

# Fungal infections

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# Vulvovaginal Candidiasis/VVC

- Although VVC is uncommon prior to menarche, an estimated 75% of women will have at least one occurrence of VVC.
- VVC can be classified as uncomplicated or complicated.
- uncomplicated infections occur sporadically, cause mild to moderate symptoms, and occur in nonimmunocompromised women.
  - often caused by *candida albicans*
- complicated infections, including recurrent, severe infections, and those in women with uncontrolled DM, or immunosuppression

## Cont....

- Recurrent VVC, defined as four or more infections per year, occurs in less than 5% of women,
- *Candida albicans* is the primary pathogen responsible for VVC, accounting for 80% to 92% of cases

# Pathophysiology

- vaginal discharge, composed of exfoliated cells, and cervical mucus cleans the vagina
- the normal pH of vaginal secretions, near 4.0, is toxic to many pathogens and is maintained by lactobacillus acidophilus, diphtheroids, and staphylococcus epidermidis
- alterations in the vaginal environment, including pH changes, allow for overgrowth of organisms that are normally suppressed

# Risk factors

- VVC is not considered to be a sexually transmitted disease, although sexual factors can be important
- oral genital contact
- diaphragm with spermicide, the contraceptive sponge
- increase the risk of VVC
- Broad-spectrum antibiotic use

# Risk factors

| Risk Factor  | Proposed mechanism   |
|--|--|
| Broad-spectrum antibiotic use<br><br>Systemic corticosteroid or<br>Immunosuppressant use | Altered vaginal flora allowing overgrowth of <i>Candida</i> organisms; risk increases with duration of antibiotic use  |
| Sexual activity  | partners may have penile or oral colonization; use of vaginal irritants or devices, including diaphragms and intrauterine systems, can irritate vaginal mucosa |
| Tight-fitting and nonabsorbent clothing  | promotes warm, moist environment for fungus growth   |
| Elevated estrogen levels, hormonal contraceptives, and pregnancy                         | Estrogen enhances <i>Candida</i> adherence to vaginal epithelial cells   |
| Diabetes   | Enhanced binding of <i>Candida</i> to epithelial cells due to hyperglycemia;   |

# Clinical Presentation

## Symptoms

- Vaginal itching
- Vaginal soreness
- Vaginal burning
- Irritation
- External dysuria
- Dyspareunia

## Sign

- Nonodorous vaginal discharge
- Yellow or yellowish green discharge
- Erythema and edema of the labia and vulva
- Fissures
- Pustulopapular lesions

# Diagnosis of VVC

- Microscopic investigation
- Asymptomatic vaginal colonization does not require treatment; therefore, the presence alone of *Candida* should not determine care.
- pH should remain normal in cases of fungal infection, whereas an elevated pH suggests bacterial infection.
- *Candida* cultures should be obtained only if signs and microscopy are inconclusive or in cases of recurrent VVC.



# Treatment

- The goals of treatment of VVC are as follows:
  - ✓ Relief of symptoms
  - ✓ Eradication of infection
  - ✓ Reestablishment of normal vaginal flora
  - ✓ Prevention of recurrent infections in complicated infections

# Treatment

- Nonpharmacologic treatment
  - ✓ Keep the genital area clean and dry
  - ✓ Avoid prolonged use of hot tubs
  - ✓ Avoid constrictive clothing
  - ✓ Avoid vaginal douching
  - ✓ Wear underwear made of cotton
  - ✓ Avoid soaps and perfumes in the genital area

# Pharmacologic Treatment of uncomplicated VVC

- 1-Day Therapies
  - **Butoconazole** 2% sustained-release cream, 5 g intravaginally as a single application
  - **Fluconazole** 150 mg, one tablet orally as SD
  - **Tioconazole** 6.5% ointment, 5 g intravaginally as a single application
- 3-Day Therapies
  - **Butoconazole** 2% cream, 5 g intravaginally for 3 nights
  - **Clotrimazole** 100-mg vaginal tablet, two tablets for 3 nights
  - **Miconazole** 200-mg vaginal suppository, one suppository for 3 nights

