Comparison of Fluconazole and Amphotericin B for Prevention and Treatment of Experimental Candida Endocarditis

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Fluconazole and amphotericin B were compared in the prophylaxis and treatment of Candida albicans aortic endocarditis in a rabbit model. In the prophylaxis study, catheterized rabbits received, prior to intravenous (i.v.) challenge with C. albicans (2 × 106 blastospores), either no therapy, single-dose i.v. amphotericin B (1 mg/kg of body weight), single-dose fluconazole (50 mg/kg or 100 mg/kg i.v. or intraperitoneally [i.p.]), or fluconazole (50 mg/kg or 100 mg/kg i.v. or i.p.) with a second dose 24 h after inoculation. A single dose of amphotericin B was significantly more effective than either the one- or two-dose regimens of fluconazole at both 50 mg/kg (P < 0.001 and P < 0.03, respectively) and 100 mg/kg (P < 0.01 and P < 0.001, respectively) in the prevention of Candida endocarditis. In parallel treatment studies of established C. albicans endocarditis, i.v. amphotericin B (1 mg/kg) or i.p. fluconazole (50 mg/kg) was begun 24 or 60 h postinfection and continued daily for 9 or 12 days. At these dose regimens, amphotericin B was consistently more effective than fluconazole in reducing fungal vegetation densities, regardless of the timing of initiation of therapy. We also examined the efficacy of fluconazole at a daily dose of 100 mg/kg i.p. administered for 21 days in the treatment of established C. albicans endocarditis. When therapy was continued for 2 weeks or longer, fluconazole was more effective than no drug and approximately twice as effective as 12 days of amphotericin B in reducing intravascular fungal densities. Our results suggest that amphotericin B is superior to fluconazole in both the prophylaxis and treatment of C. albicans endocarditis in the rabbit model. These findings may relate to the predominantly fungistatic activity of fluconazole against C. albicans in vitro.

Once considered rare, endocardial infection with Candida albicans is being reported with increasing frequency, usually in the setting of open-heart surgery or intravenous (i.v.) drug abuse or in patients undergoing long-term i.v. therapy with antibiotics or hyperalimentation (7, 10, 13, 15, 18). Even with early diagnosis, Candida endocarditis is difficult to eradicate with antifungal therapy alone, and valve replacement remains a requirement for cure in most patients (2, 15). While amphotericin B and flucytosine are synergistic in vitro against many strains of Candida and the combination has been successful in some patients without concomitant valve replacement (13), these agents are associated with significant nephrotoxicity and bone marrow suppression when used in combination (6, 19). The toxicities associated with amphotericin B and flucytosine not only render their use problematic in the therapy of documented infection but also preclude their use as antifungal agents in the prophylaxis of patients at risk for Candida endocarditis. In contrast, fluconazole, a new antifungal bis-triazole, has limited toxicity and a favorable pharmacokinetic profile, attaining high concentrations in a wide variety of tissues (14). Fluconazole is currently approved for the treatment of a number of fungal infections, including Candida peritonitis, pyelonephritis, and mucositis. Clinical trials to determine the efficacy of fluconazole in patients with hematogenously disseminated Candida infections are in progress.

Despite its increasing incidence, the relative infrequency of Candida endocarditis makes prospective human studies of fluconazole in the treatment of this infection difficult. For this reason, animal models are being used to compare the efficacy of fluconazole with the efficacies of established antifungal agents. Because of the high concentration of organisms within valvular lesions (3), the rabbit model of fungal endocarditis provides a rigorous test of the prophylactic and therapeutic efficacies of antifungal agents.

The present study was undertaken to compare the efficacy of amphotericin B with that of fluconazole in the prevention and treatment of C. albicans endocarditis in a rabbit model and to determine whether dosage, timing, and duration of therapy were important variables in determining outcome. (This study was presented in part at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 21 to 24 October 1990 [20].)

