Oral yeast infections in immunocompromised and seriously diseased patients

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Heimdahl A, Nord CE. Oral yeast infections in immunocompromised and seriously diseased patients. Acta Odontol Scand 1990;48:77–84. Oslo. ISSN 0001–6357.

The number of immunocompromised patients has increased during recent years. Most fungal infections in these patients are caused by *Candida, Aspergillus, Mucor,* and *Cryptococcus* species. Patients with low granulocyte count are at the highest risk of invasive candidal infection. The commonest type of granulocytopenia is observed in connection with malignant diseases of the hematopoietic system. Cytotoxic treatment and radiotherapy of large-body areas tend to produce a significant decrease in circulating granulocytes. Early diagnosis and adequate treatment of fungal infections are mandatory for a successful outcome. In the oral cavity it is important to differentiate between colonization and invasive infection. The optimal approach to diagnosis is a combination of histology and cultivation of specimens obtained from the same site of suspected infection. Prophylaxis of oral fungal infection in immunocompromised patients is generally aimed at preventing colonization. □ *Fungal infection; immunodeficiency; neutropenia; oral candidosis*

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The number of patients immunocompromised by disease or treatment has increased during recent years as a result of more aggressive cytotoxic therapy and increased knowledge of intensive care and management of serious infections. Therefore, fungal infections have emerged as an increasing problem in this patient population (1). Most infections are caused by *Candida, Aspergillus, Mucor,* and *Cryptococcus* species. These organisms are ubiquitous in the environment or, as with *Candida*, are commonly isolated from the normal oropharyngeal, gastrointestinal, and vaginal microflora. They have a documented virulence for the compromised host and cause a significant morbidity and mortality in those patients.

Clinicians involved in the treatment of immunocompromised patients are challenged by problems in the diagnosis, treatment, and prevention of fungal infections which differ significantly from what is to be expected in immunologically healthy persons.

Host defense mechanisms in the protection against fungal infection

Before invasive or disseminated fungal infection can take place, the causative microorganism must be acquired and a breach of body barriers such as skin or mucosal surfaces must occur.

In the immunologically healthy person, hyphal forms of *Candida* are killed by neutrophilic granulocytes (PMNs) and monocytes. Blastospores of *Candida* are also attacked by eosinophilic granulocytes. Pseudohyphae are more resistant than blastospores to phagocytosis by PMNs and can penetrate host cells, probably because of the phospholipase activity concentrated at their tips. Consequently, patients with a low granulocyte count or impaired granulocyte function are at the highest risk of both invasive candidal infection and bacterial infections.

The cell-mediated immune response is important for the protection against acquisition of fungal species on the epithelial sur-

faces of the body and against invasive disseminated yeast infections. Patients with profound defects in the cell-mediated immune response are at significant risk of invasive candidal infection.

Humoral immune function appears to play a less important role in the defense against fungal infection. Although a serologic response can be observed after fungal infections, its clinical importance is not fully understood.

Breach of body barriers

Immunocompromised patients are subjected to several occasions that may produce iatrogenic damage to skin and mucosal surfaces, predisposing to infection. Urinary, venous, or arterial catheters and skin wounds from venipuncture and bone marrow aspiration are portals of entry for infecting microorganisms.

In the oral cavity ulcers secondary to cytotoxic treatment are frequent findings in cancer patients (2). Drugs like doxorubicin, methotrexate, and ARA-C are frequently associated with ulcerations in the oropharyngeal area. Mucosal damage may also be caused by radiotherapy (3) or by reactivation of latent *Herpes simplex* virus (4). Traumatic ulceration in the oral cavity by dentures or sharp teeth further increases the risk of translocation of microorganisms from the oral cavity to the blood stream. The type of microorganism translocated is dependent on the microbial colonization and local microflora (5). If the patient is heavily colonized with, for example, *Candida* species, the risk of systemic fungal infection is obvious.

