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Enteritis Distribution among People Infected with Candidiasis

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Introduction

Candidiasis is an opportunistic infection caused by *Candida*, a type of fungi. Fungi are eukaryotic organisms found in the form of yeast, molds, or dimorphic fungi (Vanani *et al.*,2019).

Like other living organisms, fungi form a complex group with a wide range of life cycles, metabolisms, morphogenesis, and ecology including mutualism, parasitism, and commensalism. The fungal kingdom has historically been divided into four phyla, two of which share a monophyletic origin (the dikarya: Ascomycota, Basidiomycota) and two which are considered the basal fungi (Zygomycota, Chytridiomycota) (Stajich *et al*., 2009).

The genus *Candida* is a form of yeast, belongs to the phylum Ascomycota. It is considered one of the most important opportunistic pathogenic yeast-like organisms through human pathogens. This broad genus includes more than 200 species, the most prevalence of which is *Candida albicans* (Williams and Lewis, 2011, Behzadi and Behzadi, 2012).

These fungi present in healthy individuals as a commensally organisms by inhabiting various body surfaces such as oral cavity, gastrointestinal tract, vagina and healthy individual's skin. They become pathogenic and cause infections only when favorable conditions arise (Vanani *et al*., 2019) such as impaired immune system, underlying disease states, and prolonged use of antibiotics (Martins *et al*., 2014).

Candidiasis may be classified by its location into oral candidiasis (oral thrush), oropharyngeal candidiasis, genital (vulvovaginal) candidiasis, cutaneous candidiasis and invasive candidiasis (candida in the bloodstream). The most danger is invasive candidiasis or candidemia because it has the highest mortality rate among other types of *Candida* infections (CDC, 2016).

The presence of *Candida* in the gastrointestinal tract is normal, but an overgrowth may lead to serious health problems due to an imbalanced gut, causing gut-related symptoms such as bowel movement changes, excessive gas, etc. Some diseases, such as Crohn's disease and ulcerative colitis, are associated with an overgrowth of *Candida* in the gastrointestinal tract. A healthy digestive system relies on a good balance of bacteria that live in the gut, and an important role in maintaining this balance is having the ingested type of food. *Candida* overgrowth can be prevented first of all by healthy eating patterns, as susceptibility is increased by a high-sugar diet and diabetes or nutritional deficiencies causing a dysregulated immune system. Recent research has shown an increasing interest in the *Candida*-related conditions and diseases (Rusu *et al*., 2020).

Taxonomy of Genus *Candida*

Dean and Burchard (1996) classified *Candida spp.* as:

Kingdom: Fungi.

Phylum: Ascomycota.

Sub phylum: Saccharomycotina.

Class: Saccharomycetes.

Order: Saccharomycetales.

Family: Saccharomyceteae.

Genus: *Candida*.

The term *Candida* derives from the Latin word *Candida* which means white. *Candida's* spores are a commensal, harmless type of fungi that become invasive and pathogenic when the flora balance or the host homeostasis is

disrupted. This genus contains about 200 species and is the largest medically important yeast genus. At least 30 species of *candida* were identified as the causative agent of candidiasis and the number continues to grow (Miceli *et al*,. 2011). However, only five species cause around 95% of infections including *Candida ablicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei* (Turner and Butler, 2014, Gabaldon *et al*., 2016).

C. albicans is among the several species of *Candida*, the most common fungal pathogen of candidiasis (65.3%), followed by *C. glabrata* (11.3%), *C. tropicalis* (7.2%), *C. parapsilosis* (6.0%) and *C. krusei* (2.4%) (Pfaller *et al*., 2010, Giri and Kindo, 2012).

Epidemiology of Candidiasis

There is substantial geographical, centre-to-centre and unit-to-unit variability in the prevalence of *Candida spp.* (Fig.1). *C. albicans* continues to be the most prevalent *Candida spp*. causing disease in both adult and pediatric populations, but the past decades have witnessed an increase in diagnoses of *non-albicans* candidaemia in both groups (Castanheira *et al*., 2016). The prevalence of *non-albicans Candida spp*. in most regions is usually determined by factors such as background antifungal usage patterns in the region, individual patient risk factors and clonal outbreaks, that is, outbreaks involving a *Candida spp.* molecular strain that is unique in a health-care environment. In the United States and northwestern Europe, the second most common species is generally *C. glabrata* in the non-outbreak setting (Castanheira *et al*., 2016). *C. glabrata* is also generally more common among individuals of >60 years of age and among recipients of solid organ transplant (Cleveland *et al*., 2015, McCarty and Pappas, 2016). In Latin America, Southern Europe, India and Pakistan, *C. parapsilosis* and/or *C. tropicalis* are much more frequently encountered than *C. glabrata*. *C. krusei* is the least common of the five major *Candida spp.*, and it is

