Infections Caused by Fungi of the Genus *Candida*

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Colonizing mucous membranes, mainly the oral cavity, intestines, vagina, and skin, fungi of the genus *Candida* are part of the human microbiota. Vulvovaginal candidiasis (VVC) is one of the most common types of vaginal infections in women around the world and is often underestimated by both patients and doctors.

Candida epidemiology candidiasis risk factors

1. Risk Factors Associated with Superficial and Invasive Candida Infections

Colonizing mucous membranes, mainly the oral cavity, intestines, vagina, and skin, fungi of the genus *Candida* are part of the human microbiota. As commensals, they do not cause infections in healthy people. They are considered opportunistic microorganisms which cause infections only in specific clinical situations and in the presence of favorable conditions. They mainly pose a threat to immunocompromised persons or patients hospitalized for a long time. People in these risk groups suffer from mucosal infections caused by switching commensal yeast-like fungi to pathogenic ones. Importantly, the risk factors described in detail below also create a predisposition to candidemia and other invasive candidiasis [1].

Factors predisposing to infection with fungi of the genus *Candida* can be classified into immunological and non-immunological [2]. The first group includes, among others, HIV infection. As the disease progresses, more than 90% of patients suffer from superficial fungal infections affecting mainly the oropharynx, primarily related to low levels of CD4+ lymphocytes, reduced activity of NK cells, and loss of T helper cells. The dominating species in this group of patients is *C. albicans*, but infections may also be caused by *Candida tropicalis, Candida krusei,* or *Candida parapsilosis* [2].

Immunosuppressive therapy, used, for example, in transplant patients, reduces the natural immune response, which makes the body more susceptible to all kinds of fungal infections, especially with *C. albicans*. The same is true for neoplastic diseases. The disease itself and the therapy used often lead to immunosuppression and disruption of the mechanisms of both humoral and cellular immune response [2]. The incidence of candidiasis among cancer patients treated in hospitals is higher compared to patients hospitalized for other causes [3].

A lowered level of leukocytes in the blood is an important risk factor, especially for patients with haematological disorders. It may result from the ongoing disease process, as well as from the therapy used (chemotherapy or

antimicrobial treatment). It is worth adding that patients with chemotherapy-induced neutropenia are often in a serious condition that is additionally accompanied by the presence of other factors conducive to fungal infections (e.g., the use of broad-spectrum antibiotics and vascular catheters) [3].

Regarding non-immunological factors, it is worth mentioning disorders in the quantitative and qualitative composition of the microbiota, which promote the excessive multiplication of fungi. Diabetes and the associated high glycemia promote the colonization of fungi. In people with diabetes, much higher colonization of the oral mucosa with *Candida* fungi has been observed compared to the healthy population [2][4]. Reduced saliva flow or impaired neutrophil activity seem to be major factors here [4]. Hormonal disorders, especially in pregnant women, are also worth mentioning. Drugs that reduce the secretion of gastric juice or insufficient secretion of digestive enzymes promote the multiplication of fungi in the digestive tract. Inadequate diet, alcohol, lack of vitamins (especially vitamin A, vitamins B6, B12, and C) and microelements (selenium, zinc, iron), smoking, aging of the body, or chronic stress favor these types of infections [2][5]. Not without significance are also past surgeries, especially in the abdominal cavity or parenteral nutrition [6]. Patients with recurrent intestinal perforation or acute necrotizing pancreatitis have a higher risk of candidaemia [3]. The same applies to total parenteral nutrition—it increases the risk of candidiasis almost 4-fold [6]. The presence of a vascular catheter and its colonization may constitute the port of entry for the fungi to the bloodstream [3]. Past surgery, parenteral nutrition, or the use of endovascular catheters are all factors increasing the risk of (mainly systemic) infections [6].

