Acta Microbiologica et Immunologica Hungarica, 48 (3–4), pp. 479–495 (2001)

PATHOGENESIS, MICROBIOLOGICAL AND CLINICAL ASPECTS OF ORAL CANDIDIASIS (CANDIDOSIS)

(A REVIEW)*

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(Received: March 10, 2001; accepted: June 20, 2001)

The clinical significance of the oral candidiasis (either as independent disorder, or as a part of another disease) is increasing with time.

The diagnosis and local treatment of the oral candidiasis may not be satisfactory, this disorder cannot be eliminated without the correct diagnosis and management of the underlying disease. At the same time, some disorders, such as Candida induced leukoplakia, may significantly enhance tumor development.

Fungal infection of the mouth is often the initial sign of several immunodeficiency diseases. It is, therefore, very important to clarify the background of a fungal infection, since this may be critical regarding the prognosis.

Keywords: *Candida albicans*, oral candidiasis, adhesion of the *Candida albicans*

* This paper was written to commemorate to the fiftieth anniversary of the foundation of the Hungarian Society for Microbiology.

Fungi occurring in the oral cavity

The fungi are achlorophyllous heterotrophic eukaryotes, which can reproduce only by using organic matter. The fungi present in the mouth are either saprophytic or facultative pathogens. Morphologically, filamentous, dimorphous fungi and yeasts are distinguished. Since fungi are much larger than bacteria, the structure of the former has been described by Schönlein and Gruby as early as in the nineteenth century.

Of the above types that occur in the oral cavity mostly yeasts can be detected. Among them about 150 candida spp. may be present, 80% of them *C. albicans*, *C. tropicalis,* and *C. glabrata*, and 20% other species, such as *C. parapsilosis*, *C. stellatoidea, C. guillierrmondii, C. krusei, C. pseudotropicalis*, etc. The microbiological identification may be important, since during empirical treatment the pathogenic fungus may be *ab ovo* resistant to the antimycotic drug used, or resistance may develop during the treatment thereby the resistant fungi can be selected and become predominant. In such a case, both the correct identification of the strain and the determination of antimycoticum-sensitivity are of utmost importance [1].

Methods of the microbiological diagnosis

Simple and frequently used techniques are: microscopic examination of the matter to be studied using stained preparations, well as culture in a special medium. Identification is based upon morphological and biochemical characteristics. During microscopic examination the morphological properties of fungal cells are studied, such as the size, form, location and affinity for dyes of the cells. In native preparations the reproductive and metabolic activities can also be observed.

Culture is the *sine qua non* for the exact identification and determination of the antimycoticum-sensitivity of fungi. Using specific media, e.g. selective Sabouraud agar, fungi can be easily isolated from the specimen. For the identification of isolated fungi, and their antimycoticum-sensitivity, rapid tests and automatic identification techniques are available. These are based upon biomechanical characteristics, and provide results within 48–72h.

Using serological methods fungal antigens can also detected, even directly from the clinical specimen.

Candida albicans and candidiasis

Candida albicans can reproduce in different morphological types (budding or filamentous form). It is generally believed that the budding type is invasive and pathogenic, whilst the yeast cells are nonpathogenic. Data from the literature are, however, contradictory in this respect. Hyphae could not be found in some specimens taken from candida-infected tissues. Cultures of *Candida albicans* strains often undergo variations if the alimentary conditions are not optimal. At normal body temperature the budding forms occur frequently. The structure of the cells may also change, sometimes the translocation of chromosomes is seen [2, 3, 4]. In any case, the rate of reproduction plays a significant part in the pathogenecity.

Colonization and infection

The adhesion of the candida cells to host cells is necessary for colonization and it contributes to the persistence in the host. Without adhesion, the rate of multiplication of the fungus is not enough to maintain carriage of candida organisms in the oral cavity and gastrointestinal tract. The persistent adhesion is also important for providing the transition from colonization into infection. The change in the balance between colonization and infection my lead to the predominance of the latter by the alteration of expression of adhesion ligands and receptors in some patients [5, 6]. Candida cells are bound to several host cells including epithelial, endothelial cells and phagocytes. The mechanisms of adhesion are summarized in Table I [7–11].

