

Efficacy of Telavancin in the Treatment of Experimental Endocarditis Due to Glycopeptide-Intermediate *Staphylococcus aureus*[∇]

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Received 10 October 2006/Returned for modification 11 December 2006/Accepted 23 April 2007

The efficacy of telavancin, a novel lipoglycopeptide, was evaluated in experimental endocarditis in rabbits using two clinical isolates of glycopeptide-intermediate *Staphylococcus aureus*: ATCC 700788 and HIP 5836. Infected rabbits were treated for 2 days with telavancin (10 mg/kg of body weight once daily intravenously) or vancomycin (1 g twice daily intravenously), administered with a computer-controlled infusion pump system simulating human serum kinetics. Vegetations were harvested at 16 h postinoculation in the control group and at the end of treatment in the drug-treated group. For ATCC 700788, MICs and minimal bactericidal concentrations (MBCs), respectively, were 1 mg/liter and 4 mg/liter for telavancin and 8 mg/liter and 128 mg/liter for vancomycin. For HIP 5836, MICs and MBCs, respectively, were 4 mg/liter and 8 mg/liter for telavancin and 8 mg/liter and 128 mg/liter for vancomycin. Peak and trough levels were 90 µg/ml and 6 µg/ml, respectively, for telavancin and 46 µg/ml and 6 µg/ml, respectively, for vancomycin. In glycopeptide-intermediate *S. aureus* ATCC 700788, telavancin sterilized 6 of 16 vegetations (37%), whereas vancomycin sterilized 4 of 20 (20%) ($P = 0.29$) compared with 0 of 17 in the control group. In HIP 5836 experiments, telavancin and vancomycin sterilized 5 of 16 (31%) and 1 of 15 (7%) vegetations ($P = 0.17$), respectively, compared with none in the control group. Telavancin reduced vegetation titers by 2.0 and 2.3 logs greater than vancomycin for the ATCC 700788 (4.6 [2.0 to 5.8] versus 6.6 [2.0 to 6.9] log CFU/g vegetation; $P = 0.05$) and HIP 5836 (4.4 [2.0 to 7.4] versus 6.7 [4.5 to 8.7] log CFU/g vegetation; $P = 0.09$) strains, respectively; these differences did not reach statistical significance. All isolates from vegetations remained susceptible to telavancin after therapy. The results suggest that telavancin may be an effective treatment for endocarditis caused by glycopeptide-intermediate *S. aureus*.

Vancomycin is currently the American Heart Association's recommended therapy for endocarditis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (2). However, a decade has passed since the first documented case of *S. aureus* with reduced susceptibility to vancomycin surfaced in Japan (18), and strains of *S. aureus* with intermediate- and high-level resistance to vancomycin and other glycopeptide antibiotics have since appeared in several parts of the world, including Europe and the United States (6, 28, 31, 35, 37, 42). At the same time, MRSA infections have continued to increase dramatically in both health care and community settings worldwide, causing endocarditis and other severe illnesses (1, 22, 24).

In recent years, *S. aureus* has emerged as the leading cause

of infective endocarditis internationally (10, 23), with almost 40% of cases of *S. aureus* infective endocarditis resulting specifically from MRSA (10), having a high morbidity and mortality (5, 10, 23). Strains of MRSA are often resistant to a wide range of antibiotics, and therapeutic alternatives to vancomycin are limited (19, 33). Additionally, studies have shown that vancomycin is less bactericidal in *S. aureus* infective endocarditis than penicillinase-resistant β -lactam antibiotics (36) and that glycopeptides have poor diffusion into valve vegetations (7). Therefore, new antibiotics are needed.

Telavancin, a semisynthetic derivative of vancomycin, is a novel lipoglycopeptide with rapid bactericidal activity and multiple mechanisms of action against gram-positive bacteria, including methicillin-resistant, glycopeptide-intermediate, and vancomycin-resistant strains of *S. aureus* (12, 15–17, 20, 26, 27, 34). Telavancin displays potent antibacterial activity against MRSA in animal models of endocarditis (21), bacteremia (29), soft tissue infections (16), meningitis (40), and pneumonia (30). Telavancin penetrates into skin blister fluid (41), and phase 2 trials have shown that telavancin (7.5 and 10 mg/kg of body weight once daily intravenously [i.v.]) is similar in efficacy to standard therapy for the treatment of complicated skin and skin structure infections (3, 38, 39). Telavancin is being evaluated at a 10-mg/kg i.v. dose in phase 3 complicated skin and skin structure infections and hospital-acquired pneumonia trials and in a phase 2 uncomplicated *S. aureus* bacteremia trial.

