$$
\begin{aligned}
S(t+1) &= \exp\left[-\kappa(1-p\beta)\frac{I+qE}{N}\right]S(t) \\
E_1(t+1) &= \left\{1-\exp\left[-\kappa(1-p\beta)\frac{I+qE}{N}\right]\right\}S(t) \\
E_k(t+1) &= (1-\gamma_{k-1})E_{k-1}(t) \qquad \text{(A2)} \\
I_1(t+1) &= \sum_{k=1}^{i}\gamma_k E_k(t) \\
I_l(t+1) &= (1-c_{l-1})I_{l-1}(t) \\
R(t+1) &= R(t)+\sum_{l=1}^{j}c_l I_l(t)
\end{aligned}
$$

Based on the forward stepwise logistic regression result in the case-control study, and to facilitate understanding, p and β were used only to represent the use of masks. However, the protective effect, β, was obtained from the result of further multiple logistic regression which entered all other significantly associated variables (in univariate analysis). All terms shown here as products of a probability and a state variable were generated in our simulations by using random variables with binomial distributions. Under these assumptions and using mean length of incubation and symptomatic periods, the reproduction number (R) is given by:

$$R = \kappa(1-p\beta)\left(\frac{q}{\gamma}+\frac{1}{c}\right) \qquad \text{(A3)}$$

where γ^{-1} and c^{-1} are the means of the incubation and symptomatic periods in days, respectively. The basic reproduction number was estimated by

$$R_0 = \frac{R}{(1-p\beta)} \qquad \text{(A4)}$$

For the purpose of mathematical convenience, although unrealistic, our model assumed homogenous mixing as well as all infectious individuals being equally infectious.

Received August 3, 2004. Accepted for publication January 19, 2005.

Acknowledgments: H.N. would like to pay his respects to Dr. Carlo Urbani, an Italian epidemiologist who worked for the WHO Office in Hanoi, whose great achievements in controlling SARS in HFH inspired this study. The authors are grateful to Profs. Masayuki Kakehashi (Hiroshima University, Japan), Minato Nakazawa (Gunma University, Japan), and Klaus Dietz (University of Tubingen, Germany) for their helpful comments and discussions. The authors would also like to thank Dr. Nguyen Le Hang, Ms. Pham Thi Phuong Thuy, and Ms. Nguyen Thi Thu Ha for their help in our survey. H.N. is also grateful to the Japanese Foundation for AIDS Prevention for supporting his stay in the United Kingdom.

Financial support: The study was partly supported by a Health and Labor Sciences Research Grant for "Special Research" entitled "Research on the nosocomial transmission of SARS" awarded by the Ministry of Health, Labor and Welfare, Japan.

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J Infect Chemother (2006) 12:47–50
DOI 10.1007/s10156-005-0417-8

NOTE

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Emergence of rifampicin resistance in methicillin-resistant *Staphylococcus aureus* in tuberculosis wards

Received: September 21, 2005 / Accepted: November 1, 2005

Abstract To assess whether the occurrence of rifampicin (RFP) resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) is related to treatment of tuberculosis, we determined the RFP susceptibility of MRSA isolates obtained from tuberculosis patients and screened for mutation(s) in the *rpoB* gene of these isolates. The MICs of RFP for 84 MRSA isolates obtained from two hospitals in Japan were determined. DNA was sequenced in the region 1318–1602 nucleotides (nt) of the *rpoB* gene, which includes RFP resistance-determining clusters I (1384–1464 nt, 462–488 amino acids). The majority of MRSA isolates from tuberculosis wards, i.e., 48 of 51 (94%) [33 of 34 in a Tokyo hospital (97%) and 15 of 17 in a Chubu hospital (88%)], were resistant to RFP. Meanwhile, no isolates of 33 from the other wards were resistant to RFP. All RFP-resistant MRSA isolates had a mutation(s), including novel mutation(s) such as Val453→Phe, Asp471→Asn, and Ile527→Leu, in *rpoB*. An emergence of RFP-resistant MRSAs in tuberculosis wards in Japan was strongly suggested.