From biophysical aspect, the nonspecific relationship between the markers of mucous membrane and fungi can be described as a hydrophobic-hydrophobic interaction. Biochemically, the binding proteins present on the surface of candida organism bind the glycoproteins located on the mucosa surface; this is another way of adhesion [12].

In case of a specific adhesin-receptor interaction, the adhesion - protein present on the surface of the candida cells is bound to the receptor-protein of the mucosa. The adhesins are named according to the protein to which they are bound, e.g. fibronectin-binding protein, fibrinogen-binding protein, thrombin-binding protein, etc. The more binding proteins a candida strain has, the higher is its virulence. *Candida albicans* expresses adhesins which recognize the extracellular matrix proteins including laminin, fibronectin and entactin. This yeast also has surface proteins that are similar to the mammalian integrin, such as $\alpha M\beta_2$, $\alpha\gamma\beta_2$, $\alpha_5\beta_1$. These are bound to endothelial receptors, e.g. ic3b and fibronectin. The lectin-like adhesins include surface proteins that are bound to fucosil or N-acetyl glycosamine determinants or to galactosides on

epithelial cells. The adhesion of candida species to surfaces covered with saliva (e.g. dental prosthesis) may be of particular importance [10, 14].

Table I

Mechanisms of adhesion of C. albicans

Mechanism of adhesion	Adhesins of *C. albicans*	Receptors or mediators	Host (surface)
Hydrophobicity	Surface proteins	Hydrophobic surfaces	Epithelial cells, materials used in dentistry
	Integrin-like surface proteins e.g. $\alpha M\beta_2$ $\alpha\chi\beta_2$ $\alpha\beta_1$	Ic3b, c3d, polypeptides (e.g. fibronectin)	Epithelium, endothelium, extracellular matrix, blood
Protein-protein binding	Surface proteins	C3d, extracellular matrix proteins (e.g. fibrinogen, collagen, laminin, fibronectin, entactin)	Epithelial cells, endothelial cells
	Surface proteins	Fucose or N-acetyl-glucosamine residues on the host glycoproteins	Epithelial cells
Lectin-like attachment	Surface proteins	Streptococcal polysaccharides	Colonized epithelial cells, dental plaque
	Mannoproteins	Glycosphyngo-lipid receptors	Epithelial cells

The surface structure of *Candida albicans* can vary. The expression of surface macromolecules may be changed by environmental factors. These changes enable the candida organism to escape from the immune defense or to prevent the adherence to other cells, thereby promoting candidiasis. The change in glycosilation of surface proteins may give hydrophobic character to a protein, thereby the adhesive capacity may be increased. The interaction of the yeast and host cells may also be influenced by exogenous factors, e.g. drug treatment. Antibiotics, by killing competitive

microorganisms, can make new sites available for candida colonization. By contrast, the antifungal agents may reduce the adhesion [15, 16].

In case of a superficial injury, such as a decubitus ulcer caused by a denture, some receptor proteins (fibrinogen, fibronectin, thrombin) may appear on the mucosal surface. If this process reaches deeper layers, then collagen, vitronectin or laminin may also be exposed. Adhesin proteins will be attached through adequate binding proteins to the above molecules which gives rise to biofilm formation and subsequent growth of fungi. In such a way candida species can mask itself by body's markers, thus the host will recognize it as his own macromolecule. As a result, the yeast will not be available for the potentially compromized immune system. During fungal colonization on the mucosal surface hydrophobic-hydrophobic interaction takes place, and the yeast cells coalesce. Thus their virulence will be increased since they cover one another [12, 17].

