ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2003, p. 2334–2338 Vol. 47, No. 7
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.7.2334–2338.2003

In Vitro Activities of Ramoplanin, Teicoplanin, Vancomycin, Linezolid, Bacitracin, and Four Other Antimicrobials against Intestinal Anaerobic Bacteria

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Received 6 December 2002/Returned for modification 30 January 2003/Accepted 1 April 2003

By using an agar dilution method, the in vitro activities of ramoplanin, teicoplanin, vancomycin, linezolid, and five other agents were determined against 300 gram-positive and 54 gram-negative strains of intestinal anaerobes. Ramoplanin was active at ≤2 μg/ml against 287 of 300 (95.7%) gram-positive organisms, including 18 strains of *Clostridium difficile* for which MICs of ramoplanin were 0.25 to 0.5 μg/ml; for 3 of these, linezolid MICs were 8 to 16 μg/ml. Nineteen *Clostridium innocuum* strains for which the vancomycin MIC at which 90% of strains were inhibited was 16 μg/ml were susceptible to ramoplanin at 0.06 to 0.25 μg/ml and to teicoplanin at 0.125 to 1.0 μg/ml. All strains of *Eubacterium*, *Actinomyces*, *Propionibacterium*, and *Peptostreptococcus* spp. were inhibited by ≤0.25 μg of ramoplanin per ml and ≤1 μg of vancomycin per ml. Ramoplanin was also active at ≤4 μg/ml against 15 of 22 of the *Prevotella* and *Porphyromonas* strains tested, but ramoplanin MICs for all 31 strains of the *Bacteroides fragilis* group, the *Fusobacterium mortiferum-Fusobacterium varium* group, and *Veillonella* spp. were ≥256 μg/ml. Ramoplanin displays excellent activity against *C. difficile* and other gram-positive enteric anaerobes, including vancomycin-resistant strains; however, it has poor activity against most gram-negative anaerobes and thus potentially has a lesser effect on the ecological balance of normal fecal flora.

Ramoplanin, a glycolipodepsipeptide antibiotic that inhibits peptidoglycan synthesis, is currently being developed as an oral, nonabsorbable agent for the prevention of vancomycin-resistant *Enterococcus* (VRE) infection in patients with VRE gastrointestinal tract colonization (17). It has demonstrated activity against a wide spectrum of gram-positive organisms, including antibiotic-resistant strains of staphylococci and enterococci and less frequently encountered pathogens such as *Corynebacterium jeikeium*, *Listeria monocytogenes*, and *Bacillus* spp. (5, 9, 10, 11, 12, 14, 16); however, limited data are available on the drug's activity against anaerobic bacteria (3, 14).

(This study was presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, 16 to 19 December 2001, Chicago, Ill. [D. M. Citron, Y. A. Warren, K. L. Tyrrell, C. V. Merriam, H. Fernandez, and E. J. C. Goldstein, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-1417, p. 193, 2001].)

Broad-spectrum antimicrobials with activity against anaerobes may disrupt the ecological balance of the intestinal flora and promote colonization with VRE and *Clostridium difficile* (6, 7, 8, 15, 19), while antimicrobials with minimal antianaerobe activity preserve the normal intestinal anaerobic flora responsible for colonization resistance (18). Since ramoplanin is intended as treatment for intestinal colonization of VRE, we examined its potential effects on colonic flora by determining its in vitro activity against anaerobic organisms of intestinal origin, including both gram-positive and gram-negative species.

Selected for this study were strains from our collection of anaerobic gram-positive bacilli and cocci that had been isolated from bowel flora or clinical intra-abdominal specimens. Smaller numbers of gram-negative anaerobes of intestinal origin were also included. The majority of the test strains were isolated during the past 3 years. The species and numbers of strains tested are listed in Table 1. Control strains included *Staphylococcus aureus* ATCC 29213, *Eubacterium lentum* ATCC 43055, and *Bacteroides fragilis* ATCC 25285.

