

Fungal Infections in Gastroenterology



Michael AB Naafs MD*

MD, Endocrinologist, Health Consultant at Naafs, International Health Consultancy, Rhodoslaan, Oldenzaal, The Netherlands

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*Corresponding author: Michael AB Naafs, Dutch Internist Endocrinologist, Health Consultant at Naafs, International Health Consultancy, Rhodoslaan 20,7577KN, Oldenzaal, The Netherlands

Abstract

Fungal infections are increasing in gastroenterology. Cirrhotic patients, liver transplantation recipients, and patients with inflammatory bowel disease (IBD) are vulnerable to these infections. The origin of these fungal infections is frequently the GI tract. The advent of sequencing technology can identify now previously uncultivable fungi. Dysbiosis of the mycobiome and microbiome can uncheck normal commensal fungi and turn pathogenic by largely unknown mechanisms. Resistance to antifungals is becoming a global problem. New antifungals are in development and they are badly needed. In this mini-review the enteric mycobiota and fungal infections in GI disease are discussed.

Introduction

Fungi are normally present in the gastrointestinal tract as part of the gut microbiome. With the advent of sequencing technology microbes can be studied now that were previous non-cultivable. Fungal species, also called the “silent population” are known as the mycobiome [1]. Many pathogenic fungi are commensals in our bodies that cause no harm in normal conditions, but have pathogenic potential. For example, *Candida albicans*, which causes systemic candidiasis in immunocompromised patients is a normal part of the gut microflora. Why these fungi can turn pathogenic is largely unknown [2]. In a recent editorial in the American Journal of Gastroenterology Brumble and Keavney pointed to the risky business of fungal infections in patients with cirrhosis, discussing the report of Bajaj et al. [3,4]. Besides liver disease and immunocompromised patients such as in liver transplantation fungal infections occur in patients with inflammatory bowel disease (IBD). In this mini-review the enteric mycobiota and fungal infections in GI disease will be discussed.

The Mycobiome

Although fungi constitute only a very small part of the gut microbiome, the fungal community (mycobiota) has been shown to contribute actively to GI health and diseases [5-8]. Mycobiome analysis has shown that *Candida albicans* and *Candida parapsilosis* constitute most of the fungal community in the human gut [7,9,10]. Various studies have confirmed that gut fungal dysbiosis is associated with IBD [11-13]. The abundance of *C. albicans*, *Aspergillus clavatus* and *Cryptococcus neoformans* was noted

to be increased in Crohn’s disease (CD) patients [14-17]. Most *Candida* spp. can also be detected in the feces or intestinal mucosa of patients with ulcerative colitis (UC)- [18,19]. To characterize the mycobiota by sequencing variable portions of the fungi genome are targeted, which characterize the fungi to the genes level, such as the 18SrDNA of the fungal internal transcribed spacer (ITS) or the rRNA locus [20]. Each sequencing platform has its strengths and weaknesses in terms of read length, cost and coverage [21-23]. The sequences are grouped into Operational Taxonomic Units (OTUs) and the OTUs are compared with existing databases. The genus abundance is determined from multivariate analysis of the various OTUs. The role of uncultivable fungi with unknown taxonomy is not clear and new methods have to be developed to study their interactions within the gut.

A classic way to study interactions between the myco- and microbiome is to introduce dysbiosis in the gut through treatment with antifungals and anti-bacterials [24,25]. Mouse models have been used often in this way to study the gut microbiota. *C. albicans* is a commensal in the human gut but not in the murine gut. *Candida* colonization is induced in germ-free, gnotobiotic, infant mice, or conventional mice fed with anti-bacterial and antifungals. This gives some insight into the interrelation between gut bacteria and fungi [24,25]. Antibacterial can work to promote or inhibit pathogenic fungal growth [25]. It has been known for more than 30 years that anti-bacterial treatment, notably broad-spectrum antibiotics and antibiotics specific to anaerobic bacteria cause differential effects on fungal susceptibility and predisposes patients to gastrointestinal

infections by *C.albicans* [26-28]. Fungi are able to establish a niche in a perturbed gut bacterial microbiome. Studies show that the introduction of small amounts of *C.albicans* to mice after antibiotic treatment caused significant shifts to the gut microbiota, from phyla to family level, and it may not return to its pre-antibiotic stage in the long-term [29,30]. Dysbiosis studies show that the microbiome and commensal fungi interaction is a balancing act. When the microbiome is disrupted, the normally commensal elements in the mycobiome might be unchecked and turn pathogenic.

