Clinical trial of roxithromycin against respiratory tract infection and colonization of methicillin-resistant *Staphylococcus aureus*

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The antibacterial and clinical efficacies of roxithromycin (RXM) were evaluated in 12 patients with infection and colonization in the respiratory tract caused by erythomycin (EM)-sensitive MRSA: 5 with pneumonia, 1 with bronchitis, 1 with lung abscess, and 5 with MRSA colonization. All patients received a dose of 150 mg twice a day (total 300 mg/day) orally. Clinical efficacy was 71.4% (5/7) and bacterial efficacy was 100% (12/12) for EM-sensitive MRSA. However, other bacteria such as *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and even EM-resistant MRSA formed superinfection in 9 patients, although neither clinical symptoms nor inflammatory reactions were observed. After the completion of therapy, colonization by EM-resistant MRSA strains was seen in three patients. Thus, RXM showed good clinical and antibacterial efficacies against EM-sensitive MRSA infection and colonization of the respiratory tract, but it did not always prevent superinfection by other bacteria, including EM-resistant MRSA.

Key words: roxithromycin, erythromycin-sensitive MRSA

INTRODUCTION

Roxithromycin (RXM) is a new 14-membered ring macrolide developed by Roussel-Uclaf (France). This agent has almost the same antimicrobial spectrum as erythromycin (EM)[1]. Although the in vitro antibacterial activity was slightly less than that of EM, gram-positive bacteria[1], anaerobes[2], *Mycoplasma*[3], *Legionalla*[4], and *Chlamydia*[1] have all shown high sensitivity to this agent. After oral administration in humans, the serum

concentration of RXM is higher than those of other macrolides orally administered[5]. In addition, the concentration in sputum is greater than that of EM[3]. Thus, RXM is a new macrolide that offers high levels of drug concentration in the target organ, and the potential for good compliance, since its longer half life[5] allows oral administration twice a day. On the other hand, methicillin-resistant *Staphylococcus aureus* (MRSA) presents a worldwide problem as a major pathogen causing hospital infections. In our hospital, EM-sensitive MRSA strains have been isolated more frequently than EM-resistant strains[6]. Interestingly, most of the EM-sensitive MRSA isolates produce coagulase type VII. In our hospital, one of the most important issues is coping with this type of MRSA strain. Especially in the ward of internal medicine, MRSA is recovered mainly from the sputum of patients with respiratory MRSA infection or colonization. Therefore, in the present study we evaluated the antibacterial and clinical efficacies of RXM against EM-sensitive MRSA infections and colonizations in the respiratory tract.

MATERIALS AND METHODS

Bacteria

Clinical isolates of *S. aureus* were identified in the laboratory of our hospital. Those strains of *S. aureus* that showed resistance to oxacillin and EM by the Kirby-Bauer method were considered EM-resistant MRSA.

Methods

The minimum inhibitory concentrations (MICs) of these strains were determined by the microdilution method in our laboratory of the Second Department of Internal Medicine using frozen microplates supplied by Eiken Kagaku Co. Ltd. (Tokyo, Japan)[5]. Cation-supplemented Mueller-Hinton broth was used for all dilutions, and 2% NaCl was added for methicillin. The inoculum used was $1-2\times10^5$cfu/mL of a log-phase culture. Microplate wells containing serial two-fold dilutions of the antibiotics (in concentrations ranging from 128 to 0.06 μg/ml for 8 agents) were incubated overnight at 35°C for testing with MRSA. The MIC was defined as the lowest concentration of antibiotic which inhibited visible bacterial growth. Coagulase type and the production of TSST-1 were determined using commercial kits (Denka Seiken & Co. Ltd., Tokyo, Japan).

The concentration of RXM in serum and sputum was examined by bioassay cup method using *Micrococcus. luteus* ATCC 9341 as the reference strain.

Patients

Twelve patients with EM-sensitive MRSA infection or colonization were hospitalized in Fukuoka University Hospital and affiliated hospitals from November 1991 to December 1992. All of the patients discharged sputum containing significant amounts ($>10^6$—10^7/ml) of EM-sensitive MRSA. Among them, the patients who had clinical symptoms (cough, sputum, fever, fatigue) and laboratory evidence of infection (positive C-reactive protein, leukocytosis, infiltration on chest X-ray, etc.) caused by the organism were defined as having MRSA infection. Patients without clinical symptoms or inflammatory reactions were defined as having MRSA colonization. They consisted of 8 men a and 4 women with median age of 67.4 years (range 26—85 years). Included were 5 cases of pneumonia, one of bronchitis, one lung abscess, and 5 cases of MRSA colonization in the respiratory tract (see Table 1).

