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In Vitro Activities of LY333328 and Comparative Agents against Nosocomial Gram-Positive Pathogens Collected in a 1997 Global Surveillance Study

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The in vitro activity of LY333328 was evaluated for 1,479 nosocomial gram-positive pathogens isolated in 12 countries during 1997. LY333328 MICs at which 90% of the isolates tested were inhibited for *Enterococcus faecalis* (*n* = 351), *Enterococcus faecium* (*n* = 100), *Staphylococcus aureus* (*n* = 593), coagulase-negative *Staphylococcus* species (*n* = 325), and *Streptococcus pneumoniae* (*n* = 110) were 1, 1, 2, 2, and 0.015 μg/ml, respectively. LY333328 demonstrated potent activity against isolates of vancomycin-resistant enterococci, oxacillin-resistant staphylococci, and penicillin-resistant pneumococci.

Rates of nosocomially acquired infections with gram-positive bacteria and antibiotic resistance have both increased dramatically in the last decade among the most common gram-positive pathogens, *Enterococcus* species, *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) (e.g., *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*), and *Streptococcus pneumoniae* (4, 14). The emergence of glycopeptide resistance, particularly in the United States, coupled with ampicillin resistance in the majority of *Enterococcus faecium* isolates, as well as increasing high-level aminoglycoside resistance among isolates of both *E. faecium* and *Enterococcus faecalis*, can at times leave clinicians with few therapeutic options when treating enterococcal infections (14, 24). For *S. aureus* and CoNS, resistance to fluoroquinolones, aminoglycosides, macrolides, lincosamides, and penicillinase-resistant penicillins, such as oxacillin, are important treatment issues (4, 14). Vancomycin-intermediate isolates of *S. aureus* have now also been described (10). A recent study of *S. pneumoniae* isolates collected from across the United States during 1996 and 1997 reported that 32% of isolates were other than susceptible to penicillin (MIC ≥ 0.12 μg/ml) (12). Therapeutic choices are often limited for the treatment of infections with penicillin-resistant *S. pneumoniae*, as many of these isolates also demonstrate resistance to other penicillins, orally administered cephalosporins, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (4, 12, 14).

New antibacterial agents presently under development or recently made clinically available for emerging antibiotic resistance challenges in gram-positive pathogens include LY333328, quinupristin-dalfopristin (Q/D), fluoroquinolones, everninomicins, ketolides, and oxazolidinones (14, 15). LY333328 is a novel semisynthetic glycopeptide that in other studies has demonstrated promising activity against vancomycin-resistant enterococci, oxacillin-resistant staphylococci, and penicillin-resistant pneumococci (2, 6, 7, 13). To supplement the present literature, which consists principally of American- and British-based reports, the activity of LY333328 was assessed in a prospective, global multicenter in vitro surveillance study by determining its activity against 1,479 nosocomial gram-positive pathogens collected from 18 centers in 12 countries.

Between May and December 1997, 18 medical centers from 12 countries prospectively collected 110 gram-positive isolates of nosocomial origin. Isolates were restricted to 20 *E. faecalis*, 20 *E. faecium*, 35 *S. aureus*, 20 CoNS, and 15 *S. pneumoniae* isolates. All organisms were identified to the species level by individual medical centers using their own laboratory procedures. Only one isolate per patient was accepted. Isolates were accepted into the study if patients were hospitalized for two or more days prior to specimen collection, the organism isolated was obtained from a predefined infection site and met the criteria for nosocomial infection (23), and the organism was identified as the causative agent of infection. Seven North American, two South American, five European, and four Asian centers participated in the study. Twelve of the 18 centers were university and/or teaching hospitals. Community, private, and government hospitals accounted for the remaining centers. Ten centers had 900 to 2,500 beds, five centers had 500 to 899 beds, and three centers had 100 to 499 beds.

All isolates were shipped to the coordinating laboratory, Laboratories International for Microbiology Studies (Rolling Meadows, Ill.), for antibiotic susceptibility testing. Organisms of questionable identity were reidentified by the coordinating laboratory by using standard biochemicals and reagents and the Rapid ID ONE, NF, or STR systems (Remel, Lenexa, Kans.). In total, 351 *E. faecalis*, 100 *E. faecium*, 593 *S. aureus*, 325 CoNS, and 110 *S. pneumoniae* isolates were available for antibiotic susceptibility testing.

