

**RISK FACTORS FOR METHICILLIN-RESISTANT  
*STAPHYLOCOCCUS AUREUS* INFECTION AT QUEEN SIRIKIT  
NATIONAL INSTITUTE OF CHILD HEALTH  
(EMPHASIS IN INSTRUMENTAL PROCEDURE)**



**SUSITH RANJAN WADIKAWAGE**

**A THEMATIC PAPER SUBMITTED IN PARTIAL  
FULFILLMENT OF THE REQUIREMENTS  
FOR THE DEGREE OF  
MASTER OF CLINICAL TROPICAL MEDICINE  
(TROPICAL PEDIATRICS)**

**FACULTY OF GRADUATE STUDIES**

**MAHIDOL UNIVERSITY**

**2005**

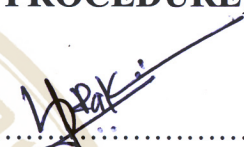
**ISBN 974-04-5704-5**

**COPYRIGHT OF MAHIDOL UNIVERSITY**

Copyright by Mahidol University


Thematic paper  
entitled

**RISK FACTORS FOR METHICILLIN-RESISTANT  
STAPHYLOCOCCUS AUREUS INFECTION AT QUEEN SIRIKIT  
NATIONAL INSTITUTE OF CHILD HEALTH  
(EMPHASIS IN INSTRUMENTAL PROCEDURE)**


  
.....  
Mr. Susith Ranjan Wadikawage  
Candidate

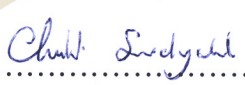
  
.....  
Assoc. Prof. Pornthep Chanthavanich,  
M.D., M.Sc. (M.C.H), D.T.C.H  
Co-Advisor

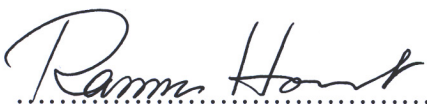
  
.....  
Asst. Prof. Kriengsak Limkittikul,  
Dip. Thai Board of Pediatrics  
Major-Advisor

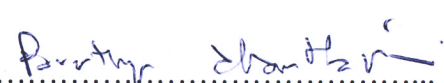
  
.....  
Special Assoc. Prof. Tawee  
Chotpitayasunondh,  
Dip. Thai Board of Pediatrics  
Co-Advisor

  
.....  
Assoc. Prof. Krisana Pengsaa,  
Dip. Thai Board of Pediatrics  
Co-Advisor

  
.....  
Mr. Porntep Suandork,  
Dip. Thai Board of Pediatrics,  
Cert. Pediatric Infectious Diseases  
Co-Advisor

  
.....  
Assoc. Prof. Chukiatt Sirivichayakul,  
Dip. Thai Board of Pediatrics  
Co-Advisor

  
.....  
Assoc. Prof. Rassmidara Hoonsawat,  
Ph.D.  
Dean  
Faculty of Graduate Studies

  
.....  
Assoc. Prof. Pornthep Chanthavanich,  
M.D., M.Sc. (M.C.H.), D.T.C.H.  
Chair  
Master of Clinical Tropical Medicine  
(Tropical Pediatrics)  
Faculty of Tropical Medicine

Thematic paper

entitled

**RISK FACTORS FOR METHICILLIN-RESISTANT  
STAPHYLOCOCCUS AUREUS INFECTION AT QUEEN SIRIKIT  
NATIONAL INSTITUTE OF CHILD HEALTH  
(EMPHASIS IN INSTRUMENTAL PROCEDURE)**

was submitted to the Faculty of Graduate Studies, Mahidol University  
for the degree of Master of Clinical Tropical Medicine (Tropical Pediatrics)

on

March 15, 2005

.....  
Mr. Susith Ratan Wadikawage

Candidate

.....  
Asst. Prof. Kriengsak Limkittikul,

Dip. Thai Board of Pediatrics

Chair

.....  
Assoc. Prof. Krisana Pengsaa,

Dip. Thai Board of Pediatrics

Member

.....  
Assoc. Prof. Chuki Sirivichayakul,

Dip. Thai Board of Pediatrics

Member

.....  
Assoc. Prof. Usa Thisyakorn,

Dip. Thai Board of Pediatrics

Member

.....  
Prof. Usa Thisyakorn

Dip. Thai Board of Pediatrics,

Cert. Pediatric Infectious Diseases

Cert. of Proficiency Board in Pediatric

Infectious Diseases

Member

.....  
Assoc. Prof. Prapat Singhasivanon,

M.B.B.S., D.T.M.&H. (Bangkok),

M.P.M., Dr.P.H. (Epidemiology)

Dean

Faculty of Tropical Medicine

Mahidol University

.....  
Assoc. Prof. Pornthep Chanthavanich,

M.D., M.Sc. (M.C.H), D.T.C.H

Member

.....  
Special Assoc. Prof. Tawee

Chotpitayasunondh,

Dip. Thai Board of Pediatrics

Member

.....  
Mr. Porntep Suandork,

Dip. Thai Board of Pediatrics,

Cert. Pediatric Infectious Diseases

Member

.....  
Assoc. Prof. Rassmidara Hoonsawat,

Ph.D.

Dean

Faculty of Graduate Studies

Mahidol University

## ACKNOWLEDGEMENT

First of all I would like to express my profound thanks and gratitude to DPDHS, PDHS, Ministry of Health and Sri Lankan Government, for giving me the opportunity to pursue this valuable, MCTM (TP) course.

With uttermost respect I would like to express my deep appreciation and gratitude to my advisor Asst. Prof. Kriengsak Limkittikul. This thematic paper would not have been possible without his tremendous skill, insight and constant source of marvelous advice.

With regards I would like to express my sincere thanks, as I owed a lot of gratitude to my co-advisors, Assoc. Prof. Pornthep Chanthavanich, Assoc. Prof. Krisana Pengsaa, Assoc.Prof.Chukiatt Sirivichayakul, Special Assoc. Prof. Tawee Chotpitayasunondh, Dr. Pornthep Suandork for their invaluable suggestions, guidance and moreover their kind helps right through this study and during preparation of the thematic paper.

My special thanks go to Dr. Keswadee Lapphra for her kindness, supports and encouragement during studying for the thematic paper.

Also my profound thanks go to my partner, Dr.Abdu- Rahman Mohamed Nuh, staff of Faculty of Tropical Pediatrics and staff at Microbiology Laboratory at QSNICH for their valuable support during my study for the thesis.

I wish to express my deep appreciation and gratitude to Department of Technical and Economic Co-operation (DTEC) and The Royal Thai Government for the sponsorship and the mandatory support. Without their contribution this study would not have been possible.

Last but not least I would like to dedicate all my gratitude and deepest in debt to my parents, mother in-law, brothers, sisters, friends, specially my loving wife and sons for their deepest understanding, encouragement and kindness in completing all possible to me.

Susith Ranjan Wadikawage

RISK FACTORS FOR METHICILLIN-RESISTANT  
*STAPHYLOCOCCUS AUREUS* INFECTION AT QUEEN SIRIKIT  
NATIONAL INSTITUTE OF CHILD HEALTH (EMPHASIS IN  
INSTRUMENTAL PROCEDURES)

SUSITH RANJAN WADIKAWAGE 4738680 TMCT/M

M.C.T.M. (Trop. Ped.)

