

EFFECT OF VANCOMYCIN THERAPY FOR OSTEOMYELITIS ON COLONIZATION BY METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*: LACK OF EMERGENCE OF GLYCOPEPTIDE RESISTANCE

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ABSTRACT

BACKGROUND: In treating orthopedic infections, the long-term impact of vancomycin therapy on colonization by methicillin-resistant *Staphylococcus aureus* (MRSA) and the emergence of vancomycin-intermediate *S. aureus* is unknown.

DESIGN: Prospective surveillance of the effect of long-term vancomycin therapy on colonization by MRSA and the emergence of vancomycin-intermediate *S. aureus*.

METHODS: Thirty-four patients with MRSA osteomyelitis that was microbiologically documented were longitudinally observed for the emergence of vancomycin-intermediate *S. aureus* at 3 body sites (wound, anterior nares, and groin) during the initial period of vancomycin therapy and at the 2-month follow-up. Twenty patients received the standard dose (20

mg/kg/d) for 34 ± 6 days and 14 patients received a high dose (40 mg/kg/d) of vancomycin for 37 ± 9 days.

RESULTS: During vancomycin treatment, global MRSA carriage (all body sites) fell from 100% to 25% in the group of patients receiving the standard dose of vancomycin, and from 100% to 40% in the group receiving the high dose. During the 2-month follow-up period after vancomycin therapy, global MRSA carriage increased from 25% to 55% in the group receiving the standard dose and decreased from 43% to 36% in the group receiving the high dose.

CONCLUSION: Therapy with a high dose of vancomycin contributes to the sustained eradication of MRSA carriage without promoting the emergence of glycopeptide resistance (*Infect Control Hosp Epidemiol* 2003;24:650-654).

The prevention and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections represent an increasingly difficult challenge due to the emergence of multidrug-resistant strains. An additional concern is the recent discovery of MRSA isolates that exhibit decreased susceptibility to glycopeptides, including vancomycin,^{1,4} which raises the possibility of organisms exhibiting global resistance to all currently available antibiotics.⁵ These isolates may demonstrate either intermediate susceptibility or resistance to vancomycin.⁶ Detection of vancomycin resistance is particularly difficult in most clinical isolates determined as either heterogeneous vancomycin-intermediate *S. aureus* (VISA)² or heterogeneous vancomycin-resistant *S. aureus* (VRSA).^{1,3}

Several clinical and epidemiologic reports indicate that nasal and extranasal carriage of MRSA may predispose targeted groups of patients to invasive infections and contribute to the nosocomial dissemination of these dangerous pathogens.⁷ Because patients with osteomyelitis caused by MRSA usually require several weeks of parenteral administration of vancomycin, they should theoretically be at risk for

the emergence of glycopeptide-resistant subpopulations.⁸⁻¹⁰ Paradoxically, there has been no study evaluating the impact of long-term vancomycin therapy on the risk of emergence of VISA or VRSA in either infected or colonized body sites of patients treated for MRSA osteomyelitis. Although the use of mupirocin for topical MRSA decontamination has shown some efficacy for prophylaxis of orthopedic infections,¹¹ its impact on multiple carriage sites of patients treated for MRSA osteomyelitis has not been reported.

The aim of this study was to evaluate the influence of prolonged vancomycin therapy for MRSA osteomyelitis on the persistence of MRSA carriage and the potential emergence of VISA or VRSA in sequentially cultured body sites during the first 4-week period of antimicrobial therapy and at the 2-month follow-up.

METHODS

Population and Study Design

Between October 1998 and September 2001, we enrolled 39 adult patients consecutively admitted to a specifically designed orthopedic septic unit at the University

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Hospital of Geneva. The criteria for eligibility included microbiologically proven osteomyelitis with a pure culture of MRSA from a bone biopsy and intravenous vancomycin therapy for a minimum of 4 weeks. Five patients were excluded due to incomplete vancomycin therapy, allergy to vancomycin, or incomplete microbiological data.

