Infections Caused by Methicillin Resistant *Staphylococcus aureus:* Distinct Risk Factors and Prognosis

Sai-Cheong Lee, Ching Hung Wang, Ning Lee[1], Shu Chu Chen, Shing-Kai Lo[2], Wen-Bien Shieh

Division of Infectious Diseases,Department of Internal Medicine & Pediatrics

[1]Department of Clinical Pathology,Chang Gung Memorial Hospital, Keelung, Taiwan

[2]Department of Public Health,Chang Gung Medical College

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are seen with increasing frequency in Taiwan. To understand the significant risk factors of MRSA infections as distinct from methicillin-sensitive *S. aureus* (MSSA) infections, we conducted a prospective daily surveillance study over a 7-month period in Keelung Chang Gung Memorial Hospital. Over 90% of MRSA infections were hospital-acquired, especially in medical wards. The length of stay in hospital, the number of major underlying diseases, the number of invasive procedures, the number and duration of antibiotics used were significantly greater than that of nosocomial MSSA infections. The usage of third generation cephalosporins was distinctly related to nosocomial MRSA infections. In cases of nosocomial MRSA infections, the mortality rate due to infection was higher than that of nosocomial MSSA infections. We conclude that the increasing frequency of MRSA infections in our hospital is probably due to the increase of these highly susceptible patients and related to the increasing usage of third generation cephalosporins, similar to MRSA infections in other countries. Effective measures are needed to control this trend.
(Nosocom Infect Control J 1996 ; 6: 131~8)

Key words: risk factor, methicillin-resistant *Staphylococcus aureus*

INTRODUCTION

Soon after methicillin was introduced in 1959, infection due to methicillin - resistant *Staphylococcus aureus* (MRSA) was reported [1]. In recent years, hospital - acquired infections due to MRSA increased in American hospitals[2,3]. In Taiwan, reports of nosocomial infections caused by MRSA are not yet too common[4-7]. In 1988, Chang and coworkers reported 95 MRSA infections from January 1983 to September 1986 in National Taiwan University Hospital[4]. They also found

Received 16 January 1996
Revised 26 February 1996
Accepted 8 April 1996
Address correspondence to: Sai-Cheong Lee,
Division of Infectious Diseases,
Chang Gung Memorial Hospital,
222 Mai Chin Road,
Keelung, Taiwan

increasing numbers of nosocomial MRSA infections from 1990 to 1992[5]. In 1994, Lin and coworkers also discovered an increasing rate of MRSA isolate among all *Staphylococcus aureus (S. aureus)* isolates from 1990 to 1992 in Tri-Service General Hospital[6]. Hwang and coworkers recently reported that 60% of MRSA isolated in Kaoshiung Medical College Hospital were hospital-acquired and they compared community-acquired MRSA infections with hospital-acquired MRSA infections to look for any significant difference[7]. However, the specific risk factors of MRSA infections that were different from MSSA infections have not yet been reported in Taiwan. Some risk factors reported in the past were common to all *S. aureus* infections. We have carried out a prospective daily microbiologic survey of MSSA and MRSA infections in Keelung Chang Gung Memorial Hospital during a 7-months period to find out the specific risk factors of MRSA nosocomial infections.

MATERIALS AND METHODS

From January 1994 to July 1994, prospective microbiologic surveillance was initiated at Keelung Chang Gung Memorial Hospital. The clinical microbiology laboratory was monitored for isolates of both MRSA and MSSA from different sites of the hospital, on a daily basis. Patients identified with *S. aureus* isolates were followed up until discharge from the hospital. The following data pertaining to the patients were recorded: age, sex, ward, isolation site, community- or hospital-acquired, major underlying diseases, invasive procedures before the isolation of the bacteria , immunosuppressive agents, stay in intensive care unit or not, total numbers and duration of antibiotics used, total duration of hospitalization and final outcome. Hospital-acquired infections were diagnosed according to the criteria of nosocomial infections published by Centers for Disease Control (CDC) in 1988[8].

S. aureus was identified by its typical morphologic characteristics of the colonies on sheep blood agar , from Gram stain, and positive tests for catalase and coagulase. All isolates were tested for antibiotic susceptibilities by the Kirby-Bauer disk method using standard zones of inhibition criteria to define sensitivity or resistance. For detection of methicillin-resistance, oxacillin disk were used. Interpretation of results was made after incubation at 35℃ for 24 hours[9,10].

Statistical analysis was performed with the use of the Fisher's exact test and Student's t test and P values of <0.05 were considered significant.

