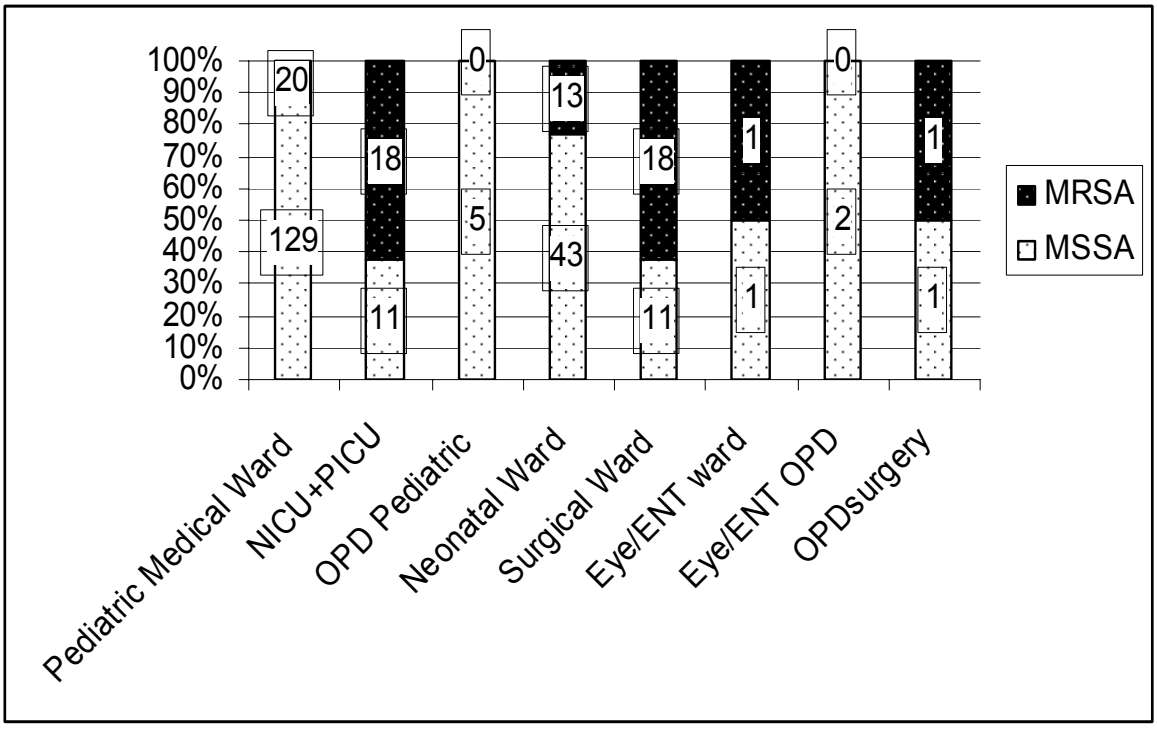

Figure 4. Distributions of MSSA and MRSA among different wards and OPD

Table 10. Distribution of source of organism acquired and methicillin susceptibility among different department

Departments	Community acquired		Hospital acquired		Total (%)
	MRSA (%)	MSSA (%)	MRSA (%)	MSSA (%)	
Pediatric Medical ward	12 (10.3)	104 (89.7)	8 (24.2)	24 (75.8)	149 (55.6)
NICU+PICU	3 (33.3)	6(66.7)	15 (75)	5 (25)	29 (10.6)
Pediatric OPD	0	5 (100)	0	0	5 (1.8)
Neonatal ward	0	21 (100)	13 (37.1)	22 (62.9)	56 (20.4)
Surgical/ENT/Eye ward	3 (23.1)	10 (76.9)	16 (89)	2 (11)	31 (11.3)
Surgery/ENT/Eye OPD	1 (25)	3 (75)	0	0	4 (1.45)
Total	19 (11%)	149	52 (49%)	54	274 (100)

