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In Vitro Activity and Spectrum of LY333328, a Novel Glycopeptide Derivative

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Reference methods were used to determine the potency of LY333328, a semisynthetic glycopeptide derivative with a key N-alkylation substitution, against 833 strains (393 gram-positive strains and representative gram-negative bacilli) with various defined resistance mechanisms. The MICs at which 90% of the isolates are inhibited (MIC_{90}s) (in micrograms per milliliter) of LY333328 and the percentages of strains inhibited at ≤8 μg/ml were as follows: for oxacillin-susceptible *Staphylococcus aureus*, 2 and 100%, and for oxacillin-resistant *Staphylococcus aureus*, 4 and 100%; for oxacillin-susceptible *Staphylococcus epidermidis*, 4 and 100%, and for oxacillin-resistant *Staphylococcus aureus*, 8 and 96%; for *Streptococcus* serogroups A, B, C, and G, 0.25 to 1 and 100%; for *Streptococcus pneumoniae*, ≤0.015 to 0.06 and 100%; for *Enterococcus faecalis*, 2 and 100%; and for vancomycin-susceptible *Enterococcus faecium*, 0.25 and 100%, and for vancomycin-resistant *Enterococcus faecium*, 4 and 100%. LY333328 was not active (MIC_{50}, ≥16 μg/ml) against more than 400 representative strains of *Enterobacteriaceae*, pseudomonads, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Haemophilus influenzae*, *Moraxella catarrhalis*, pathogenic *Neisseria* spp., and anaerobic gram-negative bacilli. Gram-positive anaerobes were LY333328 susceptible (MICs, ≤2 μg/ml). Test methods and conditions may have affected MICs of LY333328, with most (species variation) agar dilution MICs being greater than the broth microdilution MICs.

Gram-positive cocci continue to dominate the pathogens isolated from nosocomial bloodstream infections (>65%), and resistances among the staphylococci, pneumococci, and enterococci have rapidly emerged (3, 4, 6, 14). Oxacillin (methicillin)-resistant staphylococci continue to increase in prevalence, leading to widespread use of glycopeptides. In turn, the selective pressures of broad-spectrum antimicrobial use and vancomycin therapy appear to have contributed to the widespread occurrence of infections caused by vancomycin-resistant species, usually among the enterococci (3, 6). Multiply resistant strains and the potential for genetic transfer of resistance from enterococci to more virulent species require a rapid and urgent search for alternative therapeutic agents.

Compound LY333328 is a semisynthetic glycopeptide derived from the N alkylation of LY264826 (formerly A82846B), a naturally occurring, vancomycin-like drug (11–13, 15, 16). LY264826 possessed measurable activity (MICs, 1 to 8 μg/ml) against some vancomycin-resistant strains, and action against a few strains was observed (13). LY333328, among a large series of N-alkyl derivatives of LY264826, was selected as a candidate for clinical use (2, 7, 11, 12, 15, 16). Early studies by Nicas et al. (11, 12) demonstrated activity against 26 *vanA* enterococci (MIC at which 90% of the isolates are inhibited [MIC_{90}], 1 μg/ml), 20 *vanB* enterococci (MIC_{90}, 0.25 μg/ml), and 17 strains from species known to harbor *vanC* genes (MIC range, 0.06 to 0.5 μg/ml). Similar results were reported by Steele-Moore et al. (15), who showed that for all vancomycin-resistant enterococci (81 strains) and oxacillin-resistant staphylococci (67 strains), LY333328 MICs were 2 μg/ml or less.

In this study, we expand the in vitro characterization and spectrum analysis of LY333328 by testing 833 recent clinical isolates, many with multiple resistance mechanisms, using reference dilution methods (8–10). The effects of method and testing conditions on LY333328 and comparisons to five other antimicrobials (vancomycin, teicoplanin, erythromycin, quinupristin-dalfopristin, and ciprofloxacin) were also investigated (1, 5, 11).

