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Comparison of Inhibitory and Bactericidal Activities and Postantibiotic Effects of LY333328 and Ampicillin Used Singly and in Combination against Vancomycin-Resistant *Enterococcus faecium*

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One hundred ninety-five individual vancomycin-resistant *Enterococcus faecium* (VRE) isolates from five upstate New York hospitals were studied for antimicrobial susceptibilities to LY333328, quinupristin-dalfopristin, teicoplanin, ampicillin, and gentamicin. LY333328 was the most active antibiotic against VRE. The effect of media and methods on the antibacterial activity of LY333328, its synergy with ampicillin, and the postantibiotic effects (PAE) of LY333328 and ampicillin were evaluated. In microdilution tests, the MIC of LY333328 at which 90% of the isolates were inhibited (MIC_{90}) was 2 μg/ml in Mueller-Hinton II (MH II) broth and 1 μg/ml in brain heart infusion (BHI) broth. In contrast, on MH II agar the MIC_{90} was 4 μg/ml and on BHI agar it was >16 μg/ml. Bactericidal activity was observed for most strains at concentrations from 8 to ≥133 times the MIC of the tube macrodilution in MH II broth. A bactericidal effect of LY333328 plus ampicillin was demonstrated in time-kill studies, but there was great strain-to-strain variability. By the MH II agar dilution method, bacteristatic synergy (defined as a fractional inhibitory concentration of <0.5) with LY333328 and ampicillin was demonstrated for 61% of the strains tested. Under similar conditions, there was synergy with LY333328 and quinupristin-dalfopristin or gentamicin for 27 and 15% of the strains tested, respectively. The PAE of LY333328 was prolonged (23.0 h at 10 times the MIC). However, 50% normal pooled human serum decreased the PAE to 12.2 h at 10 times the MIC. Test conditions and media had a considerable effect on VRE susceptibilities to LY333328. The prolonged PAE of LY333328, a potent new bactericidal glycopeptide, and its synergy with ampicillin in a large proportion of strains suggest that further evaluation of this drug in pharmacokinetic studies and experimental infections, including those with VRE, is warranted.

Gram-positive cocci, including enterococci and staphylococci, have become common and increasingly important pathogens in nosocomial infections (7, 14, 16, 18, 21, 29). Their increasing resistance to antibiotics is well recognized (7, 16, 18, 32). Since its introduction in 1959, vancomycin has been used widely in the treatment of infections caused by gram-positive bacteria. This glycopeptide has been an effective therapeutic agent against enterococci, but it has become less effective since resistance to it was first recognized in the 1980s (9, 10, 16, 21). The development of new glycopeptides, including LY264826 and its semisynthetic derivative LY333328 (1, 2, 4, 9, 22, 33), is of special interest because of the potential use of these drugs in the treatment of infections caused by vancomycin-resistant enterococci, including vancomycin-resistant *Enterococcus faecium* (VRE). The reasons for the increased antimicrobial activity of these new glycopeptides, which inhibit cell wall synthesis, include dimerization and the increased stability of the drugs' interaction with peptidoglycan (4). In addition, LY333328 is 100 times more effective than vancomycin at inhibiting peptidoglycan transglycosylation in VRE (1, 2).

LY333328 is a new semisynthetic N-alkylated glycopeptide antibiotic with a molecular weight of 1,783 (free base), supplied as a phosphate salt. Earlier reports suggest that the susceptibilities of enterococci to LY333328 may depend on the choice of media and testing methods (3, 13, 26, 27). This study describes our observations on (i) the in vitro susceptibilities of VRE to LY333328 and five other antibiotics on several bacteriologic media by three susceptibility testing methods, (ii) the inhibitory and bactericidal effects of LY333328, (iii) LY333328 synergy with three other antibiotics, and (iv) the postantibiotic effects (PAE) of LY333328 in broth and in 50% heat-inactivated human serum.

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MATERIALS AND METHODS

Antimicrobial agents. LY333328 and vancomycin were obtained from the Eli Lilly Research Laboratories (Indianapolis, Ind.), quinupristin-dalfopristin (RP59500) was obtained from Rhône-Poulenc Rorer (Collegeville, Pa.), teicoplanin was obtained from Hoechst Marion Roussel Research Institute (Cincinnati, Ohio), and ampicillin and gentamicin were obtained from the Sigma Chemical Corporation (St. Louis, Mo.). For each drug, material from one lot number was used throughout the study. Antibiotics were reconstituted according to the manufacturers' directions, filtered through a sterile 0.45-μm-pore-size polysulfone membrane (Gelman Science, Ann Arbor, Mich.), and used the same day.

