

# Invasive candidiasis: from mycobiome to infection, therapy, and prevention

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**Abstract** *Candida* spp. are commonly found in humans, colonizing most healthy individuals. A high prevalence of invasive candidiasis has been reported in recent years. Here, we assess the relation between *Candida* spp. as part of the human mycobiome, the host defense mechanisms, and the pathophysiology of invasive disease in critically ill patients. Many hypotheses have been proposed to explain the different immune responses to the process where *Candida* goes through healthy mycobiome to colonization to invasion; the involvement of other microbiota inhabitants, changes in temperature, low nitrogen levels, and the caspase system activation have been described. Patients admitted to an intensive care unit (ICU) are at the highest risk for invasive candidiasis, mostly due to the severity of their disease, immune-suppressive states, prolonged length of stay, broad-spectrum antibiotics, septic shock, and *Candida* colonization. The first approach should be using predictive scores as screening, followed by the determination of biomarkers (when available), and, in the near future, probably immune-genomics and analysis of the clinical background in order to initiate prompt and correct treatment. Regarding treatment, the initiation with an echinocandin is strongly recommended in critically ill patients. In conclusion, prompt treatment and adequate source control in the more

severe patients remains the ultimate goal, as well as restoration of a healthy microbiota.

## Introduction

*Candida* spp. are commonly found in humans. They colonize the skin and mucosal surfaces of most healthy individuals [1], being part of what is fashionably termed microbiota or what others named the “mycobiome”. *Candida* spp. are highly prevalent fungi and have been well studied in the context of human microbiota [2, 3] (Table 1). These opportunistic fungal pathogens can cause either local or systemic infection; in recent years, the prevalence of sepsis due to fungal organisms has risen by more than 200 % [4] and they have become the third most common pathogen isolated from blood samples in large epidemiological studies in critically ill patients [5]. Patients with systemic fungal infection by *Candida* can be subdivided into three groups: those who present with bloodstream infection (candidemia), those who develop deep-seated candidiasis (most frequently intra-abdominal candidiasis), and those who develop a combination of the two. High mortality rates, ranging from 27 to 55 %, have recently been correlated with these infections [6, 7].

In the present study, we assess the relation between *Candida* spp. as part of the human mycobiome, host defense mechanisms, and the pathophysiology of invasive disease in critically ill patients, and consider future directions for their diagnosis and therapeutic management.

## Normal immune response to *Candida* and pathophysiology

As mentioned above, *Candida* spp. are opportunistic pathogens which are resident members of the healthy mycobiome.

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**Table 1** Major components of the mycobiome in different body sites

Site	Fungal composition
Oral cavity	<i>Candida</i> spp., <i>Cladosporium</i> , <i>Aspergillus</i> spp., <i>Fusarium</i>
Nasal cavity	<i>Cladosporium</i> , <i>Penicillium</i> , <i>Alternaria</i> , <i>Aspergillus</i> spp.
Gut	<i>Wallemia</i> , Trichocomaceae, <i>Saccharomyces</i> , <i>Rhodotorula</i> , <i>Candida</i> spp., uncultured fungi, <i>Aspergillus</i> , <i>Simplicillium</i> , <i>Rhodotorula</i> , <i>Galactomyces</i> , <i>Trametes</i> , <i>Pleospora</i>
Vagina	<i>Candida</i> , <i>Pichia</i> , <i>Eurotium</i> , <i>Alternaria</i>
Conjunctiva (leprosy)	<i>Candida</i> , <i>Aspergillus</i> , <i>Geotrichum</i> , <i>Acremonium</i>
Skin	<i>Candida</i> , <i>Malassezia</i> , <i>Cladosporium</i> , <i>Cryptococcus</i>

Modified from [2]