most often found among patients with underlying hematological malignancies who have received antifungal prophylaxis with fluconazole (Castanheira *et al*., 2016). A very worrisome global trend is the emergence of *C. auris* (Clancy and Nguyen, 2017). An increasing number of countries have reported cases of *Candida auris* infection. Data presented are from Australia, Brazil, Canada, Denmark, France, Japan and the United states (Cleveland *et al*., 2015). Data on *C. auris* are from the Centers for Disease Control and Prevention (last accessed 27 March 2018) (Pappas *et al*., 2018).

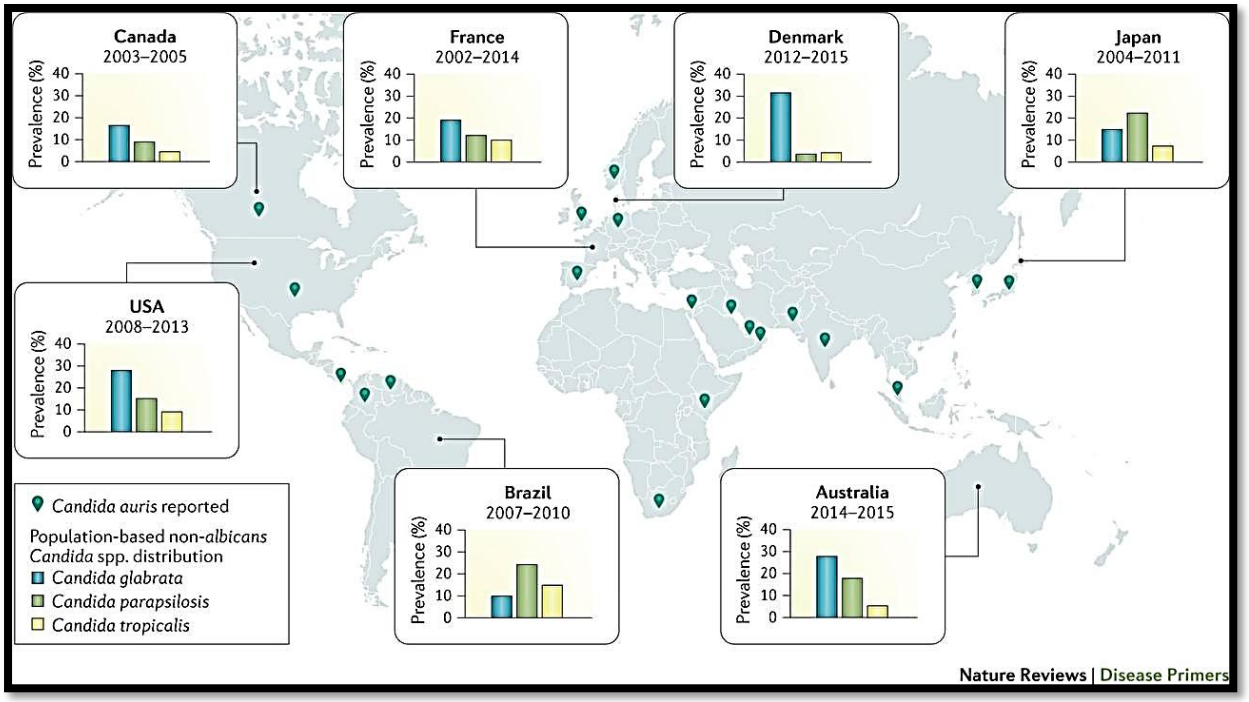

Figure 1: Geographical variations in the distribution of *Candida spp.*

Globally, *Candida albicans* is the most prevalent species associated with candidiasis, however, the distribution of *non-albicans Candida spp*. varies greatly, as exemplified in the representative countries shown. Of note, the species distribution may have changed since the data were collected (Pappas *et al*., 2018).