LY333328 was obtained from Lilly Research Laboratories (Indianapolis, Ind.), quinupristin-dalfopristin (formerly RP 59500) was supplied by Rhone-Poulenc Rorer (Collegeville, Pa.), and all other comparison compounds were either obtained from their U.S. manufacturers or purchased from Sigma Chemical Corp. (St. Louis, Mo.). The strains tested in this study were 393 gram-positive microorganisms (see Table 1) that included 206 *Staphylococcus* spp. (95 resistant to oxacillin), 13 penicillin-resistant pneumococci, and 35 vancomycin-resistant enterococci (*vanA*, *vanB*, and *vanC*), plus other organisms with a variety of defined antimicrobial resistances. Also tested were 300 gram-negative-bacillus strains representing 26 species (see Table 2). A selected group of 140 fastidious gram-negative strains that included *Haemophilus influenzae*, *Moraxella catarrhalis*, pathogenic *Neisseria* spp., and selected anaerobic bacilli (see Table 3) were tested in order to further assess the antimicrobial activity and spectrum of LY333328.

MICs were obtained for most strains by the reference broth microdilution method as outlined in documents published by the National Committee for Clinical Laboratory Standards (NCCLS), unless otherwise specified (8, 9). Antimicrobial agents were serially (twofold) diluted in cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) and incubated for 18 to 24 h in ambient air, and endpoints were determined according to NCCLS recommendations (8–10). Certain fastidious strains required testing by alternative susceptibility methods or with media, which were also added according to reference procedures as follows (8, 9): 5% lysed-horse-blood-supplemented Mueller-Hinton broth for *Bacillus cereus*, β-hemolytic *Streptococcus* spp., *Streptococcus pneumoniae*, and *Haemophilus influenzae*; Mueller-Hinton agar supplemented with 5% sheep blood for *Corynebacterium jeikeium*; *Brucella* agar supplemented with 5% sheep blood (48-h incubation) for anaerobes; and GC agar (5% CO_2 atmo-

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TABLE 1. Activities of LY333328 against 393 gram-positive strains compared to those of two glycopeptides and four other comparison compounds