LY333328 was provided by Lilly Research Laboratories (Indianapolis, Ind.) and Q/D was provided by Rhone-Poulenc Rorer (Collegeville, Pa.). Vancomycin, teicoplanin, penicillin, oxacillin, and cefuroxime were provided by Dade MicroScan Inc. (West Sacramento, Calif.). MICs were determined by the coordinating laboratory by using the National Committee for Clinical Laboratory Standards (NCCLS) M7-A4 microdilution broth method (16). Frozen 96-well panels were prepared commercially by Dade MicroScan Inc. and employed doubling antibiotic dilutions encompassing the interpretive breakpoints defined by the NCCLS (17). Enterococci were tested in cation-adjusted (Ca^{2+}, 25 μg/ml; Mg^{2+}, 12.5 μg/ml) Mueller-Hinton broth (Carr-Scarborough Microbiologicals, Inc., Decatur, Ga.) while cation-adjusted Mueller-Hinton broth supplemented with 2% NaCl was used for staphylococci. The test medium for

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TABLE 1. Antibiotic susceptibilities of *E. faecalis*, *E. faecium*, *S. aureus*, coagulase-negative *Staphylococcus* species, and *S. pneumoniae* isolates from 18 centers in 12 countries during 1997

Isolate (*n*)	Antibiotic	MIC (μg/ml)			% Susceptible[a]	% Resistant[a]
		50%	90%	Range		
Vancomycin-susceptible *E. faecalis* (346)	LY333328	0.5	1	0.008—4	—[b]	—[b]
	Vancomycin	1	2	0.5—4	100	0
	Teicoplanin	0.12	0.25	0.06—8	100	0
	Q/D	4	16	0.25—>64	5.2	87.3
	Penicillin	2	8	0.12—>16	91.9	8.1
Vancomycin-susceptible *E. faecium* (59)	LY333328	0.06	0.5	0.015—2	—	—
	Vancomycin	1	2	0.25—4	100	0
	Teicoplanin	0.5	0.5	0.06—8	100	0
	Q/D	1	2	0.5—2	74.6	0
	Penicillin	>16	>16	0.5—>16	23.7	76.3
Vancomycin-resistant *E. faecium* (40)	LY333328	1	2	0.06—2	—	—
	Vancomycin	>64	>64	32—>64	0	100
	Teicoplanin	64	>64	1—>64	5.0	92.5
	Q/D	1	1	0.25—1	100	0
	Penicillin	>16	>16	>16	0	100
Oxacillin-susceptible *S. aureus* (283)	LY333328	1	2	0.06—4	—	—
	Vancomycin	1	1	0.5—2	100	0
	Teicoplanin	0.5	1	0.03—2	100	0
	Q/D	0.25	0.5	0.12—1	100	0
	Penicillin	16	>16	0.12—>16	14.5	85.5
	Oxacillin	0.25	0.5	0.25—2	100	0
Oxacillin-resistant *S. aureus* (310)	LY333328	1	2	0.03—4	—	—
	Vancomycin	1	2	0.25—4	100	0
	Teicoplanin	1	4	0.06—8	100	0
	Q/D	0.5	2	0.12—32	89.4	4.8
	Penicillin	>16	>16	0.12—>16	0.3	99.7
	Oxacillin	>16	>16	4—>16	0	100
Oxacillin-susceptible CoNS (61)	LY333328	1	2	0.03—2	—	—
	Vancomycin	1	2	0.25—4	100	0
	Teicoplanin	2	8	0.03—32	98.4	1.6
	Q/D	0.25	0.5	0.12—2	98.4	0
	Penicillin	0.5	8	0.12—>16	31.1	68.9
	Oxacillin	0.25	0.25	0.25	100	0
Oxacillin-resistant CoNS (264)	LY333328	1	2	0.015—4	—	—
	Vancomycin	2	2	0.25—8	99.6	0
	Teicoplanin	2	16	0.06—64	97.3	2.7
	Q/D	0.25	2	0.12—8	89.8	2.7
	Penicillin	>16	>16	0.12—>16	2.3	97.7
	Oxacillin	>16	>16	0.5—>16	0	100
Penicillin-susceptible *S. pneumoniae* (51)	LY333328	0.004	0.008	0.002—0.12	—	—
	Vancomycin	0.25	0.5	0.06—0.5	100	0
	Teicoplanin	0.06	0.12	0.03—0.12	—	—
	Q/D	0.25	0.5	0.12—4	98.0	2.0
	Penicillin	0.015	0.03	0.008—0.06	100	0
	Cefuroxime	0.25	0.25	0.25—4	100	0
Penicillin-intermediate *S. pneumoniae* (31)	LY333328	0.004	0.015	0.002—0.03	—	—
	Vancomycin	0.5	0.5	0.12—1	100	0
	Teicoplanin	0.06	0.12	0.03—0.12	—	—
	Q/D	0.5	0.5	0.25—2	96.8	0
	Penicillin	0.25	1	0.12—1	0	0
	Cefuroxime	0.5	2	0.25—4	100	0
Penicillin-resistant *S. pneumoniae* (28)	LY333328	0.004	0.015	0.002—0.06	—	—
	Vancomycin	0.5	0.5	0.12—1	100	0
	Teicoplanin	0.06	0.12	0.06—0.12	—	—
	Q/D	0.25	1	0.25—1	100	0
	Penicillin	4	4	2—8	0	100
	Cefuroxime	8	8	0.25—16	21.4	0