Etiology of Candidiasis

Candidiasis is an opportunistic infection. *C. albicans* is present in healthy persons colonizing the oropharyngeal, esophageal, and gastrointestinal mucosa. *C. albicans* can cause mucosal candidiasis in these areas where they usually are present in an immunocompromised host. In patients who have leukemia, lymphoma because of the consumption of corticosteroids or cytotoxic drugs, their immunity is compromised, leading to candidal infection. Antibiotic usage is commonly associated with candidiasis. Cancer cytotoxic chemotherapy may result in fungemia caused by *C. albicans*, which develop from fungal translocation through compromised mucosal barriers. Fungal commensals in the upper and lower GI tract can transform into opportunistic pathogens due to changes in endogenous bacterial population size or composition, as well as changes in the host environment (Bertolini and Dongari-Bagtzoglou, 2019). Vaginal colonization increases in diabetes mellitus, pregnancy, and the use of oral contraceptives. Oral candidiasis is very closely associated with HIV patients. More than 90% of HIV patients present with candidiasis. Other predisposing factors of candidiasis include TB, myxedema, hypoparathyroidism, Addison's disease, nutritional deficiency(vitamin A, B6, Iron), smoking, poorly maintained dentures, IV tubes, catheters, heart valves, old age, infancy, and pregnancy (AN and Rafiq, 2020).

Classes of Candidiasis

There are several classes of candidiasis, which have become more common in recent years. Depending on body location, the mucocutaneous candidiasis can be classified as: oral candidiasis, genital candidiasis, intrauterine candidiasis, anal candidiasis and nails candidiasis (Martins *et al*., 2014).

Oral Candidiasis

Oral and perioral candidiasis is the more common type of acute mucocutaneous candidiasis (Martins *et al*, 2014). Oral candidiasis can be pseudomembranous, erythematous, and chronic hyperplastic candidiasis. Pseudomembranous candidiasis is common in chronically ill patients and infants. It is presented as white, soft, slightly elevated plaques most commonly on the tongue and buccal mucosa. Erythematous candidiasis is also known as antibiotic sore mouth. It occurs as a sequel to the use of broad-spectrum antibiotics or corticosteroids. The lesions present as consistently painful erythematous areas along with central papillary atrophy of the tongue. It is also known as kissing lesion when the palate is involved and exhibit erythema due to contact with the tongue. Chronic hyperplastic candidiasis, also known as candidal leukoplakia, presents with firm white perdistent plaques on lips, tongue, and buccal mucosa. These plaques may be homogenous or nodular and persist for years. It has premalignant potential (AN and Rafiq, 2020). Sometimes corners of the mouth could be reached, when this happens, it is labeled as angular cheilitis, being evidently a mucosal thickening and cracking. This type of candidiasis particularly affects people with immune system disorders and people with dental prostheses. It can be also found in patients receiving chemotherapy for cancer treatment, or taking immunosuppressive drugs to protect transplanted organs or in patients infected by HIV. In children and young people, it may be involved with oral (thrush) and lingual disease. In addition, and despite being very rare, esophageal candidiasis can occur in patients infected by HIV and cancer (Martins *et al*., 2014).

Genital Candidiasis

Vulvovaginal candidiasis (VVC) is the most frequent type of genital yeast infection. Approximately 75% of women experience, at least once in their

lifetime, an episode of VVC, 40-50% experience at least one additional episode of infection, 20-50% remain without any clinical manifestation, and lastly, 5% experience recurrent VVC episodes. Although, not being a threat to life, it is unpleasant and problematic (Martins *et al*., 2014), causing a variable degree of itching, burning and whitish discharge "cottage cheese-like", abundant and flocculent (AN and Rafiq, 2020). This infection is very common in pregnant women, especially in the last trimester of pregnancy, when a variation of progesterone, estradiol and glycogen, associated with an increase in vaginal pH, favors the emergence of these infections. In this case, special attention should be given due to the potential occurrence of contamination of the fetus in the uterus, or even the child during childbirth. On the other hand, it has been observed that, in individuals with diabetes, the incidence of vaginal candidiasis is higher (Martins *et al*., 2014). Similarly, patients submitted to broad-spectrum of antibiotic therapy, used to treat bacterial infections, and even the use of oral contraceptives, are also important factors associated with higher rates of incidence of VVC (Willems *et al*., 2020).

In men, balanitis, which usually appear after sexual contact, is characterized by the appearance of a rash, more or less prickly, followed by small pustules on rocking groove-preputial discharge, more or less abundant. Although this kind of injury is well defined, in particular cases it can extend to the groin and perianal region. The major factors associated with this type of infections are antibiotic therapies, diabetes and vaginal secretions of the sexual partner (Martins *et al*., 2014).