Susceptibility testing was performed according to the reference agar dilution method described by National Committee on Clinical Laboratory Standards document M11-A5 (12). Antimicrobial agents were obtained as follows: ramoplanin, Intrabiotics, Mountain View, Calif. (ramoplanin is now being developed by Genome Therapeutics Corp., Waltham, Mass.); teicoplanin, Aventis, Romainville, France; vancomycin, Eli Lilly & Co., Indianapolis, Ind.; ampicillin and bacitracin, Sigma Chemical Co., St. Louis, Mo.; linezolid and clindamycin, Pharmacia, Kalamazoo, Mich.; cefoxitin, Merck & Co., Rahway, N.J.; and metronidazole, Searle, Skokie, Ill. The antimicrobials were reconstituted according to their manufacturers' instructions, serially diluted, and added to molten supplemented brucella agar for plate preparation. The plates were inoculated on the day of preparation. Bacitracin plates were prepared on the basis of the weight of the drug. For conversion, 1 μg equals 0.066 U, or 1 U equals 15.2 μg. The binding of ramoplanin to plastic that has been reported in broth microdilution tests was not an issue in agar dilution tests (1).

Isolates were taken from frozen stock and subcultured at least twice on supplemented brucella agar (Anaerobe Systems, Morgan Hill, Calif.) to ensure purity and good growth. Colonies were suspended in brucella broth (Becton Dickinson, Sparks, Md.) to a density equal to the 0.5 McFarland standard.

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TABLE 1. In vitro activities of ramoplanin, teicoplanin, vancomycin, bacitracin, linezolid, and four other agents against intestinal strains of anaerobic bacteria

Organism (no. of strains) and drug	MIC (μg/ml)[a]		
	Range	50%	90%
Actinomyces spp. (22)[b]			
Ramoplanin	≤0.03–0.5	0.06	0.25
Teicoplanin	0.125–0.5	0.25	0.5
Vancomycin	0.5–1	0.5	1
Bacitracin	0.5–8	2	4
Linezolid	0.5–8	0.5	0.5
Cefoxitin	≤0.03–1	0.125	0.5
Ampicillin	≤0.03–0.5	0.06	0.25
Clindamycin	≤0.03–0.5	0.06	0.25
Metronidazole	≤0.03–>128	32	>128
Bifidobacterium spp. (13)[c]			
Ramoplanin	≤0.03–0.06	≤0.03	0.06
Teicoplanin	0.125–0.5	0.25	0.5
Vancomycin	0.25–1	0.5	1
Bacitracin	0.25–2	1	2
Linezolid	0.25–2	1	1
Cefoxitin	0.5–32	2	8
Ampicillin	≤0.03–1	0.125	0.5
Clindamycin	≤0.03–0.25	≤0.03	≤0.03
Metronidazole	4–>128	8	16
Clostridium bifermentans-Clostridium sordellii group (10)[d]			
Ramoplanin	0.06–0.25	0.06	0.125
Teicoplanin	≤0.06–0.125	0.125	0.125
Vancomycin	0.125–1	0.5	1
Bacitracin	0.5–32	4	32
Linezolid	1–1	1	1
Cefoxitin	0.125–4	0.5	4
Ampicillin	≤0.03–0.5	0.06	0.5
Clindamycin	≤0.03–32	0.06	0.5
Metronidazole	0.25–8	1	8
Clostridium cadaveris (10)			
Ramoplanin	0.06–4	0.06	0.125
Teicoplanin	≤0.06–0.5	≤0.06	0.25
Vancomycin	1–4	2	2
Bacitracin	2–64	32	32
Linezolid	2–4	4	4
Cefoxitin	0.5–32	0.5	1
Ampicillin	≤0.03–1	0.125	1
Clindamycin	≤0.03–2	≤0.03	1
Metronidazole	0.06–0.25	0.125	0.125
Clostridium clostridioforme (10)			
Ramoplanin	4–32	8	16
Teicoplanin	1–8	4	8
Vancomycin	0.125–1	0.5	1
Bacitracin	1–128	8	128
Linezolid	2–4	2	4
Cefoxitin	2–16	4	16
Ampicillin	0.5–128	1	2
Clindamycin	0.03–2	0.5	1
Metronidazole	0.03–1	0.06	0.25
Clostridium difficile (18)			
Ramoplanin	0.25–0.5	0.25	0.25
Teicoplanin	0.25–0.5	0.5	0.5
Vancomycin	0.5–4	1	2
Bacitracin	>128	>128	>128
Linezolid	2–16	2	16
Cefoxitin	128–>128	128	>128
Ampicillin	2–4	2	4
Clindamycin	2–>128	4	>128
Metronidazole	0.25–1	0.5	1
Clostridium innocuum (19)			
Ramoplanin	0.06–0.25	0.06	0.125
Teicoplanin	0.125–1	0.5	1
Vancomycin	8–32	16	16
Bacitracin	128–>128	>128	>128
Linezolid	2–4	4	4
Cefoxitin	8–128	64	128
Ampicillin	0.06–0.25	0.25	0.25
Clindamycin	0.125–128	0.5	128
Metronidazole	0.25–4	1	4
Clostridium paraputrificum-Clostridium tertium group (10)[e]			
Ramoplanin	0.06–0.25	0.125	0.125
Teicoplanin	≤0.06–0.25	0.125	0.25
Vancomycin	0.5–2	1	2
Bacitracin	1–128	1	128
Linezolid	1–8	4	4
Cefoxitin	1–2	1	2
Ampicillin	0.06–2	0.5	1
Clindamycin	1–8	4	4
Metronidazole	0.5–4	1	2
Clostridium perfringens (11)			
Ramoplanin	≤0.03–0.06	0.06	0.06
Teicoplanin	≤0.06–0.125	≤0.06	0.125
Vancomycin	0.5	0.5	0.5
Bacitracin	0.25–2	1	2
Linezolid	1–4	2	2
Cefoxitin	0.5–2	1	1
Ampicillin	≤0.03–0.06	≤0.03	0.06
Clindamycin	≤0.03–128	0.5	2
Metronidazole	0.5–4	2	4