[a] Susceptible and resistant breakpoints used were those suggested by the NCCLS (20).
[b] —, NCCLS susceptible and resistant breakpoints for LY333328 are not available (20).

TABLE 2. MIC distributions for isolates of vancomycin-resistant *E. faecium*

Isolate (*n*) and antibiotic	No. of isolates requiring each MIC (μg/ml) (% of total isolates tested)										
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Vancomycin-resistant *E. faecium* (40)											
LY333328	2 (5.0)	3 (7.5)	2 (5.0)	10 (25.0)	19 (47.5)	4 (10.0)	0	0	0		
Vancomycin	0	0	0	0	0	0	0	0	0	0	40 (100)
Teicoplanin	0	0	0	0	1 (2.5)	0	0	1 (2.5)	1 (2.5)	6 (15.0)	31 (77.5)
Q/D	0	0	5 (12.5)	8 (20.0)	27 (67.5)	0	0	0	0	0	0
Penicillin	0	0	0	0	0	0	0	0	40 (100)[a]	0	0

[a] All isolates demonstrated penicillin MICs of >16 μg/ml.

streptococci was cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood. Isolates were subcultured twice onto blood agar from −80°C skim milk stocks prior to MIC testing. Panels were inoculated to achieve a final concentration of approximately 5×10^5 CFU/ml in 100 μl and incubated at 35°C in ambient air for 18 to 24 h prior to reading. Oxacillin and vancomycin MICs were read at 24 h. Quality control organisms, *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619, were included each day that antibiotic susceptibility testing was performed.

The number of isolates compiled per center ranged from 67 to 110 and totaled 1,479. Of these, 235 (15.9%), 377 (25.5%), and 867 (58.6%) were from hospitals with bed sizes of 100 to 499, 500 to 899, and 900 to 2,500, respectively. The antibiotic susceptibility data collected were not considered geographically representative of any of the countries participating in the study, and isolates were analyzed strictly according to genus, species, and antibiotic resistance markers.

The MICs at which 50% of the isolates tested were inhibited (MIC_{50}s), MIC_{90}s, MIC ranges, and percentages of isolates susceptible and resistant to each antibiotic tested are presented in Table 1. For purposes of this report, MIC_{90}s differing by more than fourfold, on a weight basis, were deemed significantly different in activity. The activity of LY333328 against each gram-positive pathogen tested was consistent from country to country and for each country approximated the MIC_{90}s presented in Table 1.

