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Factors Affecting Colonization and Dissemination of *Candida albicans* from the Gastrointestinal Tract of Mice

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Male ICR Swiss mice (2 to 3 months old) were fed *Candida albicans* in their drinking water for 3 days, followed by no treatment, antibiotics in their drinking water (daily), or immunosuppressants given by intraperitoneal injection (two to three times weekly) over a 3- to 4-week period. The organs of animals were processed to determine the numbers of *C. albicans* and total aerobic bacteria per g of tissue. Untreated animals had mean *Candida* counts during the 1-month period of $10^{2.3}$ CFU/g of cecum. Animals in six of eight antibiotic-treated groups had mean cecal *Candida* counts higher than those of control animals ($P < 0.05$), with clindamycin-gentamicin producing the highest counts ($10^{4.7}$ CFU/g). Cyclophosphamide produced counts ($10^{4.3}$ CFU/g) which were higher ($P < 0.05$) than those resulting from methotrexate ($10^{3.0}$ CFU/g) or steroid ($10^{2.7}$ CFU/g) treatment. Cyclophosphamide-clindamycin-gentamicin treatment was associated with the highest ($P < 0.05$) levels of *Candida* colonization ($10^{6.5}$ CFU/g). Mice receiving immunosuppressants plus clindamycin-gentamicin were more likely to disseminate *C. albicans* than were mice receiving antibiotics alone ($P < 0.001$). Our findings suggest that colonization of the guts of mice by *C. albicans* can be facilitated by manipulating the aerobic, anaerobic, or both types of gut flora. The combined effect of immunosuppressants on both *Candida* gut colonization and dissemination appears multifactorial and deserves further investigation.

Candida albicans is commonly found in the gastrointestinal (GI) tracts of humans (4). The frequency of *C. albicans* isolation from stool varies (4, 7, 8) but is higher among immunosuppressed patients, particularly those with hematologic malignancies (2, 7). Eras et al. (7) found that 13% of 586 patients with myeloproliferative disease had histologically proven *Candida* infection of the GI tract as compared with 1.6% of patients with solid tumors. Antibiotic treatment has also been shown to increase the rate of *C. albicans* isolation in stool (15; M. Barza, M. Giuliano, and S. Gorbach, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1, 1985).

Although uncommon in healthy individuals, *C. albicans* can disseminate from the GI tracts of humans (16). The GI tract organ most commonly infected is the esophagus (7), but other sites are also involved (4, 16, 20). Guentzel and Herrera have demonstrated in immunosuppressed mice that gut *C. albicans* can disseminate to the liver, kidney, and other organs (9). Kennedy and Volz have found that in Syrian hamsters pretreated with antibiotics, *C. albicans* can disseminate similarly (12). Factors identified that facilitate this dissemination include suppression of the intestinal bacterial flora and high levels of *Candida* colonization in the gut (9, 12).

As a first step toward understanding how *C. albicans* can invade and disseminate from the GI tract, we set out to develop a model of gut colonization. Many investigators have explored this question by using animal models in which the animals were exposed to *C. albicans* in a high-dose, bolus fashion with short-term follow-up (12, 17 18). Since such an approach can produce dissemination of the organism in both animals and humans that are not immunocompromised (12, 13, 17, 18), we felt that it might be more meaningful to develop a model in which each variable was monitored over a period of weeks rather than days or hours. We examined in mice the effects of oral antibiotics, immunosuppressants, and combinations of both on quantitative colonization of the gut by *C. albicans* over 3- to 4-week periods. In addition, we investigated dissemination of the organism in mice treated with antibiotics with or without immunosuppressants. With antibiotics alone, high-level cecal colonization with *C. albicans* only occurred with a two-drug combination. Even the highest level of antibiotic-induced gut colonization by *C. albicans* did not produce dissemination of *C. albicans* without addition of an immunosuppressant. The details of these results and their implications are the subject of this report.

MATERIALS AND METHODS

Animals. Male ICR Swiss mice (2 to 3 months old) Charles River Breeding Laboratories, Indianapolis, Ind.) were used in all experiments. They were housed four to six per cage in the university animal facility. Food (Purina mouse chow) and water (deionized and autoclaved) were allowed ad libitum. Except for a pilot antibiotic experiment, all animals were housed in cages with wire mesh bottoms.