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The suspensions were applied to the antibiotic plates with a Steers replicator that delivered a final inoculum of approximately 10^5 CFU/spot. The plates were incubated in the anaerobic chamber incubator at 36°C for 44 h. The MIC was defined as the concentration of drug that completely inhibited growth or caused a marked reduction in the appearance of growth compared to the drug-free growth control.

The results are presented in Table 1. Ramoplanin was active at ≤2 μg/ml against all gram-positive strains with the exception of all 10 strains of *Clostridium clostridioforme*, 2 of 5 strains of *Clostridium symbiosum*, and 1 of 10 strains of *Clostridium cadaveris*. Moreover, teicoplanin MICs for the *C. clostridioforme* strains were 1 to 8 μg/ml, which were also higher than those for most of the other clostridia. This finding is of interest because

TABLE 1—*Continued*

Organism (no. of strains) and drug	MIC (μg/ml)[a]		
	Range	50%	90%
Clostridium ramosum (15)			
Ramoplanin	<0.03–0.06	<0.03	0.06
Teicoplanin	0.5–1	0.5	1
Vancomycin	2–8	8	8
Bacitracin	128–>128	128	>128
Linezolid	4–8	8	8
Cefoxitin	4–64	8	64
Ampicillin	0.06–0.5	0.125	0.25
Clindamycin	1–>128	2	>128
Metronidazole	0.5–4	2	4
Clostridium spp. (25)[f]			
Ramoplanin	≤0.03–8	0.125	2
Teicoplanin	≤0.06–8	0.25	1
Vancomycin	≤0.06–8	1	4
Bacitracin	0.5–>128	16	128
Linezolid	0.25–4	1	4
Cefoxitin	0.25–8	2	8
Ampicillin	≤0.03–>128	0.125	0.5
Clindamycin	≤0.03–8	0.25	0.25
Metronidazole	≤0.03–2	0.25	2
Eubacterium lentum (17)			
Ramoplanin	0.06–.5	0.25	0.25
Teicoplanin	0.125–1	0.25	0.5
Vancomycin	0.5–2	2	2
Bacitracin	0.25–>128	16	>128
Linezolid	1–2	1	2
Cefoxitin	1–16	8	8
Ampicillin	0.25–2	0.5	2
Clindamycin	≤0.03–1	0.125	1
Metronidazole	0.125–1	0.5	0.5
Eubacterium group spp. (31)[g]			
Ramoplanin	≤0.03–0.25	0.06	0.125
Teicoplanin	≤0.06–0.25	0.125	0.125
Vancomycin	0.25–2	0.5	2
Bacitracin	0.25–>128	4	>128
Linezolid	0.06–8	1	8
Cefoxitin	≤0.03–8	0.5	8
Ampicillin	≤0.03–1	0.125	0.25
Clindamycin	≤0.03	≤0.03	0.5
Metronidazole	≤0.03–>128	0.25	4
Lactobacillus spp. (37)[h]			
Ramoplanin	≤0.03–0.5	0.125	0.25
Teicoplanin	≤0.06–>64	1	>64
Vancomycin	0.25–>32	4	>32
Bacitracin	0.5–>128	8	128
Linezolid	0.5–16	4	8
Cefoxitin	≤0.06–>128	64	>128
Ampicillin	≤0.03–8	0.5	2
Clindamycin	≤0.03–>128	0.06	2
Metronidazole	0.5–>128	>128	>128
