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Narrative review

The human gut mycobiome and the specific role of *Candida albicans*: where do we stand, as clinicians?

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ABSTRACT

Background: The so-called 'mycobiome' has progressively acquired interest and increased the complexity of our understanding of the human gut microbiota. Several questions are arising concerning the role of fungi (and in particular of *Candida albicans*), the so-called 'mycobiome', that has been neglected for a long time and only recently gained interest within the scientific community. There is no consensus on mycobiome normobiosis because of its instability and variability. This review aims to raise awareness about this interesting topic and provide a framework to guide physicians faced with such questions.
Objectives: To summarize current knowledge and discuss current and potential implications of the mycobiome in clinical practice.
Sources: We performed a review of the existing literature in Medline Pubmed.
Content: This review identifies several studies showing associations between specific mycobiome profiles and health. Fungi represent a significant biomass within the microbiota and several factors, such as diet, sex, age, co-morbidities, medications, immune status and inter-kingdom interactions, can influence its structure and population. The human gut mycobiota is indeed a key factor for several physiological processes (e.g. training of the immune system against infections) and pathological processes (e.g. immunological/inflammatory disorders, inflammatory bowel diseases, metabolic syndromes). Moreover, the mycobiome (and *C. albicans* in particular) could influence an even broader spectrum of conditions such as psychiatric diseases (depression, schizophrenia, bipolar disorder) or chronic viral infections (human immunodeficiency virus, hepatitis B virus); moreover, it could be implicated in tumorigenesis.
Implications: Candida albicans is a well-known opportunistic pathogen and a major component of the mycobiome but its role in the gastrointestinal tract is still poorly understood. From a potential screening biomarker to a key factor for several pathological processes, its presence could influence or even modify our clinical practice. **Stefano Musumeci, Clin Microbiol Infect 2022;28:58**
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Introduction

The human gut microbiota, an ecological community of commensal, symbiotic and potentially pathogenic microorganisms, has acquired increasing interest in recent years as a possible key factor for several physiological and pathological processes [1]. Although research mainly focused on bacteria, this complex ecosystem includes fungi, viruses and archaea. Fungi (the so-called 'mycobiome') have been neglected and has only recently gained interest within the scientific community. Fungi represent less than 0.01%–0.1% of the human microbiota [2]; nevertheless, each genome being about 100-fold larger than that of a bacterial cell, they represent a significant biomass with numerous functions. Defining the human gut mycobiome remains challenging: there is currently no consensus on mycobiome normobiosis. The reasons are several: lack of standardized investigational approaches [2],

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mycobiome instability and variability (as a result of host characteristics such as diet [3,4], sex [5], age [6], co-morbidities, medications, immune status [7] and inter-kingdom interactions [8], for example the synergy between *Candida albicans* and *Enterococcus faecalis* [9]. This review aims to summarize current knowledge and provide a framework to guide physicians faced with such questions.

Main determinants of the mycobiome

An important limitation comes from the lack of standardized investigational techniques. Fungal databases are less accurate than bacterial ones, taxonomic information may be lacking and the wrong identification related to fungal life cycle can be challenging [10]; moreover, culture-independent techniques (i.e. ITS1, ITS2, 18S, 28S rRNA) may not be able to differentiate 'real' colonizers from those accidentally found in the gut and coming from the environment (i.e. diet) [2].

Diet seems to play a fundamental role in shaping the mycobiome. Hoffman et al. speculated that the presence of *Saccharomyces* spp. in the gut might be related to the consumption of yeast-containing foods, whereas *Candida* spp. seems to be related to the ingestion of carbohydrates [4]. David et al. showed a different mycobiome in guts of people living primarily on plant-based or animal-based diets [3]. Differences have also been observed with broad diet groups, such as vegetarians or people on a Western diet [10].

The specific roles of diet, gender and age in mycobiome composition remain poorly understood. Strati et al. found a higher number of fungal isolates of various fungal species in female individuals compared with male individuals [6]; this could be due to the role of sex hormones as well as to gender-differences in diet [11]. Furthermore, the presence of *Candida* spp. in female faecal samples can be linked to the higher prevalence of *Candida* spp. in the vaginal mycobiome [12]. Higher numbers of species in the gut mycobiome were found in infants and children compared with adults, but only when culture-independent (ITS1, ITS4) methods were used [6].

