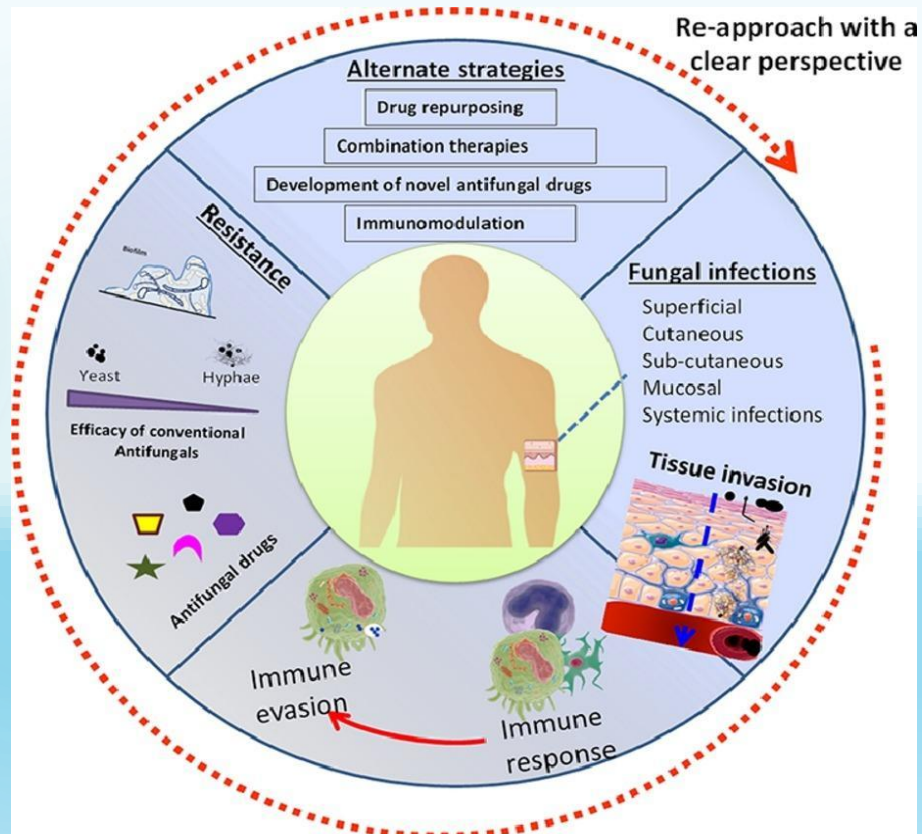


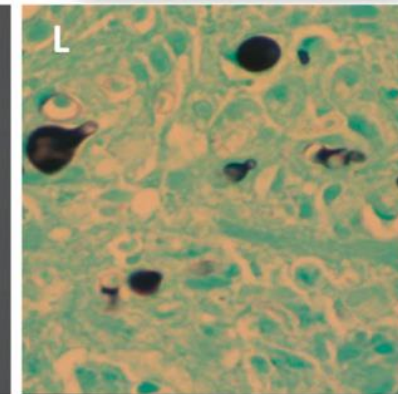
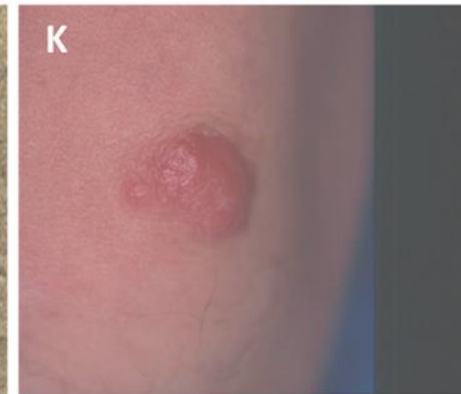
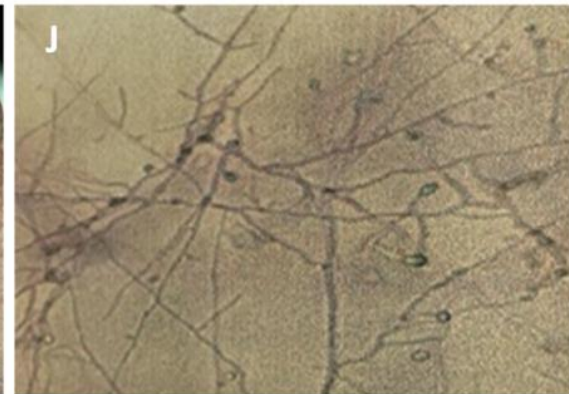
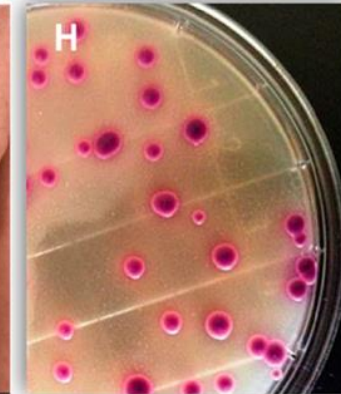
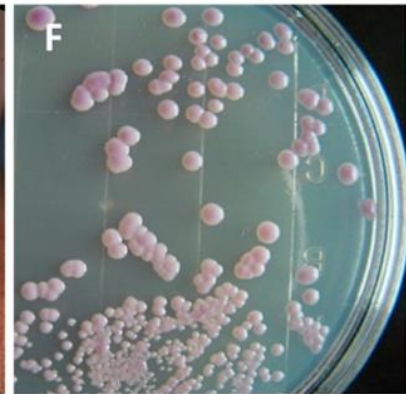
INTRODUCTION TO FUNGAL INFECTIONS



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FEATURES OF FUNGI

Cellular Structure

Eukaryotic organisms: Possess a true nucleus enclosed by a nuclear membrane. Contain typical eukaryotic organelles: Mitochondria, Golgi apparatus, Endoplasmic reticulum (with ribosomes), Cytoplasmic membrane: Contains lipids, glycoproteins, and sterols (e.g., ergosterol). Cytoskeleton: Includes microtubules, microfilaments, and intermediate filaments.

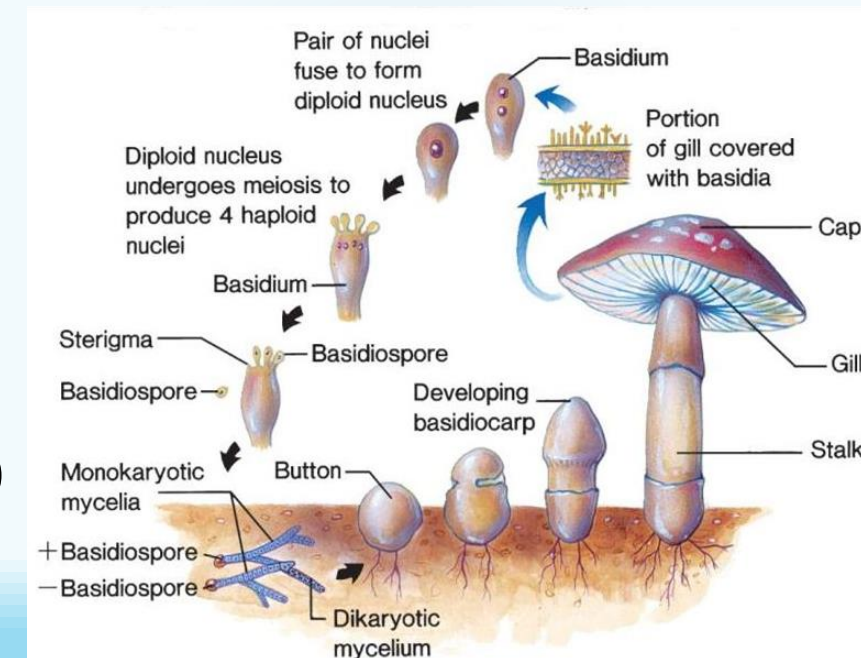
Cell Wall Composition

Rigid cell wall composed of Chitin, Cellulose, Or both

These components can be stained with: Gomori methenamine silver (GMS)
Periodic acid–Schiff (PAS)

Gram stain: Most fungi (except *Candida*) are poorly gram-positive and not clearly visible.

Special Structures: *Cryptococcus neoformans*: Surrounded by a polysaccharide capsule (important for virulence and diagnosis).



Morphological Forms: Fungi exist in two major morphological forms:

Form	Description
Molds	Multicellular - Grow as branching hyphae (filaments)
	Hyphae may be : • Septate (divided by cross-walls) • Coenocytic (non-septate, multinucleate)
Yeasts	Unicellular, oval or spherical- Grow as pasty or mucoid colonies on agar
	Reproduce by budding (daughter cell buds off parent cell)

Dimorphism (Dimorphic Fungi): Dimorphic fungi can switch between yeast and mold forms depending on:

Temperature

Environment (host vs. laboratory)

In humans (host): Exist as yeasts (parasitic form).