Peptostreptococcus asaccharolyticus (10)			
Ramoplanin	≤0.03–0.25	0.125	0.25
Teicoplanin	≤0.06–.25	0.25	0.25
Vancomycin	0.125–0.5	0.125	0.25
Bacitracin	≤0.125–1	0.25	1
Linezolid	0.5–1	1	1
Cefoxitin	≤0.03–0.5	≤0.03	0.5
Ampicillin	≤0.03–1	≤0.03	0.25
Clindamycin	≤0.03–128	0.25	64
Metronidazole	0.125–2	0.5	1
Peptostreptococcus magnus-Pepto-streptococcus-micros group (14)[i]			
Ramoplanin	≤0.03–0.125	0.06	0.125
Teicoplanin	≤0.06–0.25	0.125	0.25
Vancomycin	0.25–1	0.5	1
Bacitracin	1–32	2	32
Linezolid	0.5–4	1	2
Cefoxitin	0.25–1	1	1
Ampicillin	0.06–1	0.25	1
Clindamycin	≤0.03–1	0.06	1
Metronidazole	0.125–2	0.5	1
Peptostreptococcus spp. (13)[j]			
Ramoplanin	≤0.03–0.125	≤0.03	0.125
Teicoplanin	≤0.06–0.5	0.125	0.25
Vancomycin	0.125–1	0.5	0
Bacitracin	0.25–128	0.5	8
Linezolid	0.5–16	1	2
Cefoxitin	≤0.03–8	0.5	4
Ampicillin	≤0.03–4	0.125	0.25
Clindamycin	≤0.03–0.25	≤0.03	0.25
Metronidazole	0.06–>128	0.25	2
Propionibacterium spp. (15)[k]			
Ramoplanin	0.06–0.25	0.125	0.25
Teicoplanin	0.125–1	0.5	1
Vancomycin	0.5–1	0.5	0.5
Bacitracin	0.25–4	0.25	4
Linezolid	0.25–1	5	1
Cefoxitin	≤0.03–2	0.25	2
Ampicillin	≤0.03–0.25	0.125	0.25
Clindamycin	≤0.03–0.5	≤0.03	≤0.03
Metronidazole	64–>128	>128	>128

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C. clostridioforme and *C. symbiosum* consistently stain gram-negative, suggesting the presence of a thinner peptidoglycan layer in their cell walls. However, these strains were all susceptible to ≤1 μg of vancomycin per ml, indicating a different mechanism of activity. Ramoplanin was active (MIC, ≤0.125 μg/ml) against the 19 vancomycin-resistant (MIC, 8 to 32 μg/ml) strains of *Clostridium innocuum* and against all 15 strains of *Clostridium ramosum* (ramoplanin MIC, ≤0.06 μg/ml), for which vancomycin MICs were 2 to 8 μg/ml and teicoplanin MICs were 0.5 to 1 μg/ml. *C. difficile* strains were susceptible to ramoplanin at 0.25 to 0.5 μg/ml, including 3 of the18 strains tested for which linezolid MICs were 8 to 16 μg/ml and clindamycin MICs were >128 μg/ml. Other clostridia were susceptible to most of the agents tested, except bacitracin. These results are similar to those obtained by Romano et al. (G. Romano, C. Brunati, A. Bulgheroni, D. Jabes, and G. Privitera, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-2260, p. 196, 2001), who tested 121 *Clostrid-*

