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RESEARCH ARTICLE

Clonal relation of nasal MRSA carrier status among hospital personnel, hospitalized patients and community

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ABSTRACT

Objectives: Nasal colonization of methicillin-resistant *Staphylococcus aureus* (MRSA) among the healthcare workers (HCWs), hospitalized patients, and healthy individuals was investigated by pulsed field gel electrophoresis (PFGE) for defining of clonally distribution of them.

Methods: Totally 403 healthcare personnel, 744 patients, and 204 healthy individuals from the population were enrolled. Microbiological procedures were performed in the Bacteriological Laboratory at the Clinical Microbiology and Infectious Diseases Department of Firat University, and PFGE procedures were performed in the Microbiology Department of Inonu University.

Results: *Staphylococcus aureus* was isolated in 296 (21.9%) of 1351 nasal swabs, and 69 out of 296 (23.3%) were defined as MRSA. Nasal *S. aureus* carrier state was identical between the patients and HCWs carrier state (p=0.14). It was significantly lower in healthy subjects than the other groups (p=0.02). Seventeen (25.8%) of 66 MRSA strains were defined to be in the cluster. These strains were in 7 different clusters. Among the typed strains, 21 had close relationship, 2 had possible relationship, and 26 had no relation. PFGE pattern was defined in 33 (50%) out of 66 strains and it was inconclusive in 3 strains.

Conclusions: MRSA strains can be transferred commonly in the same hospital, among the hospitals located in the same region and the population. The results might be the indicators of increasing frequencies in population based MRSA infections. Multi-center studies are required to define clonally distribution of MRSA and the explanation of epidemiology may be helpful for preventing and controlling of MRSA related infections. *J Microbiol Infect Dis 2013; 3(2): 49-55*

Key words: MRSA, nasal carrier, PFGE.

Hastane personeli, yatan hastalar ve toplumda nazal MRSA taşıyıcılığı ve klonal bağlantı

ÖZET

Amaç: Sağlık çalışanları, hospitalize hastalar ve sağlıklı gönüllülerde nazal metisilin-dirençli *Staphylococcus aureus* (MRSA) kolonizasyonu ve klonal dağılımı pulsed field gel electrophoresis (PFGE) ile araştırıldı.

Yöntemler: Çalışmaya 403 hastane çalışanı, 744 hasta ve 204 sağlıklı toplum bireyi alındı. Mikrobiyolojik işlemler Fırat Üniversitesi Klinik Mikrobiyoloji ve Enfeksiyon Hastalıkları Anabilim Dalı Bakteriyoloji Laboratuarı'nda, PFGE işlemi ise İnönü Üniversitesi Mikrobiyoloji Anabilim Dalı'nda çalışıldı.

Bulgular: Toplam 1351 nazal sürüntü kültüründen 296 *Staphylococcus aureus* suşu izole edildi ve bunların 69 (% 23,3)'u MRSA idi. Nazal *S. aureus* taşıyıcılığı sağlık çalışanları ve hastalar arasında benzer idi (p=0,14). Sağlıklı gönüllü gurupta ise diğer guruplara göre anlamlı derecede az olarak bulundu (p=0,02). PFGE yöntemiyle 66 MRSA suşunun 17 (% 25,8)'sinin küme içinde olduğu saptandı. Bu suşlar 7 küme içinde yer almaktaydı. Tiplendirilen suşların 21 tanesi yakın ilişkili, ikisi ise muhtemel ilişkili olarak saptandı. Yirmi altı suş klonal olarak ilişkisiz bulundu. Toplam 66 suş içinde 33 (% 50) PFGE paterni belirlendi.

Sonuç: Çalışmamız sonucunda MRSA suşlarının aynı hastane içinde daha fazla olmakla birlikte bölgedeki hastaneler arasında ve hastane-toplum arasında taşınabileceğini gördük. Çalışmadan elde edilen sonuçlar toplumda artan MRSA enfeksiyon sıklığı için bir indikatör olabilir. MRSA'nın klonal dağılımının saptanması ve epidemiyolojisinin belirlenmesi için çok merkezli çalışmalara ihtiyaç olduğunu ve MRSA epidemiyolojisinin aydınlatılmasının MRSA'ya bağlı enfeksiyonların önlenmesi ve kontrolünde yardımcı olacağını düşünüyoruz.

Anahtar kelimeler: MRSA, nazal taşıyıcılık, PFGE.