THEMATIC PAPER ADVISORS: KRIENGSAK LIMKITTIKUL, M.D., DIP. THAI BOARD OF PEDIATRICS, KRISANA PENGSA, M.D., DIP. THAI BOARD OF PEDIATRICS, D.T.M.&H., CHUKIAT SIRIVICHAYAKUL, M.D., DIP. THAI BOARD OF PEDIATRICS, D.T.M.&H., PORNTHEP CHANTHAVANICH, M.D., D.T.M.&H., M.Sc. (M.C.H.), D.T.C.H., TAWEE CHOTPITASUNONDH, M.D., DIP. THAI BOARD OF PEDIATRICS, D.T.M.&H., PORNTEP SUANDORK, M.D., DIP. THAI BOARD OF PEDIATRICS.

ABSTRACT

This retrospective study was conducted at Queen Sirikit National Institute of Child Health by reviewing 274 medical records of pediatric patients from whom *Staphylococcus aureus* (*S. aureus*) was isolated from January 2002 to December 2003, to identify the ratio of MRSA and MSSA and the risk factors for methicillin-resistant *S. aureus* (MRSA) infection in children. The susceptibility patterns to the commonly used antibiotics were also reviewed.

General information of the patients as well as information about clinical specimens, site of infection, antibiotic sensitivity pattern, instrumentation procedures and surgical interventions were collected by pre-formed questionnaire.

It was found that age less than 1 year, presence of chronic or underlying disease, having instrumentation procedures and undergoing surgical interventions were significant risk factors for MRSA. The instrumentation procedures caused highest risk for MRSA isolation, with an odd ratio of 11 (95% CI 5.2-23.3). Nearly half of the patients with *S. aureus* infection (43.8%) had received instrumentation procedures.

In the hospital-acquired infections, MRSA was significantly associated with endotracheal intubation and vascular catheterization, with odds ratios of 3.3 (95% CI 1.0-10.9) and 8.3 (95%CI 9.0-36.5), respectively.

Both MRSA and MSSA were highly susceptible to vancomycin. Cotrimoxazole, erythromycin and gentamicin were effective only against MSSA. Both strains of *S. aureus* were resistant to penicillin G, implying that this drug has no place in the treatment of *S. aureus* infection.

KEY WORDS: *STAPHYLOCOCCUS AUREUS*/MRSA/ MSSA/ RISK FACTORS / CHILDREN/HOSPITAL-ACQUIRED/COMMUNITY ACQUIRED.

42 P. ISBN 974-04-5704-5

## CONTENTS

	<b>Page</b>
ACKNOWLEDGEMENTS .....	iii
ABSTRACT .....	vi
LIST OF TABLE .....	v
LIST OF ABBREVIATIONS .....	vi
CHAPTER	
I    INTRODUCTION .....	1
II   OBJECTIVES .....	4
III  REVIEW OF LITERATURE .....	5
IV  MATERIALS AND METHODS .....	11
V   RESULTS .....	15
VI  DISCUSSION .....	30
VII CONCLUSION .....	32
BIBLIOGRAPHY .....	33
APPENDIX .....	38
BIOGRAPHY .....	42

## LIST OF TABLE

	<b>Page</b>
<b>Table 1.</b> The Characteristics of Patients	16
<b>Table 2.</b> Distribution of <i>S. aureus</i> Infection according to the Admitted Wards	17
<b>Table 3.</b> Site of Infection and Surgical Intervention Presented in Number of Isolation of <i>Staphylococcus. aureus</i> Specimens	18
<b>Table 4.</b> Instrumental Procedures in <i>S. aureus</i> Infected Patients	19
<b>Table 5.</b> Source of Specimen for <i>S. aureus</i> Isolation	20
<b>Table 6.</b> Risk Factors for Hospital- and Community-Acquired <i>S. aureus</i> Infection	22
<b>Table 7.</b> Risk Factors for <i>S. aureus</i> Infection in the MRSA and MSSA	24
<b>Table 8.</b> The Antibiotic Susceptibility Pattern of MRSA and MSSA	25
<b>Table 9.</b> The Antibiotic Susceptibility Pattern of MRSA according to Hospital- and Community-Acquired Infections	26
<b>Table 10.</b> The Antibiotic Susceptibility Pattern of MSSA in Hospital- and Community-Acquired Infections	26
<b>Table 11.</b> Comparison of Diagnosis and Strains of <i>S. aureus</i> in Hospital-Acquired Infection	27
<b>Table 12.</b> Comparison of Diagnosis and Strains of <i>S. aureus</i> in Community-Acquired Infection	28
<b>Table 13.</b> Relationship of Instrumentation and Hospital-Acquired MRSA Infection	29

## 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 <i>Staphylococcus aureus</i>
MSSA	Methicillin Sensitive <i>Staphylococcus aureus</i>
NA	Not Applicable

## 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
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
SCC mec	Staphylococcal Chromosome Cassette <i>mec</i>
TSS	Toxic Shock Syndrome
U S	United State
USD	US Dollar
VISA	Vancomycin Intermediate Resistant <i>Staphylococcus aureus</i>
VRSA	Vancomycin Resistant <i>Staphylococcus aureus</i>
W/v	Weight Per Volume
%	Percent
$\beta$	Beta
<	Less Than
>	More Than
$\geq$	More Than and Equal
$\leq$	Less Than and Equal
$\chi^2$	Chi-Square

## CHAPTER I

### INTRODUCTION

*Staphylococcus aureus* (*S. aureus*) is a 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 (Stroch et al., 1986; Crossley et al., 1979).

CA-MRSA is an increasingly common pathogen in pediatric population (Sattler et al., 2002; Herold et al., 1998; Fergie, 2001).

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 analysis 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 (Soriano et al., 2000; McClelland et al., 1999; Harbarth et al., 1998).

One study (Boyce, 1998) showed that patients with serious MRSA infections stayed in the hospital for an average of 12 days longer, and had the 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.

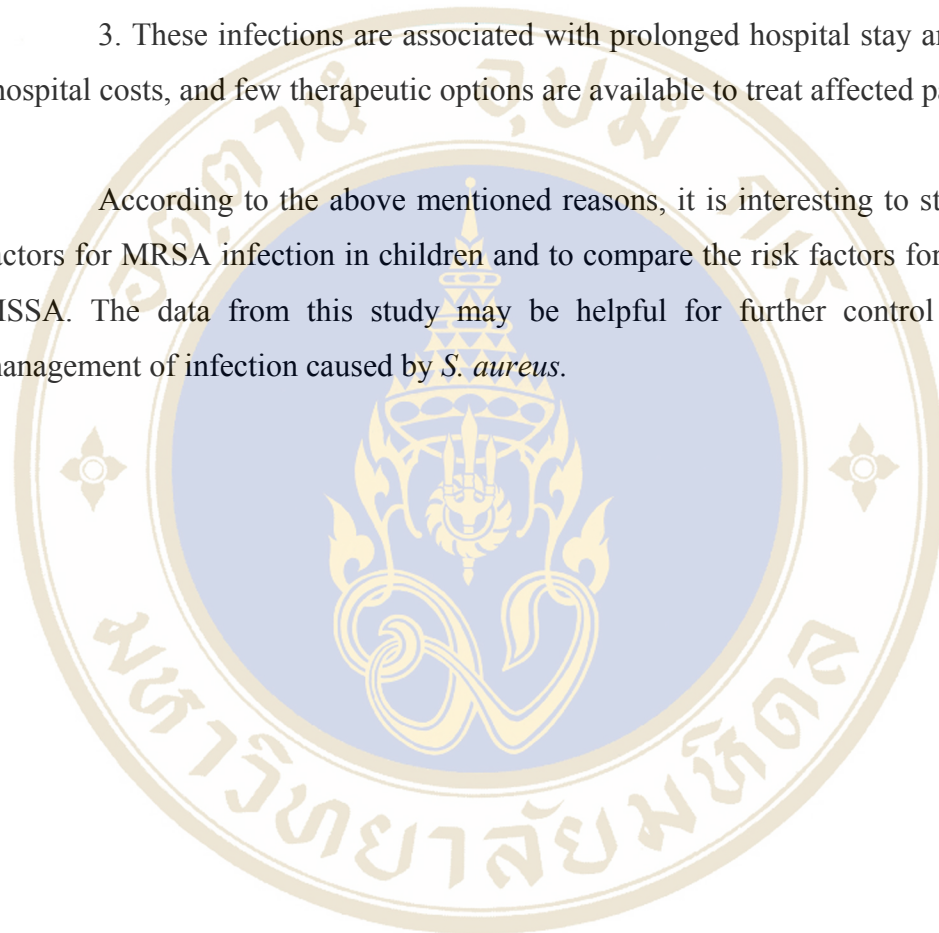
**In conclusion, MRSA infection is important because of the following reasons:**

