

Single-Dose Oral Amoxicillin or Linezolid for Prophylaxis of Experimental Endocarditis Due to Vancomycin-Susceptible and Vancomycin-Resistant *Enterococcus faecalis*[∇]

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Endocarditis prophylaxis following genitourinary or gastrointestinal procedures targets *Enterococcus faecalis*. Prophylaxis recommendations advocate oral amoxicillin (2 g in the United States and 3 g in the United Kingdom) in moderate-risk patients and intravenous amoxicillin (2 g) or vancomycin (1 g) plus gentamicin in high-risk patients. While ampicillin-resistant (or amoxicillin-resistant) *E. faecalis* is still rare, there is a concern that these regimens might fail against vancomycin-resistant and/or aminoglycoside-resistant isolates. The present study tested oral linezolid as an alternative. Rats with catheter-induced aortic vegetations were given prophylaxis simulating human pharmacokinetics of oral amoxicillin (2- to 3-g single dose), oral linezolid (600 mg, single or multiple oral doses every 12 h), or intravenous vancomycin (1-g single dose). Rats were then inoculated with the minimum inoculum infecting 90% of the animals (90% infective dose [ID₉₀]) or with 10 times the ID₉₀ of the vancomycin-susceptible *E. faecalis* strain JH2-2 or the vancomycin-resistant (VanA phenotype) *E. faecalis* strain UCN41. Amoxicillin was also tested with two additional vancomycin-susceptible *E. faecalis* strains, 309 and 1209. Animals were sacrificed 3 days later. All the tested bacteria were susceptible to amoxicillin and gentamicin. Single-dose amoxicillin provided 100% protection against all four isolates at both the ID₉₀ and 10 times the ID₉₀. In contrast, linezolid required up to four consecutive doses to provide full protection against the vancomycin-resistant isolate. Vancomycin protected only against the vancomycin-susceptible strain. The high efficacy of single-dose oral amoxicillin suggests that this regimen could be used for prophylaxis in both moderate-risk and high-risk patients without additional aminoglycosides. Linezolid appears to be less reliable, at least against the vancomycin-resistant strain.

It is generally agreed that patients at risk for infective endocarditis should receive antibiotic prophylaxis during mediocutaneous procedures that might induce bacteremia (14, 15, 33, 43). In the case of dental or upper respiratory tract procedures, antibiotics are targeted at *Streptococcus* spp., which are the most common endocarditis pathogens entering the bloodstream under these conditions (28). In the case of urogenital or gastrointestinal procedures, antibiotics are targeted at *Enterococcus faecalis* bacteria, which are the most common enterococci responsible for endocarditis. Indeed, *E. faecalis* is significantly associated with a risk of endocarditis in the case of bacteremia (22) and represents ≥86% of all speciated enterococci associated with endocarditis (1, 22, 36).

Prophylactic regimens against *Enterococcus* spp. include amoxicillin or vancomycin mostly combined with an aminoglycoside such as gentamicin. Oral amoxicillin is recommended for patients at moderate risk for endocarditis. On the other hand, patients who are allergic to beta-lactams should receive parenteral vancomycin, and patients at high risk for endocarditis should receive parenteral amoxicillin or vancomycin combined with gentamicin. These regimens are cumbersome to

implement. Moreover, they are challenged by the growing fear that they might fail to protect against antibiotic-resistant enterococci, in particular enterococci resistant to aminoglycosides, which are frequent (10, 41), and enterococci resistant to glycopeptides (34). Enterococci resistant to ampicillin (or amoxicillin) are less of a problem because they are still rare in *E. faecalis* (37, 41).