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INTRODUCTION

Although methicillin-resistant *Staphylococcus aureus* (MRSA) strains are generally known agents for nosocomial infections, caused by community acquired MRSA (CA-MRSA) strains have gained significance in the recent years. In 1999, mortal progression of CA-MRSA infections in 4 children were reported by Centers for Disease Control and Prevention (CDC), and these cases supported the hypothesis that origins of CA-MRSA could also be virulent, and MRSA infections would not be threats not only for hospitals, but for the population as well.[1]

Staphylococcus aureus, which is a member of the normal flora of anterior nasal mucosa, nasopharynx, perineal region, and skin, is shown mainly colonize in the anterior nostrils. It was reported that more than 80% of bacteremia causing microorganisms had the same genotypes with the nasally colonized strains suggesting it would be very significant to emphasize the nasal carrier state.[2] In order to perform epidemiological investigations of MRSA epidemics, methods which can differentiate or prove the similarities between strains, are required. Pulsed-field gel electrophoresis (PFGE) is useful standard method, for detection of bacterial isolate type including MRSA strains.[3]

We planned this study to emphasize once again that under the light of this information and data, MRSA strains can be disseminated in the community and among hospitals by discharge of patients without eradication of the colonization, or referral of these patients from one hospital to another, or through healthcare personnel. In order to support our hypothesis, we have employed PFGE method for epidemiological studies.

METHODS

Definition of the study group: Two basic groups were included in the study; hospital related and community based groups (this group was not related to the hospitals). Hospital related group was composed with samples from three hospitals; Elazig Community Hospital (ECH), Harput Community Hospital (HCH), and Medical Centre Hospital of Firat University (MCHFU) located in the centrum of Elazig province. Members of hospital related group were divided into two as subject hospital personnel and hospitalized patients for at least 72 hours.

Non-hospital related group members were defined according to CDC recommendations as; subjects without any previous MRSA infection or colonization history; who were not hospitalized or cared at a rescue home or without dialysis or surgery history in the last one year; and who did not have a permanent catheter or transdermal medical device.[4]

The study was conducted between September and November 2007. Microbiological procedures were performed at the Bacteriology Laboratory in the Clinical Microbiology and Infectious Diseases Department of Firat University, Elazig and PFGE procedure was performed at the Microbiology Department of Inonu University, Malatya, Turkey.

Bacterial isolation and antibiotic sensitivity

Nasal swabs were obtained with a sterile ecuvion stick from 1/3 anterior nasal concha bilaterally in a culture transport media (culture swab transport system, COPAN innovation, Italy). They were identified by using conventional methods.[5] Antibiotic sensitivities of obtained *S. aureus* strains were defined through Kirby-Bauer disc diffusion method, and methicillin resistance was defined by using 30 µg cefoxitin discs. Antibiotic sensitivity and cefoxitin resistance were evaluated according to Clinical and Laboratory Standards Institute (CLSI) standards.[6] Standard *S. aureus* ATCC 29213 strain, which sensitive to oxacillin was used as quality control strain.

Molecular typing with PFGE method

PFGE was studied in a total of 69 isolated MRSA strains. PFGE procedure was employed according to the optimization of Durmaz et al.[7]

Electrophoresis

Electrophoresis conditions in CHEF-DR II system (Bio-Rad Laboratories, Nazareth, Belgium): Duration of initial strike 5.3 seconds, duration of final strike 34.9 second, strike angle 120°, voltage 6 V/cm2, temperature 14°C, duration 20 hours (TBE tamponed pH=8.0).

Observation of results and analysis

After the electrophoresis, gel was taken into 400 ml ultra-distilled water with 5 µg/ml ethidium bromide, and stained for 20 minutes. DNA bands were photographed under UV light by using gel logic 2200 imaging system (differentiation strength: 1708x1280 pixel, Kodak Company, NY, USA), and photographs were recorded in TIFF format. Band profiles were analyzed by using GelCompar II software system (Applied Maths, Belgium). Normalization between the photographs was provided primarily by help of three standards (in the first, 7th, and 15th wells). Den-

drograms of PFGE profiles were prepared by using "Unweighted pair group method with mathematical averaging (UPGMA)", and clustering analysis was performed. Relationships between species were defined according to band related "Dice" similarity coefficient. Band and profile tolerance were taken as 1-1.5% in similarity coefficient calculation. By using the criteria developed by Tenover et al.[8], isolates were evaluated as the same, closely related, probably related and unrelated.

