Gastrointestinal Candidiasis: Fact or Fiction?

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Abstract

While *Candida albicans* has long been acknowledged as a cause of vulvovaginitis, the clinical significance of gastrointestinal candidiasis (GIC) has been a subject of controversy. Although it is acknowledged that GIC can produce a disease state in immuno-compromised patients, it now appears pathologic GIC may be more prevalent than has been generally acknowledged. In recurrent vulvovaginal candidiasis, there is ample evidence suggesting GIC is a major contributing factor, and that vaginal treatment is unlikely to cure the condition unless the intestines are also treated. There is also considerable evidence GIC can cause systemic symptoms in non-immuno-suppressed humans, and is capable of translocation from the gastrointestinal tract to internal organs. In addition, it is now known *C. albicans* produces gliotoxin, an endotoxin which has been shown to impair immune response, and can interfere with normal intracellular glutathione metabolism. Natural antifungal fatty acids, such as caprylic acid and undecylenic (10-undecenoic) acid, have been used in the treatment of GIC, with *in vitro* tests indicating undecylenic acid is a significantly more effective antifungal. *In vitro* testing also shows the essential oils from certain plants, such as oregano, possess significant activity against *C. albicans*. Various probiotic organisms, including *Lactobacillus acidophilus* and *Saccharomyces boulardii*, have been shown in animal studies to inhibit the growth and translocation of *C. albicans*. It is therefore reasonable to conclude, even in otherwise healthy individuals, *C. albicans* infections of the gastrointestinal tract can cause significant symptoms which warrant treatment.
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Introduction

Although it is an acknowledged cause of vulvovaginitis, the dimorphic fungi *Candida albicans* has been considered a normal inhabitant of the human gastrointestinal tract,[1] producing a disease state only in immuno-compromised patients — those with leukemia, AIDS, undergoing chemotherapy or radiation treatment, or being treated with immuno-suppressive drugs. Other conditions, such as diabetes mellitus, alcoholism, and the administration of systemic antibacterial drugs have also been recognized as risk factors for alimentary tract candidiasis.[2]

Since publication of *The Missing Diagnosis* by Truss in 1983,[3] followed by Crook's *The Yeast Connection: A medical breakthrough*,[4] a controversy has raged in both the popular press and scientific circles regarding the significance of gastrointestinal candidiasis (GIC) and its ability to cause systemic symptoms. Over a decade later, articles continue to appear in the

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scientific literature questioning the significance of GIC and the symptoms attributed to it.[5,6] Other research evidence, however, indicates pathologic gastrointestinal *C. albicans* infections may be more prevalent than has been generally acknowledged.[7-13]

Recurrent Vulvovaginal Candidiasis

The connection between GIC and recurrent vulvovaginal candidiasis is perhaps the one area which most clearly demonstrates the disease-causing potential of *C. albicans* infections of the gastrointestinal tract. Ninety-eight consecutive patients complaining of recurrent vaginal candidiasis (three or more episodes) were evaluated. *C. albicans* was found in both vaginal and fecal material in 52% of the patients; 47% of the patients were Candida-free in both sites. In approximately one-third of the patients, there had been no previous laboratory confirmation of candidiasis; however, in no case was Candida previously isolated from the vagina of a patient who subsequently proved to be yeast-free. In only one patient was *C. albicans* found in the stool but not in the vagina. The authors state: "The results of this study demonstrate that vaginal candidiasis does not occur naturally without the concomitant presence of *C. albicans* within the large bowel and that a 'cure' is not likely as long as the vagina remains the only treatment target."[8]

In a multicenter placebo-controlled study, a total of 258 women with vulvovaginal candidiasis who also exhibited Candida organisms in the rectum were treated with either oral nystatin or placebo, as well as with either vaginal nystatin or clotrimazole. Microscopic, culture, and symptomatic responses were superior in the group receiving combined intravaginal-oral therapy; 88% of those treated by both routes remained clear of Candida after 21 days, as compared with 75% of those receiving only intravaginal medication ($p<0.05$).[9]