Foodborne fungi are found in many animal and plant-based foods, surviving the transit through the GI tract and possibly colonizing the gut [31] Hoffmann et al. [32] reported a strong link between consumed foods and fungal abundance in the gut [32]. They found an inverse association between *Candida* and *Bacteroides* bacteria. *Bacteroides* was more abundant in high-protein diet users while *Candida* was more associated with recent carbohydrate consumption. Ultra-processed foods have been linked to a rising prevalence of autoimmune disease [33] It is not known if and how far the mycobiome is involved [33].

Fungi and Liver Disease

As mentioned before Bajaj et al. [4] studied a cirrhotic cohort of 2743 patients (1691 no infection, 918 bacterial and 134 fungal) were included. Patients with fungal infection, all of which were nosocomial, were more likely to be admitted with bacterial infections, on spontaneous bacterial peritonitis prophylaxis, and have diabetes and advanced cirrhosis. Bacterial infection types did not predict risk for fungal infections. Multi-variable analysis showed male gender to be protective, whereas diabetes, longer stay, ICU admission, acute kidney injury (AKI) and admission bacterial infection were associated with fungal infection development (AUC =0,82, area under the curve). Fungal infections were associated with significantly higher acute and chronic liver failure (ACLF), inpatient stay, ICU admission, and worse 30-day survival. The case fatality rate was 30% with most fungal infections but more than 50% for fungemia and peritonitis. On a multivariable analysis, age, AKI, end stage liver disease, ICU admission and ordinal infection variables impaired survival ($p<0,0001$; AUC=0,83)- (4).

Patients with liver cirrhosis are at an increased risk of fungal infections because the antibiotics used for prevention of spontaneous bacterial peritonitis (SPB) can select for excessive growth of fungi in the intestinal flora with subsequent fungal translocation into the peritoneal cavity and development of spontaneous fungal peritonitis (SFP)- [34,35]. Fungi are much larger than bacteria, which makes fungal translocation along the gut more difficult than in bacterial peritonitis (BT), and may require higher intestinal permeability, which is more common in advanced liver cirrhosis [36,37]. Fungal translocation may be facilitated by upper gastrointestinal bleeding, which is also common in advanced liver cirrhosis [38]. Immunosuppression and malnutrition in liver cirrhosis patients also promote this fungal translocation [35].

Direct percutaneous inoculation of fungi is the proposed route of fungal infection in patients with refractory ascites and a history of paracentesis [38].

SFP is defined as a fungal infection of ascitic fluid with no apparent intra-abdominal source of infection or malignancy [36]. A PMN (polymorph nuclear leukocytes) of $> 250/\text{cubic mm}$ in the ascitic fluid with a positive fungal culture regardless of a co-colonization of bacteria is diagnostic of SFP [39]. A positive fungal culture with a PMN count of $< 250 \text{ cells}/\text{cubic mm}$ is diagnosed as fungascites or fungal ascites [39]. Fungal ascites has a higher mortality rate than bacteriascites [39]. Of spontaneous peritonitis cases 0-7,2% are culture positive for fungi and the most frequent isolate is *Candida albicans*. Other causative fungi include *Candida glabrata*, *Candida krusei*, *Cryptococcus* spp. and *Penicillium* spp. Polymicrobial infections i.e. bacterial co-colonization occurs in 32%-74% of SFP cases, but early diagnosis by conventional microbial culture is difficult because of the time required for growth and the efficiency of PCR or assay of the fungal biomarker 1.3 beta-D-glucan in ascitic fluid has not been established [40-44].

High Child-Pugh or MELD scores increase the risk of SFP in patients with advanced liver cirrhosis [36]. The risk of SFP is increased in patients with liver cirrhosis who undergo invasive procedures [41] and increase with the length of hospital stay [42,44]. SFP mortality is estimated to be 56%-90% [36,39,41]. Hwang et al. [36] reported a high SFP mortality that was related to unresponsiveness to initial empirical treatment to suspected SBP [36]. SFP is usually diagnosed after the identification of fungi in cultures of ascitic fluid. The mortality is high because of delayed diagnosis, lack of clinical signs, lack of suspicion of SFP and delay in treatment with antifungal therapy [41]. Recent treatment guidelines on management of infections in liver cirrhosis do not include antifungals for prophylaxis or optimum treatment but do include recommendations for fungal infections [34]. Echinocandins are recommended as first-line treatment for patients with liver cirrhosis and nosocomial SFP or critically ill cirrhotic patients with community -acquired SFP [36]. Fluconazole is recommended for less severe infections [41]. However, directed antifungal therapy may not improve the outcome of some patients with SFP because of lack of response to the administration of empirical treatment and delay in antifungal therapy [44]. Although early differentiation between SFP and SBP may be difficult, the clinician is able to suspect SFP or SBP due to multidrug resistance (MDR) if spontaneous peritonitis is not improved after 48h empirical antibiotic treatment [39].