# Pharmacologic Treatment of uncomplicated VVC

- 7- to 14-Day Therapies
  - Clotrimazole 1% cream, 5 g intravaginally for 7–14 nights
  - Clotrimazole 100-mg vaginal tablet, one tablet for 7 nights
  - Miconazole 2% cream, 5 g intravaginally for 7 nights
  - Miconazole 100-mg vaginal suppository, one suppository for 7 nights
  - Nystatin 100,000-unit vaginal tablet, one tablet for 14 nights

# Pharmacologic Treatment of uncomplicated VVC

- Inability to resolve an infection may indicate
  - a mixed infection,
  - infection owing to a nonalbicans strain,
  - an infection that is not fungal, or
  - indicative of serious underlying conditions, such as DM or HIV

# Pharmacologic Treatment of uncomplicated VVC

- **Adverse effects and drug interaction**
- Topical products: burning, itching, stinging, and redness
- Systemic Fluconazole: headache, diarrhea, nausea, dizziness, abdominal pain, and taste alterations
- **Drug interaction:** Oral azoles are associated with significant drug interactions, particularly due to potent inhibition of cytochrome P-450 (CYP2C9)

# Pharmacologic Treatment of recurrent VVC

- First, any acute episodes are treated, followed by maintenance therapy.
- Although acute episodes will respond to azole therapy, some patients may require prolonged therapy
- **Two weeks of topical azole therapy** or a second dose of oral fluconazole 150 mg repeated 3 days after the first dose can be used.
- After achieving remission, recurrent VVC requires **long-term suppressive therapy for 6 months**

# Pharmacologic Treatment of recurrent VVC

- Daily
  - Itraconazole 100 mg orally once daily
  - Ketoconazole 100 mg orally once daily
- Weekly
  - Clotrimazole 500 mg vaginal suppository once weekly
  - Fluconazole 100 or 150 mg orally once weekly
- Monthly
  - Fluconazole 150 mg orally once monthly
  - Itraconazole 400 mg orally once monthly



# Treatment of VVC during pregnancy

- during pregnancy, VVC may be difficult to treat due to elevated estrogen levels, lower response rates, and frequent recurrences
- oral agents are contraindicated in pregnancy because of the concern for fetal complications.
- vaginal antifungals are the preferred treatment (clotrimazole for 1-2wks)

## Treatment of nonalbicans infections

- Treatment response rates are lower for nonalbicans infections
  - oral itraconazole 200-mg twice daily one day per month for 6 months
  - topical 4% flucytosine

# Oropharyngeal and Esophageal Candidiasis

- Oropharyngeal candidiasis (OPC), or thrush, is a localized infection of the oral mucosa caused by the yeast *Candida*
- If OPC left untreated, it will progress to esophageal candidiasis
- *Candida* is a commensal fungus found in the oral cavity in up to 65% of healthy individuals
- *Candida* carriage increases under immunocompromised conditions and hospitalized patients
- *C. albicans* is the predominant colonizing *Candida* species (70%-80%),

# Risk factors

| Factors   | Potential mechanism  |
|---|--|
| Use of steroid and antibiotics  | Suppression of cellular immunity and inhibition of phagocytosis by steroids;<br>Alteration of endogenous oral flora by broadspectrum antibiotics |
| Dentures  | Adherence of fungus to dentures, along with reduced salivary flow  |
| Xerostomia (TCA)  | Reduced cleansing and defense factors of saliva  |
| chemotherapy and radiotherapy, ulcers, endotracheal intubation trauma, and burn | Disruption of oral mucosa , Oral mucositis altered rate of mucosa regeneration   |
| HIV infection   | Decreased CD4 T lymphocytes  |
| Diabetes mellitus   | Elevated glucose levels and reduced chemotactic factor in saliva,  |
| Use of PPI  | inhibition of gastric acid by PPIs can facilitate the growth of Candida species;   |

# Pathophysiology

- Candida organisms frequently colonize the oropharynx and mucous membranes.
- in the setting of broad-spectrum antibiotic use, tissue damage (due to chemotherapy, catheter tubing, trauma, or smoking) or immune deficiency, the organisms become pathogenic