Diseases seem to alter the mycobiome; pathophysiology is nevertheless far from being elucidated. Among the hypotheses, the relationship between mycobiome and immunity could explain some of the pathological processes underlying several diseases. Iliev et al. speculate that fungi may play a role in immunological disorders by tuning the host immune response [7]: *C. albicans* is considered as the major inducer of T helper type 17 (Th17) cells [13] and has been shown to increase the production of cytokines like interleukin-22 (IL-22) [14] (a recently identify cytokine of the IL-10 family with pro-inflammatory properties) implicated in several autoimmune diseases.

A reduced fungal family diversity has been demonstrated in obese individuals [15]; similar results have also been reported in an anorexic patient [16]. Dysbiosis has been found in patients with psychiatric conditions such as depression, schizophrenia, bipolar disorder and eating disorders [17]. Interestingly, the administration of probiotics in schizophrenic patients resulted in reduced *C. albicans* serum antibodies and improved symptoms [18]. In diabetic individuals, *C. albicans* in the intestine was more prevalent compared with control individuals [19]. Chen et al. found a positive correlation between progression and severity of chronic hepatitis B infection and the variety of fungal species [20]. In human immunodeficiency virus-positive individuals (with CD4 <200 cells/μL) the prevalence of *C. albicans* in the gut was considerably higher than that in seronegative patients (age- and sex-matched) [21].

Recent studies have shown an alteration of the gut mycobiome in patients infected by severe acute respiratory syndrome coronavirus 2, independently of the severity of infection [22], and characterized by an over-representation of *C. albicans* [23]. Nevertheless, the sample was modest and could have been influenced by the use of broad-spectrum antibiotics.

Inflammatory bowel diseases remain probably the largest field of study to understand the relationship between mycobiome and diseases [24,25]. An increased *Basidiomycota*/*Ascomycota* ratio (mainly due to an increase of *C. albicans* and a decrease of *Saccharomyces cerevisiae* has been demonstrated in individuals with inflammatory bowel diseases compared with healthy volunteers [26]. Interestingly, similar epidemiological characteristics such as geographic location as well as common risk factors, genetic susceptibility and immunological abnormalities between multiple sclerosis and inflammatory bowel diseases could find a denominator in the way the mycobiome is shaped and how it similarly modulates the host immunological response [27].

Candida spp. may also be involved in graft-versus-host disease and in the pathogenesis of some tumours, like colon adenomas [28] and pancreatic ductal adenocarcinoma [29].

Although fungi are known opportunistic pathogens in immunocompromised patients [30], they can also protect against mucosal injury by modulating the immune response [31]. Antibiotics (in particular those with a broad spectrum) are the principal cause of mycobiome dysbiosis, and increase the risk of developing local and systemic fungal infections (mainly *C. albicans*) [32]. The effect of antifungals on the mycobiome is less known. In murine models, these drugs can reduce fungal diversity, and increase the number of T helper cells (such as Th1 and Th17), thus aggravating chemically induced colitis. Although these results may suggest a link between fungal dysbiosis and inflammation [33], further studies are needed to understand its relevance to humans. All these obstacles can easily cast a doubt as to whether or not a mycobiome 'normobiosis' exists.

The role of *Candida albicans* in the human gut mycobiome

The human gut mycobiome is less heterogeneous compared with fungal communities [2], with *Ascomycota* and *Basidiomycota* as the most represented phyla, while *Saccharomyces*, *Malassezia* and *Candida* are the most relevant genera [2]. *Candida* spp., and in particular *C. albicans*, are well-known members of the human mycobiome. In a group of 11 preterm infants of different gestational ages, the mycobiome was mainly composed of a single species of yeast of which *Candida* was the prevalent genus. Fungal heterogeneity increased with age and post weaning diet [34]; in a Swedish cohort of healthy infants as much as one-third of the paediatric population had yeasts (mainly *C. albicans*) colonization in the faecal microbiota by 3 years of age [35].