Table 11. Distribution of antibiotic susceptibility pattern in isolated *S. aureus*

Antibiotic	Susceptible	Intermediate	Resistant
Co-trimoxazole	206 (75.2)	0	68 (24.8)
Erythromycin	117 (42.7)	82 (29.9)	75 (27.4)
Gentamicin	202 (73.7)	0	72 (26.3)
Oxacillin	203 (74.1)	0	71 (25.9)
Penicillin G	6 (2.2)	0	268 (97.8)
Vancomycin	274 (100)	0	0

Table 12. Comparison of other antibiotic susceptibility between patients with HA and CA infection

Antibiotics	Hospital acquired				Community acquired			
	MRSA (%)		MSSA (%)		MRSA (%)		MSSA (%)	
	S	R	S	R	S	R	S	R
Co-trimoxazole	1 (1.8)	51 (98.2)	54 (100)	0	2 (10.5)	17 (89.9)	149 (100)	0
Erythromycin	1 (1.9)	51 (98.1)	32 (59.3)	21 (38.9)	0	19 (100)	84 (56.4)	65 (43.6)
Gentamicin	0	52 (100)	53 (98.1)	1 (1.9)	0	19 (100)	149 (100)	0
Penicillin G	0	52 (100)	0	54 (100)	0	19 (100)	6 (4)	143 (96)
Vancomycin	52 (100)	0	54 (100)	0	19 (100)	0	149 (100)	0

Table13. Comparison of other antibiotic susceptibility between patients with MSSA and MRSA infection

Antibiotics	Methicillin susceptibility		Total	*p* – value*
	MSSA (%)	MRSA (%)		
Co-trimoxazole				
Susceptible	203 (98.5)	3 (1.5)	206	0.00
Resistant	0 (0.0)	68 (100)	68	
Erythromycin				
Susceptible	116 (99.1)	1 (0.9)	117	0.00
Intermediate	82 (100)	0 (0.0)	82	
Resistant	5 (6.7)	70 (93.3)	75	
Gentamicin				
Susceptible	202 (100)	0 (0.0)	202	0.00
Resistant	1 (1.4)	71 (98.6)	72	
Penicillin G				
Susceptible	6 (100)	0 (0.0)	6	0.344
Resistant	197 (73.5)	71 (26.5)	268	
Vancomycin				
Susceptible	203 (74.1)	71 (25.9)	274	-
Resistant	0(0.0)	0 (0.0)	0	

*** Chi- square test**

Table14. Relationship between the disease outcome and age group

Age group	Disease outcome				
	Cure	Improved	Not improved	Died	Total (%)
≤ 2 mo	3 (2.6)	86 (75.4)	4 (3.5)	21 (18.4)	114 (42.8)
> 2 mo – 24 mo	4 (5.2)	65 (84.4)	1 (1.3)	7 (9.1)	77 (28.9)
> 24 mo – 60 mo	1 (3.1)	28 (87.5)	1 (3.1)	2 (6.3)	32 (12.0)
> 60 mo	0	39 (90.7)	2 (4.7)	2 (4.7)	43 (16.2)
Total (%)	8 (3.0)	218 (82.0)	8 (3.0)	32 (12.0)	266*(100)

*** 8 cases are missing data in the disease outcome**.

Table15. Relationship between methicillin susceptibility pattern and the disease outcome

Outcome	Methicillin susceptibility		Total (%)
	MRSA (%)	MSSA (%)	
Cure	2 (2.9)	6 (3)	8 (3)
Improved	39 (56.5)	179 (90.9)	218 (81.9)
Not improved	3 (4.3)	5 (2.5)	8 (3)
Died	25 (36.2)	7 (3.6)	32 (12)
Total	69 (100)	197 (100)	266*(100)

*** 8 cases are missing data in the disease outcome**

Table 16.Relationship between type of chronic or underlying diseases, diagnosis of previous hospitalization, type of cutenous infection and patients with CA and HA *S. aureus* infection