Statistical analysis

Statistical analysis of data was performed by using SPSS version 15.00 package program. Chi-square test was employed for risk factor analysis. Level of significance was accepted at P<0.05.

RESULTS

A total of 403 hospital personnel (170 physician, 119 healthcare personnel other than physicians (HPOP; nurses, health officers, anesthesiology technicians etc.) and 114 helping personnel (HPOP; cleaning personnel etc.), 744 patients and 204 healthy community members were included in this study. Of the participants, 628 were female, and 723 were male, and the age range was between 1 and 102 with mean ± SD 44 ± 20 years. Out of 1351 cultures, 296 *S. aureus* strains were isolated, and 69 (23.3%) of them were MRSA (Table 1).

Table 1. Demographic characteristics of all participants according to nasal *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) carrier state (N=1351)

	S. aureus (n=296)	P value	MRSA (n=69)	P value
Gender, *n* (%)				
Female (n=628)	134 (21.3)	0.68	31 (4.9)	0.89
Male (n=723)	162 (22.4)		38 (5.3)	
Age (yrs)				
0-9 (n=25)	4 (16)		2 (8)	
10-19 (n=69)	13 (18.8)		0	
20-29 (n=293)	70 (23.9)		16 (5.5)	
30-39 (n=308)	57 (18.5)	0.41	10 (3.2)	0.12
40-49 (n=159)	29 (18.2)		10 (6.3)	
50-59 (n=138)	29 (21)		11(8)	
60-69 (n=169)	41 (24.3)		6 (3.6)	
70-79 (n=147)	40 (27.2)		10 (.8)	
80 and above (n=43)	11 (25)		4 (9.3)	

Among hospitalized patients, *S. aureus* carrier state was 24.2%, and MRSA was 7.1%; whereas the rates of *S. aureus* carrier state among hospital personnel was 20.3% and 3.5%, respectively. The rates of *S. aureus* carrier state in non-hospital group were 16.7% and 1% (Table 2). There was significant differences among the hospitalized patient, hospital personnel and healthy subject groups both in nasal carrier state of *S. aureus* and MRSA (p=0.04 and p=0.0004 respectively). While no statistically significant difference was found in the *S. aureus* carrier state between hospitalized patients and hospital personnel (p=0.14); there was a significant increase in the carrier state when compared to healthy subjects (p=0.02). Band patterns of some MRSA strains, which are obtained by PFGE on the agarose gel after Sma I enzyme slicing is shown in Figure 1.

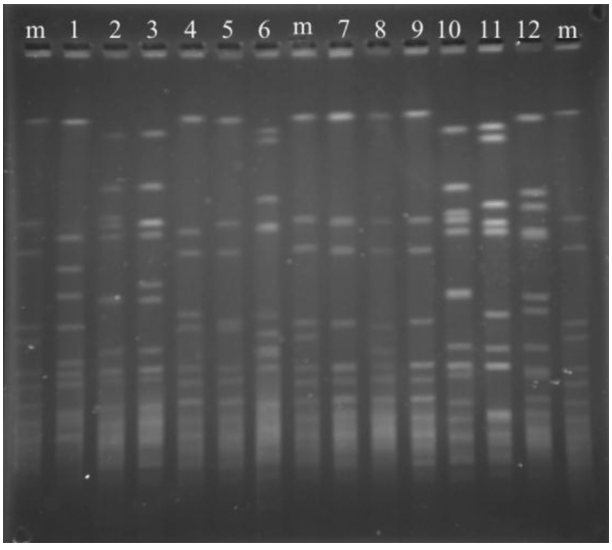

Figure 1. Some PFGE band patterns obtained by slicing with ''Sma I'' enzyme. PFGE pattern lane m: standards, lane 1: 51. MRSA strain (XXXI Clone), lane 2:52. MRSA str

(V Clone), lane 3:53. MRSA strain (V-a Clone), lane 4: 54. MRSA strain, (XXXIV-b Clone), lane 5: 55. MRSA strain (XXXIV Clone), lane 6:56. MRSA strain (XVII Clone), lane 7: 56. MRSA strain (XVII Clone), lane 8: 58. MRSA strain (XXXIV-a Clone), lane 9: 59 MRSA strain (XXXIV Clone), lane 10: 60 MRSA strain (V Clone), lane 11: 61. MRSA strain (XV Clone) and lane 12: 62. MRSA strain (XVI Clone).