Intrauterine Candidiasis

This type of infection is frequent during pregnancy. It is important to avoid the occurrence of this type of intense vaginitis in the last few weeks of pregnancy, because it can complicate and extend to the uterus, infecting the

child before birth. At childbirth, or in the first hours of life, it can be observed a widespread rash, maculopapular or pustular-vesicular. During the following weeks after birth, the clinical status may be complicated, extending to other body locations, which usually are treated with local antibiotics (Martins *et al*., 2014). Several recent studies have identified a potential role for intrauterine *Candida albicans* in adverse pregnancy outcomes, including preterm birth. There is, however, a limited understanding of the impact of intrauterine *Candida* infection on fetal well-being in early pregnancy. Using a sheep model of early pregnancy, there was a study done, the aim of which is to determine (1) the ability of experimentally induced intrauterine *C. albicans* to infect the fetus and (2) whether *C. albicans* exposure in early pregnancy is associated with alterations in fetal cardiac function, as measured by spectral tissue Doppler imaging analysis of fetal cardiac function. This study concluded that intrauterine *C. albicans* infection in a sheep model of early pregnancy causes systemic fetal candidiasis, which is associated with a robust systemic inflammatory response and progressive cardiac dysfunction detectable by spectral tissue Doppler imaging (Stock *et al*., 2017).

Anal Candidiasis

This type of infection is characterized by intense itching/pruritus, accompanied by burning sensation, and localized erythema around the anus. Skin may appear macerated with circumscribed lesions, which may eventually invade the intergluteal groove. This type of infection is most common in children; despite the frequency in women due to the use of hormonal contraceptives, intimate hygiene products, clothing and their practice of oral and anal intercourse, functioning as transient colonization of local organisms shed from the intestinal tract. As candidiasis can be sexually acquired, males can be affected (Zaidi and Lanigan, 2010).

Nails Candidiasis

Candida species are not considered normal yeasts on nails flora. Therefore, this type of infection is a sign of colonization (secondary growth) despite primary infections of nail fold and nail bed with Candida species may also occur, which are related to a disease of the nails. Onyxisdystrophy or periungal tissue is related to nail disease. This type of infection may appear, like paronychia and onychia. The paronychia is characterized by an inflammation, more or less painful, in peripheral skin nail, which appears red and brilliant. The predisposing factors are essentially, sex, different traumas (e.g., in manicure), professional activity and hormonal variations. Although infrequent in males, this infection can appear in cooks, confectioners and employees of canning factories. Usually, the nail injury itself, or onyxis (ingrown nail), is secondary to paronychia. It is characterized by a progressive striation, dyschromias (discoloration) and opacity of the nail plate, which ultimately becomes crumbly. This infection appears abruptly and painfully, leading to detachment of the nail and can spread to other nails (Martins *et al*., 2014).

Candida Colonization of the Intestine

Candida microorganisms commonly colonize the human gastrointestinal tract as a component of the resident microbiota. In the GI tract, *C. albicans* encounters and responds to varying features of the physical environment such as pH, oxygen levels and nutrient levels. *C. albicans* also responds to secretions produced in the GI tract such as bile. These findings argue that *C. albicans* is well adapted for growth in the GI tract. Their presence is generally benign (Kumamoto, 2011), however, an overgrowth may lead to serious health problems due to an imbalanced gut, causing gut-related symptoms such as excessive gas, intestinal cramps, and/or diarrhea (Rusu *et al*., 2020). Recent studies show that high level *Candida* colonization is associated with several

diseases of the gastrointestinal tract including enteritis. Further, results from animal models argue that *Candida* colonization delays healing of inflammatory lesions and that inflammation promotes colonization. These effects may create a vicious cycle in which low-level inflammation promotes fungal colonization and fungal colonization promotes further inflammation. Both inflammatory bowel disease and gastrointestinal *Candida* colonization are associated with elevated levels of the pro-inflammatory cytokine IL-17. Therefore, effects on IL-17 levels may underlie the ability of *Candida* colonization to enhance inflammation. Because Candida is a frequent colonizer, these effects have the potential to impact many people (Kumamoto, 2011).