Q/D and penicillin were less active than all glycopeptides tested against vancomycin-susceptible *E. faecalis*, with 87.3% of isolates resistant to Q/D and 8.1% resistant to penicillin. Only one isolate of vancomycin-susceptible *E. faecalis* demonstrated an LY333328 MIC of 4 μg/ml. The LY333328 MIC_{90} for the 351 isolates of *E. faecalis* tested, including vancomycin-resistant phenotypes, was 1 μg/ml. Thirty-nine of 40 (97.5%) vancomycin-resistant *E. faecium* isolates were isolated by four of the five centers in the United States. The remaining isolate was from an Italian center. LY333328 was as active as teicoplanin and more active than vancomycin, Q/D, and penicillin against vancomycin-susceptible *E. faecium*. MIC distributions for each antibiotic against vancomycin-resistant *E. faecium* are presented in Table 2. LY333328 was >32-fold more active than vancomycin and teicoplanin against vancomycin-resistant *E. faecium*. One isolate of vancomycin-intermediate *E. faecium* from a center in the United States was also identified. The MICs of LY333328, Q/D, and teicoplanin for this isolate were 0.03, 0.5, and 0.25 μg/ml, respectively. Against *E. faecium*, regardless of vancomycin susceptibility, MICs for LY333328 were ≤2 μg/ml. The LY333328 MIC_{90} for the 100 isolates of *E. faecium* tested, including vancomycin-resistant phenotypes, was 1 μg/ml.

LY333328 was equally active against oxacillin-susceptible and -resistant isolates of *S. aureus*, with all MICs being ≤4 μg/ml. MIC distributions for LY333328 and other antibiotics against oxacillin-resistant *S. aureus* isolates are presented in Table 3. LY333328 demonstrated activity similar to vancomycin and teicoplanin against oxacillin-susceptible *S. aureus* isolates. The activities of LY333328, vancomycin, teicoplanin, and Q/D were similar against oxacillin-resistant *S. aureus* isolates.

TABLE 3. MIC distributions for isolates of oxacillin-resistant *S. aureus* and oxacillin-resistant CoNS

Isolate (*n*)	Antibiotic	No. of isolates requiring each MIC (μg/ml) (% of total isolates tested)										
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Oxacillin-resistant *S. aureus* (310)	LY333328	1 (0.3)	0	2 (0.7)	24 (7.7)	184 (59.3)	92 (29.7)	7 (2.3)	0	0		
	Vancomycin	0	0	1 (0.3)	21 (6.8)	241 (77.7)	45 (14.5)	2 (0.7)	0	0	0	0
	Teicoplanin	1 (0.3)	4 (1.3)	29 (9.4)	92 (29.7)	81 (26.1)	53 (17.1)	27 (8.7)	23 (7.4)	0	0	0
	Q/D	0	4 (1.3)	39 (12.6)	118 (38.1)	116 (37.4)	18 (5.8)	12 (3.9)	2 (0.7)	0	1 (0.3)	0
	Penicillin	0	1 (0.3)	1 (0.3)	0	0	3 (1.0)	4 (1.3)	2 (0.7)	299 (96.5)[a]		
	Oxacillin	0	0	0	0	0	0	2 (0.7)	3 (1.0)	305 (98.4)[b]		
Oxacillin-resistant CoNS (264)	LY333328	3 (1.1)	5 (1.9)	6 (2.3)	22 (8.3)	103 (39.0)	117 (44.3)	8 (3.0)	0	0		
	Vancomycin	0	0	4 (1.5)	2 (0.8)	100 (37.9)	151 (57.2)	6 (2.3)	1 (0.4)	0	0	0
	Teicoplanin	1 (0.4)	13 (4.9)	15 (5.7)	16 (6.1)	18 (6.8)	84 (31.8)	25 (9.5)	85 (32.2)	0	4 (1.5)	3 (1.1)
	Q/D	0	33 (12.5)	123 (46.6)	59 (22.3)	22 (8.3)	20 (7.6)	5 (1.9)	2 (0.8)	0	0	0
	Penicillin	0	6 (2.3)	3 (1.1)	6 (2.3)	4 (1.5)	11 (4.2)	9 (3.4)	35 (13.3)	190 (72.0)[c]		
	Oxacillin	0	0	0	14 (5.3)	4 (1.5)	6 (2.3)	11 (4.2)	23 (8.7)	206 (78.0)[d]		

[a] Of these, 24 isolates demonstrated penicillin MICs of 16 μg/ml and 275 isolates demonstrated penicillin MICs of >16 μg/ml.
[b] Of these, 10 isolates demonstrated oxacillin MICs of 16 μg/ml and 295 isolates demonstrated penicillin MICs of >16 μg/ml.
[c] Of these, 54 isolates demonstrated penicillin MICs of 16 μg/ml and 136 isolates demonstrated penicillin MICs of >16 μg/ml.
[d] Of these, 23 isolates demonstrated oxacillin MICs of 16 μg/ml and 183 isolates demonstrated penicillin MICs of >16 μg/ml.