Granulocytopenia

Defects of the phagocytic system may be congenital or acquired. The congenital types are less frequent and are observed either as rare granulocytopenic diseases, such as the autosomally inherited Kostman disease, the dominant Hitzig disease, the sex-linked chronic granulomatous disease and cyclic agranulocytosis, or as defects in granulocyte function as present in Chédiak-Higashi syndrome, Shwachman's disease and myeloperoxidase deficiency. Acquired types of granulocyte defects are far commoner and are observed as agranulocytosis secondary to reactions to drugs or chemical agents. Secondary granulocyte dysfunction is observed in patients with diabetes mellitus as a result of impaired glucose metabolism of the phagocytes. However, the commonest type of granulocytopenia is observed in connection with malignant diseases of the hematopoietic system, such as acute leukemia and end-stage forms of lymphoma and myeloma. Cytotoxic treatment of malignant diseases and radiotherapy of large body areas tend to produce a significant decrease in circulating granulocytes. The more aggressive induction-remission regimens used for leukemia treatment during recent years produce long periods of pronounced granulocytopenia which increase the risk of subsequent septicemia or disseminated bacterial or fungal infections. The introduction of bone marrow transplantation for severe bone marrow diseases has added further to the number of patients at high risk of infection because of low numbers of granulocytes.

Infection is related to the number of circulating granulocytes (the most important cell type being the neutrophilic granulocytes). The frequency of infection rises as the granulocyte count drops to $< 0.5 \times 10^9/l$. The absolute level of granulocytes in blood is a reliable indicator of the infection risk. The risk of disseminated infection is significant when the granulocyte level is $< 0.1 \times 10^9$. Patients with acquired granulocyte defects often have other defects in the immunologic system, such as T-cell deficiency, which make them prime candidates for both local and disseminated yeast infection.

Cellular immune dysfunction

In rare cases cellular immunodeficiencies are congenital. The best known is the rare DiGeorge syndrome, in which the patients have hypoplasia of the thymus and the parathyroid glands. These patients have severe recurrent infections with some bacterial species and fungi, such as *Pneumocystis carinii* and yeasts. Widespread fungal colonization and infection are typical clinical

features of defects of the thymus-dependent immune response. A chronic form of mucocutaneous *Candida* infection is observed among some individuals with a selective defect in the T-lymphocyte response to *Candida* antigens, but disseminated deep infection is rare.

Acquired disturbances of cellular immunity are far commoner and may have various causes.

i) Various viral infections such as cytomegalovirus, Epstein–Barr virus, and, especially, human immunodeficiency virus (HIV) induce various grades of cellular immunodeficiencies. These types of patient usually have relatively normal phagocytic function, and, although they acquire colonization and localized invasive *Candida* infection (for example, in the oral cavity), disseminated deep infections are uncommon even in AIDS patients.

ii) Patients with Hodgkin and non-Hodgkin lymphomas often lack evidence of delayed hypersensitivity reaction as a sign of impaired cellular immune response. These patients have an increased sensitivity to viral, fungal, and intracellular bacterial infections.

iii) Treatment with cytotoxic drugs such as methotrexate, doxorubicin, and ARA-C and immunosuppressive treatment with glucocorticosteroids, cyclophosphamide, and azathioprine affect the cell-mediated immune response and the phagocytic function and increase both the risk of acquisition of yeasts and invasive infection. Cyclosporine, on the other hand, has a more selective effect on T lymphocytes and does not significantly affect the phagocytic system. Cyclosporine facilitates the acquisition of yeast in the gastrointestinal microflora.

Humoral immune function

Patients with low levels of immunoglobulins are susceptible to various types of bacterial infections (6), the type of the infection being dependent on the type of deficiency. Low levels of IgG2 impair the ability to form antibodies to polysaccharides and increase the risk of infection by respiratory tract pathogens. Salivary secretory IgA against *Candida* is considered to aggregate fungi and to prevent their mucosal attachment (7). The importance of immunoglobulins in the protection against yeast infection in immunocompromised hosts is unclear. However, humoral response may sometimes be useful for diagnostic purposes.