MATERIALS AND METHODS

Organisms. Single suspensions of C. albicans ATCC 36082 blastospores were prepared as previously described (12). Organisms used in the studies were obtained from stocks maintained at 4°C on agar slants (yeast extract; Difco Laboratories, Detroit, Mich.). Prior to use, organisms were inoculated into yeast nitrogen base broth (Difco) containing 1% dextrose and 0.15% L-asparagine (Calbiochem, San Diego, Calif.) and were grown overnight on a rotating drum at 25°C. Organisms from the 18-h broth culture were inoculated into fresh yeast nitrogen broth and incubated overnight. These stationary-phase organisms were then sonicated (model 350; Branson Sonic Power, Danbury, Conn.) for 3 s, pelleted and washed twice, and then resuspended in 0.85% NaCl. After a second sonication, organisms were diluted and counted with a hemocytometer. Confirmation of infecting inoculum was obtained by colony counts of serial dilutions of the C. albicans suspension grown in yeast potassium dextrose agar.

Antifungal agents. Fluconazole was supplied as a powder.
by Pfizer, Inc. (Groton, Conn.). In low-dose prophylaxis studies, the drug was dissolved at a concentration of 10 mg/ml in 10% dimethyl sulfoxide (Sigma, St. Louis, Mo.) in sterile water and administered i.v. Subsequent pharmacokinetic studies revealed equivalent serum levels with i.v. and intraperitoneal (i.p.) administration; therefore, fluconazole was given by i.p. injection in all subsequent studies. In the high-dose prophylaxis studies and in all treatment studies, a final drug concentration of 12.5 mg/ml was prepared by suspending fluconazole in 10% (vol/vol) Cremaphor EL (Sigma) in 0.85% sodium chloride buffered with 0.2 M sodium phosphate (pH 7.0). A 0.1% (wt/vol) solution of amphotericin B (Fungizone; Squibb) in sterile water containing 5% dextrose was administered i.v.

In vitro susceptibility testing. The drug susceptibilities of the C. albicans strain to amphotericin B and fluconazole were tested courtesy of Michael Rinaldi (Fungus Testing Laboratory, University of Texas Health Sciences Center, San Antonio, Tex.) by the broth macrodilution method in synthetic amino acid medium for fungi (11). In parallel, the in vitro susceptibilities of fluconazole and amphotericin B were determined with final inoculum sizes of \(-10^4\) and \(-10^6\) CFU/ml encompassing the range of fungal densities observed within experimental Candida vegetations in the rabbit model.

Drug levels in serum. The pharmacokinetic profile of fluconazole in the rabbit model was studied after both i.v. and i.p. administration of a single drug dose (50 mg/kg of body weight) in four rabbits each. Serum samples for measuring drug levels were drawn hourly for 4 h postdose and at 24 h postdose. The serum half-life was determined by the least-squares method, while the area under the time-concentration curve was determined by the linear trapezoidal rule. In addition, serum samples for measuring fluconazole levels were drawn \(-2\) h after i.p. administration (the anticipated peak) during the treatment of rabbits with established Candida endocarditis. Such levels were determined for 8 animals receiving i.p. fluconazole at a dose of 50 mg/kg/day and for 10 animals receiving i.p. fluconazole at 100 mg/kg/day. Fluconazole levels were determined by gas-liquid chromatography (M. Rinaldi). Peak levels of amphotericin B in serum were measured 1 h post-i.v. administration of a 1-mg/kg dose by bioassay (M. Rinaldi).

Production of C. albicans endocarditis. Female New Zealand White rabbits weighing \(-2.5\) kg were used. Animals were caged separately and given food and water ad libitum. Rabbits were anesthetized by intramuscular injection of ketamine hydrochloride (Ketaset; Aveco Co., Inc., Fort Dodge, Iowa), 35 mg/kg, and xylazine (Rompun; Mobay Corp., Shawnee, Kans.), 1.5 mg/kg. Sterile thrombotic endocarditis was produced by transaortic valvular placement of sterile polyethylene catheter (internal diameter, 0.86 mm; Becton Dickinson and Co., Parsippany, N.J.) by the method of Durack et al. (4). The catheter remained in place for the duration of the study. Endocarditis was established 48 h after catheterization by i.v. injection of \(-2 \times 10^7\) CFU of C. albicans via the marginal ear vein. Pilot studies confirmed that this challenge inoculum induced endocarditis in \(-95\%\) of catheterized animals.