Fungal infections often occur in extreme age groups: newborns, especially premature babies with low birth weight, and the elderly. Undoubtedly, the above is related to the functioning of the immune system—newborns do not have well-developed specific and nonspecific immune responses. In the case of older people, due to age, the immune system is no longer as efficient [7][8]. There may be additional factors in both groups. In the case of newborns, an important factor is the absence of microbiota in the gastrointestinal tract. A disruption in the process of acquiring a microbiota can lead to colonization by pathogenic microorganisms, including fungi. Hospitalization at an ICU, the use of vascular catheters, parenteral nutrition, and antibiotic therapy make them a group with a higher risk of infection [3][7]. It is worth adding that the risk of infection is higher for newborns with bodyweight of less than 1000 g than for newborns weighing more than 2500 g [3]. Similarly, in the case of the elderly, the use of immunosuppressive therapy, broad-spectrum antimicrobial drugs, or comorbidities such as diabetes often increase the risk of infections, especially in patients over 65 years of age [9].

The ability of fungi of the genus *Candida*, especially *C. albicans*, to colonize or infect various sites (tissues) in the human body depends on many pathogenic factors of these microorganisms. It may be worth emphasizing. However, morphological changes and phenotypic switching, expression of a number of adhesins and invasins on the cell surface, the ability to form a biofilm, or the secretion of hydrolytic enzymes are considered the most important pathogenicity factors of these microorganisms. They allow colonization, adhesion, invasion, and damage to the host tissues. Their ability to adapt to the changing pH of an environment, as well as efficient systems for obtaining nutrients [10][11], are also of great significance.

2. Most Commonly Isolated Species

C. albicans is the species most often responsible for infections. However, it is worth noting that in recent years there has been an increased incidence of isolation of species other than *C. albicans*: *Candida glabrata*, *C. tropicalis*, *C. parapsilosis*, *Candida dubliniensis*, *Candida guilliermondii*, *C. krusei*, or *Candida kefyr* [12][13]. Epidemiological data confirm this trend worldwide [13]. Recent years witnessed a particular increase in the incidence of candidiasis caused by rarely isolated *C. krusei* or *C. guilliermondii* [14].

The suspected causes of the change in the epidemiology of fungal infections are the frequent use of compounds with antifungal activity, both in the prevention and empirical treatment of infections. Abuse or improper use of antifungal drugs are most likely causes of reduced susceptibility or even resistance of fungi to antifungal drugs. Increasingly, species other than *C. albicans* are responsible for infections, and, importantly, they demonstrate a reduced susceptibility to antifungal drugs [14][15]. When analyzing the frequency of isolation of yeast-like fungi from various clinical materials, Taei et al. showed that among NCAC (Non-*Candida albicans Candida*) species, *C. glabrata* was most often isolated (it accounted for 76% of all NCACs). The next most isolated were *C. krusei* (6.6%), *C. kefyr* (5.7%), *C. parapsilosis* (4.9%), and *C. tropicalis* (2.4%). The least common (0.8%) were *C. dubliniensis*, *C. guilliermondii,* and *Candida famata*. *C. albicans* accounted for 38.5% of all isolated fungi of the genus *Candida* [13]. According to the authors of the aforementioned research, the increase in the frequency of NCAC isolation is a result of better laboratory diagnostics as well as previous exposure to polyenes and azoles or of reduced immunity, which is often related to the therapy used, e.g., cytostatics, in transplant or cancer patients. Diabetes was a common factor conducive to NCAC infections [13]. Research by Das et al. showed a similar relationship. Of the 112 *Candida* fungi isolated from vaginal swabs, 58% were non-*C. albicans* species. Among them, *C. glabrata* (20%), *C. tropicalis* (19%), and *C. parapsilosis* (9%) were isolated most often. *C. albicans* was isolated in 42% of cases [16]. Despite *C. albicans* being the most commonly isolated, an increasing share of NCAC species and their dominance in complicated vulvovaginitis was observed. The authors explain the above primarily by prolonged antifungal treatment, diabetes, older age, and poor hygienic conditions. NCAC species were also shown to have a higher resistance to antifungal drugs compared to *C. albicans* [16]. Liu et al., who focused on the assessment of risk factors for NCAC candidiasis, showed that *C. albicans*, *C. tropicalis*, *C. glabrata*, *and C. parapsilosis* were most often isolated. The above species accounted for more than 96% of all isolated fungi of the genus *Candida*. NCAC and *C. albicans* were isolated in 53.5% and 46.5% of candidiasis cases, respectively. Among NCACs, *C. tropicalis* was most isolated, primarily from patients with haematological tumors. The authors have demonstrated a higher resistance among NCAC species, particularly of *C. tropicalis* isolates [17].