	Hospital acquired		Community acquired		
	MRSA (%)	**MSSA (%)**	**MRSA (%)**	**MSSA (%)**	**Total**
Chronic and underlying disease:					
• Disease requires immunosuppressive treatment.	3 (30)	7 (70)	1 (11.1)	8 (88.9)	29
• Other chronic disease	42 (60.9)	27 (39.1)	13 (27.1)	35 (72.9)	97
Diagnosis of previous hospitalization:					
• Disease requires surgical intervention	6 (85.7)	1 (14.3)	2 (28.6)	5 (71.4)	14
• Disease require immunosuppressive treatment	1 (33.3)	2 (66.7)	1 (20)	4 (80)	8
• Other chronic disease	1 (33.3)	2 (66.7)	0	3 (100)	6
• Others	3 (60)	2 (40)	2 (22.2)	7 (77.8)	14
Type of cutaneous infection:					
• Bacterial skin infection	1 (50)	1 (50)	0	2 (100)	4

Table 17. Comparison of risk factors among patients with MSSA and MRSA infection by univariate analyses

Factor	Methicillin susceptibility		Total	Odd ratio (95% CI)	*p* –value
	MRSA (N=66)(%)	MSSA (N=192)(%)			
Age					
≤ 1 yr	59 (83.1)	108 (53.2)	167	4.3	0.001*
> 1 yr – 15 yrs	12 (16.9)	95 (46.8)	107	(2.12-9.06)	
Gender					
Male	46 (65.7)	107(53)	153	1.7	0.09*
Female	24 (34.3)	95 (47)	119	(0.93-3.12)	
School attendant					
Yes	2 (3)	26(13.9)	28	0.2	0.024*
No	66 (97)	161 (86.1)	227	(0.03-0.85)	
Day care attendant					
Yes	0 (0)	0 (0)	0	-	-
No	69 (100)	181 (100)	250		
Previous hospitalization					
Yes	17 (27.4)	27 (15.5)	44	2.1	0.06*
No	45 (72.6)	147 (84.5)	192	(0.97-4.34)	
Chronic and underlying disease					
Yes	59 (83)	77 (39)	136	7.7	< 0.001*
No	12 (17)	120 (61)	132	(3.70-16.14)	
Immune suppressive					
Yes	1 (1.5)	10 (5)	11	0.3	0.29**
No	66 (98.5)	185 (95)	251	(0.01-2.19)	
Prior cutaneous infection					
Yes	1 (1.6)	5 (2.7)	6	0.6	1.00**
No	63 (98.4)	177 (97.3)	240	(0.02-5.09)	
Surgical intervention					
Yes	39 (57.4)	57 (28.2)	96	3.4	< 0.001*
No	29 (42.6)	145 (71.8)	174	(1.86-6.30)	
Instrumental procedure					
Yes	57 (82.6)	60 (30.3)	117	10.9	< 0.001*
No	12 (17.4)	138 (69.7)	150	(5.23-23.25)	

***Chi-square test, ** Fisher Exact Test,**

Table 18.Comparison of risk factors among patients with CA-MSSA and CA-MRSA infection by univariate analyses