Extracellular (excretory) virulence factors

The excreted hydrolytic enzymes often play a significant role in the pathogenesis of microorganisms-induced diseases. *Candida albicans* can secrete several enzymes, such as lipase, phospholipase, phosphomonoesterase, hexoseaminidase, α glukosidase, proteinases [18, 19]. Mostly these latter were studied, but the final conclusion is still missing: whether extracellular protease activity is always accompanied by infection or not [20]. In addition to proteases, other factors may also contribute to the infection and the development of disease [21, 22]. Fungal toxins show versatile activities, namely cytotoxic, pharmacological, immunological, enzymatic, shock evoking and infection enhancing activities [1, 23, 24].

Defensive mechanisms of the host

Microbial interactions

The normal flora of the mouth, in addition to bacteria, also contains different fungal strains that are bound by a sialoprotein. Thus, an equilibrium can develop, and, under physiological conditions, neither bacteria nor fungi can become predominant [25, 26].

The microorganisms, present in the oral cavity compete with one another for the binding sites located on epithelial cells. In equilibrium, this prevents a massive colonization of candida sp. [27, 28]. If an obligate pathogenic microorganism, e.g. *Staphylococcus aureus*, and a candida sp. coexist, the bacterium may occupy the bindig sites on epithelial cells (e.g. displacing other microbes) which may break up the balance and lead to angular cheilitis [29, 30, 31].

Humoral defense

Non-immune factors in the saliva

Iron

The elevation of iron level in the plasma and saliva will increase the susceptibility to infections because iron as a nutrient is critically important for the growth/reproduction of fungi and bacteria [32, 33].

Lysozime (muramidase)

This enzyme acts as antimycotic in several ways. It partly impairs cytoplasmic membrane through increasing permeability and hydrolyses cell wall structures thereby damaging candida cells, partly (together with IgA antibodies) stimulates phagocytosis [34, 35].

Histidine-rich polypeptides (HRPs)

These salivary histidine-rich proteins potentiate the effect of lysozime which results in stronger antifungal activity [36, 37].

Lactoferrin

The concentration of lactoferrin in saliva significantly increases during inflammation of the mucosa and parotid gland. This protein binds iron thereby reducing salivary iron concentration which, in turn, will produce antifungal activity. It is more effective in the apolactoferrin form because its iron saturation level is lower, thus it can bind more iron. The sensitivities of different candida spp. both to lysozime and to lactoferrin vary significantly [38, 39, 40].

Lactoperoxidase

The antimicrobial effect of lactoperoxidase is also achieved through several mechanisms [41]. These include halogenization of microbial proteins, formation of aldehyde and oxidation of SH groups of thioamine-lipids [42]. Significant candidacidal activity was observed when candida spp. were incubated with a conjugate of lactoperoxidase, xanthine oxidase and specific antibodies against *Candida albicans* [43].

The salivary *glycoproteins*, that are similar to blood group antigens, appear on the mucosal surface and increase the buffer capacity of the saliva.

Salivary immune factors

The most important specific immune factor in saliva is the secretory immunoglobulin A (sIgA). This globulin represents the primary humoral specific defense against oral candida infection. It aggregates the yeast cells thereby preventing their adherence to the mucosal epithelium, and opsonizes them which facilitates phagocytosis.

Cellular defense

Extraorally several cellular and noncellular components of the immune system take part in the elimination of fungal infections. The defensive system includes neutrophil granulocytes, one of which can phagocytose up to ten yeast cells and kill a part of them mostly through the activity of myeloperoxidase [44, 45].

The fungicidal effect of human neutrophils is enhanced by interferon-α and tumor necrosis factor. Of the cytokines the granulocyte colony-stimulating factor stimulates the formation of granulocytes in the bone marrow [46, 47].

The candida cells are eliminated mostly by phagocytosis which can be achieved with the participation of the T-cell-produced cytokines/lymphokines [48, 49].