In the environment/lab: Exist as molds (saprophytic form).

Classification of Fungi

The Fungal World

FUNGI

YEASTS

Candida spp.

C. albicans

C. glabrata

C. tropicalis

C. parapsilosis

C. krusei

Cryptococcus

Trichosporon spp.

Blastoschizomyces capitatus

Rhodotorula spp.

Geotrichum spp.

Saccharomyces cerevisiae

Pichia spp.

MOLDS

Mucorales

[prev Zygomycetae]

Rhizopus spp.

Mucor spp.

Rhizomucor spp.

Lichtheimia (prev Absidia)

Septate Fungi

Aspergillus spp.

Hyalohyphomycoses

Fusarium spp.

Pseudallescheria boydii

Scedosporium prolificans

Scedosporium apiospermum

Paecilomyces spp.

FUNGAL INFECTIONS

- Fungal infections, or mycoses, are diseases caused by fungi.
- These can range from superficial (skin, nails, mucosa) to systemic and life-threatening infections, especially in immunocompromised individuals.
- They are broadly categorized as:
 - Primary (systemic) mycoses: Caused by pathogenic fungi that infect healthy or immunocompromised hosts.
 - Opportunistic mycoses: Caused by normally harmless fungi in immunocompromised individuals.

Epidemiology

- ❖ The incidence of fungal infections is increasing, especially in hospital and ICU settings.
- ❖ Nosocomial fungal infections account for a large percentage of bloodstream infections (e.g., *Candida* spp. are 4th most common).
- ❖ *Candida albicans* causes 78% of nosocomial fungal infections.
- ❖ There's a growing shift in invasive fungal infections (IFIs) from *Candida* spp. to *Aspergillus* spp., especially in stem cell transplant and hematologic malignancy patients.
- ❖ Geographic variation plays a role:
 - ❖ *Histoplasma capsulatum* → Mississippi & Ohio river valleys
 - ❖ *Coccidioides* spp. → Southwestern USA
 - ❖ *Paracoccidioides* → Central & South America

Classification of Mycoses

**Superficial
Mycoses**

**Cutaneous
Mycoses**

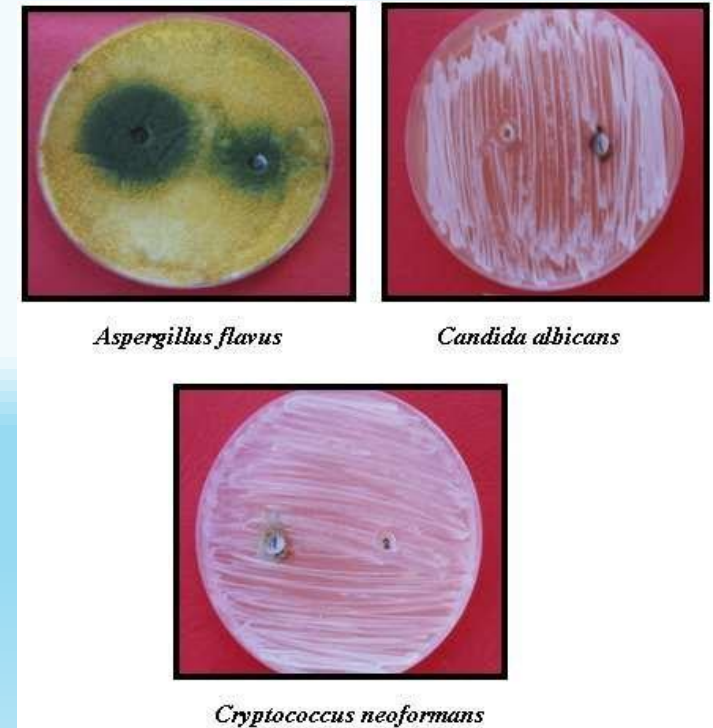
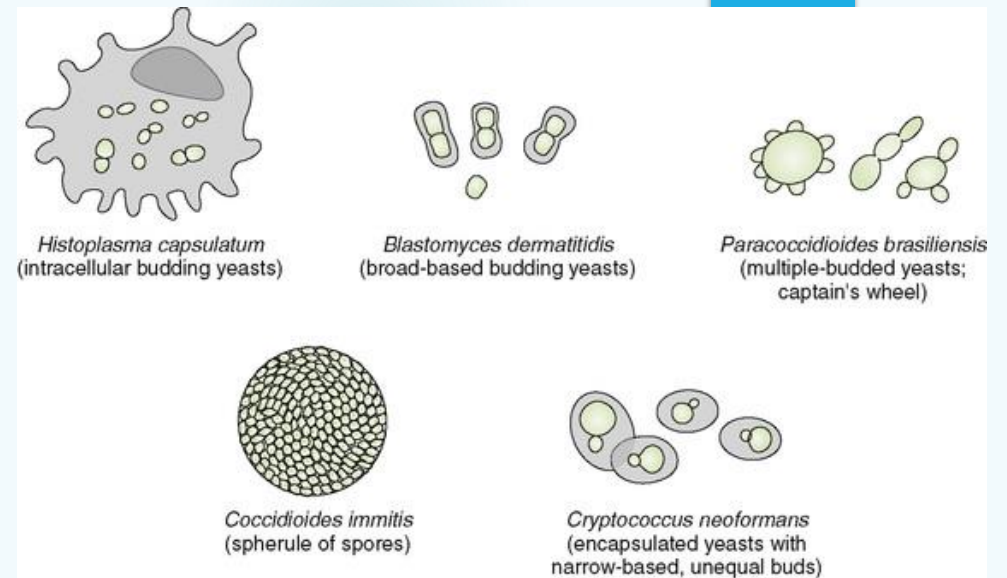
**Subcutaneous
Mycoses**

**Systemic
Mycoses**



Etiology

Type	Fungal Pathogens
Primary/ Systemic Pathogens	a. <i>Histoplasma capsulatum</i>, b. <i>Coccidioides immitis</i>, c. <i>Cryptococcus neoformans</i>, d. <i>Blastomyces dermatitidis</i>, e. <i>Paracoccidioides brasiliensis</i>, f. <i>Sporothrix schenckii</i>
Opportunistic Pathogens	i. <i>Candida albicans</i>, ii. <i>Aspergillus</i> spp., iii. <i>Mucor</i>, <i>Fusarium</i>, iv. <i>Alternaria</i>, <i>Trichosporon</i>, v. <i>Candida glabrata</i>, vi. <i>Cryptococcus neoformans</i>



Risk Factors for Fungal Infections

Host-Related Risk Factors	Procedure/Environment-Related Risk Factors	Special Population
1. Immunosuppression: 1. Hematologic malignancies 2. Stem cell/organ transplant 3. HIV/AIDS 4. Autoimmune disease treatments 2. Neutropenia: - ANC $\leq$ 500/mm³ 3. Use of Broad-Spectrum Antibiotics 4. Prior fungal colonization 5. Disruption of skin/mucosa (e.g., burns, surgery) 6. Altered gut microbiota 7. Malnutrition	1. ICU Admission 2. Central venous catheters (CVCs) 3. Parenteral nutrition 4. Prolonged mechanical ventilation 5. Renal failure and dialysis 6. Nosocomial exposure 7. Geographical exposure (e.g., caves, soil, birds)	1. Cancer Patients – receiving intensive cancer chemotherapy 2. HSCT recipient 3. Critically ill ICU Patients 4. Burn patients 5. Patients on TPN, Steroids, Multiple antibiotics

Pathophysiology

Mode of Entry:

- Inhalation of airborne conidia (e.g., *Histoplasma*, *Aspergillus*)
- Direct contact via mucosa or broken skin (e.g., *Candida*, *Sporothrix*)

Colonization:

- Some fungi, like *Candida*, are part of the normal flora of GI, skin, or mucosa.

Barrier Breach & Proliferation

- Antibiotic use or malnutrition may disturb flora balance, enabling fungal overgrowth.
- Breach in mucocutaneous barriers facilitates invasion.

Invasion & Dissemination:

- In immunocompromised hosts, fungi can invade bloodstream and disseminate to organs.
- Fungal cells may persist in macrophages due to resistance to lysosomal enzymes.

Immune Evasion:

- Altered neutrophil function or reduced numbers reduce clearance.
- Pathogens like *Cryptococcus* use capsules to avoid phagocytosis.