Antifungal regimens. (i) Prophylaxis of Candida endocarditis. Five different prophylactic regimens in catheterized rabbits were studied. In the first group, 15 rabbits received a single i.v. dose of fluconazole (50 mg/kg) 90 min prior to inoculation with C. albicans. A second group consisted of 13 rabbits which received, in addition to the dose described above, a second dose of i.v. fluconazole (50 mg/kg) 24 h after inoculation; 15 rabbits in a third prophylaxis group received a single dose of i.v. amphotericin B (1 mg/kg) 45 min before inoculation. In the two remaining prophylaxis groups, a higher dose of fluconazole was studied, again in one- and two-dose regimens. Fourteen rabbits received a single i.p. injection of fluconazole (100 mg/kg) administered 90 min prior to inoculation with C. albicans, while 15 received, in addition to the dose described above, a second i.p. dose of fluconazole (100 mg/kg) 24 h later. For these prophylaxis studies, controls consisted of catheterized rabbits inoculated with C. albicans but receiving no antifungal drugs.

Sacrifice of animals in the prophylaxis experiments was carried out either 48 (amphotericin B group and controls), or 72 (fluconazole groups) h after inoculation. Fluconazole-treated animals were sacrificed 24 h after their amphotericin B-treated counterparts because of the longer elimination half-life of fluconazole in this model.

(ii) Treatment studies. Three parallel treatment studies were performed. In the first treatment study, rabbits with established Candida endocarditis received either no drug (\(n = 45\)), daily i.p. injections of fluconazole (50 mg/kg; \(n = 46\)), or daily i.v. injections of amphotericin B (1 mg/kg; \(n = 36\)) beginning 60 h after inoculation with C. albicans. Animals treated with antifungal agents were sacrificed on days 2 to 9 of therapy, corresponding to one to eight doses of fluconazole or amphotericin B. To gain statistical power, data from days 2 and 3 of treatment were combined, as were data from days 4 and 5. Control animals either died or were sacrificed on days 1 to 7 after infection. In all groups, animals that died before their assigned sacrifice date were included in data analysis only if death occurred within 6 h of their intended sacrifice.

In the second treatment study, therapy was initiated 24 h after inoculation with C. albicans, with rabbits receiving either no drug (\(n = 20\)), daily i.p. fluconazole (50 mg/kg; \(n = 10\)), or daily i.v. amphotericin B (1 mg/kg; \(n = 35\)). One third of surviving animals in each group were sacrificed on days 4, 8, or 12 following infection. In the third treatment study, rabbits received either no drug (\(n = 18\)) or daily i.p. fluconazole (100 mg/kg; \(n = 20\)). Therapy was again initiated 24 h following infection and was continued for a total of 21 days. One third of surviving animals in each group were sacrificed on days 6, 14, or 21 of the study.

(iii) Animal sacrifices. At their assigned sacrifice times, rabbits were euthanized with 200 mg of pentobarbital sodium (Abbott Laboratories, Chicago, Ill.) administered by rapid i.v. injection. All sacrifices occurred at least 48 h after the last antifungal dose to minimize drug carryover effects within cardiac vegetations. Following sacrifice, hearts were removed and the position of the indwelling catheter was verified. Cardiac vegetations from each animal were removed, pooled, weighed, homogenized in 1 ml of sterile normal saline, serially diluted, and quantitatively cultured in yeast potassium dextrose agar at 35°C for 48 h, and the \(\log_{10}\) CFU/g of vegetation was calculated. For statistical comparisons, culture-negative vegetations were considered to contain \(\leq 2.0 \log_{10}\) CFU/g on the basis of average vegetation weight in this model. The nonnormality that this assumption introduces into the data does not affect the statistical analysis, as only nonparametric statistical tests were used (see below).

Statistical analysis. Differences in intravegetation densities of C. albicans between three treatment groups were compared with the Kruskal-Wallis test (8). If a statistically significant treatment effect was found, the pairwise compar-
isons were made by using a two-tailed Wilcoxon rank sum test (16). Comparisons between two treatment groups were made by using a two-tailed Wilcoxon rank sum test. Rates of vegetation sterility were compared by using a two-tailed Fisher's exact test (1). A maximum P value of 0.05 was considered statistically significant.