Predisposing Factors for Increase *Candida* Colonization of the Intestine

The presence of *Candida albicans* in the gastrointestinal tract is generally benign (Kumamoto, 2011), but an overgrowth may lead to serious health problems including enteritis. Inflammatory bowel diseases, etc. (Rusu *et al*., 2020). Predisposing factors that lead to increase candida colonization of the intestine include the following:

1. **Decreased Digestive Secretions**

   In a normal organism the digestive secretions, such as hydrochloric acid, bile and pancreatic enzymes have an important role not only for a correct digestion, but also to prevent *Candida* overgrowth and its penetration into absorptive surfaces in the GI tract (Guinan *et al*., 2018). Therefore, an improvement of digestive secretions is pivotal and, in some cases, is an important step to treat chronic candidiasis. Pancreatic enzymes perform an important role as therapeutic agents enabling an efficient and complete digestion of proteins and other dietary compounds. Any dysfunction on this process leads to several problems, such as food

allergies and formation of toxic substances. Furthermore, those enzymes are responsible for the preservation of the integrity of small intestine without parasites and other opportunist microorganisms (bacteria, yeasts, worms, protozoa), helping in the degradation of immunocomplexes.

The intake of antacids and antiulcer drugs has a high risk of GI infections, showing a *Candida* species overgrowth. Therefore, to restore the normal digestive secretions to proper levels, through the use of supplementary hydrochloric acid, pancreatic enzymes and substances that promote the normal bile flow, is highly important in the treatment of chronic candidiasis (Martins *et al*., 2014).

2. Dietary Factors and Nutrients Deficiency

A balanced organism needs all the macro and micronutrients in right proportions and, therefore, any unbalanced diet affects the wellbeing of the body and potentiates growing and colonization of certain invaders. Some foods, like refined sugars, sucrose, fruit juice, honey and maple syrup have an important interference, functioning like growth enhancers. Moreover, foods with high content of yeast and fungi favor the growth of *Candida*, some examples are cheeses, alcoholic beverages and dried fruits. Another food group that stimulates growth is milk and dairy products, not only because of the high content of lactose but also, in some cases, due to the presence of antibiotics. Another important situation observed in most individuals with chronic candidiasis, is the presence of food allergies, therefore all known allergens should be eliminated. Thus, dietary factors should be monitored according to the needs of each individual. Some essential nutrients usually in deficit on chronic candidiasis are zinc, magnesium, selenium, essential fatty acids, folic acid and vitamins B6 and A (Kumamoto *et al*., 2020).

3. **Impaired Immune System and Underlying Disease States**

Dysfunctions of the immune system turn the human body more vulnerable to various kinds of infections. Thus, it is of extreme importance to maintain the good conditions of the immune system in order to prevent overgrowth of certain microorganisms and opportunistic infections. By itself, a weak immune system is already sufficient to constrain the health and resistance of individuals, although with the current and prolonged or frequent consumption of antibiotics, chemotherapy, steroids, radiation, stress, as well as some environmental contaminants, the body is still more susceptible. Furthermore, any disease that, directly or indirectly, affects the immune system increases the body's susceptibility to the growth and development of pathogenic and opportunistic microorganisms. This is the case of some increasing prevalence diseases, such as cancer, diabetes, and hypothyroidism, that in addition to debilitate immune system of individuals, has led to a continuous and exacerbated prescription of immunosuppressant drugs. In fact, the most common diseases that predispose to an increased sensitivity to *C. albicans* overgrowth are diabetes mellitus, cancer, leukemia, AIDS, thyroid dysfunction and other diseases, in which host defense mechanisms are suppressed or adrenal cortex steroids, antibiotics, other similar drugs are used (immunosuppressed patients) (Bertolini and Dongari-Bagtzoglou, 2019).

4. **Prolonged Use of Antibiotics**

Antibiotics have been identified as a major responsible factor for the development of chronic candidiasis. Since its mode of action is based on the elimination of intestinal bacteria, responsible for preventing the growth of yeasts and other pathogenic organisms, as well as suppressing the immune system, antibiotics action result in a *C. albicans* overgrowth. This situation becomes shortly a vicious cycle: a person with an alteration of the immune system is more susceptible to infections and, consequently, more

infections will appear increasing the doses and frequency in the consumption of antibiotics. This fact not only favors the overgrowth of *C. albicans* and other yeasts, but particularly bacteria, which increasingly develop mechanisms of resistance against antibiotics.

An established fact is that, the indiscriminate use of antibiotics substantially increases the risk of developing complications caused by *C. albicans* and other resistant pathogens. This is particularly important in hospitals because nosocomial infections by resistant microorganisms often lead to lethal complications. Therefore, the reduction of the prescription and use of antibiotics can be considered an effective alternative to control and/or minimize the resistance problem. Another alarming factor is the widespread use of antibiotics in animals, which not only contribute to microbial resistance in animals themselves, but also indirectly affect humans: antibiotic resistance and consumption of food contaminated by antibiotics (Ben-Ami *et al*., 2012).

