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Effects of Broad-Spectrum Antibiotics on Colonization of Gastrointestinal Tracts of Mice by *Candida albicans*

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Three-month-old, male, Crl:CD1 (ICR) BR mice were fed chow containing *Candida albicans* or regular chow. Subsequently, both groups were given either antibiotics or normal saline for 10 days. Stool cultures were performed immediately before administration, at the end of antibiotic administration, and 1 week after the discontinuation of antibiotics, to determine the effect on the concentration of *C. albicans* in the stools. The stools of mice fed *C. albicans* and given antibiotics had substantially higher *Candida* counts than those of control mice fed *C. albicans* and given saline. Significantly higher candidal concentrations were observed in the stools of mice given chloramphenicol compared with those of mice given ciprofloxacin, sulfamethoxazole-trimethoprim, and ampicillin. No mice developed histopathological evidence of local gastrointestinal invasion or disseminated candidiasis. In this mouse model, *Candida* colonization increases substantially after the administration of antimicrobial agents with broad spectra and anaerobic activities.

Patients with cancer are at risk of developing disseminated candidiasis (3, 11). The gastrointestinal (GI) tract is the source of dissemination in many cases (3, 10). The administration of broad-spectrum antibiotics is associated with an increase in the concentration of *Candida* organisms in the GI lumen and hence may increase the risk of disseminated candidiasis (3, 14). We have previously described a mouse model of sustained GI colonization by *Candida albicans* (15). In the present study, we report on the effects of five antimicrobial agents on the level of GI colonization by *C. albicans* in the this mouse model. These agents were selected because of their frequent use in outpatient therapy, an approach that has gained increased interest recently.

Groups of 50 Crl:CD1 (ICR) BR mice, 3 months old and weighing approximately 25 g each (Charles River Laboratories, Wilmington, Mass.), were used with each antibiotic. Thirty of the mice were fed chow containing *C. albicans* for 2 weeks. Details of the preparation of this chow have been reported previously (15). The remaining 20 were fed regular chow which did not contain *C. albicans*. GI colonization by *C. albicans* was verified 1 week after the end of the special diet period by stool cultures, as described previously (14, 15). Subsequently, 20 mice of each group colonized with *C. albicans* received subcutaneous injections of the study antibiotics for 10 days. The remaining 10 colonized mice received the same schedule and volume (30 μl) of normal saline solution. Similarly, 10 mice of the noncolonized group were injected for the same time with either the same antibiotic or 30 μl of saline. The latter three groups served as control.

The antimicrobial agents used in this study were amoxicillin-clavulanate, chloramphenicol, ciprofloxacin, sulfamethoxazole-trimethoprim, and ampicillin and were supplied by their commercial manufacturers. The dosage schedules were equivalent to those for humans and were calculated by the method of Freireich et al. (9). The equivalence of antibiotic dosage schedules for humans and mice is shown in Table 1.

Cultures from the stools of mice were obtained on the last day of antibiotic administration and again 7 days later. Five animals from each group were randomly selected on the last day of antibiotic administration and sacrificed by cervical dislocation. The heart, lungs, kidneys, liver, and spleen were each weighed and subsequently homogenized in 10 ml of saline by using a stomacher, Lab Blender 80 (Tekmar Co., Cincinnati, Ohio). One hundred microliters of the resulting suspension was cultured onto plates containing tryptic soy agar with 5% sheep blood (Regional Media Laboratories, Lenexa, Kans.) and Sabouraud dextrose agar with cycloheximide and chloramphenicol (BBL Microbiology Systems, Cockeysville, Md.). The plates were incubated at 37°C for 48 h. Histologic examination was performed on all organs, with special emphasis on the detection of invasion of *C. albicans*. Statistical analyses were performed, by using an analysis of variance with a significance level of 0.05.

The median concentration of *C. albicans*, prior to antibiotic administration, in the stools of mice fed chow containing *C. albicans* was 4.4 $\log_{10}$ CFU/g of stool. As would be expected, there were no significant differences between groups of mice before antibiotic administration. The level of GI colonization of mice by *C. albicans* after the administration of antibiotics varied depending on the antibiotic used. The concentrations of

TABLE 1. Equivalence of antibiotic dosage schedules in humans and mice

Antibiotic	Daily dosage schedule[a]	
	70-kg human	25-g mouse
Amoxicillin-clavulanate	1.2 g q6h	5.2 mg q6h
Chloramphenicol	1.0 g q8h	4.3 mg q8h
Ciprofloxacin	200 mg q12h	1 mg q12h
Sulfamethoxazole-trimethoprim	1,200/240 mg q12h	5/1 mg q12h
Ampicillin	1 g q6h	4.2 mg q6h

[a] q, every.

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TABLE 2. Effects of antibiotics on GI colonization of mice by *C. albicans*

Antibiotic	Median *C. albicans* concn (range) (log_{10} CFU/g of stool)[a]	
	Day 10 of administration	1 wk after end of administration
Amoxicillin-clavulanate	7.74 (7.30–7.79)	7.30 (6.93–7.81)
Chloramphenicol	8.36 (8.0–8.96)	7.88 (7.81–8.0)
Ciprofloxacin	6.66 (6.40–6.92)	5.53 (5.40–5.62)
Sulfamethoxazole-trimethoprim	6.81 (5.96–6.93)	5.79 (5.54–6.38)
Ampicillin	6.0 (5.93–6.79)	5.98 (5.81–6.70)

[a] Concentration before treatment: 4.40 log_{10} CFU/g of stool (median), 4.0–4.64 (range).

C. albicans in the stools of mice receiving chloramphenicol were significantly higher than those for mice receiving any of the other antibiotics ($P < 0.03$). No other differences were statistically significant. The concentration of *C. albicans* in the stools declined during the week after cessation of antibiotic administration but remained higher than that observed prior to the onset of antibiotic administration (Table 2). The difference between the concentration at 1 week after cessation and that prior to onset of antibiotic administration was statistically significant only for chloramphenicol ($P = 0.002$) and ciprofloxacin ($P = 0.004$). It is somewhat surprising that ampicillin did not have a greater effect since its use has been associated with superficial fungal infections in humans.

The level of *Candida* concentration in the stools of mice that were colonized and received only saline remained unchanged. *C. albicans* could not be cultured from the stools of mice that received normal chow and were given either saline or the study drugs.

The results of this study indicate that the levels of GI tract colonization by *C. albicans* depended on the antibiotic used. Antibiotics with broad-spectrum activity that included anaerobes (chloramphenicol, amoxicillin-clavulanate) (12, 18) were associated with the highest increases, compared with antibiotics with minimal or no anaerobic activity (ciprofloxacin, sulfamethoxazole-trimethoprim) (7, 20) or the antibiotics with a narrower spectrum (ampicillin) (13).

Other investigators have reported findings similar to ours for humans and for animals (1, 2, 4–8, 16, 17, 19). Amoxicillin-clavulanate and chloramphenicol have been reported to cause substantial increases in GI colonization by yeasts (4, 19), while ciprofloxacin was associated with modest or small increases (7, 8, 16). Also, sulfamethoxazole-trimethoprim (1, 5, 6) and ampicillin (2, 17) have been found to promote colonization of the GI tract by yeasts.

In conclusion, in this mouse model, yeast colonization increases substantially after the administration of antimicrobial agents with broad spectra and anaerobic activities. This model may be useful in predicting the degree of GI colonization in humans after antibiotic administration, but correlations need to be made with data from humans.

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