RESULTS

**In vitro susceptibilities.** At a final *Candida* inoculum of 10⁴ CFU/ml, the MIC and mean fungicidal concentration (MFC) of fluconazole were ≤0.25 and >80 μg/ml, respectively, at both 24 and 48 h. The MIC and MFC of amphotericin B were ≤0.29 and 2.31 μg/ml, respectively, at both 24 and 48 h. At a final inoculum of 10⁵ CFU/ml, the MIC and MFC of fluconazole were 2.5 and >80 μg/ml at 24 h and >80 and >80 μg/ml at 48 h. The MICs and MFCs of amphotericin B were <0.29 and 18.5 μg/ml at 24 h and 1.16 and 18.5 μg/ml at 48 h.

**Pharmacokinetic studies.** The mean amphotericin B level in serum (± standard deviation) obtained at 1 h post-i.v. dose was 1.07 ± 0.46 μg/ml (n = 15). This value was above the MIC for the *Candida* strain at the lower inoculum (10⁴) tested in vitro and approached the MIC measured at the higher *Candida* inoculum (10⁵).

After a single 50-mg/kg i.p. dose, fluconazole levels exceeded the MIC determined at 10⁵ CFU/ml (≤1.25 μg/ml) throughout a 24-h period (Fig. 1). At this dose, the serum half-life was 8.5 h and the area under the time-concentration curve was 782 μg · h/ml. The mean peak level in serum for the 50 mg/kg fluconazole dose was 55 ± 10 μg/ml (n = 8); for the 100 mg/kg dose, the mean peak level in serum was 102 ± 32 μg/ml (n = 10).

**Prophylaxis studies.** Of 15 rabbits receiving a single prophylactic dose of amphotericin B (1 mg/kg i.v.), 12 (80%) had culture-negative cardiac vegetations. In contrast, fluconazole (50 mg/kg i.v.) given in one- or two-dose prophylaxis regimens yielded culture-negative vegetations in only 1 of 11 (9%) and 4 of 13 (31%) rabbits, respectively. Thus, a single dose of amphotericin B (1 mg/kg) was significantly more effective than either one- or two-dose regimens of fluconazole (50 mg/kg) in the prevention of *Candida* infective endocarditis (P < 0.001 and P < 0.03, respectively). Neither of the fluconazole-treated groups had rates of culture-negative vegetations significantly different from those of controls (2 of 20 [10%]).

With a higher dose of fluconazole (100 mg/kg i.p.), one- and two-dose prophylactic regimens yielded culture-negative cardiac vegetations in 4 of 14 (29%) and 2 of 15 (13%) rabbits, respectively. While a single dose of fluconazole was marginally better than control treatments in rendering vegetations culture-negative (P = 0.049), two doses were not (P = 0.212). When rates of culture-negative vegetations in the one- and two-dose groups were compared, the results again were not significantly different (P = 0.390). The prophylactic efficacy of amphotericin B was superior to that of higher-dose fluconazole in either one- or two-dose regimens (P < 0.01 and P < 0.001, respectively). (The control group had no culture-negative vegetations.)

**Treatment studies.** In the first treatment study, antifungal therapy was delayed until 60 h after infection. At all three time points studied, rabbits treated with amphotericin B had lower vegetation fungal densities than either untreated controls or animals treated with fluconazole (50 mg/kg/day) (Table 1). After 9 days of therapy, vegetation fungal densities in the amphotericin B-treated group were significantly lower than those in the fluconazole-treated group (P < 0.002). At no time point were vegetation fungal densities in the fluconazole group significantly different from those in untreated controls.

The results of the second treatment study, in which therapy was initiated 24 h after infection, are shown in Table 2. Rabbits treated with amphotericin B had lower fungal vegetation densities than those receiving fluconazole (50 mg/kg/day); these differences approached statistical significance after 8 days of therapy (P < 0.10) and attained statistical significance after 12 days of therapy (P < 0.01). Again, at all three time points, intravegetation fungal densities in the fluconazole group were not significantly different from those in the control group.

In order to determine the efficacy of a higher dose and a longer duration of therapy with fluconazole, a third study, in

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**TABLE 1. Results of treatment initiated 60 h postinfection**

<table>
<thead>
<tr>
<th>Regimen (dose)</th>
<th>C. albicans concn in cardiac vegetations on day of treatment* (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-3</td>
</tr>
<tr>
<td>Amphotericin B (1 mg/kg i.v.)</td>
<td>5.32 ± 0.37b (15)</td>
</tr>
<tr>
<td>Fluconazole (50 mg/kg i.p.)</td>
<td>5.87 ± 0.40 (15)</td>
</tr>
<tr>
<td>Control</td>
<td>6.13 ± 0.37 (18)</td>
</tr>
</tbody>
</table>

* Mean log (CFU/g) ± standard error of the mean.

b P < 0.01, relative to control value.

c P < 0.002, relative to fluconazole value.