The first subgroup of enrolled patients (from October 1998 to November 2000) were treated intravenously with a standard dose (20 mg/kg/d) of vancomycin (Eli Lilly, Geneva, Switzerland), whereas the second subgroup of enrolled patients (from December 2000 to December 2001) received a high dose (40 mg/kg/d) of intravenous vancomycin. The treatment was then adjusted to obtain a trough vancomycin concentration in the serum of 20 to 25 mg/L in the group receiving the high dose, or 10 to 15 mg/L in the group receiving the standard dose, and to have a peak less than 50 mg/L. Thereafter, samples were taken only weekly or if an increase in serum creatinine was noted.

During the first week of vancomycin therapy, all patients received applications of 4% chlorhexidine soap (Hibiscrub, Zeneca Pharma, Cergy, France) for daily body cleansing and 2% intranasal calcium mupirocin (Bactroban Nasal, SmithKline Beecham, Thörishaus, Switzerland) for 5 days. In addition, each patient remaining a MRSA carrier at any body site (wound, nose, or groin) during hospitalization was placed in contact isolation according to the established guidelines of our institution¹² until eradication was assessed by 2 consecutive negative surveillance cultures.

Microbiologic Evaluation

All patients were screened for MRSA immediately before starting vancomycin therapy. Swabs (Copanswabs, Copan Italia S.p.A., Brescia, Italy) were taken from the anterior nares, the groin, and any wound, if present.

Qualitative cultures were performed after enrichment in *Staphylococcus* Broth NaCl (Difco Laboratories, Sparks, MD) for 24 hours and subculturing on sheep blood agar. Identification of *S. aureus* was based on the morphology of colonies, the presence of clumping factor or protein A (Pastorex, Bio-Rad, Steinach, Switzerland), and the production of heat-stable nuclease (Bacto DNase test agar [Difco Laboratories] and toluidine blue O [Merck, Darmstadt, Germany]). Each MRSA isolate was routinely monitored for its overall antimicrobial susceptibility by disk diffusion (Sirscan, v2a, Montpellier, France) according to National Committee for Clinical Laboratory Standards guidelines,¹³ and finally stored at -70°C. Follow-up screening cultures for MRSA were performed weekly in all 3 sites during the initial 4-week period of therapy and at least once during the 2-month follow-up period. The eradication of MRSA was defined by at least 3 negative culture sets from body sites.

Susceptibility Testing

From each patient in whom MRSA was not eradicated during vancomycin therapy, 1 pre-therapy, 1 on-therapy (at 3 to 4 weeks), and 1 post-therapy isolate were

screened for the presence of subpopulations growing on brain–heart infusion agar supplemented with 2 µg/mL of vancomycin. One hundred microliters of a bacterial suspension adjusted to the McFarland Standard Indicator 2.0 (ATB 1550, API bioMérieux, Marcy l'Étoile, France) (approximately 5×10^8 colony-forming units [CFU]/mL) was spread onto vancomycin brain–heart infusion agar. *S. aureus* strains American Type Culture Collection 29213 and mu50 were used as the negative and positive quality control strains, respectively.² Any colony recovered from the agar at 48 hours was further tested for vancomycin minimum inhibitory concentration (MIC) by the Etest.

All strains of MRSA were also tested for the potential presence of VISA or heterogeneous VISA by the Etest (AB BIODISK, Solna, Sweden) using the McFarland 2.0 inoculum.¹⁴ VISA isolates were defined as having a vancomycin MIC ranging between 4 and 16 µg/mL, according to the breakpoints of the French Microbiology Society.¹⁵ The VISA control was the mu50 strain.

Strain Typing

Epidemiologic typing of sequential MRSA isolates was performed by pulsed-field gel electrophoresis (PFGE) (Pulsaphor system, Pharmacia LKB Biotechnology, Uppsala, Sweden) of chromosomal DNA digested with restriction endonuclease *Sma*I (Bio-Rad, Hercules, CA), according to established protocols.¹⁶ The clonality of MRSA-persistent isolates was evaluated on specimens collected at baseline, on-therapy (at 3 to 4 weeks), and during follow-up. Clonal diversity was defined by Tenover et al.¹⁷

Therapeutic Regimens and Assessment of Serum Levels of Vancomycin

Peak or trough serum levels of vancomycin were measured with the TDX Analyzer (Abbott Laboratories, Vienna, Austria) at 30 minutes following the 1-hour infusion or immediately before the next infusion, respectively.