In a separate, prospective, placebo-controlled study, patients with a history of recurrent vulvovaginitis and a current diagnosis of candidal vaginitis were treated with oral ketoconazole. All patients were initially treated for 14 days, then placed on either placebo daily or one of two oral ketoconazole regimens for six months. At the end of 12 months (six months after the treatment was discontinued), 23.8% of the women who had received placebo during the six months of treatment were asymptomatic and attack-free, as opposed to 42.9%-52.4% in the two ketoconazole groups ($p<0.05$). The authors conclude: "It appears that maintenance prophylactic therapy with oral ketoconazole is effective in preventing recurrent episodes of vulvovaginal candidiasis, but that relapse is common after withdrawal of the drug. Because of the risk of hepatotoxicity, caution is essential in selecting patients for long-term ketoconazole therapy and in following patients undergoing such treatment."[10]

In patients with recurrent or resistant vaginal candidiasis, an acquired hypersensitivity reaction to *C. albicans* has also been reported, and desensitization therapy with *C. albicans* antigen has been found to be an effective treatment.[14-16] In a clinical trial, ten women with recurrent candidal vaginitis were treated with a commercially available *C. albicans* antigen in increasing doses per a desensitization protocol. Prior to treatment the subjects' average time to relapse was 5.1 months. After treatment the mean relapse rate was 15.7 months ($p< 0.01$), with eight of the ten showing dramatic improvement.[15]

Both localized and systemic hypersensitivity responses to *C. albicans* have been demonstrated. In a study to determine whether an allergic component exists in recurrent vaginitis, vaginal washings and serum samples were examined for anti-Candida albicans IgE antibodies. In 64 subjects with recurrent vaginitis, using ELISA-modified RAST testing, specific IgE antibodies were identified in

Table 1. Comparison of *C. albicans* stool culture results with Crook's Questionnaire.[17]

Culture Results (Mean Values)	Questionnaire Results
No growth	49.5
1-2 colonies	67.0
3-6 colonies	97.9
7-11 colonies	113.3
12+ colonies	117.9

18.8% of vaginal washing samples, but only in 6.1% of sera. None of the 20 controls were positive for anti-Candida IgE. The authors state: "The detection of specific IgE antibodies vaginally but not in the peripheral circulation suggested the occurrence of a localized vaginal hypersensitivity response."[16] Although no such response has been demonstrated as yet in the intestinal tract, it is not unreasonable to postulate that possibility. If true, this would imply that various vague, generalized intestinal symptoms accompanying GIC might in fact be due to intestinal hypersensitivity responses to *C. albicans*.

Intestinal Candidiasis

While the connection between GIC and recurrent vulvovaginal candidiasis is relatively clear, other research demonstrates GIC can also cause disease-related symptoms in non-immuno-suppressed humans. A study conducted at Seattle's Bastyr University showed the degree of *C. albicans* growth on stool culture correlated well with symptomatic scores on the "Crook Questionnaire."[17] Subjects, who had a negative history of gastrointestinal disease, were asked to complete a Crook Candida Questionnaire[4] and were tested for GIC by stool culture. A strong correlation between *C. albicans* colony counts and questionnaire scores was found, consistent with the questionnaire's use for screening purposes. (See Table 1).

C. albicans has also been shown to be a cause of diarrhea.[11,12] In one three-year study, 854 patients (640 children and 214 adults) with acute or chronic diarrhea were screened. Fungal proliferation was noted in 54.8% of these patients (53.6% in children, 58.4% in adults). The predominant fungal species isolated were *Candida albicans* (64.5%), followed by *C. tropicalis* (23.3%), *C. krusei* (6.9%), and *Torulopsis glabrata* (1.6%). Trichosporon sp. and Geotrichum sp. were found to be responsible for the diarrhea in 2.3% of adults.[11]