Bacterial strains. A total of 195 recent *E. faecium* isolates obtained from five upstate New York hospitals and provided by the Wadsworth Laboratories, New York State Department of Health, Albany, were included in this study. Conventional methods for the identification and characterization of the isolates were employed (12). The isolates had been typed by pulsed-field agarose gel electrophoresis as part of another study. These typing data were used to ensure that individual isolates were not duplicates of the same strain. PCR analyses showed that 91% of the isolates contained the *vanA* gene and 9% contained the *vanB* gene.

Susceptibility testing. All susceptibility studies were performed according to National Committee for Clinical Laboratory Standards recommendations (23–25). Media were obtained from BBL Microbiology Systems, Cockeysville, Md. For each medium, material from one lot number was used throughout the study. Cation-adjusted Mueller-Hinton II (MH II) media were used (MH II broth and MH II agar provided 20 to 25 mg of Ca^{2+} and 10 to 12.5 mg of Mg^{2+} per liter).

Broth microdilution MICs were determined in MH II broth and brain heart infusion (BHI) broth. Test strains were grown overnight on MH II agar at 35°C. They were subcultured into MH II broth and grown in a shaking water bath for 4 to 6 h until a turbidity of 0.5 McFarland unit was reached. Final inocula were adjusted to 5×10^5 CFU/ml. Aliquots (0.05 ml) of these suspensions were introduced into wells (in 96-well plates [Corning/Costar, Cambridge, Mass.])

TABLE 1. Comparison of the activities of LY333328 and five other antibiotics on MH II agar against 195 VRE strains

Antibiotic	MIC (μg/ml)		
	50%	90%	Range
LY333328[a]	4	8	0.25–8
Teicoplanin	64	128	≤0.125–>128
Vancomycin	512	1,024	32–>1,024
Quinupristin-dalfopristin	2	4	0.5–32
Ampicillin	256	512	1–>512
Gentamicin	>2,048	>2,048	4–>2,048

[a] The same strains tested in MH II broth by microdilution had an MIC_{50} of 2 μg/ml and an MIC_{90} of 4 μg/ml (range, ≤0.125 to 4 μg/ml).

containing twofold dilutions (0.05 ml) of previously prepared antibiotic solutions. The plates were incubated in air at 35°C for 24 h. The MICs were considered to be the lowest antibiotic concentrations (in micrograms per milliliter) at which there was no visible growth in the wells.

Methods used for determination of broth macrodilution MICs and minimal bactericidal concentrations (MBCs) were similar to those used for microdilution except that the total volume of each antibiotic and bacterial suspension was 1.0 ml. MBCs were determined by removal of 0.1 ml from each tube in which no growth was evident and subculture on MH II agar. The plates were incubated at 35°C for 24 h in air. MBCs were read as the lowest concentrations of antibiotic that resulted in ≤0.1% survival in the subculture.

Agar dilution studies were performed on MH II agar and BHI agar. Inocula from overnight MH II agar cultures were transferred to MH II broth and incubated until the turbidity reached 0.5 McFarland unit. With a Steers replicator, bacterial inocula of 10^4 CFU were placed in spots on antibiotic-containing MH II and BHI agar plates with twofold increasing antibiotic concentrations. Following incubation for 24 h at 35°C in air, the MICs were read as the lowest antibiotic concentrations at which one or no colonies were present. A faint haze was disregarded.

The activities of LY333328-ampicillin combinations were evaluated in 96-well microdilution plates containing MH II broth. Combinations of LY333328 and ampicillin, quinupristin-dalfopristin, or gentamicin were evaluated on MH II agar by the methods described above. Bacteristatic synergy was defined as a fractional inhibitory concentration of ≤0.5.