General Clinical Features

- Fever unresponsive to antibiotics (classic in neutropenic patients)
- Unexplained sepsis or systemic inflammatory response
- Organ-specific symptoms, such as:
 1. Lungs: Cough, hemoptysis, pleuritic chest pain, dyspnea (e.g., Aspergillosis)
 2. CNS: Headache, altered sensorium, seizures (e.g., Cryptococcosis)
 3. Skin: Nodules, ulcers, necrotic lesions
 4. GI tract: Pain, diarrhea, bleeding (especially in immunosuppressed patients)
 5. Eye: Chorioretinitis or endophthalmitis (fungemia)

Clinical Presentation

Signs of dissemination: Skin lesions, ocular findings, altered mental status

Fungemia Symptoms (e.g., Candida spp.)

- Persistent fever despite antibiotic therapy
- Signs of sepsis, organ dysfunction, or shock
- Central line or catheter-related infection

Diagnosis

Traditional Diagnostic Methods

- *Histopathology may not distinguish similar-looking fungi (e.g., Aspergillus vs Zygomycetes). Also, culture may reflect colonization, not infection, especially with opportunists.*

Rapid and Advanced Diagnostic Techniques

These aim to improve speed and accuracy, especially when early treatment is critical:

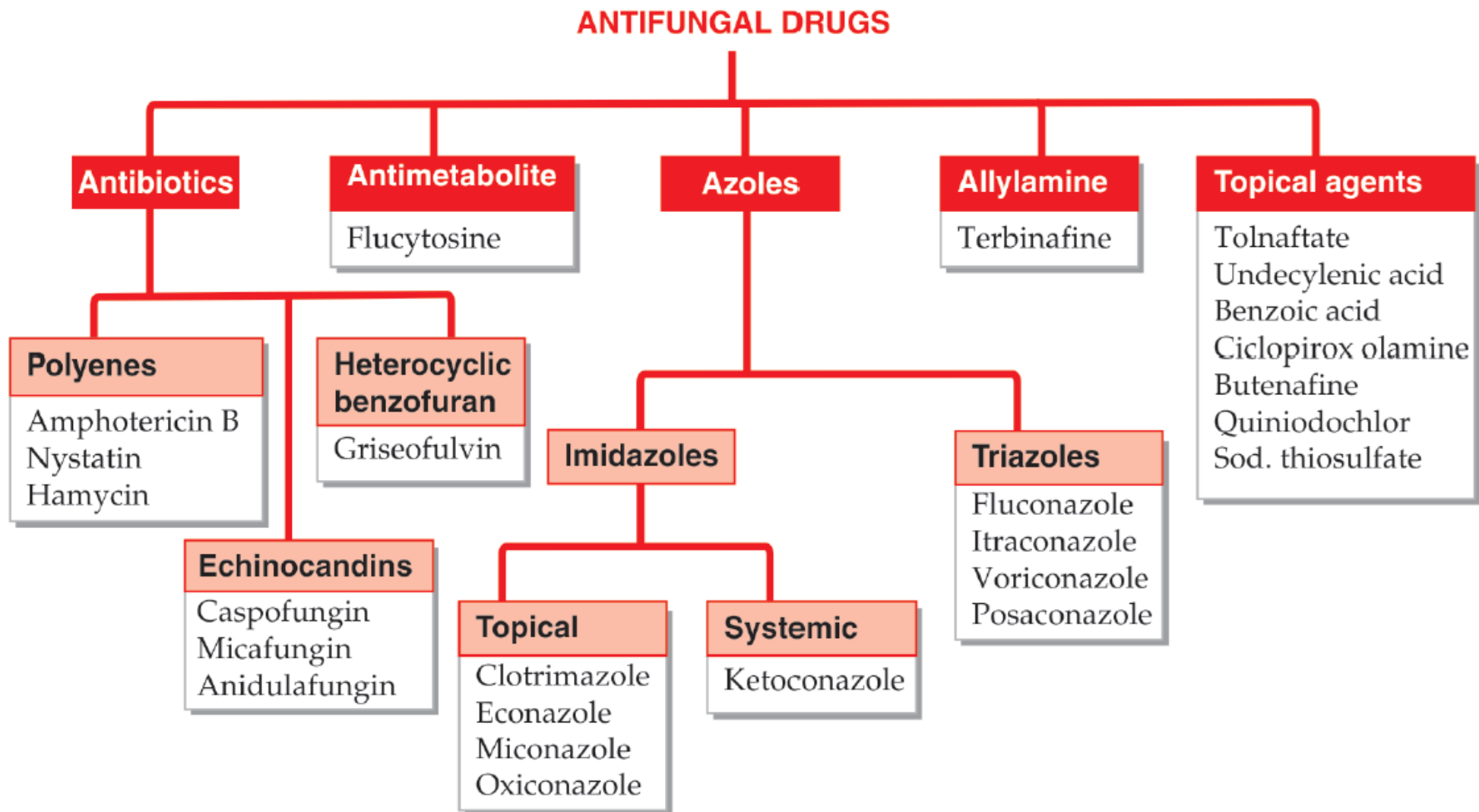
Method	Details	Limitations
Clinical Evaluation	History, immune status, signs, and symptoms	Non-specific; must guide lab investigations
Direct Microscopy	KOH mount, India ink (Cryptococcus), Calcofluor white	Rapid but low sensitivity
Histopathology	Tissue biopsy with fungal stains (PAS, GMS)	Invasive, sometimes not feasible
Culture	Blood, tissue, respiratory secretions on Sabouraud’s dextrose agar	Slow (days to weeks), some species grow poorly or not at all
Serologic tests	Detection of antibodies (e.g., Cryptococcus antigen)	Limited utility in immunocompromised hosts

Technique	Target
MALDI-TOF MS	Fungal protein fingerprint
PNA-FISH	rRNA in fungal cells
PCR-based assays	Fungal DNA
Galactomannan (GM)	Aspergillus antigen
1,3-β-D-glucan assay	Cell wall component (broad-spectrum fungi)
T2 Magnetic Resonance (T2MR)	Candida spp. DNA in blood
Cryptococcal antigen (CrAg)	Capsule polysaccharide

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Treatment



SUPERFICIAL CUTANEOUS MYCOSES

- ▶ Superficial cutaneous mycoses are fungal infections limited to the skin, hair, and nails.
- ▶ They are caused primarily by keratinophilic fungi (dermatophytes) that can invade keratinized tissues but do not penetrate deeper into the body.

Epidemiology

- ▶ These infections affect 20–25% of the global population, making them one of the most common human infections worldwide.
- ▶ They occur in both males and females, across all races and age groups.



Etiology

A. Causative Fungi

Dermatophytes (most common):

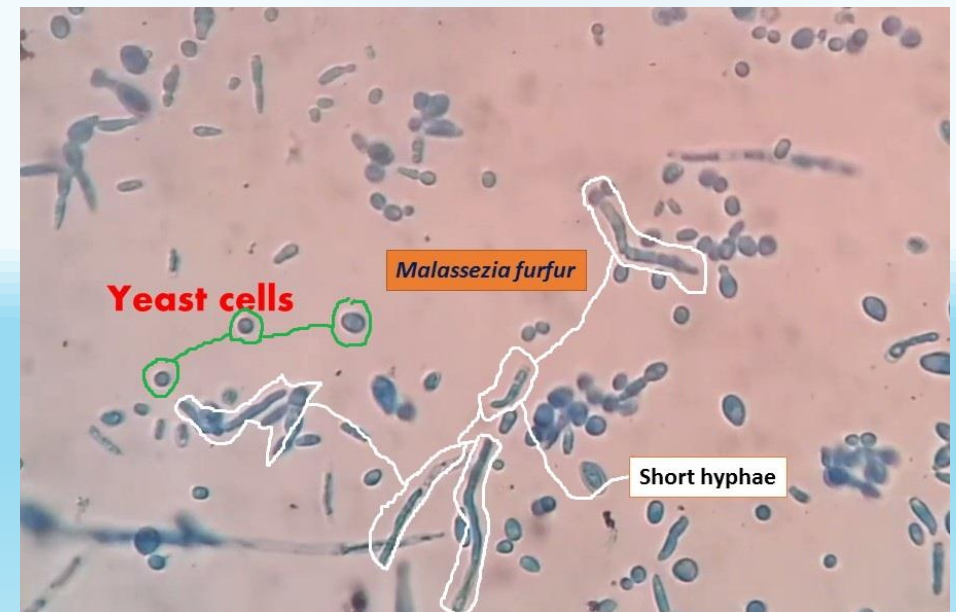
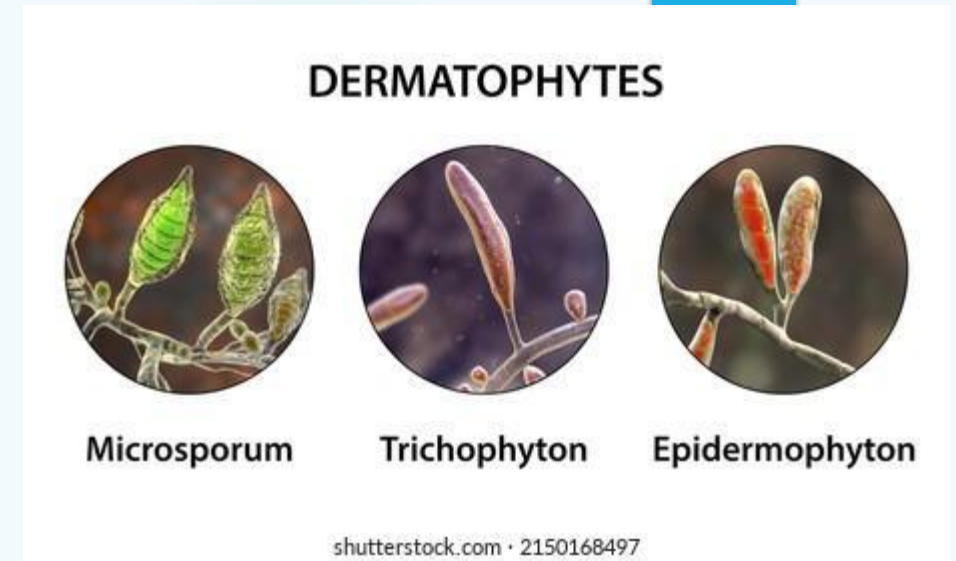
- Genera: *Trichophyton*, *Epidermophyton*, *Microsporum*
- These fungi digest keratin, allowing them to colonize the skin, nails, and hair.