TABLE 4. MIC distributions for isolates of non-penicillin-susceptible (MIC ≥ 0.12 μg/ml) *S. pneumoniae*

Isolate (*n*)	Antibiotic	No. of isolates requiring each MIC (μg/ml) (% of total isolates tested)									
		≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	≥4
Penicillin-intermediate *S. pneumoniae* (31)	LY333328	19 (61.3)	8 (25.8)	3 (9.7)	1 (3.2)	0	0	0	0	0	0	0
	Vancomycin					0	1 (3.2)	14 (45.2)	15 (48.0)	1 (3.2)	0	0
	Teicoplanin				2 (6.5)	18 (58.1)	11 (35.5)	0	0	0	0	0
	Q/D		0	0	0	0	0	15 (48.4)	14 (45.0)	1 (3.2)	1 (3.2)	0
	Penicillin	0	0	0	0	0	14 (45.2)	3 (9.7)	8 (26.0)	6 (19.4)	0	0
	Cefuroxime							15 (48.4)	5 (16.1)	5 (16.1)	3 (9.7)	3 (9.7)
Penicillin-resistant *S. pneumoniae* (28)	LY333328	17 (60.7)	2 (7.1)	7 (25.0)	1 (3.6)	1 (3.6)	0	0	0	0	0	0
	Vancomycin					0	0	9 (32.1)	18 (64.3)	1 (3.6)	0	0
	Teicoplanin				0	16 (57.1)	12 (42.9)	0	0	0	0	0
	Q/D		0	0	0	0	0	14 (50.0)	9 (32.1)	5 (17.9)	0	0
	Penicillin	0	0	0	0	0	0	0	0	0	6 (21.4)	22 (78.6)[a]
	Cefuroxime							1 (3.6)	0	0	0	27 (96.6)[b]

[a] Of these, 21 isolates demonstrated penicillin MICs of 4 μg/ml and 1 isolate demonstrated a penicillin MIC of 8 μg/ml.
[b] Of these, 5 isolates demonstrated cefuroxime MICs of 4 μg/ml, 21 isolates demonstrated cefuroxime MICs of 8 μg/ml, and 1 isolate demonstrated a cefuroxime MIC of 16 μg/ml.

Q/D was fourfold less active against oxacillin-resistant *S. aureus* isolates than oxacillin-susceptible isolates (Table 1). The LY333328 MIC_{90} for the 593 isolates of *S. aureus* tested, including oxacillin-resistant phenotypes, was 2 μg/ml. LY333328 demonstrated similar activity against both oxacillin-susceptible and -resistant CoNS isolates, with all MICs being ≤4 μg/ml. MIC distributions for antibiotics tested against oxacillin-resistant CoNS are presented in Table 3. LY333328 and vancomycin demonstrated similar activity against oxacillin-susceptible CoNS while teicoplanin was fourfold less active. The activities of LY333328, vancomycin, and Q/D were similar against oxacillin-resistant CoNS while teicoplanin was eightfold less active. One isolate of teicoplanin-resistant, oxacillin-susceptible CoNS and seven isolates of teicoplanin-resistant, oxacillin-resistant CoNS were identified (17). Isolates of teicoplanin-resistant CoNS were randomly distributed among the centers. Q/D was fourfold less active against oxacillin-resistant CoNS than oxacillin-susceptible isolates. The LY333328 MIC_{90} for the 325 isolates of CoNS tested, including oxacillin-resistant phenotypes, was 2 μg/ml.

LY333328 demonstrated MICs of ≤0.12 μg/ml against all isolates of *S. pneumoniae* tested, regardless of penicillin susceptibility. LY333328 was 32- to 64-fold more active than Q/D, 32- to 64-fold more active than vancomycin, and 8- to 16-fold more active than teicoplanin against all isolates of *S. pneumoniae* tested. MIC distributions for LY333328 and other antibiotics are presented in Table 4. The LY333328 MIC_{90} for the 110 isolates of *S. pneumoniae* tested, including penicillin-resistant phenotypes, was 0.015 μg/ml.