RESULTS

There were 75 cases of MSSA infections and 71 cases of MRSA infections during the study period. The mean age of the MSSA group was 48 years with a range of 1 month to 93 years and a standard deviation of 24 years. The mean age of the MRSA group was 55 years with a range of 1 to 90 years and a standard deviation of 20 years. The difference of age between the two groups was insignificant. There were 48 males and 27 females in the MSSA group. In the MRSA group, there were 51 males and 20 females. The difference of sex distribution between the two groups was also insignificant. However 66 out of 71 (93%) cases of MRSA infections were hospital-acquired, whereas only 25 out of 75 cases of MSSA infections were hospital-acquired. ($P<0.001$)(Table 1)

Wound and lower respiratory tract were the two most common sites of both MSSA and MRSA infections. Rate of total MRSA infections in lower respiratory tract was significantly higher than that of total

Table 1 Comparison of MSSA and MRSA Infections

	MSSA	MRSA	OR	P value
Total no. of infections	75	71		
Community-acquired	50	5		<0.001
Hospital-acquired	25	66	26.4	<0.001
Isolation site:				
sputum／tracheal aspirate	16	30	2.698	0.007
pleural effusion	1	0	1.056	1.000
blood	10	6	0.600	0.345
urine	2	0	0.521	0.497
wound discharge	32	25	0.730	0.356
CSF	0	1	1.056	0.486
CVP catheter	1	5	5.606	0.109
Other	13	4	0.285	0.028

MSSA＝methicillin sensitive *S. aureus*

MRSA＝methicillin resistant *S. aureus*

OR＝Odds ratio for MRSA infection

MSSA infections in lower respiratory tract (Table 1).However, rates of nosocomial MSSA and MRSA infections in lower respiratory tract were not significantly different (Table 2). Rates of nosocomial MSSA and MRSA infections in various departments were not different (Table 2). Mean hospital stay was longer in nosocomial MRSA infections than that in nosocomial MSSA infections (Table 3).

Although the rate of nosocomial MRSA infection with any major underlying disease was not significantly higher than that of nosocomial MSSA infections, the number of major underlying diseases in nosocomial MRSA infections was clearly higher than that in nosocomial MSSA infections (Table 3).The rate of nosocomial MRSA infections with any invasive procedure was higher than that of nosocomial MSSA infections. The number of invasive procedures in nosocomial MRSA infections was also significantly higher than that in nosocomial MSSA infections (Table 3). There was no prominent correlation of nosocomial MRSA infection with previous stay in the intensive care unit (Table 3). The number and the duration of antibiotics usage were also higher in nosocomial MRSA infections (Table 3). Among all the antibiotics used, the use of third generation cephalosporins was found related to nosocomial MRSA infections (Table 4). Mortality related to infection in nosocomial MRSA infections was higher (32/66) than that in nosocomial MSSA infections (9/25) but the difference was not significant (Table 3).

DISCUSSION

Results of our investigation revealed that nosocomial infections of MRSA was prevalent in our hospital. Similar prevalence of this infection may also be present in other hospitals in Taiwan although such reports

Table 2 Comparison of Nosocomial MSSA and MRSA Infections

	MSSA	MRSA	P value
Total no. of infections	25	66	
Isolation site:			
Sputum／Tracheal aspirate	9	29	0.493
Pleural effusion	1	0	0.275
Blood	1	6	0.669
Urine	1	0	0.275
Wound	11	21	1.000
CSF	0	1	
CVP site	1	5	1.000
Other	1	4	1.000
Location of infected cases :			
Medical ICU	7	6	0.039
Medical ward	11	42	0.090
Surgical ICU	0	4	1.000
Surgical ward	5	9	0.519
Gynecology ward	0	0	
Pediatrics ward	1	1	0.474
Neurology ward	1	4	1.000
Other	0	0	

are few[4-7]. Special attention and nation-wide re-evaluation should again be directed to this infection.

According to previous reports, MRSA infection is mainly a nosocomial infection[11-13]. In our study, 93% of MRSA infections were nosocomial in origin. However, only 33.3% of MSSA infections were hospital-acquired. Such a difference of nosocomial infection rates between MRSA and MSSA infections may indicate that some MRSA infections might have been spread in the hospital through medical personnel.

