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Antibiotics and Prevention of Microbial Colonization of Catheters

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Slime-producing staphylococci frequently colonize catheters, and when they are embedded in biofilm, they become resistant to various antibiotics. In the study that is described, the comparative efficacies of vancomycin, clindamycin, novobiocin, and minocycline, alone or in combination with rifampin, were tested in an in vitro model of colonization. The model consisted of the modified Robbins device with antibiotic-impregnated cement filling the lumen of catheter segments. The synergistic combination of minocycline and rifampin was the most efficacious in preventing bacterial colonization of slime-producing strains of *Staphylococcus epidermidis* and *Staphylococcus aureus* to catheter surfaces. A similar trend was observed when the inhibitory activities of polyurethane catheters coated with minocycline and rifampin were compared with the inhibitory activities of catheters coated with other antimicrobial agents. The inhibitory activities of catheters coated with minocycline and rifampin against *S. epidermidis*, *S. aureus*, and *Enterococcus faecalis* strains, for example, were significantly better than those of catheters coated with vancomycin ($P < 0.05$). The inhibitory activities of catheters coated with minocycline and rifampin against gram-negative bacilli and *Candida albicans* were comparable to those of catheters coated with ceftazidime and amphotericin B, respectively. We found that the combination of minocycline and rifampin is unique and highly effective in preventing the colonization of catheters with slime-producing staphylococci and that it also displays a broad-spectrum inhibitory activity against gram-negative bacteria and yeast cells.

Catheters are one of the leading causes of nosocomial infections and primary septicemia (16). Catheter-related infections are most commonly caused by coagulase-positive and coagulase-negative staphylococci, particularly slime-producing strains (1, 2). Because methicillin resistance is very prevalent among *Staphylococcus epidermidis* organisms and is increasing in frequency among *Staphylococcus aureus* strains, vancomycin remains the frontline intravenous antibiotic for the treatment of catheter-related bacteremia (12).

In developing anti-infective catheters coated with antibiotics, one must avoid such potential limitations as the inhibition of antimicrobial activity by the slime material, the emergence of drug resistance, and superinfection by *Candida* species. In an in vitro susceptibility study of 197 catheter-related staphylococcal isolates collected between 1983 and 1993 at The University of Texas M. D. Anderson Cancer Center, minocycline, novobiocin, and rifampin were shown to have antimicrobial activities equivalent to those of vancomycin and other glycopeptide antibiotics (21). In the current study, we compared the efficacies of vancomycin, clindamycin, minocycline, novobiocin, and rifampin when used alone and in combination for preventing the microbial colonization of catheters. In addition, catheters coated with either amphotericin B, vancomycin, ceftazidime, or minocycline and rifampin were tested to determine their inhibitory activities against *Candida* species, gram-positive bacteria, and gram-negative bacteria.

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MATERIALS AND METHODS

Organisms. Slime-producing strains of *S. epidermidis* and *S. aureus* isolated from the blood of patients with catheter-related bacteremia were selected. Slime production was determined as described by Christensen et al. (1, 2). The organisms were grown in Trypticase soy broth (TSB) with 0.3% yeast extract (Difco Laboratories, Detroit, Mich.), preserved in 2-ml aliquots with 15% glycerol, and stored at −70°C. Before each experiment, one aliquot was thawed at 37°C. A few colonies were again grown in TSB, and the bacterial concentrations of the suspension were standardized by using a spectrophotometer set at 600 nm (Bausch & Lomb Spectronic 20; Milton Roy Company, Analytical Products Division Rochester, N.Y.). The inoculum size was confirmed by viable counts through serial dilution cultures.

