Daptomycin Is Effective in Treatment of Experimental Endocarditis Due to Methicillin-Resistant and Glycopeptide-Intermediate *Staphylococcus aureus*[▽]

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Daptomycin is a lipopeptide antibiotic with potent in vitro activity against gram-positive cocci, including *Staphylococcus aureus*. This study evaluated the in vitro and in vivo efficacies of daptomycin against two clinical isolates: methicillin-resistant *S. aureus* (MRSA) 277 (vancomycin MIC, 2 µg/ml) and glycopeptide-intermediate *S. aureus* (GISA) ATCC 700788 (vancomycin MIC, 8 µg/ml). Time-kill experiments demonstrated that daptomycin was bactericidal in vitro against these two strains. The in vivo activity of daptomycin (6 mg/kg of body weight every 24 h) was evaluated by using a rabbit model of infective endocarditis and was compared with the activities of a high-dose (HD) vancomycin regimen (1 g intravenously every 6 h), the recommended dose (RD) of vancomycin regimen (1 g intravenously every 12 h) for 48 h, and no treatment (as a control). Daptomycin was significantly more effective than the vancomycin RD in reducing the density of bacteria in the vegetations for the MRSA strains (0 [interquartile range, 0 to 1.5] versus 2 [interquartile range, 0 to 5.6] log CFU/g vegetation; $P = 0.02$) and GISA strains (2 [interquartile range, 0 to 2] versus 6.6 [interquartile range, 2.0 to 6.9] log CFU/g vegetation; $P < 0.01$) studied. In addition, daptomycin sterilized more MRSA vegetations than the vancomycin RD (13/18 [72%] versus 7/20 [35%]; $P = 0.02$) and sterilized more GISA vegetations than either vancomycin regimen (12/19 [63%] versus 4/20 [20%]; $P < 0.01$). No statistically significant difference between the vancomycin HD and the vancomycin RD for MRSA treatment was noted. These results support the use of daptomycin for the treatment of aortic valve endocarditis caused by GISA and MRSA.

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are common causes of severe community-acquired and health care-associated infections, causing over one-quarter of all cases of *S. aureus* infective endocarditis (IE) (14). When vancomycin is used to treat IE caused by MRSA, vancomycin may exhibit slow bactericidal activity and diffuse poorly into bacterial vegetations (25, 32). Over the years, the use of vancomycin has been associated with treatment failures in patients with IE and bacteremia, even in instances in which the patients' MRSA

isolates remained in the susceptible MIC range (15, 21). Furthermore, recent studies showed a shift in the vancomycin MIC for MRSA strains from ≤ 0.5 µg/ml to MICs of 1 or 2 µg/ml (20, 34). Sakoulas and colleagues found that clinical success correlated with vancomycin MICs: the failure of vancomycin for the treatment of MRSA bacteremia was significantly more likely when the vancomycin MIC was 1 to 2 µg/ml than when it was ≤ 0.5 µg/ml (31). Two other studies showed similar results (20, 33). Moreover, the emergence of glycopeptide-intermediate *S. aureus* (GISA) and heterogeneous GISA (in addition to vancomycin-resistant *S. aureus*) strains has mandated the development of alternatives to vancomycin for the clinical care of patients with drug-resistant *S. aureus* infections (1, 10, 35, 36).

Daptomycin is a cyclic lipopeptide antibiotic with rapid bactericidal activity against most antibiotic-resistant gram-positive pathogens in vitro, including GISA and MRSA strains (7, 16). It is approved by the FDA and the EMEA for the treatment of complicated skin and skin structure infections and bacteremia, including those involving right-sided IE caused by methicillin-susceptible *S. aureus* and MRSA strains (Cubicin, daptomycin for injection, package insert, 2006; Cubist Pharmaceuticals, Lexington, MA). A randomized clinical study (13) found that

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daptomycin is not inferior to standard therapy for *S. aureus* bacteremia and right-sided IE. A total of 44% of daptomycin-treated patients infected with MRSA had successful clinical outcomes, whereas 32% of patients receiving vancomycin had successful clinical outcomes (13).

