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Prospective Evaluation of Effects of Broad-Spectrum Antibiotics on Gastrointestinal Yeast Colonization of Humans

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This study evaluated the effects of broad-spectrum antibiotics on the gastrointestinal (G.I.) yeast flora of humans and correlated the findings with those obtained from a mouse model of G.I. colonization by *Candida albicans*. We prospectively studied 46 adult cancer patients who received one of five broad-spectrum antibiotics (ceftriaxone, ceftazidime, ticarcillin-clavulanic acid, imipenem-cilastatin, and aztreonam) as therapy for infections. Quantitative examination of yeast colonization of stools was conducted at the baseline, at the end of antibiotic treatment, and 1 week after discontinuation of therapy. Antibiotics with anaerobic activity (ticarcillin-clavulanic acid) or high G.I. concentrations (ceftriaxone) caused a higher and more sustained increase in G.I. colonization by yeasts than did antibiotics with poor anaerobic activity (ceftazidime and aztreonam) or a low G.I. concentration (imipenem-cilastatin). These results were similar to those obtained with a mouse model of G.I. colonization by *C. albicans* that involved the same antibiotics. Hence, the mouse model may be useful for evaluation of yeast colonization of the human G.I. tract.

Immunocompromised patients are at risk of developing serious fungal infections. Prominent among these infections is disseminated candidiasis (1, 3, 4, 20, 21). The source of this infection often is the gastrointestinal (G.I.) tract (3, 9, 14, 15, 34). Administration of broad-spectrum antimicrobial agents to these patients increases their risk of candidal infections by increasing the frequency and magnitude of G.I. colonization by *Candida* spp. (9, 14, 18, 28, 30, 32, 33).

We recently described the effects of broad-spectrum antimicrobial agents on yeast colonization of the G.I. tract in a mouse model (30). The purpose of the current study was to determine whether the mouse model of G.I. colonization by *Candida albicans* (30, 31) is predictive of G.I. colonization by yeasts in humans and to study the impact of the various antimicrobial agents used in the mouse model study on yeast colonization of the human G.I. tract.

MATERIALS AND METHODS

Adult cancer patients, cared for at the Department of Medicine of the University Hospital of Heraklion, Crete, Greece, were eligible if they had suspected or documented bacterial infections. Patients were enrolled in the study if they were to receive any of the five antibiotics to be examined. When a total of nine patients was accrued for each antibiotic, enrollment was stopped for that antibiotic.

The antibiotics used were ceftriaxone, ceftazidime, ticarcillin-clavulanic acid, imipenem-cilastatin, and aztreonam, and they were supplied by their commercial manufacturers. The dosage schedules used are shown in Table 1, and they are the equivalents of the ones used in the previously reported study of our mouse model (30) as calculated by the method of Freireich et al. (10). Exclusion criteria were antibacterial, antifungal, and/or corticosteroid therapy in the preceding 30 days; hepatic and renal dysfunction; chronic inflammatory bowel diseases; and a short life expectancy (<30 days).

Patients were evaluable if they completed at least a 7-day course of the antibacterial agent, had not received concomitant antimicrobial agents or corticosteroids during therapy and the 1 week after discontinuation of treatment, and had no deterioration of liver and kidney function tests during therapy.

Stool specimens from each patient were obtained immediately before treatment, at the end of treatment, and 1 week after its discontinuation. Each stool specimen was homogenized and inoculated directly onto Sabouraud dextrose agar (SDA-gelose de sabouraud + chloramphenicol; Diagnostics Pasteur, Marnes le Coquette, France). For preparation of quantitative fungal stool cultures, a stool specimen was weighed and homogenized in a volume of sterile isotonic saline so that the final mixture contained 0.1 g of stool per ml. The specimen was vortexed for 2 min. Tenfold serial dilutions with saline were made, and 100 μl of each dilution was inoculated onto Sabouraud dextrose agar. Cultures were incubated at 30°C for 48 h, and quantitation of fungal colonies was done at 48 h. Yeasts were identified on the basis of the API 20C AUX (Bio Merieux S.A., Marcy-l'etoile, France).

RESULTS

From 1 October 1990 until 31 January 1992, a total of 72 patients were entered in the study and divided into five different therapeutic groups. Twenty-six patients could not be evaluated for the following reasons: early discontinuation of the study drug (<6 days; 9 patients), administration of another antimicrobial agent along with the study drug (12 patients), addition of corticosteroids (3 patients), renal dysfunction during the treatment course (1 patient), and early death (1 patient). There were no significant differences in the distribution of nonevaluable patients among the five groups.