Antibiotic-impregnated methacrylic acid. One gram of methacrylic acid (cement) was dissolved in 0.5 ml of sterile water that contained no antibiotics (negative control) or one of the following: 60 mg of minocycline (Lederle Laboratories, American Cyanamid Co., Pearl River, N.Y.), 60 mg of vancomycin (Lymphomed Inc., Rosemont, Ill.), 60 mg of novobiocin (Upjohn Laboratories, The Upjohn Co., Kalamazoo, Mich.), 60 mg of clindamycin (Upjohn Laboratories), 30 mg of rifampin (Marion Merrell Dow, Inc., Kansas City, Mo.); 30 mg of rifampin and 60 mg of minocycline, 30 mg of rifampin and 60 mg of vancomycin, or 30 mg of rifampin and 60 mg of novobiocin. The resulting methacrylic acid gel alone or in combination with antibiotics was then used to fill the lumen of the 1-cm catheter segments that were assembled in a modified Robbins device (MRD) as described below. The use of antibiotics in combination with cement is based on the principle that the antibiotic will be released gradually from the cement (28). The antibiotic released from the cement in the lumen of the catheter will coat the catheter surface exposed to the contaminated infusate.

In vitro model of colonization. An MRD was used to study the colonization of silicone catheter segments with *S. epidermidis* or *S. aureus* in the presence or absence of antibiotics (9, 13). Unlike traditional testing methods that study free-floating planktonic bacteria, the MRD allows the quantitation of bacteria that are sessile and adherent to catheter surfaces. The device is constructed of an acrylic block (42 cm long) with a lumen (2 by 10 mm). Twenty-five evenly spaced sampling ports were used. Equal-size catheter segments (1 cm in length) from a urinary silicone catheter (Baxter Healthcare Corp., Valencia, Calif.) were attached to the sampling ports in such a way that the cross-sectional pores of the catheter segment (0.3 cm^2), including the lumen, lay flush with the inner surface and were exposed to the flow without disturbing flow characteristics. After placing the catheter segments in the sampling ports, the entire apparatus was sterilized with ethylene oxide gas. The lumens of the catheter segments were then

filled with 35 mg of sterile methacrylic acid gel (Howmedica, Inc., Rutherford, N.J.), alone or mixed with antibiotics. The MRD was connected to an intravenous administration set (Imed Corp., San Diego, Calif.) which was connected to a 1-liter bag of 5% glucose in water (D_5W). The D_5W bag was inoculated with either *S. epidermidis* or *S. aureus* to produce a bacterial suspension of 10^3 to 10^5 CFU/ml. The contaminated infusate of D_5W was circulated from the bag through the intravenous tubing into the MRD by a peristaltic pump (Imed Corp.) that was set to deliver the infusate at a flow rate of 60 ml/h for 2 h.

At the end of 2 h of flow, 2-ml aliquots of the contaminated infusate were obtained from the MRD for colony counts. In addition, catheter segments containing methacrylic acid with and without antibiotics were removed in duplicate. The methacrylic acid was removed from the lumen, and the catheter surface (0.3 cm^2 per segment) of the cut end of the catheter segment was cultured by dragging it back and forth four times across a blood agar plate in a manner comparable to the semiquantitative technique previously described by Maki et al. (17). An equal number of catheter segments without antibiotics (controls) and with antibiotics were left in place. The contaminated D_5W bag was removed and replaced with a 1-liter bag of sterile normal saline. To remove free-floating nonadherent organisms from the surface of the catheter segments, the saline solution was flushed through the MRD for 4 h at 40 ml/h, after which the remaining sampling ports were removed. The flushed catheter segments were then detached, and the methacrylic acid cement was removed from the lumen. The cut ends of the catheter segments were cultured semiquantitatively as described above.