Compared with the amount of data on the activity of daptomycin against MRSA strains, far fewer data are available on the activity of daptomycin against *S. aureus* strains with reduced susceptibility to glycopeptides (GISA), including vancomycin. The objective of this study was to compare a daptomycin regimen with two vancomycin regimens (in which the recommended dose [RD] or a high dose [HD] of vancomycin was used) in an experimental model of aortic valve endocarditis in rabbits infected with MRSA or GISA by the use of a humanized pharmacokinetics (PK) model.

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MATERIALS AND METHODS

Bacterial isolates. The MRSA strain used in the study (strain 277) was isolated from a patient with bacteremia at the Hospital Clínic Universitari in Barcelona, Spain, while the GISA strain was isolated from a patient in the United States (29) and is currently included in the American Type Culture Collection of strains (strain ATCC 700788). Both strains were stored at -80°C in skim milk.

Antibiotics. Daptomycin powder was supplied by Cubist Pharmaceuticals. Vancomycin, gentamicin, and rifampin were purchased from Sigma (St. Louis, MO).

Susceptibility testing. The gentamicin, rifampin, and vancomycin MICs and minimal bactericidal concentrations (MBCs) were determined by the microdilution method in liquid medium, cation-adjusted Mueller-Hinton broth (Oxoid, Hampshire, England), according to the procedures of the Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards) (28). Daptomycin susceptibility testing was performed in Mueller-Hinton broth in which the calcium concentration was adjusted to 50 $\mu\text{g/ml}$ by the standard methodology. *S. aureus* ATCC 29213 was used as the test control strain.

Time-kill curve studies. All time-kill curve studies were performed in duplicate, according to the criteria of the CLSI. An inoculum of 10^5 CFU/ml was used. Bactericidal activity was defined as at least a 3-log reduction in the numbers of CFU at 24 h in comparison with the numbers of CFU in the initial inoculum. Viability counts were determined at 0, 4, and 24 h (12).

Study animals. Experimental aortic valve endocarditis was induced in New Zealand White rabbits (body weight, 2 kg), which were obtained from San Bernardo Farm (Pamplona, Spain). The animals were housed in the animal facilities of the Facultad de Medicina, Universidad de Barcelona, which is equipped with an automatic air-exchange system with a high-efficiency particulate air filter and a circadian light cycle. They were nourished *ad libitum*.

Human PK simulation studies. Antibiotics were administered by using a computer-controlled infusion pump system designed to reproduce human serum PKs in rabbits after an intravenous (i.v.) infusion. Animal drug doses were chosen to simulate the PK profiles of daptomycin (6 mg/kg of body weight i.v. every 24 h [q24h]) (4, 9, 10) and vancomycin (30 mg/kg i.v. divided into two doses; for an adult of 70 kg, 1 g i.v. every 12 h [q12h]) in humans. These are the current RDs for the treatment of *S. aureus* endocarditis (2, 13). In addition, the vancomycin HD was also tested in order to achieve the proposed optimal PK/pharmacodynamic (PD) index of the area under the concentration-time curve (AUC)/MIC ratio of >350 (27) for the treatment of serious infections due to MRSA. For this vancomycin HD treatment, the animals received 60 mg/kg i.v. vancomycin divided into four doses (equivalent to 1 g i.v. every 6 h [q6h] for a 70-kg adult). If an MIC for MRSA of 2 $\mu\text{g/ml}$ is assumed, this dose would simulate the human PK profile necessary to achieve the aforementioned PK/PD ratio.