***C. albicans* stock culture preparation.** A blood culture isolate of *C. albicans* was obtained from the university hospital clinical microbiology laboratory. It came from a 79-year-old patient who died of disseminated candidiasis. Stock cultures were prepared from the original blood isolate and stored at −70°C. Several colonies from a 48-h-old growth on Sabouraud dextrose agar (BBL Microbiology Systems, Cockeysville, Md.) were inoculated into 100 ml of tryptic soy broth (Difco Laboratories, Detroit, Mich.) and incubated at 37°C with constant agitation in a rotary shaker (150 to 180 rpm) for 24 h. Volumes (10 ml each) of this broth were then centrifuged at 400 × *g* for 10 min. The supernatant was decanted, and the pellet was washed three times in 10 ml of sterile, nonpyrogenic saline. The final saline-*Candida* mixture was stored in 1-ml aliquots at −70°C.

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Oral inoculation of *C. albicans*. *C. albicans* was given to each mouse by allowing it to drink the organism mixed with its drinking water for 3 days. The organism was prepared by taking 1 ml of the stock culture and proceeding as described for stock culture preparation. The final pellet of washed *C. albicans* was then added to deionized, autoclaved water (pH 5.5) and diluted to a concentration of approximately 2×10^6 CFU/ml. The exact concentration was determined by serial dilutions and surface plating on Sabouraud dextrose agar.

Specimen processing and enumeration of organisms. On each processing day (once or twice weekly), three or four mice in each experimental group were killed by cervical dislocation and dissected under aseptic conditions. Various organs (stomach, large and small intestines, cecum, liver, spleen, and kidney) were removed and weighed. The organs were ground in 2 to 4 ml of tryptic soy broth in sterile glass-glass tissue homogenizers (Ten Broeck Tissue Grinders; Fisher Scientific Co., Pittsburgh, Pa.). Serial dilutions of each homogenate were then plated on tryptic soy agar (Difco) and Sabouraud dextrose agar and incubated aerobically at 37°C. Blood was aspirated from the heart (0.5 to 1.0 ml) and pour plated with tryptic soy agar. Total aerobic bacteria (TAB) were counted after 24 h on tryptic soy agar; *Candida* colonies were counted after 48 h on Sabouraud dextrose agar plates. Identification of *C. albicans* was by colony morphology and Gram stain. *C. albicans* was easy to distinguish morphologically from bacteria because of its characteristic cream-colored colonies and the fact that none of the control animals (not fed *C. albicans*) had any detectable yeasts by our assay methods. This was true even for mice given tetracycline (data not shown).

Effects of antibiotics. Animals, after *C. albicans* inoculation, were fed antibiotics in their drinking water (deionized and autoclaved) for the duration of the experiment. The ceca of animals sacrificed at weekly intervals were processed for *Candida* and TAB counts. In a pilot study (data not shown), tetracycline (Sumycin; E. R. Squibb & Sons, Princeton, N.J.) was compared with four other antibiotics (gentamicin [Schering Corp., Bloomfield, N.J.], trimethoprim-sulfamethoxazole [Burroughs Welcome Co., Research Triangle Park, N.C.], vancomycin [Eli Lilly & Co., Indianapolis, Ind.], and metronidazole [Searle Pharmaceuticals, Inc., Chicago, Ill.]). Tetracycline was associated with slightly higher gut levels of *C. albicans* than the other antibiotics without affecting the TAB counts. This suggested that anaerobic bacteria might be more important than aerobic flora in preventing *Candida* colonization of the gut.

