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Noncandidal Fungal Infections of the Mouth

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Background

Candidiasis is the most common fungal infection of the mouth. This article, however, focuses on noncandidal oral fungal infections. Other Medscape Reference articles on candidiasis include Candidiasis, Chronic Mucocutaneous;Candidiasis, Mucosal; and Candidiasis, Cutaneous.

This article discusses 6 noncandidal oral infections: aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, and zygomycosis (mucormycosis). Although these noncandidal fungal infections are considerably less common than oral candidiasis, they commonly produce subclinical infection, especially pulmonary infections.

In rare cases, these infections can produce clinical disease in healthy persons. Systemic mycoses in healthy individuals are more common in endemic areas than elsewhere, and they are often asymptomatic and may spontaneously resolve. In otherwise healthy persons, acute pulmonary and primary mucocutaneous symptomatic lesions may resolve without treatment. However, chronic pulmonary infection tends to progress and disseminated infections can be fatal. Immunocompromised persons are at particular risk from these mycoses, and clinical manifestations of infection by these organisms often suggest impaired immune competence.[1]

Patients at greatest risk include those with leukemia, leukopenia, solid tumors, transplants,[2] or HIV disease.[3, 4] Also at risk are premature infants.

Noncandidal fungal infections have the potential for serious injury to the oral cavity and sometimes also the paranasal sinuses, the orbit, and the cranial base. Orofacial lesions caused by the main systemic mycoses may occasionally be seen in isolation, but they are typically associated with lesions elsewhere, often in the respiratory tract. The oral lesions associated with these deep fungal infections are chronic, may mimic neoplasms, and progress to form solitary, chronic deep ulcers with the potential for local destruction and invasion and systemic dissemination.

Chronic oral ulceration, chronic maxillary sinus infection, or bizarre mouth lesions, especially in patients with HIV disease, those with lymphoproliferative disorders, persons with diabetes mellitus, or those who have been in endemic areas, may suggest the diagnosis and patients should be treated in consultation with a physician with appropriate expertise.

Most of these mycoses are diagnosed on the basis of a history of foreign travel or an immunocompromised state. Investigations include smears, biopsy, staining with periodic acid-Schiff (PAS) or Gomori methenamine silver,

culture of the affected tissues, polymerase chain reaction (PCR), serodiagnosis (sometimes), physical examination, and chest radiography. Definitive diagnosis is achieved by means of microbiologic or histologic identification and serodiagnosis. DNA probes are available for several species. Unfortunately, specific laboratory studies for an accurate diagnosis of many mycoses is available only in a few laboratories.

However, prompt identification and treatment, usually with systemic antifungal drugs, are essential; delayed treatment or no treatment can result in considerable orofacial destruction, systemic dissemination, or death.

Most systemic mycoses can be treated with systemic amphotericin. Azoles are often considered better, but their cost is usually prohibitive where they are most needed, that is, in the developing world.

Pathophysiology

Aspergillosis

More than 160 species and variants of *Aspergillus* organisms have been discovered, although only 10 are pathogenic in humans. *Aspergillus fumigatus* is the most common pathogen, but *Aspergillus flavus, Aspergillus glaucus, Aspergillus nidulans, Aspergillus terreus, Aspergillus repens, Aspergillus parasiticus,* and *Aspergillus niger* are also encountered. *A flavus* is the most virulent.

Aspergillus species are the most common environmental fungi, being prolific saprophytes in soil and decaying vegetation. Inhalation of the conidia is very likely extremely common, but, unless the inhalation is massive or unless the host is immunocompromised, clinical disease is rare. Nevertheless, aspergillosis is found worldwide. Its prevalence is increasing, and this is now the most prevalent mycosis second only to candidosis.

The organisms exist as prolific saprophytes in soil and decaying vegetation. Inhalation of the organisms allows for their germination and colonization in the mucosa of the respiratory tract, including the mouth. Lesions may be established primarily in the oral mucosa, but they more commonly begin in the mucosa of the maxillary sinus. They may appear in the oral cavity after local invasion and/or destruction of the surrounding structures. Inhalation of the spores is common, although clinical disease is rare unless the individual is immunocompromised by medication (eg, chemotherapy,[4] organ transplantation immunosuppression) or disease (eg, HIV infection, leukemia, lymphoma).