Infection and disease develop if a) candida organisms can produce pathogenecity and virulence factors continuously and in large amounts, b) adhesion and colonization cannot be prevented by the host for any reason. As a result, candida-biofilm is formed under which the extracellular enzymes and toxins of the yeast damage the tissues continuously thereby being ready to produce systemic infection.

In summary, the pathogenesis of oral candidiasis is rather complex: in addition to the microbiological properties of candida spp., the actual status of the host also plays a significant role.

Factors influencing candida carriage

It is generally accepted that, including healthy population, the candida carriage in women somewhat exceeds that seen in men. This is thought to be due to the extensive use of oral anticoncipients [50]. Yeast carriage appears to be more frequent in summer which may be explained by the change in circulatory regulation. It is not clear whether temperature influences candida-virulence. It has been established, however, that at lower temperature yeast cells are more resistant to the killing effect of leukocytes.

Salivary factors

Reduction in the amount of saliva leads to the decrease in the buffer capacity of the saliva. Saliva contains some proteins (lysozime, lactoferrin) and histidine which have antifungal activity. If the volume of saliva becomes less, the antimycotic effect will also be reduced which in turn results in the increased rate of reproduction of the oral candida strains [29]. Decrease in the salivary pH also increases the number of candida organisms. The saliva freshly secreted by the parotid gland is more resistant to the candida-produced proteases than the saliva mixed with other materials [51].

Diurnal variations

During sleep, when salivary secretion is reduced, there is more chance for candida carriage. Sleeping with dentures also increases yeast carriage since the hydrophobicity of denture material is greater than that of mucosa. Thus, the adherence of the yeast to the denture will increase, and during sleep with dentures the number of fungi will be significantly higher than during sleep without dentures [52, 53].

Smoking

Some authors reported that smoking increases the number of candida organisms by 30–70%. This may be due to localized epithelial changes, and to the fact that some substances present in cigarette smoke (such as polycyclic aromatic hydrocarbons) provide aliment, primarily carbon, to the yeast; they also serve a source of energy to other candida species. Thus, smoking accelerates the reproduction of candida organisms [21].

Distribution in oral cavity

There are some distinguished sites in oral cavity that are particularly important for candida colonization. Such regions include the posterior dorsal part of the tongue and the bony palate where the proliferation of candidal hyphae is obvious. In persons with dentures, primarily the fitting surface serves as a reservoir for the yeasts. The inner buccal surface and corners of the mouth are also preferential sites for adherence and reproduction [52, 54–56].

Immune status

Candida carriage was found to be greater in persons with blood group 0 or in whom the blood group antigens are not secreted in saliva. Candida carriage is also modified by the amounts of specific antibodies (IgA, IgG) against *Candida albicans* as well as by reduced ratio of T_{helper} to $T_{suppressor}$ lymphocytes [57].

Oral microflora

Several microorganisms can be isolated from the normal oral cavity whose quantitative and qualitative distribution can produce a normal balance in microflora. This balance may be broken by several factors. The loss of balance, however, does not necessarily mean candida infection, but it may facilitate adhesion, multiplication and finally the predominance of the yeast. The causative factors include use of broad spectrum antibiotics, corticosteroids or oral anticoncipients as well as overuse of solutions for mouth irrigation [25]. Oral sex can also change the normal flora significantly. The composition of the oral microflora may be altered unnoticeably by diets containing broad spectrum antibiotics. Some of these are admixed to animal food to increase meat production. Such drugs include tetracyclines, aminoglycosides and macrolides. In some countries, fluoroquinolons are used to eradicate salmonella infection in pigs. The regular consumption of the meat of these animals provide a chance for the overgrowth of resistant bacteria.

Hospitalization

Hospitalization may also be a factor modifying candida carriage. The oral carriage of yeast is significantly higher in hospitalized than ambulant patients. The high counts alone, however, do not necessarily mean that the patient will have a manifest candidiasis [58]. The factors promoting or modifying oral candidiasis are summarized in Table II.