Data Analysis

In this study, the demographic and clinical information that was recorded included age and gender, underlying diseases, type and stage of osteomyelitis, type of vancomycin regimen, serum levels of vancomycin, and other associated antibiotics. Continuous variables were presented as the mean and standard deviation or median if their distribution was skewed. Yates-corrected chi-square or Fisher's exact tests were used to assess changes between the observed proportions of unrelated samples. A *P* value of less than .05 was considered statistically significant. Statistical analysis was performed using Analyse-it software (version 1.62; Analyse-it Software LTD, Leeds, England) or Excel 2002 (Microsoft Corp., Redmond, WA).

RESULTS

Patients and Vancomycin Treatment

Thirty-four patients (20 men and 14 women) with a mean age of 66.2 ± 16.1 years (range, 37 to 77 years) treat-

TABLE
CHARACTERISTICS OF ORTHOPEDIC PATIENTS TREATED WITH VANCOMYCIN

Characteristic	Vancomycin Regimen	
	Standard Dose (20 mg/kg/d)	High Dose (40 mg/kg/d)
No. of patients	20	14
Mean age, y (\pm SD)	67 (\pm 18)	66 (\pm 12)
Male (%)	10 (50)	8 (57)
No. with underlying diseases (%)		
Chronic renal failure	4 (20)	4 (29)
Diabetic disease	6 (30)	7 (50)
No. with osteomyelitis (%)		
Cierny-Mader, stage 3 or 4*	7 (35)	6 (43)
Localization of osteomyelitis		
Foot-phalangeal	9 (45)	7 (50)
Femur-hip	4 (20)	3 (21)
Tibia-knee	4 (20)	3 (21)
Other [†]	3 (15)	1 (8)
Implant-associated infection (%)	4 (20)	4 (29)
No. who underwent surgical procedures (%)	17 (84)	11 (79)
Vancomycin regimen		
Mean trough serum level, mg/L (\pm SD)	11.4 (\pm 7.1)	21.8 (\pm 5.9)
Mean duration of treatment, d (\pm SD)	34 (\pm 6)	37 (\pm 9)
No. of patients with other antibiotics (%) [‡]	5 (25)	4 (29)

SD = standard deviation.

*Cierny-Mader classification: stage 1 = intramedullary osteomyelitis (infected intramedullary rod); stage 2 = superficial osteomyelitis; stage 3 = localized osteomyelitis (full-thickness, cortical sequestration); and stage 4 = diffuse osteomyelitis (fracture with non-union, infected prosthesis).

[†]Included ankle, wrist, or phalangeal.

[‡]Rifampin and ciprofloxacin were used in combination with vancomycin in 8 patients and 1 patient, respectively.

ed for MRSA osteomyelitis with vancomycin for a minimum of 4 weeks fulfilled all criteria to be enrolled in this study. There was no significant difference in the major baseline demographic and clinical characteristics of patients treated with the standard ($n = 20$) or high ($n = 14$) dose of vancomycin, including age, gender, duration of therapy, implant-associated infection, and major underlying diseases (Table). The localization and severity of osteomyelitis was similar in patients treated with the standard dose or the high dose of vancomycin. Nine patients (4 in the group receiving the standard dose and 5 in the group receiving the high dose) were diagnosed as having an acute osteomyelitis, whereas 25 patients suffered from a chronic infection (duration, longer than 4 weeks). Twenty-six patients (14 receiving the standard dose and 12 receiving the high dose) initially presented with an open wound (chronic fistula or breakdown of a wound following surgery).

Twenty patients received a standard dose (20

mg/kg/d) and 14 patients a high dose (40 mg/kg/d) of vancomycin for 34 ± 6 and 37 ± 9 days, respectively. Serum levels of vancomycin were used for adjusting the standard- or high-dose regimens of intravenous vancomycin to target trough serum levels of 10 to 15 mg/L and 20 to 25 mg/L, respectively. The mean (\pm standard deviation) serum trough levels in patients receiving the standard and high doses of vancomycin were 11.4 ± 7.1 mg/L and 21.8 ± 5.9 mg/L, respectively. Eight patients received another systemic antibiotic combined with vancomycin; 3 receiving the standard dose and 4 receiving the high dose, respectively, received rifampin and 1 patient receiving a high dose received ciprofloxacin.