Origin of infecting microorganisms and shift in microbial flora

Hospitalization in itself increases the risk of microbial shift in the normal oropharyngeal, gastrointestinal, and skin microflora. The more severely ill the patient is, the greater is the risk of acquisition of potentially pathogenic microorganisms in the gastrointestinal microflora (8). Treatment that alters the normal physiologic properties of the oropharyngeal tract (for example, radiotherapy and drugs with xerostomic side effects) facilitates colonization and overgrowth with *Candida* species (3, 9). Treatment that suppresses the cell-mediated immune response further enhances growth of yeasts. It also appears that malignant disease in itself for unclear reasons predisposes to a shift in the gastrointestinal microflora. The administration of antimicrobial agents to immunocompromised patients induces significant disturbances in the normal oropharyngeal and gastrointestinal microflora. Agents with pronounced effects on the normal microflora should be avoided if possible in these groups of patients since this increases the risk of superinfection (5, 10).

Most infections in immunocompromised patients are caused by organisms that have colonized epithelial surfaces near the site where the infection develops (11). For example, bacterial pneumonia is often preceded by oropharyngeal colonization with the infecting microorganisms, and *Candida* pharyngitis and esophagitis are more often observed in patients heavily colonized with *Candida* species in the oral cavity (12). Thus surveillance cultures are often useful in immunocompromised patients at high risk of infection. Cultures from the oral cavity and pharynx should be obtained before the patient enters a period of profound granulocytopenia and should be repeated

weekly during the period of increased risk of infection. Nonendogenous bacteria and yeasts and filamentous fungi should be isolated and identified, and their susceptibility to antimicrobial agents determined.

Diagnostic problems in immunocompromised patients

In immunocompromised patients fungal infections are often suspected as the cause of unclear fever, septic symptoms, or localized inflammatory signs. Early diagnosis and adequate treatment are mandatory for a successful outcome. Superficial localized lesions are easily detected, whereas deep-seated fungal infections remain extremely difficult to diagnose in the immunocompromised host. In the oral cavity it is important to differentiate between colonization and invasive infection. The definite diagnostic test for invasive fungal infection is demonstration of hyphae or fungal pathogens invading the tissue. Furthermore, the invasive microorganism should be isolated and identified by microbiologic methods. These criteria are difficult to fulfill in most immunocompromised hosts, as life-threatening disease may contradict the excision of tissue. Other noninvasive methods such as cultivation from mucous membranes and blood, in combination with, for example, serology, must therefore often be used as alternatives to histology. In most patients the infecting organism is *Candida albicans*, but other *Candida* species, such as *C. tropicalis, C. krusei, C. parapsilosis,* and the closely related yeast *C. glabrata*, are also often involved in the infection (2, 13, 14). Three different diagnostic 'tools' can be used in the diagnosis of fungal infection: cultivation, histology, and serology (15).

Cultivation

The causative microorganism can be correctly identified only by microbiologic methods. Antimicrobial susceptibility testing is only possible after isolation of the microorganism. The significance of fungal isolates from clinical specimens must be put in relation to what may be isolated from that specific site during normal circumstances. Isolation of *Candida* species from the oral cavity without clinical signs of local or systemic infection provides little information and is often only an indication of colonization. Isolation of fungi from subsequent blood samples is, however, strong evidence of deep-sited invasive infection. Most deep mycoses cannot be detected by blood culture, even though autopsy reveals disseminated infection (15).

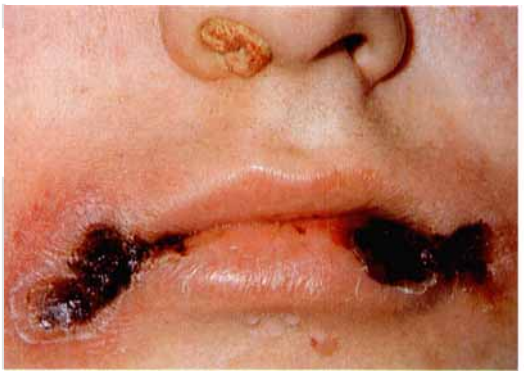
Histology

Histologic examination of biopsy specimens and the demonstration of fungus in tissue is essential for the diagnosis of invasive *Candida* infection in immunocompromised patients. Histology is the best diagnostic tool for differentiation between infection and colonization, as culture alone will not always give the diagnosis.