Translocation and Systemic Dissemination

A further area of candida-related controversy relates to the ease with which *C. albicans* can become systemically disseminated in non-immuno-suppressed patients. Individuals can be predisposed to *C. albicans* colonization of the gastrointestinal tract by antibiotic administration, as demonstrated through both animal and human studies. Antibiotic treatment decreased the total population levels of the indigenous bacterial flora in 86% of Syrian hamsters, and predisposed animals not only to gastrointestinal overgrowth but also subsequent systemic dissemination (to liver, kidneys, and spleen) by *C. albicans* following intragastric inoculation. None of the non-antibiotic-treated control animals showed any *C. albicans* when visceral organs were cultured. In 10% of antibiotic-treated animals whose intestinal flora had been reestablished prior to *C. albicans* inoculation, *C. albicans* was cultured from the liver, but not from either the kidneys or spleen. Examination of the mucosal surfaces of the intestinal tract also indicated that animals with an intact intestinal microflora had significantly lower numbers of *C. albicans* adhered to the gut walls than did antibiotic-treated animals.[18]

The authors state: "The results indicate that the indigenous microflora reduced the mucosal association of *C. albicans* by

forming a dense layer of bacteria in the mucus gel, out-competing yeast cells for adhesion sites, and producing inhibitor substances (possibly volatile fatty acids, secondary bile acids, or both) that reduced *C. albicans* adhesion. It is suggested, therefore, that the indigenous intestinal microflora suppresses *C. albicans* colonization and dissemination from the gut by inhibiting Candida-mucosal association and reducing *C. albicans* population levels in the gut."[18]

In infant mice (15-19 days old), systemic and gastrointestinal infection was established after oral-intragastric challenge with *C. albicans*. High levels of organisms in the liver, kidney, spleen, stomach and intestine were found in all animals up to the 24th post-infection day.[19]

Gastrointestinal colonization and systemic dissemination by *C. albicans* and *C. tropicalis* have been compared in both intact and immuno-compromised mice. Five-day-old CFW mice were inoculated orally with two *C. albicans* and two *C. tropicalis* strains isolated from the blood of patients with acute leukemia. Both *C. albicans* and *C. tropicalis* spread to the lungs, liver, and kidneys within 30 minutes following inoculation. In animals colonized with *C. albicans*, immuno-suppression with cortisone acetate and cyclophosphamide on days 30 and 33 after inoculation increased the number of fungal organisms in the stomach 40- to 370-fold, and in the intestines by 30- to 80-fold. *C. albicans* disseminated to the internal organs more frequently and in greater numbers than *C. tropicalis*. However, 20% of mice infected with *C. tropicalis* died, compared with only 4% infected with *C. albicans*.[20]

In 1969, Krause et al demonstrated intact *C. albicans* organisms are capable of escaping the intestinal tract and reaching the blood and urine in humans. Krause, himself the subject, was examined to exclude any intestinal, pulmonary or renal disease, and had not used local or systemic antibiotics in the previous 10 years. Following an extensive evaluation to eliminate the possibility of any preexisting yeast infection, he ingested a large dose (10^{12} organisms) of *C. albicans* orally. Within 2 hours he developed pyrexia, shivering, and headache. Although most of the fungal organisms probably remained in his gastrointestinal tract, the organism was cultured from blood samples at 3 and 6 hours, and from urine specimens collected 2 3/4 and 3 1/4 hours after inoculation. All colonies grown were found to be identical to the strain administered.[21] Clearly, it is possible for *C. albicans* to cross the intact gut wall and cause systemic effects in non-immuno-suppressed human subjects.

Toxin Production

Endotoxins have recently been shown to stimulate both *in vitro* and *in vivo* bacterial translocation across the gut mucosa.[22] *C. albicans* produces a variety of endo- and exotoxins,[23-27] including a toxic epipolythiodioxopiperazine metabolite called gliotoxin, which has been shown to possess immunomodulating and antiphagocytic properties.[28-29] Significant levels of gliotoxin have been found in the vaginal secretions of patients who were symptomatic for vaginal candidiasis.[26] In one study, 32 out of 50 *C. albicans* strains obtained from patient cultures were found to contain gliotoxin and related toxins, suggesting the possibility that these substances "may contribute to the virulence of the organism."[27]

