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## AN OVERVIEW ON FUNGAL INFECTION IN DIABETES

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### 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.

## INTRODUCTION

Several thousand species of fungi have been described, but fewer than 100 are routinely associated with invasive diseases of humans. In general, healthy humans have a very high level of natural immunity to fungi, and most fungal infections are mild and self-limiting. Intact skin and mucosal surfaces and a functional immune system serve as the primary barriers to colonization by these ubiquitous organisms, but these barriers are sometimes breached.

Unlike viruses, protozoan parasites, and some bacterial species, fungi do not require human or animal tissues to perpetuate or preserve the species. Virtually all fungi that have been implicated in human disease are free-living in nature. However, there are exceptions, including various *Candida* spp., which are frequently found on mucosal surfaces of the body such as the mouth and vagina, and *Malassezia furfur*, which is usually found on skin surfaces that are rich in sebaceous glands. These organisms are often cultured from healthy tissues, but under certain conditions they cause disease. Many fungal infections, or mycoses, of

humans and animals affect only the outer layers of skin, and although they are sometimes difficult to cure, they are not considered dangerous. Athlete's foot and ringworm are among the common superficial fungal infections.

Sporotrichosis is an infection of farmers, horticulturists, and others who come into contact with plants or mud. Blastomycosis is caused by yeast like fungus that reproduces by budding. Wart like lesions appears most often on the skin, sometimes spreading to the bones and other organs. The South American variety of blastomycosis is caused by *B. brasiliensis*. Chytridiomycosis, caused by *Batrachochytrium dendrobatidis*, is a deadly fungal skin infection in amphibians, which it kills by damaging to the animals' normally permeable skin, thus disrupting the transport of air and moisture.<sup>(1)</sup>

Histoplasmosis, which is caused by spores of the fungal genus *Histoplasma*, is a severe infection that shows varied symptoms. In acute cases ulcers of the pharynx and enlargement of the liver and spleen are present.

In other forms tubercular like lesions of the lung occur. In its benign form no symptoms may be present. Fungal infections sometimes follow the use of antibiotics, which kill nonpathogenic as well as pathogenic bacteria, thereby providing a free field in the body for fungal invasion. <sup>(2)</sup>

### **FUNGAL INFECTION IN DIABETIC PATIENT**

It is widely accepted by both the medical profession and the general public that diabetics have an increased propensity to develop infections. Despite a number of both systemic and local host factors that can contribute to infections, whether diabetics truly are at greater risk for infection and the magnitude of the effect of diabetes on the risk of infection remain active questions. In addition, the types of infections observed in patients with diabetes mellitus (DM) are also complex. <sup>(3)</sup>

Host and organism-specific factors that may explain why people with DM are more susceptible to particular infections will be reviewed here. The clinical features, diagnosis, and treatment of specific infections that appear either to be more prevalent in diabetics or to have

unique features when they occur in diabetics are discussed separately. These infections include: <sup>(4)</sup>

- Vaginal yeast infection
- Foot infections. ( Diabetic infections of the lower extremities)
- Urinary tract infections, including fungal infections. (Emphysematous urinary tract infections)
- Superficial fungal infections, such as oral candidiasis, onychomycosis, and intertrigo. (Oropharyngeal and esophageal candidiasis and Onychomycosis and Candidal intertrigo.)
- Mucormycosis. (zygomycosis)
- Malignant external otitis. (necrotizing)
- Emphysematous cholecystitis.
- Pyomyositis, which is a primary bacterial infection of skeletal muscle characterized by the formation of one or more intramuscular abscesses. ( Pyomyositis)

### **Risk Factors for Developing Fungal Infections**

- Diabetes
- Use of drugs that suppress the immune system
- Cancer chemotherapy drugs

- Corticosteroids
- Drugs to prevent rejection of an organ transplants,
- AIDS
- Burns, if extensive
- Hodgkin lymphoma or other lymphomas
- Kidney failure
- Lung disorders, such as emphysema
- Leukemia