Organism and type (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]			%[b]	
		50%	90%	Range	Susc.	≤4 (≤8) μg/ml
Staphylococcus aureus						
Oxacillin susceptible (66)	LY333328	1	2	0.25–8		94 (100)
	Vancomycin	0.5	0.5	0.25–1	100	
	Teicoplanin	0.25	0.5	≤0.12–1	100	
	Erythromycin	0.5	>8	0.25–>8	86	
	Quinu.-dalfo.[c]	0.25	0.5	≤0.12–0.5	100	
	Ciprofloxacin	0.25	0.5	0.06–2	97	
Oxacillin resistant (50)	LY333328	1	4	0.25–8		92 (100)
	Vancomycin	0.5	1	0.5–2	100	
	Teicoplanin	0.25	1	0.25–2	100	
	Erythromycin	>8	>8	>8	0	
	Quinu.-dalfo.	0.5	0.5	0.25–1	100	
	Ciprofloxacin	>4	>4	0.25–>4	28	
Staphylococcus epidermidis						
Oxacillin susceptible (23)	LY333328	2	4	0.5–8		96 (100)
	Vancomycin	1	1	0.25–2	100	
	Teicoplanin	1	2	0.25–16	96	
	Erythromycin	0.25	>8	0.25–>8	74	
	Quinu.-dalfo.	≤0.12	≤0.12	≤0.12–0.25	100	
	Ciprofloxacin	0.25	0.25	0.06–0.25	100	
Oxacillin resistant (27)	LY333328	2	8	0.5–16		89 (96)
	Vancomycin	1	2	1–2	100	
	Teicoplanin	1	2	0.25–4	100	
	Erythromycin	>8	>8	1–>8	0	
	Quinu.-dalfo.	0.25	0.25	≤0.12–0.5	100	
	Ciprofloxacin	0.25	0.25	0.06–0.25	100	
Staphylococcus haemolyticus						
Oxacillin susceptible (7)	LY333328	1		0.12–1		100
	Vancomycin	0.5		0.25–1	100	
	Teicoplanin	1		≤0.12–4	100	
	Erythromycin	0.25		0.25–>8	71	
	Quinu.-dalfo.	0.25		≤0.12–0.5	100	
	Ciprofloxacin	0.12		0.12–0.5	100	
Oxacillin resistant (13)	LY333328	2	2	1–4		100
	Vancomycin	1	2	1–2	100	
	Teicoplanin	4	16	0.5–>16	77	
	Erythromycin	0.5	>8	0.5–>8	54	
	Quinu.-dalfo.	0.25	0.25	≤0.12–0.5	100	
	Ciprofloxacin	>4	>4	4–>4	0	
Other coag.-neg. *Staphylococcus* spp. (20)[d]	LY333328	0.5	1	0.03–2		100
	Vancomycin	0.5	1	0.25–2	100	
	Teicoplanin	0.5	2	≤0.12–4	100	
	Erythromycin	0.25	>8	0.12–>8	55	
	Quinu.-dalfo.	0.25	0.5	≤0.12–1	100	
	Oxacillin	0.25	>8	≤0.12–>8	75	
	Ciprofloxacin	0.12	0.5	0.03–>4	95	
Streptococcus spp.						
Serogroup A (20)	LY333328	0.25	0.5	0.06–1		100
	Vancomycin	0.25	0.25	0.25	100	
	Teicoplanin	≤0.12	≤0.12	≤0.12	100	
	Erythromycin	0.12	0.25	≤0.06–0.25	100	
	Quinu.-dalfo.	≤0.12	0.25	≤0.12–0.5	100	
	Oxacillin	≤0.12	≤0.12	≤0.12	100	
	Ciprofloxacin	0.25	0.5	0.12–2	95	