Factor	Community acquired		Total	Odd ratio (95% CI)	*p* –value
	MRSA (N=19)(%)	MSSA (N=141)(%)			
Age					
≤ 1 yr	16 (18.6)	70 (81.4)	86	6.02	0.01*
> 1 yr – 15 yrs	3 (3.8)	79 (96.3)	82	(1.56 – 27.21)	
Gender					0.3*
Male	13 (14.4)	77 (85.6)	90	2	
Female	6 (7.8)	71 (92.2)	77	(0.66 -6.27)	
School attendant					0.1**
Yes	0	21 (15.3)	21	0.00	
No	18 (100)	116 (84.7)	134	(0.0 -1.67)	
Day care attendant					
Yes	0	0	0	-	-
No	19 (12.6)	132 (87.4)	151		
Previous hospitalization					
Yes	5 (20)	20 (80)	25	2.27	0.2**
No	12 (9.9)	109 (90.1)	121	(0.62 – 22.70)	
Chronic and underlying disease					
Yes	14 (24.6)	43 (75.4)	57	6.64	< 0.001*
No	5 (4.7)	102 (95.3)	107	(2.06 – 22.7)	
Immune suppressive					
Yes	1 (16.7)	5 (83.3)	6	1.54	0.5**
No	18 (11.5)	139 (88.5)	157		
Prior cutaneous infection					
Yes	0	4 (100)	4	0.00	1.0**
No	17 (11.6)	130 (88.4)	147	(0.0 – 13.02)	
Surgical intervention					
Yes	3 (7)	40 (93)	43	0.58	0.6**
No	14 (11.4)	109 (88.6)	123	(0.13 – 2.34)	
Instrumental procedure					
Yes	27 (73)	10 (27)	37	0.21	0.01*
No	118 (92.9)	9 (7.1)	127	(0.07 – 0.62)	

*** Chi-square test, ** Fisher Exact Test**

Table 19.Comparison of risk factors among patients with HA-MSSA and HA-MRSA infection by univariate analyses

Factor	Hospital acquired		Total	Odd ratio (95% CI)	*p* – value
	MRSA (N=49) (%)	MSSA (N=51) (%)			
Age					
≤ 1 yr	43 (53.1)	38 (46.9)	81	2.0	0.2*
> 1 yr – 15 yrs	9 (36.0)	16 (64.0)	25	(0.73 – 5.63)	
Gender					
Male	33 (52.4)	30 (47.6)	63	1.5	0.45*
Female	18 (43.0)	24 (57.0)	42	(0.80 – 1.86)	
School attendant					
Yes	2 (28.6)	5 (71.4)	7	0.4	0.4**
No	48 (51.6)	45 (48.4)	93	0.05 – 2.35)	
Day care attendant					
Yes	0	0	0	-	-
No	50 (50.5)	49 (49.5)	99		
Previous hospitalization					
Yes	12 (63.2)	7 (36.8)	19	1.9	0.3*
No	33 (46.5)	38 (53.5)	71	(0.63 – 6.36)	
Chronic and underlying disease					
Yes	45 (57)	34 (43)	79	3.4	0.01*
No	7 (28)	18 (72)	25	(1.17 – 10.22)	
Immune suppressive					
Yes	0	5 (100)	5	0.0	0.06**
No	48 (51.1)	46 (48.9)	94	(0.0 – 1.19)	
Prior cutaneous infection					
Yes	1 (50)	1 (50)	2	1.0	
No	46 (49.5)	47 (50.5)	93	(0.0 – 38.74)	1.0**
Surgical intervention					
Yes	36 (67.9)	17 (37.1)	53	5.1	< 0.001*
No	15 (29.4)	36 (70.6)	51	(2.04 – 12.84)	
Instrumental procedure					
Yes	47 (58.2)	33 (41.3)	80	9.5	< 0.001*
No	3 (13)	20 (87)	23	(2.39 – 43.96)	

Chi-square, ** Fisher Exact Test

Table 20. Comparison of risk factors among patients with MSSA and MRSA infection by multivariate analyses

Factor	Methicillin susceptibility		Total	*P* –value
	MRSA (N=66)(%)	MSSA (N=192)(%)		
Age				
≤ 1 yr	59 (83.1)	108 (53.2)	167	< 0.001*
> 1 yr – 15 yrs	12 (16.9)	95 (46.8)	107	
School attendant				
Yes	2 (3)	26(13.9)	28	0.52 *
No	66 (97)	161 (86.1)	227	
Chronic and underlying disease				
Yes	59 (83)	77 (39)	136	< 0.001*
No	12 (17)	120 (61)	132	
Surgical intervention				
Yes	39 (57.4)	57 (28.2)	96	< 0.01 *
No	29 (42.6)	145 (71.8)	174	
Instrumental procedure				
Yes	57 (82.6)	60 (30.3)	117	< 0.001 *
No	12 (17.4)	138 (69.7)	150	