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 stay 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

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

#### OBJECTIVES OF STUDY:

##### General Objectives

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

##### Specific Objectives

1. To study risk factors of MRSA comparing with MSSA infection.
2. To study risk factors of hospital comparing with community acquired *S. aureus* infection.
3. To compare the antibiogram pattern of MRSA and MSSA.
4. To study risk factors of MRSA infection in association with instrumentation.

## 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 include enzymes, hemolysins, leukocidins, toxins and the cell surface proteins and cell wall components. These biological active components including 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 *S. aureus*, resistance to methicillin and related  $\beta$ -lactam antibiotics is encoded by the *mecA* 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

*mecA* gene. This alteration does not allow the drug to bind well to the bacterial cell, causing resistance to  $\beta$ -lactam antimicrobial agents.

### **Mechanism of Resistance to Antimicrobial Agents**

Penicillin is inactivated by  $\beta$ -lactamase, a serine protease that hydrolyzes the  $\beta$ -lactam ring. Methicillin is  $\beta$ -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 et al., 1986; Sanford et al., 1994). Persons colonized with *S. aureus* are at increased risk for subsequent infections (Wenzel et al., 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 LTCs, 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 State (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 et al., 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 (Charlebios 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 that the 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, no significant difference in the exposure between the two groups was found (Sattler et al., 2002).

### **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 ° 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 AND STUDY SITE

This was a retrospective study, under the management of Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University. It was conducted at Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand. Data collection was carried out from the first week of November 2004 to the first week of January 2005.

#### DATA COLLECTION

In this retrospective study, children from whom *S.aureus* was isolated from any body site by microbiology laboratory at QSNICH were identified.

Two hundred and seventy-four medical records and susceptibility results of clinical specimens collected since January 2002 to December 2003 were reviewed.

Demographic data of patients as well as the information about clinical specimens, site of infections, the antibiotic sensitivity pattern, instrumentation, surgical interventions and past illnesses were collected by using pre-formed questionnaires.

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

#### 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

$Z_{\alpha/2}$  = the standard normal number deviate for two sided  $\alpha$  Where  $(1-\alpha)$  is the confidence level (since  $\alpha=0.05$  for a 95% confidence level,  $Z_{\alpha/2} = 1.96$ )

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

$\delta$  = the effect size, is the difference of estimate that we wish to detect

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

$$= 246 \text{ patients}$$

## OPERATIONAL DEFINITION

### Immunosuppressive drug

Immunosuppression would be concerned when its effect was considered during *S. aureus* infection onset; e.g. If the patient was treated with prednisolone, a dose of 2 mg/kg/day more than 2 weeks, the immunosuppression effect should exist until 2 weeks after stopping.

### Staphylococcal Resistant Pattern

In this retrospective study, identified *S.aureus* infections were stratified into MRSA and MSSA on the basis of the property of methicillin resistance or methicillin sensitive, respectively.

The MRSA was classified into CA-MRSA or HA-MRSA on the basis of preset criteria.

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 defferentiation are shown in the following table. The criteria are different from those for coagulase-negative Staphylococci (CoNS).

<b>Minimal Inhibitory Concentration (MICs)</b>	<b>Oxacillin Susceptible</b>	<b>Oxacillin Intermediate</b>	<b>Oxacillin Resistant</b>
<i>S. aureus</i>	≤ 2 µg/ml	no intermediate MIC	≥ 4 µg/ml
CoNS	≤ 0.25 µg/ml	no intermediate MIC	≥ 0.5 µg/ml
<b>Zone Sizes</b>	<b>Oxacillin Susceptible</b>	<b>Oxacillin Intermediate</b>	<b>Oxacillin Resistant</b>
<i>S. aureus</i>	≥ 13 mm	11-12 mm	≤ 10 mm
CoNS	≥ 18 mm	no intermediate zone	≤ 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 will be defined if a clear zone of inhibition is  $\leq 10$  mm and  $\geq 13$  mm, respectively.

#### **Hospital Acquired (HA)-*Staphylococcus aureus* Infection**

1. Any isolate of *S. aureus* infection occurred > 48 hours after hospitalization.
2. Any new infection or super infection occurred 48 hours after hospitalization.

#### **Community Acquired (CA)-*Staphylococcus aureus* Infection**

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

### **INCLUSION AND EXCLUSION CRITERIA**

#### **Inclusion Criteria**

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

#### **Exclusion Criteria**

The infection was assumed as contamination, which defined by in charge physician or laboratory unit.

### **DATA ANALYSIS**

Descriptive statistics were used to describe the demographic characteristics, clinical symptoms and signs and laboratory tests of subjects. The data was analyzed by utilizing statistical test with a preset confidence interval (CI) 95 % ( $p < 0.05$ ) and  $\chi^2$ -tests for categorical variables was used for comparison. The statistical software package of SPSS was used.

## CHAPTER V

### RESULTS

#### DEMOGRAPHIC DATA OF THE SUBJECTS AND CHARACTERISTIC OF SPECIMENS

In this study, 274 medical records that met the inclusion and exclusion criteria were reviewed. There were 154 male (56.2%) and 120 female (43.8%) patients. Their age ranged from neonate to 15 years with average age 25.3 months. Their mean (SD) weight and height were 9.0 (8.5) kilograms and 75.6 (24.7) centimeters, respectively. Eleven percent of subjects had a history of school attendance and 91.2 % had no information of daycare attendance. Sixteen percent of children had a history of previous hospitalization, 50.7 % of children had chronic and underlying diseases, 4.0 % of the children took immunosuppressive medications and 2.2% had prior cutaneous infections. According to 78 children, which the number of family members was available, the mean (SD) of number of family member was 4.3(1.4) (Table 1).