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TABLE 1—*Continued*

Organism and type (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]			%[b]	
		50%	90%	Range	Susc.	≤4 (≤8) μg/ml
Serogroup B (20)	LY333328	0.12	0.25	0.06–0.25		100
	Vancomycin	0.25	0.25	0.25	100	
	Teicoplanin	≤0.12	≤0.12	≤0.12	100	
	Erythromycin	≤0.06	≤0.06	≤0.06	100	
	Quinu.-dalfo.	0.25	0.25	0.25	100	
	Oxacillin	0.25	0.25	0.25	100	
	Ciprofloxacin	0.5	1	0.25–1	100	
Serogroup C (10)	LY333328	0.25	1	≤0.015–1		100
	Vancomycin	0.25	0.5	0.25–0.5	100	
	Teicoplanin	≤0.12	≤0.12	≤0.12	100	
	Erythromycin	0.06	>8	≤0.06–>8	80	
	Quinu.-dalfo.	0.25	0.5	≤0.12–0.5	100	
	Oxacillin	≤0.12	0.25	≤0.12–0.25	100	
	Ciprofloxacin	1	1	0.25–1	100	
Serogroup G (10)	LY333328	0.5	1	0.06–1		100
	Vancomycin	0.25	0.5	≤0.12–0.5	100	
	Teicoplanin	≤0.12	≤0.12	≤0.12	100	
	Erythromycin	0.06	>8	≤0.06–>8	70	
	Quinu.-dalfo.	0.25	0.5	0.25–0.5	100	
	Oxacillin	≤0.12	≤0.12	≤0.12	100	
	Ciprofloxacin	0.25	0.5	0.12–0.5	100	
Streptococcus pneumoniae						
Penicillin susceptible (17)	LY333328	≤0.015	≤0.015	≤0.015–0.12		100
	Vancomycin	0.25	0.25	≤0.12–0.5	100	
	Teicoplanin	≤0.12	≤0.12	≤0.12–0.25	100	
	Erythromycin	≤0.06	>8	≤0.06–>8	88	
	Quinu.-dalfo.	0.25	0.5	0.25–0.5	100	
	Ciprofloxacin	1	1	0.5–4	92	
Penicillin resistant (13)[e]	LY333328	≤0.015	0.06	≤0.015–0.25		100
	Vancomycin	0.25	0.25	≤0.12–0.25	100	
	Teicoplanin	≤0.12	≤0.12	≤0.12–0.25	100	
	Erythromycin	>8	>8	≤0.06–>8	8	
	Quinu.-dalfo.	0.5	0.5	0.25–1	100	
	Ciprofloxacin	1	1	0.25–4	92	
Enterococcus faecalis						
Vancomycin susceptible (10)	LY333328	0.5	2	0.25–2		100
	Teicoplanin	≤0.12	0.25	≤0.12–0.25	100	
	Erythromycin	1	>8	0.5–>8	20	
	Quinu.-dalfo.	4	8	4–8	60	
	Ciprofloxacin	1	>4	1–>4	60	
Vancomycin resistant (10)[f]	LY333328	1	2	0.25–2		100
	Teicoplanin	≤0.12	>16	≤0.12–16	60	
	Erythromycin	>8	>8	2–>8	0	
	Quinu.-dalfo.	8	16	4–16	30	
	Ciprofloxacin	>4	>4	0.5–>4	20	
Enterococcus faecium						
Vancomycin susceptible (10)	LY333328	0.12	0.25	0.06–0.5		100
	Teicoplanin	0.25	0.5	≤0.12–1	100	
	Erythromycin	>8	>8	0.25–>8	10	
	Quinu.-dalfo.	2	2	0.25–2	100	
	Ciprofloxacin	4	4	0.5–4	40	
Vancomycin resistant (10)[g]	LY333328	1	4	0.12–4		100
	Teicoplanin	>16	>16	2–>16	50	
	Erythromycin	>8	>8	4–>8	0	

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TABLE 1—*Continued*

Organism and type (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]			%[b]	
		50%	90%	Range	Susc.	≤4 (≤8) μg/ml
	Quinu.-dalfo.	0.5	0.5	0.5	100	
	Ciprofloxacin	>4	>4	2–>4	0	
Other *Enterococcus* spp. (20)[h]	LY333328	0.25	0.5	0.06–1		100
	Vancomycin	4	4	0.25–4	100	
	Teicoplanin	0.25	0.5	≤0.12–1	100	
	Erythromycin	4	>8	0.12–>8	35	
	Quinu.-dalfo.	2	8	0.25–16	80	
	Ciprofloxacin	1	4	1–>4	50	
Corynebacterium jeikeium (10)	LY333328	0.12	0.12	0.06–0.12		100
	Vancomycin	0.5	0.5	0.25–0.5	100	
	Teicoplanin	0.5	0.5	≤0.12–0.5	100	
	Erythromycin	>8	>8	8–>8	0	
	Quinu.-dalfo.	≤0.12	0.5	≤0.12–0.5	100	
	Ciprofloxacin	>4	>4	0.12–>4	10	
Bacillus cereus (7)	LY333328	0.5		≤0.015–0.5		100
	Vancomycin	0.5		0.5–1	100	
	Teicoplanin	≤0.12		≤0.12	100	
	Erythromycin	2		0.12–2	14	
	Quinu.-dalfo.	2		1–2	100	
	Ciprofloxacin	0.03		0.015–0.12	100	
Clostridium spp. (10)[i]	LY333328	0.5	2	0.25–2		100
Peptostreptococcus spp. (10)	LY333328	0.25	0.5	0.3–1		100