Vancomycin and other glycopeptides have a singular mech-

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[∇] Published ahead of print on 7 May 2007.

anism of action, namely inhibition of the synthesis of cell walls by targeting peptidoglycan synthesis. Telavancin, besides inhibiting cell wall synthesis, also causes disruption of cell membrane integrity (17, 26, 27). This multifunctional mechanism of action may help to minimize the potential for the selection of resistance (16, 27). In several studies, telavancin has exhibited *in vitro* activity superior to that of vancomycin (12, 15, 20, 26, 33).

In vivo data about the activity of telavancin in experimental endocarditis are few, and no clinical data about the efficacy of telavancin in infective endocarditis exist. A study comparing the efficacies of telavancin and vancomycin in a rabbit model of aortic valve infective endocarditis found telavancin to be significantly more effective than vancomycin in endocarditis induced by a strain of vancomycin-intermediate *S. aureus* and at least as effective in endocarditis caused by a strain of MRSA (21). The researchers, however, did not simulate the human pharmacokinetics of telavancin and vancomycin in their experimental model. Because drugs are eliminated more rapidly in animals than in humans, antibiotic pharmacokinetics in animals and humans may vastly differ. Therefore, the present study was conducted to evaluate the efficacy of telavancin administered using a humanized pharmacokinetics model in the treatment of experimental aortic valve endocarditis in rabbits infected with either of two glycopeptide-intermediate *S. aureus* (GISA) strains.

(This work was presented in part at the 16th European Congress of Clinical Microbiology and Infectious Diseases, Nice, France, 1 to 4 April 2006 [23a].)

MATERIALS AND METHODS

Antimicrobial agents. Telavancin powder was obtained from Theravance, Inc. Vancomycin hydrochloride powder was obtained from Sigma-Aldrich Corporation (St. Louis, MO). Agents were prepared for the study experiments according to the manufacturers' recommendations.

Bacterial strains. Two strains of *S. aureus*, both having resistance to methicillin and reduced susceptibility to glycopeptides, were used in the study: GISA strain ATCC 700788, a clinical isolate available from the American Type Culture Collection, and HIP 5836, a GISA strain isolated from a patient in New Jersey and supplied by Theravance, Inc. These strains were kept frozen in skim milk at -80°C . Before each experiment, an aliquot was thawed and inoculated onto plates containing Columbia agar with 5% sheep blood (bioMérieux, Marcy-l'Étoile, France).

***In vitro* susceptibility studies.** The MICs and minimal bactericidal concentrations (MBCs) of telavancin and vancomycin were determined by the microdilution method in liquid medium cation-adjusted Mueller Hinton broth (Oxoid, Hampshire, England) as described by the guidelines of the Clinical and Laboratory Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards [NCCLS]) (25). *S. aureus* ATCC 29213 was used as the test control strain.

In accordance with CLSI criteria, duplicate time-kill curve studies were performed with each isolate, using an inoculum of 10^5 CFU/ml. Bactericidal activity was defined as at least a 1,000-fold increase ($\geq 3 \log_{10}$ CFU/ml) in killing at 24 h in comparison with the initial inoculum. Bacterial viability counts were performed at 0, 4, and 24 h.

Simulation of human serum pharmacokinetics. A computer-controlled infusion pump system was designed to administer telavancin and vancomycin to rabbits at dosing volumes and intervals that produced pharmacokinetic serum profiles in rabbits that were similar to those observed in humans after *i.v.* infusion of the antimicrobials. Doses of telavancin and vancomycin that were representative of the pharmacokinetic profiles of the drugs in humans (10 mg/kg *i.v.* telavancin every 24 h and 1 g *i.v.* vancomycin every 12 h) were selected.