### **TYPES OF FUNGAL INFECTION**

- Superficial Fungal infections
- Systemic Fungal infections
- Opportunistic Fungal infections
- Cutaneous Fungal infections
- Subcutaneous Fungal infections

#### **Superficial Fungal infections**

- Superficial fungal infections (e.g., yeast vaginitis, oral thrush, and athletes' foot) affect millions of people worldwide. These affect the outer layers of the skin, the nails and hair.<sup>(5)</sup>
- Four infections are classified in the superficial mycoses. Black piedra, caused by *Piedraia hortai*, and white piedra, caused by *Trichosporon beigelii*, are infections of the hair. The skin infections include tinea nigra, caused by *Exophiala*

*werneckii*, and tinea versicolor, caused by *M. furfur*. Where the skin is involved, the infections are limited to the outermost layers of the stratum corneum; in the case of hairs, the infection is limited to the cuticle. In general, these infections cause no physical discomfort to the patient, and the disease is brought to the attention of the physician for cosmetic reasons.

- Although rarely life-threatening, they can have debilitating effects on a person's quality of life and may in some cases spread to other people or become invasive (systemic).
- Most superficial fungal infections are easily diagnosed and can be treated effectively.
- The main groups of fungi causing superficial fungal infections are:
  - Dermatophytes (tinea)
  - Yeasts i.e. candida, malassezia, piedra
  - Moulds.
- Fungal infections of the skin are among today's most common infectious diseases, and they occur worldwide.

➤ Superficial fungus infections fall into three broad categories:

- Dermatophytes (ringworm),
- Tinea versicolor, and
- Cutaneous candidiasis (yeast infection).

#### **Systemic Fungal infections:-**

➤ Systemic infections occur when fungi get into the bloodstream and generally cause more serious diseases.

➤ Systemic fungal infections may be caused either by an opportunistic organism that attacks a person with a weakened immune system, or by an invasive organism that is common in a specific geographic area, such as cocci and histoplasma. Unlike superficial infections, systemic fungal infections can be life-threatening.

➤ Systemic mycoses may result from breathing in the spores of fungi, which normally live in the soil or rotting vegetation or as opportunistic disease in immune compromised individuals. Although uncommon, some may infect healthy individuals. The result is most often a mild infection and long lasting resistance

to further attack, but occasionally these infections are more serious and chronic (especially in the immune suppressed).

➤ The initial focus of the systemic mycoses is the lung. The vast majority of cases in healthy, immunologically competent individuals are asymptomatic or of short duration and resolve rapidly, accompanied in the host by a high degree of specific resistance.

➤ The organisms causing systemic fungal infections include:

- Histoplasmosis
- Coccidioidomycosis (North and South America)

#### **Opportunistic Fungal infections**

➤ Opportunistic fungal infections constitute an increasing proportion of infections seen in immunocompromised patients; these infections are associated with a very high mortality rate. On the other hand, the endemic mycoses affect tens of thousands of persons who encounter the fungi that cause these infections in the course of every day activities in certain geographic areas.

- These infections are often asymptomatic, but endemic fungi can cause severe and even fatal infection in the appropriate host. New antifungal agents have changed the treatment of many fungal infections in the past few years. One can now choose from multiple effective drugs for many of the invasive mycoses. The following "clinical pearls" emphasize some clinical syndromes that aid in the diagnosis of fungal infections and highlight various nuances of treatment with antifungal agents. <sup>(7)</sup>

#### **Cutaneous Fungal infections**

- The cutaneous mycoses are caused by a homogeneous group of keratinophilic fungi termed the dermatophytes. Species within this group are capable of colonizing the integument and its appendages (the hair and the nails).
- In general, the infections are limited to the nonliving keratinized layers of skin, hair, and nails, but a variety of pathologic changes can occur depending on the etiologic agent, site of infection, and immune status of the host. The diseases are

collectively called the dermatophytoses, ringworms, or tineas. They account for most of the fungal infections of humans. <sup>(8)</sup>

