Journal of Infection (2007) **54**, 337–342

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Risk factors for isolation of low-level mupirocin-resistant versus -susceptible methicillin-resistant *Staphylococcus aureus* from patients in intensive care units

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Accepted 15 June 2006
Available online 24 July 2006

KEYWORDS
MRSA;
Mupirocin;
Resistance;
Risk factors;
Piperacillin–tazobactam

Summary *Objectives:* The aim of this study was to determine the risk factors for the recovery of low-level mupirocin-resistant (mup^r) or -susceptible (mup^s) MRSA from patients in intensive care units (ICUs).
Methods: A case–case–control study was conducted from November 2003 to April 2004. Two case groups consisted of patients with low-level mup^r MRSA and mup^s MRSA. A control group was frequency matched.
Results: Mup^r MRSA and mup^s MRSA were isolated from 20 to 51 patients, respectively, during a six-month period. Risk factors identified for mup^r MRSA were as follows: exposure to piperacillin–tazobactam (odds ratio [OR] 13.8; 95% confidence intervals [CI], 1.8–105.0), third-generation cephalosporins (OR, 5.0; 95% CI, 1.6–15.5) and quinolones (OR, 3.4; 95% CI, 1.1–10.7). Risk factors identified for mup^s MRSA were as follows: length of ICU stay (OR, 1.1; 95% CI, 1.0–1.1), surgery (OR, 3.7; 95% CI, 1.5–9.0), exposure to third-generation cephalosporins (OR, 8.4; 95% CI, 3.3–21.7) and quinolones (OR, 7.7; 95% CI, 2.8–21.3).
Conclusions: Our results suggest that nosocomial isolation of low-level mup^r MRSA may be affected by piperacillin–tazobactam.

Introduction

Mupirocin, produced by *Pseudomonas fluorescens* was introduced into clinical practice in 1985 in the UK. It is known as the most clinically effective antibiotic for the elimination of methicillin-resistant *Staphylococcus aureus*

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0163-4453/$30
doi:10.1016/j.jinf.2006.06.008

(MRSA) from nasal carriage.[1,2] Treatment with nasal mupirocin ointment appears to be effective in reducing the onset of infections as well as the severity of infections at surgical sites[3–5]; treatment with this antibiotic has been adopted as a control measure against MRSA infections.[6,7] However, mupirocin-resistant MRSA has already been reported.[8–10]

Mupirocin-resistant (mup^r) strains are separated arbitrarily into two phenotypes: the low-level resistant strain (MIC = 8–256 μg/mL), which is usually associated with a mutation in the gene (*ileS*) for target enzyme, and the high-level resistant strain (MIC ≥ 512 μg/mL), which is mediated by a plasmid containing the *ileS-2* gene encoding a second novel IRS, which has no affinity for muopirocin.[11]

As low-level mupirocin resistance is now more prevalent in clinical isolates,[12–14] concerns regarding treatment failure for nasal decolonization of MRSA are increasing[15–18]; therefore, routine monitoring for potential resistance is prudent in the hospital setting. Prior mupirocin use is a significant risk factor for widespread low-level resistance.[8–10] However, interestingly, recent studies have reported the isolation of mup^r *S. aureus* strains in the absence of any apparent exposure to mupirocin,[13,15] indicating that other factors may be involved.

In this study, we conducted a case–case–control study to identify the risk factors associated with the recovery of low-level mup^r MRSA, compared with the recovery of mupirocin-susceptible (mup^s) MRSA, from clinical cultures in intensive care units (ICUs). Antibiotic exposure was a potential risk factor of particular interest. This is the first study conducted to identify risk factors associated with the isolation of low-level mup^r MRSA.

Materials and methods

Study design and definitions

A case–case–control study was performed retrospectively from November 2003 to April 2004 at a 750-bed tertiary care hospital equipped with three ICUs containing 54 beds.

Cases were defined as patients with clinical cultures that grew low-level mup^r MRSA (case 1 group) and mup^s MRSA (case group 2). The controls consisted of patients who were admitted to the ICUs for more than 48 h, and were selected from the same ICUs that were being used for cases during the same calendar month that mup^r MRSA was isolated (frequency-matched controls).