TABLE 1—*Continued*

Organism (no. of strains) and drug	MIC (μg/ml)[a]		
	Range	50%	90%
Bacteroides fragilis group (17)[l]			
Ramoplanin	>32–>256	256	>256
Teicoplanin	16–128	64	128
Vancomycin	16–128	64	128
Bacitracin	16–>256	>256	>256
Linezolid	2–4	4	4
Cefoxitin	4–128	32	64
Ampicillin	8–>128	32	>128
Clindamycin	≤0.03–>128	2	>128
Metronidazole	0.5–4	1	2
Fusobacterium-Veillonella spp. (15)[m]			
Ramoplanin	32–>256	>256	>256
Teicoplanin	64–>256	>256	>256
Vancomycin	128–>256	>256	>256
Bacitracin	16–>256	>256	>256
Linezolid	0.25–2	0.5	1
Cefoxitin	0.5–16	4	4
Ampicillin	0.125–8	2	4
Clindamycin	0.06–4	0.06	4
Metronidazole	0.25–4	0.5	4
Porphyromonas asaccharolytica (10)			
Ramoplanin	≤1–4	≤1	4
Teicoplanin	≤1	≤1	≤1
Vancomycin	≤1–4	2	4
Bacitracin	≤1–4	≤1	2
Linezolid	2–2	2	2
Cefoxitin	0.06–0.25	0.125	0.25
Ampicillin	≤0.03	≤0.03	≤0.03
Clindamycin	≤0.03	≤0.03	≤0.03
Metronidazole	0.06–0.125	0.06	0.125
Prevotella spp. (12)[n]			
Ramoplanin	4–128	32	128
Teicoplanin	0.25–4	0.5	4
Vancomycin	2–64	32	64
Bacitracin	0.5–32	2	32
Linezolid	0.25–2	0.5	1
Cefoxitin	≤0.03–16	0.5	1
Ampicillin	≤0.03–32	0.125	4
Clindamycin	≤0.03	≤0.03	≤0.03
Metronidazole	0.125–1	0.25	

[a] 50% and 90%, MICs at which 50 and 90% of strains are inhibited, respectively.
[b] *A. israelii* (four strains), *A. meyeri* (four), *A. naeslundii* (four), *A. odontolyticus* (five), *A. viscosus* (four), and *Arcanobacterium pyogenes* (one).
[c] *B. adolescentis* (two strains), *B. bifidum* (one), *B. breve* (two), *B. catenulatum* (two), *B. dentium* (one), *B. longum* (one), and no good fit (four).
[d] *C. bifermentans* (five strains) and *C. sordellii* (five).
[e] *C. paraputrificum* (five strains) and *C. tertium* (five).
[f] *C. aminovalericum* (one strain), *C. baratii* (one), *C. butyricum* (five), *C. cochlearium* (one), *C. glycolicum* (two), *C. leptum* (one), *C. novyi A* (one), *C. sphenoides* (one), *C. sporogenes* (one), *C. subterminale* (three), *C. symbiosum* (five), and no good fit (three).
[g] *Collinsella aerofaciens* (nine strains), *E. alactolyticum* (one), *E. brachy* (one), *E. combesii* (one), *E. contortum* (two), *E. limosum* (six), and no good fit (eleven).
[h] *L. acidophilus* (three strains), *L. brevis* (two), *L. casei* (seven), *L. catenaformis*, (two), *L. confusus* (one), *L. delbrueckii* (one), *L. fermentum* (one), *L. jensenii* (one), *L. lactis* (one), *L. plantarum* (two), *L. rhamnosus* (one), and no good fit (fifteen).
[i] *P. magnus* (seven strains) and *P. micros* (seven).
[j] *Gemella morbillorum* (one strain), *P. anaerobius* (nine), and *P. prevotii* (three).
[k] *P. acnes* (five strains), *P. avidum* (seven), and *P. granulosum* (three).
[l] *B. caccae* (two strains), *B. distasonis* (three), *B. fragilis* (three), *B. ovatus* (two), *B. stercoris* (two), *B. thetaiotaomicron* (three), and *B. vulgatus* (two).
[m] *F. mortiferum* (six strains), *F. varium* (five), *Fusobacterium* sp. (one), and *Veillonella* sp. (three).
[n] *P. bivia* (four strains), *P. buccae* (three), *P. intermedia* (two), *P. melaninogenica* (two), and *P. oris* (one).

ium strains representing 17 species and reported only one isolate of *Clostridium rectum* for which the ramoplanin MIC was >256 μg/ml; ramoplanin MICs for the remaining *Clostridium* strains were ≤4 μg/ml. Their study also included 76 strains of *C. difficile* for which ramoplanin MICs were ≤0.007 to 0.125 μg/ml. Our results are also in agreement with those of Biavasco et al. (3), who tested ramoplanin, teicoplanin, and vancomycin against 70 strains of *C. difficile* and obtained MICs that were virtually identical to those in our present study. Since *C. difficile* is frequently isolated from the same types of patients who are colonized with VRE, and since ramoplanin is active against both organisms, it may eradicate both of them (8, 15).