Therefore, we focused on antibiotics with substantial anaerobic activity (vancomycin, tetracycline, chloramphenicol [Parke, Davis & Co., Detroit, Mich.], and clindamycin [The Upjohn Co., Kalamazoo, Mich.]) in contrast to antibiotics with largely aerobic activity (gentamicin, trimethoprim-sulfamethoxazole). Metronidazole was not studied because it had no detectable effect on *C. albicans* in the pilot study. The concentrations of antibiotics used were calculated on a weight basis to deliver the approximate dose that is used in humans for gut decontamination (vancomycin, 0.2 mg/ml; gentamicin, 0.1 mg/ml) (19) or the dose used parenterally for serious infections (tetracycline, 1 mg/ml; chloramphenicol, 0.5 mg/ml; clindamycin, 0.24 mg/ml; trimethoprim-sulfamethoxazole, 0.06 mg/ml of trimethoprim). This dosage was based on an approximate daily water consumption of 5 ml per mouse.

Effect of immunosuppressants alone. Immunosuppressive agents were given by intraperitoneal injection two or three times weekly at the following doses: cyclophosphamide (Cytoxan; Mead Johnson & Co., Evansville, Ind.), at 3 mg per mouse per day; methotrexate (Lederle Laboratories, Pearl River, N.Y.), 0.15 mg per mouse per day; cortisone acetate (Merck, Sharp & Dohme, West Point, Pa.), 1 mg per mouse per day. The same dose was used whether the immunosuppressant was used alone or in combination with other immunosuppressants or antibiotics. The immunosuppressant doses were found by Guentzel and Herrera to facilitate *Candida* colonization and dissemination in mice (9).

To better understand any effect immunosuppressants might have on GI *Candida* colonization and dissemination, we studied the effect of each immunosuppressant (except cortisone acetate) on the peripheral leukocyte count and differential cell count during a 3-week period. Counts were done three times per week with a hemacytometer. Four animals were counted for each drug at each point in time, and the count of each animal represented the average of two counts.

Effect of combination treatment with antibiotics and immunosuppressants. Antibiotics (clindamycin-gentamicin) were given in drinking water, and immunosuppressive agents were given by intraperitoneal injection as follows: cyclophosphamide, 3 mg twice per week; methotrexate, 0.15 mg three times per week; and methylprednisolone (Depomedrol; Upjohn), 1 mg three times per week. Methylprednisolone was substituted for the cortisone acetate used in the previous experiment because it is more potent in humans and cortisone seemed to have little effect.

Statistical analysis. Data analysis was by one-way analysis of variance and Student's *t* test (two tailed) or Fisher's exact test. Statistical testing for Table 1 was done by choosing mice that were sacrificed in each experimental group at 7, 14, 21, and 28 (± 1) days with similarly chosen mice in the control group. The selection process was carried out so that for each comparison respective pools were equally weighted with animals from the different time periods. For example, the control group had four mice sacrificed at 8 days, four at 15 days, four at 22 days, and four at 29 days. The methotrexate-steroid-treated group had four mice sacrificed at 8 days, four at 15 days, four at 21 days, and two at 28 days. Only mice from the first three time intervals were pooled and compared.

RESULTS

Effect of coprophagia on colonization of the GI tract with *C. albicans*. At 8 days after the 3-day oral *C. albicans* inoculation, mice housed in cages with wire mesh bottoms had lower *Candida* counts than did mice in solid-bottom cages (mean; log 2.0 versus 2.7 $P < 0.05$). Thereafter, the differences between the groups were not significant, but there was greater variation in *Candida* counts among mice housed in solid-bottom cages. For this reason, only data obtained from animals housed in wire mesh-bottom cages were reported (no data are displayed from the pilot antibiotic study).

Localization of *C. albicans* in the GI tract. *Candida* counts in the stomach, small intestine, cecum, and large intestine were compared (Fig. 1). Except on day 8 of sampling, when the stomach counts were slightly lower than the cecal and large intestinal counts ($P < 0.05$), there were no differences among these four sample sites. For this reason and ease of anatomic identification, the cecum was chosen as the site of sampling for all remaining experiments.

