



FUNGAL INFECTIONS IN DIABETES MELLITUS: AN OVERVIEW

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Accepted on: 15-02-2011; Finalized on: 12-04-2011.

ABSTRACT

Prevalence of diabetes mellitus is being increasing globally as well in India. India has become the diabetic capital of the world. Fungal infections are often common in diabetes mellitus and however prevalence data of fungal infections in patients with diabetes mellitus availability is less. The study was undertaken to know the different fungal organisms, types, infections and their treatment among diabetes mellitus. Education on disease and precautionary measurements can prevent these infections. Hence pharmacist as a health care profession may help these patients in preventing infections through educational programs, patient information leaflets (PILS) and some video aids.

Keywords: Diabetes mellitus, fungal infections, pharmacist.

INTRODUCTION

A fungal infection usually appears on the skin, as the organisms live on a protein called keratin. This protein makes up the nails, skin and hair. The various symptoms of a fungal infection depend on the type of fungus that has caused the infection. Fungi are aerobic and eukaryotic cells; they are more complex than bacteria, which grow best at 25°C to 35°C. Fungi that cause only cutaneous and subcutaneous disease grow poorly at temperatures >37°C. Table 1 shows the clinical classification of fungal organisms.

Fungal organisms are broadly classified as follows

Hyphae (Moulds): Hyalohyphomycoses, *Aspergillus* spp., *Pseudallescheria boydii*, Dermatophytes: *Epidermophyton floccosum*, *Trichophyton* spp., *Microsporum* spp. Phaeohyphomycoses, *Alternaria* spp., *Anthopsis deltoidea*, *Bipolaris hawaiiensis*, *Cladosporium* spp., *Curvularia geniculata*, *Exophiala* spp., *Fonsecaea pedrosoi*, *Phialophora* spp., *Fusarium* spp. Zygomycetes *Absidia corymbifera*, *Mucor indicus*, *Rhizomucor pusillus*

Dimorphic Fungi: *Blastomyces* spp., *Coccidioides* spp., *Paracoccidioides* spp., *Histoplasma* spp., *Sporothrix* spp

Yeasts: *Candida* spp., *Cryptococcus neoformans*

Coccidioidomycosis

Coccidioidomycosis is caused by *C. immitis*, a thermal dimorphic fungus like *H. capsulatum* and *B. dermatitidis*. In soil, it grows as a mold with Arthroconidia but converts to a spherule containing 200 to 400 endospores each in host tissues. The number of multiplying coccidioidal organisms is significantly higher than *H. capsulatum* or *B. dermatitidis*, which may explain the higher incidence of clinical infection following exposure to *C. immitis*. Primary pulmonary infection occurs in the susceptible host when airborne Arthroconidia generated by dust storms or strong winds are inhaled. T-cell immunity is critical for

control of infection. Host immune response results in the production of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies; although they do not confer specific protection to disease development, serologic tests measuring antibody levels have diagnostic and prognostic value.

Patients with diabetes mellitus are more likely to be affected. One third of the cavities may close spontaneously within 2 years of its discovery, whereas the remainder may be complicated by secondary bacterial infections or persistent hemoptysis that requires excision.

Diagnosis: Definitive diagnosis is made with fungal culture and stains of blood, tissue, and fluids. However, blood cultures are frequently negative. Growth of the organism on appropriate media typically is apparent in 3 to 5 days.

Cryptococcosis

Cryptococcus neoformans is an opportunistic fungal pathogen that causes invasive diseases primarily in patients with underlying immunodeficiency and rarely in hosts with normal defenses. It exists as an encapsulated yeast surrounded by a polysaccharide capsule and has a worldwide distribution. Infection is acquired via inhalation of the spores of *C. neoformans* into the lungs. In patients with intact T-cell immunity, primary infection usually is contained within the lungs, whereas rapid dissemination to other sites, most notably the CNS, occurs in immunocompromised hosts.