Non - dermatophyte fungi:

- *Malassezia furfur* (especially in pityriasis versicolor)
- Yeasts: *Candida* species (especially in mucocutaneous infections)

B. Reservoirs of Infection

- Humans (anthropophilic)
- Animals (zoophilic)
- Soil (geophilic)

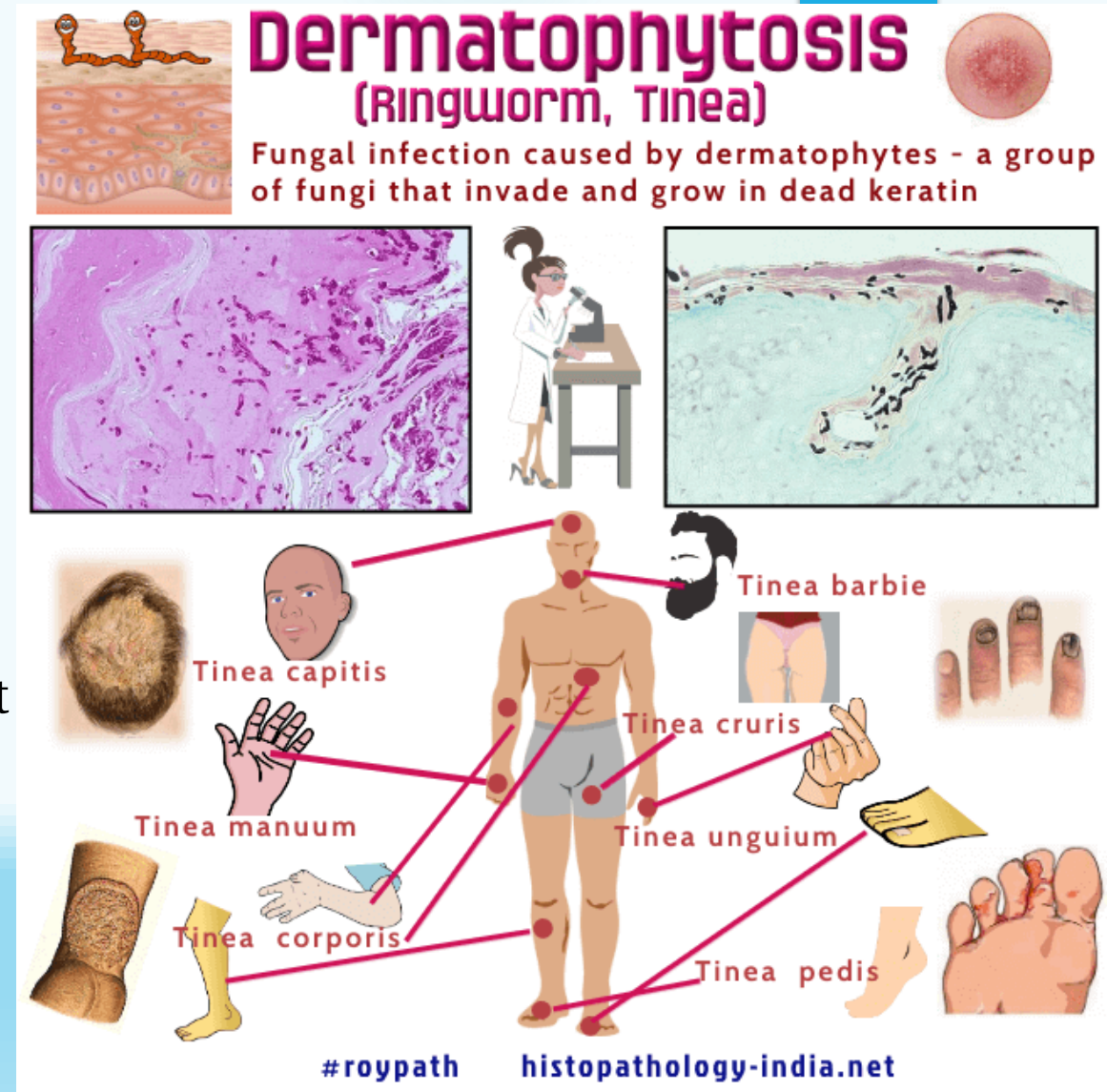


Risk Factors

- ▶ Warm, moist environments
- ▶ Prolonged sweating or water exposure
- ▶ Maceration (softening of skin due to moisture)
- ▶ Intertriginous areas (skin folds)
- ▶ Sharing personal items (combs, towels)
- ▶ Crowded living conditions (e.g., dormitories, military barracks)

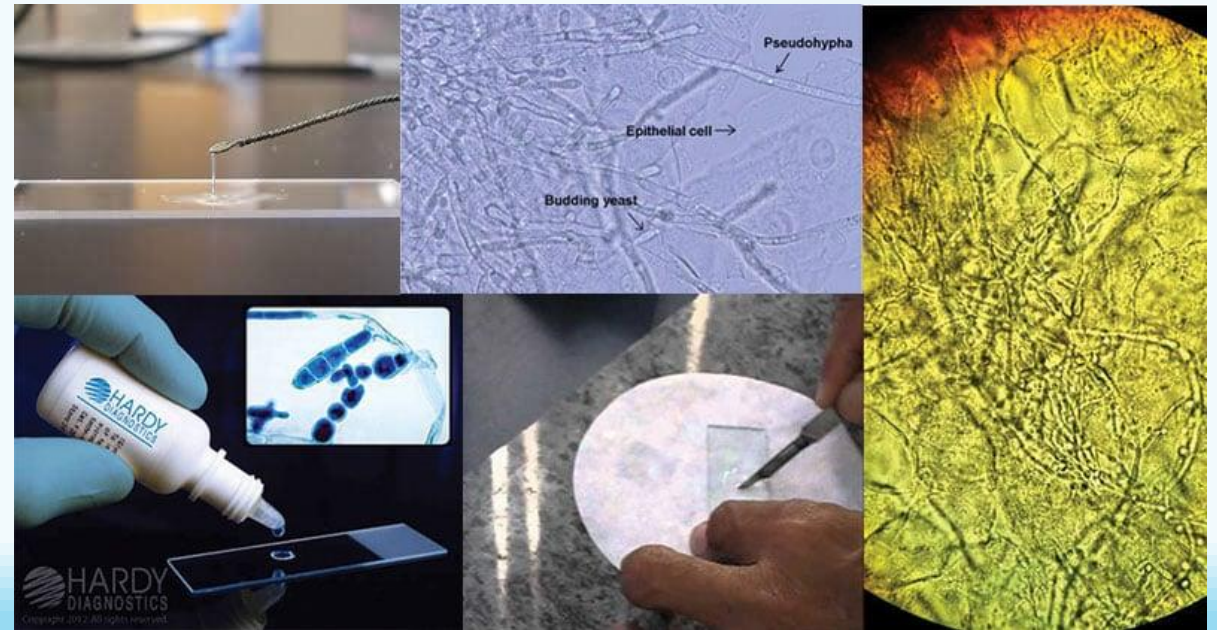
Pathophysiology

- ▶ Dermatophytes adhere to the stratum corneum, penetrate keratin, and begin to grow outward in a ring-shaped (annular) pattern.
- ▶ This causes the classic lesion with:
 - ▶ A central clearing
 - ▶ A red, scaly, elevated "active" border
- ▶ In contrast to conditions like psoriasis or lichen planus, dermatophyte lesions often have this distinct pattern.
- ▶ Nail infections (onychomycosis) present as chalky, brittle, discolored nails—usually dull yellow or white.