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![FIG. 1. Serum concentration of fluconazole after a 50 mg/kg i.p. dose (n = 4). The error bars show the standard error of the mean for each time point. The MIC of fluconazole is shown by the horizontal dashed line (1.25 μg/ml).](http://aac.asm.org/)
which therapy was initiated 24 h after infection with a daily i.p. dose of 100 mg/kg for 21 days, was performed (Table 3). After 6 days of therapy, fungal vegetation densities in the fluconazole-treated animals were no different from those in the control group. However, after 14 or 21 days of therapy, significantly lower fungal vegetation densities were seen in the fluconazole group (\( P < 0.05 \) for both time points). Furthermore, there was a trend toward an increased number of culture-negative vegetations in the fluconazole group after 14 or 21 days of therapy compared with untreated controls, although this trend did not achieve statistical significance (data not shown).

**DISCUSSION**

The placement of prosthetic cardiac material, including valves, patch grafts, ventricular-assist devices, and artificial hearts, may be complicated by the development of device-associated fungal endocarditis (13, 15, 18). Such infections are invariably refractory to medical therapy alone and require surgical intervention for definitive cure (2, 15). The role of antifungal prophylaxis in the surgical placement of such prosthetic devices has been neglected because of significant problems associated with previously available drugs, including systemic and end-organ toxicity (amphotericin B), rapid selection of drug resistance (fluconazole), and lack of parenteral preparations (ketocazole); similar problems have limited the use of antifungal treatment alone for established fungal prosthetic-device infections. Fluconazole circumvents many of these problems, since it possesses few intrinsic toxicities and is available in both oral and parenteral forms (9).

In this study, we found amphotericin B to be a highly effective agent in the prophylaxis of *C. albicans* endocarditis in the rabbit model. In contrast, fluconazole at doses of 50 or 100 mg/kg in either one- or two-dose regimens was ineffective in this model. Similarly, amphotericin B was generally more effective than fluconazole in the treatment of established *C. albicans* endocarditis, although therapeutic outcome with fluconazole was directly related to dosage and duration of treatment. Specifically, when therapy was delayed until 60 h postinfection, fluconazole was substantially less effective than amphotericin B, despite serum fluconazole levels well in excess of the MIC for the organism. However, we found that when higher doses of fluconazole (100 mg/kg/day) were initiated 24 h postinfection and continued for 14 days or longer, the efficacy of this agent appeared to be equivalent to a 12-day course of amphotericin B.

Walsh and coworkers have also documented that the timing of the initiation of fluconazole therapy is an important variable in determining its efficacy in the prevention and treatment of disseminated *Candida* infections in the granulocytopenic rabbit model (17). As in our study, they found fluconazole to be significantly less effective than amphotericin B plus fluconazole when fluconazole therapy was initiated late postinfection (144 h). However, in contrast to our observations, fluconazole was equivalent to amphotericin B plus fluconazole in both preventive and early-initiated therapy (24 h postinfection) in their model. Such disparate observations may reflect the smaller *Candida* inocula used in their study (10^2 to 10^4 compared with 10^7 in the current study) as well as differences in the two models of *Candida* infection. Walsh et al. suggested that the lack of efficacy of fluconazole was multifactorial and related to (i) an in vivo inoculum effect, with more chronic dissemination yielding abscesses containing high fungal densities; (ii) poor diffusion of the drug into large or fibrotic lesions of deep visceral candidiasis; (iii) reduced metabolic activity of fungi in the center of large lesions, leading to decreased susceptibility to triazoles; and/or (iv) emergence of resistance among fungi exposed to subinhibitory concentrations of poorly diffusing antifungal agents. The observations of Walsh et al. are concordant with those of Filler et al., who recently reported that amphotericin B was more effective than fluconazole in the treatment of hematogenously disseminated candidiasis and endophthalmitis in a nongranulocytopenic rabbit model (5).