**Table 1. The Characteristics of Patients**

<b>Characteristic</b>	<b>Number of patients with available data</b>	<b>Mean (SD)</b>	<b>Number (%)</b>
Gender Male: Female	274		154 (56.2):120 (43.8)
Age (month)	274	25.3 (39.6)	
Weight (kg)	268	9.0 (8.5)	
Height (cm)	120	75.6 (24.7)	
School attendance	255		28 (11.0)
Previous hospitalization	236		44 (16.1)
Chronic & underlying diseases	268		136 (50.7)
Immunosuppressive drug	262		11 (4.0)
Prior cutaneous infection	246		6 (2.2)
Number of family member	78	4.27 (1.4)	

Most of the patients from whom *S. aureus* was isolated, were from pediatric ward (54.4%) followed by neonatal ward (20.4%) and surgical ward (10.6%). About eleven percent of isolates were from the patient in critical care units (ICU and NICU). Only 3.2% of the isolated specimens were from the outpatient department (Table 2).

**Table 2. Distribution of *S. aureus* Infection according to the Admitted Wards**

Admitted ward	Number (N= 274; %)
Pediatric ward	149 (54.4)
Neonatal ward	56 (20.4)
Surgical ward	29 (10.6)
Pediatric ICU	16 (5.8)
NICU	13 (4.8)
Pediatric OPD	5 (1.8)
ENT/EYE OPD	2 (0.7)
Surgical OPD	2 (0.7)
ENT/EYE ward	2 (0.7)

According to the site of *S. aureus* infection, skin and soft tissues (32.5%) was the most common site followed by systemic (more than 1 organs) (28.1%) and respiratory tract (15.7%). The least common site was gastrointestinal tract (2.1%), including pus from double lumen catheters, fluids from mouth in palatoplasty, fluid from peritoneal cavity, pus from exploratory laparotomy and pus from colostomy.

Sixty-four percent of patients did not get surgical procedure. In those who underwent surgical procedures the most common one was abdominal surgery (14.2%) followed by soft tissue surgery (6.9%) and a surgery on musculoskeleton system (6.2%) (Table 3).

**Table 3. Site of infection and Surgical Intervention Presented in Number of Isolation of *Staphylococcus aureus* Specimens**

	Site of infection Number (%)	Surgical procedure Number (%)
Skin & soft tissues	89 (32.5)	19 (6.9)
Genitourinary tract	8 (2.9)	5 (1.2)
Musculoskeleton	8 (2.9)	17 (6.2)
Gastrointestinal tract	6(2.1)	39 (14.2)
Multi organ system (>1 organs)	77 (28.1)	1 (0.4)
Respiratory tract	43 (15.7)	8 (2.9)
Eye	22 (8.1)	1 (0.4)
ENT	7 (2.6)	3 (1.1)
Others*	14 (5.1)	8 (2.9)
No surgical intervention	-	174 (63.5)
<b>Total</b>	<b>274</b>	

**Other\*:**sites of infection: stoma wound, oral cavity, mandible, bleb of toe.

**surgical procedures:** palatoplasty, excision of bleb of toe, drainage of mandibular abscess.

Nearly half of the patients with *S. aureus* infection had received instrumentation procedure and 18% of the patients had received more than one instrumental procedure. Forty-one percent of the procedures were endotracheal intubation and 27% were central vascular catheterizations (Table 4).

**Table 4. Instrumental Procedures in *S. aureus* Infected Patients**

<b>Instrumental Procedures</b>	<b>Number of patients (%)</b>
No procedure	150 (56.2)
Procedures (at least 1)	117 (43.8)
Procedures (at least 2)	48 (18.0)
Procedures (at least 3)	11 (4.1)
<b>Procedures</b>	<b>Number (%)</b>
Endotracheal intubation	72 (40.9)
Vascular catheterization	48 (27.3)
Urinary catheterization	29 (16.5)
Endoscopy	1 (0.6)
Bronchoscopy	3 (1.7)
Intercostal drainage	4 (2.3)
Other	19 (10.8)

## PERCENTAGE OF MRSA AND MSSA IN *S. AUREUS* ISOLATED SPECIMENS

In this study, the ratio of MRSA: MSSA was 1:2.9. The skin and soft tissues (36.5%) was the most common source of specimen for isolation of *S. aureus*. On the other hand, ear discharge (1.8%) was the least common specimen being submitted. The blood (30.3%) was the most common source of sterile specimen collected followed by tracheal secretion (12.0%). (Table5)

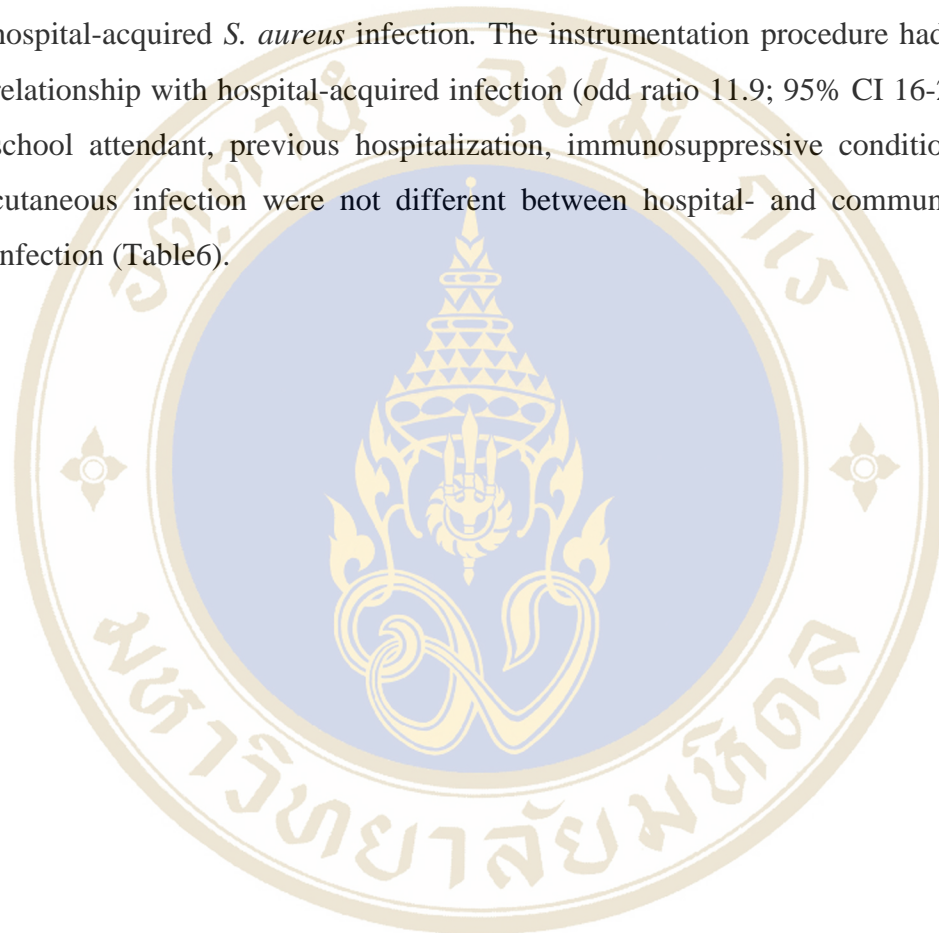
From the total 274 specimens, there were 71 (25.9%) and 203 (74.1%) isolated MRSA and MSSA, respectively. Isolation of MRSA from blood and sputum were more common than MSSA (Table 5).