Clinical Presentation & Diagnosis

- ▶ Clinical history and physical exam are the first steps.
- ▶ Mycotic infections of the skin have a classic appearance that consists of a central clearing surrounded by an advancing red, scaly, elevated border, also referred to as an “active” border.
- ▶ Direct KOH microscopy:
 - ▶ Quick and inexpensive
 - ▶ Detects fungal hyphae
- ▶ Fungal culture:
 - ▶ Confirms species
 - ▶ Takes longer and is more costly
- ▶ Diagnostic tests are strongly recommended when:
 - ▶ Systemic (oral) therapy is considered
- ▶ The diagnosis is uncertain



Goals of Treatment

1. Eradication of the fungal organism.
2. Clinical cure and nail appearance improvement. Even after successful treatment, nails may remain dystrophic due to preexisting damage—this should be explained to patients to avoid dissatisfaction.

General Approach

1. Keep area clean and dry
2. Avoid contact with infectious sources
3. Address predisposing factors (e.g., excessive moisture, poor hygiene)
4. Onychomycosis affects quality of life (pain, cosmetic issues, reduced mobility).
5. Treatment is not always necessary for mild, asymptomatic cases.
6. Untreated cases may lead to cellulitis, reduced mobility, and fungal transmission (e.g., in diabetics or communal settings).
7. Individualized treatment decisions are key—consider disease severity, comorbidities, and patient preferences.
8. Success assessment requires months of follow-up due to slow nail growth (~1 mm/month).
9. Patient adherence and education are crucial for success and preventing recurrence.

Non-Pharmacologic Therapy

▶ **Mechanical/chemical nail avulsion:**

- ▶ Adjunct to oral therapy.
- ▶ Used in total dystrophic onychomycosis with severe thickening or onycholysis.
- ▶ Enhances antifungal penetration into nail unit.

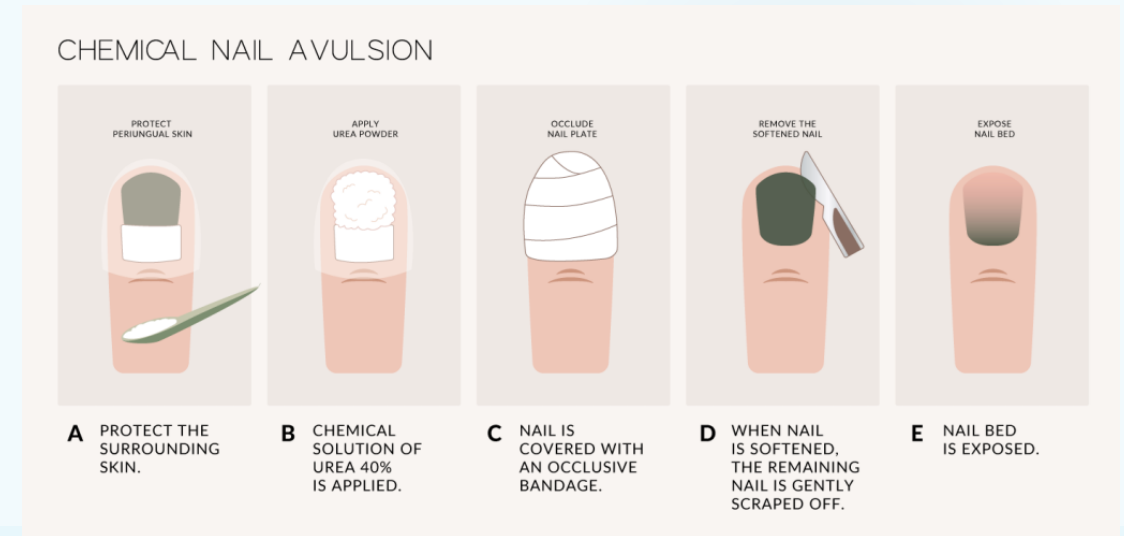
Pharmacologic Therapy

Topical antifungals:

- First-line for localized skin infections
- Examples: azoles, allylamines, ciclopirox

Oral antifungals:

- Used for extensive or severe infections, tinea capitis, and onychomycosis
- Examples: terbinafine, itraconazole, griseofulvin



A. Topical Therapy

- Formulations: Creams, ointments, powders, solutions, lacquers.
- Best for:
 - Superficial infections, limited nail involvement (<50%), no matrix involvement.
 - Early distal subungual onychomycosis or when oral therapy is contraindicated.
- **Nail Lacquers:**
 - Ciclopirox 8% (Penlac) – FDA-approved; requires daily use for 1 year, cure rate ~9–32%.
 - Amorolfine 5% – Higher cure rates (not FDA-approved in US).
- **Advantages:**
 - Minimal systemic side effects.
 - Useful in mild or early infections.
- **Limitations:**
 - Poor penetration if nail plate intact.
 - Requires prolonged application and good adherence.

B. Systemic Therapy

First-line:

- Terbinafine (fungicidal, best for dermatophytes).
- Itraconazole (fungistatic, broader spectrum incl. Candida, molds).

Alternative:

- Fluconazole (off-label, lower efficacy).

Old drugs (less used due to poor efficacy and safety): Griseofulvin, Ketoconazole.

1. Terbinafine

- Dose: 250 mg/day for 12 weeks (toenails); 6 weeks (fingernails).
- Mycologic cure: 77–100%.
- Persists in nail up to 36 weeks post-treatment.
- Well tolerated, rare hepatotoxicity (check LFTs).
- Few drug interactions (inhibits CYP2D6).

2. Itraconazole

- Pulse therapy preferred: 200 mg twice daily for 1 week/month × 2–3 months.
- Alternative: Daily for 6 weeks (fingernails) or 12 weeks (toenails).
- Persists in nails for ~27 weeks.
- Avoid in heart failure and liver disease.
- Many CYP3A4 drug interactions.

3. Fluconazole

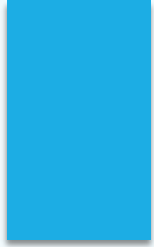
- Dose range: 50 mg/day to 300 mg/week for 6–12 months.
- Mycologic cure ~48%.
- Not FDA-approved but well tolerated, fewer interactions.

Different Types Of Mycotic Infections Of The Skin, Hair, And Nails

Infection	Site Affected	Key Features	Causative Organisms	Treatment	Notes
Tinea Pedis (Athlete's foot)	Interdigital spaces, plantar surface, soles	Interdigital scaling, fissuring, moccasin-type thickening, vesicles	T. rubrum, T. mentagrophytes	Topical antifungals (2–4 wks); Oral for severe cases	Recurrs in up to 70%; often with onychomycosis
Tinea Manuum	Palms (usually one hand), can involve feet	Dry, hyperkeratotic palms; vesicles if nails involved	Usually same as tinea pedis	Topical/oral antifungals; emollients with lactic acid	Often coexists with tinea pedis
Tinea Cruris (Jock itch)	Groin, inner thighs, buttocks	Red, scaling plaques with raised, active border; scrotum often spared	T. rubrum	Topical antifungals; oral for severe; short-term steroids	Examine feet as possible source
Tinea Corporis (Ringworm)	Glabrous skin – trunk, limbs, face	Annular lesion with central clearing and raised edge	T. rubrum, T. mentagrophytes	Topical; oral if widespread	KOH test confirms; steroids may mask typical appearance
Tinea Capitis	Scalp, hair follicles	Hair loss, scaling; mainly in children	T. tonsurans, M. canis	Oral antifungals (e.g., griseofulvin); antifungal shampoo	Treat family carriers to prevent spread
Tinea Barbae	Beard and mustache areas	Follicular pustules, nodules; hair loss	T. verrucosum, T. mentagrophytes	Oral antifungals; shaving recommended	Adult males only
Pityriasis Versicolor (Tinea versicolor)	Trunk, face, extremities	Hyper/hypopigmented scaly macules	Malassezia spp.	Topical azoles; oral if extensive	High recurrence; ketoconazole shampoo effective
Onychomycosis (Tinea Unguium)	Fingernails or toenails	Nail thickening, discoloration, crumbling	T. rubrum, T. mentagrophytes, Candida, molds	Long-term oral antifungals; topical if superficial	Toenails > fingernails; affects QOL; recurs easily