Western diet and antibiotics can influence gut colonization by *C. albicans* [36]; interestingly, colonization rates are much lower in non-Western societies [37].

Diet, bacterial microbiota and antibiotics

A positive correlation has been found between *C. albicans* abundance in the stool and high carbohydrate consumption [38], whereas a negative correlation has been found for diets rich in amino acids, proteins and fatty acids [4]. In particular, glucose triggers yeast-to-hyphal transition, a fundamental step leading to increased virulence of *Candida* spp. by improving the capacity to penetrate the tissues, colonize indwelling devices and produce biofilm, as well as by contributing to the ability to escape the immune system [39]. The hyphal form is in effect predominant in patients with candidiasis [40].

Bacteria, as mentioned, are fundamental to keep a balanced gut microbiota, and to avoid fungal overgrowth (in particular that of

C. albicans). Anaerobic bacteria (mainly clostridial *Firmicutes* and *Bacteroidetes*) are capable of activating hypoxia-inducible factor-1α and decreasing intestinal colonization and mortality from invasive candidaemia [32]. Moreover, fatty acid metabolites produced by the bacterial microflora may exert immunomodulatory effects and inhibit *C. albicans* germination [8]. It has been shown that *Pseudomonas aeruginosa* can kill hyphal *C. albicans* by producing 15-hydroxyeicosatetraenoic acid from exogenous arachidonic acid [41].

Antibiotics use is considered one of the main destabilizers of the gut microbiota. In mice, the use of broad-spectrum antibiotic treatment facilitates *C. albicans* gastrointestinal overgrowth [42]. Mason et al. showed the role played by *C. albicans* in shaping the microbiota by interacting with bacteria in different ways: by boosting the recovery of certain populations such as Bacteroidetes while down-regulating others (such as *Lactobacillus*) [43].

Gutierrez et al. showed that higher concentrations of substrates such as carbohydrates, sugar alcohols and primary bile acids, normally used by gastrointestinal bacteria, were available after cefoperazone treatment, because of the decrease of the bacterial population and could promote *C. albicans* growth [44].

The role of probiotics

The preventive role of probiotics (both bacterial and fungal) has been used to reduce gastrointestinal problems including those related to antibiotics use. Their mechanism of action, composition and efficacy are nevertheless far from being elucidated and not all probiotic formulations seem beneficial for preventing the potential pathogenicity of *Candida* spp. [45].

In order to explain the anti-*Candida* activity of probiotic bacteria, Payne et al. proposed several mechanisms, such as nutritional competition, antimicrobial compounds (bacteriocins, hydrogen peroxide), enhancement of phagocyte activities, regulation of peristalsis, epithelial cell renewal rates and pH alteration [46].

Saccharomyces boulardii is probably one of the best known fungal probiotics used in acute infectious gastroenteritis and antibiotic-associated diarrhoea [47]. Pappas et al. showed that probiotic yeasts, such as *Saccharomyces cerevisiae* var. *boulardii*, may have a synergistic effect on the survival of probiotic bacteria [48]. Roy et al. reported in a preterm and low birthweight infant population (112 patients included) that *Lactobacillus* and *Bifidobacterium* species significantly lowered *C. albicans* levels in the gastrointestinal tract, and reduced the incidence of candidaemia [49]. Also, Kumar et al. showed in a paediatric intensive care population in India that those receiving a probiotic cocktail had fewer positive tests for *C. albicans* (rectal swab) compared with those receiving a placebo during broad-spectrum antibiotic courses [50]. Nevertheless, this reduction did not reflect a lower prevalence of candidaemia.

Beneficial and detrimental role of C. albicans in the mycobiome

The high prevalence of *C. albicans* in the gastrointestinal tract of humans, shown in several studies, in otherwise healthy individuals raises questions whether any beneficial effect could be related to its gastrointestinal tract carriage.

