Gastrointestinal Colonization and Systemic Dissemination by *Candida albicans* and *Candida tropicalis* in Intact and Immunocompromised Mice

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Gastrointestinal colonization and systemic dissemination by *Candida albicans* and *Candida tropicalis* were compared in intact and immunocompromised mice. Five-day-old CFW mice were inoculated by the oral-intragastric route with 1.0 x 10^7 CFU of two *C. albicans* and two *C. tropicalis* strains isolated from the blood of patients with acute leukemia and with *C. albicans* 4918 and its cerulenin-resistant mutant 4918-10. *C. albicans* and *C. tropicalis* spread to the lungs, liver, and kidneys within 30 min postinoculation, and organ CFU of the two species were comparable over the following 10 days. Close association of blastoconidia with the villous surface of the small intestine resulted in lysis of microvilli and then progressive invasion of villi. Blastocystidia within villi were surrounded by a conspicuous zone of clearing. Persistent colonization of the small and large intestines by *C. albicans* blood isolates and strains 4918 and 4918-10 was similar for 31 days after inoculation, but consistently exceeded that of *C. tropicalis*. In mice colonized with *C. albicans*, immunosuppression with cortisone acetate and cyclophosphamide on days 30 and 33 after inoculation increased stomach CFU 400- to 370-fold and intestinal CFU 300- to 80-fold. In contrast, persistent colonization by *C. tropicalis* was undetectable before immunosuppression and only became apparent after treatment. *C. albicans* disseminated more frequently and with higher organ CFU than *C. tropicalis*. Despite this fact, 20% of mice infected with *C. tropicalis* died, compared with 4% infected with *C. albicans* blood isolates. Indirect immunofluorescence revealed penetrative growth by *Candida* hyphae exclusively in the mucosa and submucosa of the stomach from immunosuppressed, persistently colonized mice. Taken together, the data indicate that *C. tropicalis* appears to be more virulent than *C. albicans* and that factors responsible for gastrointestinal colonization, systemic dissemination, and mortality in immunocompromised mice may not be identical.

Invasive candidiasis is the most frequent opportunistic fungal infection in immunocompromised patients, especially those with acute leukemia (3, 28). Penetration of the *Candida* species through the gastrointestinal mucosa is thought to be the most frequent mechanism leading to systemic dissemination (39). Autopsy studies conducted in patients who had culture-proven disseminated *C. albicans* or *C. tropicalis* infections with involvement of the alimentary tract have demonstrated submucosal invasion by blastocystidia and pseudohyphae, preceded by a band of advancing tissue necrosis only in those with *C. tropicalis* infections (40). Investigations of the pathophysiology of this process in experimentally infected animals have suggested a complex interplay (15) involving lysis of the mucin layer, microvilli, and villi by candidal hydrolytic enzymes (13), adherence to gastrointestinal mucosa (19, 22, 36, 37), suppression of the strictly anaerobic intestinal microflora by antibiotic therapy (20, 21), and neutropenia secondary to cytotoxic chemotherapy (12, 18). Depletion of CD4+ lymphocytes, however, predisposes to mucosal candidiasis of the alimentary tract but not to systemic dissemination (1, 6-8, 29).

Several animal models have been devised to reproduce gastrointestinal and systemic candidiasis as they occur in humans (10-13, 15, 16, 18, 20-23, 30, 31, 34, 41). Ideally, persistent gastrointestinal colonization by the *Candida* species should precede immunocompromising treatments which give rise to invasion and systemic dissemination. Persistent colonization of adult mice in the absence of compromising procedures has only been achieved with prolonged feeding of *C. albicans* incorporated in solid chow, which may partially protect the fungus from gastric acidity (34). The infant mouse model, however, circumvents these problems since gastrointestinal colonization with *C. albicans* initiated in infancy persists for at least 30 days (16, 31). Immunosuppression of the persistently colonized mice with cortisone and cyclophosphamide results in penetrative growth by the filamentous form of *Candida* species in the cardial-atrium fold of the stomach and dissemination to deep organs (10-12, 18).