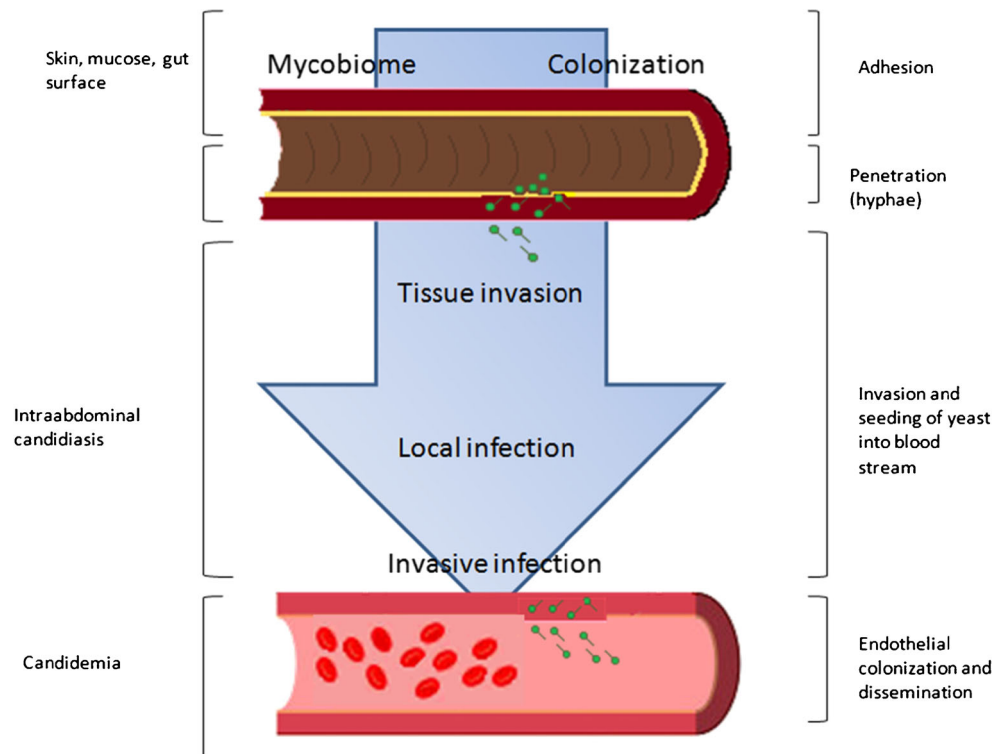
Only in certain circumstances do they become pathogenic and cause life-threatening infections. The composition of the mycobiome differs according to body region and, therefore, its local role in the development of disease may vary.

Gut microbiota form part of the first line of antimicrobial defense, along with the mucosal barrier, antibodies, antibiotic peptides, and the intestinal epithelium. Members of the intestinal microbiota secrete bacteriocins—toxins produced by bacteria to inhibit the growth of similar or closely related bacterial strains—and compete with pathogens for nutrients, surfaces, and substrates [8, 9].

A crucial step in the process in which *Candida* spp. become invasive is their ability to form hyphae and become virulent, adhering to and invading into deeper tissues (Fig. 1). When loss of integrity occurs in a normal

ecosystem such as the gut, other microbiota inhabitants such as *Pseudomonas aeruginosa* and *Enterococcus faecalis* have been shown to inhibit hyphal morphogenesis [10]. Other environmental factors such as temperature below 35 °C inhibit hyphal development through the action of the heat shock protein 90 (HSP90). Low nitrogen levels due to starvation have been associated with activation of hyphal development through mitogen-activated protein kinase (MAPK) [11]. These morphogenic changes are associated with proteins localized in the cell wall that act as adhesins and invasins, and these simultaneously modulate immune responses [12].

Increased activity of peritoneal macrophages, more efficient neutrophil activity, and a re-balanced cytokine response have all been noted after lactobacilli supplementation. All of these mechanisms have been found to be altered during *Candida* infection. In a recent randomized controlled trial (RCT) in a pediatric population, probiotics were shown to decrease the rate of fungal colonization by more than 30 % and as early as day 7 [13, 14]. It is clear that the morphogenesis of *Candida* is regulated by a complex network which depends on the microenvironmental status and host innate immunity, and can lead to a range of clinical scenarios. The recognition of *Candida* by innate immune cells is mediated by at least three families of pattern recognition receptors (PRRs): toll-like receptors (TLRs), C-type lectin receptors, and the nucleotide-binding oligomerization domain-like receptors. These PRRs initiate the pro- and anti-inflammatory cascade upon recognition of invasion.

**Fig. 1** Pathogenesis in invasive candidiasis

Several hypotheses have been proposed to explain the different immune responses to the dimorphic *Candida* form. One of the most recent involves caspase 1 related to the activation of T<sub>H</sub>17 cells (a T cell subset) in the mucosal lining, depending on the load and morphology of *Candida*, which may be able to differentiate between colonization and infection [15]. However, definitive information is still scarce.

### Risk factors for invasive candidiasis

Any variable that alters the commensal relation between *Candida* spp. and the host could be interpreted as a risk factor for invasive candidiasis. Its clinical manifestations may differ, depending on the clinical conditions in which the invasion takes place (Table 2) [16, 17].