Diagnosis: Diagnosis of cryptococcosis is made by isolating the organism from a sterile body site, by histopathology, or by cryptococcal capsular antigen testing. Blood cultures are positive in 70% of patients with AIDS who are infected with *C. neoformans*. India ink stain outlines the polysaccharide capsule of the yeast.



Aspergillosis

Aspergillosis, the most common invasive mold infection worldwide, is caused by the ubiquitous fungus *Aspergillus* spp. Approximately 150 species have been identified thus far. Pathogenic species that commonly cause invasive diseases include *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans*. *A. fumigatus* is the predominant species causing invasive aspergillosis; it accounts for approximately 90% of all cases. The rate of progression of invasive diseases may be closely related to the growth rate of the organisms. Macrophage ingestion and killing of the spores and extracellular killing of hyphae by neutrophils are the primary host defenses against *Aspergillus* in the lungs. Corticosteroids can substantially impair the functions of macrophages and neutrophils. T-cell function is thought to be important in the more chronic forms of invasive aspergillosis.

Signs and symptoms are more prominent and tend to extend over weeks or months; they include chronic productive cough, mild to moderate hemoptysis, low-grade fever, malaise, and weight loss. In contrast, patients who are the most immunocompromised are least likely to have symptoms and may progress within 7 to 10 days from onset of disease to death.

Candidiasis

Candida species are opportunistic pathogens that are a part of the normal human commensals. *Candida* as a cause of oral lesions was first identified in the 1840s. Over the past decade, the incidence of infections owing to *Candida* sp has increased dramatically. Based on a case-control study well matched for age, sex, service, underlying diagnosis, and duration of hospital stay, nosocomial candidemia was found to result in a crude mortality of 61% compared with 12% among cases and controls respectively, with an excess mortality of 49%. Those who survived spent an extra 11 days in the hospital.

Candida organisms are yeasts that exist microscopically as small (4–6 µm), thin-walled, ovoid cells that reproduce by budding. Other morphologic forms, such as pseudohyphae and hyphae, also can be seen in clinical specimens for most *Candida* sp except *C. glabrata*. More than 150 *Candida* sp have been identified previously; however, approximately 10 are considered important human pathogens. The pathogenic species include *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata* (formerly classified as *Torulopsis glabrata*), *C. krusei*, *C. guilliermondii*, *C. lusitanae*, *C. kefyr* (*C. pseudotropicalis*), *C. rugosa*, *C. dubliniensis*, and *C. stellatoidea* (now considered *C. albicans*). Speciation of the pathogens is important owing to the varied pathogenic potential and susceptibility to antifungal agents. A rapid presumptive identification of *Candida albicans* usually can be made by performing the specific germ tube test. Breakdown of the normal host defense mechanisms is necessary for *Candida* organisms to become pathogens. An intact integument is required for protection against cutaneous

invasion. When invasion occurs, functioning neutrophils, macrophages, and lymphocytes are important host defenses against the development of systemic disease.

Vulvovaginitis

Vulvovaginal candidiasis is estimated to occur at least once during reproductive years in 75% of women with no recognizable predisposing factors. However, identifiable risk factors include broad-spectrum antibiotics, high estrogen-containing oral contraceptives, poorly controlled diabetes, and pregnancy. Among patients infected with HIV, one large cross-sectional study found similar incidence (9%) of vaginal candidiasis compared with patients who do not have HIV. Clinical signs and symptoms include whitish cheesy discharge, vulvovaginal pruritus, irritation, soreness, dyspareunia, and burning on micturition.

FUNGAL INFECTIONS AND THE DIABETES

About 15% of the populations have fungal infections of the feet. Diabetic patients are very often prone to fungal infections, because of higher blood glucose levels which help for the growth of fungi. Common types of fungi are yeasts, moulds, mushrooms and all are not harmful. Most of the fungal infections can be treated and cured if diagnosed early. Table 2 shows the common fungal infections in diabetes mellitus.

Infections involving fungi may occur on the surface of the skin, in skin folds, and in other areas kept warm and moist by clothing and shoes. They may occur at the site of an injury, in mucous membranes, the sinuses, and the lungs. Fungal infections trigger the body's immune system, can cause inflammation and tissue damage, and in some people may trigger an allergic reaction. Many studies have shown that incidence of fungal infections are common in diabetes.