Coating catheters with antibiotics. Polyurethane triple-lumen central venous catheters (20 cm long and 13 gauge) that had been pretreated with the cationic surfactant tridodecylmethylammonium chloride to enable subsequent bonding of anionic antibiotics were obtained (Bio-Guard AB Coating; Cook Inc., Bloomington, Ind.). These catheters were used as such as controls or were coated with antimicrobial agents. The following solutions of antimicrobial agents were prepared: (i) vancomycin (Eli Lilly and Co.), 60 mg/ml of sterile water; (ii) ceftazidime (Eli Lilly & Co.), 60 mg/ml of sterile water; (iii) amphotericin B, 60 mg/ml of sterile water; and (iv) a combination of minocycline (Lederle Laboratories, Pearl River, N.Y.), 60 mg/ml of sterile water, and rifampin (Ciba-Geigy Pharmaceutical Div., Summit, N.J.), 30 mg/ml of sterile water. Bio-Guard catheters were dipped in one of the four solutions for 15 min and were then removed and allowed to dry overnight.

Modified Kirby-Bauer technique. The antimicrobial activities of the antibiotic-packed catheter segments (packed with cement) and antibiotic-coated catheter segments were assessed in vitro by the modified Kirby-Bauer technique described previously by Sherertz et al. (25, 26). Four strains of each of *S. epidermidis*, *S. aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter calcoaceticus*, and *Candida albicans* that had been cultured from the blood of patients with septicemia were grown for 18 h in TSB. The broth inoculum was diluted to 10^6 CFU/ml in phosphate-buffered saline, and a swab that was placed in this suspension was rubbed across the surface of a TSB agar plate.

Two-centimeter segments of polyurethane antibiotic-coated Bio-Guard catheters were tested in quadruplicate. The polyurethane segments coated with vancomycin or with the combination of minocycline and rifampin were pressed into agar plates overlaid with *S. epidermidis*, *S. aureus*, or *E. faecalis* strains. Segments coated with ceftazidime or with the combination of minocycline and rifampin were pressed into agar plates overlaid with *P. aeruginosa*, *S. maltophilia*, or *Acinetobacter baumanii* strains. The segments coated with amphotericin B or with the combination of minocycline and rifampin were pressed into agar overlaid with *C. albicans*. All agar plates were incubated for 24 h at 37°C. Zones of inhibition were determined by measuring the diameter perpendicular to the long axis of the catheter as described by Sherertz et al. (25, 26).

The antibiotic-packed catheter segments containing cement impregnated with vancomycin, vancomycin plus rifampin, or minocycline plus rifampin were tested as follows. The catheter segments were unpacked, and the empty catheter segments and cement pieces were then independently tested in triplicate against *S. epidermidis* and *S. aureus* by the modified Kirby-Bauer technique outlined above. The unpacked catheter segments and cement pieces were transferred every day to a new plate until no zones of inhibition could be demonstrated.

Statistics. The significance of differences between the frequencies of categorical variables was determined by the chi-square test or the Fisher exact test. Continuous variables with normal distributions were compared by Student's *t*-test. Continuous variables that were not normally distributed were compared by the Mann-Whitney rank sum test.

RESULTS

MRD. Experiments were conducted to compare the efficacy of minocycline-rifampin with that of vancomycin alone or vancomycin-rifampin exposed to a contaminated infusate consisting of 10^3 CFU of *S. epidermidis* or *S. aureus* per ml of suspension. Catheter segments packed with cement were tested in duplicate. Vancomycin alone failed to prevent the colonization with *S. epidermidis* before flushing and decreased the concentration of colonized bacteria by only 25% after flushing. Vancomycin reduced the level of colonization of *S. aureus* by 28% before flushing and 32% after flushing. Although the addition of rifampin to vancomycin resulted in a 42 to 81% reduction of *S. epidermidis* and *S. aureus* colonization before and after flushing, the combination of vancomycin and rifampin was not synergistic (it did not achieve a >10-fold reduction in the number of colonies). The combination of minocycline and rifampin, on the other hand, led to the total prevention of colonization by staphylococci and was more effective than the combination of vancomycin and rifampin.