Study Design

All patients received a dose of 150 mg of RXM twice a day (total 300 mg/day) for at least three days. Appropriate follow-up cultures and X-ray examinations were performed during the course of therapy. Complete blood counts, C-reactive protein determinations, and other biochemical examinations were performed before, during and after therapy. Then, the clinical and bacteriological efficacies were evaluated.

Evaluation of responses

Clinical response was classified in one of the following 4 categories: "excellent" referred to successful improvement in clinical condition and laboratory data, and defervescence within 3 days; "good" referred to similar results obtained within four to seven days; "fair" referred to recovery

Table 1. Background of patients with erythromycin-sensitive MRSA infection

#	Age	Sex	Type of infection	Underlying disease	Concomitant bacteria	Pre-administered antibiotics	Days from admission to detection
1	81	M	Pneumonia	Pancreas cancer	–	–	14
2	71	M	Pneumonia	End-stage renal disease	*K. oxytoca*	–	14
3	85	M	Pneumonia	Lung cancer	*K. pneumoniae*	piperacillin	8
4	26	F	Pneumonia	Subarachnoid hemorrhage	–	cefmetazole	10
5	68	M	Pneumonia	Acute myocardial infarction	–	ceftazidime	10
6	57	M	Lung abscess	Bulbo-spinal muscular atrophy	*P. aeruginosa*	–	1
7	60	F	Colonization	Pemphigus	*P. aeruginosa*	imipenem+ cefotiam	8
8	69	M	Colonization	Hepatoma	–	cefazolin	11
9	64	M	Colonization	Thalamus bleeding	–	amikacin	12
10	74	F	Colonization	Cerebral infarction	*E. aerogenes*	cefazolin	8
11	71	M	Colonization	Lung cancer	–	–	13
12	83	F	Bronchitis	Hypertension	*K. pneumoniae*	arbekacin	23

from fever and improvements in clinical condition and laboratory findings after seven days or a tendency for improvement within seven days; "poor" referred to no resolution of fever after seven days or more, or changes required in antibiotic therapy due to clinical deterioration after four days or more. Bacteriological efficacy was classified in the following six categories: eradication, decrease, persistence, superinfection, emergence of a resistant strain, and reacquisition of MRSA.

RESULTS

Efficacy

The efficacy rating was defined as the percentage of cases that showed "excellent" and "good" responses divided by the total number of cases. As shown in Table 2, 5 patients showed a good response while 2 had a fair response. The overall clinical efficacy of RXM against respiratory infection was 71.4% (5/7). MRSA was eradicated in all cases, so the antibacterial efficacy against MRSA was 100% (12/12). Superinfections with pathogens other than MRSA, such as *Pseudomonas aerugionosa and Enterococcus faecalis*, were seen in 8 patients, and one patient had a superinfection with EM-resistant MRSA during therapy with RXM. After therapy, EM-resistant MRSA was detected in three cases (Table 2).

Side effects

Neither clinical adverse effects nor abnormalities in laboratory data were noted.

Bacteriological features of MRSA strains (see Tables 3, 4)

The EM-sensitive and EM-resistant MRSA isolated from case #12 failed to be subcultured because of incomplete preservation, so these strains were not evaluated bacteriologically. Of the 11 strains of EM-sensitive MRSA evaluated, 7 produced coagulase type VII. One strain produced mixed coagulase types II and III. No strain of EM-sensitive MRSA produced TSST-1. Only one strain produced enterotoxin. Except for the mixed-coagulase type, the strains showed resistance to imipenem, arbekacin, minocyline, and ofloxacin. All strains were susceptible to rifampicin, RXM, clindamycin, vancomycin, and sulfamethoxazole/trimethoprim. Of 3 strains of superinfecting EM-resistant MRSA, one produced coagulase type VII. No strain of EM-resistant MRSA produced both TSST-1 and enterotoxin. All strains were susceptible to vancomycin and

Table 2. Clinical and bacterial efficacies of roxithromycin against MRSA infection in the respiratory tract