Each group included 9 evaluable patients, except for the

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TABLE 1. Effects of antibiotics on G.I. colonization of humans by yeasts

Antibiotic and daily dosage schedule	No. of patients studied	Yeast concn (log_{10} CFU/g of stool)[a]		
		Before treatment	On last day of treatment	1 week after end of treatment
Ceftriaxone, 2 g/8 h	9	3.7, <3.0–5.2 (7)	6.9, 3.0–7.9 (9)	5.3, <3–6.8 (9)
Ceftazidime, 2 g/8 h	9	3.6, <3–5.5 (8)	5.4, <3–6.9 (8)	3.8, <3–5.0 (8)
Ticarcillin-clavulanate, 3.1 g/4 h	10	3.2, <3–5.8 (7)	5.8, 3.0–8.4 (10)	4.8, <3–7.5 (9)
Imipenem-cilastatin, 1 g/6 h	9	4.2, <3–7.4 (6)	5.0, <3–8.5 (7)	4.5, <3–6.8 (7)
Aztreonam, 2 g/6 h	9	4.6, <3–8.6 (7)	5.0, <3–9.4 (7)	3.5, <3–8.8 (7)

[a] The median and range of yeast concentrations and number of patients colonized are shown.

ticarcillin-clavulanic acid group, which included 10. There were no significant differences in patient characteristics among the five study groups, including age (median, 65 years), sex (male/female ratio, 30/16), underlying disease (38 patients with solid tumors and 8 with hematologic malignancies), infectious diseases (neutropenic fever, 17 patients; pneumonia, 18 patients; urinary tract infection, 5 patients; fever of undetermined origin, 5 patients; cholecystitis, 1 patient), and duration of antibiotic treatment (mean and median, 9 days; range, 8 to 10 days).

Of these 46 patients, 35 had baseline stool cultures positive for yeasts including *C. albicans* (20 patients), *Torulopsis glabrata* (7 patients), *C. parapsilosis* (4 patients), *C. tropicalis* (2 patients), *C. norvegensis*, and *C. rugosa* (1 patient each).

Six patients acquired yeasts during antibiotic therapy. Five acquired *C. albicans*, and one acquired *T. glabrata*. All of the patients who were not colonized initially and who received ceftriaxone or ticarcillin-clavulanic acid became colonized during therapy, whereas this did not occur among the patients who received ceftazidime or aztreonam.

An increase in the concentration of yeasts was observed in the stools of 41 patients during antibiotic therapy, and its degree was dependent on the antibiotic used. Five patients had negative stool cultures for yeasts prior to, during, and after antibiotic therapy. Ceftriaxone and ticarcillin-clavulanic acid caused the highest degree of increase in yeast concentrations (medians, 3.2 and 2.6 log_{10} CFU/g of stool, respectively). Ceftazidime and imipenem-cilastatin caused a lesser increase (medians, 1.8 and 0.8 log_{10} CFU/g of stool, respectively). On the other hand, aztreonam had a lower impact on yeast concentration (median increase, 0.4 log_{10} CFU/g of stool) (Table 1).

A persistent but smaller increase in yeast concentrations was seen 1 week after the end of therapy with ceftriaxone and ticarcillin-clavulanic acid compared with the pretreatment results. This was not true for the other three antibiotics (Table 1).

DISCUSSION

These results indicate that ceftriaxone and ticarcillin-clavulanic acid, which are antibiotics with either good anaerobic activity or high concentrations in the G.I. tissues and contents (5, 8, 17, 24), are associated with substantial increases in the yeast flora of the gut. On the other hand, antibiotics with poor anaerobic activity, like ceftazidime (7, 8, 23) and aztreonam (13, 25, 35), or with low concentrations in the G.I. contents, like imipenem (22, 26, 27), were associated with smaller increases in the yeast flora of the gut.

These findings are similar to those obtained earlier with a mouse model of G.I. colonization by *C. albicans* (30). Hence, this model may be useful in predicting the impact of antimicrobial agents on the level of yeast colonization of the human G.I. tract. Similar findings were shown by other investigators who used animals and humans (2, 6, 11, 12, 14, 16, 18, 19, 25, 29). However, this study was the first to compare directly the findings obtained with animals with those obtained with humans by using the same antimicrobial agents.

Since candidal infections can be life threatening (1–4, 9, 20) and since the activities of various broad-spectrum antibiotics appear to be similar in this patient population, the use of antibiotics which cause lower levels of G.I. colonization may, perhaps, result in a decrease in fungal infections.

In conclusion, we have shown that the concentration of yeasts in the human gut increases significantly after administration of antibiotics with good anaerobic activity and/or high G.I. concentrations. These findings could have been predicted from our model of G.I. colonization of mice by *C. albicans*. This model may improve our ability to decrease the incidence of fungal infections in cancer patients by selecting antibacterial regimens that have minimal impact on colonization by yeasts.

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