Patients in the intensive care unit (ICU) are at the highest risk for invasive candidiasis, mostly due to the severity of their disease, immune-suppressive states, prolonged length of stay, septic shock, and *Candida* colonization. Colonization occurs in the ICU population during the first week in up to 80 % of cases [5, 18], but few develop an ensuing severe infection [19]. The pathophysiology route of infection will determine the clinical scenario [20]; indeed, during a large recent study [7] focusing on intra-abdominal candidiasis, only 14 % of patients also developed candidemia.

A well-known risk factor for invasive candidiasis is the use of broad-spectrum antibiotics [21]. Cephalosporins have been associated with specific species such as *C. glabrata* [22]. In recent studies, patients using ciprofloxacin-containing regimens presented a higher risk [hazard ratio (HR) 3.4, 95 % confidence interval (CI): 1.4–8.0] of developing invasive *Candida* spp. infection; this effect was not observed with other antibiotics such as meropenem, piperacillin/tazobactam, or cefuroxime [23]. In contrast to bacterial infection, the process between *Candida* colonization and infection requires time, around 7 days according to some authors [20], and, so, treatment should be individualized. Oncohematological patients and solid organ transplant (SOT) recipients have an altered neutrophil function, due to the disease or due to chemotherapy or immunosuppressive agents; in some cases, their complex healthcare routine also makes them a high-risk population.

**Table 2** Clinical scenario and specific risk factors for invasive candidiasis

Type of patient	Risk factor
Oncohematological	Mucositis, altered neutropenic function
Solid organ transplant recipient	Immunosuppressive agents
Surgical patients (multiple abdominal surgeries, severe acute pancreatitis)	Contamination of peritoneum if repeated interventions
Non-surgical critically ill patient	Septic shock, broad-spectrum antibiotics, biofilms in central venous catheters, endotracheal tube, nasogastric tube, or urinary catheters
Surgical critically ill patients	Contamination of peritoneum plus ICU specific risk factors

### Diagnosis

The diagnosis of invasive candidiasis [24] is still difficult because of the “common” presence of yeast cells in certain tissues. The gold standard for diagnosis remains culture from sterile sites. However, the sensitivity of blood cultures is nowhere near optimal, ranging between 21 and 71 % in autopsy studies [25]. Efforts have been made to identify predictive rules in order to initiate antifungal therapy. Some of the most widely used are characterized by their high negative predictive value and are validated in candidemia only [21, 26, 27]; this means that they are useful for screening patients to rule out invasive candidiasis, but not for initiating treatment. In recent years, the development of fungal biomarkers has emerged as a promising tool in patients in whom suspicion is high but culture remains negative, and also to identify patients who are at the highest risk for developing an intra-abdominal candidiasis episode and are, therefore, likely to benefit most from appropriate early treatment.

### Mannan antigen and anti-mannan antibodies

Mannan is a polysaccharide present in the fungal structure of *Candida*. When invasive candidiasis is present, mannan can be detected in plasma along with its antibodies. Recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend the use of these antibodies to diagnose invasive candidiasis with a level of evidence of II [28].

### Beta D-glucan

Beta D-glucan (BDG) is a component of the inner layer of the fungal wall, not specific for *Candida* spp. In high-risk critically ill surgical patients, it has been identified as a good predictor for intra-abdominal candidiasis; two consecutive BDG serum levels above 80 pg/ml were positive-predictive around ~5 days earlier than regular cultures, and also achieved high sensitivity and specificity [29]. In patients with prolonged ICU stay who developed severe sepsis, a cutoff value of

80 pg/ml was again identified as a marker of early detection of invasive candidiasis [30].

Other specific biomarkers for *Candida* infection include polymerase chain reaction (PCR) detection and the *Candida albicans* germ tube specific antibody (CAGTA), but these methods are still to be validated in large populations and are currently not recommended in the guidelines [28].