Fungal Infections in Liver Transplantation

Invasive fungal infections (IFIs) are frequent causes of morbidity and mortality in liver transplantation patients. Candidiasis is the most common opportunistic fungal infection of the oral cavity caused by fungi of the genus *Candida* in immunosuppressed individuals. Bertoncello dos Santos et al. performed a cross

sectional study in 49 liver transplant recipients at different stages of immunosuppression by the collection of oral samples with a sterile swab [45]. In these 49 patients' samples, 39% had the yeast of the genus *Candida* Isolated and of these patients, 12% had candidiasis, 60% of atrophic type and 34% pseudomembranous. Eleven yeast species were (58%) *Candida* non-albicans and eight (42%) *Candida albicans*. The high incidence of *Candida* non-albicans in the oral cavity with a long history of transplantation warrants a more effective control of health of these patients, the authors concluded [45].

Pasternak et al. investigated the incidence and risk factors of IFIs in pediatric liver transplant recipients during the early post transplantation period (<3 months) - [46]. Data were collected for all pediatric liver transplant recipients registered in a national transplantation center from 2004-2014. Ten IFIs were identified in 81 liver transplant recipients (12,5%) all occurring during the first month post transplantation. *Candida* species were responsible for nine cases (90%) of which four were non-albicans *Candida* (44%). Significant risk factors were multiple blood products transfusion during transplantation, prolonged use of indwelling catheters, prolonged IV antibiotic treatment, surgical complications, pulse steroid treatment and living donor transplantation. The predictive model used two clinical parameters to define high -risk patients: a living donor transplantation and duration of IV antibiotic treatment (area under the ROC curve 0,98). The authors concluded that IFIs are a significant complication occurring in the first month post transplantation and future studies targeting antifungal prophylaxis in these high -risk patients are needed [46]. To date, only small studies and case-series analyzing clinical presentation and risk of IFIs in liver transplantation (LTs) are available.

Bassetti et al. [47] performed a retrospective multinational study in 10 centers in Europe and Brazil. All consecutive LTs developing IFI during the period January 2011 to December 2013 were included in the study [47]. A total of 42 LTs were included. Median age was 52,5 years and 78,6% of patients were men. Viral hepatitis was the most common cause for liver transplantation (49,2%). Candidemia represented the majority of cases (24,6%), followed by intra-abdominal candidiasis (18,4%). Overall 30-day mortality was 23,8% with higher mortality in patients with candidemia compared with intra-abdominal candidiasis (37,5% vs 5,6%; p=0,02). Multivariate analysis showed candidemia to be a risk factor associated with mortality among LTs presenting IFIs (odds ratio: 11,86; 95% CI 1,5-280; p=0,01). *Candida albicans* represented the most common isolate (59,5%). High rates of antifungal resistance were found with 16,7% and 4,8% of isolates displaying resistance to azoles and caspofungin respectively [47].

Fungal Infections in IBD

Patients with inflammatory bowel disease (IBD) are at increased risk of complications caused by bacteria, viruses, fungi and

parasites. Various factors have been associated with an increased risk of infection in these patients including immunosuppressive and immunomodulatory therapy, severity of disease activity, comorbidity, narcotic analgesic treatment, surgery, malnutrition, leucopenia and older age [48-52]. Stamatides et al. [53] performed a systematic PubMed search for studies providing data on clinical, microbiology, treatment and outcome of fungal infections in patients with IBD. Fourteen studies with data on 1524 patients were included in the final analysis. The most common fungal infections in patients with IBD were caused by *Candida* species (903 infections). The most commonly reported site of *Candida* infection was the GI tract. Available evidence shows that most fungal infections occur within 12 months of IBD treatment and within 6 months when anti-TNF-alpha agents are used [53].

Various studies have confirmed that gut fungal dysbiosis is associated with IBD, as mentioned above [11-13]. The abundance of *C.albicans*, *Aspergillus clavatus* and *Cryptococcus neoformans* was increased in Crohn's disease [14-17]. Sokol et al. [54] studied the fecal fungal microbiota in patients with IBD. Bacterial and fungal composition of the microbiota of 235 patients with IBD and 36 healthy subjects (HS) was determined using 16 S and ITS2 sequencing, respectively. The obtained sequences were analysed using the Qime pipeline to assess composition and diversity. The authors observed that fungal microbiota is skewed in IBD, with an increased Basidiomycota/Ascomycota ratio, a decreased proportion of *Saccharomyces cerviciae* and an increased proportion of *Candida albicans* compared with HS. They also identified disease specific alterations in diversity, indicating that a Crohn's specific gut environment may favour fungi at the expense of bacteria. The concomitant analysis of bacterial and fungal microbiota showed a dense and homogenous correlation network in HS but a dramatically unbalanced network in IBD, suggesting the existence of disease specific inter-kingdom alteration [54].