The control group 1, for the case group 1, did not have mup^r MRSA isolated from cultures during their hospitalization. We randomly selected six controls for each mup^r MRSA patient. The control group 2, for the case group 2, was identical to control group 1 with the exception that patients with mup^s MRSA were excluded. All cultures were drawn at least 48 h after admission. All clinical specimens were cultured in search of an infectious etiology for patient deterioration.

The rationale for a case–case–control study design was to identify risk factors for the isolation of low-level mup^r MRSA by contrasting two multivariable models: risk factors for isolation of mup^r MRSA and risk factors for isolation of mup^s MRSA.

Data collection

Patients' data were collected from medical charts and electronic databases. The following variables, as possible risk factors, were collected for each patient: age, sex, comorbid conditions and the Charlson score[19] [obtained by using the codes from the tenth revision of the International Classification of Diseases], surgery prior to the outcome of interest, transfer from another hospital, hospitalization during the prior year, length of ICU stay prior to the outcome of interest (for cases, length of ICU stay prior to MRSA isolation, and for controls, complete length of ICU stay), and treatment with antimicrobial drugs. For the cases, treatment with antimicrobials was included in the analysis only when the agents were given within 14 days prior to isolation of mup^r MRSA or mup^s MRSA. For controls, treatment with antimicrobial agents within 14 days of isolation of any organisms or during the 14 days prior to discharge was analyzed. Because we believed that antibiotics received early in the admission were unlikely to be related to the isolation of mup^r MRSA, we chose the antibiotics within 14 days prior to isolation of organism to avoid analyzing antibiotics that patients had received during the initial phase of a lengthy admission. We assessed prior use of mupirocin in both cases and controls on the basis of information obtained from the hospital computerized databases from January 2002 to December 2004; this information was collected because of the previous reports that low-level resistance to mupirocin emerges after long-term use.[8–10]

MRSA detection and mupirocin susceptibility

MRSA isolates were identified by the standard disk diffusion method[20] and the detection of the *mecA* gene was by polymerase chain reaction (PCR). The primer pair was MecA1 (5′-ATG CTA AAG TTC AAA AGA GTA TTT ATA A) and MecA2 (5′-TGA TGA TTC TAT TGC TTT TAA GTC), yielding a 400-bp product. The MICs of mupirocin, ranging from 0.125 to 1.024 μg/mL, were determined by the standardized agar dilution method.[21] A microinoculator (Sakuma Co. Ltd, Japan) was used to inoculate the bacterial suspensions (10^4 cfu/spot). *S. aureus* ATCC 29213 was used as a control.

Sequencing the *ileS* and *ileS-2* genes

To identify point mutations of the *ileS* gene, the 690-bp product was amplified using a primer pair Lmr1 (5′-GTA AAT CTT TAG GTA ATG TGA TTG TAC) and Lmr2 (5′-TCT TCT TTA ACA TGT GGT GTA TGA GA). To detect the *ileS-2* gene, a 410-bp region in the *ileS-2* gene was amplified using a primer pair Mup1 (5′-TAT ATT ATG CGA TGG AAG GTT GG) and Mup2 (5′-AAT AAA ATC AGC TGG AAA GTG TTG).[14] PCR products were purified with the QIAquick-spin PCR purification kit (Qiagen) and sequenced by Bioneer Corporation, Korea.

Pulsed-field gel electrophoresis (PFGE)

Chromosomal DNA from *S. aureus* was prepared in agarose blocks and was cleaved with *Sma*I (New England Biolabs

Inc.).[22] Electrophoresis was performed with the GeneNavigator System (Amersham Biosciences Ltd.) with 130 V and at 16 °C; 5 s pulse time for 4 h, 25 s pulse time for 6 h, 45 s pulse time for 20 h, and 75 s pulse time for 6 h. Total running time was 36 h. The band patterns were compared using the criteria for bacterial strain typing.[23]

Statistical analysis

All statistical analyses were performed with SAS software, version 8 (SAS Institute). Bivariable analysis was performed separately for each of the variables. Odds ratio (OR) and 95% confidence intervals (CI) were calculated for categorical variables. *P* values were calculated using Fisher's exact test for categorical variables, by the Chi-square test for ordinal variables, and by the Student *t* test or the Wilcoxon rank sum test for continuous variables.