Like MSSA infections, the most frequent sites of MRSA infections were lower respiratory tract, wound and blood (Table 1 and Table 2). However, other unusual sites of MRSA infections including central nervous system and central venous pressure catheter wound were also found (Table 1and Table 2). This indicates that any site of the body can be infected by MRSA during hospitalization. Nosocomial MRSA infections were not confined to any unit. Most nosocomial MRSA infections occurred in medical or surgical patients. These patients had most of the predisposing factors of nosocomial MRSA infections. Multiple major underlying diseases, multiple invasive procedures, prolonged use of multiple antibiotics, use of third generation cephalosporin were found to be distinct risk factors of MRSA infections. The overall mortality of MRSA infections was higher than that of MSSA infections although the difference was not significant (Table 1 and Table 2). Although mortality of

Table 3 Risk Factors and Outcome of Nosocomial MSSA and MRSA Infections

		MSSA	MRSA	P value
Duration of hospital stay (days):	range	11-100	13-219	
	mean ±S.D.	31±23	60±42	<0.001
Major underlying diseases		21	63	0.087
No. of major underlying diseases:	range	0-4	0-6	
	mean ±S.D.	1±1.17	2.44±1.49	<0.001
Invasive procedure	range	1-4	1-6	
	mean ±S.D.	1.4±0.89	2.51±1.45	<0.001
Previous stay in ICU		4	18	0.262
No. of antibiotics used before isolation:				
	range	0-9	0-11	
	median	2	4	
	mean ±S.D.	2±2	4±2	0.0001
Duration (days) of antibiotics used befor isolation:				
	range	0-68	0-181	
	median	6	18	
	mean ±S.D.	9±14	30±36	0.0001
Outcome: Cured		8	22	0.904
Improved		5	8	0.335
Expired , related to infection		9	32	0.285
Expired , not related to infection		2	0	0.070
Unevaluable		1	4	1.000

nosocomial MRSA infections was not significantly higher, the mean duration of hospital stay was longer than that of MSSA nosocomial infections. This indicates that MRSA nosocomial infections prolong hospitalization. From all these data, we conclude that vigorous control of MRSA is definitely necessary and beneficial in Taiwan. Measures used to control MRSA in North America and Europe should be practiced to control MRSA in Taiwan. After this investigation, we used the following measures to manage nosocomial MRSA infections.

Microbiology laboratory results were reviewed daily for early detection of all MRSA infections[14]. Barrier precautions were carried out for all patients colonized or

Table 4 Comparison of Antibiotic Usage in Nosocomial MSSA and MRSA Infections

	MSSA	MRSA	P value
Specific antibiotic used before isolation:			
First generation cephalosporins	12	38	0.412
Second generation cephalosporins	1	12	0.104
Third generation cephalosporins	1	27	0.001
Aminoglycoside	8	16	0.453
Sulfonamide	0	2	1.000
Clindamycin	2	19	0.036
Ampicillin	0	11	0.031
Penicillin	7	25	0.378
Methicillin	2	14	0.218
Ticarcillin	1	3	1.000
Erythromycin	0	0	
Negacide	0	1	1.000
Imipenem	0	2	1.000
Tetracycline	0	0	
Others	11	37	0.304

infected by MRSA, including the use of gloves on secretion contact and handwashing by personnel after contact with all these patients. Masks are not needed and gowns are indicated only if soiling is likely. Nurses caring for MRSA patients did not care for non-colonized patients when nursing personnel were adequate. Patients colonized or infected by MRSA were discharged from hospital as soon as possible.

Nosocomial MRSA infections subsequently diminished but were not completely eradicated. It was difficult to prevent all nosocomial MRSA infections. The acceptable rate of nosocomial MRSA infections is still uncertain.

Placing patients with MRSA in private or same room is helpful to control MRSA nosocomial infections[15,16]. However, private rooms are frequently inadequate when the number of these patients is large. Culturing all exposed personnel periodically and treating all MRSA nasal carriers with intranasal mupirocin can be very time-consuming, expensive and has a relatively low yield[15,16]. The epidemic MRSA strain may not be the same as the MRSA strain in nasal carriers among personnel[17]. Rational use of third-generation cephalosporins may be helpful in the control of MRSA nosocomial infections[7]. However, in some teaching hospital, there is no or inadequate number of infectious diseases specialists to effectively control the use of third generation cephalosporins. Problems of controling nosocomial MRSA infections still exist in Taiwan .