Time-kill assays were performed with the MICs determined by the tube macrodilution method described above. Suspensions of bacteria in log phase were used to inoculate flasks containing MH II broth and antibiotics at 1, 2, 4, 10, 20, 30, and 40 times the MIC. The final inoculum size was 10^5 CFU/ml. Flasks were incubated in a shaking water bath at 35°C, and sampling was done at 0, 2, 6, 24, and 48 h. Samples (0.1 ml) were 10-fold serially diluted in 0.9% NaCl, and 25-μl aliquots were plated in duplicate on MH II agar. Undiluted 0.1-ml samples were also plated directly from the flasks, providing a lower limit of detection of 10^1 CFU/ml. Plates were incubated at 35°C, and colony counts were determined 24 h later with an electronic colony counter (New Brunswick Scientific, Edison, N.J.). Synergy was defined as a ≥2-$\log_{10}$-unit difference when two drugs were compared with the most effective single drug and at least one of the drugs was present in a concentration that did not affect the growth curve of the test organism when used alone. Complete bactericidal activity was defined as the inability to recover viable organisms in an undiluted sample and subsequent inability to recover viable organisms from the same flask up to the final time point. The potential antibiotic carryover for each assay was assessed by plating concurrent samples from the highest drug concentrations and controls at all dilutions. Aliquots were washed once in MH II broth to remove antibiotic. No evidence of antibiotic carryover was found.

PAE. The method of Craig and Gudmundsson was used to determine PAE (11). Three or four colonies from an MH II agar plate were used to inoculate MH II broth. The inoculated broth was then serially diluted fivefold with MH II broth. All tubes were incubated overnight at 37°C. Following incubation, the tube in each set with an optical density at 580 nm closest to but not higher than 0.3 was selected as the inoculum. One milliliter of each inoculum was then individually added to 9 ml of antibiotic-containing medium and a drug-free control. The final inoculum size was 10^6 to 10^7 CFU/ml. After a 90-min incubation, the antibiotic was removed from the bacterial suspension by centrifugation (1,200 × *g*) and washing in warm MH II broth. This procedure was performed twice. Thereafter, sampling for PAE was done at 0, 1, 2, 3, 4, 5, 12, and 24 h by the same procedure as described for kinetics-kill curves. The PAE (in hours) was determined by counts of CFU per milliliter and the formula $PAE = T - C$, where T is the time required for a 1-$\log_{10}$-unit increase in CFU per milliliter of the test culture after removal of the antibiotic and C is the time required for a 1-$\log_{10}$-unit increase in CFU per milliliter for a similarly treated control. The PAE studies were performed in MH II broth and in 50% heat-inactivated pooled normal human serum (PNHS).

RESULTS

Table 1 shows the MICs at which 50 and 90% of the isolates were inhibited (MIC_{50} and MIC_{90}) and the range of MICs of LY333328, teicoplanin, vancomycin, quinupristin-dalfopristin, ampicillin, and gentamicin against 195 VRE strains tested by agar dilution on MH II agar. MIC_{90}s of LY333328 and quinupristin-dalfopristin were in the susceptible range, while those of the other four antibiotics were in the highly resistant range. Table 2 shows the activities of LY333328, vancomycin, and teicoplanin against 189 of the same isolates, grouped into VanA and VanB phenotypes and tested in MH II broth. All VanA strains were highly resistant to vancomycin and were *vanA* positive by PCR. They were divided into two subgroups, VanA and VanA′, based on their levels of resistance to teicoplanin. All VanB strains were resistant to vancomycin and susceptible to teicoplanin and were *vanB* positive by PCR. The microdilution method with MH II broth was used for the studies comparing VanA and VanB, because the methods and testing conditions can markedly influence the results of LY333328 susceptibility tests. The MIC_{90} of LY333328 decreased as susceptibilities to teicoplanin and vancomycin decreased. The highest MIC_{90} of LY333328 was for VanA strains highly resistant to teicoplanin (4 μg/ml). In contrast, the LY333328 MIC_{90} for VanA strains with intermediate resistance to teicoplanin was 2 μg/ml. The LY333328 MIC_{90} for VanB strains was still lower (1 μg/ml).

The susceptibilities of 26 VRE strains to LY333328, quinupristin-dalfopristin, teicoplanin, ampicillin, vancomycin, and gentamicin were tested on MH II and BHI agars. The MIC_{90} of LY333328 was markedly higher on BHI agar than on MH II agar (>16 versus 4 μg/ml), while susceptibilities to the other antibiotics were similar on both agars.