Telavancin concentrations in plasma were assayed by Theravance, Inc., using a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantitation of 0.25 $\mu\text{g/ml}$ (16). Vancomycin concentrations were assayed at the Centre de Diagnòstic Biomèdic, Hospital Clínic, Barcelona, Spain. Vancomycin concentrations were measured by an immunoturbidimetric method

with boosting by latex (ADVIA Chemistry, Bayer Health Care LLC, Germany). The limit of detection of the procedure was 0.8 $\mu\text{g/ml}$ (range from 0.8 to 72.9 $\mu\text{g/ml}$), and the precision coefficients represented by the inter- and intra-assay coefficients of variation ranged from 2.2% to 2.7%, evaluated for three levels of concentrations: 10.9, 39.3, and 73.1 $\mu\text{g/ml}$.

In vivo experimental pharmacokinetic studies were performed in five healthy rabbits to simulate the pharmacokinetic profiles of vancomycin and telavancin in humans at doses of 1 g *i.v.* twice daily and 7.5 mg/kg *i.v.* once daily, respectively. Two polyethylene catheters (inner diameter, 0.81 mm; outer diameter, 1.27 mm [Portex SA, Hythe, England]) were inserted: one through the carotid artery for sampling and the other into the cava vein through the jugular vein for infusion. Both lines were tunneled subcutaneously and brought to the interscapular region. The external portion of the jugular catheter was connected to a flowthrough swivel, and the other portion was connected to a computer-controlled infusion pump system, in accordance with *in vivo* experimental pharmacokinetic studies previously described by Gavaldà and colleagues (14). The pump system was programmed to deliver an *i.v.* infusion at previously calculated flow rates. To determine the antibiotic concentrations, 1 ml of blood was sampled at 0, 0.25, 0.5, 1, 2, 3, 4, 5, and 6 h after the start of the infusion. Because the telavancin pharmacokinetic disposition in rabbits exhibits dose linearity, infusion parameters for the 10-mg/kg *i.v.* human dose were projected from the pharmacokinetic data obtained from the simulated 7.5-mg/kg *i.v.* human dose.

Experimental endocarditis model. This research project fulfills the requirements stipulated in Spanish Royal Decree 223/1988 on the protection of animals used in experiments. The Ethical Committee on Animal Research of the University of Barcelona approved the animal studies. New Zealand White rabbits, 2 kg each, were obtained from San Bernardo Farm, Pamplona, Spain. The animals were housed in the animal facilities of the Faculty of Medicine, University of Barcelona, and nourished *ad libitum*.

Experimental aortic valve infective endocarditis was induced in the rabbits according to the technique described by Garrison and Freedman (13). Briefly, a polyethylene catheter was inserted through the right carotid artery into the left ventricle and was kept in place during the experiment. One or two catheters (inner diameter, 0.81 mm; outer diameter, 1.27 mm; Portex SA) were inserted into the inferior cava vein through the jugular vein, in accordance with the method of Garrison and Freedman, to administer the test antimicrobials.

The infusion pump delivered 2 ml/h of 0.9% saline solution to keep the catheter accessible until the initiation of dosing; 24 h after the placement of the intracardiac catheter, the animals were infected via the marginal ear vein with 1 ml of saline solution containing 7×10^5 CFU/ml of ATCC 700788 ($n = 40$) or strain HIP 5836 ($n = 32$).

A 1-ml sample of blood was obtained 18 h after infection and just before the initiation of antimicrobial therapy to confirm the presence of endocarditis. The bacteremia was interpreted as indicative of infective endocarditis. Infected rabbits were randomly assigned to one of three groups: control without treatment, treatment with telavancin simulating 10 mg/kg *i.v.* every 24 h, and treatment with vancomycin simulating 1 g *i.v.* every 12 h. Antimicrobial therapy administered using the computer-controlled infusion pump system was initiated 18 h after inoculation and maintained for 48 h. Following 48 h of treatment and 6 half-lives of the antibiotic after ending antimicrobial therapy, the rabbits in the treatment groups were killed with a lethal *i.v.* injection of sodium pentobarbital. The animals in the control group were killed 16 h after infection.

Each animal having proper placement of the catheter, macroscopic evidence of vegetations at the time of death, and *S. aureus* in cultures of blood obtained before the start of antimicrobial therapy was studied. The chest cavity was immediately opened, the heart was excised and opened, and the aortic valves were removed aseptically. Aortic valve vegetations were weighed and homogenized with 2 ml of tryptic soy broth (Difco Laboratories Incorporated, Detroit, MI) in a tissue homogenizer (Stomacher 80; Seward Limited, London, England). Homogenates were quantitatively cultured onto plates containing Columbia agar with 5% sheep blood (bioMérieux). The plates were incubated over 48 h at 37°C in room air. Two additional plates were cultured with 0.1 ml of the homogenate. The remaining homogenate was qualitatively cultured in tryptic soy broth for a week. The bacteria recovered were retested to confirm their telavancin and vancomycin MICs.