Among the other gram-positive strains, all *Eubacterium* spp., *Propionibacterium* spp., *Peptostreptococcus* spp., *Actinomyces* spp., and *Bifidobacterium* spp. were inhibited by ≤0.25 μg of ramoplanin per ml and ≤1 μg of vancomycin per ml. While all 37 *Lactobacillus* strains were susceptible to ramoplanin at ≤0.5 μg/ml, vancomycin MICs for 16 of these strains were >32 μg/ml and teicoplanin MICs were >64 μg/ml.

Among the gram-negative strains, for the *B. fragilis* group, the *Fusobacterium mortiferum-Fusobacterium varium* group, and *Veillonella* strains, ramoplanin MICs were ≥256 μg/ml. The *Prevotella* and *Porphyromonas* strains were somewhat more susceptible, with ramoplanin and vancomycin MICs ranging from ≤1 to 128 μg/ml. All 10 of the *Porphyromonas* and 5 of the 12 *Prevotella* strains were susceptible to ≤4 μg of ramoplanin per ml. A previous study also found that ramoplanin inhibited *Prevotella bivia* and *Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*) at concentrations of 0.5 to 4 μg/ml (13).

Ramoplanin exhibited potent activity against most gram-positive anaerobes while having little or no effect on most of the gram-negative strains; therefore, ramoplanin appears to have less impact on the anaerobic bowel flora than some of the other more broad-spectrum agents that we tested. Our vitro data do not necessarily predict in vivo effect, and clinical data on the impact of ramoplanin on normal fecal flora are needed. Our susceptibility study used an inoculum of 10^5 CFU/spot that resulted in MICs that were ≤2 μg/ml for 95.7% of the gram-positive strains; however, concentrations of anaerobes are typically in the range of 10^9 to 10^{12} CFU/g of feces; therefore, ramoplanin may have even less impact on normal anaerobic gram-positive flora than would be suggested by our test results. Ramoplanin dosed at 400 mg twice daily results in a fecal

concentration of 1 to 1.5 mg per g of stool (Timothy Leach [Genome Therapeutics Corp.], personal communication). While enzymatic breakdown of the drug by fecal flora does not occur, there is a nonspecific and reversible adsorption of about 80 to 90% of the drug (2). High concentrations of ramoplanin in feces induce high levels of free antibiotic, and the binding with subsequent release can maintain long-lasting levels in the gastrointestinal tract (2) and provide effective therapy for VRE without causing the major perturbation of the gastrointestinal ecosystem that can occur with administration of broad-spectrum antimicrobials, especially the expanded-spectrum cephalosporins, metronidazole, and the fluoroquinolones (4). Significantly, ramoplanin exhibited excellent activity against the 18 strains of *C. difficile* tested and might provide an alternative therapy for this pathogen in addition to VRE.

This study was supported by a grant from Intrabiotics.