To determine the concentrations of daptomycin and vancomycin in serum samples from five healthy rabbits, blood was drawn from a carotid catheter at different times after a single i.v. injection of the antibiotic. Rabbits received 25 mg/kg of vancomycin and 15 mg/kg of daptomycin. The daptomycin concentrations in plasma were assayed by the disk-plate bioassay method (11) with *Micro-*

coccus luteus (ATCC 9341) as the bioassay microorganism and Mueller-Hinton agar as the growth medium. The sensitivity of the daptomycin bioassay was 0.5 $\mu\text{g/ml}$. Vancomycin concentrations were assayed at the Centre de Diagnòstic Biomèdic, Hospital Clínic, Barcelona. The concentration was measured by an immunoturbidimetric test, boosted by the latex method (Advia chemistry system; Bayer Health Care LLC, Leverkusen, Germany). The limit of detection of the procedure was 0.8 $\mu\text{g/ml}$. The concentration detection range was from 0.8 to 72.9 $\mu\text{g/ml}$, and the inter- and intraassay coefficients of variation were from 2.2% to 2.7% and were evaluated with three concentrations: 10.9, 39.3, and 73.1 $\mu\text{g/ml}$.

In order to ensure that rabbits were dosed appropriately in the experimental IE model, it was necessary to first obtain the values of the PK parameters of daptomycin and vancomycin in healthy, uninfected rabbits. Different PK parameters were estimated on the basis of an open two-compartment model in order to compare the PKs in rabbits, the human-adapted model, and humans (18, 19), as described previously (26).

An infusion pump system was set up to deliver antibiotics to rabbits i.v. at previously calculated flow rates to simulate the human kinetics of 6 mg/kg daptomycin daily ($n = 5$), 1 g vancomycin q12h ($n = 5$), or 1 g vancomycin q6h ($n = 4$). To determine the antibiotic concentrations in the rabbits' serum, 1 ml of blood was sampled at different times after the start of drug infusion.

Endocarditis model. Experimental aortic valve IE was induced by the method described by Garrison and Freedman (17). A catheter was inserted through the right carotid artery into the left ventricle, and the catheter for antibiotic administration was placed into the inferior vena cava through the jugular vein, as described previously (26).

The infusion pump delivered 2 ml/h of 0.9% saline solution until the beginning of antimicrobial administration. Twenty-four hours after placement of the intracardiac catheter, all animals were infected via the marginal ear vein with 1 ml of saline solution containing 7×10^5 CFU/ml of the MRSA strain or 8×10^5 CFU/ml of the GISA strain. One milliliter of blood was obtained 16 h after infection and immediately before the initiation of antimicrobial therapy to confirm the presence of bacteremia, which was interpreted to indicate IE. The infected rabbits were then randomized to the following treatments: saline solution only (control; $n = 20$ for MRSA, $n = 17$ for GISA), daptomycin ($n = 19$ for MRSA, $n = 19$ for GISA), the vancomycin RD ($n = 20$ for MRSA, $n = 23$ for GISA), and the vancomycin HD ($n = 18$ for MRSA, $n = 22$ for GISA). Eighteen hours after the inoculation of MRSA or GISA, daptomycin and vancomycin treatments were initiated; also at that time, control animals were killed and the vegetations were quantitated for bacterial CFU. Antibiotics were administered via the computer-controlled infusion pump system for 48 h. After completion of the 48-h treatment, the animals were killed after an additional six half-lives of either daptomycin (48 h) or vancomycin (6 h) had elapsed. This provided growing time for the residual viable bacteria contained within the endocardial vegetations.

Analysis of endocardial vegetations. After antibiotic treatment, the rabbits were killed and the aortic valve vegetations were removed and processed as described previously (26).

The bacteria recovered were retested to measure daptomycin and vancomycin MICs for comparison to the pretreatment MICs. The results were expressed as the number of $\log_{10}$ CFU of MRSA or GISA per gram of vegetation. The result was assigned a value of 2 if there was no growth on the quantitative plates but there was growth in the qualitative culture (the rest of the homogenate in tryptic soy broth). The result was assigned a value of 0 and the vegetation was considered sterile if there was no growth from the initial quantitative culture or from homogenates cultured for a week.