*C. tropicalis* is an increasingly frequent cause of invasive candidiasis in neutropenic patients being treated for acute leukemia or undergoing bone marrow transplantation (35, 43). The virulence of *C. albicans* and *C. tropicalis* was similar after intravenous inoculation of intact mice (2, 42) and was comparably enhanced in animals rendered neutropenic with cyclophosphamide (2) or cytarabine (41). However, differentiation of *C. tropicalis* was greater than that of *C. albicans* after gastrointestinal inoculation of adult mice pretreated with gentamicin and cytarabine (41, 42). In this study, the infant mouse model was used to compare the gastrointestinal persistence of these two species and their invasiveness after immunosuppression.

*Candida* species may need to adhere to gastrointestinal epithelium before invasion can take place. *C. albicans* 4918 differs from its cerulenin-resistant mutant 4918-10 in the capacity to adhere to vaginal mucosa (25) or fibrin-platelet clots (5), but not to disks of mouse duodenal tissue in vitro.

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Gastrointestinal colonization and invasion by the parental and mutant strains were also compared in the infant mouse model.

MATERIALS AND METHODS

Microorganisms and culture conditions. *C. albicans* 177 and 194 and *C. tropicalis* 117 were donated by G. St-Germain (Laboratoire de santé publique du Québec, Sainte-Anne-de-Bellevue, Quebec, Canada), and *C. tropicalis* 83-48062 was obtained from the collection of E. Reiss (Centers for Disease Control, Atlanta, Ga.). All four strains were originally isolated from the blood of patients with acute leukemia and immediately lyophilized. *C. albicans* 4918 and its cerulenin-resistant mutant strain 4918-10 were kindly provided by R. A. Calderone (Georgetown University, Washington, D.C.) (5). Yeasts were cultured in 100 ml of Sabouraud dextrose broth (GIBCO Laboratory, Grand Island, N.Y.) for 18 h at 37°C. The culture was washed once by centrifugation, counted in a hemacytometer, and diluted in sterile 0.01 M phosphate-buffered saline (PBS) (pH 7.2), to yield 2.0 × 10⁸ yeasts per ml.

Infant mouse model. The infant mouse model (18, 31) was used to assess long-term colonization and systemic dissemination by *C. albicans* and *C. tropicalis*. Pregnant Crl:CFW (SW) Br mice (Charles River Canada Inc., St-Constant, Quebec, Canada) were housed in individual cages and maintained with their offspring after delivery. Five-day-old infant mice were isolated from their mothers and kept at 37°C for 1 h before inoculation with 1.0 × 10⁷ CFU of *C. albicans* or *C. tropicalis* contained in 50 μl of PBS. Mice inoculated with PBS alone, or unoinoculated, served as controls. The mice were returned to their respective mothers after inoculation.

Quantitative cultures of lung homogenates and gastric contents performed immediately after gavage demonstrated no pulmonary aspiration of *Candida* species and reproducible delivery of greater than 95% of the inoculum into the stomach. After weaning at 3 weeks of age, mice were maintained under conventional conditions and fed mouse chow (Prolab Animal Diet; Agway Inc., Syracuse, N.Y.) and water ad libitum.

Acute dissemination to deep organs. Three mice per *Candida* strain tested were sacrificed by cervical dislocation 30 min, 3 h, 3 days, and 10 days after inoculation. Individual mice were dissected, and the lungs, kidneys, and liver were mechanically homogenized (Stir-R model S63C; Tri-R Instruments, Rockville Center, N.Y.) in 10 ml of sterile isotonic saline. Samples were serially diluted and plated on Sabouraud dextrose agar (GIBCO) containing 50 μg of chloramphenicol per ml. Plates were incubated for 48 h at 37°C, and the number of CFU per organ was calculated.