TABLE 1. Relative efficacies of antibiotics in preventing colonization of catheters with *S. epidermidis*

Antibiotic packed	Mean ± SD CFU/0.3 cm^2 of catheter surface	
	Before flush	After flush
None (control)	441 ± 61	107 ± 23
Novobiocin	174 ± 16	154 ± 25
Vancomycin	210 ± 36	63 ± 20
Clindamycin	122 ± 10	14 ± 2
Rifampin	15 ± 6	19 ± 4
Minocycline	48 ± 21	15 ± 4
Vancomycin + rifampin	67 ± 6	4 ± 2
Clindamycin + rifampin	28 ± 6	15 ± 6
Novobiocin + rifampin	5 ± 3	0
Minocycline + rifampin	0	0

Further experiments were conducted with the same MRD model to simultaneously compare the efficacies of vancomycin, clindamycin, minocycline, and novobiocin, alone and in combination with rifampin that had been mixed with methacrylic acid, in preventing *S. epidermidis* colonization. Two catheter segments contained methacrylic acid mixed with each of these antibiotics or antibiotic combinations. The mean volumes of CFU cultured from the 0.3-cm^2 segment are given in Table 1. The combinations of rifampin with novobiocin and rifampin with minocycline were more effective in preventing the colonization of catheter surfaces with *S. epidermidis* than any other antibiotic or antibiotic combination tested.

Modified Kirby-Bauer technique. Bio-Guard catheters coated with the combination of minocycline and rifampin were significantly more active ($P < 0.05$ by the Mann-Whitney test) against *S. epidermidis*, *S. aureus*, and *E. faecalis* than vancomycin, which is the therapeutic drug of choice for treating infections caused by these organisms (Fig. 1). These results are consistent with previous data obtained with the MRD model (Table 1). In addition, the efficacy of this combination of antibiotics was comparable to that of ceftazidime against *S. maltophilia* or *P. aeruginosa* (Fig. 2). Unexpectedly, this combination had an in vitro antimicrobial activity against *C. albicans* that was comparable to that of amphotericin B (Fig. 2).

The antibiotic-impregnated cement maintained zones of inhibition with a diameter of >10 mm for at least 5 days, irrespective of the antibiotic or combination used. The diameters of the zones produced by cement impregnated with minocycline-rifampin were 37.3 ± 0.9 mm, compared with diameters of 27.7 ± 0.5 mm for cement impregnated with vancomycin-rifampin and 18.8 mm for cement impregnated with vancomycin. The unpacked catheter segments (from which antibiotic-impregnated cement had been removed) maintained zones of inhibition for at least 2 days. Those were 33.3 ± 2.0 mm for catheter segments previously packed with minocycline-rifampin, 27.6 ± 0.9 mm for those previously packed with van-

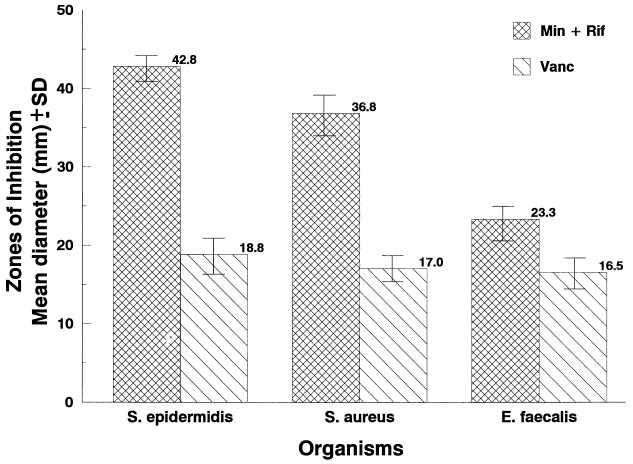

FIG. 1. Zones of inhibition of catheters coated with either minocycline and rifampin (Min + Rif) or vancomycin (Vanc) against four bacteremic isolates of each of the following organisms: *S. epidermidis*, *S. aureus*, and *E. faecalis*. The zones of inhibition produced by the combination of minocycline and rifampin were significantly larger than those produced by vancomycin ($P < 0.05$) for all three types of organisms.

comycin-rifampin, and 16.3 ± 0.5 mm for those previously packed with vancomycin alone.