#	Infection	Clinical efficacy	Bacterial efficacy against MRSA	Superinfection	Reacquisition during administration	Reacquisition after administration
1	Pneumonia	good	eradicated	CNS, *X. maltophilia*	EMR-MRSA	–
2	Pneumonia	fair	eradicated	*E. faecalis*, CNS	–	–
3	Pneumonia	fair	eradicated	*E. faecalis*, CNS	–	EMR-MRSA
4	Pneumonia	good	eradicated	–	–	–
5	Pneumonia	good	eradicated	*P. aeruginosa*	–	–
6	Lung abscess	good	eradicated	–	–	–
7	Colonization	–	eradicated	*P. aeruginosa*	–	EMR-MRSA
8	Colonization	–	eradicated	*E. faecalis*	–	–
9	Colonization	–	eradicated	–	–	–
10	Colonization	–	eradicated	*E. faecalis*	–	–
11	Colonization	–	eradicated	*E. faecalis*	–	–
12	Bronchitis	good	eradicated	*E. cloacae*	–	EMR-MRSA

EMR: erythromycin-resistant

sulfamethoxazole/trimethoprim.

Concentration of RXM in serum and sputum

After roxithromycin administration, serum and sputum were taken from two patients, cases #5 and #10. Case #5 was a 68-year-old male patient with acute myocardial infarction who suffered from MRSA pneumonia 10 days after admission. Laboratory data before therapy revealed decreased renal function and elevated liver enzymes, suggesting the patient had impairment of the liver and kidney before therapy. In case #5, the serum and sputum were taken one hour after oral administration of 150 mg of RXM on the seventh day after the beginning of RXM therapy. As shown in Table 5, the concentration in serum was 30.8 μg/ml and that in sputum was 2.91 μg/ml. In case #10, the respiratory tract or a 74-year-old female patient with cerebral infarction was colonized with MRSA. Laboratory data before therapy showed elevated liver enzyme, suggesting the patient had obstructive liver dysfunction. In addition, although the creatinine clearance was 110 ml/min, she suffered from urinary tract infection by *Serratia marccescens* at the time, suggesting renal impairment. In this case, the concentration in serum was examined twice. The first examination was carried out one day after the beginning of RXM therapy, the second examination five days after. As shown in Table 6, in the first examination the concentration one hour after oral administration of 150 mg of RXM was 26.5 μg/ml, and that after two hours was 24.7 μg/ml. In the second, the concentration one hour after oral administration of 150 mg of RXM was 25.3 μg/ml, that after two hours 41.6 μg/ml, and that after three hours 42.2 μg/ml.

Case Report (Case #6 in Table 1)

A 57-year-old male patient with pneumonia was transported to our hospital from an other hospital because his pneumonia had not been cured. He had a several-year history of gait disturbance, dysarthria, tetraplegia and muscular atrophy. He had been diagnosed with bulbospinal muscular atrophy and was undergoing ambulatory treatment.

On January 19, 1992, he abruptly became comatose. When he was admitted to a local hospital, he suffered cardiac arrest. Apnea was caused by atrophy of the respiratory muscles. The patient gradually improved with artificial breathing following a tracheotomy. However,

Table 3. Bacteriological and biological characteristics of erythromycin-sensitive MRSA strains

Cases	MPIPC	IPM/CS	TOB	GM	ABK	RFP	EM	RXM	CLDM	VCM	MINO	OFLX	ST	Coag.	TSS-T1	Enterotoxin
#1	>16	>16	>16	>16	16	<0.13	1	0.5	0.25	1	>16	>16	1	VII	(−)	(−)
2	>16	>16	>16	>16	16	<0.13	1	0.5	0.25	1	>16	>16	1	VII	(−)	A
3	>16	>16	>16	>16	16	>16	2	0.5	0.5	1	16	>16	1	VII	(−)	(−)
4	>16	>16	>16	>16	8	<0.13	1	0.5	<0.13	1	16	>16	1	VII	(−)	(−)
5	>16	8	>16	>16	>16	<0.13	1	0.5	0.25	2	>16	>16	1	UT	(−)	(−)
6	>16	>16	>16	>16	>16	<0.13	1	0.5	0.25	2	>16	>16	2	UT	(−)	(−)
7	>16	>16	>16	>16	16	<0.13	1	0.5	0.25	1	16	>16	1	UT	(−)	(−)
8	>16	>16	>16	>16	8	<0.13	1	0.5	0.25	1	16	>16	1	VII	(−)	(−)
9	>16	0.25	>16	>16	2	<0.13	1	1	0.25	1	<0.13	0.5	0.5	II,III	(−)	(−)
10	>16	>16	>16	>16	8	<0.13	2	0.5	0.25	1	>16	>16	1	VII	(−)	(−)
11	>16	>16	>16	>16	16	>16	1	0.5	0.25	1	16	>16	1	VII	(−)	(−)