Blastomycosis

Blastomycosis is a term sometimes used to include a range of granulomatous systemic mycoses, including North American blastomycosis (Gilchrist disease), South American blastomycosis (paracoccidioidomycosis or Almeida disease), coccidioidomycosis, and cryptococcosis. However, the nomenclature is now restricted mainly to the North American and South American forms of blastomycosis, which involve the viscera, lymph nodes, and mucocutaneous tissues.

Blastomyces dermatitidis causes the North American form, whereas *Paracoccidioides brasiliensis* causes the South American form. As expected, North American blastomycosis is seen predominantly in North America, in the Mississippi, Missouri, and Ohio River valleys in the United States and in southern Canada. However, it is also seen in Africa, India, the Middle East, and Australia, and sporadic cases are seen worldwide.

B dermatitidis, which is found in soil and spores, may be inhaled to produce respiratory tract and sometimes disseminated disease. Serotype 1 is seen in North America, and serotype 2 is seen in Africa. Outdoor workers are particularly affected, but blastomycosis is increasingly recognized in persons with HIV disease.

Coccidioidomycosis

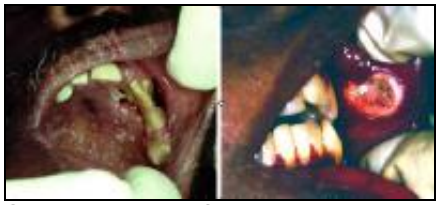
Coccidioidomycosis is seen mainly in arid parts of the Western hemisphere, such as the southwestern United States, Mexico, Central America, and parts of South America. Inhalation of spores of *Coccidioides immitis,* found in soil, produces subclinical infection in up to 90% of the population in such areas.

Cryptococcosis

Cryptococcosis is seen worldwide in humans and animals. Aspiration of *Basidiobolus* spores, mainly capsular serotype A but sometimes serotype D of *Cryptococcus neoformans* (a ubiquitous yeast found especially in pigeon feces and present in soil), may lead to infection. Two varieties have been described, which are *C neoformans* var

neoformans (synonymous with capsular serotypes A, D, and AD) and the less common *C neoformans* var *gattii* (synonymous with capsular serotypes B and C). *C neoformans* var *neoformans* is found in excreta from pigeons, canaries, parrots, and budgerigars and in rotting fruit and vegetables. *C neoformans* var *gattii* is associated with a particular tree, the Red River gum tree (*Eucalyptus camaldulensis*).

Note the image below.



Cryptococcosis. Left image shows solitary, destructive lesion resulting in necrosis of alveolar bone and palatal mucosa; note the superficial pseudomembranous candidiasis of the palate. Right image shows nonspecific chronic ulceration of the buccal mucosa due to cryptococcosis; this is associated with submucosal induration and regional adenopathy. Courtesy of David Sirois, DMD, PhD.

Histoplasmosis

Histoplasmosis is the most frequently diagnosed systemic mycosis in the United States. Sporadic cases are seen worldwide.

Histoplasma capsulatum, the causal organism, is a soil saprophyte found particularly in northeastern and central states such as Missouri, Kentucky, Tennessee, Illinois, Indiana, and Ohio (mainly in the Ohio and Mississippi valleys). The organism has also been found in Latin America, India, the Far East, and Australia.

H capsulatum var *duboisii* is the type mainly found in equatorial Africa.

Histoplasma species are commonly found in bird and bat feces. In endemic areas, the organism is a soil saprophyte, and more than 70% of adults appear to be infected, typically with subclinical manifestations, as a result of inhaling spores.