# Clinical presentation

- **Oropharyngeal candidiasis**
- Sore, painful mouth and tongue
- Burning tongue
- Dysphagia
- Metallic taste
- **Sign**
- Diffuse erythema on the surface of buccal mucosa, throat, tongue, and gums
- White patches on tongue, gums, or buccal mucosa
- Angular cheilitis presents with small cracking lesions at the corners of the mouth

# Clinical presentation

- **Esophageal candidiasis**
- **Symptoms**
- Fever
- Odynophagia
- Dysphagia
- Retrosternal pain
- **Signs**
- Fever
- Hyperemic or edematous white plaques
- Ulceration of esophagus
- Narrowing of lumen

# Diagnosis

- **Oropharyngeal candidiasis**
- Based on clinical presentation and culture
- **Esophageal candidiasis**
- Endoscopy: reveal whitish plaques
- Cytology and culture
- Mucosal biopsy



# Treatment

- Desired outcome
  - Clinical cure
  - Prevent progression to esophagus
  - Improve quality of life
  - Minimize number of recurrence
  - Minimize toxicities and DI of antifungals

# General approach to management

- Management depends on
  - ✓ immune status of the patient
  - ✓ other concurrent mucosal and medical disease
  - ✓ concomitant medication
- Selection of antifungal drug depends on
  - ✓ Drug adherence
  - ✓ Drug interaction
  - ✓ Adequate saliva for dissolution of topical ppn
  - ✓ Presence of liver disease

# General approach to management

- topical agents require frequent applications because of the short contact time with the oral mucosa
- sufficient saliva is needed to dissolve topical preparation (xerostomia)
- Nystatin suspension might be a better choice for patients with xerostomia
- Miconazole 50 mg tablet offer once daily dosing
- Systemic therapy is required
  - for those with refractory to topical treatment
  - moderate-to-severe disease, and
  - those at high risk for disseminated invasive candidiasis

# Treatment of Oropharyngeal Candidiasis

| Initial Episodes of OPC (7-14 Days)  | Common side effect   |
|--|--|
| <b>Clotrimazole</b> 10 mg troche: hold 1 troche in mouth for 15-20 minutes . 5 times daily | Altered taste, mild nausea, vomiting                                     |
| <b>Nystatin</b> 100,000 units/mL suspension: 5 mL swish and swallow 4 times daily          | Mild nausea, vomiting, diarrhea  |
| <b>Miconazole</b> 50 mg mucoadhesive buccal tablets 50 mg daily                            | Diarrhea, headache, nausea, upper abdominal pain, and vomiting           |
| <b>Fluconazole</b> 100 mg tablets: 100-200 mg daily  | GI upset, hepatitis not common   |
| <b>Itraconazole</b> 10 mg/mL solution: 200 mg daily  | GI upset, hepatotoxicity, CHF, pulmonary edema with long-term use (rare) |
| <b>Posaconazole</b> 40 mg/mL suspension: 400 mg daily with a full meal                     | GI upset, fever, headache, increased hepatic transaminases not common    |

# Treatment of Oropharyngeal Candidiasis

| Fluconazole-Refractory OPC: Treat for $\geq 14$ Days  | Common side effect   |
|---|--|
| <b>Itraconazole</b> 10 mg/mL solution: 200 mg daily   | Altered taste, mild nausea, vomiting   |
| <b>Voriconazole</b> 200 mg tablets: 200 mg twice daily ( $>40$ kg), taken on empty stomach                      | GI upset, rash, reversible visual disturbance, increased hepatic transaminases, hallucinations     |
| <b>Posaconazole</b> 40 mg/mL suspension: 400 mg twice daily $\times$ 3 days, then 400 mg daily $\times$ 28 days |  |
| <b>Amphotericin B</b> 100 mg/mL suspension: 1-5 mL swish and swallow 4 times daily                              | IV: fever, chills, sweats, nephrotoxicity, electrolyte disturbances, bone marrow suppression       |
| <b>Caspofungin</b> 50 mg IV daily   | Fever, headache, infusion-related reactions, hypokalemia, increased hepatic transaminases, anemia, |