5. Inflammatory Conditions of the GI Tract

Like antibiotic treatment, the presence of inflammation in the GI tract alters bacterial colonization and the activities of the host, creating conditions that favor both high level *Candida* colonization and exacerbation of disease (Kumamoto, 2011).

Some of these inflammatory conditions are Crohn's disease and ulcerative colitis:

- Crohn's disease

  The inflammation that is characteristic of Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is thought to arise as a result of dysregulated immune interactions between the host and components of the intestinal microbial flora. To test for an association between Candida colonization and CD, a large-scale study of families in which multiple members suffered from CD was

conducted. The authors studied both CD patients and their unaffected, healthy relatives (HR). Healthy relatives often exhibit characteristics that have been noted in patients such as increased intestinal permeability or defects in oral tolerance, but they do not have clinical disease. HRs are therefore less likely to have been treated with medications that might increase the likelihood of Candida colonization, such as antibiotics and immunomodulators.

Stool samples from both patients and HRs are more frequently contained significant levels of *C. albicans* than stool samples from control individuals (individuals who lived in the same geographic region and had no history of IBD). In addition to increased frequency of colonization, patients and HR carried *C. albicans* at higher levels than control individuals. A similarity in colonization between patients and HR was observed when family members lived together in the same household and when they did not. Therefore, similarity in carriage within families was not simply due to a shared environment. The authors suggest that subclinical inflammation is present in HRs, this effect could influence *C. albicans* colonization. Thus, this study demonstrated an association between familial Crohn's disease and intestinal colonization by *C. albicans* (Kumamoto, 2011).

- Ulcerative colitis

  Patients with ulcerative colitis (UC), another form of IBD, are also frequently colonized by *Candida*. For example, in one study, many patients with long standing disease (duration >5 year) had high level colonization detected in stool or brush smears from inflamed mucosa. Among the control group (individuals with diarrhea but not UC), only one person was highly colonized. Further, in patients with active disease who were colonized with *Candida*, treatment with the antifungal drug fluconazole led to a reduction in clinical signs and in

the size of inflammatory lesions. Although these effects may be direct or indirect, the results argue that reducing Candida colonization reduced disease severity (Kumamoto, 2011).

6. **Impaired Liver Function**

The modifications of the liver functions, as a result of injury or chemical causes, can change detoxification mechanisms. In this situation, as the liver is not able to perform its functions properly, toxins are absorbed by the intestine being accumulated, which affects more the liver and other organs function, and increase the body's sensitivity to chemicals. The accumulation of toxins in the body, as a result of liver damage, associated with changes in the mechanisms of detoxification, also stimulates *C. albicans* overgrowth. One way to diagnose if liver function is affected or if the mechanism of filtration of the blood is not properly being done, is through the manifestation of symptoms (e.g., psoriasis, premenstrual syndrome, among others) of chronic candidiasis outside of digestive tract (Martins *et al*., 2014).

7. **Altered Bowel Flora**

As described, drugs and other chemical compounds greatly affect the wellbeing of the body. If the liver does not work properly, products and metabolites resulting from poor digestion are accumulated in the body causing toxicity and, at the same time, favoring pathogenic strains, and also *C. albicans* overgrowth. Therefore, intestinal flora is of utmost importance in maintaining proper intestinal health and balance, being involved in the maintenance of nutritional status, immune system function, cholesterol metabolism, carcinogenic agents and aging. It is imperative to promote healthy and growth of beneficial intestinal flora, not only after taking antibiotics, but also in other situations. It should also be noted that chronic stress greatly affects the balance of intestinal flora and suppresses the immune system function. In other hand, especially in women, the hormonal

balance is very important and the oral routine of contraceptive use is itself a predisposing factor to *C. albicans* overgrowth once it is a causative agent of variation in the balance of the intestinal microflora (Martins *et al*., 2014).