The immune system is weakened in this case and the cellular immune response in particular is hampered so that the system cannot fight fungal infection as well. Other causes for fungal infections are chronic diseases or conditions such as in patients with AIDS, tuberculosis, leukemia and other illnesses where the immune system is overtaxed or paralyzed. Patients with chronic conditions such as diabetes, kidney failure or extensive burns are all at a high risk for developing fungal infection.^{1, 2, 3}

Pathology of fungal infections in diabetes: Leukocyte function is compromised and immune responses are blunted. Patients with well controlled diabetes are much susceptible to infections. However, urinary tract infections continue to be problematic because glucose in the urine provides an enriched culture medium. This problem is further complicated if patients have developed autonomic neuropathy leading to urinary retention from poor bladder emptying. Ascending infection from the bladder (pyelonephritis) is thus a constant concern. Renal papillary necrosis may be a devastating complication of bladder infection. A dreaded infection complication of



poorly controlled diabetes is mucormycosis. This often fatal fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain.⁴

Women and fungal infections: In women with diabetes, vaginal secretions contain more glucose, or sugar, due to higher amounts of glucose in the blood. Yeast cells are nourished by this excess glucose, causing them to multiply and become a fungal infection. Also, hyperglycemia interferes with the immune functions that help prevent fungal infections.

Fungal infections in women with diabetes can mean that blood glucose levels are not well-controlled or that an infection can spread to another part of the body. When a woman with diabetes has a fungal infection, she is more likely to get other infections as well. This is because the combination of yeast and high blood sugar inhibits the body's ability to fight off other bacteria and viruses. Any infection in a person with diabetes poses a risk because blood sugars may be much higher or lower than normal while the body tries to fight infection.

Diabetic children: Angular stomatitis due to *Candida* is a classic complication in diabetic children and an occasional complication in diabetic adults. Increased concentrations of salivary glucose reportedly accounts for its occurrence, but not for the predilection for younger patients. Clinically it is appreciated as white, curd-like material which adheres to erythematous, fissured areas at the angle of the mouth or as white patches on the buccal mucosa and palate. Diagnosis is readily confirmed by examination of a potassium hydroxide preparation. Success in treatment may depend on normalization of blood sugar and the supplemental use of anticandidal lozenges.

One study in South Africa of 100 people with diabetes and another 100 without diabetes found that fungal infections were two and a half times as likely with diabetes, especially in people whose average blood sugar was above 160 mg/dl.⁶ Table no 3, 4 shows the commonly used drugs in the treatment of the fungal infections.

Table 1: Clinical Classification of Mycoses (fungal)

Classification	Site Infected	Example
Superficial	Outermost skin and hair	Malasseziasis (Tinea versicolor)
Cutaneous	Deep epidermis and nails	Dermatophytosis
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis
Systemic	Disease of more than one internal organ	
Opportunistic		Candidiasis, Cryptococcosis, Aspergillosis, Mucormycosis
Nonopportunistic		Histoplasmosis, Blastomycosis, Coccidioidomycosis

Table 2: Common fungal infections in Diabetes mellitus^{1, 4, 5}

Significantly increased incidence	Mucormycosis	a. Rhino cerebral, b. Cutaneous
	Candidiasis	a. Vulvovaginal, b. Oral, c. Candiduria, d. Ascending pyelonephritis
	Aspergillosis	a. External otitis
Slightly increased incidence	Candidiasis	a. Cutaneous, b. Prostatic abscess c. Peritonitis in patients undergoing peritoneal dialysis
Possible increased incidence	Dermatophytoses	
	Candidiasis	a. Biliary tract infection, b. Postoperative peritonitis
	Pulmonary mucormycosis	
	Invasive aspergillosis	
Incidence similar to that in general population		a. Systemic candidiasis, b. Candidaemia, c. Candida sinusitis