Condition	Topical Treatments	Oral Regimen
Tinea pedis	1. Butenafine, daily 2. Luliconazole, daily 3. Naftifine, daily	Fluconazole 150 mg once/week × 1–4 weeks
Tinea corporis	1. Econazole, daily 2. Miconazole, twice daily 3. Terbinafine, daily	Terbinafine 250 mg/day × 2 weeks
Tinea cruris	1. Clotrimazole, twice daily 2. Luliconazole, daily 3. Naffine cream, daily	Itraconazole 200–400 mg/day × 1 week
Tinea capitis	Topical shampoos only (adjunct): 1. Selenium sulfide 2. Ketoconazole 3. Undecylenic acid	Terbinafine 250 mg/day × 4–8 weeks



Onychomycosis	1. Ciclopirox 8% lacquer (48 weeks) 2. Efinaconazole 10% (48 weeks) 3. Tavaborole 5% (48 weeks)	Terbinafine 250 mg/day × 6–12 weeks Itraconazole 200 mg twice daily (pulse) Fluconazole 50–300 mg/week ≥6 months
Pityriasis versicolor	1. Clotrimazole, twice daily 2. Ketoconazole, daily 3. Sulconazole, twice daily	Fluconazole or Itraconazole 200 mg daily × 3–7 days

Mucocutaneous Candidiasis

- ▶ Mucocutaneous Candidiasis : Persistent or recurring infection with candida species effecting mouth, scalp, skin, nails or other sites.
- ▶ Mucocutaneous Candidiasis occurs in 3 forms
 1. Oropharyngeal
 2. Esophageal
 3. Vulvovaginal

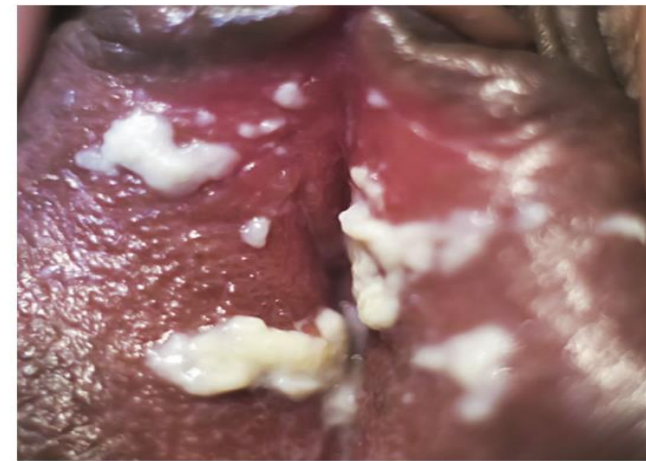


Figure 2. Genitalia with candidiasis, showing swollen labias and reddened vagina.

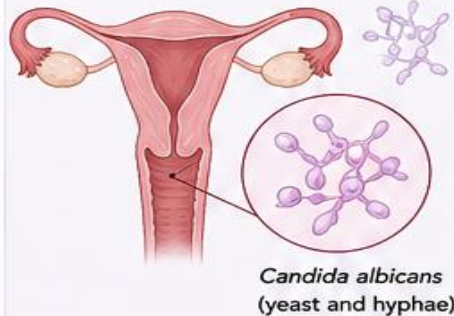
VULVOVAGINAL CANDIDIASIS (VVC)

Infection of the vulva and vagina caused predominantly by *Candida* species.
May occur with or without symptoms in women with positive vaginal cultures for *Candida*.

1. DEFINITION & CLASSIFICATION

DEFINITION

VVC refers to infections in individuals with or without symptoms who have positive vaginal cultures for *Candida* species.



Candida albicans
(yeast and hyphae)

EPISODIC FREQUENCY

SPORADIC VVC

Infrequent episodes

RECURRENT VVC (RVVC)

≥ 4 episodes in 1 year

CLINICAL CLASSIFICATION

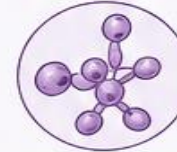
UNCOMPLICATED VVC

- Sporadic infection
- Usually caused by *C. albicans*
- Susceptible to all forms of antifungal therapy regardless of the duration of treatment

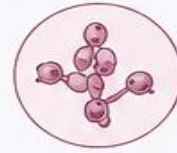
COMPLICATED VVC

- Recurrent VVC
- Severe disease
- Non-*C. albicans* candidiasis
- Host factors:
 - Diabetes mellitus
 - Immunosuppression
 - Pregnancy

IMPORTANT ETIOLOGIC ORGANISMS



C. albicans
80–92% of cases



C. glabrata
Most common non-*C. albicans* species



Other non-*C. albicans* *Candida* species

The number of cases of non-*C. albicans* candidiasis appears to be increasing.

2. RISK FACTORS FOR VVC

SEXUAL FACTORS



- Increased frequency after becoming sexually active
- Oral-genital contact increases risk
- Not considered a sexually transmitted disease (STI)
- Treatment of asymptomatic partners is not recommended

CONTRACEPTIVE AGENTS



Diaphragm with spermicide



Contraceptive sponge



Intrauterine device (IUD)



Vaginal contraceptive ring (*Candida* can adhere to its surface)



Oral contraceptives (High-estrogen pills increase risk)

ANTIBIOTIC USE



- Broad-spectrum antibiotic use
- Alters normal vaginal microbiota
- Increases *Candida* colonization and symptomatic infection

HOST FACTORS



Diabetes mellitus



Immunosuppression



Pregnancy

FACTORS WITH NO PROVEN ASSOCIATION



Excess refined carbohydrate intake



Douching



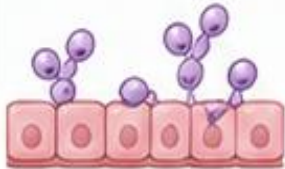
Tight-fitting clothing



Antibiotic use is significant in only a small number of women.
Three days of antibiotics increased the prevalence of asymptomatic vaginal colonization of *Candida* and the incidence of symptomatic VVC.

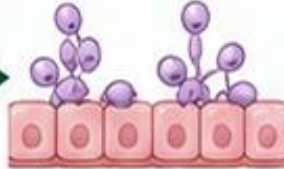
3. PATHOPHYSIOLOGY OF VVC

1 VAGINAL COLONIZATION



- *Candida* normally exists as part of vaginal flora.
- Asymptomatic colonization occurs in 10–20% of reproductive-age women.
- Colonization mainly occurs in the blastospore (yeast) form.

2 ADHESION TO EPITHELIUM



- *Candida* attaches to vaginal mucosal cells.
- Attachment requires:
 - Fungal adhesins (surface proteins)
 - Appropriate epithelial receptors
- Variations in receptors explain why some women are more susceptible.

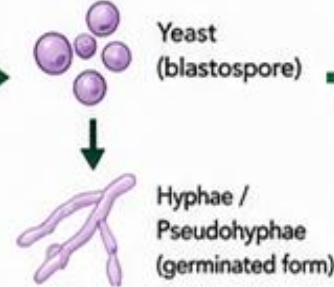
3 ENVIRONMENTAL OR HOST CHANGES



Triggering factors include:

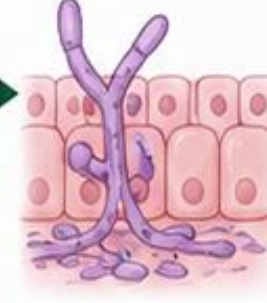
- Antibiotic therapy
- Diabetes mellitus
- Pregnancy
- Immunosuppression
- Hormonal influences

4 MORPHOLOGIC TRANSFORMATION



- Yeast form → colonization
- Hyphae form → tissue invasion

5 TISSUE INVASION



- Hyphae penetrate vaginal epithelial tissue.
- Local inflammation develops.

6 CLINICAL DISEASE



Results in:

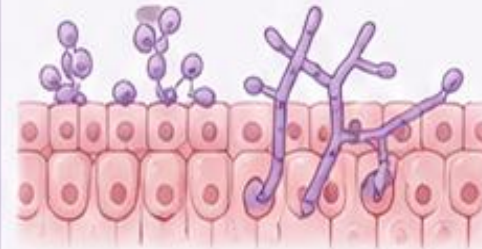
- Vulvar itching (pruritus)
- Burning sensation
- Vaginal soreness
- Thick white “cottage cheese” discharge
- Dyspareunia
- Dysuria



KEY POINTS

- *C. albicans* causes 80–92% of VVC cases.
- VVC is NOT a sexually transmitted disease.
- Antibiotic use predisposes to VVC by altering normal vaginal flora.
- Blastospores = colonization; Hyphae = invasion and symptomatic disease.
- Complicated VVC includes recurrent infection, severe disease, non-*C. albicans* species, pregnancy, diabetes, and immunosuppression.