Statistical analysis. The results were expressed as the median and the interquartile range of the number of $\log_{10}$ CFU of MRSA or GISA per gram of vegetation. The Mann-Whitney rank-sum test was used to compare the $\log_{10}$ CFU/g values between the different treatment groups. The Fisher exact test was used to compare the rate of sterilization of the vegetations and assess whether there were differences between the treatment groups.

RESULTS

Susceptibility testing. The MRSA strain was susceptible to vancomycin and daptomycin (MICs, 2 $\mu\text{g/ml}$ and 0.12 $\mu\text{g/ml}$, respectively; MBCs, 2 $\mu\text{g/ml}$ and 0.25 $\mu\text{g/ml}$, respectively) but resistant to gentamicin and rifampin (MICs, >256 $\mu\text{g/ml}$ for both), according to the CLSI standard MIC breakpoints (28). The GISA strain was susceptible to daptomycin and gentamicin (MICs, 0.5 $\mu\text{g/ml}$ and 0.25 $\mu\text{g/ml}$, respectively; MBCs, 1

FIG. 1. Results of time-kill experiments for MRSA 277 incubated with daptomycin (DAP) (A) or vancomycin (VAN) (B). The cell density ($\log_{10}$ CFU/ml) was determined at the indicated time points.

FIG. 2. Results of time-kill experiments for GISA ATCC 700788 incubated with daptomycin (DAP) (A) or vancomycin (VAN) (B). The cell density ($\log_{10}$ CFU/ml) was determined at the indicated time points.

$\mu\text{g/ml}$ and $128 \mu\text{g/ml}$, respectively) but presented intermediate resistance to vancomycin (MIC, $8 \mu\text{g/ml}$) and resistance to rifampin (MIC, $>256 \mu\text{g/ml}$). The MBC/MIC ratio (13) for the GISA isolate ($128 \mu\text{g/ml}/8 \mu\text{g/ml}$) indicated that it was tolerant to vancomycin (22).

In vitro time-kill experiments. The in vitro activities of daptomycin and vancomycin against MRSA 277 are presented in Fig. 1A and B, respectively; and the in vitro activities of daptomycin and vancomycin against GISA ATCC 700788 are presented in Fig. 2A and B, respectively. At the concentrations tested (between 4 and 0.5 times the MIC), daptomycin showed bactericidal activity over the MIC for both strains, while vancomycin was bacteriostatic.

PK studies. The PK parameters obtained from the human-adapted model were similar to those in humans (3) (Table 1). The mean trough concentration of daptomycin was well above the daptomycin MICs of both the MRSA and the GISA strains, and the mean trough concentrations of the vancomycin

RD and the vancomycin HD exceeded the vancomycin MIC of MRSA ($2 \mu\text{g/ml}$). Studies with vancomycin were also performed with GISA strains as a negative control. The mean trough concentrations in the 38 treated rabbits (18 infected with MRSA and 20 infected with GISA) in the vancomycin HD arms were $20 \mu\text{g/ml}$ at 24 h and $19 \mu\text{g/ml}$ at 48 h. We do not have the concentrations for the treated rabbits in the vancomycin RD arm.

Treatment of established endocarditis. The relative effectiveness of the daptomycin and vancomycin therapeutic regimens for the treatment of established endocarditis (control, daptomycin, the vancomycin RD, and the vancomycin HD) is shown in Table 2. One rabbit treated with daptomycin (from the MRSA arm), three treated with the vancomycin RD (from the GISA arm), and two treated with the vancomycin HD (from the GISA arm) died during the experiment; and the data for those rabbits were not included in the analyses.