Out of 66 MRSA strains, 17 (25.8%) were defined in the cluster by PFGE method. These strains were present in 7 clusters. Strains range differed 2-3 in the clustering. Among the typed strains, 21 were closely and 2 were probably related, where 26 strains were defined as unrelated. In a total of

66 strains, 33 (50%) were defined to have PFGE pattern, and no result was detected in 3 strains by PFGE. Purity of these three strains and presence of *S. aureus* were tested biochemically. Despite three repetitions with the markers and the same protocol, no result was obtained (Figure 2).

Table 2. Comparison of nasal *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) carrier state among the groups.

Nasal carriage (microorganism)	Hospitalized Patients (n=744)	Hospital Personnel* (n=403)	Healthy Subjects (n=204)	P value
Staphylococcus aureus, n (%)	180 (24.2)	82 (20.3)	34 (16.7)	0.040
Methicillin-resistant *Staphylococcus aureus (MRSA), n (%)*	53 (7.1)	14 (3.5)	2 (1.0)	0.0004

* Physicians, other than healthcare and helping personnel except physicians.

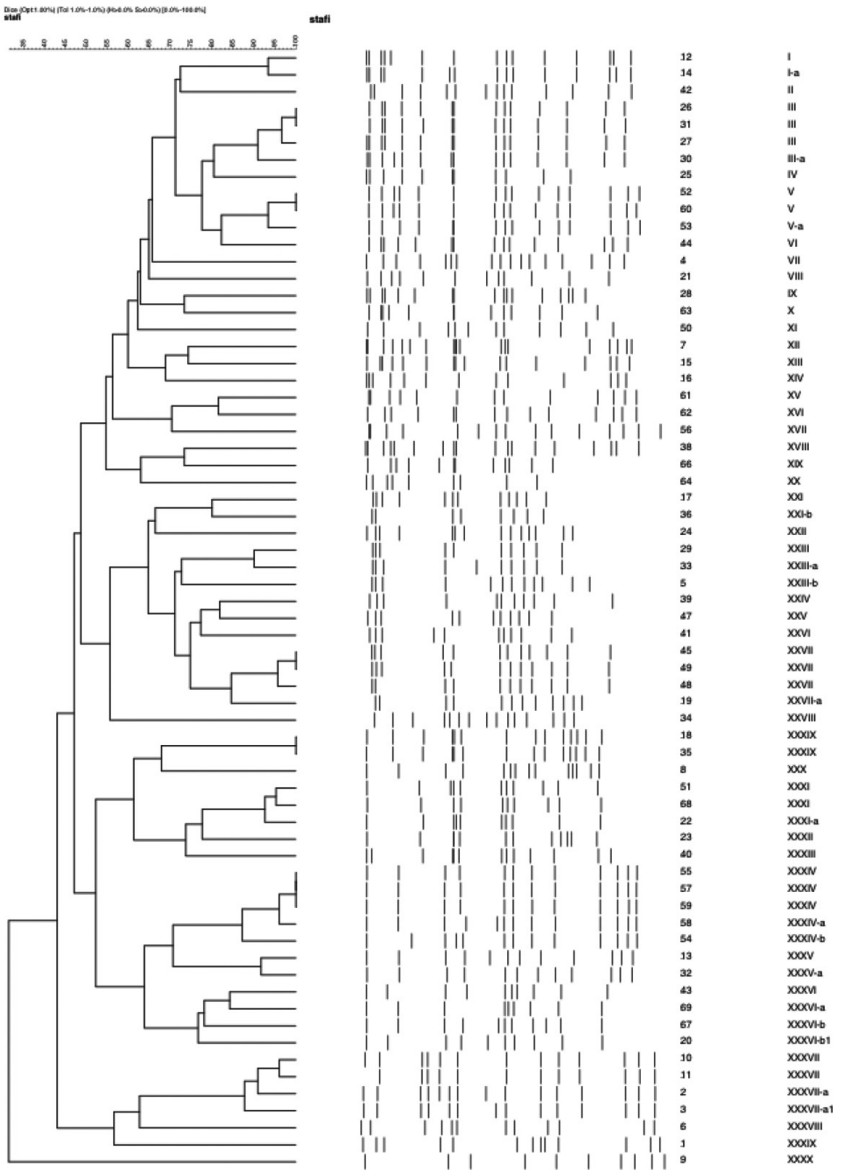

Figure 2. UPGMA dendrogram derived from PFGE data and PFGE banding patterns (a, possible; a1, closely related to a; b probably related)

Thirty-seventh clone (XXXVII): It is made up of four strains. Two strains formed the same cluster, and the other two are closely related among themselves. Two of these strains were isolated in the infectious disease clinic, one was isolated in ENT, and the other was isolated in nephrology clinic among the hospitalized patients. The common characteristics of strains, which belonged to this colon, were that the four patients were internalized in MCHFU Anesthesiology intensive care unit between the same dates, and they had longer hospital stay histories.