Effect of antibiotics on cecal colonization with *C. albicans*. A summary of the relative impact of the different antibiotic regimens on cecal *Candida* counts is shown in Table 1. A combination of clindamycin-gentamicin produced signifi-

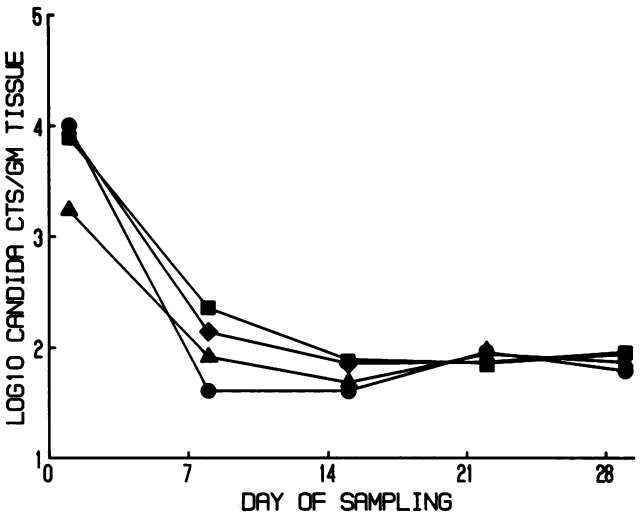

FIG. 1. Localization of *C. albicans* in the GI tracts of mice. Comparison of four gut segments (stomach, ●; small intestine, ▲; cecum, ■; and large intestine, ◆). Counts are given in CFU per g of tissue. Each point on this graph and in subsequent figures represents a mean of 3 to 4 animals.

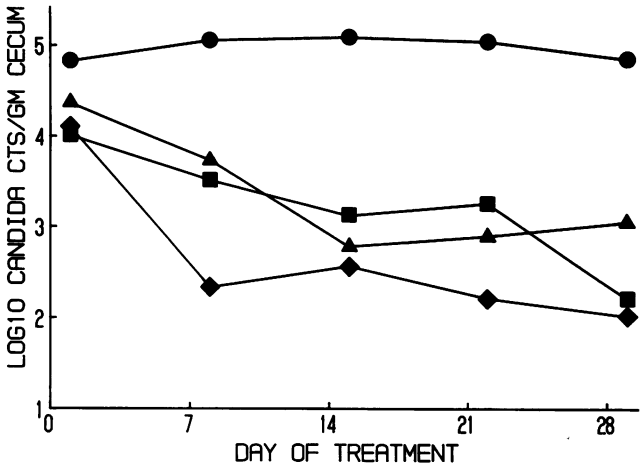

FIG. 2. Effect of antibiotics on cecal colonization with *C. albicans*. Symbols: ●, clindamycin-gentamicin; ▲, gentamicin; ■, clindamycin; ◆, untreated control.

cantly higher *Candida* levels ($P < 0.05$). Vancomycin and trimethoprim-sulfamethoxazole had no effect when compared with untreated animals. An example of the changes in cecal *Candida* counts with time can be seen in Fig. 2.

Striking differences were seen in the effects of antibiotics on cecal TAB counts. Tetracycline by itself had no detectable effect on TAB when compared with control animals (data not shown), although we cannot rule out counterbalancing effects on different organisms. In contrast, gentamicin resulted in a several-log drop in TAB (Fig. 3). Yet both of these drugs had similar effects on cecal *Candida* counts (Table 1). This suggests that modifying either the anaerobic or aerobic GI flora can facilitate *Candida* colonization. This consideration is further suggested by the finding that clindamycin and gentamicin together had an effect on cecal TAB that was significantly different from that of each drug individually ($P < 0.05$; Fig. 3).

Effect of immunosuppressant alone on *Candida* GI colonization. Cyclophosphamide produced significantly higher *Candida* counts than those of all other groups (Fig. 4) ($P < 0.05$). Methotrexate and cortisone acetate were not significantly different from the control group. Addition of cortisone to the cyclophosphamide or methotrexate group had no additional effect. None of the immunosuppressants, alone or in combination with other immunosuppressants, were associated with any mouse deaths.

Parallel with the cecal *Candida* findings, cyclophosphamide had the greatest effect on peripheral blood leukocyte counts (Table 2). It produced lower total leukocyte, lymphocyte, and granulocyte counts than those of the methotrexate, steroid (methylprednisolone), or control group ($P < 0.05$).