Data analysis. The results were expressed as \log_{10} CFU of ATCC 700788 or HIP 5836 per gram of vegetation. Vegetations were assigned a value of 2 \log_{10} CFU/g when growth was detected in the culture of the remaining homogenate in tryptic soy broth but not detected in the quantitative cultures on plates containing Columbia agar with 5% sheep blood. Vegetations in which no growth was detected in any of the cultures were assigned a value of 0 \log_{10} CFU/g and considered sterile.

Results were expressed as the median (interquartile range) of the number of

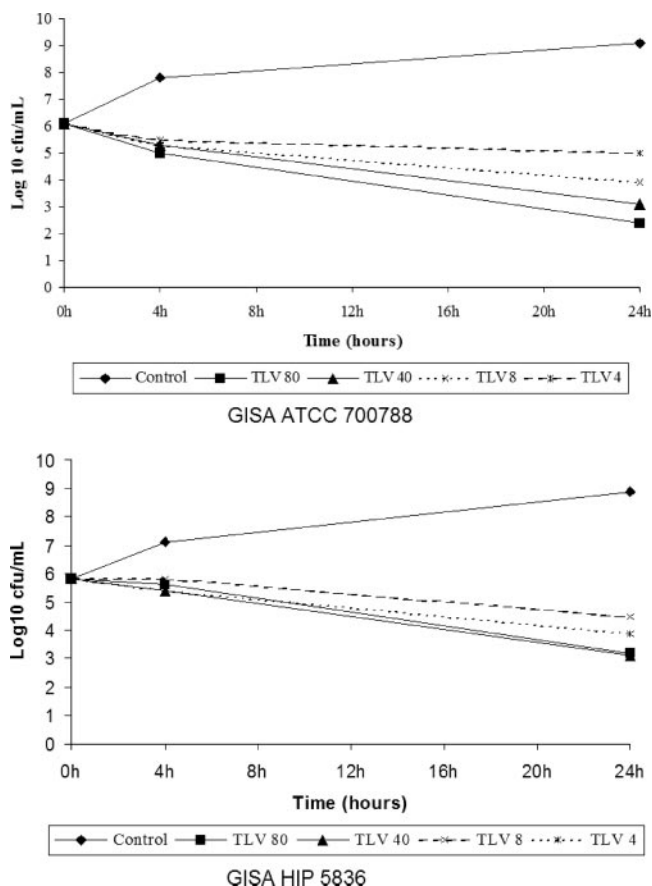


FIG. 1. Time-kill curves with telavancin.

log₁₀ CFU/g tissue of ATCC 700788 or HIP 5836. The Fisher exact test was used to compare the rate of sterile vegetations and assess whether there were differences between treatment groups. The Mann-Whitney rank sum test was used to compare the log₁₀-CFU/g tissue values between the different treatment groups.

RESULTS

In vitro susceptibility studies. The respective MICs/MBCs of telavancin and vancomycin were 1/4 and 8/128 for ATCC 700788 and 4/8 and 8/128 for HIP 5836. The in vitro activity of telavancin for ATCC 700788 is presented in Fig. 1A, and that for HIP 5836 is presented in Fig. 1B. At the concentrations tested, telavancin demonstrated activity to some extent and caused a reduction in bacterial counts of approximately 2 to 2.5 log₁₀ CFU/ml at 24 h (Fig. 1). Vancomycin was bacteriostatic.

Simulation of human serum pharmacokinetics. The rabbit pharmacokinetic data used in the mathematical model are shown in Table 1. The computer-controlled infusion pump system produced serum kinetics in rabbits similar to those found in humans for telavancin (Fig. 2). The pharmacokinetic parameters obtained from the humanized model in rabbits were similar to those in humans (Table 1).