Table 21.Comparison of risk factors among patients with CA-MSSA and CA-MRSA infection by multivariate analyses

Factor	Community acquired		Total	*p* –value
	MRSA (N=19)(%)	MSSA (N=141)(%)		
Age				
≤ 1 yr	16 (18.6)	70 (81.4)	86	0.09*
> 1 yr – 15 yrs	3 (3.8)	79 (96.3)	82	
Chronic and underlying disease	14 (24.6)	43 (75.4)	57	< 0.001*
Yes	5 (4.7)	102 (95.3)	107	
No				
Instrumental procedure				
Yes	27 (73)	10 (27)	37	0.19*
No	118 (92.9)	9 (7.1)	127	

Table 22.Comparison of risk factors among patients with HA-MSSA and HA-MRSA infection by multivariate analyses

Factor	Hospital acquired		Total	*p* – value
	MRSA (N=49) (%)	MSSA (N=51) (%)		
Chronic and underlying disease				
Yes	45 (57)	34 (43)	79	0.22*
No	7 (28)	18 (72)	25	
Surgical intervention				
Yes	36 (67.9)	17 (37.1)	53	< 0.01*
No	15 (29.4)	36 (70.6)	51	
Instrumental procedure				
Yes	47 (58.2)	33 (41.3)	80	< 0.01*
No	3 (13)	20 (87)	23	

CHAPTER VI
DISCUSSION

Over the last decade, the prevalence of MRSA infection in different countries and hospitals all over the world has been increasing.

Surveillance data from European Antimicrobial Resistance Surveillance System (Tiemersma et al., 2004) showed that proportion of MRSA significantly increased in Belgium (27.3%), Germany (19.2%), Ireland (45%) and United Kingdom (44.5%). Reports from African hospitals showed that MRSA accounted for 21.3 – 30% of all clinical samples (Kesah et al., 2003). In Thailand, the rate of MRSA ranged from 26.6 – 38.7% (Vitipatarapak 1998; Napaporn 2003), which was not much different to the proportion of MRSA isolates observed in our study (26%).

Sixty-one percent of patients were ≤ 1year of age and 71% were ≤ 2yrs of age. In this study we found that 83% of MRSA infected patients were ≤ 1year of age. Storch and Rajagopalan reported that MRSA bacteremia occurred mainly in infants and had history of prematurity.

Previous reports have shown that MRSA infections occurred most often in intensive care unit and surgical wards because these patients received more antibiotics, undergone more intensive instrumental procedures and surgical interventions and have longer hospital stay than those admitted to medical wards (Myers and Linnemann, 1982; Swanston, 1999). During the period of this study, we also documented that MRSA infection were more common than MSSA in intensive care units and surgical wards which is similar to the previous report (Endo et al., 1996).

MRSA is associated with infection of various body sites. In this study, the most common site of infection was skin and soft tissue infection, followed by systemic (>1 organs), respiratory tract infection, eye and genito-urinary tract system. Similar finding was reported by investigator (Locksley et al., 1982).

MRSA is resistant not only to the semi synthetic penicillinase resistance penicillins such as methicillin but also to multiple antibiotics including all beta-lactam antibiotics, aminoglycosides, cephalosporins and other anti staphylococcal antibiotics ((Myers and Linnemann, 1982; Richmond et al., 1997). In this study, about one-fourth of MRSA isolates were resistant to four of six tested antibiotics. Almost all MRSA isolates were resistant to co-trimoxazole, erythromycin, gentamicin and penicillin G. Fortunately, all MRSA isolates were still sensitive to vancomycin.