Persistence in small and large intestines. Three mice per *Candida* strain studied were sacrificed 17, 24, and 31 days after oral-intra gastric inoculation. Total contents from the small or large intestine were serially diluted in sterile isotonic saline and spread on Sabouraud dextrose agar with chloramphenicol. Plates were incubated at 37°C for 48 h, and the number of CFU per intestinal segment was determined. Weights of control and inoculated mice were recorded at 3, 10, 17, 24, and 31 days after gavage.

Immunosuppression and systemic dissemination in persistently colonized mice. Systemic dissemination and mortality were examined in mice persistently colonized by *C. albicans* or *C. tropicalis* and immunosuppressed with cortisone acetate and cyclophosphamide (18). A portion of the mice surviving oral-intra gastric inoculation were sacrificed after 28 days to verify long-term colonization of the stomach and small intestine and to exclude persistent infection of the lungs, liver, or kidneys before immunosuppression. Persistently colonized mice were immunosuppressed with 1.25 mg of cortisone acetate (Merck, Sharp & Dohme Canada, Kirkland, Quebec, Canada) per g and 0.10 mg of cyclophosphamide (F. W. Horner Inc., Town of Mount Royal, Quebec, Canada) per g intraperitoneally on days 30 and 33 after inoculation, and survivors were sacrificed on day 36. Control mice including colonized animals sham-immunosuppressed with saline intraperitoneally, unoinoculated mice immunosuppressed with cortisone and cyclophosphamide, and mice inoculated with PBS were also sacrificed. All mice were dissected, and the number of *Candida* CFU was quantitated in the stomach, small intestine, lungs, liver, and kidneys. Weights of the mice were recorded in each group before and after immunosuppression.

Susceptibility to cerulenin. The stability of susceptibility or resistance to cerulenin in vivo was verified by testing *C. albicans* 4918 and 4918-10 isolated from stomach, intestine, liver, kidneys, and lungs of persistently colonized and immunosuppressed mice sacrificed 36 days after oral-intra gastric inoculation. Sixteen isolates of each strain were cultured on L agar (20 g of agar, 10 g of Bacto Peptone, 5 g of yeast extract) with or without 5 μg of cerulenin (Sigma Chemical Co., St. Louis, Mo.) per ml for 48 h at 37°C (9). Pairs of plates were compared for the presence and abundance of growth.

Immunofluorescence and immunoperoxidase. Indirect immunofluorescence and immunoperoxidase assays were conducted to specifically visualize *Candida* species in sections of the esophagus, stomach, and small intestine. Fresh tissues were fixed in 10% buffered neutral Formalin, processed for embedding in paraffin, and cut in sections 4 μm thick. Tissue sections were deparaffinized with toluene and hydrated in a graded ethanol series. The sections were washed in PBS for 10 min, and nonspecific adsorption was blocked by incubating with normal goat serum for 20 min. The sections were incubated with a 1/10 dilution of rabbit anti-*C. albicans* 3181A (serotype A) cell wall antiserum for 1 h at 22°C. After being washed four times with PBS, fluorescein-conjugated heavy- and light-chain-specific goat anti-rabbit immunoglobulin G (Meloy Laboratories, Inc., Springfield, Va.) diluted 1/20 in PBS was added. The sections were incubated for 45 min, washed four times with PBS, and examined in a fluorescence microscope. The indirect immunoperoxidase assay was conducted identically except for the use of peroxidase-conjugated heavy- and light-chain-specific goat anti-rabbit immunoglobulin G (Meloy Laboratories) diluted 1/20 in PBS. The sections were incubated for 45 min, washed four times with PBS, and substrate, a solution containing diamobenzidine tetrahydrochloride (0.1% in 0.1 M Tris buffer [pH 7.2] mixed with an equal volume of 0.02% hydrogen peroxide), was added. The color was developed in the dark for 5 min at 22°C, and the reaction was stopped by washing the sections several times in distilled water. The slides were examined by light microscopy.