Currently, linezolid is the sole molecule that could circumvent all of these resistance phenotypes and yet be administered orally with 100% bioavailability (32). Therefore, we tested the ability of oral linezolid to prevent experimental endocarditis in rats challenged with one vancomycin-susceptible and one vancomycin-resistant (VanA phenotype) isolate of *E. faecalis*. Prophylaxis with linezolid simulated in rats the kinetics produced in the sera of humans by an oral administration of 600 mg (9). Control rats received either no prophylaxis or prophylaxis simulating the kinetics in the sera of humans following the administration of 2 to 3 g of amoxicillin and 1 g of parenteral vancomycin, which are the prophylactic regimens recommended in the United States and Europe (14, 15, 33, 42). Two-gram and 3-g oral doses of amoxicillin produce quite comparable pharmacokinetic profiles in the sera of humans (13, 27, 42). Eventually, amoxicillin prophylaxis was also tested against endocarditis isolates of *E. faecalis* that were used in the original experiments of endocarditis prophylaxis performed in the 1980s.

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TABLE 1. MICs of various antibiotics for the vancomycin-susceptible and vancomycin-resistant *E. faecalis* strains used in experimental endocarditis

Antibiotic	MIC (mg/liter) for ^a :			
	Van ^s <i>E. faecalis</i> strain JH2-2	Van ^r <i>E. faecalis</i> strain UCN41	Van ^s <i>E. faecalis</i> strain 309	Van ^s <i>E. faecalis</i> strain 1209
Amoxicillin	0.25	0.25	0.5	1
Linezolid	1	2	2	4
Vancomycin	1	>256	4	4
Teicoplanin	2	32	0.25	0.25
Gentamicin	2	1	64	16

^a Van^s, vancomycin susceptible; Van^r, vancomycin resistant.

MATERIALS AND METHODS

Microorganisms, antibiotics, and chemicals. The four *E. faecalis* isolates tested in animals are described in Table 1. The vancomycin-susceptible laboratory strain JH2-2 (30) and the vancomycin-resistant strain UCN41 (VanA phenotype) were used with all the drugs tested. In addition, two vancomycin-susceptible isolates (strains 309 and 1209) (25) were used in supplementary prophylaxis experiments with amoxicillin alone. Unless otherwise stated, bacteria were grown at 35°C either in brain heart infusion (Difco Laboratories, Detroit, MI) without aeration or on Columbia agar plates (Becton Dickinson, Cockeysville, MD) supplemented with 3% blood. Stocks of the culture were kept at -70°C in brain heart infusion supplemented with 10% (vol/vol) glycerol.

Amoxicillin was purchased from GlaxoSmithKline (Münchenbuchsee, Switzerland), linezolid was purchased from Pfizer (Zürich, Switzerland), and vancomycin was purchased from Eli Lilly (Vernier/Genève, Switzerland). All other chemicals were commercially available reagent-grade products.

In vitro susceptibility studies. The MICs of the tested drugs were determined by the broth microdilution method according to CLSI (formerly NCCLS) methods and criteria (35). MICs were defined as the lowest concentration of antibiotic that completely inhibits visible growth after 24 h of incubation at 35°C.

Time-kill curves were determined by inoculating tubes containing 10 ml of prewarmed medium with 10⁶ CFU/ml (final concentration) from an overnight culture of bacteria. Immediately after inoculation, antibiotics were added to the tubes at final concentrations approximating the peak and trough levels of the drugs in human sera (see Results). Samples were removed from the tubes just before and at various times after antibiotic addition, serially diluted, and plated onto blood agar for colony counts. Antibiotic carryover was minimized both by appropriate sample dilution for all the drugs and by supplementation of the plates with 2,000 U/ml penicillinase (Bacto-Penase concentrate; Difco Laboratories, Detroit, MI) for amoxicillin. Each time-kill experiment was performed on at least two independent occasions.

Production of sterile aortic vegetations and infusion pump installation. All animal experiments were carried out according to Swiss federal and cantonal regulations. Sterile aortic vegetations were produced in female Wistar rats (180 to 200 g) by the insertion of a polyethylene catheter via the right carotid artery, as previously described (29). In addition, a permanent intravenous (i.v.) line was placed in the superior vena cava to infuse the antibiotics (24). The distal portion of the catheter was connected to a programmable delivery pump (pump 44; Harvard Apparatus, South Natick, MA) as described previously (24).