Key words Rifampicin · Drug resistance · MRSA · *rpoB* · Tuberculosis

Rifampicin (RFP) is one of the first-line antituberculous agents and also a potent antimicrobial agent against methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2] RFP acts by interacting in a specific manner with the β-subunit of the bacterial RNA polymerase encoded by the *rpoB* gene.[3] In MRSA infections, RFP is often used in combination with antibiotics with lower penetrability, such as vancomycin.[4,5] The combination therapy with RFP revealed strong activity and good tissue penetration that is required to reach deep-seated infections effectively.[4,5] In such a situation, there is a high risk of emergence of RFP-resistant MRSA. Most RFP-resistant MRSA organisms and other bacteria are known to have a mutation(s) in the particular regions, clusters I and II in the *rpoB* gene encoding the RNA polymerase β-subunit.[4–7]

In the present study, we examined RFP susceptibility of MRSA isolates obtained from inpatients with tuberculosis and screened for mutations in the *rpoB* gene of these isolates. A total of 84 MRSA isolates obtained from hospitals in Tokyo[8–12] and Chubu district[13] were analyzed. *S. aureus* ATCC29213 and ATCC700699 strains were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Of these isolates, 51 were obtained from tuberculosis wards in both hospitals (34 from a hospital in Tokyo during an MRSA outkreak in 2001[12] and MRSA surveillance studies done before and after the outbreak in 2000–2003[8–11] and 17 from a hospital in Chubu during an MRSA outbreak[13]), and 33 other isolates were from other wards in a Tokyo hospital.[8] All MRSA isolates were analyzed by pulsed-field gel electrophoresis (PFGE) as described previously.[8–13] Differences between tuberculosis wards and the other wards in the isolation numbers of MRSA were analyzed by Fisher's exact probability test. A P value <0.05 was considered statistically significant.

The minimum inhibitory concentration (MIC) of RFP was determined by an E-test (AB BIODISK, Dalvagen, Sweden), and the result was interpreted according to the guidelines of the National Committee for Clinical Laboratory Standards.[14] The staphylococcal breakpoint for resistance to RFP is defined as ≥4 μg/ml (susceptible is defined as ≤1 μg/ml).[14]

The distribution of RFP MICs for the MRSA isolates obtained from tuberculosis and other wards is shown in Fig. 1. The MICs of RFP ranged from ≤0.002 to ≥256 μg/ml.

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Among the 84 MRSA isolates, 48 were resistant to RFP with MIC ≥48 μg/ml. The other isolates were susceptible to RFP with MIC ≤0.015 μg/ml. The majority of MRSA isolates from tuberculosis wards, i.e., 48 of 51 (94%) [33 of 34 in a Tokyo hospital (97%) and 15 of 17 in a Chubu hospital (88%)], were resistant to RFP (Fig. 1, Table 1). Meanwhile, 0 of 33 isolates from the other wards were resistant to RFP ($\chi^2 = 72.47$, $P < 0.001$) (see Table 1).