# Treatment of esophageal Candidiasis

| Esophageal Candidiasis( 14-21 Days                              | Common side effect |
|---|--------------------|
| <b>Fluconazole</b> 100 mg tablets: 200-400 mg (3-6 mg/kg) daily | See above          |
| <b>Amphotericin B</b> : 0.3-0.7 mg/kg/day IV daily              | See above          |
| <b>Posaconazole</b> 40 mg/mL suspension: 400 mg twice daily     | See above          |
| <b>Itraconazole</b> 200 mg daily                                | See above          |
| <b>Voriconazole</b> 200 mg twice daily                          | See above          |

# Treatment of esophageal Candidiasis

| Fluconazole-Refractory 21-28 Days  | Common side effect |
|--|--------------------|
| <b>Itraconazole</b> 200 mg daily   | See above          |
| <b>Posaconazole</b> 40 mg/mL suspension:<br>400 mg twice daily                             | See above          |
| <b>Voriconazole</b> 200 mg twice daily   | See above          |
| <b>Caspofungin</b> 50 mg IV daily<br><b>Amphotericin B</b> : 0.3-0.7 mg/kg/day<br>IV daily | See above          |
| <b>Amphotericin B</b> : 0.3-0.7 mg/kg/day<br>IV daily                                      | See above          |

# Mycotic infections of the skin, hair, and nails

- Tinea infections are superficial fungal infections in which the pathogen remains within the **keratinous layers** of the **skin** or **nails**
- The common tinea infections are tinea pedis, tinea corporis (body), and tinea cruris(groin)
- are primarily caused by dermatophytes such as Trichophyton, Microsporum, and Epidermophyton.
- The causative dermatophyte typically invades the stratum corneum without penetration into the living tissues (local infection)



# Pathophysiology

- primary mode of transmission is direct contact with other persons or surface reservoirs
- upon contact, the dermatophytes attach to the keratinized cells, leading to thickening of the cells
- Although infection remains localized, bacterial superinfections may develop

# Risk factors

- Prolonged exposure to sweaty clothing
- Excessive skin folds
- Warm, humid climate
- Use of public pools
- Walking barefoot in public areas
- Skin trauma
- Poor nutrition
- Diabetes mellitus
- Immunocompromise
- Impaired circulation

# Tinea Pedis (athlete's foot)

- Most common dermatophytoses (70%)
- occurs in hot weather and with use of occlusive footwear
- Common presentation
  - fissuring, maceration and scaling of the spaces between the toes
  - itching and burning
  - erythema of the soles, heels, and sides of the foot
  - formation of vesicles and pustules typically on the soles of the foot

# Tinea Pedis (athlete's foot)

- complication : streptococcal cellulitis (disruption of skin integrity )
- **Topical treatment**
  - Butenafine, daily
  - Sertaconazole, twice daily
  - Luliconazole daily
  - Naftifine cream daily,
- **Systemic treatment**
  - Fluconazole 150 mg 1 per week × 1-4 weeks

# Tinea Cruris

- is an infection of the proximal thighs and buttocks
- more common in males
- high humidity and warm temperatures along with wet or tight-fitting clothes has contribution
- the lesions are red and patients complain itching and burning
- pustules or vesicles and maceration are usually found
- **Topical treatment**
  - Luliconazole, Naftifine cream, Econazole, Ketoconazole cream (daily) , Miconazole, twice daily
  - Itraconazole 200-400 mg/day × 1 week

# Tinea Cruris

- topical therapy should be continued for 1 to 2 weeks after symptom resolution
- Topical hydrocortisone can be used for pruritus and burning
- **Systemic therapy**
  - Itraconazole 200-400 mg/day × 1 week
- **Patient counseling**
- keeping the area dry or avoiding prolonged exposure to moisture