First clone (I): It is made up of two strains, which are closely related, and they were detected in two patients, who were internalized at the same time interval in ENT clinic of MCHFU. Third clone (III): It is made up of four strains, and three of them were the same, whereas one was closely related. These strains were isolated from hospitalized patients in the MCHFU Anesthesiology intensive care unit.

Twenty-seventh clone (XXVII): It is made up of four strains, and three of them were the same, whereas one was closely related. All of these strains were obtained from MCHFU. Two of these strains were obtained from patient in plastic surgery clinic, and one was obtained from a patient in nephrology clinic. These two clinics were at the same floor. The other one was isolated form a patient in the neurology clinic, but no relationship was defined with the other strains.

Fifth clone (V): It is made up of three strains; two strains were the same, whereas one was closely related. All three patients had COPD. Two of these strains were obtained at MCHFU, and the other one was obtained at Harput Community Hospital (HCH). When isolated from HCH were examined, it was determined that the patient was previously internalized in the department of chest diseases at the MCHFU.

Thirty-fourth clone (XXXIV): It is made up of five strains; three strains were the same, one was closely and the other was probably related. All of these isolated were obtained from ECH, and the four strains were from patients, who were hospitalized at the same floor, whereas the other one was obtained from helping healthcare personnel.

Two MRSA isolates, which were obtained from the community, belonged to different clones. Strains belonging to XXXIst clone were also closely related with the patient internalized in the HCH. When this hospitalized patient and subjects with community isolated MRSA strains were retrospectively examined, no relationship was detected.

DISCUSSION

Nasal *S. aureus* carrier state is an important risk factor in the development of both community and hospital acquired staphylococcus infections. Sources of MRSA, which become endemics for many hospitals, are generally colonized or infected patients or healthcare personnel. The most important tools transmitting a disease between patients are hands of healthcare personnel. MRSA has been shown on hands of healthcare personnel after procedures like wound debridement, tracheal aspiration, catheter care and changing the clothes. Transmission through hands of healthcare personnel, who is a nasal carrier, is more commonly encountered.[9] It has been shown that strains on hands are almost always the same with that of in the nose in subjects with concomitant presence of *S. aureus* strains in the nose and hands.[10] While carrier rate of nasal *S. aureus* is 10-20% in healthy adults, this rate is increased up to 20.3-43.6% among the hospital personnel.[11-13] Although these results may show variability between centers, they are important because they have shown that approximately 1/3 of hospital personnel can be carriers. When nasal MRSA carrier state was concerned, it was more commonly encountered among healthcare personnel than subjects from the community. While nasal MRSA carrier rate was changing between 2-6% among the hospital personnel,[14-16] this rate has been reported as 0-3% in the community.[15,17,18] Rashid et al.[19] investigated a total of 129 nasal swabs and epidemiological information concerning risk factors for nasal carriage were obtained from physicians, nurses, sanitary workers and administrative staff. The prevalence of *S. aureus* and MRSA nasal carriage was significantly higher in physicians (51.8%, 18.5%), nurses (66.6%, 27.3%) and sanitary workers (59%, 13.6%) as compared to administrative staff (27.6%, 2.1%) were reported.

Durmaz et al.[20] reported in their study nasal *S. aureus* carrier rate among healthcare personnel as 32%, and MRSA carrier rate as 11%. Nasal *S. aureus* carrier rate was reported as 33% among 61 subjects from the community and there was no MRSA carrier state in this group. Also Kilic et al.[21] reported that nasal swabs were obtained from 4,050 children during a 4-month period in Ankara and they found that 1,001 (24.7%) of them were colonized with *S. aureus*. In that study, the rate of MRSA among all children was reported as 0.07% and the MRSA strains revealed three different PFGE pattern. Caylan et al.[22] reported *S. aureus* carrier rate in nasal swabs of 278 hospital person-