Table 3: Drugs used in the treatment

Topical agents	Systemic agents	Other treatment options
Clotrimazole	Itraconazole	Surgical debridement
Miconazole	Terbinafine	Topical steroids
Ketaconazole	Fluconazole	Radiation therapy
Econazole	Amphotericin	
Other agents:	Nystatin	
Benzoic acid with Salicylic acid	Griseofulvin	
	Voriconazole	



Table 4 : Treatment ^{7, 11, 13}

FDA LABELED INDICATIONS	DOSAGE	ADR
DRUG: CLOTRIMAZOLE		
Candidal vulvovaginitis Candidiasis Oropharyngeal candidiasis	Vaginal tablet: Insert 100 mg (1 tablet) INTRAVAGINALLY daily for 7 days or 200 mg (2 tablets) INTRAVAGINALLY daily for 3 days Cream: Insert 1 applicatorful (5 g) of 1% cream INTRAVAGINALLY daily for 7 to 14 days TOPICAL: apply thin layer of 1% cream twice daily for up to 4 wk Slowly dissolve 1 lozenge ORALLY 5 times/day for 14 days	Pruritus, Skin irritation, Nausea, Vomiting
DRUG: MICONAZOLE		
Oropharyngeal candidiasis	Tablet: 50 mg BUCCALLY against the upper gum above the incisor tooth once daily in the morning for 14 day	Pruritus (2%), Diarrhea (6%), Infectious disease (11.9%), Anaphylaxis reaction
DRUG: ECONAZOLE		
Candidiasis of skin	Apply topically to affected areas twice daily for 2 wk	Erythema, Pruritus, Stinging of skin, Burning sensation
DRUG: ITRACONAZOLE		
Aspergillosis Candidiasis Oropharyngeal candidiasis	Capsule: 200 mg ORALLY every 12 hr for 3 days, followed by 200 mg ORALLY once daily up to a MAX of 200 mg ORALLY twice daily; continue for at least 3 months and until evidence of clinical and laboratory improvement	Rash, Hypokalemia, Diarrhea, Nausea and vomiting Serious: Stevens-Johnson syndrome, Neutropenic disorder
DRUG: FLUCONAZOLE		
Candidiasis Candidal vulvovaginitis Candidemia Candidiasis Candidiasis of the esophagus Candidiasis of urogenital site Oropharyngeal candidiasis	Candidal vulvovaginitis: (uncomplicated) 150 mg ORALLY as a single dose Candidal vulvovaginitis: (complicated) 150 mg ORALLY every 72 hr for 3 doses. loading dose, 800 mg IV or ORALLY, then 400 mg (6 mg/kg) IV or ORALLY daily; continue for 14 days after first negative blood culture result and resolution of signs and symptoms of candidemia Systemic candidiasis, up to 400 mg ORALLY or IV once daily for 4 to 6 wk	Nausea, Vomiting Hepatic: Increased liver enzymes Neurologic: Headache SERIOUS Dermatologic: Stevens-Johnson syndrome Immunologic: Anaphylaxis (rare)
DRUG: AMPHOTERICIN		
Candidiasis Fungal infection of central nervous system (Severe) Fungal infection of lung (Severe) Mucormycosis	0.25 to 1 mg/kg/day IV over 2 to 6 hours; MAX of 1.5 mg/kg when given on alternate days	Weight loss; Gastrointestinal: Diarrhea, Indigestion, Loss of appetite, Nausea, Vomiting; Immunologic: Complication of infusion, Chills, fever, headache; Other: Malaise SERIOUS: Cardiovascular: Cardiac dysrhythmia, Hypotension, Thrombophlebitis; Endocrine metabolic: Hypokalemia, Hematologic: Anemia, Thrombocytopenia Immunologic: Anaphylaxis Ophthalmic: Blurred vision, Diplopia Renal: Nephrotoxicity
DRUG: NYSTATIN		
Candidal vulvovaginitis Candidiasis of skin, Gastrointestinal candidiasis, Oropharyngeal candidiasis	1 tablet (100,000 units) INTRAVAGINALLY daily for 2 wk Ointment or cream, apply liberally to affected areas TOPICALLY twice daily until healing complete Tablet: 1 to 2 tablets (500,000 to 1,000,000 units) ORALLY 3 times per day; continue treatment for at least 48 hr after clinical cure oral suspension, 4 to 6 mL (400,000 to 600,000 units) ORALLY (retained in mouth as long as possible prior to swallowing) 4 times daily; continue treatment for at least 48 hr after perioral symptoms disappear	Nausea and vomiting, With large doses (5 MU/day)