#### **Subcutaneous Fungal infections**

- The subcutaneous mycoses include a wide spectrum of infections caused by a heterogeneous group of fungi.
- The infections are characterized by the development of lesions at sites of inoculation, commonly as a result of traumatic implantation of the etiologic agent.
- The infections initially involve the deeper layers of the dermis and subcutaneous tissues, but they eventually extend into the epidermis. <sup>(9)</sup>

#### **PATHOPHYSIOLOGY OF FUNGAL INFECTION**

**Mycosis** (plural: Mycoses) is a condition in which fungi pass the resistance barriers of the human or animal body and establish infections. Mycoses can result when the climate is hot and humid, and when people live in crowded conditions. Some fungi reproduce

through tiny spores in the air. People inhale those spores or they land on the skin. Therefore, fungal infections often start in the lungs or on the skin. People are at risk of fungal infections when they are taking strong antibiotics for a long period of time because antibiotics kill not only damaging bacteria, but healthy bacteria as well. This alters the balance of microorganisms in the mouth, vagina, intestines and other places in the body, and results in an overgrowth of fungus. Individuals with weakened immune systems are also at risk of developing fungal infections. This is the case of people with HIV/AIDS, people under steroid treatments, and people taking chemotherapy. People with diabetes also tend to develop fungal infections. Very young and very old people, also, are groups at risk. <sup>(10)</sup>

## **SOME FUNGAL INFECTION IN DIABETIC PATIENT**

### **VAGINAL YEAST INFECTION**

Vaginal yeast infections are a common problem in women. Vaginal yeast infections are also called yeast vaginitis or vaginal candidiasis. Although many women experience yeast infections,

women with type 2 diabetes have them more often.

Most women have yeast organisms as part of their normal flora, the tiny microorganisms that live on and inside our bodies.

“No one knows exactly why yeast infections are more common [in women with type 2 diabetes] but there is a definite association with how well a person's diabetes is controlled,” says Vincent Woo, MD, chair of the clinical and scientific section of the Canadian Diabetes Association. The increased level of blood sugar in diabetes affects the whole body, not just the blood. “Elevated blood sugars appear in the mucus of the vagina and vulva, so they serve as an excellent culture medium for yeast,” says Daniel Einhorn, MD, vice president of the American Association of Clinical Endocrinologists. Yeast gets energy from sugar. So in an environment that is moist with sugar, yeast may overgrow.

The effects of diabetes on the body become more obvious as time goes on. People who don't keep good control of their blood sugar may develop complications related to the constantly

high levels. One complication is difficulty in fighting off infections, either bacterial or fungal.

Yeast infections occur mainly in women who are menstruating (having monthly periods). They are less common in postmenopausal women who do not take estrogen and in girls who have not yet started menstruating.

## **VAGINAL YEAST INFECTION**

### **SYMPTOMS**

The most common symptoms of a yeast infection include:

- Itching or irritation of the vulva and around the vaginal opening.
- Pain with urination, vulvar soreness or irritation,
- Pain with intercourse
- Reddened and swollen vulvar and vaginal tissues.
- Some women have no abnormal vaginal discharge. Others have white clumpy (curd-like) or watery vaginal discharge.

Symptoms of a yeast infection are similar to a number of other conditions, including bacterial vaginosis (a bacterial infection of the vagina), trichomoniasis (a sexually transmitted infection), and dermatitis (irritated skin).

## **VAGINAL YEAST INFECTION**

### **RISK FACTORS**

In most women, there is no underlying health problem that leads to a yeast infection. There are several risk factors that may increase the chances of developing an infection, including:

- Antibiotics — most antibiotics kill a wide variety of bacteria, including those that normally live in the vagina. These bacteria protect the vagina from the overgrowth of yeast. Some women are prone to yeast infections while taking antibiotics.
- Hormonal contraceptives (eg, birth control pills, patch, and vaginal ring) — the risk of yeast infections may be higher in women who use birth control methods containing estrogen.
- Contraceptive devices — vaginal sponges, diaphragms, and intrauterine devices (IUDs) may increase the risk of yeast infections. Spermicides do not usually cause yeast infections, although they can cause you to have vaginal or vulvar irritation.
- Weakened immune system — Yeast infections are more common in people who have a weakened

immune system due to HIV or use of certain medications (steroids, chemotherapy, post-organ transplant medications).