REFERENCES

1. **Barry, A. L., M. A. Pfaller, and P. C. Fuchs.** 1993. Ramoplanin susceptibility testing criteria. J. Clin. Microbiol. **31:**1932–1935.
2. **Bertazzoni Minelli, E., A. Benini, L. Vicentini, and A. Muner.** 1995. Antibiotics and their interaction with intestinal contents. Microecol. Ther. **25:**360–367.
3. **Biavasco, F., E. Manso, and P. E. Varaldo.** 1991. In vitro activities of ramoplanin and four glycopeptides antibiotics against clinical isolates of *Clostridium difficile*. Antimicrob. Agents Chemother. **35:**195–197.
4. **Carmeli, Y., G. M. Eliopoulos, and M. H. Samore.** 2002. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant *Enterococcus*. Emerg. Infect. Dis. **8:**802–807.
5. **Collins, L. A., G. M. Eliopoulos, C. B. Wennersten, M. J. Ferraro, and R. C. Moellering, Jr.** 1993. In vitro activity of ramoplanin against vancomycin-resistant gram-positive organisms. Antimicrob. Agents Chemother. **37:**1364–1366.
6. **Donskey, C. J., T. K. Chowdhry, M. T. Hecker, C. K. Hoyen, J. A. Hanrahan, A. M. Hujer, R. A. Hutton-Thomas, C. C. Whalen, R. A. Bonomo, and L. B. Rice.** 2000. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. N. Engl. J. Med. **343:**1925–1932.
7. **Edlund, C., L. Barkholt, B. Olsson-Liljequist, and C. E. Nord.** 1997. Effect of vancomycin on intestinal flora of patients who previously received antimicrobial therapy. Clin. Infect. Dis. **25:**729–732.
8. **Hacek, D. M., P. Bednarz, G. A. Noskin, T. Zembower, and L. R. Peterson.** 2001. Yield of vancomycin-resistant enterococci and multidrug-resistant *Enterobacteriaceae* from stools submitted for *Clostridium difficile* testing compared to results from a focused surveillance program. J. Clin. Microbiol. **39:**1152–1154.
9. **Jones, R. N., and A. L. Barry.** 1989. In vitro evaluation of ramoplanin (A16686 or MDL62198). A new depsipeptide complex for potential topical use. Diagn. Microbiol. Infect. Dis. **3:**279–282.
10. **Lawrence, T., C. Rotstein, T. Beam, E. A. Gorzynski, D. Amsterdam.** 1993. In vitro activities of ramoplanin, selected glycopeptides, fluoroquinolones, and other antibiotics against clinical bloodstream isolates of gram-positive cocci. Antimicrob. Agents Chemother. **37:**896–900.
11. **Manzor, O., J. Pawlak, and L. Saravolatz.** 1999. In-vitro activity of 29 antimicrobial agents against penicillin-resistant and -intermediate isolates of *Streptococcus pneumoniae*. J. Antimicrob. Chemother. **43:**31–36.
12. **Mobaraki, N., J. M. Quale, and D. Landman.** 1994. Bactericidal activity of peptide antibiotics against multidrug-resistant *Enterococcus faecium*. Antimicrob. Agents Chemother. **38:**385–387.
13. **NCCLS.** 2001. Methods for antimicrobial susceptibility testing of anaerobic bacteria. Approved standard, 5th ed. M11-A5. National Committee for Clinical Laboratory Standards, Wayne, Pa.
14. **O'Hare, M. D., G. Ghosh, D. Felmingham, and R. N. Gruneberg.** 1990. In-vitro studies with ramoplanin (MDL 62,198): a novel lipoglycopeptide antimicrobial. J. Antimicrob. Chemother. **25:**217–220.
15. **Poduval, R. D., R. P. Kamath, M. Corpuz, E. P. Norkus, and C. S. Pitchumoni.** 2000. *Clostridium difficile* and vancomycin-resistant *Enterococcus*: the new nosocomial alliance. Am. J. Gastroenterol. **95:**3513–3515.
16. **Rolston, K. V. I., N. Dholakia, D. H. Ho, B. Leblanc, T. Dvorak, and H. Streeter.** 1996. In-vitro activity of ramoplanin (a novel lipoglycopeptide), vancomycin, and teicoplanin against Gram-positive clinical isolates from cancer patients. J. Antimicrob. Chemother. **38:**265–269.
17. **Somner, E. A., and P. E. Reynolds.** 1990. Inhibition of peptidoglycan biosynthesis by ramoplanin. Antimicrob. Agents Chemother. **34:**413–419.
18. **Vollard, E. J., and H. A. Clasener.** 1994. Colonization resistance. Antimicrob. Agents Chemother. **38:**409–414.
19. **Wong, M. T., C. A. Kaufman, H. C. Stanford, P. Linden, G. Fort, H. J. Fuchs, S. B. Porter, R. P. Wenzel, and the Ramoplanin VRE2 Clinical Study Group.** 2001. Effective suppression of vancomycin-resistant *Enterococcus* species in asymptomatic gastrointestinal carriers by a novel glycolipodepsipeptide, ramoplanin. Clin. Infect. Dis. **33:**1476–1482.