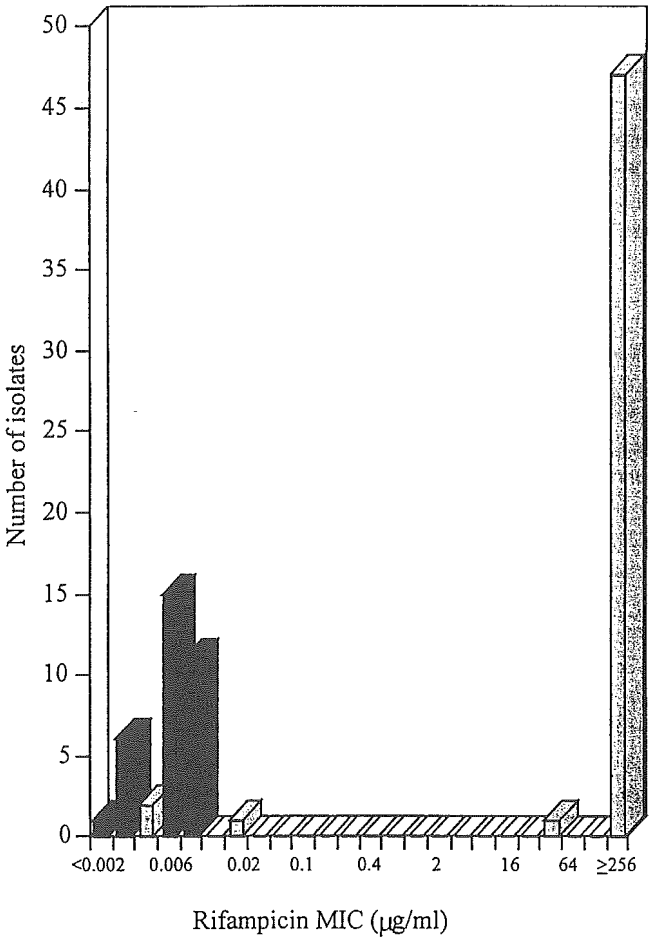

Fig. 1. Distribution of rifampicin minimum inhibitory concentrations (*MICs*) for 84 methicillin-resistant *Staphylococcus aureus* (MRSA) strains isolated in Tokyo and Chubu hospitals. *Gray bars* represent MRSA isolates obtained from tuberculosis wards; *black bars* represent MRSA isolates from other wards

The DNA sequence of the region of 1318–1602 at nucleotide positions (nt) of *rpoB*, corresponding to codons 440–534 (amino acid number, aa number), which includes the RFP resistance-determining cluster I (1384–1464 nt, 462–488 aa)[4] and cluster II (1543–1590 nt, 515–530 aa)[4] of *S. aureus* were amplified by polymerase chain reaction (PCR) with the primers rpoB-F (5′-CCG TCG TTT ACG TTC TGT AGG-3′) and rpoB-R (5′-AAA GCC GAA TTC ATT TAC ACG-3′). PCR products were sequenced with the same primers by the dideoxy chain termination method with an ABI PRISM 3100 sequencer (Applied Biosystems, Foster City, CA, USA). Of 84 isolates analyzed, 32 had one mutation and 16 had two mutations in clusters I and II of *rpoB* (Table 2). A total of 64 mutations were identified, and all mutations resulted in amino acid substitution. Of them, 60 mutations were located in cluster I: 19 were Ala 477→Asp, 14 were Ser 486→Leu, 12 were His 481→Asp, 12 were Ala 473→Thr, 1 was Ser 464→Pro, 1 was Gln 468→Leu, and 1 was Asp 471→Asn. Three mutations were located in cluster II; all three were Ile 527→Leu. One was found in the region upstream from cluster I, i.e., Val453→Phe. All mutations except for the three mutations, Asp471→Asn, Ile527→Leu, and Val453→Phe, were already reported to be related to RFP resistance in *S. aureus*.[4–7] Type 3 isolates were resistant to RFP and had a single mutation of Asp471→Asn, indicating that the *rpoB* mutation was associated with RFP resistance. The mutations at 527 aa, Ile527→Phe or Ile527→Met, were known to be related to RFP resistance.[2] However, whether the mutation Ile527→Leu at the same position was associated with RFP resistance is unclear, because additional mutations known to be related to RFP resistance were present (see type 4 and 5 isolates, Table 2). The association of Val453→Phe with RFP resistance is also unclear because there was an additional mutation associated with RFP resistance (see type 11 isolates, Table 2). Nevertheless, three novel mutations of Asp471→Asn, Ile527→Leu, and Val453→Phe were identified in *S. aureus*.