The effects of BHI and MH II media on the susceptibilities of 26 VRE strains to LY333328 were also compared by the broth microdilution method. Results were the opposite of those obtained on agar media. Susceptibilities to LY333328 were lower in BHI broth than in MH II broth (MIC_{50}, 0.5 versus 2 μg/ml; MIC_{90}, 1 versus 2 μg/ml). In contrast, susceptibilities to vancomycin were essentially the same in both media. Agar dilution and microdilution tests comparing susceptibilities in MH II and BHI media were repeated two to four times. The results were highly reproducible.

In order to assess the importance of the method used for susceptibility testing, the susceptibilities of 14 VRE strains to LY333328 were determined in MH II medium with the micro-

TABLE 2. Activities of LY333328, teicoplanin, and vancomycin tested by microdilution in MH II broth against VRE strains

Antibiotic	Phenotype[a] (no. of isolates)	MICs (μg/ml)		
		50%	90%	Range
LY333328	VanA (156)	2	4	1–4
	VanA′[b] (16)	1	2	0.25–4
	VanB (17)	0.25	1	0.125–2
Teicoplanin	VanA (156)	64	>128	32–>128
	VanA′[b] (16)	16	16	16
	VanB (17)	0.5	2	0.25–8
Vancomycin	VanA (156)	512	1,024	256–>1,024
	VanA′[b] (16)	256	512	128–>1,024
	VanB (17)	256	256	64–1,024

[a] PCR analyses were predictive of VanA and VanB phenotypes.

[b] VanA′ strains are highly resistant to vancomycin and intermediate in teicoplanin resistance (MIC = 16 μg/ml).

TABLE 3. Comparison of the inhibitory and bactericidal activities and MBC/MIC ratios of LY333328 and ampicillin against 14 VRE strains in MH II broth macrodilution assays

Strain no.	LY333328			Ampicillin		
	MIC (μg/ml)	MBC (μg/ml)	MBC/MIC	MIC (μg/ml)	MBC (μg/ml)	MBC/MIC
1	≤0.03	2	≥67	256	512	2
2	≤0.06	8	≥133	ND[a]	ND	
3	≤0.06	8	≥133	ND	ND	
4	≤0.06	8	≥133	128	512	4
5	0.06	4	67	16	64	4
6	0.125	16	128	256	512	2
7	0.125	8	64	256	>512	>2
8	0.125	1	8	16	64	4
9	0.25	16	64	512	ND	
10	0.25	16	64	128	256	2
11	0.25	8	32	512	>512	>1
12	0.25	8	32	64	>512	>8
13	0.25	8	32	256	>512	>2
14	0.5	4	8	512	>512	>1

[a] ND, not done.

and macrodilution and agar dilution methods. The MIC_{90} varied from 0.25 μg/ml for macrodilution to 4 μg/ml for microdilution and agar dilution.

MICs, MBCs, and MBC/MIC ratios for LY333328 and ampicillin are shown in Table 3. These studies were performed with the macrodilution method in MH II broth. The MIC of LY333328 varied from ≤0.03 to 0.5 μg/ml, and that of ampicillin ranged from 16 to ≥512 μg/ml. The MBCs of LY333328 were from 8- to ≥133-fold higher than the MICs.

Bacteristatic synergy against VRE was observed for combinations of LY333328 and either ampicillin, quinupristin-dalfopristin, or gentamicin. In microdilution tests with MH II broth, there was synergy between LY333328 and ampicillin for 14 of 20 strains (70%). In tests with the MH II agar technique, the percentages of 33 strains for which synergy was observed for LY333328 and either ampicillin, quinupristin-dalfopristin, or gentamicin were 61, 27, and 15%, respectively.