Variables, for which *P* values were $\leq$0.05 in the bivariable analysis, were included in the logistic regression model for multivariable analysis. A backward stepwise selection method was used. Risk factors were evaluated for confounding and interaction. All tests were 2-tailed, and a *P* value of $\leq$0.05 was considered significant.

Results

During the study period, 20 patients with mup^r MRSA (case group 1) and 51 patients with mup^s MRSA (case group 2) were identified. A total of 120 control patients were included in control group 1. Of the control patients, 16 patients with mup^s MRSA isolates were not included in control group 2 ($n = 104$).

MRSA isolates were primarily recovered from sputum, with 90% mup^r and 94% mup^s MRSA. Other sites of isolation included urine and wound secretions for mup^r and blood for the mup^s MRSA. The mupirocin MIC of mup^r isolates ranged from 16 to 64 μg/mL. PCR results showed that *mec*A and *ileS* genes were detected in all MRSA isolates; however, the *ileS-2* gene conferring a high-level mupirocin resistance was not detected in any of the MRSA isolates. Sequence analysis of the amplified *ileS* gene fragment identified a point mutation V588F in the IRS conferring low-level mupirocin resistance from all of 20 mup^r isolates (Table 1). PFGE analysis of 53 MRSA isolates, including 20 mup^r isolates, showed five clonal types (A–E). Twenty mup^r MRSA isolates were separated into five PFGE types and subtype A1, and the remaining 33 mup^s MRSA isolates belonged to the aforementioned five types (data not shown).

Diagnosis at admission to ICU in case group 1 patients included neurologic disorder (30%), respiratory disorder (25%), gastrointestinal–hepatobiliary disorder (20%), genitourinary disorder (15%) and cardiovascular disorder (10%). For the case group 2, the diagnoses included infectious disorder (35%), neurologic disorder (18%), gastrointestinal–hepatobiliary disorder (19%), respiratory disorder (12%), cardiovascular disorder (12%) and hematologic disorder (4%).

Results from the bivariate risk factor analyses for both low-level mup^r and mup^s MRSA are outlined in Table 2. The results of the multivariate risk factor analyses for both low-level mup^r and mup^s MRSA are outlined in Table 3. The multivariable logistic regression analysis demonstrated that exposure to the following antibiotics was significantly associated with the isolation of mup^r MRSA: piperacillin–tazobactam (OR, 13.8; 95% CI, 1.8–105), third-generation cephalosporins (OR, 5.0; 95% CI, 1.6–15.5) and quinolones (OR, 3.4; 95% CI, 1.1–10.7). The independent risk factors for the isolation of mup^s MRSA were the length of ICU stay (OR, 1.1; 95% CI, 1.0–1.1), surgery (OR, 3.7; 95% CI, 1.5–9.0), exposure to third-generation cephalosporins (OR, 8.4; 95% CI, 3.3–21.7) and quinolones (OR, 7.7; 95% CI, 2.8–21.3).

Table 1 Results obtained from mupirocin-resistant MRSA isolates by mutational analysis of the *ileS* gene and PFGE

Isolate	MIC[a]	Culture site	ICU	Isolated date	V588F	PFGE pattern
1	32	Wound	MICU	Nov, 2003	+[b]	A1
2	64	Sputum	MICU	Nov, 2003	+	A0
3	32	Sputum	MICU	Nov, 2003	+	A0
4	64	Sputum	SICU	Nov, 2003	+	B
5	64	Sputum	CICU	Dec, 2003	+	B
6	64	Sputum	CICU	Dec, 2003	+	B
7	64	Sputum	MICU	Dec, 2004	+	A0
8	32	Sputum	MICU	Feb, 2004	+	C
9	32	Sputum	MICU	Mar, 2004	+	C
10	32	Sputum	MICU	Mar, 2004	+	C
11	32	Sputum	SICU	Mar, 2004	+	C
12	32	Sputum	MICU	Mar, 2004	+	D
13	32	Sputum	CICU	Mar, 2004	+	C
14	32	Sputum	CICU	Mar, 2004	+	D
15	32	Sputum	MICU	April, 2004	+	D
16	32	Sputum	SICU	April, 2004	+	E
17	32	Sputum	CICU	April, 2004	+	C
18	32	Sputum	MICU	April, 2004	+	C
19	16	Urine	SICU	April, 2004	+	A0
20	64	Sputum	CICU	April, 2004	+	C

ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; CICU, medico-surgical ICU; V588F: F, phenylalanine; V, valine; and PFGE, pulsed-field gel electrophoresis.
[a] MIC, MIC for mupirocin, μg/mL.
[b] +, Presence of indicated amino acid change by mutation in *ileS* gene.