Several investigators (Thompson et al., 1982; Locksley et al., 1982; Strausbaugh et al., 1991) have reported risk factors for MRSA infection including, prolonged hospitalization, hospitalization in intensive care unit and existing chronic illness. In this study we documented risk factors for MRSA infection included younger age (≤ 1year), had chronic and underlying diseases, had instrumentation procedures and surgical intervention and admitting to intensive care unit.

In our study the risk factors for CA-MRSA was different from risk factors for CA-MSSA, as we found that age ≤ 1year and chronic or underlying disease were risk factors for CA-MRSA infection. This was different from report from Sattler et al., 2002, which found no difference risk factors for CA-MRSA and CA-MSSA infection.

This study has several limitations. The retrospective design increased the chances that patients may misclassified. Because medical records were not always completed and patients were not available for interview, HA infection criteria may have been missed.

Because of this limitation we couldn’t prove any association between household contacts, previous hospitalization, school attendance, prior cutaneous skin infection, immunosuppressive drugs and MRSA.

CHAPTER VII
CONCLUSION

This study was conducted to study risk factors, ratio of MRSA and MSSA and the antibiogram pattern of MRSA and MSSA in 274 pediatric patients with *S. aureus* infection.

MRSA was an important cause of infection in children, especially children aged ≤ I year. Skin and soft tissue infection was the most common system involved in non-invasive S. *aureus* infection on the other hand systemic (> 1 system, include blood) were common site in invasive *S. aureus* infection.

Younger age (≤ 1 year), chronic and underlying disease, instrumentation procedure and surgical intervention were found to be associated with MRSA infection while household contact, prior cutaneous skin infection, and immunosuppressive drugs were not.

The proportion of MRSA was less than MSSA but the proportion of HA – MRSA infection was more than CA – MRSA infection.

Nearly 26% of *S. aureus* isolates were resistant to co-trimoxazole, erythromycin, gentamycin and oxacillin while almost (98%) of the isolates were resistant to penicillin G. All the isolates were sensitive to vancomycin.

RECOMMENDATION

Therefore, base on the result of this study we suggest that:

- Penicillin G should not be used for treatment of *S. aureus* infection unless its sensitivity is proved.
- Vancomycin could be used for treatment of invasive *S. aureus* infection with resistant to methicillin.
- It should be careful for treatment of children with invasive *S. aureus* infection, especially ≤ 2 months. The possibility of methicillin resistance *S. aureus* should be kept in mind.
- Initiative to control MRSA and continues surveillance system should be initiated, especially in intensive care unit and surgical wards, include health care personal.

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APPENDIX

PATIENT'S CASE RECORD FORM Subject No___ ___ ___

Hospital Number ___ ___ ___ ___ ___ ___/___ ___

Admission Number ___ ___ ___ ___ ___/___ ___

Date of Admission __ __ /__ __/__ __ Date of Discharge __ __ /__ __/__ __ (DD/MM/YY)

1. Patient Profile

1.1 Birth Date __ __ /__ __/__ __ (DD/MM/YY) or Age __ __ years __ __ mo

1.2 Gender ____ Male=1/Female=2

1.3 Weight ___ ___. ___ kg
☐ no data

1.4 Height or Length ___ ___ ___ cm
☐ no data

1.5 School attendant:
☐ no school attendant
☐ kindergarten
☐ elementary school (Gr. I-VI)
☐ primary school (Gr. VII-IX)
☐ secondary school (Gr. X-XII)
☐ no data

1.6 Is there any day-care attendance in the last six months?
☐ No ☐ Yes, if yes, how long?_____ months ☐ no data

1.7 Is there any previous hospitalization within 1 year?
☐ No ☐ Yes, if yes, how many times? _____ ☐ no data
The latest admission date: __ __/__ __/__ __ (DD/MM/YY)
Duration of hospitalization: _____ days(last admission)
Diagnosis: _____