The most commonly used stains for demonstration of fungal organisms in tissue specimens are Gomori methenamine silver (GMS), periodic acid-Schiff stain (PAS), and Gridley fungus (GF). A factor complicating the histologic interpretation in specimens from immunologically defective patients is the great variation of the inflammatory response evoked by host–parasite interactions. The optimal approach to diagnosis is a combination of histology of biopsy specimens and cultivation of microbiologic specimens obtained from the same site of suspected infection (16). In severely compromised patients excision of tissue specimens may pose a serious risk for the patient, as bleeding and superinfection may ensue. It is therefore not always possible to perform histology, and the diagnosis has to rely on cultivation and clinical observations in these cases.

Serology

Serologic determination of circulating antibodies against fungi has been used to detect invasive infections (17). Various methods have been used, such as immuno-



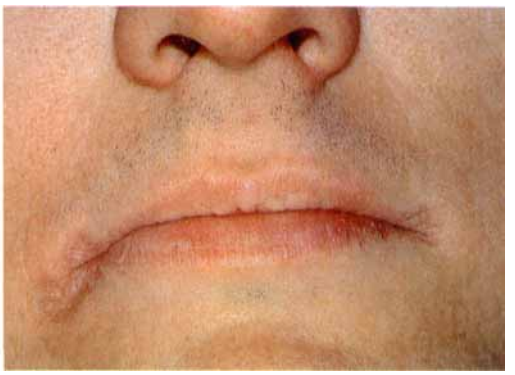


Fig. 1A. A neutropenic bone marrow recipient patient (acute lymphatic leukemia, neutrophils $<0.1 \times 10^9$/l blood) with angular cheilitis caused by *Staphylococcus aureus* and *Candida albicans*. 1B. The same patient 11 days later after engraftment of new bone marrow (neutrophils $>1 \times 10^9$/l blood).

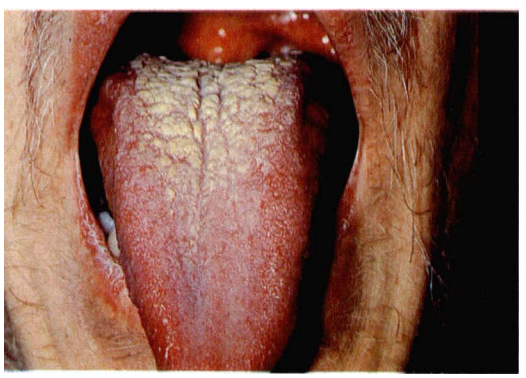


Fig. 2. Heavy colonization with *Candida albicans* in spite of nystatin prophylaxis in a neutropenic patient with chronic myeloic leukemia in blast crisis treated with chemotherapy.

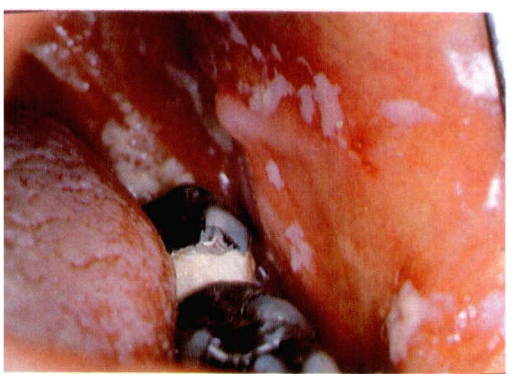


Fig. 3. Bone marrow recipient (acute myeloic leukemia, neutrophils $<0.1 \times 10^9$/l blood) with invasive *Candida albicans* infection of the oral and pharyngeal mucous membranes.