CANDIDA AS COMMENSAL FLORA

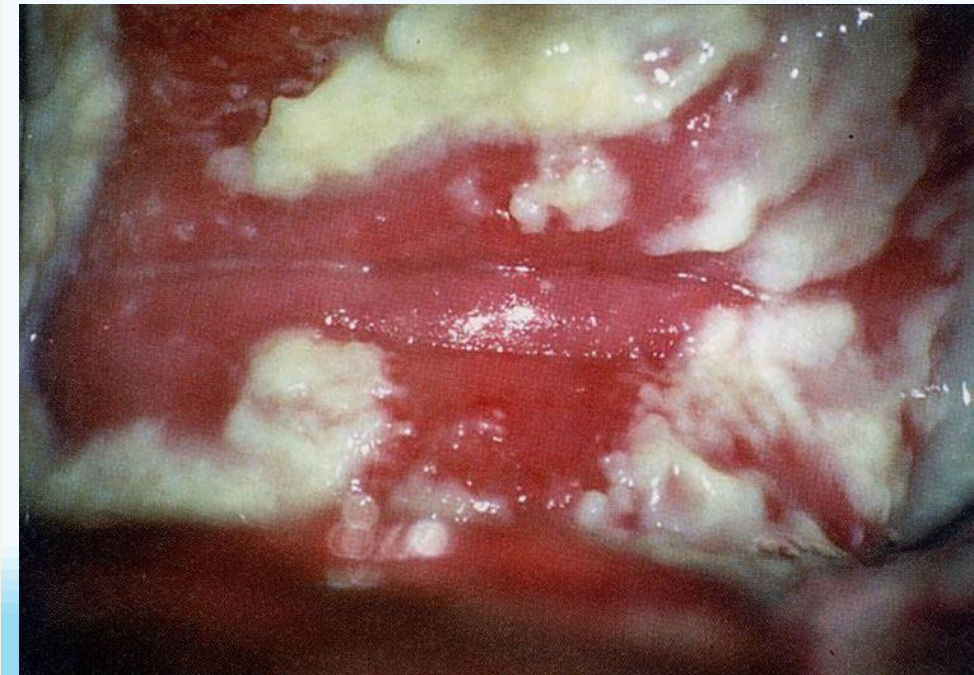


- *Candida* species can act as commensal members of the vaginal flora.
- To colonize the vagina, *Candida* must be able to attach to the mucosa.
- Changes in the host's vaginal environment or response are necessary to induce a symptomatic infection.
- In most cases of symptomatic VVC, no precipitating factor can be identified.

Sign and symptoms and Diagnosis

General	Often involves both the vulva and the vagina
Symptoms	Intense vulvar itching, soreness, irritation, burning on urination, and dyspareunia
Signs	Erythema, fissuring, curdy "cheese"-like discharge, satellite lesions, edema
Laboratory tests	Vaginal pH—normal, saline, and 10% KOH microscopy—blastospores or pseudohyphae
Other diagnostic tests	<i>Candida</i> cultures not recommended unless classic signs and symptoms with normal vaginal pH and microscopy are inconclusive or recurrence is suspected

KOH, potassium hydroxide.



Treatment

Goals of Therapy

The goal of therapy is complete resolution of symptoms in patients who have symptomatic VVC.

General Approach

1. Remove or improve any predisposing factors, if they can identify
2. Avoid use of harsh soaps, perfumes, tight or constrictive clothing, prolonged or frequent hot tub use and douching (Rinsing or washing inside of vagina)
3. Keep genital areas clean and dry

Non Pharmacological treatment

Use of oral lactobacillus, yogurt

Pharmacological Treatment

Effective antimycotic agent should have limited local and systemic side effects, high cure rate and easy administration.

Treatment for uncomplicated VVC

Active Ingredient	Preparation	Regimen
Nonprescription/Topical Vaginal Products		
Butoconazole	2% cream	One applicator × 3 days
Clotrimazole	1% cream	One applicator × 1 day
	100 mg tablet	One 100 mg tablet × 7 days
	2% cream	One applicator × 1 day
	200 mg tablet	One 200 mg tablet × 3 days
	10% cream	One applicator × 1 day
	500 mg tablet	One 500 mg tablet × 1 day
	1,200 mg ovule	One ovule × 1 day
Miconazole ^a	2% cream	One applicator × 1 day
	100 mg suppository	One 100 mg suppository × 7 days
	200 mg suppository	One 200 mg suppository × 3 days
Ticonazole	2% cream	One applicator × 3 days
	6.5% cream	One applicator × 1 day
Prescription/Topical		
Nystatin	100,000 unit tablet	One tablet × 14 days
Terconazole	0.4% cream	One applicator × 7 days
	0.8% cream	One applicator × 3 days
Oral Products		
Fluconazole	150 mg	One tablet × 1 day

^aThe FDA warns of the possible increase in the anticoagulant effects of warfarin with concomitant use.

Treatment for complicated VVC

1. Occurs majorly in patients with immunocompromised, uncontrolled DM, pregnancy
2. Treatment is aggressive for 10 to 14 days
3. Antimycotic agents used for 10 to 14 days → Two dose regimen of fluconazole cure 80% of complicated VVC and 2nd dose given after 72 hours of 1st dose
4. Pregnant female should be treated with topical imidazoles for 7 days, oral therapy is contraindicated due to birth defects. Most effective drug is Nystatin

Antifungal resistant VVC

Individuals resistant to azoles or antimycotic agents → Boric acid 600 mg Intravaginal Capsule OD for 14 days followed by maintenance regimen for 2 weeks

Or

- 5- Flucytosine cream administered intravaginally 1000 mg inserted nightly for 7 days

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

- ▶ These are common and localized infections that occur in patients with HIV infection, DM, Leukemia and other malignancies and also associated with antimicrobial therapy, steroid use, radiation therapy and denture use.
- ▶ OPC is referred to as Thrush or candidiasis caused by yeast candida majorly by candida albicans,
- ▶ Infection extending into the esophagus called esophageal candidiasis.

Etiology

1. Candida albicans
2. Candida glabrata
3. Candida tropicalis
4. Candida dubliniensis



RISK FACTORS FOR CANDIDIASIS (Local & Systemic Factors)

LOCAL FACTORS		
Factor	Examples / Details	Illustration
Use of steroids and antibiotics	Prolonged or frequent use of corticosteroids and antibiotics.	 Steroids  Antibiotics
Dentures	Poorly fitting dentures or continuous denture use.	 
Xerostomia (dry mouth)	Caused by drugs (eg, tricyclic antidepressants and phenothiazine), chemotherapy, radiotherapy to the head/neck, and various diseases (eg, Sjögren's syndrome, HIV, and cancer of the head/neck), as well as bone marrow transplant recipients.	  Drugs  Chemo/ Radiotherapy  Sjögren's Syndrome  HIV / Cancer  BMT Recipients
Smoking	Tobacco use increases risk of oral candidiasis.	 
Disruption of oral mucosa	Chemotherapy and radiotherapy, ulcers, endotracheal intubation trauma, and burns.	 Chemotherapy  Radiotherapy  Ulcers  Intubation trauma  Burns

SYSTEMIC FACTORS		
Factor	Examples / Details	Illustration
Drugs	Cytotoxic agents, corticosteroids, immunosuppressants (after organ transplant), omeprazole, and environmental chemicals (eg, benzene and pesticides).	 Cytotoxic agents  Corticosteroids  Immunosuppressants (Organ transplant)  Omeprazole  Benzene / Pesticides
Extremes of age	Neonates or the elderly.	 Neonate  Elderly
HIV infection / AIDS	Immunodeficiency increases susceptibility to candidiasis.	 
Diabetes mellitus	Poor glycemic control predisposes to <i>Candida</i> infections.	 220 mg/dL 
Malignancies	Leukemia and head/neck cancers.	 Leukemia  Head / Neck cancer
Nutritional deficiencies	Deficiencies of iron, folate, and vitamins B1, B2, B6, B12, and C.	 Iron  Folate  B1  B2  B6  B12  B12  Vitamin C

PATHOGENESIS OF ORAL CANDIDIASIS (OPC)

1. COLONIZATION

Candida species (commensal) colonize the oral mucosa.