Effects of antibiotics plus immunosuppressants on cecal *Candida* counts. The combination cyclophosphamide-clindamycin-gentamicin produced the highest cecal *Candida*

TABLE 1. Effects of antibiotics and immunosuppressants on *C. albicans* colonization in the ceca of mice[a]

Antibiotic(s)	Immunosuppressant(s)		No. of mice	Log_{10} *Candida* counts/g of cecum (±SD)	*P* value[b]
	Alone	Plus antibiotics			
		Cld-Gen-Cyclo	18	6.46 ± 1.37	<0.0001
		Cld-Gen-Pred	13	5.53 ± 0.95	<0.0001
		Cld-Gen-Metho	15	5.31 ± 1.40	<0.0001
Cld-Gen			39	4.74 ± 1.17	<0.0001
	Cyclo		15	4.31 ± 0.73	<0.0001
	Cyclo-Cort		14	4.09 ± 0.48	<0.0001
Tet			32	3.04 ± 0.71	0.0002
Cld			16	3.02 ± 0.87	0.008
Chl			16	3.00 ± 0.63	0.002
Gen			32	2.97 ± 0.87	0.001
	Methotrexate		12	2.97 ± 1.36	0.12
	Cort		16	2.74 ± 1.01	0.13
Van			16	2.57 ± 0.94	0.30
TSX			16	2.52 ± 0.97	0.40
	Metho-Cort		14	2.43 ± 0.55	0.46
No treatment			16	2.28 ± 0.53	

[a] Abbreviations: Cld, clindamycin; Gen, gentamicin; Tet, tetracycline; Cld, clindamycin; Chl, chloramphenicol; Van, vancomycin; TSX, trimethoprim-sulfamethoxazole; Cort, cortisone acetate; Cyclo, cyclophosphamide; Pred, methylprednisolone; Metho, methotrexate.

[b] *P* value determined by Student's *t* test comparing specified drug regimen with the control group of animals (no treatment). The respective pools were equally weighted with animals from different time periods (see Materials and Methods for details).

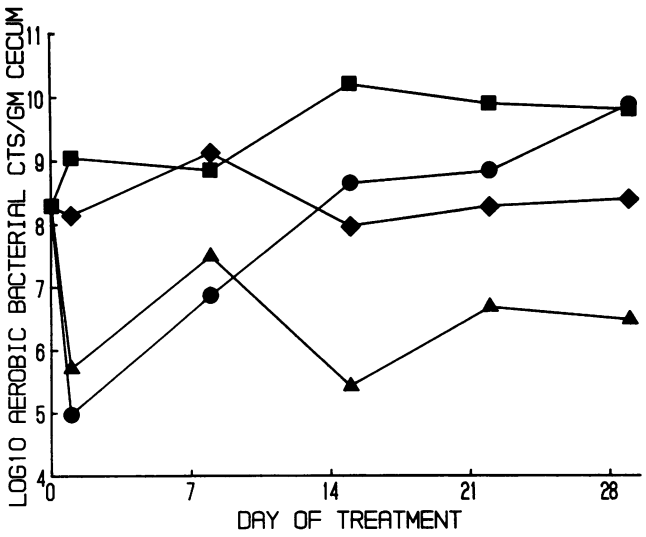

FIG. 3. Effect of antibiotics on cecal TAB counts. Symbols: ■, clindamycin; ◆, untreated control; ▲, gentamicin; ●, clindamycin-gentamicin.

counts observed in the whole study (Fig. 5) and was uniformly different from the clindamycin-gentamicin group ($P < 0.05$). The methotrexate and steroid (methylprednisolone)-antibiotic groups had *Candida* counts intermediate between those of the cyclophosphamide-antibiotic and antibiotic alone groups and were significantly different ($P < 0.05$) from the clindamycin-gentamicin group on only a single sample day. Mortality rates were 31% for the cyclophosphamide group, 12% for the methotrexate group, and 0% for the steroid group.