MPIPC: methicillin, IPM/CS: imipenem/cilastatin, TOB: tobramycin, GM: gentamycin, ABK: arbekacin, RFP: rifampicin, EM: erythromycin, RXM: roxithromycin, CLDM: clindamycin, VCM: vancomycin, MINO: minocycline, OFLX: ofloxacin, ST: sulfamethoxazole/trimethoprim, Coag: coagulase, TSST-1: toxic shock syndrome toxin-1

ND: not done, UT: untypable

Table 4. Bacteriological and biological characteristics of erythromycin-resistant MRSA strains

Cases	MPIPC	IPM	TOB	GM	ABK	RFP	EM	RXM	CLDM	VCM	MINO	OFLX	ST	Coag.	TSS-T1	Enterotoxin
#1	>16	>16	>16	>16	16	>16	>16	>16	>16	2	>16	>16	1	Ⅶ	(−)	A
3	>16	>16	>16	>16	8	>16	>16	>16	>16	1	>16	>16	1	UT	(−)	(−)
7	>16	>16	>16	>16	8	<0.13	>16	>16	>16	1	16	>16	1	UT	(−)	A

MPIPC: methicillin, IPM/CS: imipenem/cilastatin, TOB: tobramycin, GM: gentamycin, ABK: arbekacin, RFP: rifampicin, EM: erythromycin, RXM: roxithromycin, CLDM: clindamycin, VCM: vancomycin, MINO: minocycline, OFLX: ofloxacin, ST: sulfamethoxazole/trimethoprim, Coag: coagulase, TSST-1: toxic shock syndrome toxin-1

ND: not done, UT: untypable

Table 5. Serum and sputum concentrations of roxithromycin one hour after oral administration of 150 mg for patient #5