Based on RFP susceptibility testing, PFGE genotyping, and DNA sequencing of *rpoB*, the MRSA isolates from tuberculosis wards were classified into 23 types (see Table 2). Among 84 isolates, 12 isolates from a Chubu district hospital (type 7) were resistant to RFP (MIC, >256 μg/ml), showed PFGE pattern A2(M1), and had a mutation of Ala 477→Asp; 11 isolates from a Tokyo hospital (type 12) were resistant to RFP (MIC, >256 μg/ml), showed PFGE pattern

Table 1. Frequency of rifampicin-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in tuberculosis wards

Rifampicin susceptibility	No. (%) of isolates			
	Tuberculosis wards			Other wards
	Tokyo[a] ($n = 34$)	Chubu district[b] ($n = 17$)	Total ($n = 51$)	T ($n = 33$)
Resistant	33 (97%)	15 (88%)	48 (94%)	0 (0%)
Susceptible	1 (3%)	2 (12%)	3 (6%)	33 (100%)

[a] Tokyo hospital
[b] Chubu district hospital

Table 2. Resistance to rifampicin and mutations in the *rpoB* gene of *S. aureus* in tuberculosis wards

Hospital[a]	Specimen or reference strain	No. of isolates	Rifampicin MIC (μg/ml)	PFGE genotype[b]	*rpoB* gene		Type no. assigned
					Nucleotide changes[c]	Amino acid changes[d]	
T	Sputum	1	48	A14	TCT→CCT	Ser464→Pro	1
T	Sputum	1	>256	A2(M1)	CAA→CTA	Gln468→Leu	2
T	Sputum	1	>256	F6	GAC→AAC	Asp471→Asn[e]	3
T	Sputum	1	>256	F2	GCT→GAT, ATT→CTT	Ala477→Asp, Ile527→Leu[e]	4
T	Sputum	2	>256	F4	GCT→GAT, ATT→CTT	Ala477→Asp, Ile527→Leu[e]	5
C	Gastric juices	1	>256	M2(A18)	GCT→GAT	Ala477→Asp	6
C	Sputum	12	>256	A2(M1)	GCT→GAT	Ala477→Asp	7
C	Sputum	1	>256	AO	GCT→GAT	Ala477→Asp	8
C	Sputum	1	>256	M7	GCT→GAT	Ala477→Asp	9
T	Sputum	1	>256	G2	GCT→GAT	Ala477→Asp	10
T	Sputum	1	>256	J1	GTT→TTT, TCA→TTA	Val453→Phe[e], Ser486→Leu	11
T	Arterial blood	1	>256	J1	TCA→TTA	Ser486→Leu	12
	Sputum	9					
	Nasal cavity	1					
T	Nasal cavity	1	>256	J2	TCA→TTA	Ser486→Leu	13
T	Sputum	1	>256	J4	TCA→TTA	Ser486→Leu	14
T	Thorax drain	1	>256	R1	GCA→ACA, CAT→GAT	Ala473→Thr, His481→Asp	15
	Sputum	1					
T	Sputum	3	>256	J7(R2)	GCA→ACA, CAT→GAT	Ala473→Thr, His481→Asp	16
	Arterial blood	1					
	Urine	1					
T	Sputum	1	>256	J8	GCA→ACA, CAT→GAT	Ala473→Thr, His481→Asp	17
T	Sputum	1	>256	A1	CAT→TAT	His481→Asp	18
T	Sputum	1	>256	A2(M1)	CAT→TAT	His481→Asp	19
T	Urine	1	>256	S	CAT→GAT	His481→Asp	20
T	Sputum	1	>256	A22	CAT→TAT	His481→Asp	21
T	Sputum	1	0.015	AU1	No change	No change	22
C	Sputum	2	0.005	A3	No change	No change	23
	ATCC29213		0.005	–	No change	No change	
	N315		0.004	–	–	–	

MIC, minimum inhibitory concentration; PFGE, pulsed-field gel electrophoresis
[a]T, Tokyo hospital; C, Chubu district hospital
[b]Data from references 8–13
[c]Base changes are underlined
[d]The numbering of the amino acids is based on that of *S. aureus* N315 (GenBank accession no. NC-002745)
[e]Novel mutation

J1, and had mutation Ser486→Leu; and 5 isolates from Tokyo (type 16) were resistant to RFP (MIC, >256μg/ml), showed PFGE pattern J7(R2), and had two mutations of Ala 473→Thr and His 481→Asp, indicating that there was clonal expansion of these RFP-resistant MRSA strains in tuberculosis wards in both hospitals. Sixteen isolates of types 1–4, 6, 8–11, 13, 14, and 17–21 were resistant to PFP, but showed different genotypes (PFGE patterns and *rpoB* mutations), indicating that individual strains of RFP-resistant MRSA existed in tuberculosis patients. Collectively, these results suggest that there were two types of transmission mode of MRSA isolates: some were transmitted within tuberculosis wards and the others were brought from outside the wards.