**Table 5. Source of Specimen for *S. aureus* Isolation**

Source of specimen	MRSA (N=71)	MSSA (N=203)	Total Number (N=274)(%)
Skin & soft tissues	10	90	100 (36.5)
Blood	39	44	83 (30.3)
Tracheal suction	8	25	33 (12.0)
Eye discharge	2	22	24 (8.8)
Urine	2	5	7 (2.6)
Sputum	4	2	6 (2.2)
Ear discharge	0	5	5 (1.8)
Other	6	10	16 (5.8)

## **RISK FACTORS FOR *S. AUREUS* INFECTION**

In comparison between the hospital-acquired and community-acquired *S. aureus* infection, age (less than 1 year), having chronic and underlying disease, surgical intervention and having instrumentation were significantly related to the hospital-acquired *S. aureus* infection. The instrumentation procedure had the highest relationship with hospital-acquired infection (odd ratio 11.9; 95% CI 16-23). Gender, school attendant, previous hospitalization, immunosuppressive condition and prior cutaneous infection were not different between hospital- and community-acquired infection (Table6).



**Table 6. Risk Factors for Hospital- and Community-Acquired *S. aureus* Infection**

Risk factors	HA (%)	CA (%)	Odd ratio (95%CI)	p value
<b>Age</b>				
<1y	80 (75.5)	80 (47.6)	3.4	<0.001
1-15y	26 (24.5)	88 (52.4)	(1.9-6.0)	
<b>Gender</b>				
Male	64 (60.4)	90 (53.6)	1.3	0.33
Female	42 (39.6)	78 (46.4)	(0.8-2.2)	
<b>School attendant</b>				
Yes	7 (7.0)	21(13.5)	0.5	0.15
No	13 (93.0)	134 (86.5)	(0.2-1.3)	
<b>Previous hospitalization</b>				
Yes	19 (21.1)	25 (17.1)	1.3	0.55
No	71 (78.9)	121 (82.9)	(0.6-2.7)	
<b>Chronic &amp; underlying disease</b>				
Yes	79 (75.9)	57 (34.8)	5.9	<0.001
No	25 (24.1)	107 (65.2)	(3.3-10.8)	
<b>Immunosuppression</b>				
Yes	5 (5.1)	6 (3.7)	3.6	0.75*
No	94 (94.9)	157 (96.3)	(0.9-14.7)	
<b>Prior cutaneous infections</b>				
Yes	2 (2.1)	4 (2.6)	0.8	1.00*
No	93 (97.9)	147 (97.4)	(0.1-5.1)	
<b>Surgical intervention</b>				
Yes	53 (51.0)	43 (25.9)	2.9	<0.001
No	51 (49.0)	123 (74.1)	(1.7-5.2)	
<b>Instrumentation procedure</b>				
Yes	80 (77.7)	37 (22.6)	11.9	<0.001
No	23 (22.3)	127 (77.4)	(16.4-22.6)	

Fishers exact test\*

Considering the strains of *S. aureus* infection, age less than 1 year, having chronic and underlying disease, having instrumentation intervention and surgical intervention were the significant risk factor for MRSA infection. The instrumentation intervention had highest risk for MRSA infection with odd ratio 11 (95%CI 5-23). In our study, school attendant was found as a protective risk for MRSA isolation (Table 7). Gender, previous hospitalization, immunosuppressive condition and prior cutaneous infection were not different between MRSA and MSSA infections.



**Table 7. Risk Factors for *S. aureus* Infection in the MRSA and MSSA**

Risk factors	MRSA	MSSA	Odd ratio (95% CI)	p value
<b>Age</b>				
<1y	57 (83.9)	103 (51.8)	4.8	<0.001
1-15y	11 (16.1)	96 (48.2)	(2.3-10.4)	
<b>Gender</b>				
Male	45 (66.1)	109 (52.9)	1.7	0.076
Female	23 (33.9)	97 (47.1)	(1.0-3.2)	
<b>School attendant</b>				
Yes	2 (2.9)	26(13.9)	0.2	0.024
No	66 (97.1)	161(86.1)	(0.03-0.9)	
<b>Previous hospitalization</b>				
Yes	17 (27.4)	27 (15.5)	2.1	0.06
No	45 (72.6)	147 (84.5)	(1.0-4.3)	
<b>Chronic &amp; underlying disease</b>				
Yes	59 (83.1)	77 (39.1)	7.7	<0.001
No	12 (16.9)	120 (60.9)	(3.7-16.3)	
<b>Immunosuppression</b>				
Yes	1 (1.5)	10 (5.1)	0.3	0.29*
No	66 (98.5)	185 (94.9)	(0.01-2.1)	
<b>Prior cutaneous infections</b>				
Yes	1 (1.5)	5 (2.8)	0.6	1.00*
No	63 (98.5)	177 (97.2)	(0.02-5.1)	
<b>Surgical intervention</b>				
Yes	39 (57.4)	57 (28.2)	3.4	<0.001
No	29 (42.6)	145 (71.8)	(1.9-6.3)	
<b>Instrumentation procedure</b>				
Yes	57 (82.6)	60 (30.3)	10.9	<0.001
No	12 (17.4)	138 (69.7)	(5.2-23.3)	

Fishers exact test\*

**ANTIBIOGRAM OF *S. AUREUS***

Both MRSA and MSSA were susceptible to vancomycin. Most of MSSA was still susceptible to co-trimoxazole, erythromycin and gentamicin, which were not benefit for MRSA treatment. Almost all of both strains of *S. aureus* resisted to penicillin G, which implied that this drug should not be used for *S. aureus* infection (Table 8).

**Table 8. The Antibiotic Susceptibility Pattern of MRSA and MSSA**

Antibiotics	MRSA (N=71)		MSSA (N=203)	
	Susceptible(%)	Resistant(%)	Susceptible(%)	Resistant(%)
Co-trimoxazole	3 (4.2)	68 (95.8)	203 (100)	0
Erythromycin	1 (1.4)	70 (98.6)	116 (95.9)	5 (4.1)
Gentamicin	0	71 (100)	202 (99.5)	1 (0.5)
Penicillin G	0	71 (100)	6 (3.0)	197 (97.0)
Vancomycin	71 (100)	0	203 (100)	0

When the susceptibility pattern of MRSA was compared between hospital- and community-acquired organisms, we found that both strains had similar pattern of resistance to co-trimoxazole, erythromycin, gentamicin, penicillin G and vancomycin (Table9).

**Table 9. The Antibiotic Susceptibility Pattern of MRSA according to the Hospital- and Community-Acquired Infections**

Antibiotics	MRSA-HA (N=52)		MRSA-CA (N=19)		p value
	Susceptible (%)	Resistant (%)	Susceptible (%)	Resistant (%)	
Co-trimoxazole	1 (1.9)	51 (98.1)	2 (10.5)	17 (89.5)	0.17*
Erythromycin	1 (1.9)	51 (98.1)	0	19 (100)	0.7*
Gentamicin	0	52 (100)	0	19 (100)	NA
Penicillin G	0	52 (100)	0	19 (100)	NA
Vancomycin	52 (100)	0	19 (100)	0	NA

\* Fischer Exact test

When the susceptibility pattern of MSSA was compared between hospital- and community-acquired, we found that both strains also had the similar pattern of resistance to co-trimoxazole, erythromycin, gentamicin, penicillin G and vancomycin (Table10).