Rate of MRSA Colonization During and After Glycopeptide Therapy

At baseline, 100% of the patients had MRSA osteomyelitis that was microbiologically documented (by bone biopsy). In the group receiving the standard dose of vancomycin, 9 (45%) of the 20 patients were colonized in the anterior nares and 6 (30%) in the groin. In comparison, at the onset of therapy with a high dose of vancomycin, 10 (71%) of the 14 patients were colonized in the nares and 9 (64%) in the groin.

During vancomycin treatment, MRSA nasal carriage fell from 45% to 5% in the group receiving the standard dose of vancomycin, and from 71% to 14% in the group receiving the high dose (no significant difference). MRSA groin carriage fell from 30% to 10% in the standard-dose group, and from 64% to 21% in the high-dose group (no significant difference). The global MRSA carriage (all body sites) fell from 100% to 25% in the standard-dose group, and from 100% to 40% in the high-dose group (no significant difference). During the 2-month period following therapy with the standard dose of vancomycin, 6 of 15 previously decolonized patients were recolonized with MRSA, shifting the overall colonization rate for this period from 25% to 55%.

During the 2-month follow-up period after therapy with a high dose of vancomycin, overall MRSA carriage at any site did not increase, but marginally decreased from 43% to 36% (Figure). Patients treated with a high dose of vancomycin had a significantly higher probability ($P = .048$) of remaining free of MRSA during the follow-up period than did patients treated with the standard dose.

An analysis of risk factors showed that among the residual MRSA carriers treated with vancomycin, most still had open wounds. Except for the vancomycin dose, no factors (eg, underlying diseases, implant-associated infection, or other associated antibiotics) should be associated with a risk of residual MRSA carriage.

Genetic Relatedness of MRSA Specimens

In the 16 patients who were persistently or recurrently colonized with MRSA during follow-up screening, PFGE was used to evaluate the genetic relatedness of pre-treatment and follow-up strains. In all 16 patients, 11 who received the standard dose and 5 who received the high dose, the relatedness of persistently or recurrently colo-

nizing strains of MRSA was confirmed and no patient became recolonized with a new strain.

Analysis of Vancomycin Susceptibility

The potential emergence of VISA or heterogeneous VISA was determined by comparing follow-up isolates with related pretreatment isolates in the 16 persistent or recurrent MRSA carriers. Among the 51 MRSA isolates tested, none yielded any significant subpopulation (more than 10 CFU) that demonstrated decreased vancomycin susceptibility on agar supplemented with 2 µg/mL of vancomycin. The screening of subpopulations on brain-heart infusion agar supplemented with 2 µg/mL of vancomycin was used to avoid extensive population analysis studies on all MRSA isolates. For the few MRSA isolates that yielded colonies growing on agar containing 2 µg/mL of vancomycin, further testing demonstrated that none of these colonies could grow on agar supplemented with higher concentrations (ie, 4 or 6 µg/mL) of vancomycin, nor did any exhibit a significant increase in vancomycin MIC by the Etest.

Evaluation of the 51 MRSA isolates by the Etest yielded identical MICs (median MIC, 1.5 µg/mL; range, 1 to 2 µg/mL) for follow-up MRSA isolates from 11 carriers treated with the standard dose of vancomycin and 5 carriers treated with the high dose. In no patient was there any trend for the emergence of VISA or heterogeneous VISA during the long-term intravenous therapy with either the standard or high dose.

DISCUSSION

This study evaluated the impact of long-term parenteral vancomycin therapy on MRSA carriage or eradication at 3 body sites and the potential emergence of vancomycin resistance in hospitalized orthopedic patients treated for osteomyelitis. The 2 groups of patients treated with vancomycin received a similar 1-week protocol of topical decontamination with mupirocin and chlorhexidine, but differed from each other by receiving either a standard or high dose of parenteral vancomycin. Whereas eradication of MRSA carriage occurred in 75% and 57% of the patients treated for 4 weeks with the standard or high dose of vancomycin, respectively, recolonization observed during the 2-month post-therapy period occurred mainly in the group receiving the standard dose. Decolonization of the nares essentially occurred during the first week of therapy. Overall, these data indicate the efficacy of mupirocin applied intranasally. But this efficacy is temporary because previously decolonized patients in the group receiving the standard dose of vancomycin were recolonized with MRSA during the fourth week and 2-month period of follow-up. However, no recolonization occurred among patients in the group receiving the high dose. All persisting or relapsing MRSA isolates were identical to pre-therapy isolates and remained fully susceptible to vancomycin during the observation period, regardless of the serum levels of vancomycin obtained during therapy or duration of antibiotic exposure.