Electron microscopy. Fresh portions of the esophagus, stomach, and small intestine were fixed in 0.1 M cacodylate-buffered 2.5% glutaraldehyde (pH 7.4) for 2 h at 4°C. Specimens were postfixed with 1% osmium tetroxide for 2 h at 22°C. After fixation, samples were washed in the same buffer, dehydrated through a series of graded ethanol, and embedded in Araldite 502. Thin sections were mounted on 400-mesh naked-nickel grids and counterstained with uranyl.
RESULTS

Acute dissemination to deep organs. All C. albicans and C. tropicalis strains disseminated to the lungs, liver, and kidneys within 30 min postinoculation, and total numbers of viable units of the two species were similar after 30 min, 3 h, 3 days, and 10 days, decreasing continuously over this period (Fig. 1). Cultures of organs from mice inoculated with PBS alone, or unoinoculated, were uniformly negative. Cumulative mortalities scored 28 days after inoculation ranged from 0 to 32% for C. albicans strains and 0 to 19% for C. tropicalis isolates (Table 1). No mortalities were recorded in uninoculated control mice or animals inoculated with PBS alone.

Numerous blastoconidia were observed in the stomach and small intestine 30 min after oral-intragastric inoculation with C. albicans or C. tropicalis, but could not be seen after 24 h, 4 days, or 8 days. Immunoperoxidase staining revealed blastoconidia in the lumen of the small intestine and deep between villi (Fig. 2a and b). Close association of blastoconidia with the villous surface resulted in lysis of microvilli and then progressive invasion of villi (Fig. 2b to d). Blastocconidia within villi were surrounded by a conspicuous zone of clearing (Fig. 2d).

Persistence in small and large intestines. Colonization of the small and large intestines by two C. albicans blood isolates and strains 4918 and 4918-10 was similar for 31 days after oral-intragastric inoculation. However, persistent colonization by the four C. albicans strains consistently exceeded that of the two C. tropicalis strains (P < 0.001, two-way analysis of variance with multiple comparisons) (Fig. 3). Infant mice inoculated with C. albicans gained weight less rapidly than uninoculated controls or mice inoculated with C. tropicalis strains (17 to 26 mice per strain; P < 0.05, weighted linear regression [14]).

Immunosuppression and systemic dissemination in persistently colonized mice. Persistent colonization of the stomach and small intestine was demonstrated 28 days after inoculation with the C. albicans strains but was undetectable in mice inoculated with C. tropicalis or PBS (Table 2). No deaths or systemic dissemination was observed in uninoculated mice, in animals inoculated with PBS, C. albicans, or C. tropicalis and sham-immunosuppressed, and in immunosuppressed mice inoculated with PBS. However, immunosuppression increased stomach CFU 40- to 370-fold and intestinal CFU 30- to 80-fold in mice colonized with C. albicans. Gastrointestinal colonization by C. tropicalis, undetectable before immunosuppression, only became apparent after treatment with cortisone and cyclophosphamide. C. albicans disseminated to the liver, kidneys, and lungs more frequently and with higher organ CFU than C. tropicalis (P < 0.002, Wilcoxon two-sample test). Despite this fact, 14 of 69 mice (20%) infected with C. tropicalis died, compared with 3 of 70 mice (4%) infected with C. albicans blood isolates (P = 0.004, chi-square). C. albicans 4918 disseminated to a greater extent than strain 4918-10 (P < 0.001, Wilcoxon) and produced higher mortality (15 of 48 mice [31%] compared with 1 of 55 mice [2%]; P < 0.001, chi-square). All isolates of C. albicans 4918 and 4918-10 recovered from persistently colonized and immunosuppressed mice remained susceptible and resistant to cerulenin, respectively.

