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Diagnosis and treatment of mucosa *Candida* spp. infections – a review article

SUMMARY

Candida albicans is the most common cause of fungal infections worldwide. Non-albicans *Candida* species play an important role in vulvovaginal candidiasis and invasive infections. Most cases of infections are endogenous. In case of patients with immune disorders this opportunistic pathogen causes both surface, systemic infections, and candidemia. Symptoms depend on the area affected. Candidiasis are treated with antimycotics; these include clotrimazole, nystatin, fluconazole, voriconazole, amphotericin B, and echinocandins. The emergence of drug resistance and the side effects of currently available antifungals are becoming a major problem in the management of *Candida* spp. infection.

Keywords: *Candida* spp., mucosa, treatment, recommendation

INTRODUCTION

Candidiasis is a fungal infection caused by yeasts that belong to the class *Saccharomycetes*. *Candida albicans* is the most common cause of fungal infections worldwide (24) There are over 20 species of *Candida* spp. yeasts that can cause infection in humans, five most common of them are *C. albicans, C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis.* In the majority of cases, there are infections with yeast of *Candida* genus that were previously present in the body (endogenous infec-

tions), and the reason of disease process is the disturbance of the balance between yeast and host. Exogenous infections are rare. In case of patients with immune disorders, this opportunistic pathogen causes both surface (the oral cavity, oropharynx, oesophagus, and vagina), systemic infections and candidemia. Another reason for the development of infections caused by *Candida* spp. is the disruption of the balance in the microorganism of the human body (42). The most common causes of the occurrence of candidiasis are: immunosuppressant or steroids treatments, long-term catheterization, invasive medical procedures, treatment with broad-spectrum antibiotic, destruction of skin by deep skin burns, local disorders of the gastrointestinal tract, diabetes mellitus, premature very low birth weight infants, immunologically compromised individuals, spread of HIV infection (31, 42). Pathogenesis of candidiasis depends on the virulence factors of the fungus allowing colonization and invasion of tissues, as well as avoiding host immune responses. *C. albicans* virulence factors include: complexity of cell wall structure, adhesion, pleomorphism, enzymatic activity, molecular mimicry, phenotypic variation. To the difficulty in treating patients with *Candida* spp. infections contribute also biofilms and secreted aspartyl proteinases. Biofilms are having influence to higher resistance to both antifungal drugs and the host immune response. Secreted aspartyl proteinases (SAP) are a degradative enzymes which is associated with invasion (22).

Diagnosis of fungal infections is based on microscopic studies, microbiological cultures and identification of cultured fungal species, serological tests (detection of antigens and antibodies) and molecular ones (14). Respiratory, gastrointestinal, and oesophageal candidiasis require an endoscopy to diagnose (10).

Candidiasis symptoms depend on the area affected (16). Most candidal infections result in complications such as redness, itching, and discomfort, though untreated complications in certain populations may be severe or even fatal. In immunocompetent people, candidiasis is usually a localized infection of the skin, nails or mucosal membranes, including the oral cavity and pharynx, esophagus, and vagina (penis) (29); less commonly in healthy individuals, the gastrointestinal tract, urinary tract and respiratory tract are sites of candida infection (26). Candidiasis is treated with antimycotics; these include clotrimazole, nystatin, fluconazole, voriconazole, amphotericin B, and echinocandins. Infectious Diseases Society of America in 2016 carried out a revision of the clinical practice guideline for candidiasis depending on the site of infection and its severity (27). The supplementation of pharmacological treatment is lowcarbohydrate diet and probiotic preparations.