Inter-kingdom alterations between fungi and bacteria at the gut may also be implicated in the gut mycobiome-gut-brain-axis (GBA). These alterations influence extraintestinal immune responses. Dectin-1 is one of the most important pattern recognition receptors (PRRs) expressed by immune cells that interact with fungal beta-glucan. Dectin-1 knockout mice have severe colitis [55]. Fungi are able to synthesize and release neurotransmitters, similar to many bacteria. *S.cervisiae* and *Penicillium chrysogenum* can produce high concentrations of norepinephrine. *C.albicans* is able to produce histamine, another neuromediator involved in appetite regulation, sleep-wake rhythm and cognitive activity [56-58].

Sivamaruthi reviewed the clinical outcome of probiotic and symbiotic therapy for inflammatory bowel diseases. The studies suggested that the intervention of multistrain probiotic preparation or symbiotic preparation performed better than single strain therapy. Moreover, several studies were conducted with VSL#3 and proved that VSL#3 was safe and recommended by many clinicians to support the remission of UC, and for maintenance therapy. Most

of the clinical trials were conducted with a minimum number of patients on short treatment duration or no proper follow-up. Apart from the formulation of best probiotic or symbiotic preparation, dosage, duration, mode of intervention and form of formulation are playing a critical role in the outcome of a clinical trial. Future studies are required to select the probiotic strain or combinations to treat or control IBD [59].

Antifungal Resistance and *Candida Auris*

Antifungal resistance is becoming a global problem [60]. Only a few classes of antifungal drugs are available, so the emergence of resistance to single drug classes and now multidrug resistance is a serious problem in patient management. Azole resistance among *Candida* and *Aspergillus* species is one of the greatest challenges, followed by echinocandin among some *Candida* species, especially *Candida glabrata*. The spread of agriculturally derived azole-resistant *Aspergillus fumigatus* and emerging threats such as *Candida auris* are alarming. The molecular mechanisms that cause drug resistance are naturally occurring in less susceptible species and are acquired in strains of susceptible organisms. Drug resistance mechanisms include altered drug interactions, reduced cellular drug concentrations mediated by drug efflux transporters and permeability barriers associated with biofilms. Although *C. auris* is inherently multidrug resistant, other strains typically develop resistance through stepwise selection of multiple drug resistance mechanisms.

The GI tract is a major source of echinocandin drug resistance. *Candida* species are a part of the human microbiome and can cause systemic infection upon immune suppression. *Candida glabrata* infections are increasing and have greater rates of antifungal resistance than other species. Healy et al. showed that *C. glabrata* echinocandin resistance can arise within the GI tract in a murine model and that resistant mutants can readily disseminate upon immune suppression [61]. Various investigational antifungals are currently in preclinical or clinical development, including several of them that have the potential to overcome resistance observed against the azoles and echinocandins. These include agents that also target ergosterol and beta-glucan biosynthesis, as well as compounds with novel mechanisms of action that may also overcome the limitations of currently available antifungal classes, including both resistance and adverse effects toxicity [62].

Conclusion

Fungal infections are increasing in gastroenterology. Cirrhotic patients, liver transplant recipients and patients with inflammatory bowel disease (IBD) are vulnerable to these infections. The origin of these infections is frequently the GI tract. The advent of sequencing technology can identify now previously uncultivable fungi. Dysbiosis of the mycobiome and microbiome can uncheck normal fungal commensals and turn them pathogenic by largely unknown mechanisms. Antibiotics can work to promote or inhibit pathogenic fungal growth. Dysbiosis can also be induced by diet and foodborne pathogens, including fungi.

The mortality of fungal infections in patients with acute and chronic end-stage liver cirrhosis is high (>50%) in cases of spontaneous fungal peritonitis (SFP). Age, acute kidney injury (AKI), end-stage liver disease, ICU admission and ordinal infection variables all impair survival. Invasive fungal infections (IFIs) are frequent causes of morbidity and mortality in liver recipients' patients. Significant risk factors were multiple blood products transfusions during liver transplantation, prolonged use of indwelling catheters, pulse steroid treatment and living donor transplantation. Various studies have confirmed that gut dysbiosis is associated with IBD. Fungal microbiota is skewed in IBD patients and Crohn's specific gut microenvironment may favor fungi at the expense of bacteria. Antifungal resistance is becoming a global problem. Various investigational antifungals are currently in preclinical and clinical development. They are badly needed to meet the challenge of increasing fungal infections in gastroenterology.

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