Experimental endocarditis model. The results of the therapeutic regimens tested in the experimental model of GISA endocarditis are shown in Table 2. All control rabbits had infected vegetations with high mean bacterial counts (>9 log CFU) per gram of vegetation. For both vancomycin and teta-

TABLE 1. Pharmacokinetic parameters

Parameter ^a	Vancomycin	Result for:	
		Telavancin	
		Dose 1	Dose 2
Humans^b			
Dose	1 g i.v.	7.5 mg/kg i.v.	10 mg/kg i.v.
C _{max} /C _{min} (µg/ml)	52/10	89/6	
k (h ⁻¹)	0.15	0.110	0.095
t _{1/2β} (h)	4.6	6.18	7.41
AUC (µg · h/ml)	358.6	604	785
Protein binding (%)	50	90	90
Animals (n = 5)			
Dose	25 mg/kg i.v.	15 mg/kg i.v.	
k (h ⁻¹)	0.53 ± 0.14	0.57 ± 0.06	
t _{1/2β} (h)	1.3 ± 0.4	1.2 ± 0.11	
AUC (µg · h/ml)	101 ± 16	269.8 ± 52.2	
Protein binding (%)	65	90	90
Humanlike (n = 3 or 5)			
Dose	1 g i.v.	7.5 mg/kg i.v.	10 mg/kg i.v.
k (h ⁻¹)	0.18 ± 0.03	0.19 ± 0.09	ND ^c
t _{1/2β} (h)	3.8 ± 1.2	4.6 ± 2.8	ND
AUC (µg · h/ml)	298.8 ± 18	638 ± 38	ND
C _{max} /C _{min} (µg/ml)	46/6	90/6	114/6
AUC/MIC			
HIP 5836	37.3	159.5	
ATCC700788	37.3	638	

^a k, first-order elimination rate constant; t_{1/2β}, half-life at β phase; AUC, area under the concentration-time curve; C_{max}, maximum concentration of drug; C_{min}, minimum concentration of drug.

^b Vancomycin values were obtained from Blouin and colleagues (4); telavancin values were obtained from data on file at Theravance, Inc.

^c ND, not determined. Infusion parameters for the 10-mg/kg i.v. human dose were projected from the pharmacokinetic data obtained from the simulated 7.5-mg/kg i.v. human dose.

vancin, the bacterial counts after 2 days of treatment were reduced in the vegetations of treated animals, compared with those of the control group (P < 0.001). Telavancin also reduced vegetation titers by 2.0 and 2.3 log CFU greater than vancomycin for the ATCC and HIP strains, respectively, but the difference did not reach statistical significance (P = 0.09 and P = 0.05, respectively). All isolates from vegetations remained susceptible to telavancin.

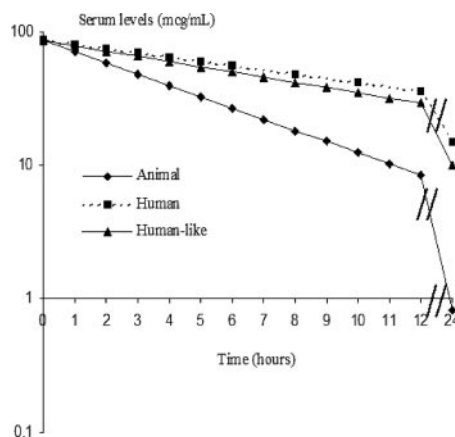


FIG. 2. Serum pharmacokinetics of telavancin.

TABLE 2. Treatment of experimental endocarditis caused by ATCC 700788 and HIP 5836 strains^a

Treatment group ^b	No. surviving/total (%)	No. with sterile vegetation/total (%)	Median log CFU/g of vegetation (interquartile range)
GISA ATCC 700788			
Control		0/17 (0)	9.5 (8.3–9.8)
Telavancin	16/17 (94)	6/16 (37)*	4.6 (2.0–5.8)†
Vancomycin	20/23 (87)	4/20 (20)*	6.6 (2.0–6.9)‡
HIP 5836			
Control		0/20 (0)	9.1 (9.1–9.4)
Telavancin	16/17 (94)	5/16 (31)*	4.4 (2.0–7.4)‡
Vancomycin	15/15 (100)	1/15 (7)*	6.7 (4.5–8.7)‡

^a *, not significant; †, $P = 0.05$; ‡, $P = 0.09$.

^b Results for telavancin represent simulation of a dose of 10 mg/kg every 24 h i.v. Results for vancomycin represent simulation of a dose of 1 g every 12 h i.v.