Effects of Candida Colonization on the Intestine

1. **High level *C. albicans* colonization triggers the development of enteritis and IBD**

   CD patients and HRs share many characteristics, such as increased intestinal permeability or defects in oral tolerance, yet HRs do not have disease. To date, no single factor that explains why some people develop CD and others do not has been identified. It is clear that development of CD requires the microbiota. In human patients surgically treated for CD, recurrence of the disease was not observed when the fecal stream was diverted but recurred after fecal transit was restored. In laboratory studies, mice that are genetically susceptible to colitis but are germ free do not develop colitis. Upon colonization with bacterial flora, these mice develop disease. Thus, it is thought that in CD patients, homeostasis between the normal intestinal flora and the host has somehow broken down so that components of the commensal flora evoke an aberrant immune response. It is most likely that some individuals are highly susceptible to CD because of a combination of genetic and environmental factors. In these individuals, one or more triggering event(s) occur that can result in the development of CD. Once the triggering event occurs, immune responses that culminate in recurrent inflammatory conditions are set in motion. The nature of the putative triggering events is not known. One possible triggering event may be antibiotic use. Analysis of a large database of patient records showed a statistically significant association between antibiotic use, especially tetracycline use, and subsequent diagnosis with CD. Antibiotic use may alter both the total

level of bacteria colonizing the intestinal tract and the composition of organisms. Antibiotic use also results in increased *Candida* colonization. Because different organisms differ in their propensity to lead to inflammation, these effects of antibiotics may influence the amount or type of stimulation that the immune system receives and affect inflammation (Kumamoto, 2011).

Recently, attention has focused on the role of a subset of T-helper cells, Th17 cells, in IBD. Biopsies of inflamed mucosa or blood cells from IBD patients produce higher levels of IL-17, a cytokine secreted by Th17 cells. Increased levels of IL-17 are also produced by gastric ulcer biopsies in comparison to non-ulcer tissue. Further, IL-23, a cytokine that promotes the expansion and maintenance of Th17 cells, is required for induction of T-cell mediated colitis in murine models. These findings favor a role for IL-23 and IL-17 in IBD. Intriguingly, colonization by *C. albicans* increases IL-17 and IL-23 production by murine gastric and oral tissues. Therefore, *Candida* colonization could enhance inflammation by increasing levels of these cytokines. High-level colonization by *Candida* occurring in a susceptible individual with subclinical inflammation could thus exacerbate inflammation and trigger CD, a possibility discussed by Standaert-Vitse et al (Standaert-Vitse *et al*., 2009). Further studies will be required to investigate this possibility (Kumamoto, 2011).

2. ***C. albicans* colonization inhibits the healing of inflammatory lesions of the intestine and increase their severity**

To elucidate the interplay between *Candida* and the host during disease, animal models of GI tract disease have been employed. For studies of ulcers, rats or mice are treated with ulcer inducing chemicals such as cysteamine, a compound that concentrates in the duodenum producing duodenal ulcers. When rats received cysteamine treatment and *C. albicans* inoculation on the same day, almost all rats (16/17)

developed perforated duodenal ulcers. Rats who received cysteamine but no *Candida* exhibited perforated ulcers at a lower frequency (4/15). The area and depth of the ulcers were also greater in the presence of *C. albicans* than in its absence. Rats receiving *C. albicans* alone without cysteamine did not develop ulcers. Therefore, in this model, ulcers were more severe when C. albicans was present(Kumamoto, 2011).

In a subsequent study, *C. albicans* was administered to rats beginning 3 days after cysteamine treatment. The duodenum of these rats was examined several days later, when ulcer healing should have begun. Duodenal ulcers were observed in 70% of the rats treated with both cysteamine and *C. albicans* compared to 33% of rats that received only cysteamine. The area of the ulcers was significantly larger in the animals that received both cysteamine and *C. albicans*. Ulcer scarring was observed in animals that did not receive *C. albicans*, but rarely in animals that received *C. albicans*. Therefore, the presence of *C. albicans* delayed ulcer healing in this animal model (Jin *et al*., 2008).

IBD has been modeled by treating animals with chemicals or by using mutant strains of mice. For example, dextran sulfate sodium (DSS), which injures epithelial cells and causes inflammation, or trinitrobenzene sulfonic acid (TNBS), which produces ulceration, have been used to produce colitis. Poulain and coworkers treated mice with DSS and some mice were also inoculated with *C. albicans* by oral gavage. The presence of *C. albicans* led to a modest increase in disease severity. For example, in the presence of *C. albicans*, the mice exhibited severe inflammation with massive influx of neutrophils and tissue destruction. Tissue levels of myeloperoxidase (MPO), indicative of neutrophils in the tissue, were elevated in mice that received *C. albicans* compared to those who did not. Tissue expression of the cytokine TNF-α was also higher in DSS-treated mice that received *C. albicans* (Jawhara *et al*., 2008).