	Serum	Sputum
Concentration (μg/ml)	30.8	2.91

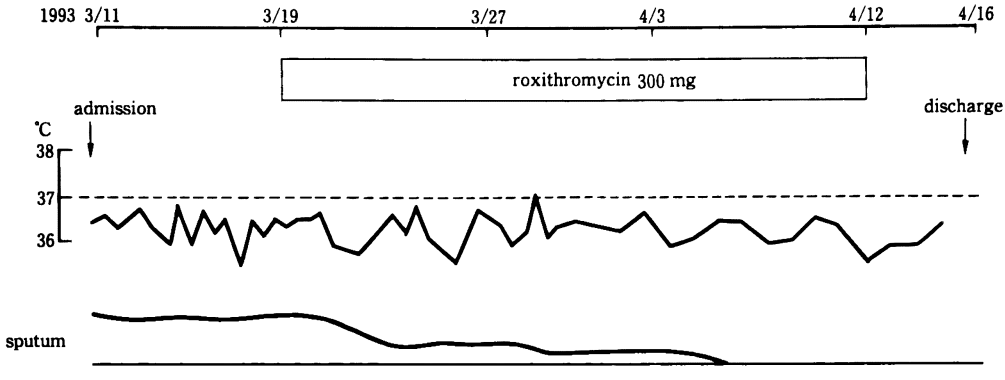
Bioassay cup method
M. luteus ATCC 9341

on February 20, aspiration pneumonia developed. Although antibiotics were used, the pneumonia did not improve. The patient was transported to our hospital on March 11, 1992. His clinical course is shown in Fig. 1. On admission, he was fatigued and debilitated. His body weight was 45 kg, and his height was 156 cm. The breath sounds were diminished over the right lower lung field. Neurological examination showed gait disturbance, dysphagia, dysarthria and static ataxia; thus, systemic dyskinesia was severe. Laboratory findings included WBC 9,100 and CRP 6.8 mg/dl. Blood gas examination showed mild hypoxemia (PO_2 64.1 mmHg). Chest X-ray and computer tomography revealed the cavity and niveau of the right lung, and surrounding infiltration, suggesting that the lung abscess and pneumonia caused by MRSA in the cavity had originated after pneumonis was cured (Figs. 2 a, b). However, dyspnea and fever were mild at that point, despite a cough and discharge of purulent sputum; artificial breathing was not considered necessary. The patient was followed up without antibiotics for several days. The amount of C-reactive protein and volume of sputum increased gradually, and his general condition deteriorated. In addition, 10^6/ml of EM-sensitive MRSA was detected in sputum. On May 19, oral administration of RXM 300 mg/day was begun. By May 27, the inflammatory reaction had become negative, and the niveau and infiltration had disappeared (Figs. 3 a, b). MRSA in the sputum was also eradicated; the patient was discharged on April 15. During hospitalization, no superinfection with any other bacteria, such as EM-resistant MRSA or *P. aeruginosa*, was found.

Table 6. Time course of serum concentration of roxithromycin after oral administration for patient #10

	Serum concentration (μg/ml)		
Time after oral administration	1 h	2 h	3 h
Experiment #1	26.5	24.7	ND
Experiment #2	25.3	41.6	42.2

Bioassay cup method
M. luteus ATCC 9341
ND: not done



WBC	9,100	10,500	7,600	6,900	7,100	5,200
CRP	1.2	5.3	2.0	0.1	<0.1	<0.1
ESR (/1h)	34	72	29	19	13	6
sputum culture	MRSA 1×10^6 *P. aeruginosa* 3×10^5	MRSA+	MRSA++	NF	NF	NF

NF: normal flora

Fig.1. Clinical course of case #6.

DISCUSSION

MRSA strains are becoming highly resistant to various antibiotics. In our country, the main agents used to treat MRSA infection are changing from β-lactams and minocycline to arbekacin and vancomycin. However, in our hospital, EM-sensitive MRSA strains producing coagulase type VII are frequently recovered from various clinical specimens and often cause infection[6]. In this study, we evaluated the clinical and bacteriological efficacies of RXM against infections caused by EM-sensitive MRSA. Our main focus was on repiratory tract infection or colonization by MRSA because of the high incidence in the field of internal medicine.

RXM showed good clinical and antibacterial efficacies against EM-sensitive MRSA infection and colonization in the respiratory tract. Although in general RXM is thought to be less effective against bacteria than EM or clarithromycin *in vitro*[7~9], RXM showed better antibacterial activities against MRSA clinical isolates in present study (Table 3). Besides, there have been reports that RXM was particularly effective for respiratory tract infection[10,11] This may be because RXM not only has high concentrations in serum and sputum[3,5] but also is makedly taken up by polymorphonuclear leukocytes, aiding phagocytosis[12,13] In our case, the concentrations of RXM in serum and sputum were much higher

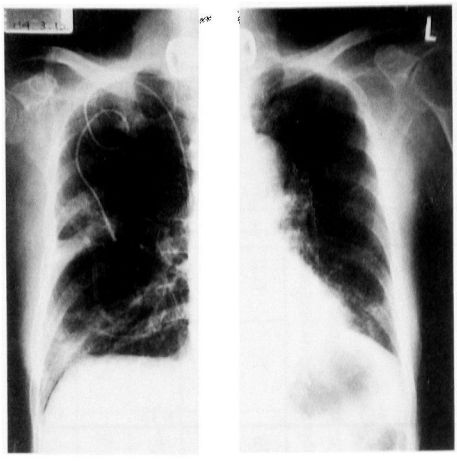


Fig. 2a. Chest X-ray finding before roxithromycin therapy.

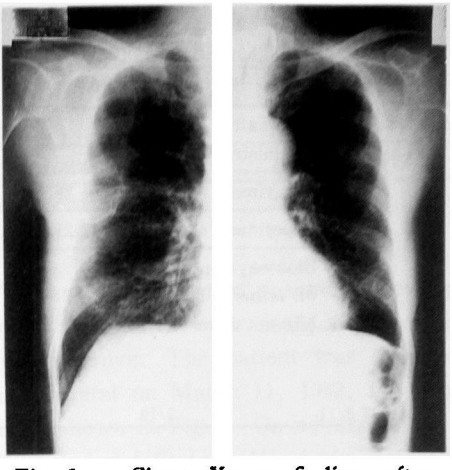


Fig. 3a. Chest X-ray finding after roxithromycin therapy.