**Table10. The Antibiotic Susceptibility Pattern of MSSA in Hospital- and Community-Acquired Infections**

Antibiotics	MSSA-HA (N=54)		MSSA-CA (N=149)		p value
	Susceptible (%)	Resistant (%)	Susceptible (%)	Resistant (%)	
Co-trimoxazole	54 (100)	0	149 (100)	0	NA
Erythromycin	32 (59.3)	22 (40.7)	84 (56.4)	65 (43.6)	0.71
Gentamicin	53 (98.2)	1 (1.8)	149 (100)	0	0.26*
Penicillin G	0	54 (100)	6 (4.1)	143 (95.9)	0.15
Vancomycin	54 (100)	0	149 (100)	0	NA

\* Fischer Exact test

**RELATION OF DIAGNOSIS, STRAIN OF *S. AUREUS* AND SOURCE OF INFECTION**

In the hospital-acquired infection, we found that there was no significant difference between both MRSA and MSSA in systemic and soft tissue infections, however in case of systemic infection, the percentage of MRSA was slight higher than those of MSSA.

**Table 11. Comparison of Diagnosis and Strains of *S. aureus* in Hospital-Acquired Infection**

Diagnosis	HA (N=106)		Odd ratio (95%CI)	p value
	MRSA (%)	MSSA (%)		
Skin & soft tissues infection				
Yes	5 (9.6)	10 (20.4)	0.4	0.174
No	47 (90.4)	43 (79.6)	(0.1-1.4)	
Systemic infection				
Yes	30 (55.8)	20 (37.0)	2.2	0.06
No	23 (44.2)	34 (63.0)	(1.0-5.2)	

In the community-acquired infection, we found that the MSSA was higher percentage than MRSA in skin and soft tissue infections ; on the other hand, the MRSA was significantly higher than MSSA in systemic infection.

**Table 12. Comparison of Diagnosis and Strains of *S. aureus* in Community-Acquired Infection**

Diagnosis	CA (N=168)			p value
	MRSA (%)	MSSA (%)	Odd ratio (95%CI)	
Skin & soft tissues infection				
Yes	3 (15.8)	72 (48.3)	0.02	0.01*
No	16 (84.2)	77 (51.7)	(0.04-0.77)	
Systemic infection				
Yes	8 (36.8)	21 (14.8)	3.87	0.01*
No	12 (63.2)	122 (85.2)	(1.26-11.81)	

\* Fischer Exact test

## RELATIONSHIP OF MRSA INFECTION AND INSTRUMENTAL PROCEDURE

In the hospital-acquired infection, we found that the MRSA infection was more common in patients who had received endotracheal intubation and central vascular catheterization comparing to those who had not received those procedures. There was no significant association between strain of *S. aureus* infection and urinary catheterization (Table 13).

**Table 13. Relationship of Instrumentation and Hospital-Acquired MRSA Infection**

Instrumental Procedure	HA (N=164)		Odd ratio (95%CI)	p value
	MRSA (%)	MSSA (%)		
Endotracheal intubation				
Yes	6 (31.6)	18 (12.4)	3.3	0.04
No	13 (68.4)	127 (87.6)	(1.0-10.9)	
Vascular catheterization				
Yes	5 (26.3)	6 (4.1)	8.3	0.003
No	14 (73.7)	139 (95.9)	(1.9-36.5)	
Urinary catheterization				
Yes	1 (5.3)	10 (6.9)	0.8	0.79
No	18 (94.7)	135 (93.1)	(0.02-5.9)	

## CHAPTER VI

### DISCUSSION

The pediatric patients who are commonly found to be infected with *S. aureus* infection was the focus of this study. Previous studies showed even neonates were at risk of *S. aureus* infection (Endo et al., 1996). There were numbers of risk factors contributing for the emergence and spreading of MRSA infections (Sattler et al., 2002; Herold et al., 1998; Fergie and Percell, 2001).

In our study, it was found that most *S. aureus* infections had been isolated from children in pediatrics and neonatal wards. The finding that large proportion of *S. aureus* had been isolated from blood stream gives an impression that this organism can easily invade the blood stream and can cause serious consequences. Gastrointestinal surgery was the most common procedure among the surgical intervention that associated with *S. aureus* infection. Skin and soft tissue was the most common site of infection, however it may not represent the real pathogen, because it might be only colonization.

From this study, it is noted that half of *S. aureus* isolated patients had undergone instrumentation procedures. The three most common procedures were endotracheal intubation, vascular catheterization and urinary catheterization. It may be because these three procedures were necessary for general intensive care.

Identifying risk factors and taking appropriate measures to control those are very important in order to control the spreading of the organism within the community. MRSA infection was more common in children whose aged less than 1 year, which confirmed the previous study by Napaporn (2003). Moreover having chronic or underlying disease as risk factors supports the study by Layton (1995), and undergoing instrumentation were the risk factors for MRSA infection. The finding from Benerjee et al (1991) and Steinberg et al (1996) showed that vascular device was a factor increasing the *S. aureus* infection and selective antibiotic pressure may increase the resistance strains, this confirm the findings by Panlilio (1992). School attendance in this study was shown to be a protective factor for MRSA infection,

which was a confounding factor with older age, confirmed by multivariate analysis. (data not shown).

When susceptibility to antibiotics pattern was concerned, glycopeptides was very effective against both MRSA and MSSA infection. co-trimoxazole, gentamicin and erythromycin were still effective against MSSA infection. Penicillin G had no place for the treatment of both MRSA and MSSA infection. This finding suggests that co-trimoxazole, erythromycin and gentamicin might be the alternative drugs for MSSA infection in case of cloxacillin allergy. This study does not find any significant difference between MRSA acquired from community and hospital, and between MSSA acquired from community and hospital, which implied that the source of the organism might not be helpful for choosing antibiotics.

In hospital-acquired *S. aureus* infection, 60% of systemic infection was caused by MRSA; therefore glycopeptides should be considered when the patients had nosocomial systemic infection.

The community-acquired skin and soft tissue infection was commonly caused by MSSA strain. It implied that the first line antibiotics used for the skin and soft tissue infection occurred in community should be cloxacillin.

This study also showed the relationship between instrumentation procedure and strain of pathogen in hospital-acquired *S. aureus* infection. The vascular catheterization in hospital-acquired infections was related to MRSA strain. Endotracheal intubation was also a risk factor for MRSA infection.

## CHAPTER VII

### CONCLUSION

Proper management of *S. aureus* infection in pediatric patients is becoming more and more important as it may lead to emergence of resistant strains, serious clinical manifestations.

Age less than 1 year, presence of chronic or underlying diseases, exposure to instrumentation and undergoing surgical procedures were the most important risk factors for emergence of hospital-acquired MRSA strains.

Skin and soft tissue infections were more common than systemic (involving more than one system) infection.

Gender, previous hospitalization, presence of immunosuppressive conditions and prior cutaneous infection were not significant risk factors for MRSA infection both in hospital- and community-acquired.

Almost all of both community- and hospital-acquired MRSA strains were resistant to co-trimoxazole, erythromycin, gentamicin, and penicillin G but sensitive to vancomycin.

Penicillin G is no longer effective against both MRSA and MSSA strains. Most of the MSSA were still susceptible to co-trimoxazole, erythromycin, and gentamicin. Vancomycin was effective against both MRSA and MSSA isolations. It is worth to preserve glycopeptides for the resistant staphylococcal infections.

Identification of potential risk factors of *S. aureus* infection and judicious use of antimicrobials are mandatory in order to see the better outcome.