Increasing numbers of clinical isolations of gram-positive pathogens resistant to one or more antibiotics have encouraged research and development of new antibiotics targeting these bacteria (4, 14). One of these investigational agents, LY333328, is an *N*-alkylated epivancosamine derivative of LY264826, a naturally occurring structural analog of vancomycin (18). Pharmacodynamic studies have demonstrated LY333328 to possess concentration-dependent, bactericidal activity in vitro (2, 9, 21) and in vivo (20; C. J. Boylan, K. Campanale, T. R. Parr, D. Philips, T. Nicas, and M. Zeckel, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-41, p. 13, 1998; M. E. Rupp and J. S. Ulphani, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-111, p. 260, 1998). These findings are in bold contrast to the bacteriostatic action on enterococci exhibited by vancomycin and teicoplanin (2, 9; Boylan et al., 38th ICAAC). LY333328 demonstrates an extremely long serum half-life in humans (132 to 356 h), bestowing potential pharmacokinetic advantages over clinically available glycopeptides and other antibiotics (J. Chien, S. Allerheiligen, D. Philips, B. Cerimele, and H. R. Thomasson, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-55, p. 18, 1998).

Previous work has demonstrated that LY333328 possesses excellent in vitro activity against vancomycin-susceptible and -resistant *E. faecalis*, *E. faecium*, *E. gallinarum*, and *E. casseliflavus* (2, 6, 7, 13, 18, 21). LY333328 activity against both vancomycin-susceptible *E. faecalis* and *E. faecium* was similar in all (2, 7, 13, 18, 21) but a single study (6). In that study, LY333328 was reported to possess marginally better activity against *E. faecium* than *E. faecalis* (6). The presence of *vanA* or *vanB* resistance determinants has been demonstrated not to affect (2, 9, 18, 19) or only moderately influence (8) the activity of LY333328. In addition, the activity of LY333328 against vancomycin-resistant enterococci cannot be accounted for by its failure to induce expression of resistance in inducible *vanA*- and *vanB*-positive isolates (15, 18). LY333328's mechanism of action against vancomycin-resistant isolates has been hypothesized to result from its inhibition of the transglycosylation step of cell wall biosynthesis, which contrasts with vancomycin's inhibition of D-Ala-D-Ala transpeptidation (1).

Q/D was considerably less active against isolates of *E. faecalis* than those of *E. faecium*, with 87.3% of *E. faecalis* isolates resistant to Q/D (Table 1). Q/D resistance rates similar to those found in this study have previously been reported in the United States and Canada (11) and raise an important concern regarding the clinical use of Q/D. The slowly bactericidal effects (bacteriostatic) of Q/D against vancomycin-resistant isolates of *E. faecium* strains with concurrent macrolide resistance may also be a consideration (3).

Clinical isolates of *S. aureus* with reduced susceptibility to teicoplanin have been regularly reported in Europe and the United States (4). Resistance to teicoplanin is usually encountered among CoNS, such as *S. haemolyticus* and *S. epidermidis*, and is more common among oxacillin-resistant isolates (4). Vancomycin resistance is less common, but there are reports of laboratory selection of low-level resistance in *S. haemolyticus* (22) and clinical isolates of vancomycin-intermediate *S. aureus* (10). In the present study, LY333328 was equally active against oxacillin-susceptible and -resistant isolates of *S. aureus* and

CoNS, with all MICs being ≤4 μg/ml. LY333328 was also very active against all isolates of *S. pneumoniae* tested regardless of penicillin susceptibility and was substantially more potent than Q/D against *S. pneumoniae*, as has been previously demonstrated (5).

In conclusion, the potent inhibitory activity of LY333328 suggests that in the future it may represent an alternative choice in the treatment of infections with antibiotic-resistant gram-positive bacteria. Animal models to evaluate LY333328 activity in life-threatening infections, synergy studies to determine LY333328 activity in combination with other antibiotics, particularly against vancomycin-resistant enterococci, studies to monitor for LY333328 resistance development during monotherapy, and LY333328 clinical trials will further define the therapeutic roles of this novel glycopeptide (19).

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