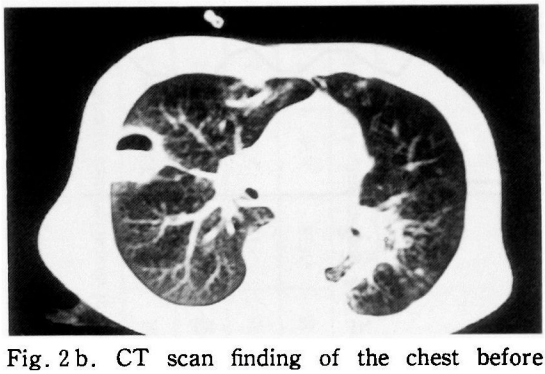


Fig. 2b. CT scan finding of the chest before roxithromycin therapy.

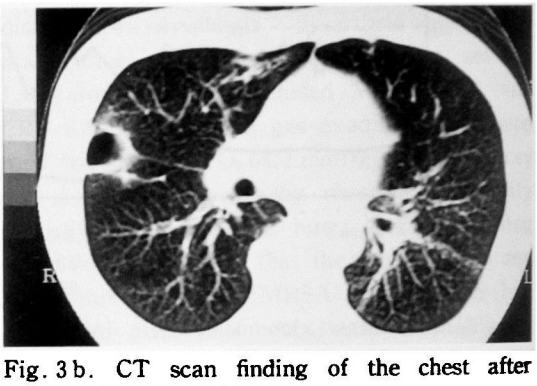


Fig. 3b. CT scan finding of the chest after roxithromycin therapy.

than those in other reports[3,5], probably due to dysfunction of the liver and kidney in our patients.

Thus, RXM may be useful as one of the first-choice oral agents to eliminate MRSA, in addition to rifampicin and sulfamethoxazole/trimethoprim.

However, during and after therapy, the emergence of EM-resistant MRSA strains or the reacquisition of MRSA occurred in spite of the high rate of eradication of EM-sensitive MRSA. This seems to be a big problem in therapy with macrolides such as EM, and a major issue is the prevention of resistance and reacquisition[14]. If MRSA is negative, even for a temporary period, isolation precautions can be lifted and the hospital staff can work more easily. Nevertheless, the emergence of resistant strains is too dengerous for a hospital to overlook. Although sulfamethoxazole/trimethoprim, new quinolones such as ciprofloxacin, and rifampicin are recommenede to decolonize MRSA according to the U. K. guidelines, their usefulness should be carefully reviewed.

The systemic administraction of antibiotics for the eradication of colonized organisms may be appropriate only in the following situations: 1) the preventive use of antibiotics is recommended when a patient has a poor general con dition and high risk of infection; 2) the preperative use of antibiotics is permitted in patients waiting for surgery; 3) when patients are to be

transferred to another ward of hospital. The use of antibiotics for patients in the third category is becoming essential for the general management of hospitals, since some hospitals or nursing homes for senior citizens now refuse to take MRSA-positive patients[15].

In conclusion, RXM appears to be useful for EM-sensitive MRSA infection and colonization. We will continue our clinical study of the usefulness of RXM by evaluating additional cases.

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MRSA 呼吸器感染症に対する roxithromycin の臨床的検討

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Erythromycin 感受性 MRSA（メチシリン耐性黄色ブドウ球菌）による呼吸器感染 12 症例に対する roxithromycin の臨床的・細菌学的効果が検討された。疾患の内訳は，肺炎 5 例，気管支炎 1 例，肺膿瘍 1 例，colonization 6 例であった。投与量は 1 日 300 mg（1 回 150 mg 1 日 2 回）であった。臨床効果は 71.4%（5/7），細菌学的効果は 100%（12/12）であった。*Pseudomonas aeruginosa* や *Enterococcus faecalis* や erythromycin 耐性 MRSA による菌交代が 9 例でみられたが，それらによる臨床症状や炎症反応は認めなかった。治療終了後，erythromycin 耐性 MRSA の colonization が 3 例でみられた。roxithromycin は erythromycin 感受性 MRSA による呼吸器感染に対して良好な臨床的・細菌学的効果を示したが，erythromycin 耐性 MRSA などによる菌交代を必ずしも阻止できなかった。

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