Effects of antibiotics plus immunosuppressants on cecal aerobic bacterial counts. Immunosuppressants, in combination with clindamycin-gentamicin, had markedly different effects on cecal TAB counts as compared with the antibiotics alone (Fig. 6). On day 3 of the experiment, the cyclophosphamide-antibiotic regimen produced a peak in cecal TAB counts ($10^{10.2}$ CFU/g), while the antibiotic alone regimen

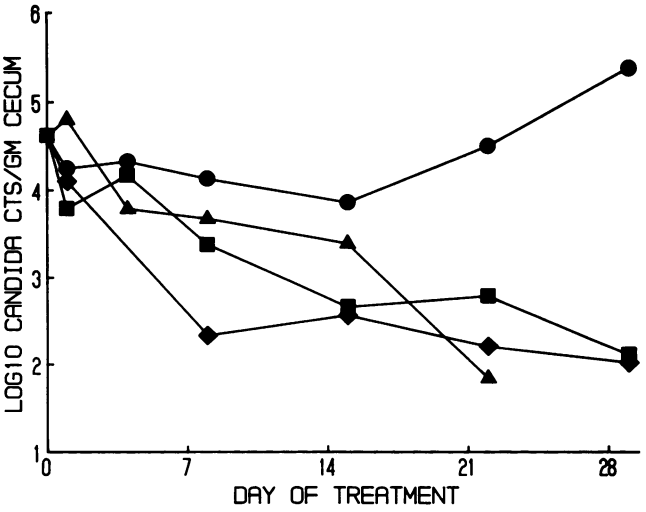

FIG. 4. Comparison of the effects of immunosuppressants on cecal *C. albicans* colonization. Symbols: ●, cyclophosphamide; ▲, methotrexate; ■, cortisone acetate; ◆, untreated control.

TABLE 2. Effects of immunosuppressants in mice over a 3-week period on mean peripheral blood leukocyte count[a]

Drug	Mean (±SD) leukocyte count[b]		
	Total	Lymphocyte	Granulocyte
Methotrexate	5,600 ± 3,900	4,200 ± 2,500	1,800 ± 1,700
Saline	3,600 ± 1,800	2,900 ± 1,500	720 ± 460
Steroid	2,300 ± 1,100	1,700 ± 870	490 ± 340
Cytoxan	1,500 ± 1,500	1,300 ± 1,300	200 ± 250

[a] Twice weekly, two mice were sacrificed in each group.
[b] All cell counts in different treatment groups were statistically different ($P < 0.05$), except in the comparison between steroid versus saline granulocyte counts.

reached its nadir ($10^{5.7}$ CFU/g). The methotrexate and steroid groups produced intermediate effects. These findings suggest that the cytotoxic agents had an effect on the GI bacterial flora independent of those of antibiotics. Whether this was due to a direct effect on the bacteria or an indirect effect related to gut dysmotility and bacterial overgrowth is unknown at this time.

Dissemination of *C. albicans* versus bacteria. In spite of producing the highest levels of *Candida* colonization seen with antibiotics alone, the clindamycin-gentamicin group had almost no *Candida* dissemination (Table 3). *Candida* dissemination was more common in the immunosuppressant plus antibiotic groups than in the antibiotic alone group (11/46 versus 1/23; $P < 0.001$). However, the steroid plus clindamycin-gentamicin group was the only immunosuppressant plus antibiotic combination that had significantly greater *Candida* dissemination than the antibiotic alone group (5/13 versus 1/23; $P = 0.016$). Bacterial dissemination occurred more frequently than *Candida* dissemination except in the steroid plus antibiotic group. This must be interpreted with caution because of the large number of mice not processed in the cyclophosphamide group because of death followed by rapid autolysis. *C. albicans* disseminated most commonly to the liver (8 mice; mean, 170 ± 340 [standard deviation] CFU/g of tissue), followed by kidney (5 mice; 370 ± 500 CFU/g) and spleen (3 mice; 400 ± 530 CFU/g). Data were