Oropharyngeal candidiasis

Infection of the mucous membranes of the mouth and throat (colloquially called a thrush) is quite a common disease in non-healthy people. However, it most often affects people with immune disorders. Additional factors that favour the occurrence of such an infection are: salivary gland dysfunction, blood group 0, carbohydrate-rich diet, neonatal period, pregnancy. *Candida albicans* is the most common species associated with thrush, seven other species within the *Candida* genus have been attributed to the disease in the oral cavity: *C. glabrata*, *C. guillermondii*, *C. kruesi*, *C. lusitaniae*, *C. parapsilosis*, *C. pseudotropicalis*, *C. stellatoidea*, and *C. tropicalis* (38). An estimated 30–60% of healthy adults carry *Candida* species within the oral cavity. The majority of these microorganisms exist as commensal colonization rather than as a pathologic process (25). The diagnosis of oral candidiasis is based on the clinical appearance alone. If empiric treatment is ineffective, the material should be taken from pathological changes for mycological examination. Basic diagnostics also includes cultures on an agar medium and biochemical identification with a susceptibility mark. Histologic examination, serological tests and detection of genetic material of the fungus using molecular biology techniques may be a supplement to the diagnosis which is important in the diagnosis of invasive and systemic fungi. In order to distinguish commensal carriage from infection, a salivary examination is performed, based on a quantitative analysis of the colony forming units (CFU) (21).

Oral thrush is characterized by the presence of whitish, usually painless plague mainly in the mucous membrane of the cheeks and palate. Changes can also occur around the corners of the mouth (angular cheilitis), on the tongue (acute atrophic glossitis) and gums (stomatitis). Very often changes in the mouth coexist with the candidiasis in the throat and esophagus – there is discomfort during swallowing. Oral candidiasis is classified by the duration of symptoms on acute candidiasis (pseudomembranous, atrophic) and chronic candidiasis (pseudomembranous, atrophic, hyperplasia) (30).

The treatment should primarily include minimizing the impact of risk factors, the use of topical antifungal agents (suspensions, solutions, gels) and oral hygiene. In case of patients with immunodeficiency who suffer from severe course of oral mycosis, general treatment should be used. Antifungal drug should be selected on the basis of the micogram. Treatment should be continued for at least 2 weeks after the symptoms have resolved.

Oesophagus candidiasis

Candida spp. are a component of the physiological flora of the digestive tract in 40–80% of the population. In some situations, usually associated with immune disorders, these fungi can cause opportunistic infections. According to H. Daniell research, the use of proton pump inhibitors is an additional risk factor for developing oesophagia (7). The clinical picture of candidiasis varies from benign asymptomatic mucous membrane infections to generalized multi-organ infections with mortality up to 50% (15). Symptoms of oesophagus mycosis include dysphagia, sodynophagia, pain and burning sensation in the epigastrium and behind the breastbone, as well as secondary weight loss. The test of choice is endoscopy of the upper gastrointestinal tract, histologic confirmation of candida in the esophagus is the gold standard for diagnosis (18). The current first-line treatment is fluconazole administered orally at a dose of 200–400 mg / day (3–6 mg / kg / day) for 14–21 days, which can then be administered long-term at a dose of 100–200 mg 3 × during the week to prevent the recurrence of the disease. In case of patients with difficult swallowing, intravenous fluconazole 400 mg / day (6 mg/ kg/ day) is recommended. Resistant and refractory infections can occur and may require alternative agents for treatment or long-term antifungal prophylaxis to reduce recurrence. For fluconazole resistance, itraconazole 200 mg/ day or voriconazole 2 × 200 mg orally or intravenously for 14–21 days are used (13, 17) Amphotericin B deoxycholate 0.3 to 0.7 mg/kg daily can be used in patients with refractory candida esophagitis, but it has serious medication side effects and should be avoided if possible. Posaconazole 400 mg twice daily has been effective in refractory esophageal candidiasis as well (13, 27). Empirical antifungal therapy is recommended when there is a suspicion of oesophagus mycosis in case of patients with impaired immune system (e.g. during chemotherapy or with AIDS) (27). The lack of effective treatment of oesophagia can lead to complications such as bleeding or secondary esophageal stenosis and to the development of esophago-bronchial fistula.

Gastrointestinal candidiasis

Candida spp., despite their natural occurrence in the digestive tract, are rarely the cause of mycosis of the stomach or intestines. *Candida* spp. are common in the stomach of healthy people, without causing any lesions. In immunocompetent patients with ulcerations or erosions of the gastric mucosa, yeasts can colonize them, but they do not affect the healing process (8). However, results from animal models argue that *Candida* spp. colonization delays healing of inflammatory lesions and that inflammation promotes colonization (20). Candidiasis almost always has a secondary character to previous pathological changes occurring in the stomach and most frequently relates to patients with neoplastic diseases (8). Colonization of *Candida albicans* may enhance inflammation because it is associated with elevated levels of the pro-inflammatory

cytokine IL-17 and IL-23 (20). In the course of gastro-intestinal candidiasis, ulcers are most often found, with superficial erosions, whitish plaques or purulent membranes. The lesions located in the small and large intestine have a similar appearance, and the frequency of their occurrence in these parts of the intestine is similar. Clinical symptoms are usually non-specific. These include diarrhea, nausea, vomiting, flatulence and abdominal pain, as well as gastrointestinal bleeding (8, 9). The treatment recommendations are the same as for esophageal candidiasis (27).