## BIBLIOGRAPHY

- Banerjee SN, Emori TG, Culver DH, et al. Secular trends in nosocomial primary blood stream infections in the United States, 1980-1989. *Am J Med* 1991; 91:S86-9.
- Barret FF, McGehee RF, Finland M. Methicillin resistant *Staphylococcus aureus* at Boston City Hospital. *N Engl J Med* 1968;279:441-8.
- Blot SI, Vendewound KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin susceptible and methicillin resistance *Staphylococcus aureus*. *Arch Intern Med* 2002;162:2229-35.
- Boyce JM and Causey WA. Increasing occurrence of methicillin-resistant *Staphylococcus aureus* in the United States. *Infect Control* 1982;3:377-83.
- Buckingham SC, McDougal LK, Cathey LD, et al. Emergence of community-associated Methicillin-resistant *Staphylococcus aureus* at a Memphis, Tennessee Child's Hospital. *Pediatr Infect Dis J* 2004; 23:619-24.
- Casewell MW and Hill RLR. The carrier state: methicillin-resistant *staphylococcus aureus*. *J Antimicrob Chemother* 1986;18:S1-12.
- Chambers HF. Methicillin resistance in staphylococci: molecular and biochemical basis and clinical implications. *Clin Microbiol Rev* 1997;10:781-91.
- Charlebois ED, Perdreau-Remington F, Kreiswirth B, et al. Origins of community strains of Methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2004; 39:47-54.
- Classics in infectious disease; "on abscess"; Alexander ogstan (1844-1929) *J Infect Dis* 1989;6:122-8.
- Conterno LO, Wey SB, Castelo A. Risk factors for mortality in *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol* 1998;19:32-7.

- Crossly K, Loesch D, Landesman B, et al. An outbreak of infections caused by strains of *Staphylococcus aureus* resistant to methicillin and aminoglycosides. *J Infect Dis* 1979;239:273-9.
- Embil J, Ramotar K, Romance L, et al. Methicillin-resistant *Staphylococcus aureus* in tertiary care institutions on the Canadian prairies 1990-1992. *Infect Control Hosp Epidemiol* 1994;15:646-51.
- Endo A, Masunaga K, Masaki R, et al. Bacterial changes in neonatal intensive care unit. *Acta Paediatr Jpn* 1996;38:12-6.
- Fergie JE and Purcell K. Community-acquired methicillin-resistant *Staphylococcal aureus* infections in South Texas children. *Pediatr Infect Dis J* 2001;20:860-3.
- Frank AL, Marcinak JF, Mangat PD, Schreckenberger PC. Community acquired and clindamycin-susceptible methicillin-resistant *Staphylococcus aureus* in children. *Pediatr Infect Dis J* 1999;18:993-1000.
- Haddadin AS, Fappiano SA, Lipsett PA. Methicillin resistant *Staphylococcus aureus* (MRSA) in the intensive care unit. *Postgrad Med J* 2002;78:385-92.
- Harbarth S, Rutschmann O, Sudre P, Pittet D. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus*. *Arch Intern Med* 1998;158:182-9.
- Heley RW, Cushion NB, Tenover FC, et al. Eradication of endemic methicillin-resistant *Staphylococcus aureus* infection from a neonatal intensive care unit. *J Infect Dis* 1995;171:614-24.
- Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. *JAMA* 1998;279:593-8.
- Hussain FM, Boyle-Vavra S, Bethel CD, Daum RS. Current trend in community acquired methicillin resistant *Staphylococcus aureus* at a tertiary care pediatric facility. *Pediatr Infect Dis J* 2000;19:1163-6.
- Kloos WE and Bannerman TL. *Staphylococcus and Micrococcus*. In: Murray PR, ed. *Manual of Clinical Microbiology*. 7th ed revised. Washington, DC: ASM Press, 1999:pp.267-9.

- Layton MC, Hierholzer WJ, Patterson JE. The evolving epidemiology of methicillin-resistant *Staphylococcus aureus* at a university hospital. *Infect Control Hosp Epidemiol* 1995;16:12-7.
- Levine DP, Cushing RD, Jui J, Broun WJ. Community acquired methicillin –resistant *Staphylococcus aureus* endocarditis in the Detroit Medical centre. *Ann Intern Med* 1982;97:330-8.
- Locksley RM, Cohen ML, Quinn TC, et al. Multiply antibiotic-resistant *Staphylococcus aureus*: introduction, transmission, and evolution of nosocomial infection. *Ann Intern Med* 1982;97:317-24.
- Lowy FD. *Staphylococcus aureus* infection. *N Engl J Med* 1998;339:520-32.
- McClelland RS, Fowler VG Jr, Sanders LL, et al. *Staphylococcus aureus* bacteremia among elderly vs. younger adult patients: comparison of clinical features and mortality. *Arch Intern Med.* 1999;159:1244-7.
- Napaporn C. Methicillin-resistant *Staphylococcus aureus* infections in children at Queen Sirikit National Institute of Child Health. *J Infect Dis Antimicrob Agents* 2003;20:73-9.
- Ogston A. micrococcus poisoning. *J Anat* 1882;17:24-58.
- Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975-1991. *Infect Control Hosp Epidemiol* 1992;13:582-6.
- Richmond AS, Simberkoff MS, Schaeffler S, Rahal JJ. Resistance of *Staphylococcus aureus* to semi-synthetic penicillins and cephalothin. *J Infect Dis* 1997;135:108-12.
- Romero-vivas J, Rubio M, Fernandez C, Piacazo JJ. Mortality associated with nosocomial bacteremia due to methicillin resistant *Staphylococcus aureus*. *Clin Infect Dis* 1995;21:1417–23.
- Sanford MD, Widmer AF, Bale MJ, Jones RN, Wenzel RP. Efficient detection and long term persistence of carriage of methicillin resistant *Staphylococcus aureus*. *Clin Infect Dis* 1994;19:1123-8.