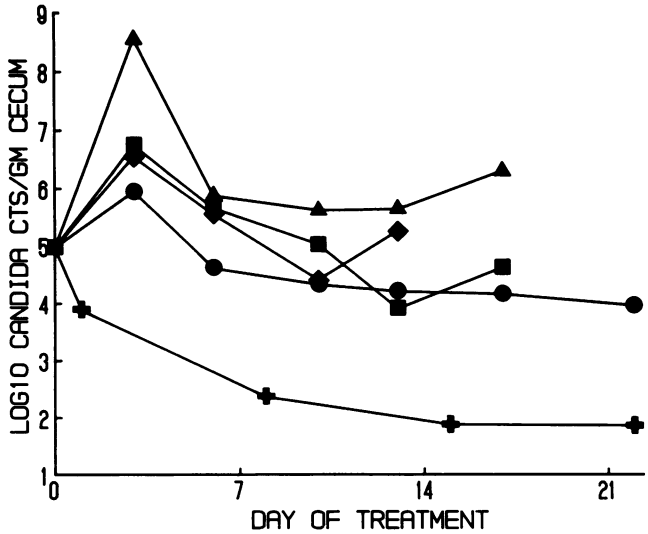

FIG. 5. Comparison of the effects of cyclophosphamide-clindamycin-gentamicin (▲), methotrexate-clindamycin-gentamicin (■), steroid-clindamycin-gentamicin (◆), clindamycin-gentamicin (●), and no antibiotics (✚) on cecal *Candida* colonization.

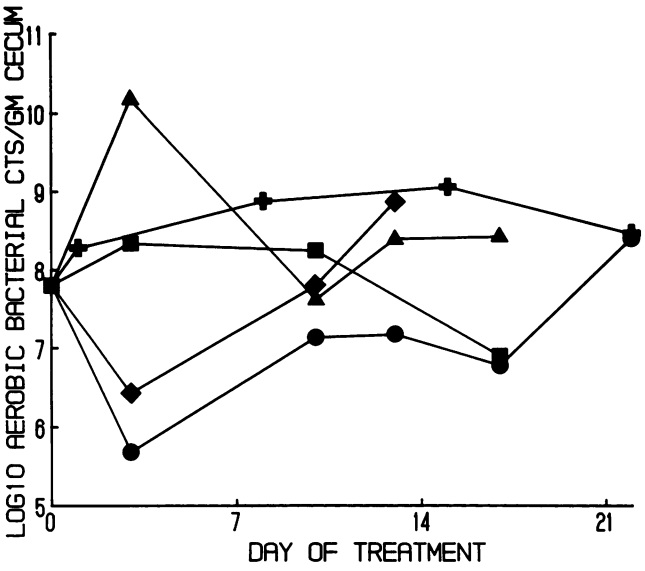

FIG. 6. Comparison of the effects of cyclophosphamide-clindamycin-gentamicin (▲), methotrexate-clindamycin-gentamicin (■), steroid-clindamycin-gentamicin (◆), clindamycin-gentamicin (●), and no treatment (✚) on cecal aerobic bacterial colonization.

not displayed by treatment group because of the small number of animals with dissemination. No blood cultures positive for *C. albicans* were detected. The pattern for bacterial dissemination was similar; the liver was the most common site (16 mice; 270 ± 440 CFU/g), followed by kidney (8 mice; 140 ± 350 CFU/g) and spleen (8 mice; 52 ± 85 CFU/g).

DISCUSSION

In our study, a combination of two antibiotics (clindamycin and gentamicin) was required to achieve high-level and prolonged colonization of the gut with *C. albicans*. Individually, clindamycin and gentamicin had an equal effect on *Candida* GI colonization (Table 1). Gentamicin did this in association with a striking effect on the aerobic bacterial flora, whereas clindamycin had relatively little effect. In addition, tetracycline produced cecal *Candida* levels to similar to those produced by clindamycin and gentamicin without causing any detectable effect on the TAB. This suggests indirectly that the tetracycline effect on cecal *C. albicans* may be mediated through suppression of anaerobic bacteria. In combination, these data may indicate that the greater effect of the two-drug combination results from combined suppression of aerobic gram-negative rods by gentamicin and other organisms (probably including anaerobes) by clindamycin.

The only other study which longitudinally examined the effects of different antibiotics on *Candida* GI colonization was with humans. Barza et al. (25th ICAAC) found that in human volunteers given intravenous cefoperazone, cefoxitin, piperacillin, or aztreonam, cefoperazone produced the greatest fall in both anaerobic and aerobic stool bacterial counts. Cefoperazone also resulted in significantly higher stool *C. albicans* counts ($P < 0.05$) than did the other three drugs. These data support our hypothesis that both anaerobic and aerobic bacteria are likely to have an effect on *Candida* gut colonization.