TABLE 2. Treatment of experimental endocarditis caused by MRSA 277 and GISA ATCC 700788

Treatment group	No. of sterile vegetations/ total no. (%)	Median (IQR ^a) log ₁₀ CFU/g of vegetation
MRSA 277		
Control ^a	0/20 (0)	9 (8.6–9.3)
Daptomycin ^b	13/18 (72) ^{c,g}	0 (0–1.5) ^{d,i}
Vancomycin RD ^e	7/20 (35) ^{c,h}	2 (0–5.6) ^{d,j}
Vancomycin HD ^f	9/18 (50) ^{g,h}	1 (0–2) ^{i,j}
GISA ATCC 700788		
Control ^a	0/17 (0)	9.5 (8.3–9.8)
Daptomycin ^b	12/19 (63) ^{k,m}	2 (0–2) ^{l,o}
Vancomycin RD ^e	4/20 (20) ^{k,n}	6.6 (2–6.9) ^{l,p}
Vancomycin HD ^f	4/20 (20) ^{m,n}	2.4 (2–4) ^{o,p}

^a The control animals were killed 18 h after the infection was started.^b Simulating a regimen of 6 mg/kg q24h i.v.^c $P = 0.02$.^d $P = 0.02$.^e Vancomycin RD simulating treatment at 1 g q12h i.v.^f Vancomycin HD simulating treatment at 1 g q6h i.v.^g $P = 0.17$.^h $P = 0.35$.ⁱ $P = 0.19$.^j $P = 0.13$.^k $P < 0.01$.^l $P < 0.01$.^m $P < 0.01$.ⁿ $P = 1.00$.^o $P = 0.02$.^p $P = 0.03$.^q IQR, interquartile range.TABLE 1. Values of PK and PD parameters^a

Regimen	Previously reported human values (single dose)						Animal values (<i>n</i> = 5)				Human-like values (<i>n</i> = 5)				AUC/MIC ratio	
	Dose	$C_{\text{max}}/C_{\text{min}}$ ($\mu\text{g}/\text{ml}$)	K (h^{-1})	$t_{1/2\beta}$ (h)	AUC ($\mu\text{g} \cdot \text{h}/\text{ml}$)	% Protein binding	K (h^{-1}) ^b	$t_{1/2\beta}$ (h) ^b	AUC ($\mu\text{g} \cdot \text{h}/\text{ml}$) ^b	% Protein binding	$C_{\text{max}}/C_{\text{min}}$ ($\mu\text{g}/\text{ml}$)	K (h^{-1}) ^b	$t_{1/2\beta}$ (h) ^b	AUC ($\mu\text{g} \cdot \text{h}/\text{ml}$) ^b	MRSA 277	GISA ATCC 700788
Vancomycin RD	1 g i.v. ^a	52/10	0.15 ^a	4.8 ^a	358.6 ^a	50	0.53 $\pm$ 0.14	1.3 $\pm$ 0.4	101 $\pm$ 16	65	46/6	0.18 $\pm$ 0.03	3.8 $\pm$ 1.2	298.8 $\pm$ 18	149.4 ^e	37.4 ^e
Vancomycin HD	1 g i.v. ^a	NA	0.15 ^a	4.8 ^a	NA	50	0.53 $\pm$ 0.14		665.7 $\pm$ 90	65	50/15	0.18 $\pm$ 0.03		665.7 $\pm$ 90.43	332.8 ^e	83.2 ^e
Daptomycin	6 mg/kg i.v. ^b	86/15	0.07 ^b	9.5 ^b	973.9 ^b	92	0.19 $\pm$ 0.01	3.57 $\pm$ 0.19	439.8 $\pm$ 132.4	90	86/15	0.09 $\pm$ 0.01	7.6 $\pm$ 1.3	845.7 $\pm$ 207	7,047.5 ^d	1,691.4 ^f

^a Data from Blouin et al. (4).^b Cubist, data on file (10, 11), and data from Benvenuto et al. (3).^c Vancomycin MIC for MRSA 277, 2 $\mu\text{g}/\text{ml}$.^d Daptomycin MIC for MRSA 277, 0.12 $\mu\text{g}/\text{ml}$.^e Vancomycin MIC for GISA ATCC 700788, 8 $\mu\text{g}/\text{ml}$.^f Daptomycin MIC for GISA ATCC 700788, 0.5 $\mu\text{g}/\text{ml}$.^g C_{max} , maximum concentration in serum; C_{min} , minimum concentration in serum; K , elimination rate constant; $t_{1/2\beta}$, terminal half-life; NA, not available.^h Values are means $\pm$ standard deviations.