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[b] Susc., percentage of strains susceptible per NCCLS criteria for all other drugs or at ≤4 μg/ml for quinupristin-dalfopristin (10). ≤4 (≤8) μg/ml, percentage of strains inhibited at this concentration of drug. The concentration utilized to define LY333328's MIC population distribution was ≤4 μg/ml (≤8 μg/ml if the percentage was less than 100%).
[c] Quinu.-dalfo., quinupristin-dalfopristin (30/70 ratio); formerly RP59500.
[d] Includes *Staphylococcus auricularis* (two strains), *Staphylococcus capitis* (two strains), *Staphylococcus cohnii* (two strains), *Staphylococcus hominis* (four strains), *Staphylococcus saprophyticus* (four strains), *Staphylococcus sciuri* (two strains), *Staphylococcus simulans* (two strains), and *Staphylococcus warneri* (two strains).
[e] Includes strains that are penicillin resistant (six strains) and penicillin intermediate (seven strains).
[f] Includes *vanA* (four strains) and *vanB* (six strains) genotypes.
[g] Includes *vanA* (five strains) and *vanB* (five strains) genotypes.
[h] Includes *Enterococcus avium* (three strains), *Enterococcus casseliflavus* (six strains), *Enterococcus durans* (two strains), and *Enterococcus gallinarum* (nine strains). Furthermore, vancomycin-susceptible (5 strains) and *vanC* (15 strains) genotypes were characterized.
[i] Includes *Clostridium difficile* (two strains), *Clostridium perfringens* (four strains), *Clostridium tertium* (two strains), and *Clostridium septicum* (two strains).

sphere) for *Neisseria gonorrhoeae*. A selected set of 25 gram-positive strains was used to assess the effects on LY333328 potency of the addition of 5% sheep blood to Mueller-Hinton agar and three divalent cation concentrations, namely, 6.1/4.3, 25/12.5, and 50/25 mg of calcium-magnesium/liter. Possible method effects were evaluated by comparing reference agar MICs with broth microdilution MICs for the same selected strains (1, 5, 11).

Table 1 illustrates the activities of LY333328 compared to those of five other representative antimicrobial agents. Two potential concentrations were utilized in these analyses to assess the limits of the MIC population distribution for LY333328, each concentration having been previously utilized for similar glycopeptide drugs as breakpoints and substantiated by early animal pharmacokinetic or in vivo infection results (3, 7, 10). Against the tested staphylococci, LY333328 was generally less active (MIC_{90}s, 2 to 8 μg/ml) than either vancomycin or teicoplanin (two- to fourfold more potent). Oxacillin-resistant strains were inhibited by 8 μg of LY333328/ml or less (except one strain of *Staphylococcus epidermidis*), and these results were not significantly higher than those with oxacillin-susceptible strains of the same *Staphylococcus* species. Vancomycin and quinupristin-dalfopristin were effective against 100% of the staphylococci at ≤2 and ≤1 μg/ml, respectively.

The β-hemolytic streptococci and *Streptococcus pneumoniae* strains were generally very susceptible to LY333328 (MIC_{90}s, ≤0.015 to 1 μg/ml), vancomycin (MIC_{90}s, 0.25 to 0.5 μg/ml), teicoplanin (MIC_{90}s, ≤0.12 μg/ml), and quinupristin-dalfopristin (MIC_{90}s, 0.25 to 0.5 μg/ml). Ciprofloxacin and erythromycin were less potent, especially against penicillin-nonsusceptible *Streptococcus pneumoniae* strains (MICs, ≥0.12 μg/ml). The enterococci that were resistant to vancomycin (*vanA*, *vanB*, and *vanC*; 35 strains) were consistently inhibited only by LY333328 (MIC_{90}s, 0.5 to 4 μg/ml) of the agents tested. The agents tested against this diverse, drug-resistant set of 60 *Enterococcus* spp. (Table 1), in order of effectiveness, were LY333328 (100% inhibited at ≤4 μg/ml), teicoplanin (85% susceptible), quinupristin-dalfopristin (75% inhibited at ≤4

TABLE 2. Activities of LY333328 against 300 gram-negative bacillus strains[a] compared to those of two glycopeptides and three other compounds