DRUG: GRISEOFULVIN		
Onychomycosis due to dermatophyte, Tinea unguium; onychomycosis	1 g ORALLY once a day for at least 4 months (fingernails) or at least 6 months (toenails)	Dermatologic: Photosensitivity, Rash, Urticaria Gastrointestinal: Diarrhea, Nausea, Vomiting Neurologic: Headache SERIOUS: Neurologic: Acroparesthesia (rare)
DRUG: VORICONAZOLE		
Aspergillosis, Invasive Candidemia Candidiasis of the esophagus, Disseminated candidiasis, of the skin and infections in abdomen	200 mg ORALLY every 12 hr (guideline dosing) Maintenance, 200 to 300 mg ORALLY every 12 hr for patients weighing 40 kg or more; 100 to 150 mg ORALLY every 12 hr for patients under 40 kg; treat for a minimum of 14 days following symptom resolution or following last positive culture, whichever is longer 200 to 300 mg ORALLY every 12 hr for patients weighing 40 kg or more; 100 to 150 mg ORALLY every 12 hr for patients under 40 kg; treat for a minimum of 14 days following symptom resolution or following last positive culture, whichever is longer	COMMON Cardiovascular: Peripheral edema (less than 2%), Dermatologic: Rash (7%) Gastrointestinal: Diarrhea (less than 2%), Nausea (5.4%), Vomiting (4.4%), Neurologic: Headache (3%), Ophthalmic: Visual disturbance (21%), Psychiatric: Hallucinations (2.4% to 16.6%), Other: Fever (5.7%) SERIOUS: Cardiovascular: Prolonged QT interval (less than 2%), Torsades de pointes (less than 2%), Dermatologic: Erythema multiforme (less than 2%), Stevens-Johnson syndrome (less than 2%), Toxic epidermal necrolysis (less than 2%), Gastrointestinal: Pancreatitis (less than 2%); Hepatic: Hepatitis, Increased liver function test, Liver failure; Immunologic: Anaphylactoid reaction (less than 2%); Neurologic: Toxic encephalopathy, Ophthalmic: Optic disc edema, Optic neuritis, Renal: Renal failure
DRUG: MICAFUNGIN		
Candidemia Candidiasis of the esophagus Disseminated candidiasis	100 mg/day IV over 1 hr 150 mg/day IV over 1 hr; mean duration of therapy, 15 days (range 10 to 30 days) (manufacturer dosing) 50 mg/day IV over 1 hr ; mean duration for prophylaxis, 19 days (range 6 to 51 days)	COMMON Cardiovascular: Phlebitis (1.6%), Dermatologic: Rash (1.6%) Gastrointestinal: Abdominal pain (1%), Diarrhea (1.6%), Nausea (2.8%), Vomiting (2.4%), Hematologic: Anemia , Hepatic: Liver function tests abnormal, Neurologic: Headache (2.4%); Other: Fever (1.5%), Rigor (1%) SERIOUS: Hematologic: Febrile neutropenia (36.5%), Hemolysis, Hemolytic anemia, Intravascular hemolysis, Neutropenia, Thrombocytopenia, Thrombotic thrombocytopenic purpura; Hepatic: Hepatitis; Renal: Renal impairment, acute; Other: Drug-induced anaphylaxis



CONCLUSION

Hence it can be concluded that patient education is necessary to prevent the infections earlier and the management of infections. Diabetes mellitus are affected more commonly with these infections so care should be taken while preventing these infections. Pharmacist can play an important role in the education and management of these infections.

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