Our data support the concept of an in vivo inoculum effect; at an inocula of \( \sim 10^6 \) CFU/ml (similar to fungal densities found within cardiac vegetations in vivo), the inhibitory activity of fluconazole was substantially lower than at an inoculum of \( \sim 10^7 \) CFU/ml. In contrast, amphotericin B MICs at both 24 and 48 h remained within levels achievable in serum in vivo, irrespective of inoculum size. We reasoned that it was possible to overcome the effect of such a large intravascular inoculum by increasing the fluconazole dose. Although we found that higher-dose fluconazole treatment (100 mg/kg/day) begun 24 h after infec-

**TABLE 2. Results of treatment initiated 24 h postinfection**

<table>
<thead>
<tr>
<th>Regimen (dose)</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B (1 mg/kg i.v.)</td>
<td>4.27 ± 0.43 (10)</td>
<td>3.47 ± 0.38 (10)</td>
<td>3.04 ± 0.34 (13)</td>
</tr>
<tr>
<td>Fluconazole (50 mg/kg i.p.)</td>
<td>ND*</td>
<td>5.83 ± 0.38 (2)</td>
<td>4.59 ± 0.36 (8)</td>
</tr>
<tr>
<td>Control</td>
<td>6.60 ± 0.27 (6)</td>
<td>4.54 ± 0.91 (6)</td>
<td>5.59 ± 0.82 (8)</td>
</tr>
</tbody>
</table>

* Mean log (CFU/g) ± standard error of the mean.

**TABLE 3. Treatment with fluconazole initiated 24 h postinfection**

<table>
<thead>
<tr>
<th>Regimen (dose)</th>
<th><em>C. albicans</em> concn in cardiac vegetations on day of treatment* (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Fluconazole (100 mg/kg i.p.)</td>
<td>4.23 ± 0.58 (7)</td>
</tr>
<tr>
<td>Control</td>
<td>4.18 ± 0.85 (7)</td>
</tr>
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</table>

* Mean log (CFU/g) ± standard error of the mean.

b \( P < 0.05 \), relative to control value.
tion and continued for 14 to 21 days reduced vegetation fungal densities, our studies were not designed to systematically determine whether timing, duration, or dosage of fluconazole was the dominant factor in achieving this reduction. The lack of efficacy of lower-dose fluconazole (50 mg/kg) initiated 24 h after infection suggests that both drug dosage and the duration of treatment are important. It is also possible that the in vivo development of fluconazole resistance may be an important mechanism in the treatment failures seen with this drug. However, we did not specifically examine pre- and posttreatment isolates for fluconazole resistance. These factors will require characterization in future studies.

The relative lack of efficacy of fluconazole in the treatment of Candida endocarditis in our study contrasts with results recently reported by Longman et al. (9) in a similar experimental model. In their prophylaxis study, i.p. fluconazole (30 mg/kg) given 2 h before and 8 h after an i.v. inoculum of \(-10^6\) C. albicans or Candida parapsilosis prevented endocarditis in five of five catheterized animals, while all untreated controls had positive qualitative vegetation cultures. In their treatment study of established Candida endocarditis in which therapy was begun 72 h after infection and continued for 14 days, they found i.p. fluconazole (50 mg/kg/day) to be as effective as i.p. amphotericin B (3 mg/kg/day) with or without fluycytosine (35 mg/kg/day) in rendering vegetation cultures negative. Their protocols differed substantially from ours in several regards: (i) their Candida challenge inoculum was \(-1 \log_{10}\) CFU lower than that in our study; (ii) no comparative amphotericin B limb was included in their prophylaxis study; (iii) quantitative fungal cultures were not performed in their treatment study; and (iv) their sample sizes were very small, making statistical comparisons problematic.

In conclusion, our data suggest that amphotericin B is superior to fluconazole in the prophylaxis of experimental C. albicans endocarditis at the inoculum, dosage, and treatment schedules studied. Moreover, in short-term treatment studies (<2 weeks), amphotericin B was superior to lower-dose fluconazole. However, it appears that fluconazole may be equivalent to amphotericin B in the treatment of established Candida endocarditis when given for longer duration (>2 weeks) at a higher dosage.

ACKNOWLEDGMENT

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