The amount of 2% mupirocin ointment usage, supplied in a 22-g tube, had gradually decreased in hospitalized patients over the past three years (average, 244,295 inpatients per year); 893 tubes in 2002, 599 tubes in 2003, and 407 tubes in 2004. Most of the mupirocin had been prescribed for the treatment of skin infections in the Dermatology ward and only a small amount was used in the three ICUs; where the estimated use was 24–49 tubes per year. Mupirocin had not been prescribed to the study population except for three patients with mup^s MRSA isolates during the study period; the reasons for its prescription were not shown in the medical records.

Discussion

In the present study we assessed the risk factors associated with the recovery of low-level mup^r MRSA, and the risk factors associated with the recovery of mup^s MRSA from

Table 2 Bivariate risk factors for the isolation of mupirocin-resistant and mupirocin-susceptible MRSA

Variable	Mupirocin-resistant MRSA			Mupirocin-susceptible MRSA		
	Control ($n = 120$)	Case ($n = 20$)	*P* value	Control ($n = 104$)	Case ($n = 51$)	*P* value
Demographics and comorbidities						
Sex (m/f)	71/49	11/9	0.81	61/43	32/19	0.73
Mean age (yrs)	61.24 ± 17.48[a]	67 ± 16.27[a]	0.17	60.35 ± 18.09[a]	65.77 ± 11.48[a]	0.05
Charlson score (mean)	1.683 ± 1.61[a]	1.7 ± 1.72[a]	0.97	1.75 ± 1.68[a]	2.04 ± 1.85[a]	0.33
Variables related to hospitalization						
ICU stay (mean days)	13.38 ± 32.00[a]	18 ± 18.07[a]	<0.01	9.49 ± 9.06[a]	29.65 ± 59.71[a]	<0.01
Surgery	28 (23.33)	2 (10)	0.25	22 (21.15)	23 (45.10)	<0.01
Admission in past year	32 (26.67)	6 (30)	0.79	28 (26.92)	16 (31.37)	0.57
Transfer	5 (4.17)	0 (0)	1.00	3 (2.88)	3 (5.88)	0.40
Antibiotics						
Penicillin	0 (0)	0 (0)	1.00	0 (0)	2 (3.92)	0.11
Ampicillin–sulbactam	4 (3.33)	1 (5)	0.54	4 (3.85)	1 (1.96)	1.00
Piperacillin–tazobactam	2 (1.67)	4 (20)	<0.01	1 (0.96)	3 (5.88)	0.10
Ceph 1 or Ceph 2	15 (12.50)	1 (5)	0.47	14 (13.46)	4 (7.84)	0.43
Ceph 3	43 (35.83)	15 (75)	<0.01	33 (31.73)	34 (66.67)	<0.01
Cefepime	0 (0)	1 (5)	0.14	0 (0)	4 (7.84)	0.01
Vancomycin	7 (5.83)	5 (25)	0.02	5 (4.81)	8 (15.69)	0.03
Metronidazole	4 (3.33)	2 (10)	0.20	2 (1.92)	9 (17.65)	<0.01
Clindamycin	13 (10.83)	4 (20)	0.27	6 (5.77)	10 (19.61)	0.01
Quinolone	19 (15.83)	8 (40)	0.03	11 (10.58)	19 (37.25)	<0.01
Imipenem	5 (4.17)	3 (15)	0.09	4 (3.85)	8 (15.69)	0.02
Aminoglycoside	15 (12.50)	3 (15)	0.72	10 (9.62)	18 (35.29)	<0.01
Macrolide	3 (2.50)	1 (5)	0.46	1 (0.96)	5 (9.80)	0.02