2. BREAKDOWN OF HOST DEFENSES

Changeover from commensal → pathogenic

A. IN HIV-INFECTED INDIVIDUALS

PRIMARY DEFENSE (First line)

- Cell-mediated immunity at mucosal surfaces (mediated by CD4 T cells)
- When CD4 T cells fall below protective threshold → protection decreases

SECONDARY / LOCAL DEFENSES (When primary fails)

- CD8 T cells
- Salivary cytokines
- Innate immune cells: neutrophils, macrophages, epithelial cells
- Role of antibodies – unclear

FACTORS AFFECTING DEFENSES

- Low CD4 T-cell count (hallmark predictor)
- High HIV viral load (may have stronger association with OPC)
- Dysfunction of CD8 T cells due to reduced E-cadherin → impaired migration

B. IN NON-HIV-INFECTED INDIVIDUALS

PREDISPOSING FACTORS

- Broad-spectrum antibiotics
- Steroids, immunosuppressants
- Xerostomia, smoking, systemic diseases
- Altered oral microflora, malnutrition, etc.

CANDIDA ADHERENCE

Ability of *Candida* to adhere to buccal epithelial cells

EXPRESSION OF VIRULENCE FACTORS

- Adaptation to host environment (temperature, pH, nutrients, etc.)
- Morphologic transition: yeast ↔ pseudohyphae ↔ hyphae
- Adhesion to epithelial cells & proteins
- Secretion of enzymes (phospholipases, proteinases) → invasion & tissue damage

INVASION & MULTIPLICATION

Candida invades mucosa and multiplies

INFLAMMATION & CLINICAL DISEASE

Development of oral candidiasis (pseudomembranous, erythematous, etc.)

Types Of Oropharyngeal Candidiasis		
Type	Population at Risk	Clinical Signs & Appearance
Pseudomembranous (Thrush)	- Neonates - HIV or cancer patients - Elderly, debilitated - Broad-spectrum antibiotics/steroids - Dry mouth, smokers	- White/yellowish "cottage cheese" plaques on buccal mucosa, tongue, gums - Easily scraped off, may leave red/bleeding areas - Bald, depapillated tongue dorsum
Erythematous (Atrophic)	- HIV patients - Those on antibiotics/steroid inhalers	- Painful red mucosa - Few or no white plaques - Flat red patches on palate or tongue - Loss of papillae on tongue - Acute or chronic
Hyperplastic (Candidal Leukoplakia)	- Smokers - Rare in HIV	- Thick white, adherent keratotic plaques on buccal mucosa, tongue borders, lips - Cannot be scraped off easily - May progress to dysplasia or malignancy
Angular Cheilitis	- HIV patients - Denture wearers	- Painful, red cracks at corners of mouth - May be punctate or extend along the skin folds
Denture Stomatitis (Chronic Atrophic)	- Elderly denture wearers - Poor oral hygiene	- Red, flat mucosa under dentures - More common with maxillary dentures
Central Papillary Atrophy (<i>Median Rhomboid Glossitis</i>)	- Rare (<1%) - More in men (3:1)	- Rhomboid red/atrophic or hypertrophic area - Midline dorsal tongue- May not completely resolve

Clinical Presentation and Diagnosis of OPC and EC

Feature	Oropharyngeal Candidiasis (OPC)	Esophageal Candidiasis
General	- Often diverse in presentation - Common in immunocompromised patients	- Often occurs as an extension of OPC - May also occur alone - Affects distal two-thirds of esophagus most commonly
Symptoms	- Can be asymptomatic - Sore or painful mouth - Burning tongue- Metallic taste - Dysphagia (difficulty swallowing) - Odynophagia (painful swallowing), especially if hypopharynx involved	- Dysphagia, odynophagia- Retrosternal chest pain - Rare: epigastric pain - Sometimes asymptomatic
Signs	- Erythema and white patches on buccal mucosa, tongue, throat, gums - No constitutional signs (e.g., fever)	- Fever may occur - White or beige plaques in esophagus - Hyperemic/edematous mucosa - May have ulceration, mucosal friability, lumen narrowing - Rare: Perforation or aorto-esophageal fistula
Laboratory Tests	- Microscopy (scraping → pseudohyphae, budding yeast) - Culture usually not needed unless resistant case	- Upper GI endoscopy is the best test - Helps exclude other causes (viral, aphthous ulcers) - Biopsy to confirm Candida - Culture needed in resistant or non-responding cases

TREATMENT

Goals of Treatment :

1. Primary outcome → Elimination of clinical sign and symptoms
2. Prevent complications
3. Minimizing no of future occurrences
4. Minimize toxicities, DDI of systemic antifungal agents

General Approach :

1. Management of OPC should be individualized for each patients by taking into consideration of patients immune status, other concurrent mucosal and medical devices, concurrent medication exogenous infections sources.
2. Minimize predisposing factors such as administration of corticosteroids, chemotherapeutic against and antimicrobials.

Pharmacologic therapy :

1. Management of OPC should be individualized for each patients by taking into consideration of patients immune status, other concurrent mucosal and medical devices, concurrent medication exogenous infections sources.
2. Minimize predisposing factors such as administration of corticosteroids, chemotherapeutic against and antimicrobials
3. Selection of antifungal agents
 - a. Patients drug adherence
 - b. Adequate saliva for dissolution of solid topic medicine
 - c. Risk of caries from sucrose or dextrose containing preparations
 - d. Potential DDI
 - e. Co existing medical conditions
 - f. Location and severity of infection
 - g. Need for long term therapy
 - h. Resistance

Topical antimycotic therapy :

1. First line therapy for milder forms of infection
2. Topical agents include Nystatin and Clotrimazole
3. Available in different formulations - Oral suspensions, trouches, mucoadhesive tablets, creams and powders
4. Requires frequent applications because of short contact time period with oral mucosa.
5. Clotrimazole troches $\Rightarrow$ Needs saliva for dissolution, difficult in xerostomia patients, contain dextrose.
6. Nystatin suspension $\Rightarrow$ Drug of choice in xerostomia patients, Bad taste, cause N/V, Contain high sugar content caution in DM and dentate patients
7. Miconazole mucoadhesive tablet - 50mg $\Rightarrow$ Taste less, odour less, sugar less tablets used in patients > 16 years of age OD
8. Topical creams $\rightarrow$ Clotrimazole, Ketoconazole, Miconazole, Nystatin + Steroid
Best to treat angular cheilitis (cracks at mouth corners, inflammation and drying) * 3 days

Systemic antimycotic therapy :

1. Indicated in moderate to severe cases, refractory OPC, immunocompromised patients, EC, and patients who cannot tolerate topic agents.
2. Systemic agents include Fluconazole, Ketoconazole, Itraconazole, Amphotericin B, Voriconazole, Posaconazole, Echinocandins → Caspofungin, micafungin
3. Fluconazole ⇒ Most common, inexpensive, well tolerated , over use may lead to resistance.

OPC - Treat patient for 7 to 14 days

1. Clotrimazole 10 mg Troche Q5D
2. Nystatin solution 10,00,000 units/ml - 5 ml Q5D
3. Mucoadhesive miconazole tablet 50 mg OD
4. Fluconazole 100 mg - 200 mg OD
5. Itraconazole 10 mg/ml - 200 mg OD

EPC - Treat for 14 to 21 days

1. Fluconazole 100 mg tablet 3 - 6 mg/kg od
2. Amphotericin B 50 mg IV - 0.3 - 0.7 mg/kg/day
3. Posaconazole 40mg/ml suspension — 400 mg BD
* 3 days followed by 400 mg OD * 28 days
4. Itraconazole 10 mg/ml - 200 mg OD
5. Voriconazole 200 mg tablet BD

OPC - Fluconazole Refractory - Treat > 14 days

1. Itraconazole 10 mg/ml - 200 mg OD
2. Voriconazole 200 mg tablet BD
3. Posaconazole 40mg/ml suspension — 400 mg BD
* 3 days followed by 400 mg OD * 28 days
4. Amphotericin B 100 mg/ml suspension - 1-5 ml Q5D

50 mg IV - 0.3 - 0.7 mg/kg/day

5. Caspofungin 50 mg IV OD

EPC - Fluconazole Refractory - Treat 21 to 28 days

1. Itraconazole 10 mg/ml - 200 mg OD
2. Posaconazole 40mg/ml suspension — 400 mg BD
3. Voriconazole 200 mg tablet BD
4. Caspofungin 50 mg IV OD
5. Micafungin 150 mg IV OD

⇒ Side effects of this therapies

- ① GI upset ⇒ N/V, diarrhea, abd discomfort, dyspepsia
- ② Hepatotoxicity ⇒ specific for systemic therapy
- ③ Neurologic & CNS disturbances ⇒ altered light perception, photopsia, color changes, hallucinations, confusion

↓
Particularly for voriconazole

- ④ IV related — fever, HA, chills, sweating, Rash, flushing
- ⑤ Nephrotoxic → Amphotericin B.
- ⑥ Anaphylaxis.
- ⑦ Bone marrow suppression.
- ⑧ CHF, Pulmonary edema ⇒ Itraconazole.