TNBS-treated rats inoculated with *C. albicans* exhibited a larger area of colonic damage, and increased MPO activity in colon tissue (Zwolinska-Wcislo *et al*., 2009). When fluconazole was administered to the rats along with *C. albicans*, the damage and MPO activity were reduced. Thus, the presence of *C. albicans* enhanced colitis in these animal models. Taken together, these studies show that *C. albicans* exacerbates damage and delays healing of inflammatory lesions in animal models (Kumamoto, 2011).

3. *C. albicans* colonization of the intestine is associated with invasive candidiasis

Invasive candidiasis refers to bloodstream infections with *Candida spp.* (candidemia). It is an emerging infection closely linked to advances in medical technology and is widely recognized as a major cause of morbidity and mortality in the health-care environment. One of the possible risk factors for the development of invasive candidiasis is the escape of *C. albicans* through the gastrointestinal barrier (for example, owing to gastrointestinal perforation) and enter the bloodstream (Pappas *et al*., 2018).

In a recent study that supports this view, Miranda et al (Miranda *et al*., 2009) recovered *Candida* organisms from the blood of patients with candidiasis and compared those organisms to organisms cultured from the rectum or skin of the same patient. In most cases of *C. albicans* candidemia, the strain identified in a patient's blood sample and the strain identified in the same patient's rectum sample were identical. These findings support the model that commensal organisms residing in the GI tract can escape from this niche and reach the bloodstream (Miranda *et al*., 2009).

Evaluation of *Candida ssp.*

A vaginal discharge sample can help to diagnose vaginal candidiasis by examining under a microscope or by fungal culture in a laboratory. Under the microscope, budding yeast is visible. Oral thrush is mostly a clinical diagnosis but can also be confirmed by looking at the scrapings of the rash under the microscope. For systemic candidiasis, a blood culture is a diagnostic tool (Valente *et al*., 2020).

Treatment of *Candida ssp.*

Candida infections are treated with antifungal medications such as nystatin, clotrimazole, amphotericin B, miconazole. Mild or moderate genital *Candida* infections can have treatment with antifungal vaginal cream. The antifungal creams come in 1, 3 or 7-day treatment. Econazole or fluconazole 150 mg orally one-time dose can also be prescribed (Fang *et al*., 2020). Oral and topical treatments have similar efficacy, but oral medications are more expensive. Clinicians should avoid prescribing fluconazole in the first trimester of pregnancy (Zhang *et al*., 2019). For recurrent vaginal candida infections, fluconazole dosing is on days 1, 4, and 7, and then weekly for six months is given. Similar treatment can be used for oral thrush, with oral lozenges as a substitute dose form. Systemic candidiasis requires treatment with oral or intravenous antifungal medications, including caspofungin, fluconazole, and amphotericin B (Nirmala *et al*., 2019).

Prognosis of *Candida ssp.*

Vaginal and skin infections, although the most common *Candida* infections are localized. Therefore these can be treated with antifungal drugs to obtain complete recovery and excellent prognosis and outcomes. An untreated *Candida* infection can affect other organs and may lead to a systemic infection.

The long term prognosis with systemic candidiasis depends on the severity and location of the *Candida* infection, the general health of the infected person, and the timing of diagnosis and treatment. Almost one-third of the patients with candidemia develop septic shock according to host factors such as age and source of the infection than intrinsic virulence factors of organisms (Bassetti *et al*., 2020).

Conclusion

Candida micoorganisms commonly colonize the human gastrointestinal tract as a component of the resident micrbiota, but we concluded from this study that an overgrowth of this organism can make it an opportunistic pathogen that may lead to serious health problems in the predisposed patients.

As the studies discussed above show, high-level *Candida* colonization is frequently observed in immunocompromised patients, after prolonged use of antibiotics, nutritional deficiencies and due to changes in endogenous bacterial population size or composition, as well as, changes in host environment. *Candida* colonization is also frequently observed in IBD patients. The presence of *Candida* in those patients delays healing and exacerbates the disease. This vicious cycle in which inflammation promotes *Candida* colonization and *Candida* colonization delays healing may impact many patients. The effects of antifungal treatment on UC patients argue that reduction in fungal colonization could be beneficial for colonized patients.

C. albicans may invade gastrointestinal barrier and enter the bloodstream causing candidemia, but absence of predisposing conditions, such as gastrointestinal perforation, doesn’t permit the invasion.

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