When discussing species other than *C. albicans*, *Candia auris* is worth mentioning. First isolated in Japan in 2009 from a patient with otitis, it has become a causative agent of invasive infections around the world. It is characterized by ease of spreading, resistance to antifungal agents and disinfectants, a wide range of pathogenic factors, and the fact that it causes severe infections with a high, estimated at even 72%, mortality rate [18][19][20]. Most often, it causes infections in patients who are artificially ventilated, hospitalized in the intensive care unit, catheterized, HIV-infected, diabetic and immunosuppressed. Other factors predisposing to *C. auris* infections include parenteral nutrition, previous surgery, or long-term use of antimicrobials [18][19][21]. *C. auris* is currently a global threat, causing severe epidemic outbreaks of invasive infections most often associated with medical care [20].

3. Infections Caused by Fungi of the Genus Candida

Among the infections caused by *Candida* spp. fungi, one can distinguish surface infections and systemic infections [10][18][19][22]. Surface infections are not generally life-threatening [10]. Among them, one can mention infections of the skin and nails, mucous membrane of the mouth, throat, esophagus, intestines, and vagina [10][23]. Systemic infections, on the other hand, are characterized by a severe course and pose a direct threat to human life. Systemic candidiasis is associated with high mortality, and neutropenia, as well as damage to the gastrointestinal mucosa, are quoted as the most common factors predisposing to this type of infection. Other factors include the use of central venous catheters or antibacterial therapy, most often with broad-spectrum agents [10].

Skin infections are most often surface infections, while infections involving the dermis and subcutaneous layer occur very rarely. The changes most often affect skin folds, e.g., inguinal folds, and often occur in overweight people. *Candida* spp. may also be the causative agent of paronychia or onychomycosis [22]. Oral candidiasis is mainly caused by *C. albicans* and most often occurs in people with impaired immune function. The most common risk factors are HIV infection, followed by wearing prostheses and braces, old age, xerostomia, or poor oral hygiene [10][22]. Esophageal candidiasis is most often caused by *C. albicans* and occurs primarily in people with an impaired immune system or with concomitant diseases, e.g., diabetes. Often, it is manifested by odynophagia and dysphagia, but it can also be completely asymptomatic [22]. Intestinal mycosis is most often superficial, but it can also occur with intestinal perforation. Fungal infections of the intestines are most often associated with inflammatory bowel disease [22].

According to statistical data, about 75% of women have experienced vulvovaginal candidiasis (VVC) at least once in their lifetime, and in about 5–8% of them, it has a recurrent character (occurs at least four times per year) [10].

Invasive infections are most commonly caused by *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. kefyr* [22]. These fungi are some of the most common etiological factors of invasive infections, primarily in patients in intensive care units [24]. The entry of fungi into the bloodstream may result in the spread of fungi into tissues and organs [23]. It can cause, among others, meningitis, peritonitis, and abdominal infections, endocarditis, or infections affecting the patient's bones and joints [22]. The above-mentioned risk factors for invasive infections also include old age, parenteral nutrition, cancer, and immunosuppressive treatment [24].

Candida spp. fungi are also causative agents of infections associated with a foreign element (biomaterial) introduced into the human body. In this context, the adhesive properties of fungi and their ability to form biofilm are important. The possibility of fungal colonization in hip replacements, vascular catheters, urinary catheters, endotracheal tubes, dental implants, artificial valves, pacemakers, or even contact lenses has been demonstrated [25][26]. Infections that occur with the formation of biofilm often have a chronic, recurrent character and are characterized by a high mortality rate of more than 40% [26]. Biofilm plays an important role, protecting the fungal cells against the immune mechanisms of the human body as well as against antifungal agents. The therapeutic

options for infections with biofilm-forming organisms are extremely limited [26]. The formation of biofilm structures on the biomaterial may result in blood infection or systemic infection of tissues and organs [27].

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