REFERENCES

1. Jevons MP: Celbenin-resistant staphylococci

(Letter). Br Med J 1961; 1: 12405.
2. Boyce JM, Causey WA: Increasing occurrence of methicillin-resistant *Staphylococcus aureus* in the United States. Infect Control 1982; 3: 377-83.
3. Haley RW, Hightower AW, Khabbaz RF, et al: The emergence of methicillin-resistant *Staphylococcus aureus* infections in United States hospitals. Possible role of the house staff-patient transfer circuit. Ann Intern Med 1982; 97: 297-308.
4. Chang SC, Hsu LY, Luh KT, et al: Methicillin-resistant *Staphylococcus aureus* infections. J Formosan Med Assoc 1988; 87: 157-63.
5. 孫春轉，楊麗瑟，張上淳等：北部某教學醫院methicillin抗藥性金黃色葡萄球菌院內感染之回顧。感控通訊1993; 3(4): 6-11。
6. 林金絲，楊祖光，王志堅等：Methicillin抗藥性金黃色葡萄球菌院內感染之討論。疫情報導1994; 10: 275-81。
7. 張桐榮，黃高彬：比較社區與住院病人感染MRSA的危險因子，醫療行爲與預後。感控通訊1993; 3(1): 1-4。
8. Garner JS, Jarris WR, Emori TG, et al: CDC definitions for nosocomial infection, 1988. Am J Infect Control 1988; 16: 128-40.
9. Boyce JM: Reevaluation of the ability of the standardized disk diffusion test to detect methicillin-resistant of *Staphylococcus aureus.* J Clin Microbiol 1984; 19: 813-7.
10. Thornsberry C, Sevenson JM, Baker CN , et al: Methods for determining susceptibility of fastidious and unusual pathogens to selected antimicrobial agents. Diag Microb Infect Dis 1988; 9: 139-53.
11. Peacock JE Jr, Marsik FJ, Wenzed RP: Methicillin-resistant *Staphylococcus aureus* : introduction and spread within a hospital. Ann Intern Med 1980; 93: 526-32.
12. Thompson RL, Cabezudo I, Wenzel RP: Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus.* Ann Intern Med1982; 97: 309-17.
13. 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.
14. Boyce JM: Should we vigorously try to contain and control methicillin-resistant *Staphylococcus aureus?* Infect Control Hosp Epidemiol 1991; 12: 46-54.
15. Dacre J, Emmerson AM, Jenner EA: Gentamicin-methicillin-resistant *Staphylococcus aureus* : epidemiology and containment of an outbreak. J Hosp Infect 1986; 7: 130-6.
16. Bitar CM, Mayhall CG, Lamb VA, et al: Outbreak due to methicillin-and rifampin-resistant *Staphylococcus aureus* : epidemiology and eradication of the resistant strain from the hospital. Infect Control 1987;8:15-23.
17. Ellison RT III, Judson FN, Peterson LC, et al: Oral rifampin and trimethoprim/sulfamethoxazole therapy in asymptomatic carriers of methicillin-resistant *Staphylococcus aureus* infections. West J Med 1984; 140: 735-40.

Methicillin 抗藥性金黃色葡萄球菌感染之特異誘因與預後

李細祥　王清虹　李寧[1]　陳淑珠　盧成皆[2]　謝文斌

基隆長庚醫院感染科及小兒科

[1]基隆長庚醫院臨床病理科

[2]長庚醫學院公共衛生科

在臺灣，methicillin抗藥性金黃色葡萄球菌感染有逐漸增多之趨勢，為了瞭解methicillin抗藥性金黃色葡萄球菌感染之特異誘因，與methicillin感受性葡萄球菌感染不同之誘因，我們在基隆長庚醫院進行研究發現methicillin抗藥性金黃色葡萄球菌感染大多為院內感染，且在內科病房較多。住院日數，潛在重大疾病之數目，侵入性檢查之數目，分離前使用之抗生素數目及日數，在methicillin抗藥性金黃色葡萄球菌院內感染者，明顯比methicillin感受性金黃色葡萄球菌院內感染者為高；methicillin抗藥性金黃色葡萄球菌院內感染與第三代頭孢子素使用特別有關，死亡率亦比methicillin感受性金黃色葡萄球菌感染高。我們的結論是，methicillin抗藥性金黃色葡萄球菌感染在各醫院增多，可能是由於此類病患增多及第三代頭孢子素使用增多，與外國報告之methicillin抗藥性金黃色葡萄球菌相同，必需有效之措施，來控制此趨勢，我們探討各種methicillin抗藥性金黃色葡萄球菌處理措施之可行性。(感控雜誌 1996；6： 131～8)

關鍵詞：誘因，methicillin 抗藥性金黃色葡萄球菌