Antibiotic prophylaxis and bacterial challenge. Twenty-four hours after catheterization, groups of 10 rats were given antibiotic prophylaxis with amoxicillin, linezolid, or vancomycin. Antibiotics were delivered at changing flow rates, using the delivery pump described above, in order to mimic in the animals the human serum kinetics produced by a single oral dose of 2 to 3 g of amoxicillin (24, 27, 42), a single or multiple consecutive oral doses (every 12 h) of 600 mg of linezolid (9), or a single i.v. dose of 1 g of vancomycin (6). Control rats were given i.v. saline.

Rats were inoculated at the time corresponding to the peak antibiotic concentration in the serum. They were challenged i.v. with the minimal size of bacterial inoculum producing endocarditis in 90% of untreated control rats (90% infective dose [ID₉₀]). A 10-times-greater inoculum (10 times the ID₉₀) was used in certain experiments.

Antibiotic concentrations in the serum. Drug concentrations in the serum were determined for groups of three to five animals by an agar diffusion bioassay using *Bacillus subtilis* ATCC 6633 as the indicator organism for amoxicillin and

vancomycin and *Staphylococcus aureus* ATCC 29213 as the indicator organism for linezolid. The limits of detection (in mg/liter) were 0.39 for amoxicillin, 3.12 for linezolid, and 1.76 for vancomycin. Standard curves were linear ($r < 0.995$), and intraplate and interplate variations were consistently <10%.

Evaluation of infection. Control rats were sacrificed 48 h after inoculation and treated rats 72 h after the end of prophylaxis, when no antibiotic was detected in the blood anymore. The cardiac vegetations were sterilely removed, homogenized, serially diluted, and plated on blood agar. The detection limit of the dilution technique was $\geq 2 \log_{10}$ CFU/g of vegetation. Valve lesions were considered sterile when no bacteria grew on the plates.

Statistical evaluation. Fisher's exact test was used to compare the incidences of valve infection. The mean peak and trough serum values of different linezolid regimens were compared by one-way analysis of variance. *P* values were corrected by Bonferroni's correction for multiple-group comparisons. Statistical significance was considered at a *P* value of ≤ 0.05 .

RESULTS

Antibiotic susceptibility and time-kill curves. Table 1 shows the MICs of various antibiotics for the four tested organisms. They were all susceptible to amoxicillin, as are the majority

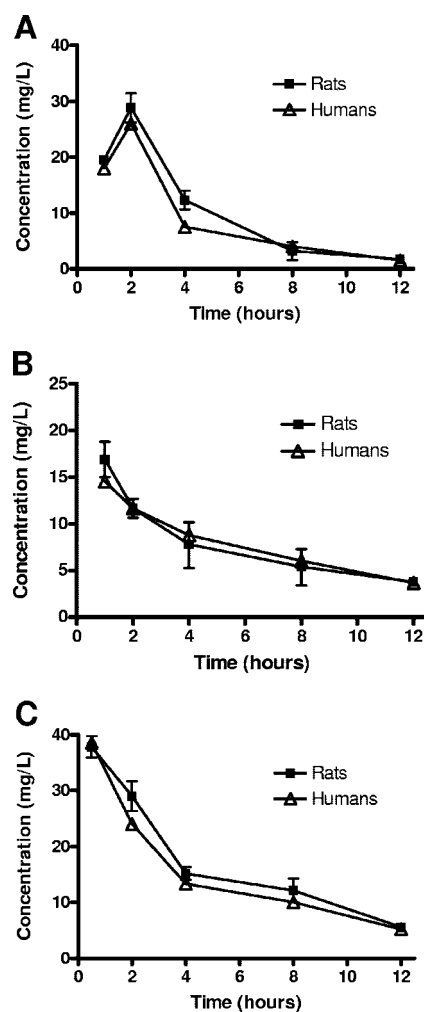


FIG. 1. Simulation, in the sera of rats, of the kinetics in the sera of humans following the administration of either a single oral dose of 2 to 3 g of amoxicillin (A), a single oral dose of 600 mg of linezolid (B), or a single intravenous dose of 1 g of vancomycin (C). Each data point on the curve represents the mean \pm standard deviation of three to seven determinations for individual animals.