Clinical types of oral candidiasis

Oral candidiases can be classified clinically from several aspects. Classification is based upon the clinical manifestation of fungal infection, histopathological alterations and the potential presence of an underlying disease. The clinical manifestation of candida infection may vary considerably. There may be overlaps of the individual diseases; their differential diagnosis and classification are often difficult.

Pseudomembranous candidiasis

This is the most common form of oral candida infections. It is characterized by white patches which can be wiped off from the surface of the tongue or the mucosa. Underneath an erythematous base with punctate bleeding is seen. This form of candidiasis is observed mostly in infants and elderly patients. In the former group, the immune system, due to its underdevelopment, is not yet able to eliminate the fungus, and in the elderly the immune defense is not able to do so for any longer.

Table II

Factors influencing oral candidiasis

Exogenous factors
Chronic local irritation
Yeast content of food
Alimentary factors
Antibiotic and/or hormone content of food
Radiotherapy of head and neck regions
Age
Hospitalization
Smoking
Dentures
Ill-fitting denture
Improper use of denture
Oral hygiene
Endogenous factors
Change in oral microflora
Immunologic and endocrine disorders
Malignant and chronic diseases
Haemopoietic disorders, blood group
Dysplasia of oral epithelium

Treatments with immunosuppressive agents, used to manage underlying diseases, diminish the natural defence of the body. In these cases, one should pay more attention to the potential candida infection and be ready to introduce antifungal prophylaxis. The pseudomembranous candidiasis is also common in the initial stage of Human Immunodeficiency Virus (HIV) infection. Candidiasis may be the first premonitory sign of this viral disease. The removable white patches seen in pseudomembranous candidiasis comprise necrotic tissue and desquamative parakeratotic epithelium. Under this, on the outer surface of epithelium, microabscesses containing polymorphonuclear neutrophils and oedema can be observed. The candida cells and hyphae reach the stratum spinosum [27].

Erythematous (atrophic) candidiasis

This form is primarily seen on the dorsum of the tongue, palate and buccal mucosa. The patient complains of burning, sharp sensation which is due to the loss of papillae on the dorsum of the tongue. Previous corticosteroid and tetracycline treatments are thought to be predisposing factors. Erythematous (atrophic) candidiasis may follow persisting pseudomembranous candidiasis, but it can also develop "de novo". Red areas are often seen in the palate which result from increased vascularization and reduced epithelial thickness [59, 60].

Candida leukoplakia (hyperplastic candidiasis)

Candida leukoplakia is a white patch (<5 mm in diameter) firmly attached to the oral mucosa. Bánóczy et al. have reported [54, 61–64] that, in many cases, the histologically diagnosed leukoplakia is not white. The histologic characteristics include parakeratosis and epithelial hyperplasia. The malignant transformation depends on the degree of dysplasia. It is still unclear, whether *Candida albicans* is a causative factor of leukoplakia, or this disorder is the consequence of a secondary infection. It has been corroborated that this group of leukoplakia, the so called nonhomogeneous form, is a severe disorder which is prone to malignant transformation. While the malignancy rate amounts to 2–6% for all kinds of leukoplakia, this ratio for the nonhomogeneous form is 9–40%. It is therefore very important to concentrate the treatment on the candida infection in the case of candida leukoplakia, and to try to change the nonhomogeneous into the homogeneous form [65–68].

Candida-associated denture stomatitis

This disorder is primarily observed in patients with upper dentures. Erythematous and oedematous areas are seen in the mucosa which alteration contacts the fitting surface of the denture. Otherwise the patients appear to be completely healthy, no pathological symptoms or signs are found in their history. The pH of saliva between the denture and mucosa is lower than in normal persons; this is favourable for candida reproduction. Yeasts could be detected in 78–100% of patients with denture stomatitis, but this does not necessarily mean that these patients will have manifest candidiasis. The yeast count in persons with dentures is ten times higher than in those without dentures. In addition, sleeping with denture also increases candida count. Newton [69] distinguished three clinical types of candida-associated denture stomatitis:

I. hyperaemic
II. erythematous
III. granular

Denture stomatitis is not associated exclusively with candidiasis. Bacterial infection, mechanical irritation and allergic reaction may also play a part in stomatitis [53, 70].