1.8 Does the patient have any chronic disease?
☐ No ☐ Yes, if yes, define_____ ☐ no data

1.9 Does the patient take any immunosuppressive drug?
☐ No ☐ Yes, if yes, define_____ ☐ no data

1.10 Is there any history of prior cutaneous infection within 6 months?
☐ No ☐ Yes, if yes, define_____ ☐ no data
When did the latest occur? ____/____/____(DD/MM/YY)

1.11 Number of persons in the household: _____ (include the patient) ☐ no data

2. The clinical features

2.1 System of *S. aureus* infection:

☐ skin and soft tissue ☐ musculoskeleton ☐ respiratory tract
☐ cardiovascular system ☐ gastrointestinal system ☐ hepatobiliary system
☐ genitourinary tract ☐ systemic (>1 organ) ☐ nervous system
☐ other, define_____

2.2 System of surgical intervention (can be >1)

☐ skin and soft tissue ☐ musculoskeleton ☐ respiratory tract
☐ cardiovascular system ☐ gastrointestinal system ☐ hepatobiliary system
☐ genitourinary tract ☐ systemic ☐ nervous system
☐ other, define_____ ☐ no any intervention ☐ no data

2.3 Instrumental procedure (can be >1)

☐ endotracheal tube ☐ urinary catheter ☐ endoscope
☐ vascular catheter ☐ no any instrument ☐ no data
☐ other, define _____

2.4 Admitted ward

☐ pediatric ward ☐ newborn ward ☐ surgical ward ☐ ENT or eye ward
☐ ICU pediatric ☐ NICU ☐ ICU surgery ☐ OPD ENT or eye
☐ OPD pediatric ☐ OPD well baby ☐ OPD surgery ☐ other, define_____

2.5 Type of infection:

☐ community acquired ☐ hospital acquired

2.6 Antibiotic treatments and their outcome:

Before the result of culture:

_____dose _____mg/kg/day start date ___/___/___ stop date ___/___/___
_____dose _____mg/kg/day start date ___/___/___ stop date ___/___/___
_____dose _____mg/kg/day start date ___/___/___ stop date ___/___/___

After isolation:

☐ No change Outcome ☐ cure ☐ improve ☐ not improve ☐ dead

☐ Change(1) ATB: name _____, dose ____ mg/kg/day, duration __ days
ATB: name _____, dose ____ mg/kg/day, duration __ days
Outcome after change(1) ☐ cure ☐ improve ☐ not improve ☐ dead

☐ Change(2) ATB: name _____, dose ____ mg/kg/day, duration __ days
ATB: name _____, dose ____ mg/kg/day, duration __ days
Outcome after change(2) ☐ cure ☐ improve ☐ not improve ☐ dead

☐ Change(3) ATB: name _____, dose ____ mg/kg/day, duration __ days
ATB: name _____, dose ____ mg/kg/day, duration __ days
Outcome after change(3) ☐ cure ☐ improve ☐ not improve ☐ dead

3. Pathogen

3.1 Lab specimen No. ___ ___ ___ ___ ___/__ ___

3.2 Date of specimen collection: ____/____/____

3.3 Source of specimen:

☐ blood ☐ CSF ☐ pleural fluid ☐ pericardial fluid
☐ ear discharge ☐ sputum ☐ tip of catheter ☐ skin and soft tissue
☐ urine ☐ other, define_____

3.4 Resistance of *Staphylococcus aureus*:

☐ MSSA ☐ MRSA ☐ VISA ☐ VRSA

3.5 Susceptibility pattern:

Antibiotic	Susceptible	Intermediate	Resistant	Method	MIC
Amikacin					
Ampicillin					
Cefotaxime					
Ceftriaxone					
Ceftazidime					
Chloramphenicol					
Ciprofloxacin					
Co-trimoxazole					
Erythromycin					
Gentamicin					
Imipenam					
Oxacillin					
Meropenam					
Nalidixic acid					
Netilmicin					
Nitrofurantoin					
Norfloxacin					
Penicillin G					
Tetracycline					
Vancomycin					

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