Table 4 shows killing kinetics for two of the five VRE strains tested following exposure to increasing concentrations of LY333328 and ampicillin, used singly or in combination. The effect of LY333328 on strain VRE-30 was rapid. Even at zero time (≈5 s, the time that elapsed between the start of the experiment and the removal of the first sample), bactericidal activity was seen, and by 6 h no surviving bacteria could be detected at 10 to 30 times the MIC. In contrast, with ampicillin no bactericidal effect for this strain was observed at zero time, and some viable organisms persisted at 48 h even at the highest drug concentration tested. Combinations of LY333328 and ampicillin had complete bactericidal activity at 2 h for 20 and 30 times the MIC and at 6 h for 10 times the MIC. Viable *E. faecium* (strain VRE-30) organisms were detected at 48 h only at the lowest drug concentrations studied (4 times the MIC for both drugs). A beneficial drug interaction was seen at this and higher concentrations, but true synergy was not demonstrated. Used alone, LY333328 inhibited growth of strain VRE-31 at all concentrations tested (Table 4). However, the number of viable organisms present at 48 h was significantly lower than in the untreated control only at 40 times the MIC. Ampicillin also inhibited growth at all concentrations, but in contrast to LY333328, the number of surviving microorganisms present at 48 h was at least 5 $\log_{10}$ units lower at every concentration tested than in the untreated control. Only the combination of LY333328 and ampicillin having the highest drug concentrations (40 times the MIC) had complete bactericidal activity against this isolate, and that effect was seen only at 48 h. In contrast, the combination of LY333328 and ampicillin at 30 times the MIC eliminated all detectable viable organisms of strain VRE-30 within 2 h. Three additional VRE isolates were studied at drug concentrations of 1 to 20 times the MIC, singly or in combination with ampicillin. These studies showed

TABLE 4. Bacterial killing of two VRE strains by LY333328, ampicillin, and LY333328 plus ampicillin

Antibiotic(s)	Concentration (no. of times the MIC)	Bacterial killing ($\log_{10}$ CFU/ml)[a]							
		Strain VRE-30[b]				Strain VRE-31[c]			
		2 h	6 h	24 h	48 h	2 h	6 h	24 h	48 h
LY333328	0	+1.27	+2.36	+3.72	+3.65	+1.20	+3.10	+3.80	+3.90
	4	−0.97	−2.30	−2.99	+2.27	−0.26	−0.24	+0.82	+3.26
	10	−2.15	>−4.0	>−4.0	>−4.0	+0.13	+0.06	+3.17	+3.63
	20	−1.30	>−4.0	>−4.0	>−4.0	−0.17	−0.20	+0.87	+2.70
	30	−2.17	>−4.0	>−4.0	>−4.0	ND	ND	ND	ND
	40	ND[d]	ND	ND	ND	−0.43	−0.74	−3.59	−3.70
Ampicillin	4	−0.78	−1.62	−4.24	−3.62	−0.58	−0.94	−2.64	−2.74
	10	−0.57	−0.89	>−4.0	−3.87	−0.55	−0.83	−2.77	−2.48
	20	−0.82	−1.45	−4.14	>−4.0	−0.44	−0.85	−1.93	−2.83
	30	−0.76	−1.10	>−4.0	−3.88	ND	ND	ND	ND
	40	ND	ND	ND	ND	−0.43	−0.74	−3.23	−4.82
LY333328 + ampicillin	4	−2.50	>−4.0	>−4.0	−3.67	−0.27	−0.20	−0.63	−2.52
	10	−3.0	>−4.0	>−4.0	>−4.0	−0.26	−0.67	−1.89	−2.67
	20	>−3.0	>−4.0	>−3.0	>−3.0	−0.40	−0.70	−1.83	−3.61
	30	>−3.0	>−4.0	>−3.0	>−3.0	ND	ND	ND	ND
	40	ND	ND	ND	ND	−0.47	−0.86	−3.13	>−5.0

[a] Bacterial count following incubation minus initial inoculum (10^5 CFU/ml). A negative value indicates net killing, and a positive value indicates net growth.
[b] MIC = 0.125 μg of LY 333328 per ml and 16 μg of ampicillin per ml.
[c] MIC = 0.06 μg of LY333328 per ml and 4 μg of ampicillin per ml.
[d] ND, not done.

up to a 1.5-$\log_{10}$-unit drop in CFU per milliliter at 72 h (data not shown).

The PAE of LY333328 and ampicillin at 10 times the MIC, used alone and in combination, were evaluated in MH II broth and in 50% PNHS. The PAE of LY333328 was clearly longer than that of ampicillin (18.7 h versus 4.0 h at 10 times the MIC). This PAE was extended to 23 h when the drugs were used in combination. PNHS decreased the PAE of LY333328 by 30%, while no change was observed for the PAE of ampicillin. For combinations of LY333328 and ampicillin evaluated with 50% PNHS, the PAE decreased by 30 to 50%.