Antimicrobial agent	MIC (μg/ml)[b]			% [c]	
	50%	90%	Range	Susc.	≤4 (≤8) μg/ml
LY333328	>32	>32	8–>32		0 (<1)
Vancomycin	>16	>16	>16	0	
Teicoplanin	>16	>16	>16	0	
Erythromycin	>8	>8	>8	0	
Quinupristin-dalfopristin	>16	>16	16–>16	0	
Oxacillin	>8	>8	2–>8	<1	

[a] Include *Acinetobacter* spp. (10 strains), *Citrobacter freundii* (20 strains), *Citrobacter koseri* (10 strains), *Enterobacter aerogenes* (20 strains), *Enterobacter cloacae* (20 strains), *Enterobacter sakazakii* (2 strains), *Enterobacter taylorae* (2 strains), *Escherichia coli* (20 strains), *Hafnia alvei* (1 strain), *Klebsiella oxytoca* (10 strains), *Klebsiella ozaenae* (1 strain), *Klebsiella pneumoniae* (20 strains), *Morganella morganii* (10 strains), *Pantoea agglomerans* (10 strains), *Proteus mirabilis* (20 strains), *Proteus vulgaris* (10 strains), *Providencia rettgeri* (10 strains), *Providencia stuartii* (10 strains), *Pseudomonas aeruginosa* (30 strains), *Salmonella enteritidis* (10 strains), *Salmonella typhi* (2 strains), *Serratia marcescens* (20 strains), *Serratia liquefaciens* (2 strains), *Shigella* spp. (10 strains), *Stenotrophomonas maltophilia* (10 strains), and *Yersinia enterocolitica* (10 strains).

[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

[c] Susc., percentage of susceptible strains (10). ≤4 (≤8) μg/ml, percentage of strains inhibited at this concentration of drug. The concentration of LY333328 utilized was ≤8 μg/ml if the percentage was less than 100%.

TABLE 3. Activities of LY333328 against 140 gram-negative fastidious strains, including *Haemophilus influenzae*, *Moraxella catarrhalis*, pathogenic *Neisseria* spp., and selected anaerobic bacilli

Organism group (no. tested)	MIC (μg/ml)[f]			% ≤4 (≤8) μg/ml[g]
	50%	90%	Range	
Haemophilus influenzae (50)[a]	>32	>32	16–>32	0 (0)
Moraxella catarrhalis (30)[b]	16	16	8–16	0 (30)
Neisseria gonorrhoeae (30)[c]	>32	>32	16–>32	0 (0)
Neisseria meningitidis (10)	>32	>32	8–>32	0 (10)
Neisseria spp. (10)[d]	>32	>32	32–>32	0 (0)
Anaerobic gram-negative bacilli (10)[e]	>32	>32	16–>32	0 (0)

[a] Includes strains that are β-lactamase positive (20 strains), β-lactamase negative and ampicillin susceptible (20 strains), and β-lactamase negative and ampicillin resistant (10 strains).

[b] Includes strains that are β-lactamase negative (10 strains), β-lactamase positive and BRO-1 (10 strains), and β-lactamase positive and BRO-2 (10 strains).

[c] Includes strains that are β-lactamase positive (10 strains), β-lactamase negative and penicillin susceptible (10 strains), and β-lactamase negative and penicillin resistant (10 strains).

[d] Includes strains of *Neisseria mucosa* (two strains), *Neisseria sicca* (four strains), and *Neisseria subflava* (four strains).

[e] Includes strains of *Bacteroides fragilis* (five strains), *Prevotella bivia* (three strains), and *Prevotella disiens* (two strains).

[f] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

[g] % ≤4 (≤8) μg/ml, percentage of strains inhibited by this concentration of LY333328; the concentration used was ≤8 μg/ml if the percentage was less than 100%.