Kumamoto et al. bring up the capacity of *C. albicans* to train our immune systems not only against systemic candidiasis, but also against other pathogen-related infections [51], such as *Staphylococcus aureus* [52], *Aspergillus fumigatus* or *Pseudomonas aeruginosa* [52]. Panpetch et al. showed that in murine models, the administration of *C. albicans* right before challenge with *Clostridium difficile* resulted in a more severe disease [53], whereas gut colonization of *C. albicans* before *C. difficile* challenge protected against lethal *C. difficile* infection [54]. These results may highlight the role of *C. albicans* in reducing the inflammatory response under certain conditions [55]. Lopez-Medina et al. showed in a neutropenic mouse model that *C. albicans* was able to inhibit *P. aeruginosa* virulence (by suppressing the expression of specific genes), but without affecting its colonization capacity, increasing survival from *P. aeruginosa* infection [56].

From SIFO to candidaemia

Different unexplained gastrointestinal symptoms (belching, bloating, indigestion, nausea, diarrhoea, flatulence) in otherwise immunocompetent patients have been attributed to an excessive number of fungal organisms in the gut (hence the names 'small intestinal fungal overgrowth', or SIFO [57], 'intestinal candida/fungal overgrowth' [38] and 'Candida/Yeast hypersensitivity syndrome' [58]). Although fungal overgrowth could indeed facilitate generalized, yet non-specific, gastrointestinal tract symptoms, the lack of diagnostic tests makes the validity of these clinical entities controversial [33]. Jobst and Kraft did not to find any correlation between several different complaints potentially related to intestinal fungal overgrowth (for example migraine, abdominal discomfort, eczema) and the presence of *C. albicans* in the stool [59]. Instead, a correlation between the expansion of the intestinal mycobiome and the onset of fungaemia in allogeneic haematopoietic cell transplant patients has been described [60]. Therefore, it could be interesting to monitor the dynamics and composition of the mycobiome to identify patients at high risk of fungaemia, and to develop prophylactic and/or therapeutic strategies.

Implications for clinical practice

Whether current knowledge and future progress on this topic will finally influence or even modify our clinical practice is difficult to foresee. One of the biggest challenges in this field remains the lack of standardized investigational techniques.

Nevertheless, several works that we have summarized in this paper seem to point to the mycobiome as an impactful key player in health in the near future. Among the most relevant issues, is the possibility for diets to modulate *C. albicans* physiology in the gut [38,61]. Moreover, more diagnostic approaches could stem from an in-depth understanding of the mycobiome; for example, gut mycobiome signature could be harnessed as potential screening biomarker. Indeed Nagpal *et al.* showed an association between mycobiome signature and Alzheimer disease markers in patients with mild cognitive impairment [61] (and suggested a potential role of mycobiome-modifying diets in disease evolution), while Luan *et al.* described the mycobiome of patients with intestinal adenomas and suggested that the mycobiome can be used as a diagnostic biomarker in differentiating among adenomas of different stages [28]. Antibiotics are major destabilizers of the gut microbiota. Besides the well-known association between antibiotics overprescription and the worldwide rise in antimicrobial resistance, inappropriate antibiotic usage can damage the microbiota, allowing the overgrowth of fungi with pathogenic potential such as *C. albicans* [37,38]. There is increasing evidence that the gut mycobiome and different chronic conditions (e.g. neoplasms, immunological/inflammatory disorders, psychiatric diseases, metabolic syndromes, inflammatory bowel diseases) can mutually interact; it will be of great importance to determine the clinical significance of such interactions in clinical practice (see Table 1 and Fig. 1).

Table 1
The potential roles of *Candida albicans* and *Candida* spp. in human health

	Examples	References
Training the immune system:		
Against fungal infections	Systemic candidiasis and *Aspergillus fumigatus*	[31,51,52,62]
Against bacterial infections	*Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Clostridium difficile*	[51,53–56,62]
Non-specific gastrointestinal tract symptoms	Due to *Candida* overgrowth	[33,38,57–59]
Increased risk of fungaemia	Allogeneic haematopoietic cell transplant patients	[60]
Increased virulence of *Candida*	Glucose intake eases yeast to hyphae transition	[4,39,40,63]
Favours/aggravates:		
Neoplasic diseases	Graft-versus-host disease, tumours (colon adenomas and pancreatic ductal adenocarcinoma)	[28,29]
Immunological/inflammatory disorders	Rheumatoid arthritis, multiple sclerosis	[7,13,14,27,64]
Psychiatric conditions	Depression, schizophrenia, bipolar disorder and eating disorders	[16–18]
Metabolic syndromes	Obesity, diabetes type 1 and 2	[15,16,19]
Inflammatory bowel diseases	Crohn's disease and ulcerative colitis	[26,27]
Viral infections	Hepatitis B virus, human immunodeficiency virus type 1	[20,21]