In conclusion, MRSAs obtained from tuberculosis wards in two hospitals in Japan had resistance to RFP and mutation(s) in the particular regions of *rpoB*. It is difficult to conclude that RFP-resistant MRSA isolates were emerging in the wards during RFP therapy. Nevertheless, the present results strongly suggest an emergence of such MRSAs in tuberculosis wards in Japan. It is necessary to monitor PFP resistance in both tuberculosis and other wards.

The DNA sequences of part of the *rpoB* of MRSA reported here were registered in the DDBJ, EMBL, and GenBank nucleotide sequence databases under the following accession numbers: AB195713, AB195714, and AB195715.

Acknowledgments This work was supported by a grant for Research on Emerging and Re-emerging Infectious Diseases from the Ministry of Health, Labour and Welfare in 2005 (H15-SHINKO-11).

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病院感染対策の基本

組織としての対応を理解する

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臨床医
Vol. 31　No. 8　別刷
2005年8月10日発行

中外医学社

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組織としての対応を理解する

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感染症は微生物の身体への侵入が発症原因であるが，宿主の防御機構（解剖学的構造および免疫能・感受性）の他に宿主の生活する環境（施設の構造および運営システム）が重要な因子となっている．そのため環境感染の観点から，病院感染を管理する必要がある．すなわち，施設の空調などの構造・設備の改善や運営方針の決定など，組織として病院感染に対応しなければならない．また，病院感染の防止は，感染発症や感染伝播に対する個人個人の知識と医療技術が基礎とはなるが，一部の職員の油断が二次感染拡大に直接つながることからも，組織としての対応が重要である．種々の規程や管理を決める感染対策委員会 Infection Control Committee（ICC）と，実働部隊である感染対策チーム Infection Control Team（ICT）が大きな役割を果たす．

ICCとICT，リンクナースの存在意義と役割

病院感染は，「医療事故の1つ」であるとの認識により，患者および職員の安全管理の観点から病院長の諮問機関である各種委員会の1つではなく，病院長直属の組織とすることが望ましい．すなわち，ICCの委員長は病院長もしくは看護部長など管理職が担当し，その委員会での議決がそのまま直接組織としての決定事項となり，即座に実行へと移される体制である．そのために，委員会のメンバーには，感染症や微生物学の専門家以外に，予算執行の責任者である会計課長や種々の条例解釈や規程の担当である庶務課長などの事務職員，外来，手術室，検査室，薬剤部などの責任者が入っていることが好ましい．したがって，ICCの委員は個人名による指名ではなく，役職で決めることが重要である．

現場での指導や相談対応はICTが行うことになる．現場でのマニュアル，手順書の活用，問題が発生した場合の相談と対処方法など，即座に対応しなければならない場合もあるため，少なくとも数人の専任は必要であろう．また，マニュアルの定期的見直しや改定，抗菌薬の使用指針，分離菌の種類と抗菌薬感受性の推移の情報発信，ターゲットサーベイランス実施と評価，職員・出入り業者への教育研修など，ICTの役割は多種にわたり，また重要である．ICTの提案はICCで承認されなければならない．

病院感染は，外来の待合室等でも二次感染という形で発生することもあるが，通常は入院後48時間以降に発症した感染で，感染症の潜伏期に入院したものを除くということになっている．したがって，病院感染の舞台は病棟ということになるが，一番患者に接し観察しているのは医師でなく看護師である．そのために最前線の感染管理はリンクナースがキーパーソンとなる．リンクナースとICTの連携とそれらの役割を，職員が充分に理解してはじめて実効性を発揮する．