nel as 15.1%, and MRSA carrier rate as 4%. In the same study, 104 subjects from the community were screened, and carrier rates for nasal *S. aureus* was 10.4%, whereas it was 3.8% for MRSA. MRSA carrier rates from hospitals and community are very close, and the high rate in the community was also noteworthy.[23] Rafee Y et al.[24] reported that the prevalence of MRSA colonization in the study group was significantly higher than in the control group (23% vs. 3.9%). The prevalence of *S. aureus* colonization was 28/77 (36%) in the study group and 16/77 (21%) in the control group. The prevalence of *S. aureus* nasal colonization among patients was 6/24 (25%); one with methicillin-susceptible *S. aureus* (MSSA) and 5 with MRSA. In the study (patient) group, 14/24 (58%) families had at least one household member who was colonized with MRSA compared to 2/29 (6.9%) in the control group. In our study, nasal *S. aureus* carrier rate was 16.7% in the community, and it was 20.3% among healthcare personnel. MRSA carrier rates were 7.1% among hospitalized patients, 3.5% among healthcare personnel, and 1% in the community.

In recent years, increased isolations of MRSA have indicated that effective strategies should be developed to control staphylococcal infections and microbial resistance against antibiotics. Therefore, epidemiology, pathogenesis and population genetics of *S. aureus* should be well-known. Definition of MRSA strains having the same antibiotic susceptibility pattern as the same strains is not true in every time and these strains may be genotipically different.[25] In the past, definition of epidemiological relationship between the nosocomial isolates obtained from different sites has been based on phenotypic characteristics such as biotype, serotype, bacteriophage or bacteriocin types. This approach has been started to change in the last 20 years due to developments of DNA based new technologies or molecular analysis. DNA based molecular typing is made up by using PFGE and other restriction based methods, plasmid analysis and polymerase chain reaction (PCR) based typing methods. PFGE is one of the available methods with the highest reproducibility and differentiation strength, and it is a generally preferred method for epidemiological evaluations.[26] Alone it has been employed successfully in molecular typing of MRSA. Layton et al.[27] performed PFGE analysis of 68 MRSA strains, and they defined five main clones with isolate analysis of 38 MRSA strains, and different band patterns in the remaining 30 isolates in their study about epidemiology of hospital and CA-MRSA infections. They defined different patterns in both community and hospital acquired MRSA isolates, so they concluded that cross-transmission between patients were low. Robert et al.[28] typed 270 MRSA isolates, which they obtained from 12 hospitals, by using PFGE, and they defined five main clones. They reported that 14.9% of isolates belonged to the same clone, and this clone was present all hospitals. They also reported that 9 out of 12 hospitals had the same MRSA clone.

Molecular epidemiological studies on MRSA are very limited in our country. In a study performed with 80 MRSA strains in Erciyes University by PFGE analysis, 10 main clones were defined, and 76.3% of strains belonged to the same clone.[29] Four different clones; A, A1-A5, B, C and D, were detected in a study performed at the Karadeniz Technical University by using PFGE analysis. Out of 23 isolates, 20 (87%) were clustered in A clone and its subtypes (A1-A5).[30] As a result of our study, nasal MRSA carrier state acquired from the community has been defined as rare (1%). Close relationship between the strains isolated from community (XXXI-a) and the species isolated from Harput Community Hospital indicated that hospital acquired MRSA strains might spread from hospitals to the community or vice versa. Also the fifth clone in our study was made up of three strains; two of them were the same, whereas one was closely related. All 3 patients had chronic obstructive pulmonary diseases (COPD), and two of them were obtained from MCHFU, and one was from HCH. When the isolate from HCH was examined, the patient was defined to be internalized in the chest diseases department of MCHFU. It was observed that strains could be transmitted between hospitals by means of colonized patients. Thirty fourth clone was made up of five strains; three of them were the same, whereas one was closely and the other was probably related. All of these isolated were from ECH, and 4 strains were obtained from patients in the same floor, and one was isolated from a helping healthcare personnel, who was working at the same hospital. When the other clones were examined, MRSA was observed to be transmitted between wards at the MCHFU. Common features of these strains were that the wards were located at the same floor or patients were previously hospitalized into anesthesiology ICU. As there was no database related to clonal distributions of MRSA in our region, correlations between the obtained clones could not be investigated.

As a result of our study, we observed that MRSA strains could be transmitted between the regional hospitals, and between the hospital and community, the commonest being within the same hospital. Moreover, obtained data from this study might

interpret as we could meet increased CA-MRSA infection frequency in the near future. We think that national and multicenter clinical trials are needed to define MRSA clonal distributions and epidemiologic feature in our country. Such studies would be helpful for preventing and control of MRSA related infections.

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