Gliotoxin exhibits profound immunosuppressive activity *in vivo*,[30] which could account for the GIC-related immune system suppression reported by Truss[3] and Crook.[4] Gliotoxin induces apoptosis in thymocytes, splenocytes, and mesenteric lymph node cells, and can selectively deplete bone marrow of mature lymphocytes. The molecular mechanism by which gliotoxin is thought to exert these effects is by preventing the activation of transcription factor NF-kappaB in response to

a variety of stimuli in T and B cells.[31] In addition, gliotoxin may interfere with normal glutathione metabolism within the cell,[32,33] providing at least a theoretical basis for the increased chemical sensitivity frequently reported to be caused by GIC.[34]

Therapeutic Approaches

In addition to Crook's diversified, fresh-foods diet which restricts all refined carbohydrates, specific antifungal agents have typically been employed to combat GIC.[4] Pharmaceutical antifungals such as nystatin, ketoconazole, amphotericin B, fluconazole and itraconazole have all been utilized, as well as various natural antifungal agents.

Antifungal Fatty Acids and Essential Oils

Fatty acids have been known and used for centuries as antimicrobial agents, originally in the manufacture of soaps. In the last 50 years, however, they have found use both *in vitro* as yeast and mold inhibitors in food stuffs, and as topical, intestinal, and systemic antifungals. In recent years, both caprylic acid and undecylenic acid have been used to treat GIC.

Undecylenic acid (10-undecenoic acid) is an eleven-carbon, mono-unsaturated fatty acid, $C_{11}H_{20}O_2$. A substance found in the body (naturally occurring in sweat), undecylenic acid is produced commercially by the vacuum distillation of castor bean oil, as a result of the pyrolysis of ricinoleic acid. It has been used orally in humans as an unsuccessful treatment for psoriasis and neurodermatitis,[35-37] and as an economical antifungal agent,[38] as well as being commonly used as a topical antifungal in such over-the-counter products as Desenex®.

Undecylenic acid has very low toxicity. In humans, as much as 20 grams per day has been taken orally with only mild gastrointestinal symptoms,[36] and up to 400 mg/kg/day has been given orally to rats for 6-9 months, with no toxicity being noted.[39]

Caprylic acid, although present in small quantities in coconut oil, can be produced commercially from the oxidation of octanol.[40] Classified by some authors as an hepatic failure toxin when used intravenously,[41] caprylic acid ($C_8H_{16}O_2$), is a direct isomer of the anticonvulsant valproic acid.

Most organic fatty acids are fungicidal. As early as 1945, Wyss et al demonstrated that the greater the number of carbon atoms in the fatty acid chain, the greater the fungicidal activity, up to the point exceeding eleven carbons where solubility becomes the limiting factor.[42] In 1954, Neuhauser evaluated both undecylenic and caprylic acids *in vitro* against *C. albicans*, and concluded caprylic acid was more effective.[38] However, she used a questionable method of applying the fatty acids which may have rendered the results inaccurate. The pH of the test environment is critical to accurate *in vitro* testing of antifungal agents. Peck and Rosenfeld had earlier demonstrated an acid environment alone (pH less than 5.8) is sufficient to inhibit fungal growth in several species, including *C. albicans*.[43] Therefore, great care must be exercised so that pH is accurately controlled, to reflect only the antifungal effect of the substance tested, and not just its hydrogen ion (pH) effect.

Neuhauser tested undecylenic and caprylic acids by adding *C. albicans* culture to Sabourand's agar media, adjusting the pH to either 5.6 or 7.5, and then pouring the broth into petri dishes and allowing it to cool. The plates were then dusted with the fatty acid (in a resin matrix) being tested, incubated, and evaluated.[38] This method does not control pH at the interface between the fatty acid and the C. a*lbicans* organisms. Since both fatty acids have an intrinsically low pH, it can be assumed the resultant pH at the actual point of contact between the fatty acid and the C. al*bicans* in Neuhauser's study was actually lower than reported.

Peck and Rosenfeld circumvented this problem by mixing the fatty acid being tested into the Sabourand's media prior to adjusting the pH, so the test conditions could be more precisely controlled. Their study showed undecylenic acid was approximately six times more effective as an antifungal than caprylic acid,[43] a finding which is consistent with the research of Wyss et al.[42]

Essential oils of various plants also have been shown to be antifungal, including thyme, cloves, cinnamon, and oregano.[44] A recent *in vitro* evaluation of essential oil of oregano (*Oreganum vulgare*) showed the minimum inhibitory concentration against *C. albicans* to be <0.1µg per ml. In contrast, the minimum inhibitory concentration for a mixture of the calcium and magnesium salts of caprylic acid was <0.5 mg per ml, indicating that caprylates are significantly less potent antifungals than essential oil of oregano.[45] Although no clinical studies have been published supporting their use in GIC, essential oils are recommended by some practitioners based on clinical experience.