- **Pregnancy** — vaginal discharge becomes more noticeable during pregnancy, although yeast infection is not always the cause.
- **Diabetes** — Women with diabetes are at higher risk for yeast infections, especially if blood sugar levels are often higher than normal.
- **Sexual activity** — vaginal yeast infections are not a sexually transmitted infection. They can occur in women who have never been sexually active, but are more common in women who are sexually active.

#### **VAGINAL YEAST INFECTION TREATMENT**

- Treatment of a vaginal yeast infection may include a pill that you take by mouth or a vaginal treatment.<sup>(11)</sup>
- **Vaginal treatment** — Treatment for a vaginal yeast infection often includes a vaginal cream or tablet. You apply the cream or tablet inside the vagina at bedtime with an

applicator. There are prescription and non-prescription treatments, so ask your doctor or nurse which to use. One, three, and seven-day treatments are equally effective.

- **Oral treatment** — A prescription pill called fluconazole (Diflucan®) is another option for treating yeast infections. Most women only need one dose, although women with more complicated infections (such as those with underlying medical problems, recurrent yeast infections, or severe signs and symptoms) may require a second dose 72 hours (3 days) after the first dose.
- Side effects of fluconazole are mild and infrequent, but may include stomach upset, headache, and rash. Fluconazole interacts with a number of medications; ask your doctor, nurse, or pharmacist if you have concerns. Fluconazole is not usually recommended during the first trimester of pregnancy due to the potential risk of harm to the fetus.

#### **PREVENTION**

Sporadic attacks of vulvovaginal candidiasis usually occur without an identifiable precipitating factor.

Nevertheless, a number of factors predispose to symptomatic infection:

- Diabetes mellitus — Women with diabetes mellitus who have poor glycemic control are more prone to vulvovaginal candidiasis than euglycemic women. Maintaining good glycemic control can help to prevent vaginal infection.
- Antibiotics — one-quarter to one-third of women are prone to vulvovaginal candidiasis during or after taking broad spectrum antibiotics. These drugs inhibit normal bacterial flora, which favors growth of potential pathogens such as candida. In women susceptible to symptomatic yeast infections with antibiotic therapy, a dose of fluconazole (150 mg orally) at the start and end of antibiotic therapy may prevent postantibiotic vulvovaginitis.
- Increased estrogen levels — Vulvovaginal candidiasis appears to occur more often in the setting of increased estrogen levels, such as oral contraceptive use (especially when estrogen dose is high), pregnancy, and estrogen therapy.
- Immunosuppression — Candidal infections are more common in immunosuppressed patients, such as those taking corticosteroids or with HIV infection.
- Contraceptive devices — Vaginal sponges, diaphragms, and intrauterine devices have been associated with vulvovaginal candidiasis, but not consistently. Spermicides are not associated with candida infection.
- Behavioral factors — Vulvovaginal candidiasis is not traditionally considered a sexually transmitted disease since it occurs in celibate women and since candida is considered part of the normal vaginal flora. This does not mean that sexual transmission of candida does not occur or that vulvovaginal candidiasis is not associated with sexual activity. As an example, there is an increase in the frequency of vulvovaginal candidiasis at the time most women begin regular sexual activity. Partners of infected women are four times more likely to be colonized than partners of uninfected women, and colonization is often the

same strain in both partners. Individual episodes of vulvovaginal candidiasis do not appear to be related to lifetime numbers of sexual partners or the frequency of coitus, but may be linked to orogenital and, less commonly, anogenital sex.

### **EMPHYSEMATOUS URINARY TRACT INFECTION**

Emphysematous urinary tract infections (UTIs) are infections of the lower or upper urinary tract associated with gas formation. They may manifest as cystitis, pyelitis, or pyelonephritis. Issues related to emphysematous UTIs will be reviewed here. Diabetes mellitus is a major risk factor for these infections and is also associated with an increased risk of asymptomatic bacteriuria and certain symptomatic UTIs such as cystitis, renal and perinephric abscess, and *Candida* infections.