DISCUSSION

This study clearly demonstrates that the susceptibilities of VRE to LY333328 are both medium and method dependent. In comparative studies using the microdilution method in MH II broth (cation adjusted), the MIC_{90} of LY333328 was 2 μg/ml, while in BHI broth the MIC_{90} was 1 μg/ml. Tested by macrodilution in MH II broth, the MIC_{90} was only 0.25 μg/ml. In agar dilution studies, the MIC_{90} on MH II agar was 4 μg/ml while on BHI agar it was >16 μg/ml. Nicas et al. noted in earlier studies with two other semisynthetic glycopeptides the importance of medium and method selection in evaluation of antimicrobial activities against *E. faecium* (26, 27). Higher MIC_{90}s than those obtained in this study (8 versus 2 μg/ml) have previously been reported by Biavasco et al. for LY333328 tested in MH II broth (BBL) by microdilution (5). Schwalbe et al. obtained an MIC_{90} of 1 μg/ml by microdilution, but information on medium type was not provided (30). On Iso-Sensitest agar (Unipath Ltd., Basingstoke, United Kingdom), the MIC_{90} was 0.25 μg/ml for VanA phenotypes and 0.12 μg/ml for VanB strains (13). Jones et al. found the MIC_{90} for *E. faecium* strains in cation-adjusted MH broth (Difco) to be 4 μg/ml (17). The reasons for these variations in reported susceptibilities are not clear, but the importance of different medium cation concentrations has been noted previously in reports evaluating antimicrobial susceptibilities of *Pseudomonas aeruginosa* to aminoglycosides and imipenem (8, 19). It has been noted that susceptibility results for vancomycin may depend on the media used, the method employed, and the physicochemical characteristics of the drug, independent of the growth rate of the microorganism (15).

We found LY333328 to be bactericidal when evaluated by macrodilution subcultures in time-kill analyses. This activity was dependent upon drug concentration and was enhanced by ampicillin (Table 4). However, true synergy between LY333328 and ampicillin was not demonstrated. The inability to demonstrate synergy may be due to the very rapid killing of susceptible VRE at the drug concentrations tested. In our studies, LY333328 was bactericidal only at concentrations 8 to ≥133 times the MIC. However, bactericidal activity was demonstrated at 4 to 8 or 2 to 64 times the MIC in two other studies (5, 30). While Biavasco et al. (5) found that a 2-$\log_{10}$-unit decrease in CFU per milliliter required an LY333328 concentration of 8 times the MIC and a 3-$\log_{10}$-unit decrease required 16 times the MIC in kill curves, for three of five strains we demonstrated that concentrations of LY333328 as high as 20 times the MIC caused only a 1.5-$\log_{10}$-unit drop in CFU per milliliter. However, bactericidal activity of LY333328 against two additional strains at 20 to 40 times the MIC was observed. The differences in these observations may be strain related.

In a multiple-dose in vitro pharmacodynamic model, Zelenitsky et al. demonstrated synergy of LY333328 with gentamicin and rapid bactericidal action (34). Our MH II broth microdilution data demonstrated bacteristatic synergy of LY333328 with ampicillin in 70% of the strains tested. Furthermore, bacteristatic synergy with ampicillin, quinupristin-dalfopristin, or gentamicin was observed in tests with MH II agar (for 61, 27, and 15%, respectively, of the strains tested).

Our data indicate that the PAE for LY333328 is prolonged (18.7 h at 10 times the MIC). Furthermore, the presence of ampicillin (10 times the MIC) increased the PAE to 23 h. However, 50% serum decreased the PAE by 30 to 50%. These data indicate the persistence of the effect of LY333328 for many hours and therefore the possibility that therapy may require infrequent dosing. Although their method was different than ours, Novelli et al. (28) also demonstrated a prolonged PAE for LY333328 (at 8 times the MIC the PAE was 7.4 ± 2.2 h).

Pharmacokinetic studies in rats have shown that the half-life for LY333328 is 9.7 h, that 77% of the drug is bound to protein, and that there is no evidence of drug accumulation in plasma but that there is evidence for deep compartmentalization (20). LY333328 has been shown to be effective in the treatment of mice with renal infection and in leukopenic mice bacteremic with VRE (6, 31).

In summary, of the drugs evaluated in this study, LY333328 is the most active, and it can be rapidly bactericidal against VRE. The susceptibilities to LY333328 vary with media and study methods. The PAE is prolonged. Bacteristatic synergy with LY333328 was observed with ampicillin, quinupristin-dalfopristin, and gentamicin. Further evaluation of this new semisynthetic glycopeptide against VRE is highly recommended.

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