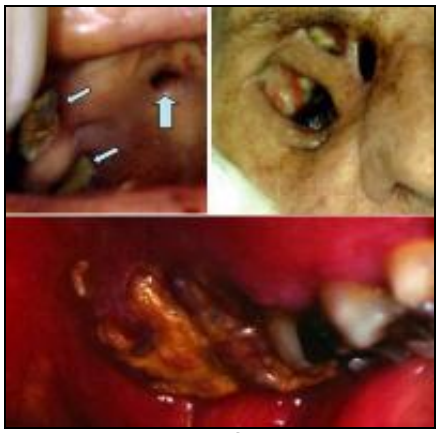
Zygomycosis

Mucor and *Rhizopus* species are the most common agents to cause zygomycosis.[5] Fungi of the order Mucorales (of the class Zygomycetes) are responsible for most mucormycosis. However, in addition to *Mucor* and *Rhizopus* species, organisms from the genera *Absidia, Apophysomyces, Mortierella, Saksenaea, Rhizomucor,* and *Cunninghamella* may also be involved. Therefore, the condition is probably better termed zygomycosis.

These fungi are ubiquitous worldwide in soil, manure, and decaying organic matter. Classic zygomycosis occurs worldwide. In some warmer regions, other Zygomycetes such as *Conidiobolus coronatus* infect a range of animals and can also occasionally cause rhinofacial zygomycosis in humans. Most human cases have been recorded from the Caribbean, Latin America, and Central and West Africa. Sporadic cases are seen worldwide.

Mucoraceae are commonly cultured from the nose, throat, mouth, and feces of many healthy individuals, but infection is virtually unheard of in otherwise healthy individuals.

Note the image below.



Mucormycosis. Top left image shows multiple, deep ulcerations (arrows) of the hard palate. Top right image shows destruction of the

palate and the floor of the orbit (failed skin graft of the right eye after orbital enucleation); this infection originated in the maxillary sinus. Bottom image shows similar deep, destructive ulceration of the left posterior maxillary alveolar bone and mucosa due to mucormycosis of the maxillary sinus. Courtesy of David Sirois, DMD, PhD.

Paracoccidioidomycosis

South American blastomycosis (paracoccidioidomycosis or Almeida disease) is found mainly in Colombia, Ecuador, Venezuela, Uruguay, Argentina, and, particularly, Brazil.[6] In Brazil, the disease is endemic in the states of Sao Paulo, Rio de Janeiro, and Minas Gerais. *P brasiliensis* is responsible and is presumably being inhaled as spores. Subclinical infection is not uncommon in endemic areas. Sporadic cases are seen worldwide.

Epidemiology

Frequency

United States

Because of the ubiquitous presence of these fungi in the environment, exposure is common. However, clinical disease is uncommon except in persons with iatrogenic or pathologic immunosuppression.

International

Because of the ubiquitous presence of these fungi in the environment, exposure is common in endemic areas, and travelers may present with manifestations even years after exposure. However, clinical disease is uncommon except in persons with iatrogenic or pathologic immunosuppression.

Mortality/Morbidity

In a healthy individual, infection is typically self-limited, although latency is commonly established, rather than elimination. Reactivation of latent infection may subsequently occur if the infected individual becomes immunosuppressed.

- Primary infection or reactivation in individuals with impaired immune surveillance presents a different scenario in which the disease may continue as a locally invasive and destructive process. Once the organism breaks through local barriers and enters the blood or lymphoreticular system, dissemination is rapid and difficult to control.
- Untreated, these fungal infections can be fatal, and among patients who are immunosuppressed (eg, those with AIDS, diabetes, leukemia, lymphoma, or iatrogenic immunosuppression as in organ transplantation), death rates dramatically increase.
- Regional destruction of the maxilla by paranasal infections leads to considerable morbidity, including oroantral fistula with oronasopharyngeal insufficiency and orbital invasion, which may result in loss of the eye.

Race

The deep mycoses can affect individuals of all races; no racial predilection is recognized.

Sex

The mycoses affect both sexes equally.

Age

The deep mycoses can affect individuals of all ages, although they are more common in adults than in children. Elderly individuals may be at increased risk, although this is often secondary to impaired immunity.

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