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fluorescence measure of antibodies against cell surface components (18), immunodiffusion tests using cytoplasmic candidal antigens, and enzyme-linked immunosorbent assay (19). A lack of standardization of reagents makes comparisons between different laboratories difficult. The value of detecting antibodies against *Candida* is controversial, as they may have been preexisting as a result of an earlier infection or colonization. Immunocompromised patients often have a decreased ability to produce antibodies, and interpretation of the serologic response is therefore complicated. Kostiala et al. (20), however, could detect increased levels of antibodies against *Candida* in patients with hematologic malignancies and found it useful to differentiate between *Candida* infections and septicemia with bacterial species.

The detection of fungal antigen is of great value in the diagnosis of cryptococcosis and has also been applied for detection of antigenic components (mannan, mannose) or metabolites (arabinitol) in blood from patients with disseminated candidal infection. These approaches are, however, still limited by frequent cross-reactions and both false-positive and false-negative reactions (20).

Clinical aspects of oropharyngeal candidosis in immunocompromised patients

Clinical diagnosis and management of candidosis in immunocompromised patients should aim at early diagnosis and treatment of infection and colonization of different body sites. Weekly surveillance cultures and daily clinical investigations should be performed. Oral and pharyngeal inspection should be carried out daily in patients who are at high risk of infection (granulocytes $< 0.5 \times 10^9/l$). Additional cultures and, if possible, material for microscopic examination should be obtained if colonization or local oropharyngeal infection is suspected. Mucosal ulcerations and cheilitis should be regarded as potentially infected in these patients, and bacterial species and yeasts are frequently isolated from such lesions (Fig. 1). Heavy colonization of oral mucosal surfaces are generally characterized by a white pseudomembranous lesion initially appearing on the dorsum of the tongue and subsequently also on buccal and alveolar mucosa (Fig. 2). It is difficult to differentiate between yeast colonization and epithelial sloughing caused by cytotoxic treatment on the basis of only clinical evidence, and additional laboratory investigations should be performed. The absence of pseudomembranes on the tongue does not exclude colonization, and invasive infection may occur without previous clinical signs of colonization. However, if microbiologic cultures are performed regularly, it will be observed that invasive oropharyngeal yeast infections are always preceded by colonization of mucosal surfaces. As a consequence of this, much interest has been focused on the possibility of preventing colonization of different body sites in severely compromised patients.

Invasive yeast infection in the oropharyngeal tract is characterized by clinical findings such as intensive signs of inflammation in the mucous membranes, often in connection with multiple widespread 'colonies' (Fig. 3). Definite diagnosis is established by microscopic investigation of tissue specimens from the suspected site. In most patients the state of the underlying disease makes invasive procedures hazardous, and diagnosis has to rely on clinical observations and microbiologic findings. Important factors to consider are the clinical picture at the site of infection, the kind and number of microorganisms isolated from the lesion, and the grade of immunosuppression and systemic signs of infection. Treatment of invasive fungal infection in severely immunocompromised patients is complicated and difficult. Topical treatment is insufficient, and systemic treatment is mandatory, to avoid fatal complications. The prognosis of treatment is dependent on several factors, such as susceptibility of infecting microorganism to antimicrobial agents and toxicity of treatment given. The most important factor, however, is the recovery of the patient's immune function with circulating functional neutrophils in high numbers ($>1 \times 10^9/l$ blood) (Fig. 1).

Fungal prophylaxis

The frequent finding of *Candida* species in the normal oropharyngeal and gastrointestinal microflora in immunocompromised patients in connection with the findings of invasive *Candida* infections in the oropharynx, esophagus, and rectum has suggested that the suppression of endogenous *Candida* species may decrease the events of infection (22). Most antifungal agents have been used for this purpose. In general, nonabsorbable agents have been used to prevent colonization and thereby, it is hoped, also decrease the number of subsequent infections. Systemically administered agents have aimed at the prevention of colonization and also at prevention and early treatment of invasive infection. In patients wearing dentures fungal prophylaxis should include these also (23).