DISCUSSION

Recent reports have indicated that biofilm-embedded organisms adherent to catheter surfaces become resistant to various antimicrobial agents that are effective against these same organisms when they exist as dispersed free-floating cells (6, 9, 10). On the basis of these findings, the antimicrobial activities of various agents in preventing the colonization of catheter surfaces is better tested by using an in vitro model of catheter colonization, such as the MRD model, rather than an in vitro susceptibility model of dispersed organisms, such as the microtiter broth dilution method (9, 13).

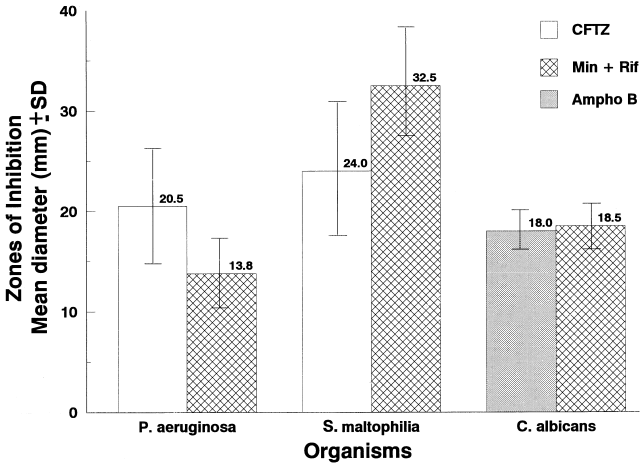

FIG. 2. Zones of inhibition of catheters coated with either ceftazidime (CFTZ), minocycline-rifampin (Min + Rif), or amphotericin B (Ampho B) against four of each of the following isolates that cause septicemia: *P. aeruginosa*, *S. maltophilia*, and *C. albicans*. The zones of inhibition produced by the combination of minocycline plus rifampin were comparable to those produced by ceftazidime against gram-negative bacilli and comparable to those produced by amphotericin B against *C. albicans* ($P > 0.1$).

By using an established in vitro model of colonization, rifampin in combination with minocycline was shown to act synergistically to completely prevent the colonization of slime-producing *S. epidermidis* and *S. aureus* on catheter surfaces (Table 1). This combination was generally superior to all other rifampin-containing combinations such as rifampin plus vancomycin, rifampin plus clindamycin, and rifampin plus novobiocin. Only after flushing was the efficacy of rifampin plus novobiocin in preventing staphylococcal colonization on catheter surfaces comparable to that of rifampin plus minocycline (Table 1). Vancomycin alone was relatively inferior in preventing colonization of *S. epidermidis* and *S. aureus*, and the addition of rifampin resulted in a marked improvement in efficacy (Table 1). These findings agree with those presented in a report by Farber and colleagues (10), who demonstrated that slime extract obtained from *S. epidermidis* inhibits glycopeptide antibiotics but does not affect the antimicrobial activity of rifampin. In our study, clindamycin was one of the most effective single agents in preventing colonization after flushing, but it was not very effective in preventing the colonization of planktonic bacteria before flushing (Table 1). Khardori and colleagues (13), who used the same in vitro model of colonization, reported similar findings with subinhibitory concentrations of clindamycin.

Minocycline and rifampin had both been reported to have excellent in vitro activity by microtiter susceptibility test methods against methicillin-resistant *S. epidermidis* and *S. aureus* (15, 19, 31, 32). The activity of the combination of minocycline and rifampin has occasionally been shown to be synergistic (24, 30) but never antagonistic. In a recent susceptibility study of 197 methicillin-resistant and methicillin-susceptible *S. epidermidis* and *S. aureus* bacteremic isolates from the M. D. Anderson Cancer Center, the MICs of minocycline, rifampin, and ciprofloxacin at which 90% of strains are inhibited were 1.0, 0.5, and 32.0 μg/ml, respectively (7). Such a high MIC of ciprofloxacin at which 90% of strains are inhibited deterred us from using quinolones, even though recent reports have indicated that such agents have unique activities against bacteria adherent to foreign bodies (32). Time-kill kinetic studies with 48 randomly selected isolates failed to show any antagonism between rifampin and minocycline (7). Data from the present study also suggest that the antimicrobial activity of minocycline-rifampin against dispersed organisms is preserved against slime-producing organisms that adhere to catheter surfaces.