DISCUSSION

Telavancin exhibited rapid action against the two GISA strains both in vivo and in vitro. The MICs/MBCs of telavancin for HIP 5836 were 4 mg/liter and 8 mg/liter, respectively, and 1 mg/liter and 4 mg/liter for ATCC 700788, respectively, versus vancomycin MICs/MBCs of 8 mg/liter and 128 mg/liter for both strains. In vivo results show that after 2 days of therapy, telavancin sterilized more vegetations and reduced more vegetation titers to a greater degree than vancomycin, although the difference was not statistically significant.

Madrigal and colleagues conducted a previous study of telavancin in a rabbit model of aortic valve endocarditis caused by COL, an MRSA strain, or by HIP 5836, and found that after 4 days of therapy a twice-daily regimen of 30 mg/kg telavancin reduced mean aortic valve vegetation titers and sterilized vegetations of COL at least as effectively as vancomycin at 30 mg/kg twice daily. However, the observed difference was not statistically significant (21). The researchers also found that telavancin was significantly more effective than vancomycin in endocarditis due to HIP 5836, resulting in a 5.5- \log_{10} CFU/g reduction in vegetation titers, versus no reduction in CFU with vancomycin. The investigators concluded that telavancin may be an effective treatment for endocarditis and other serious staphylococcal infections. However, the results of the present study support the assessment of the efficacy of telavancin for staphylococcal endocarditis because it is the first study to use a humanized pharmacokinetics model to compare the activity of telavancin with that of vancomycin in GISA endocarditis. The present study also tested the activity of telavancin in vegetations of a greater density in control rabbits than those tested in the previous rabbit *S. aureus* endocarditis study (~ 9.5 log CFU/g ATCC 700788 and ~ 9.1 log CFU/g HIP 5836, versus ~ 7.4 log CFU/g COL and ~ 6.7 log CFU/g HIP 5836). Furthermore, the present study was of a shorter duration than the earlier study, showing a clear trend of more potent activity by telavancin compared with vancomycin in only 2 days of antimicrobial therapy, versus 4 days of therapy in the prior study. Additionally, resistance against telavancin was not selected in vivo after 2 days of therapy. The results of the present study of GISA-induced endocarditis can also be extrapolated to MRSA

infections, as both GISA strains used in the study were resistant to methicillin.

The bactericidal activity of telavancin may be further enhanced by the addition of gentamicin or rifampin, as suggested by recommendations for prosthetic valve endocarditis and in vitro synergy data (8, 9). In addition, controversial clinical outcomes associated with other drugs for gram-positive infections, including linezolid and daptomycin, have heightened the need for an alternative to vancomycin for the treatment of *S. aureus* endocarditis and other serious staphylococcal infections. Linezolid has been associated with adverse events and reports of clinical failure that have rendered it inappropriate for MRSA endocarditis (9, 19). Daptomycin has showed a good in vivo activity against MRSA experimental endocarditis (32), and in a recent published trial (11), the efficacy of daptomycin in patients with *S. aureus* bacteremia or right-sided or left-sided endocarditis was similar to that of comparator-based therapy (nafcillin or vancomycin). However, for methicillin-susceptible *S. aureus* or MRSA left-sided endocarditis, its efficacy was poor and similar to those of the comparators (nafcillin or vancomycin). Furthermore, the daptomycin MIC increases in some patients with microbiological failure were a cause of concern (11).

In summary, telavancin was efficacious in a rabbit model of *S. aureus* endocarditis simulating antimicrobial pharmacokinetics in humans. Telavancin was bactericidal in vitro and in vivo against two GISA isolates that are resistant to methicillin. Telavancin was as effective as vancomycin in the treatment of experimental endocarditis from GISA. These results suggest that telavancin may be an effective alternative to vancomycin in the treatment of GISA endocarditis and other serious staphylococcal infections, including those with decreased susceptibility to vancomycin.

ACKNOWLEDGMENTS

This work was supported in part by a medical school grant from Theravance, Inc.: Red Española de Investigación en Patología Infecciosa (V-2003-REDC14A-O). This work was also supported in part by Fondo de Investigaciones Sanitarias (FIS) grants FIS 00/0475, FIS 02/0322, and FIS 05/0170. J. M. Miró was a recipient of a research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and the Conselleria de Salut de la Generalitat de Catalunya, Barcelona (Spain).

The authors also thank Fundación Máximo Soriano Jiménez for its technical support.

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