Whereas many studies have been performed to evaluate the efficacy of topical or systemic antimicrobial

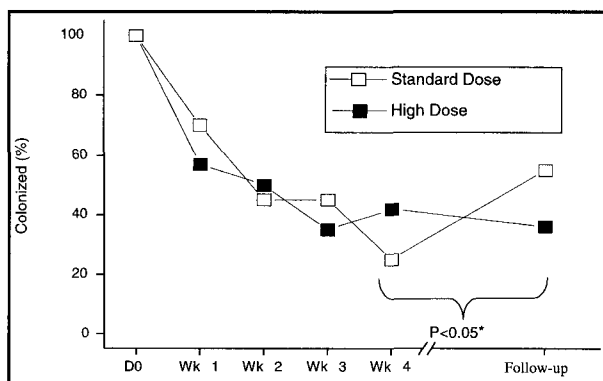


FIGURE. Global (nares, groin, and wound) rate of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization during and after vancomycin therapy: standard dose (20 mg/kg/d) versus high dose (40 mg/kg/d). *During the 2-month follow-up period after therapy with a high dose of vancomycin, overall MRSA carriage at any site did not increase, but marginally decreased from 43% to 36%. Patients treated with a high dose of vancomycin had a higher probability ($P = .048$) of remaining free of MRSA during the follow-up period than did patients treated with a standard dose.

regimens for nasal and extranasal MRSA carriage, conflicting data on their efficacy have been reported.¹⁸ True comparisons among the different studies are difficult because more than 40 different decolonization regimens have been tested in past decades¹⁸; intranasal application of mupirocin, by far the most effective topical agent, has limited effectiveness in eradicating extranasal MRSA colonization^{18,19}; and randomized or nonrandomized prospective studies were performed mostly with noninfected patients in attempts to decrease the incidence of *S. aureus* infections in special risk groups^{20,21} or before orthopedic¹¹ or cardiothoracic surgery.^{22,23} When topical decontamination, frequently associated with systemic antimicrobial therapy, was used for controlling endemic or epidemic conditions of MRSA transmission, even more heterogeneous results have been reported.²⁴⁻³⁰ The discrepancy in the success rates reported in these studies may result not only from the different regimens of antimicrobials used for MRSA decontamination such as co-trimoxazole, rifampin, ciprofloxacin, minocycline, rifampin, and fusidic acid, but also from the highly different clinical and epidemiologic situations of targeted groups. However, these studies did determine that combined regimens of antimicrobial agents were superior to single agents such as rifampin, quinolone, or fusidic acid, with each of these potentially leading to the rapid emergence of antibiotic resistance.³¹⁻³⁴

This study was facilitated by the well-established MRSA surveillance system in the orthopedic septic unit of our hospital, which involves routine preoperative and postoperative microbiological screening of each patient. To optimize the penetration of vancomycin into bones infected with MRSA and its efficacy, therapy with a higher dose of vancomycin was initiated in our institution in 2001.^{10,35,36} The possible relationship between the duration or amount of vancomycin therapy and the development of resistance

is still under debate.³⁷⁻⁴⁰ Despite that more than 50% of patients presenting with VISA received long-term vancomycin treatment (29 days to 18 weeks), these isolated cases did not establish a statistically valid relationship between overall vancomycin use and the emergence of glycopeptide resistance.³⁸ Because most clinical isolates present as heterogeneous VISA, and thus might represent an intermediate step toward the development of more highly resistant organisms,⁴¹ we found it appropriate to perform our screening assays at a low concentration (2 µg/mL) of vancomycin. This procedure, added to the Etest with a high inoculum, was rapid and efficient for the detection of trends of emerging vancomycin resistance.

Therapy with a high dose of vancomycin may contribute to the elimination of MRSA carriage without promoting the emergence of glycopeptide resistance. Further studies are warranted to evaluate a larger group of patients during longer follow-up periods.

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