TABLE 2. Pharmacokinetic parameters and activities of amoxicillin, linezolid, and vancomycin in the prophylaxis of experimental endocarditis due to vancomycin-susceptible and vancomycin-resistant *E. faecalis* strains^a

Prophylactic regimen ^b	C _{max} (mg/liter)	T _{max} (h)	C _{min} (mg/liter)	T/MIC (h)	No. of infected rats/total no. of rats			
					Van ^s <i>E. faecalis</i> strain JH2-2 inoculated with ID ₉₀		Van ^r <i>E. faecalis</i> strain UCN41 inoculated with:	
					ID ₉₀	10 × ID ₉₀	ID ₉₀	10 × ID ₉₀
None					9/9		10/10	12/12
AMX	29.4 ± 6.59	2	0.52 ± 0.08	12	0/10 ^d		0/10 ^{d,e}	0/9 ^{d,e,f}
LNZ-1	17.5 ± 5.13	1	3.81 ± 0.61	12	2/9 ^d		8/11	9/9
LNZ-2	18.6 ± 4.47	1	4.57 ± 1.10	24	ND		4/10 ^d	7/9
LNZ-4	19.3 ± 5.34	1	5.93 ± 1.69	48	ND		0/12 ^d	3/11 ^d
VAN	37.8 ± 3.29	0.5	5.57 ± 0.56	12 ^c	0/9 ^d		3/3	ND

^a C_{max}, peak concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; C_{min}, trough concentration of drug in serum; T/MIC, time above MIC; ND, not determined; Van^s, vancomycin susceptible; Van^r, vancomycin resistant. Values represent means ± standard deviations.

^b AMX, human simulation of a single oral dose of 2 to 3 g amoxicillin; LNZ-1, human simulation of a single oral dose of 600 mg linezolid; LNZ-2, human simulation of two consecutive oral doses of 600 mg linezolid every 12 h; LNZ-4, human simulation of four consecutive oral doses of 600 mg linezolid every 12 h; VAN, human simulation of a single i.v. dose of 1 g vancomycin.

^c Time above the MIC for the susceptible strain.

^d P < 0.05 versus no treatment.

^e P < 0.05 versus treatment with LNZ-1.

^f P < 0.05 versus treatment with LNZ-2.

(>95%) (37, 42) of clinical isolates of *E. faecalis*, as well as linezolid and gentamicin. Strain UCN41 was resistant to vancomycin and teicoplanin, as expected.

The rates of killing were determined with antibiotic concentrations approaching peak and trough levels in the serum, i.e., 20 mg/liter and 1 mg/liter for amoxicillin, 20 mg/liter and 4 mg/liter for linezolid, and 40 mg/liter and 5 mg/liter for vancomycin, respectively. No concentration-dependent killing was observed with any of the drugs. Amoxicillin produced some killing activity (1.8- to 2.3-log₁₀ CFU/ml reduction in viable counts after 24 h of exposure). Linezolid was purely bacteriostatic against both isolates. Vancomycin induced a loss of 1 log₁₀ CFU/ml against the vancomycin-susceptible isolate and failed against the resistant one.

Antibiotic concentrations in the serum and results of prophylaxis. Figure 1 depicts the simulation of the human pharmacokinetics of a 2- to 3-g single dose of amoxicillin, 600 mg of oral linezolid, and a 1-g i.v. dose of vancomycin in rats. Simulations of the human pharmacokinetics of any of the drugs were as previously described (6, 9, 21, 24, 27, 42). For linezolid, repeating the doses every 12 h for up to four times tended to increase both peak and trough concentrations, but these fluctuations were not statistically significant (Table 2).