Candida cells disseminated most extensively to the liver and then to the kidneys and lungs (Table 2). Typical candidal microabscesses were most abundantly observed on the surface of the liver, but were also found on the kidneys, stomach, intestine, lungs, skin, urinary bladder, and myocardium of immunosuppressed mice infected with C. albi-
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but not immunosuppressed. Marked atrophy of the thymus and spleen was observed in control and infected mice immunosuppressed with cortisone and cyclophosphamide. Uninfected mice and animals inoculated with C. albicans or C. tropicalis steadily lost about 17% of their body weight in the 6 days following the initiation of immunosuppression, while sham-immunosuppressed animals continued to gain weight.

Indirect immunoperoxidase and immunofluorescence as-

dys performed on sections of the esophagus, stomach, and small intestine from immunosuppressed, persistently colonized mice 36 days after inoculation revealed penetrative growth by hyphae of C. albicans or C. tropicalis exclusively in the mucosa and submucosa of the stomach. Candida cells were not seen in sections from unoinoculated control mice.

**DISCUSSION**

C. tropicalis is an increasingly frequent cause of invasive candidiasis in neutropenic patients being treated for acute leukemia or undergoing bone marrow transplantation (35, 43). However, the precise microbial and host factors which favor C. tropicalis as a cause of gastrointestinal and systemic candidiasis in these patients are presently unknown (17). The virulence of C. albicans and C. tropicalis was similar after intravenous inoculation of intact mice (2, 42) and was comparably enhanced in animals rendered neutropenic with cyclophosphamide (2) or cytarabine (41). In contrast, dissemination of C. tropicalis was greater than that of C. albicans after gastrointestinal inoculation of adult mice pretreated with gentamicin and cytarabine (41, 42). To reproduce the clinical condition in humans, however, persistent gastrointestinal colonization by the Candida species should preferably precede immunocompromising treatments which give rise to invasion and systemic dissemination. The infant mouse model is ideally suited for this purpose, since oral-intragastric inoculation of 5-day-old mice results in sustained colonization in the absence of compromising procedures (31). Immunosuppression of the persistently colonized mice with cortisone acetate and cyclophosphamide results in penetrative growth by the filamentous form of Candida strains in the cardia-atrium fold of the stomach and systemic dissemination (10–12). The model also reproduces the human condition because patients with culture-proven disseminated C. albicans or C. tropicalis infections and involvement of the alimentary tract had submucosal invasion by both blastoconidia and pseudohyphae (40). Findings obtained after immunosuppression of persistently colonized mice are thus considered to be more clinically relevant than those produced immediately after oral-intragastric inoculation, in which rapid transcytosis of Candida blastoconidia

**FIG. 2.** Blastoconidia of C. tropicalis 117 in sections of small intestine 1 h after oral-intragastric inoculation. Immunoperoxidase staining (a, b, and d) revealed blastoconidia in the lumen (a) and deep between villi (b). Close association of Candida cells with intestinal epithelium resulted in lysis of the villous surface (b, arrow) and destruction of microvilli (c). A conspicuous zone of clearing surrounded blastoconidia within villi (d, arrow). Magnification (a, b, and d), × 1,008.
GASTROINTESTINAL COLONIZATION AND SYSTEMIC CANDIDIASIS

CANDIDA ALBICANS

CANDIDA TROPICALIS

DAYS AFTER INOCULATION

FIG. 3. Total viable units of C. albicans or C. tropicalis in the small and large intestines of infant mice inoculated by the oral-intragastric route. Each point represents the mean of three mice.

nonimmunocompromised, persistently colonized mice (10), which may correlate with the band of advancing tissue necrosis preceding submucosal invasion by blastoconidia and pseudohyphae which was demonstrated in humans (40).