Vulvovaginal candida infection (VVC)

Vulvovaginal candidiasis is, after bacterial vaginosis, the second most common abnormality associated with vaginal biocenosis (2). The infection usually occurs by self-infection as a result of disturbance of the normal bacterial flora or reduced immunity of the organism. It is estimated that 75% of women will experience at least one episode of VVC over a lifetime, and approximately 40–45% will be treated for this reason at least twice (2). In 5–10% of patients, the recurrent form of mycosis will develop. Asymptomatic colonization affects 10–15% of women (36). The most common pathogen is *Candida albicans* (70–89% of cases), less often *C. glabrata* (3.4–20%), *C. crusei*, *C. tropicalis*, *C. kefyr*, *C. parapsilosis*. (34, 41). Factors conducive to vulvovaginal candidiasis include conditions of reduced immunity of the body, an important factor conducive to infection are hormonal changes. Estrogens increase the adherence of yeasts to mucous membranes (contraception, hormone replacement therapy), while progesterone reduces cellular immunity, and thus promotes infections in the second phase of the menstrual cycle and in the third trimester of pregnancy (28, 45). A diagnosis of *Candida* VVC can usually be made clinically. Signs include pruritus, irritation, vaginal soreness, external dysuria, and dyspareunia often accompanied by a change in vaginal discharge (white, thick, curd-like), vulvar edema, erythema, excoriation, fissures. These symptoms and signs are nonspecific and can be the result of a variety of infectious and noninfectious etiologies. Diagnosis should be confirmed by a wet mount preparation with the use of saline and 10% potassium hydroxide to demonstrate the presence of yeast or hyphae, before proceeding with empirical antifungal therapy. Vulvovaginal candidiasis is associated with pH <4.5. For those with negative wet mount findings, vaginal cultures for *Candida* spp. should be obtained.

VVC can be classified as either uncomplicated (as in ~90% of cases) or complicated (~10% of cases) (5). Complicated VVC is defined as severe or recurrent disease (more than 4 episodes of symptomatic VVC within 1 year (40).), infection due to *Candida* species other than *C. albicans*, and/or VVC in an abnormal host (5). Recommended treatment of uncomplicated VVC is 150 mg dose of fluconazole. Several topical antifungal agents are effective therapy for VVC, and no agent is clearly superior (1, 35) and oral and topical antimycotics achieve entirely equivalent results (3, 25, 27, 43, 44). For recurring *Candida* VVC, 10–14 days of induction therapy with a topical or oral azole, followed by fluconazole at a dosage of 150 mg once per week for 6 months, is recommended (40). Complicated VVC requires topical therapy administered intravaginally daily for around 7 days or multiple doses of fluconazole (150 mg every 72 h for 3 doses) (35). Therapy with azoles is less effective in treating non–*C. albicans* VVC (1). Candidiasis due to *C. glabrata* is frequently resistant to azole (including voriconazol). Topical boric acid at a dosage of 600 mg daily for 14 days (in gelatin capsule), may be successful (39). Other alternative treatments include topical 17% flucytosine cream alone or in combination with 3% AmB cream administered daily for 14 days; these agents must be compounded by a pharmacy. Results of many studies indicate that there is no need to implement treatment in sexual partners of patients suffering from VVC / rVVC (5). The Polish Gynecological Society recommends gathering an interview for the appearance of symptoms of a yeast infection in a sexual partner and, if confirmed, treatment by topical preparations (43).