Table 2 also presents the results of prophylaxis against the vancomycin-susceptible and vancomycin-resistant isolates JH2-2 and UCN41. It can be seen that single-dose oral amoxicillin successfully prevented experimental endocarditis due to the two tested isolates. Moreover, amoxicillin prevented endocarditis both in rats inoculated with the ID₉₀ and in rats inoculated with 10 times the ID₉₀, as shown with the vancomycin-resistant isolate. In contrast, single-dose oral linezolid prevented valve infection only against the vancomycin-susceptible isolate JH2-2, whereas it failed against the resistant UCN41. At least two to four consecutive doses of linezolid were required to fully restore efficacy in rats challenged with the ID₉₀ or with 10 times the ID₉₀ of this strain. This underlines the potential failure of linezolid against *E. faecalis* isolates.

Finally, single-dose vancomycin successfully protected ani-

mals inoculated with the susceptible isolate JH2-2 but failed against the resistant isolate UCN41, as expected.

Prophylactic efficacy of amoxicillin against two additional *E. faecalis* organisms. Because single-dose amoxicillin prophylaxis was the sole regimen that was effective against the JH2-2 and UCN41 strains, we further studied its efficacy against two additional isolates, *E. faecalis* 309 and 1209, which were used in seminal experiments of endocarditis prophylaxis in the 1980s (25). Table 3 shows that single-dose amoxicillin prophylaxis protected rats challenged with both the ID₉₀ and 10 times the ID₉₀ of these two strains.

DISCUSSION

Simulating single-dose oral amoxicillin prophylaxis successfully prevented experimental endocarditis against the vancomycin-susceptible and vancomycin-resistant strains JH2-2 and UCN41 as well as against two more isolates used in earlier experiments of endocarditis prophylaxis (*E. faecalis* 309 and 1209) (25). In contrast, simulating oral linezolid required up to four consecutive doses to provide full protection against the vancomycin-resistant isolate, and vancomycin failed against this strain, as expected.

The good performance of amoxicillin against the four isolates probably results from the fact that we simulated the whole

TABLE 3. Activity of amoxicillin in the prophylaxis of experimental endocarditis due to either of two additional vancomycin-susceptible *E. faecalis* isolates

Prophylactic regimen	No. of infected rats/total no. of rats			
	<i>E. faecalis</i> 309 inoculated with:		<i>E. faecalis</i> 1209 inoculated with:	
	ID ₉₀	10 × ID ₉₀	ID ₉₀	10 × ID ₉₀
None	5/5	5/5	5/5	4/4
AMX ^a	0/10 ^b	0/9 ^b	1/9 ^b	0/10 ^b

^a AMX, human simulation of single oral dose of 2 to 3 g amoxicillin.

^b P < 0.005 versus no treatment.

human pharmacokinetics of the drug in animals and did not inject the drug in single bolus as in earlier studies (25). Those prior studies suggested that single-dose amoxicillin prophylaxis was poorly effective because it protected only rats challenged with the ID₉₀ (25). Therefore, combining amoxicillin with gentamicin provided a greater margin of safety. However, using single-bolus injections completely overlooked the fact that most drugs have a much shorter half-life in rodents than in humans. Thus, it underestimated the importance of the more prolonged presence of antibiotics in the sera of humans (2, 19, 25, 26). The critical importance of this aspect was demonstrated in further studies (5, 7, 8, 11, 23, 24, 40, 46). For instance, a single-bolus injection of amoxicillin, mimicking only the peak drug concentration produced during prophylaxis, afforded a marginal protection limited to the ID₉₀ of the infecting organism (24). In contrast, mimicking the entire human kinetics of amoxicillin prophylaxis extended successful protection to >100 times the ID₉₀ (24).

The present experiments simulated the entire human pharmacokinetics of the drugs in rats and confirmed the excellent performance of amoxicillin in rats when profiles of the drug in human serum were mimicked. Hence, single-dose oral amoxicillin might be suggested for prophylaxis against ampicillin-susceptible *E. faecalis* endocarditis in humans. This does not preclude the addition of aminoglycosides, as currently recommended for ampicillin-resistant strains and also as suggested for experiments with penicillin-resistant streptococci (31a).