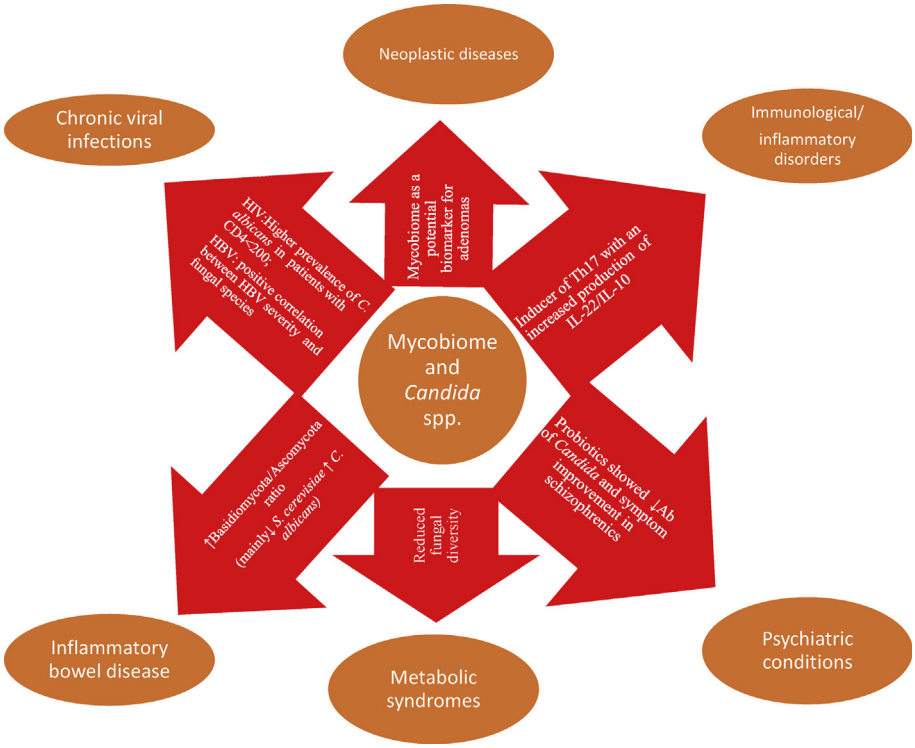

Fig. 1. Relationship between the mycobiome and *Candida* spp. in different diseases.

Conclusions

Although interest in the human gut mycobiome has grown in the last decade, progress on this subject is substantially hampered by the lack of standardized investigational approaches, and many key issues still remain unanswered (e.g. the interaction with the human host and its impact).

Although *C. albicans* is a well-known opportunistic pathogen, and a major component of the mycobiome, its role in the gastrointestinal tract remains poorly understood, but is likely to be crucial. Given its main reservoir in the gut, *C. albicans* can influence a plethora of processes, like digestion and immunity, and could be responsible for hitherto unexplained medical syndromes.

Transparency declaration

The authors declare that they have received no support for the present manuscript, nor grants, royalties or licenses, consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, payment for expert testimony, support for attending meetings and/or travel. Moreover, no patents are planned, issued or pending, nor participation on a data, safety monitoring board or advisory board, and they have no leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid, stock or stock options, receipt of equipment, materials, drugs, medical writing, gifts or other services, or other financial or non-financial interests. No external funding was received.

Authors' contributions

SM contributed to conceptualization, methodology and writing the original draft; MC contributed to conceptualization, methodology, supervision, writing the original draft, and reviewing and editing; AL contributed to conceptualization, and to reviewing and editing; and JS contributed to conceptualization, supervision, and to reviewing and editing.

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