All control rabbits inoculated with the two strains of *S. aureus* tested had infected aortic valve vegetations and a high median bacterial titer per gram of vegetation ($\geq 9 \log_{10}$ CFU). Comparisons between treated groups revealed that after 48 h of treatment, daptomycin was significantly more effective than the vancomycin RD in sterilizing the MRSA and GISA vegetations ($P = 0.02$ and $P < 0.01$, respectively). In comparison with the vancomycin HD, daptomycin sterilized more vegetations in the MRSA group, but the differences did not reach statistical significance ($P = 0.17$), and compared to HD vancomycin, daptomycin was significantly more effective against the GISA isolates ($P < 0.01$). Daptomycin also reduced the median number of MRSA and GISA CFU in the vegetations of the treated animals to a greater extent than either of the vancomycin regimens. These differences were statistically significant for both strains in the vancomycin RD arm (for MRSA, $P = 0.02$; for GISA, $P < 0.01$) and against GISA in the vancomycin HD arm ($P = 0.02$).

The vancomycin HD was more active than the vancomycin RD for the MRSA strain, but there were no statistically significant differences either in the proportion of sterilized vegetations ($P = 0.35$) or in the reduction of the density of the bacteria within the vegetations ($P = 0.13$). The vancomycin HD showed more activity than the vancomycin RD ($P = 0.03$) against GISA experimental endocarditis, but the proportion of sterilized vegetations was low and the same (20%) in both arms.

All the MRSA and GISA isolates from the endocardial vegetations had the same MICs as the strains used as inocula after daptomycin, the vancomycin RD, and the vancomycin HD treatments.

DISCUSSION

The in vitro susceptibility and time-kill curve study results provided here indicate that daptomycin has bactericidal activity against MRSA 277 and GISA ATCC 700788, with MICs/MBCs of 0.12/0.25 $\mu\text{g/ml}$ and 0.5/1 $\mu\text{g/ml}$, respectively. This is consistent with the results of previous studies, in which daptomycin was found to be active against GISA isolates. The results of animal model experiments for determination of the efficacy of daptomycin against IE infections caused by enterococci (6, 24), as well as *S. aureus* and MRSA (5, 30), have previously been published in the peer-reviewed literature, but there are limited data from animal models on its efficacy against GISA IE infections (23). The present study used a rabbit model simulating human-like PKs to investigate the efficacy of daptomycin against aortic valve IE caused by MRSA or GISA. Here, daptomycin was significantly more effective for the treatment of GISA aortic valve IE than either of the vancomycin regimens used after 48 h of treatment ($P < 0.01$). Daptomycin was also significantly more effective for the treatment of MRSA aortic valve IE than the vancomycin RD ($P < 0.01$), but its effectiveness was not significantly different from that of the vancomycin HD. For both the MRSA and the GISA isolates studied, the effectiveness of the vancomycin HD (60 mg/kg i.v. divided into four doses; for an adult of 70 kg, 1 g i.v. q6h) was not significantly different from that of the vancomycin RD (30 mg/kg i.v. divided into two doses; for an adult of 70 kg, 1 g i.v. q12h), except that it reduced the numbers of bacteria within the vegetations in the GISA-infected animals ($P = 0.03$). In order to reach an optimal PK/PD index of an AUC/MIC ratio of >350 (27), we needed to simulate in rabbits a schedule of 1 g i.v. q6h. With this regimen, we obtained with the vancomycin HD regimen an AUC/MIC ratio of 333 and a mean steady-state trough serum vancomycin concentration of close to 20 $\mu\text{g/ml}$ in the 38 treated rabbits. In humans, the efficacy of this vancomycin HD regimen for the treatment of episodes of endocarditis caused by MRSA strains with vancomycin MICs of 2 $\mu\text{g/ml}$ must be counterbalanced with the increased risk of the renal toxicity of this regimen (20).