Angular stomatitis

Angular stomatitis is an uni- or bilateral disorder of the angles of the mouth which is characterized by inflamed and erythematous fissuring. It may be ulcerated in severe cases. Inducing factors include B_{12}- or iron-deficiency, but the disease may accompany HIV infection. Angular stomatitis is induced not only by fungi, but also by *Staphylococcus aureus*, which reproduces as a result of synergism of pathogenic microorganisms. The disease often associates with denture stomatitis, but it may be caused by saliva accumulation resulting from the lowering of the physical biting height. It may also accompany other underlying diseases such as chronic multifocal oral candidiasis [31, 55].

Median rhomboid glossitis

This disorder is characterized by an atrophic lesion which is elliptical or rhomboid in shape, symmetrically located at the midline of the tongue. Usually, there is a chronic candidiasis in the background, and manifested primarily by smoking and diabetes mellitus. The gustatory buds are atrophic, the hyphae infiltrate the upper layer of parakeratotic epithelium and form a biofilm. Usually, a mixed flora (bacteria and fungi) can be isolated [59].

Chronic multifocal oral candidiasis

This disorder is a group of lesions in multiple oral sites, usually appearing during a prevailing chronic candida infection. This disease comprises a tetrad that include a) leukoplakia [14], the most constant component of the tetrad, b) angular cheilitis [61], especially in denture wearers, c) median rhomboid glossitis [54], d) palatal lesions.

Holmstrup and Bessermann proposed additional criteria: the lesion lasts longer than one month and no predisposing factors are found in the medical history. The patients who underwent radiotherapy or received antibiotic or cytostatic treatment are excluded from the above syndrome [71].

Pindborg reported that this disease occurs most commonly in smoking men aging 50–60 years. The successful antifungal treatment and the prevention of recurrence necessitate the reduction or stop of smoking [68].

Oral candidiasis associated with systemic disease

Oral candidiasis is often a manifestation of some systemic disease. This can be an immunological and/or haematological disorder which may lead to candida infection by compromising the defensive system of the body. The symptoms of systemic diseases are present not only in the oral cavity but also in horny tissues (e.g. skin, nail) and on the mucosal surface (e.g. vagina, intestines) [31].

Treatment of candidiasis

The antifungal agents used for treating fungal infections are listed in Table III. It is crucially important to treat the potential underlying disease together with the mycosis, otherwise the recurrence will be inevitable. In each case, the dentist taking part in the diagnosis and treatment of oral candidiasis should cooperate with the patient's doctor to find the adequate therapy. Because of the different antifungal-sensitivity of candida species, it is reasonable to obtain a specimen before starting the treatment and send it to a laboratory in order to determine the antimycotic sensitivity. In case of unsuccessful treatment, it is compulsory to stop the previously used medicine and switch to the effective antifungal agent [12, 72–76]; see Table III.

Table III

Antimycotics used for the treatment of candidiasis

Polyenes (bind irreversibly to the ergosterol of fungal cells)
Nystatin
Amphotericin-B
Azole-derivatives (inhibit ergosterol synthesis)
Clotrimazole
Miconazole
Ketoconazole
Fluconazole
Itraconazole
DNA-analogues (inhibit protein synthesis of fungi at DNA-level)
5-Fluorocytosine

Acknowledgements. This review is a part of the accredited Ph.D. program of Semmelweis University, entitled "Studies on the immune-biological examination of effects of microorganisms and their products at molecular, cellular and organism level".

This work was partly supported by the National Scientific Research Fund of Hungary, grant no.: OTKA TV32473.

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