#### **Asymptomatic Bacteriuria**

Presence of bacteria in the urine as a result of a bacterial infection in the urinary tract. A small amount of bacteria may produce no symptoms. Large amounts of bacteria usually indicate a urinary tract infection.

#### ***Cystitis***

Cystitis or bladder infection, is the most common urinary tract infection. It occurs in the lower urinary tract (the bladder and urethra) and nearly always in women. In most cases, the infection is brief and acute and only the surface of the bladder is infected. Deeper layers of the bladder may be harmed if the infection becomes persistent, or chronic, or if the urinary tract is structurally abnormal.

#### **Pyelonephritis (Kidney Infection)**

Sometimes the infection spreads to the upper tract (the ureters and kidneys). This is called pyelonephritis, or more commonly, a kidney infection.<sup>(12)</sup>

#### **FOURNIER'S GANGRENE OF THE PENIS**

Fournier's gangrene is a necrotizing infection that involves the soft tissues of the male genitalia.[ Asc R, Sarikaya S, et al.1998] Fournier's gangrene is a specific form of necrotizing fasciitis, a general term introduced in 1951, by Wilson, to describe infection of the soft tissue, which involves the deep and superficial fascia, regardless of the location. Originally, the term Fournier's

gangrene was used to describe idiopathic gangrene of the genitalia; however, it has also been used to describe most soft tissue necrotizing infections of the perineum, independent of the cause. Modern day use of the term Fournier's gangrene should be restricted to describe infections that primarily involve the genitalia.

In his presentation, Fournier reviews the systemic and local factors that influence this fulminant process. Local factors related to the trauma of the genitalia accounted for a vast majority of the cases of genital gangrene. Although Fournier has not emphasized the role of diabetes in this article, diabetes was known as the leading predisposing systemic factor.[Ayumba BR,et.al 1998] Fournier describes in anecdotes some of the misconceptions of the times that created this condition, including the practice of nighttime ligation of the prepuce to control enuresis or an attempted birth control technique practiced by an adulterating man to avoid impregnating his married lover. Since Fournier's description, subsequent knowledge has shown that it has an identifiable cause, which frequently

manifests in a more indolent fashion. Trauma to the genitalia continues to be a frequently recognized vector for the introduction of bacteria that initiate the infectious process.<sup>(13, 14)</sup>

### **FOOT INFECTIONS (DIABETIC INFECTIONS OF THE LOWER EXTREMITIES)**

Diabetic foot infections are associated with substantial morbidity and mortality. Important factors for development of diabetic foot infections include neuropathy, peripheral vascular disease, and hyperglycemia. In the setting of sensory neuropathy there is diminished perception of pain and temperature, so delays in injury presentation are common. Autonomic neuropathy can cause diminished sweat secretion resulting in dry, cracked skin, facilitating microorganism entry, while motor neuropathy can lead to foot deformities. Peripheral artery disease can lead to impaired blood supply needed for healing of ulcers and infections. Hyperglycemia impairs neutrophil function and reduces host defenses. Trauma in patients with one or more of these risk factors precipitates development of wounds that can be slow

to heal and predispose to secondary infection. Most diabetic foot infections are polymicrobial, with up to five or seven different specific organisms involved. The microbiology of diabetic foot wounds is variable depending on the extent of involvement. <sup>(15)</sup>

**MANEGEMENT OF FUNGAL INFECTION IN DIABETIC PATIENTS**

**Drugs used in the treatment**

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

The 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. <sup>(16)</sup>

**Treatment <sup>(17)</sup>**

<b>DRUG</b>	<b>FDA LABELED INDICATIONS</b>	<b>DOSAGE</b>	<b>ADR</b>
CLOTRIMAZOLE	Candidal vulvovaginitis  Candidiasis  Oropharyngeal candidiasis	Vaginal tablet: Insert 100 mg (1 tablet) INTRA VAGINALLY daily for 7 days or 200 mg (2 tablets) INTRA VAGINALLY 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
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
ECONAZOLE	Candidiasis of skin	Apply topically to affected areas twice daily for 2 wk	Erythema, Pruritus, Stinging of skin,