### Immunogenomics

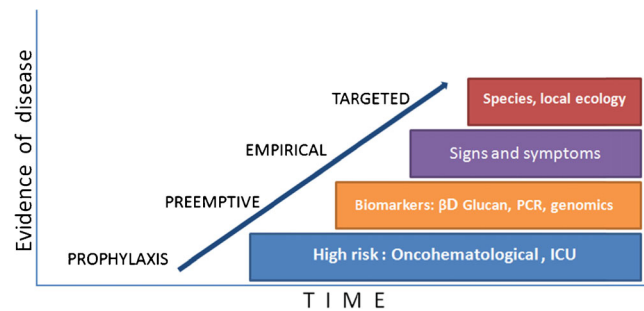
Recently, a secondary analysis by the FUNGINOS group [31] evaluated the influence of genetic polymorphisms on the susceptibility to *Candida* colonization and intra-abdominal candidiasis. They found one single-nucleotide polymorphism (SNP) associated with *Candida* colonization located in TLR4 and two associated with intra-abdominal candidiasis: one located in the tumor necrosis factor alpha (TNF $\alpha$ ) gene (rs1800629, AA/GA) and the other in the  $\beta$ -defensin 1 gene (DEFB1) (rs18 00971, GG/CG). If these results are confirmed in larger cohorts, this may lead to a change in approach, since the identification of these SNPs may predict patients at high risk who have a genetic predisposition to develop invasive candidiasis.

Sites other than blood or peritoneum may be involved. As mentioned above, *Candida* can infect locally or systemically. Central nervous system manifestations can occur due to disseminated candidiasis, or as a complication of a neurosurgical procedure. It may present as meningitis or as small, solitary, or epidural abscesses. Ocular involvement should be ruled out in every patient with candidemia, paying particular attention to those who cannot report visual alterations [32]. Patients with neutropenia should be evaluated when the neutrophil count recovers.

*Candida* endocarditis is one of the most serious manifestations of invasive candidiasis. The optimal therapy is a combination of valve replacement and a long course of antifungal therapy (according to current guidelines, liposomal amphotericin B is preferred). Urinary tract involvement is common in critically ill patients; however, asymptomatic candiduria should only be treated in patients with high-risk factors, such as severely immune-compromised patients with fever and candiduria in whom an invasive candidiasis must be ruled out.

### Treatment

The opportunities for initiating antifungal treatment during the ICU stay are numerous and illustrated in Fig. 2. According to current Infectious Diseases Society of America (IDSA) and ESCMID guidelines, invasive candidiasis patients must receive prompt treatment, and the selection of the antifungal agent should be based on the patient's clinical situation. Initiation with an echinocandin is strongly recommended



**Fig. 2** Opportunities for the treatment of invasive candidiasis

when septic shock, hemodynamic instability, or high risk of an azole-resistant causal agent is suspected or present [33, 34].

Echinocandins were associated with better outcome in a recent review analysis [35]. With regard to intra-abdominal candidiasis, there is little evidence to favor the choice of a particular antifungal agent. A small recent analysis showed that micafungin in plasma and peritoneal fluid in critically ill patients with proven or suspected intra-abdominal infection achieved low to moderate penetration into the peritoneal fluid after the first dose in around 30 % of cases [36]. Nevertheless, the usefulness of biomarkers to guide initiation or cessation of empirical antifungal treatment is still to be determined [37].

### Prophylaxis

Given the high mortality, prophylaxis for invasive candidiasis has been widely analyzed. Fluconazole has proved to be effective for preventing colonization and intra-abdominal candidiasis in high-risk surgical patients when compared to placebo [38, 39]. However, mortality rates were not compared and the incidence of candidemia in those patients when analyzed was too low to allow assessment (2.2 %) [40].

Other attempts have been made to introduce prophylaxis with newer antifungals. In one trial, micafungin was compared to placebo in high-risk ICU patients, but benefit was not demonstrated in mortality or in proven candidiasis [41]. It should be borne in mind that administering prophylaxis with a broad-spectrum antifungal may increase resistance and the cost could be excessive [42].

A recent meta-analysis [43] concluded that echinocandins are as effective as triazoles administered for prophylaxis. However, the RCTs presented a large variability in terms of patients and scenarios. In a recent survey [44], up to 7.5 % of ICU patients received systemic antifungal therapy without evidence of infection.

Probably the best recommendation is to use predictive scores as first screening, excluding patients with a low probability of presenting invasive candidiasis, followed by the determination of biomarkers (when available), and, in the near future, probably immune-genomics and analysis of the clinical background in order to initiate prompt and correct treatment.

## Conclusion

*Candida* spp. is part of the healthy mycobiome but can become invasive, depending on microenvironmental determinants and host immunity status. Invasive candidiasis is a high-prevalence infection with a high mortality rate in critically ill patients. Prompt treatment and adequate source control in the more severe patients remains the ultimate goal. Strict antimicrobial policies should be imposed in order to prevent infection and restore the mycobiome.

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