μg/ml), ciprofloxacin (37% susceptible), and erythromycin (17% susceptible). LY333328 was also active against *Corynebacterium jeikeium* (MIC_{90}, 0.12 μg/ml), *Bacillus* spp. (MIC_{50}, 0.5 μg/ml), and anaerobic gram-positive species (two genera were tested).

Table 2 lists the MIC results of LY333328 and five other drugs for 300 gram-negative bacilli. Less than 1% of LY333328 MICs were at 8 μg/ml or less, and all other comparison drugs were also inactive against these tested species. Table 3 also demonstrates that LY333328 had little potency against *Haemophilus influenzae*, *Moraxella catarrhalis*, pathogenic *Neisseria* spp., and anaerobic gram-negative bacilli (all MICs, ≥8 μg of LY333328/ml).

Studies comparing agar- and broth-based reference MICs of LY333328 are found in Table 4. A species-dependent variation was observed, where MICs determined on agar were elevated compared to MICs determined by a broth microdilution assay using enterococci and coagulase-negative staphylococci other than *Staphylococcus epidermidis*. The effect of increasing calcium and magnesium broth concentrations on LY333328 potency was a slight but insignificant increase in the MIC ($P > 0.05$; data not shown). Furthermore, the addition of 5% sheep blood to the Mueller-Hinton agar dilution plates slightly increased LY333328's activity by a 0.52 $\log_2$ dilution step.

Preliminary in vitro test results (11, 12, 15) and in vivo studies (2) of LY333328 indicate that this N-alkyl derivative of LY264826 (13, 16) has a great potential for the therapy of infections caused by resistant gram-positive species (3, 4, 6, 14). Although the potency of LY333328 in this study was slightly less than that of vancomycin or teicoplanin against some susceptible strains, LY333328's spectrum was complete and superior to those of all comparison drugs when tested against our collection of 393 gram-positive cocci (Table 1). LY333328 has been described as bactericidal (11, 12, 15) and concentration dependent (10). Static effects were observed for LY333328 when tested against some vancomycin-resistant enterococci (15).

Variable MIC results have already been reported for LY333328, even though each investigator was said to be using reference procedures (8, 9, 11, 12, 15). By our quantitative assessment, LY333328's potency was generally two- to fourfold less than that reported by Steele-Moore et al. (15) and Nicas et al. (12), although no potentially resistant strains were observed in any published study. Great care appears to be necessary when testing this compound, since method, supplements, other test conditions, such as choice of the broth medium (11), and the physicochemical characteristics of the drug itself may influence the MIC results.

If the in vivo animal infection model results (50-fold lower 50% effective dose than that of vancomycin) and preliminary pharmacokinetic data (half-life, 13.5-fold greater than that of vancomycin in the rat) are substantiated in humans (2, 7), LY333328 should be a welcome addition to our chemotherapeutic choices for severe invasive gram-positive infections.

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TABLE 4. Comparison ratios (agar dilution MIC/broth microdilution MIC) for LY333328 MICs as determined by NCCLS methods (8)

Organism group (no. tested)	No. of occurrences at ratio:						
	0.25	0.5	1	2	4	8	16
Staphylococcus aureus (4)	0	2	1	1	0	0	0
Staphylococcus epidermidis (4)	1	1	2	0	0	0	0
Other coagulase-negative staphylococci (7)[a]	0	0	0	1	2	3	1
Enterococci (10)[b]	0	0	0	1	4	5	0

[a] Includes strains of *Staphylococcus hominis* (one strain), *Staphylococcus haemolyticus* (two strains), *Staphylococcus saprophyticus* (one strain), *Staphylococcus sciuri* (one strain), *Staphylococcus simulans* (one strain), and *Staphylococcus warneri* (one strain).

[b] Includes strains of *Enterococcus casseliflavus* (two strains), *Enterococcus durans* (two strains), *Enterococcus faecalis* (two strains), *Enterococcus faecium* (two strains), and *Enterococcus gallinarum* (two strains).

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