The activity of daptomycin in our study is in partial agreement with the activities described in two earlier studies. In a rat model that did not use human-like PKs, Voorn et al. (36) showed that daptomycin (5 mg/kg given twice a day [b.i.d.]) was more effective than vancomycin (100 mg/kg b.i.d.) or teicoplanin (15 mg/kg b.i.d.) for the treatment of cloxacillin-tolerant or cloxacillin-nontolerant aortic valve *S. aureus* endocarditis. In addition, Cha and Rybak (8) used an in vitro simulated endocardial vegetation model, in which daptomycin (6 mg/kg) achieved 99.9% killing of the GISA isolates by 8 h, while vancomycin was ineffective after the same period. In contrast, Kaatz et al. demonstrated that daptomycin (8 mg/kg every 8 h) and teicoplanin (12.5 and 40 mg/kg q12h) were as efficacious as vancomycin (17.5 mg/kg q6h) in reducing the numbers of MRSA organisms found in rabbit endocardial vegetations after 4 days of treatment (23), but that study did not use a human-like PK model. While the computer-controlled drug infusion system used in the present study can simulate the PKs of drugs in humans and is automated for technical ease, it has only recently been developed and, thus, confounds comparisons with studies that used different vegetations models, different

animals, and different dosing methods and frequencies. The other important limitation is bacterial strain heterogeneity.

Preclinical studies such as those presented here will continue to be important as physicians look to optimize the vancomycin dosage for the treatment of endocarditis caused by MRSA isolates with a vancomycin MIC of 2 $\mu\text{g/ml}$ and to look for alternatives to vancomycin for the treatment of MRSA endocardial infections and, potentially, those caused by vancomycin-resistant *S. aureus* isolates. Limited clinical data on the use of other antibiotics in lieu of vancomycin for the treatment of MRSA IE are available. The recent clinical study with daptomycin published by Fowler et al.—the largest study performed with patients with bacteremia and/or IE caused by *S. aureus*, including isolates with methicillin resistance—demonstrated that the activity of daptomycin alone against these infections is comparable to that of dual antibiotic therapy with semisynthetic penicillin or vancomycin plus gentamicin (13). In that trial, the efficacy of daptomycin against right-sided endocarditis caused by methicillin-susceptible *S. aureus* or MRSA strains was good. However, against left-sided endocarditis, its efficacy was as poor as that of current treatment options, antistaphylococcal penicillin (nafcillin, oxacillin, flucloxacillin) or vancomycin, with the penicillin and vancomycin given after initial gentamicin therapy. Furthermore, the increase in the MICs of daptomycin and vancomycin in some patients with microbiological failure is a cause for concern. In our experimental study, daptomycin was better than the vancomycin RD for the treatment of MRSA or GISA IE and was also more effective than the vancomycin HD for the treatment of GISA IE. We did not detect an increase in the MIC of the strains after 2 days of therapy. However, we cannot rule out the possibility of the development of heteroresistance to vancomycin or daptomycin, because population analyses were not performed with bacteria harvested from the vegetations.

In conclusion, in the rabbit experimental system described here, daptomycin was effective in sterilizing GISA and MRSA aortic valve endocarditis vegetations, was more effective than the vancomycin HD in treating MRSA experimental endocarditis, and was more potent than the vancomycin RD and the vancomycin HD in treating GISA experimental endocarditis. The results of the present study may provide a foundation for the use of daptomycin for the treatment of left-sided MRSA and GISA endocarditis in humans.

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