運営方針

職員の健康管理は，感染の伝播の観点とともに感染源の観点からも，病院感染対策の第一歩である．職員採用時の健康診断では既往歴や予防接種歴の確認が重要で，特に結核，麻疹，水痘など空気感染する疾患，B型肝炎など事故により感染する疾患に関しては本人の申請だけでなく胸部X線写真や血清抗体価などで客観的に確認し，結核予防法や労働基準法などの条例に規程のない対応

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0388-2969/05/¥500/論文/JCLS

の決定は，組織としてなされる必要がある．特に臓器移植を行う施設や制がん剤やステロイド剤などを多用するがん患者や自己免疫疾患患者を多く取り扱う施設について，欧米では臓器移植学会など学術団体やCDCなどが学術論文を根拠としてだしている勧告やマニュアルで規定している．たとえば，水痘の既往のない，または予防接種をしていない，あるいは水痘の予防接種をしていても接種後6週間経過していない職員の移植病棟への配属禁止は，移植患者が水痘に罹患した場合の死亡率および死亡しなくても軽快するまでの患者の苦痛・負担と医療経済学などの論文を根拠としている[1]．日本では老健施設などでの患者および職員に対するインフルエンザ予防接種は，日本では条例にはないが，厚生労働省および地方自治体から接種奨励の通達がでている．

手術室の下足履き替え問題，内視鏡検査の消毒方法，ディスポ製品の採用なども施設として，どの根拠を用いるのか，どのように対処するのかは組織の方針を決める必要がある．

面会者の制限，盲導犬の導入，ペット，切花・植木などの植物，食べ物などの許可も施設および組織として方針を決める必要がある．CDCはこれらの問題に関して，たとえば盲導犬など動物は禁止するのでなく，そのようにすれば許可できるという条件をあげている[2]．

設備

空気感染によって感染伝播する疾患の対応は，その施設の構造および運営方針が大きな要素になる．結核，麻疹，水痘，アスペルギルス症など空気感染する疾患管理は，施設の構造と空調システムによるところが大きい．特に多剤耐性結核には陰圧病室管理が好ましい．また，小児病棟やがん病棟には陰圧・陽圧を調整できる病室設置が好ましいが，経費がかかるため，施設としての方針により決定される．欧米では，建築学会などと共同研究を行い，医療施設における構造や扉・窓の位置の基準を決めている．

洗浄水，透析室，空調の冷却塔の管理も施設としてモニターし管理する必要がある．

ゾーニングと人や物の動線に対する理解と協力

清潔・不潔（汚染）区域の設定と，それをもとにした手順の決定は，感染伝播の防止に大きな役割を果たす．ことに飛沫感染，接触感染の感染伝播経路の遮断の観点から，1つの病棟内での患者のベッド配置，病室の決定，診療・看護者の行動順番，清掃順番は，その病棟に勤務する全員が充分に理解し，動線と手順を統一しなければ効果を発揮しない．MRSAやVRE感染症の場合は特に重要である．

廃棄物の分別と種類に対する理解と協力

医療施設の廃棄物は，一般廃棄物（可燃性，不燃性）の他に，医療廃棄物，感染性廃棄物，鋭利廃棄物などに分類され，それを職員全員が充分に理解しなければならない．廃棄物は一次貯蔵場所の管理（欧米では虫や動物が入り込めない構造と管理を規定している国もある），委託業者への周知徹底も問題になることがある．

●おわりに

病院感染は，安全な医療の提供の観点から，科学的な根拠に基づく防止対策が重要であるが，絶対という方法はないため，施設としてどのように対処するか，また医療経済学的な観点からも妥当な方法を施設・組織として理解し，実施していく必要がある．

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厚生労働科学研究費補助金　医療技術評価総合研究事業

院内感染地域支援ネットワーク及び相談体制の改善・普及や、
データベースおよびバックアップ体制の構築に関する研究

平成17年度　総括研究報告書

発行日　平成18年4月10日
発行者　倉辻忠俊
〒157-8535　東京都世田谷区大蔵2丁目10－1
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製作　株式会社メヂカルフレンド社