In contrast, while single-dose linezolid prophylaxis protected against the vancomycin-susceptible strain JH2-2, as also observed against one enterococcal isolate in rabbits (4), it required up to four consecutive doses to protect against the vancomycin-resistant strain UCN41. This raises concerns about the systematic use of linezolid for the prophylaxis of enterococcal endocarditis. In the present experiments, linezolid was purely bacteriostatic in vitro, whereas amoxicillin did display some killing against both strains. Several studies indicate that bactericidal drugs are more effective than bacteriostatic compounds when administered for equivalent periods of time (20, 38). The times above MIC (12 h) for linezolid were not an issue because they were similar for both single-dose linezolid and single-dose amoxicillin (i.e., 12 h (Table 2)). Therefore, pure bacteriostasis might be one explanation for the limited efficacy of single-dose linezolid.

Nevertheless, more-subtle pharmacodynamic parameters cannot be excluded. The major parameter for linezolid efficacy was shown to be the ratio of the area under the concentration-time curve (AUC) to the MIC (AUC/MIC), both in animals and in humans (3, 12, 39). In the present experiments, the AUC/MIC ratio of single-dose linezolid was two times greater for strain JH2-2 (MIC, 1 mg/liter) than for strain UCN41 (MIC, 2 mg/liter). Thus, differences in AUC/MIC ratios could be important. Eventually, adjuvant host defense mechanisms could also play a role. These include platelet-microbicidal proteins (PMPs), which may promote the eradication of susceptible streptococci and staphylococci from cardiac vegetations (16, 18, 31, 45, 49) and were shown to synergize with antibiotics in experimental endocarditis therapy (17, 48). A hypothetical greater PMP susceptibility of strain JH2-2 over that of strain UCN41 could be additional speculation for the differential successes and failures of single-dose linezolid against the two

strains. However, the susceptibility of the strains to PMPs was not tested.

Since prophylaxis with linezolid was suboptimal, the question arises as to whether amoxicillin and vancomycin are still suitable in a world of growing antibiotic resistance. Epidemiologic surveillances indicate that they still are. Indeed, resistances to ampicillin and glycopeptides are not reported primarily for *E. faecalis*, which is the most frequent *Enterococcus* sp. responsible for endocarditis, but rather for *Enterococcus faecium*, which is a very rare cause of endocarditis (1, 22, 36). In one nationwide study in the United Kingdom, the frequency of ampicillin resistance was 0.3% in *E. faecalis* versus 85% in *E. faecium* (41). Likewise, in two nationwide studies in the United Kingdom and the United States, the frequency of vancomycin resistance was 10 to 30 times lower in *E. faecalis* than in *E. faecium* (41, 47). Moreover, the risk of endocarditis due to vancomycin-resistant enterococci is still very low, as only 12 cases, which were all of nosocomial origin, have been described so far (44). Since the large majority of patients at risk for endocarditis reside outside the hospital, these patients will still benefit from prophylaxis with amoxicillin or vancomycin.

In summary, three practical conclusions can be drawn from these observations. First, single-dose oral amoxicillin and vancomycin can still be recommended for the prophylaxis of enterococcal endocarditis in the large majority of situations, including for high-risk patients. Indeed, amoxicillin protected rats challenged with >10-times-greater inocula than in previous studies, which used a single-bolus injection(s) (4, 25), contributing to the current recommendations (including the use of drug combinations with aminoglycosides). Second, amoxicillin without gentamicin addition was highly protective against susceptible enterococci. This also appeared to be true for vancomycin. Thus, one might consider abandoning the systematic use of aminoglycosides in the prophylaxis recommendations. Third, single-dose oral linezolid was not reliable for the prophylaxis of enterococcal endocarditis in these experiments because it provided a limited window of activity.

The rationale for antibiotic prophylaxis of endocarditis is not evidence based and thus tends to be debated. The present results provide an experimental ground for downscaling and simplifying current recommendations by proposing single-dose oral amoxicillin for the prophylaxis of *E. faecalis* endocarditis, as proposed for endocarditis due to oral streptococci.

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