Little is known about the relative abilities of C. albicans and C. tropicalis to persistently colonize the normal gastrointestinal tract. Sustained colonization of the small and large intestines by C. albicans strains reproducibly exceeded that of C. tropicalis strains for 31 days after oral-intragastric inoculation and was correlated with significantly decreased weight gain compared with mice colonized with C. tropicalis or uninfected controls. Potential factors responsible for lower colonization by C. tropicalis include enhanced susceptibility to the suppressive effect of the anaerobic flora (20, 21), increased bacteria-yeast or yeast-yeast interactions (22), and decreased adhesion to gastrointestinal epithelium. C. tropicalis adheres less efficiently than C. albicans to fibrin-platelet clots (27), but adhesion of the two species to gastrointestinal epithelium in vitro has not been directly studied (33). The decreased weight gain of mice colonized with C. albicans may result from competition for or malabsorption of nutrients. The absence of systemic spread of both Candida species in persistently colonized mice before immunosuppression demonstrates that the normal gastrointestinal tract and host defense mechanisms effectively prevent invasion by Candida species.

Immunosuppression of persistently colonized mice with cortisone acetate and cyclophosphamide resulted in weight loss, increases in viable units in the stomach and small intestine, and systemic dissemination especially to the liver, all consistent with previous findings in studies on C. albicans (12, 18). In contrast, C. tropicalis only became detectable in the stomach and small intestine after immunosuppression. C. albicans hyphae have been demonstrated in the stratified squamous epithelium of the stomach of infant mice 10 days after oral-intragastric inoculation (30) and may have been the source of systemic dissemination by C. tropicalis after immunosuppression. In addition, C. tropicalis appeared more virulent than C. albicans, since it produced higher mortalities despite lower viable units in the liver, kidneys, and lungs. Taken together, these results suggest that factors responsible for gastrointestinal colonization, systemic dissemination, and mortality by Candida species in mice immunosuppressed with cortisone acetate and cyclophosphamide may not be identical. The finding of invasive Candida hyphae in the gastric mucosa but not other segments of the gastrointestinal tract after immunosuppression identifies the cardial-atrium fold as the portal of entry in mice with gastrointestinal and systemic candidiasis, in agreement with other reports (1, 6, 10-12, 18).

C. albicans 4918 disseminated to a greater extent than its cerulenin-resistant mutant 4918-10 and produced higher mortalities. This may have resulted from the 37-fold-greater stomach content of strain 4918 compared with strain 4918-10 before immunosuppression. Both strains have comparable abilities to adhere to disks of mouse duodenal tissue in vitro (38), but their relative adhesion to the cardial-atrium region of the stomach has not been determined. Such a study would be of interest to evaluate the potential role of adhesion in persistence of colonization at this portal of entry for invasive candidiasis.

Features of the virulence factors of C. albicans and C. tropicalis and their interactions with the microbial flora, epithelial cells, and host defense mechanisms of the gastrointestinal tract should further our understanding of the
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<th>No. colonized/no. inoculated&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment</th>
<th>No. dead/no. treated&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mortality (%)</th>
<th>Systemic dissemination (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>0/4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imunosuppressed</td>
<td>9/62</td>
<td>15</td>
<td>6 (0-1.5 × 10&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (0-1.0 × 10&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Colonization of stomach and small intestine 28 days after inoculation with PBS, C. albicans, or C. tropicalis.

<sup>b</sup> Cumulative mortalities, days 30 to 36 after inoculation.

<sup>c</sup> Percentage of persistently colonized and PBS-control mice with growth of Candida species in the liver, kidneys, or lungs, 36 days after inoculation.

<sup>d</sup> 36 days after inoculation.

<sup>e</sup> Persistently colonized and PBS-control mice were sham-immunosuppressed with saline intraperitoneally on days 30 and 33 after inoculation.

<sup>f</sup> Persistently colonized and PBS-control mice were immunosuppressed with 1.25 mg of cortisone acetate per g and 0.10 mg of cyclophosphamide per g intraperitoneally on days 30 and 33 after inoculation.
relative propensities of these two species to cause invasive candidiasis.

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REFERENCES


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