Cutaneous candidiasis

Candida spp. dermatitis can occur under several clinical forms. The most common form of yeast dermatitis is Candidal intertrigo (candidosis in tertriginosa, intertrigo candidamycetica), which locates in the skin folds, especially in case of obese people. In these places acute or subacute inflammation is observed with an exudation. Epidermis shows significant maceration, cracks are present. Around the main changes there are satellite eruptions with vesicles and pustules (16). Erosio interdigitalis blastomycetica (in tertrigo erosiva interdigitalis candidamycetica) is associated with people working in wet conditions. The most frequent location of the disease is the interdigital space, between the third and fourth finger of the hand. In the depths of this fold, inflammation develops with painful cracks. The infection may spread to adjacent interdigital spaces. A characteristic feature is the maceration of the epidermis, which exfoliates with collar around the circumference of candida inflamatory focus (16). Candidal folliculitis (folliculitis candida – cetica) is more common in people with reduced immunity, within the beard there are nasal pustular eruptions, from which *Candida albicans* are isolated. In the treatment of the cutaneus candidiasis, there are effective topical azoles and polyenes including clotrimazole, miconazole and nystatin. The infected area must be dry. The basic meaning in the treatment of candidiasis of the nail shaft has drainage. Paronychia is a *Candida* infection of the hand or foot where the nail and skin meet at the side or the base of a nail. Inflammation manifested by edema, pain and purulent secretion. Skin typically presents as red, itchy, and hot, along with intense pain. Pus is usually present, along with gradual thickening and browning discoloration of the nail plate. The process is usually chronic and shows a period of remission and exacerbation. Nail plates undergo partial destruction, are grayed out, gray-brown, lose gloss, stratify and separate from the nail bed (3). In the nail infections caused by *Candida* spp. local treatment is usually ineffective. In typical cases, more effective oral terbinafine or itraconazole is used instead of oral griseofulvin (19). Terbinafine has a short and variable activity, which is confirmed by clinical trials. On the other hand, itraconazole seems to be effective at a dose of 200 mg 2 times a day for 7 days a month for 3–4 months (6, 37).

CONCLUSION

The epidemiology of *Candida* spp. infections has changed in recent years. *Candida albicans* is the most common etiological factor responsible for oral, esophagus and skin candidiasis. In invasive infections and vaginal candidiasis (26, 43), other species of the *Candida* play an important role. *Candida* spp. sensitivity to antifungal drugs can be predicted based on knowledge of the species. However, the sensitivity of individual isolates may be different than standards. In case of HIV positive patients with recurrent candidiasis of the oral cavity and esophagus, and in rare cases of adults with generalized candidiasis, isolates of *C. albicans* resistant to azoles are isolated. Pfaller and colleagues (33) reported susceptibility data for fluconazole and voriconazole:

- 90.2% of the *Candida* spp. isolates were found to be susceptible to fluconazole; however, reduced fluconazole susceptibility (defined as <75.0% susceptible) was observed in 13 of 31 species;
- resistance to fluconazole was shown to increase throughout time for *C. parapsilosis*, *C. guilliermondii*, *C. lusitaniae*, *C. sake*, and *C. pelliculosa*;

- fluconazole resistance was found to be emerging in isolates of *C. guilliermondii*, *C. inconspicua*, *C. rugosa*, and *C. norvegensis*;
- resistance to voriconazole was generally uncommon during the study;
- one-third of fluconazole-resistant isolates of *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. rugosa*, *C. lipolytica*, *C. pelliculosa*, *C. apicola*, *C. haemulonii*, *C. humicola*, *C. lambica,* and *C. ciferrii* remained susceptible to voriconazole (32).

Resistance to the echinocandins is generally uncommon, with incidence rates ranging from 0%–1.7%. In total, 38% of echinocandin-resistant *C. glabrata* isolates is also found to be resistant to fluconazole (33). Resistance to both azoles and echinocandins is an important concern.

The majority of *Candida* spp. isolates are still sensitive to amphotericin B. Resistance to amphotericin B is very rare among *C. albicans*, *C. tropicalis*, and *C. parapsilosis* isolates. *C. lusitaniae* strains very often show clinically significant resistance to amphotericin B, but the frequency of this phenomenon has not been precisely determined (11). Some reports indicate that it is necessary to use this antibiotic at maximum doses in infections caused by *C. glabrata* and *C. krusei* (46). The intrinsic resistance to antifungal therapy observed in some species, along with the development of acquired resistance during treatment in others, is becoming a major problem in the management of *Candida* spp. infections.

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