Results from the MRD model encouraged us to coat catheters with the combination of minocycline and rifampin in order to compare the activity of this combination with those of selected antimicrobial agents that have been shown to be effective clinically in the treatment of infections caused by gram-positive bacteria (vancomycin), gram-negative bacilli (ceftazidime), and yeasts (amphotericin B). Using a rabbit model, Sherertz et al. (26) have shown that coated catheters with zone sizes of ≥15 mm were highly predictive of in vivo efficacy, whereby colonization of the indwelling catheter is prevented. Catheters coated with minocycline and rifampin demonstrated high levels (zone sizes, ≥20 mm) of inhibitory activity against gram-positive cocci. This activity was significantly better than that of vancomycin (Fig. 1). The inhibitory activity of vancomycin against the gram-negative bacilli tested was not significantly different from that of ceftazidime, and in most cases, the zone sizes were >15 mm. The inhibitory activity of vancomycin against *C. albicans* was comparable to that of amphotericin B, and in all cases the zone sizes were >15 mm. The broad-spectrum inhibitory activity of the combination of minocycline and rifampin, especially against *C. albicans*, adds to the potential role of this combination in coating catheters because *C.*

albicans is emerging as one of the organisms commonly associated with catheter-related infections (8, 14, 22). When high drug concentrations were tested, minocycline and rifampin were independently reported to have in vitro activity against *C. albicans* (11, 29). Another advantage favoring the use of the combination of minocycline and rifampin as a prophylactic regimen for coating catheters is that, unlike the glycopeptides, penicillins, cephalosporins, aminoglycosides, quinolones, azoles, and amphotericin B, these two antibiotics are not used as primary therapeutic agents in the treatment of bloodstream infections.

The clinical relevance and applicability of the two in vitro models (MRD with antibiotic-packed catheter segments and the modified Kirby-Bauer technique with coated catheters) have recently been demonstrated. In a recent prospective randomized clinical trial involving 234 patients, central venous catheters coated with minocycline and rifampin were demonstrated to be highly efficacious in significantly reducing the rate of catheter colonization and preventing catheter-related bacteremia (4, 21).

Coating of catheters with antibiotics rather than antiseptic agents such as chlorhexidine raises concern about the potential emergence of antibiotic-resistant strains. The frequency of developing rifampin resistance is about 10^{-6} to 10^{-8} (18, 23). Unlike heavily contaminated areas such as the gastrointestinal tract, catheters are rarely heavily colonized or exposed to high-grade bacteremia (27). In vitro (24, 30) and in vivo (3, 5) studies have demonstrated that minocycline protects against the emergence of staphylococcal strains that are resistant to rifampin. In addition, neither rifampin nor minocycline was found to be associated with cross-resistance to other beta-lactam or glycopeptide antibiotics (7). In a recent prospective randomized clinical study involving catheters coated with minocycline and rifampin in which catheters and samples from skin insertion sites were cultured, no organisms resistant to minocycline and rifampin were isolated (21).

In summary, the combination of minocycline and rifampin was highly effective in preventing the colonization of catheter surfaces by slime-producing *S. epidermidis* and *S. aureus* isolates and displayed broad-spectrum inhibitory activity against gram-positive cocci, gram-negative bacilli, and *C. albicans* organisms. On the basis of these findings, this antibiotic combination should be considered as an alternative prophylactic antimicrobial regimen for the coating of indwelling vascular catheters.

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