Ceph 1, first generation cephalosporin; ceph 2, second generation cephalosporin; and ceph 3, third-generation cephalosporin.
[a] mean ± standard deviation.

patients in ICUs by a case–case–control study design. The advantages of the case–case–control study design have been described in prior reports on risk factors for nosocomial isolation of antibiotic-resistant pathogens from clinical cultures.[15,16,24,25]

In this study, we found that the exposure to piperacillin–tazobactam, third-generation cephalosporins and quinolones was significantly associated with isolation of low-level mup^r MRSA. In cases with mup^s MRSA, length of ICU stay, exposure to third-generation cephalosporins and quinolones were significantly associated variables. Exposure to piperacillin–tazobactam was shown to be the sole risk factor for the isolation of low-level mup^r MRSA. In this retrospective analysis, we could not identify the acquisition time of mup^r MRSA or mup^s MRSA strains during the ICU stay; however, we assumed that there was no difference in the acquisition time between the two groups.

The identification of third-generation cephalosporins and quinolones as common risk factors, in both low-level mup^r MRSA and mup^s MRSA groups, is probably due to their common use in treatment for severe gram-negative infections in ICUs where the MRSA strain is commonly colonized. Vancomycin was not identified as a risk factor for the groups studied, although it was commonly used as a treatment for gram-positive infections, especially MRSA infections.

Prior mupirocin use has been reported as a significant factor for the recovery of low-level mup^r MRSA in the previous studies.[8–10] In our study, however, none of the

Table 3 Selected variables in the multivariate analysis for mupirocin-resistant and mupirocin-susceptible MRSA

Mupirocin-resistant MRSA		Mupirocin-susceptible MRSA	
Variable	OR (95% CI)	Variable	OR (95% CI)
Piperacillin–tazobactam	13.8 (1.8–105.0)	ICU stay	1.1 (1.0–1.1)
Ceph 3	5.0 (1.6–15.5)	Surgery	3.7 (1.5–9.0)
Quinolone	3.4 (1.1–10.7)	Ceph 3	8.4 (3.3–21.7)
		Quinolone	7.7 (2.8–21.3)

Ceph 3, third-generation cephalosporin.

patients with low-level mup^r MRSA had apparent exposure to mupirocin during hospitalization. Only three patients with mup^s MRSA isolates were given mupirocin; under the unidentified reasons for its prescription. In addition, we do not routinely use mupirocin for surgical prophylaxis; its use is limited to the elimination of nasal MRSA carriage among HCWs in this hospital.

One previous study suggested that the isolation of low-level mup^r MRSA from patients, who had not been exposed to mupirocin, might be related to nosocomial transmission by medical staff.[13] However, this association seems unlikely based on the results of our study. By the PFGE analysis, mup^r MRSA and mup^s MRSA isolates could be separated into five PFGE profiles belonging to our endemic strains. A dominant PFGE type of mup^r MRSA was recovered from both contemporary and clustered patients; suggesting the possibility of horizontal spread from month to month. Our unpublished active surveillance data to detect MRSA nasal carriage among 225 HCWs showed that none of 14 MRSA isolates had low- or high-level mupirocin resistance. As a result, it is not clear if there was horizontal transmission of mup^r MRSA.

In this study, we have shown that piperacillin–tazobactam was statistically associated with the recovery of low-level mup^r MRSA, although the confidence interval was wide, due to the small sample size in case group 1. Broad-spectrum antimicrobials have been reported as risk factors for other antibiotic-resistant pathogens.[24–28] However, case–control studies, similar to this study, have not identified a causal association. Hence, our results require validation by future studies.

In conclusion, we have demonstrated that low-level mup^r MRSA was prevalent among the patients in ICUs, who had no apparent exposure to mupirocin. Furthermore, our study suggests that piperacillin–tazobactam may be a risk factor associated with the recovery of low-level mup^r MRSA as demonstrated by the multivariate logistic analysis. This is the first study that specifically assessed risk factors for nosocomial isolation of low-level mup^r MRSA or mup^s MRSA using a case–case–control study design.

Acknowledgements

We thank Seung Eun Lee, Sang Hoon Park, Young Mi Kim, and Hee Sun Sim for their invaluable help with data handling and laboratory work.

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