			Burning sensation
ITRACONAZOLE	Aspergillosis	Capsule: 200 mg ORALLY every 12 hr for 3 days, followed by 200 mg	Rash, Hypokalemia, Diarrhea, Nausea and vomiting
	Candidiasis	ORALLY once daily up to a MAX of 200 mg ORALLY twice daily;	Stevens-Johnson syndrome, Neutropenic disorder
	Oropharyngeal candidiasis	continue for at least 3 months and until evidence of clinical and laboratory improvement	
AMPHOTERACIN	0.25 to 1 mg/kg/day IV over 2 to 6 hours; MAX of 1.5 mg/kg when given on alternate days		
NYSTATIN	Candidal vulvovaginitis Candidiasis of skin,	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 cureoral suspension, 4 to 6 mL (400,000 to 600,000 units)	Nausea and vomiting, With large doses (5 MU/day)
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)

## REFERENCES

1. Edwards JE, Tillman DB, Miller ME, Pitchon HE.1979; Infection and diabetes mellitus. *West J Med* 130:515-521.
2. Drachman RH, Root RK Jr, WB Wood.1966; Studies on the effect of experimental nonketotic diabetes on antibacterial defense—I. Demonstration of a defect in phagocytosis. *J Exp Med* 124:227-40.
3. Hosking DJ, Bennett T, Hampton JR.1978; Diabetic autonomic neuropathy *Diabetes* 27:1043-54.
4. Kaslow RA.1985; Infections in diabetics. In *Diabetes in America*.Harris MI, Hamman RF, eds. NIH publ. no. 85-1468, 1-18.
5. Drake LA, Dinehart SM, Farmer ER, et al.1996; Guidelines of care for superficial mycotic infections of the skin: Onychomycosis. Guidelines/Outcomes Committee. American Academy of Dermatology. *J Am Acad Dermatol.* 34: 116-121.
6. Ellenberg M, Weber H.1967; The incipient asymptomatic diabetic bladder. *Diabetes* 16:331-35.
7. Drake LA, Dinehart SM, Farmer ER, et al.1996; Guidelines of care for superficial mycotic infections of the skin: Pityriasis (tinea) versicolor. Guidelines/Outcomes Committee. American Academy of Dermatology. *J Am Acad Dermatol.* 34: 287-289.
8. Trent JT, Federman D, Kirsner RS.2001; Common bacterial skin infections. *Ostomy Wound Manage.* 47: 30-34.
9. Rex JH, Walsh TJ, Sobel JD, et al. 2000; Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. *Clin Infect Dis.*30:662.
10. Asci R, Sarikaya S, Buyukalpelli R, Yilmaz AF, Yildiz S. 1998; Fournier's gangrene: Risk assessment and enzymatic debridement with lyophilized collagenase application. *Eur Urol.* 34:411–8.
11. Ayumba BR, Magoha GA. 1998; Management of Fournier's gangrene at the Kenyatta National Hospital, Nairobi. *East Afr Med J.* 75:370–3.
12. Sonck CE, Somersalo O1963; The yeast flora of the anogenital region in diabetic girls. *Arch Dermatol* 88:846-852.

13. Basoglu M, Gul O, Yildirgan I, Balik AA, Ozbey I, Oren D. 1997; Fournier's gangrene: Review of fifteen cases. *Am Surg.* 63:1019–21.
14. Yumura Y, Chiba K, Saito K, Hirokawa M. 2000; Fournier's gangrene of penis in a patient with malignant lymphoma: A case report. *Hinyokika Kiyo.* 46:735–37.
15. Murphy RA.1965; Skin lesions in diabetic patients: The "spotted leg" syndrome. *Lahey Clin Found Bull* 14:10-14.
16. National guideline for the management of vulvovaginal candidiasis. 1999; Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). *Sex Transm Infect.* 75 Suppl 1:S19.
17. Ferris DG, Nyirjesy P, Sobel JD, et al. 2002; Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. *Obstet Gynecol.* 99:419.