Probiotics

While ingestion of probiotic organisms such as La*ctobacillus acidophilus* has been used empirically for treating candidiasis, only one recent, controlled study has been performed. In a crossover trial lasting 12 months (six months with no yogurt, six months with 8 oz. of yogurt taken orally daily), Hilton et al evaluated the effects of consumption of yogurt containing *L. acidophilus* on patients with recurrent candidal vulvovaginitis. Patients had significantly fewer vaginal candidal infections while consuming yogurt (0.38±0.51) than during the control period (2.54±1.66, P=0.001).[46]

Oral ingestion of four different probiotic bacteria has also been shown to protect both athymic and euthymic mice from mucosal and systemic candidiasis. The presence of *L. acidophilus*, *L. reuteri*, *L. casei GG* or *Bifidobacterium animalis* prolonged the survival of the mice, decreased the severity of mucosal and systemic candidiasis, and decreased the C. albicans colony count in the alimentary tract.[47]

Oral administration of at least one probiotic micro-organism, *Saccharomyces boulardii*, has been shown in animal studies to inhibit the translocation of *C. albicans* from the gastrointestinal tract. Antibiotic-treated, pathogen-free mice were orally inoculated with C. *albicans* to promote intestinal overgrowth and subsequent translocation of this organism. The oral *S. boulardii* regimen reduced the incidence of mesenteric lymph node (MLN) cultures positive for *C. albicans* but did not decrease the numbers of *C. albicans* per gram of MLN in immuno-competent mice. However, steroid-induced immuno-suppression increased translocation of *C. albicans* to the MLN, and allowed translocating *C. albicans* to spread systemically to the spleen, liver, and kidneys. In these immuno-suppressed mice, orally administered *S. boulardii* decreased both the incidence of *C. albicans* translocation to the MLN, liver, and kidneys, and the number of translocating *C. albicans* per gram of MLN, spleen, and kidneys.[48]

Conclusion

Although additional research needs to be done in order to definitively determine the systemic effects of GIC, upon taking an overall view of the published literature it is possible to make the following observations:

1) Oral antibiotics can dramatically increase C. *albicans* levels in the intestinal tract.

2) GIC may cause localized vaginal and perhaps intestinal hypersensitivity responses.

3) GIC has been shown to cause significant symptoms in non-immuno-compromised humans.

4) Under certain conditions, even in the presence of an intact immune system, *C. albicans* may translocate across the intestinal wall and

spread systemically, as shown in both experimental animals and in humans.
5) Certain strains of *C. albicans* and other fungal organisms known to inhabit the human gastrointestinal tract produce endotoxins which can impair immune response and perhaps even cause chemical hypersensitivity.
6) Various natural antifungal agents and probiotics can exert antifungal or other protective actions to inhibit *C. albicans* growth or prevent translocation.

It is therefore reasonable to conclude, even in otherwise healthy individuals, C. al*bicans* infections of the gastrointestinal tract can cause significant symptoms which warrant treatment.

Over forty years ago, Irene Neuhauser, M.D., stated: "Intestinal infections due to *Candida albicans* have recently become a subject of much interest. The appearance of large numbers of this organism in the feces of patients receiving certain antibiotics was noted soon after the introduction of these drugs into clinical medicine.... It is fortunate that the undesired symptoms caused by antibiotic therapy and the greatly increased numbers of *C. albicans* organisms found in the feces of such patients usually disappear within a relatively short time after the use of the drug has been discontinued. However, in a few cases this is not so and the patient continues to have more or less severe symptoms which parallel the presence of large numbers of *C. albicans* organisms in the feces.... Intractable intestinal moniliasis is serious and is being seen much more frequently than formerly."[38] Dr. Neuhauser's assertions are still true today.

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