It has been suggested by Kennedy and Volz (12) that the anaerobic bacterial gut flora is more important than aerobic bacteria at preventing *Candida* colonization and dissemination from the gut. In their hamster model, penicillin G reduced total gut anaerobic bacterial counts, increased facultative bacterial counts, and led to increased levels of *C. albicans* in the gut, with a high frequency of *C. albicans* dissemination to the liver, spleen, or kidney. A major concern about their conclusions, however, is that these findings were recorded only 24 h after three large intragastric inocula of *C. albicans* (10^7 organisms). Krause et al. (13), using a similar inoculum (on a weight basis) in a human volunteer, demonstrated that dissemination of *C. albicans* to blood and urine occurs within hours. Thus, it seems reasonable to question what relevance results derived from such short-term experiments have in relation to *C. albicans* gut colonization under more steady-state conditions.

A nonlethal, leukopenia-producing dose of cyclophosphamide produced high-level, sustained colonization of the mouse cecum with *C. albicans*. Methotrexate and cortisol had no effect on *C. albicans* in comparison with untreated mice. Guentzel and Herrera (9), using mice colonized with *C. albicans* shortly after birth, reported that cyclophosphamide produced higher *Candida* levels than those in control animals 15 days after treatment was begun. Methotrexate resulted in higher levels 8 days after treatment was begun, and cortisone had a similar effect at 14 days. The lack of effect of methotrexate and cortisol in our model may be related to the possibility that the effects of these drugs on *Candida* colonization are small and short lived (days 7 to 14, Fig. 4) and that we did not detect them because we had only four animals in each experimental group. A more likely explanation is that it is due to the different colonization states achieved by the two models. In our model, with *Candida* inoculation into adult mice, sustained high-level colonization did not occur, whereas it did in the other model, in which mice were inoculated perorally as neonates (9).

In parallel to the findings with immunosuppressants alone, addition of cyclophosphamide to clindamycin-gentamicin produced higher levels of *Candida* gut colonization than adding either methotrexate or steroid to the antibiotic treatment. Two factors that may contribute to this effect are the lower peripheral leukocyte counts (both granulocytes and

TABLE 3. Organism dissemination: effects of immunosuppressants combined with antibiotics[a]

Drug group	No. of mice			No. of mice with positive organ cultures		
	Total	Died	Sacrificed	Total	Bacteria	*C. albicans*
Cyclo-Cld-Gen	26	8*†	18	9	9‡	3‡
Meth-Cld-Gen	17	2	15	7	7	3
Pred-Cld-Gen	13	0*	13	5	2	5
Cld-Gen	24	1†	23	5	5	1

[a] For definitions of drug name abbreviations, see Table 1, footnote *a*. The differences between groups indicated by pairs of symbols *, †, and ‡ were statistically significant ($P < 0.05$; Fisher exact test).

lymphocytes) and higher TAB counts seen in association with cyclophosphamide ($P < 0.05$). Existing data do not suggest that the changes in aerobic bacteria seen with cyclophosphamide are due to antibacterial activity (1, 11). A more likely possibility may be that cyclophosphamide has a direct effect on the gut that brings about these changes. Although frank gut ileus has not been reported with cyclophosphamide, the drug is known to produce structural and functional changes in gut mucosal cells (3, 6, 10). Thus, it is conceivable that bacterial and candidal overgrowth may occur in a manner similar to that seen with blind loops or dysmotility syndromes (5, 14).

Although steroids and methotrexate had relatively little effect in our model on cecal levels of *C. albicans*, they both had rates of *Candida* dissemination similar to those found with cyclophosphamide. This indicates that factors other than gut levels of *C. albicans* or peripheral leukocyte counts (or both) may be important determinants of whether *C. albicans* disseminates from the gut. Additional work is necessary to understand the combined effects of antibiotics plus immunosuppressants on *Candida* GI colonization and dissemination and its importance in the management of immunosuppressed patients.

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