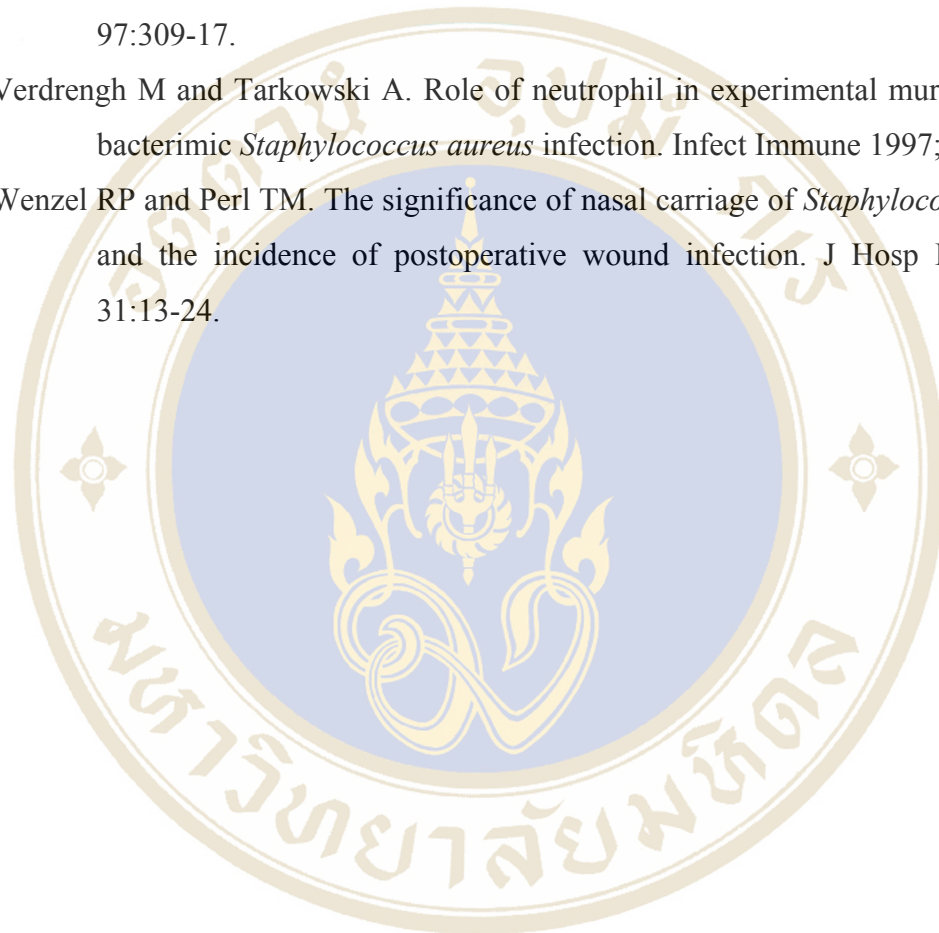
- Saravolatz LD, Markowitz N, Arking L, Pohlod D, Fisher E. Methicillin resistant *Staphylococcus aureus*: epidemiologic observations during a community acquired outbreak. *Ann Intern Med* 1982;96:11-6.
- Sattler CA, Mason EO Jr, Kaplan SL. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* infection in children. *Pediatr Infect Dis J* 2002;21:910-7.
- Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase-negative staphylococcus. *N Engl J Med* 1987; 316:927-31.
- Soriano A, Martinez JA, Mensa J et al. Pathogenic significance of methicillin resistance for patients with *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2000;30:368-73.
- Speller DC, Johnson AP, James D, Marples RR, Charlett A, George RC. Related Articles, links resistance to methicillin and other antibiotics in isolates of *Staphylococcus aureus* from blood and cerebrospinal fluid, England and Wales, 1989-95. *Lancet* 1997;350:323-5.
- Steinberg JP, Clark CC, Hackman BO. Nosocomial and community acquired *Staphylococcus aureus* bacteremias from 1980 to 1993: Impact of intravascular devices and methicillin resistance. *Clin Infect Dis* 1996;23:255-9.
- Storch GA and Rajagopalan L. Methicillin-resistant *Staphylococcus aureus* bacteremia in children. *Pediatr Infect Dis J* 1986;5:59-67.
- Strausbaugh LJ, Jacobson C, Sewell DL, Potter S, Ward TT. Antimicrobial therapy for methicillin-resistant *Staphylococcus aureus* colonization in residents and staff of a Veterans Affairs nursing home care unit. *Infect Control Hosp Epidemiol* 1992;13:151-9.
- Swanston WH. Methicillin resistant *Staphylococcus aureus*. *West Indian Med J* 1999; 48:20-2.
- Tenover FC, Lancaster MV, Hill BC, et al. Characterization of staphylococci with reduced susceptibilities to vancomycin and other glycopeptides. *J Clin Microbiol*, 1998; 36: 1020-7. (Erratum in: *J Clin Microbiol* 1998;36:2167.)

Tiemersma EW, Bronzwaer S L.A.M, Lyytikainen O, et al. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999-2002. *Emerg Infect Dis* 2004; 10:1627-34.

Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; 97:309-17.

Verdrengh M and Tarkowski A. Role of neutrophil in experimental murine mode of bacteremic *Staphylococcus aureus* infection. *Infect Immune* 1997;65:2517-21.

Wenzel RP and Perl TM. The significance of nasal carriage of *Staphylococcus aureus* and the incidence of postoperative wound infection. *J Hosp Infect* 1995; 31:13-24.





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:

<input type="checkbox"/> skin and soft tissue	<input type="checkbox"/> musculoskeleton	<input type="checkbox"/> respiratory tract
<input type="checkbox"/> cardiovascular system	<input type="checkbox"/> gastrointestinal system	<input type="checkbox"/> hepatobiliary system
<input type="checkbox"/> genitourinary tract	<input type="checkbox"/> systemic (>1 organ)	<input type="checkbox"/> nervous system
<input type="checkbox"/> other, define _____		

2.2 System of surgical intervention (can be >1)

<input type="checkbox"/> skin and soft tissue	<input type="checkbox"/> musculoskeleton	<input type="checkbox"/> respiratory tract
<input type="checkbox"/> cardiovascular system	<input type="checkbox"/> gastrointestinal system	<input type="checkbox"/> hepatobiliary system
<input type="checkbox"/> genitourinary tract	<input type="checkbox"/> systemic	<input type="checkbox"/> nervous system
<input type="checkbox"/> other, define _____	<input type="checkbox"/> no any intervention	<input type="checkbox"/> no data

2.3 Instrumental procedure (can be >1)

<input type="checkbox"/> endotracheal tube	<input type="checkbox"/> urinary catheter	<input type="checkbox"/> endoscope
<input type="checkbox"/> vascular catheter	<input type="checkbox"/> no any instrument	<input type="checkbox"/> no data
<input type="checkbox"/> other, define _____		

2.4 Admitted ward

<input type="checkbox"/> pediatric ward	<input type="checkbox"/> newborn ward	<input type="checkbox"/> surgical ward	<input type="checkbox"/> ENT or eye ward
<input type="checkbox"/> ICU pediatric	<input type="checkbox"/> NICU	<input type="checkbox"/> ICU surgery	<input type="checkbox"/> OPD ENT or eye
<input type="checkbox"/> OPD pediatric	<input type="checkbox"/> OPD well baby	<input type="checkbox"/> OPD surgery	<input type="checkbox"/> 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:

- |  |  |  |   |
|--|--|--|---|
| <input type="checkbox"/> blood         | <input type="checkbox"/> CSF                 | <input type="checkbox"/> pleural fluid   | <input type="checkbox"/> pericardial fluid    |
| <input type="checkbox"/> ear discharge | <input type="checkbox"/> sputum              | <input type="checkbox"/> tip of catheter | <input type="checkbox"/> skin and soft tissue |
| <input type="checkbox"/> urine         | <input type="checkbox"/> 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					

## BIOGRAPHY

**NAME:** Susith Ranjan Wadikawage

**DATE OF BIRTH:** 28 September 1968

**PLACE OF BIRTH:** Walasmulla, Sri Lanka.

**INTITUTIONS ATTENDED:** M.B.B.S, (1996)  
Faculty of Medicine, University of Ruhuna,  
Sri Lanka.  
National Institute of Health Services (NIHS)  
Kalutara, Sri Lanka (2003).  
D.T.M.&H, (2004)  
Faculty of Tropical Medicine, Mahidol University,  
Thailand.

**OFFICIAL ADDRESS:** District Medical Officer,  
Base Hospital, Tangalle,  
Sri Lanka (2002-up to now).  
TP-0094 472240261.

**HOME ADDRESS:** No 31, Indipokunugoda Road, Tangalle,  
Sri Lanka.  
TP-0094 472242044.  
-0094 777 250568.

**E –MAIL:** [susithranjan@yahoo.com](mailto:susithranjan@yahoo.com)