Nystatin

The effect of nystatin alone (4×10^5 units to 1.2×10^6 units daily) in the prophylaxis of invasive fungal infections has been evaluated in several studies with conflicting results (24–26). As a conclusion of these studies it can be stated that nystatin had an effect on colonization rate, but its effectiveness with regard to disseminated *Candida* infection could not be proved.

Nystatin appears to be more effective in preventing *Candida* infection when given in combination with various nonabsorbable antibacterial agents. Levine et al. (27) showed that, to suppress endogenous yeasts adequately, nystatin was effective only if the patients could be prevented from acquiring yeasts by staying in laminar air flow rooms and eating a diet free from fungi. The incomplete effect of nystatin in preventing acquisition of *Candida* in the gastrointestinal tract has resulted in the use of other antifungal agents in combination with bacterial decontamination regimens as prophylaxis for infection in immunocompromised patients.

Amphotericin B

Amphotericin B has been used in several studies in combination with antibacterial agents for prophylaxis of infection in immunocompromised patients, either as lozenges or incorporated in multidrug decontamination regimens. Colonization of the gastrointestinal tract by *Candida* can be prevented with amphotericin B, whereas it is more complicated to prevent colonization of the oropharynx (28, 29). When studies using nystatin are compared with studies using amphotericin B, no significant difference is obtained with regard to the rate of invasive fungal infection (30–32).

Imidazole and triazole agents

At present the main interest in antifungal prophylaxis has aimed at agents such as clotrimazole, miconazole, ketoconazole, and fluconazole. Clotrimazole is only available as a topical agent, and the absorption after oral administration is minimal. Miconazole is an agent for parenteral use, whereas ketoconazole and fluconazole are absorbed from the gastrointestinal tract and have both topical and systemic effects after peroral administration. Miconazole and ketoconazole administration may decrease the incidence of oral *Candida* infection, without decreasing *Candida* colonization, suggesting a systemic rather than a topical effect (33, 34). Several disseminated infections due to inherently ketoconazole-resistant *Aspergillus* species and *Candida glabrata* were observed in patients receiving ketoconazole prophylaxis (33) and may limit the use of this agent in hospitals with frequent infections with these microorganisms. Ketoconazole has several side effects, such as endocrine disturbances, hepatitis, and interaction with cyclosporine, which is important in organ transplant patients. In patients with chronic mucocutaneous candidosis ketoconazole has shown promising results (35) and is considered the drug of choice. Fluconazole has recently been shown to eliminate effectively oropharyngeal and esophageal candidosis in patients with HIV infection and also to prevent relapse for a considerable period of time (36).

Chlorhexidine

Chlorhexidine is widely used as an oral

'antiseptic' and has also been used as prophylaxis against colonization with fungi in immunocompromised patients in several studies. Conflicting results have been reported with regard to the effect of a 0.1% solution on colonization rate (37, 38). Chlorhexidine, 0.2%, is less effective against candida stomatitis than, for example, clotrimazole (22). Selection of resistant bacterial strains with subsequent overgrowth should be considered (39). Furthermore, chlorhexidine interacts in vitro with nystatin (40). Intraoral use of chlorhexidine should probably be avoided together with antifungal drugs in immunocompromised patients.

Treatment of invasive *Candida* infections

Invasive fungal infections in severely immunocompromised patients should always be treated with systemic antifungal therapy. Amphotericin B is the drug most commonly used. The main limitation of this drug is toxicity. Amphotericin B encapsulated into liposomes has an enhanced antifungal effect, and promising data from patient studies have been reported (41). Recently developed agents for peroral use, such as fluconazole, have made treatment of some invasive *Candida* infections less toxic to patients. However, treatment with any antifungal agent is only beneficial if circulating neutrophil levels are normalized.

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Received for publication 15 June 1989