# Tinea Corporis

- is an infection of the skin of the trunk, extremities, or face
- the lesions may be singular or multiple and appear as round, scaly lesions.
- if the infection is very widespread systemic antifungal therapy may be necessary
- **Topical treatment**
- naftifine cream, daily
- oxiconazole, sulconazole, terbinafine, tolnaftate, (twice daily)
- **Systemic treatment**
  - terbinafine 250 mg/day  $\times$  2 weeks
  - fluconazole 150 mg once weekly  $\times$  4 weeks

# Tinea Capitis

- mycotic infection involving the scalp and hair follicles
- It primarily affects children
- objects such as hats, brushes, or pillowcases are often the source of transmission
- The diagnosis of tinea capitis can be made in children based on the presence
  - scalp scaling, scalp pruritis, occipital adenopathy and diffuse patchy or discrete alopecia
- **Treatment**
  - Terbinafine 250 mg/day × 4-8 weeks
  - Fluconazole 150 mg/week × 4 weeks



# Onychomycosis

- is a fungal infection of the nail apparatus and is most common single cause of nail dystrophy
- more commonly affects the toenails (due to slow growth of toe nails)
- *C. albicans* is the most commonly isolated yeast that typically affects fingernails
- **Risk factors**
- increasing age, immunodeficiency , DM, psoriasis, peripheral vascular disease, smoking, prevalence of tinea pedis and frequent nail trauma

# Pathophysiology

- The pathophysiology depends on the clinical type
- In distal lateral subungual, the fungus spreads from the plantar skin and invades the underside of the nail through the distal lateral nail bed, leading to inflammation of the area.
- In cases of white superficial onychomycosis, the fungus invades the surface of the nail plate directly.
- Proximal subungual onychomycosis infections begin in the cuticle and the proximal nail fold, then penetrate the dorsum of the nail plate.

# Treatment

- Factors that impact treatment decision includes
  - Type and severity of onychomycosis
  - Causative organism—dermatophyte vs molds or yeast
  - Infection of the finger vs toenail
  - Extent of disease-number of nails
  - Other sites of mycotic infection (palms, soles)
  - Age and underlying medical conditions (diabetes, poor perfusion, immunocompromised)
  - Drug interactions and adverse effects
  - Cost of therapy

# Treatment

- **Treatment options**
  - oral and topical therapies,
  - mechanical or chemical nail avulsion
    - used primarily in patients with severe onycholysis and extensive nail thickening
    - it enhance penetration of the antifungal agent to the entire nail plate
- in general, onychomycosis of the toenail is more difficult to treat than fingernails,
- they requires longer treatment duration, and associated with a higher recurrence

# Treatment

- Adequate treatment is essential to prevent spread to other sites, secondary bacterial infections, cellulitis, or gangrene.
- topical agents have low efficacy due to the chronic nature of nail infections
  - Terbinafine 250 mg/day  $\times$  6 weeks (fingernail), 12 weeks (toenail)
  - Itraconazole 200 mg BID  $\times$  1 week/month for 2 months (fingernail); 200 mg daily  $\times$  12 weeks (toenail)
  - Fluconazole 50 mg daily or 300 mg once weekly for  $\geq 6$  months (fingernail) or 12 months (toenail) (not FDA approved)

# Treatment

- terbinafine persisting in nails for 30 to 36 weeks after completion of treatment while itraconazole persist for 27 weeks
- The more common adverse effects reported with terbinafine are GI (eg, diarrhea, dyspepsia, nausea, and abdominal pain), dermatologic (eg, rash, urticaria, and pruritus), and headache
- stevensJohnson's syndrome, toxic epidermal necrolysis, pancytopenia, lupus erythematosus, psoriasis, hair loss, and hepatotoxicity
- itraconazole therapy due to its negative inotropic effects( avoid in patients with CHF)

# Treatment

- Griseofulvin has a narrow antifungal spectrum, low clinical efficacy, especially for toenail infections, high relapse rates, and the need for prolonged treatment duration (up to 12-18 months for toenails)
- use of ketoconazole is also associated with high relapse rates, and the prolonged treatment duration carries an increased risk of hepatotoxicity

THANK YOU