



COMMUNICABLE DISEASES: A GLOBAL PERSPECTIVE EMPHASIZING FUNGI.

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What are these?



Champignons *Agaricus*



Chanterelle *Cantharellus*
cibarius



FotoosVanRobin from the Netherlands

Objectives:

At the end of the of the presentation participants should be able to discuss:

- World- wide mapping of occurrence of fungal infections
- Resistance patterns
- Prevention and control of fungal infections particularly nosocomial infections
- Use of antifungal agents for common occurring infections.

Communicable Diseases

Definition (GlobalHealth.gov)

- Infection spreading from one person to another or from an animal to a person.
- spread often happens via airborne viruses or bacteria
- also spread through blood or other bodily fluid
- aka infectious or contagious disease

Communicable Diseases

-A Global Perspective



- Essential data for Ministries of Health
 - burden of diseases
 - injuries
 - risk factors

- Currently lifestyle and behaviour are linked to 20-25% of the global burden of diseases

Communicable Diseases

-A Global Perspective



- Poorer developing countries face triple burden
 - Communicable disease
 - Non-communicable disease
 - Socio-behavioural illness
- Epidemiological transition is already well advanced
- Significant emphasis on communicable disease is still necessary

Communicable Diseases

-A Global Perspective

- Reportable communicable diseases
 - **Caused by different types of micro-organisms**
 - Viruses – Human Immunodeficiency Virus
 - Bacteria - Anthrax
 - Protozoan – Cryptosporidiosis
 - Fungus – Coccidioidomycosis
- Most fungal infections are not reportable communicable diseases.

Communicable Diseases

-A Fungal Emphasis

- Fungal infections affect both plants and animals
- Because fungal spores are often present in the air or in the soil, fungal infections usually begin in the lungs or on the skin.
- Fungal infections usually progress relatively slowly

Communicable Diseases

-A Fungal emphasis

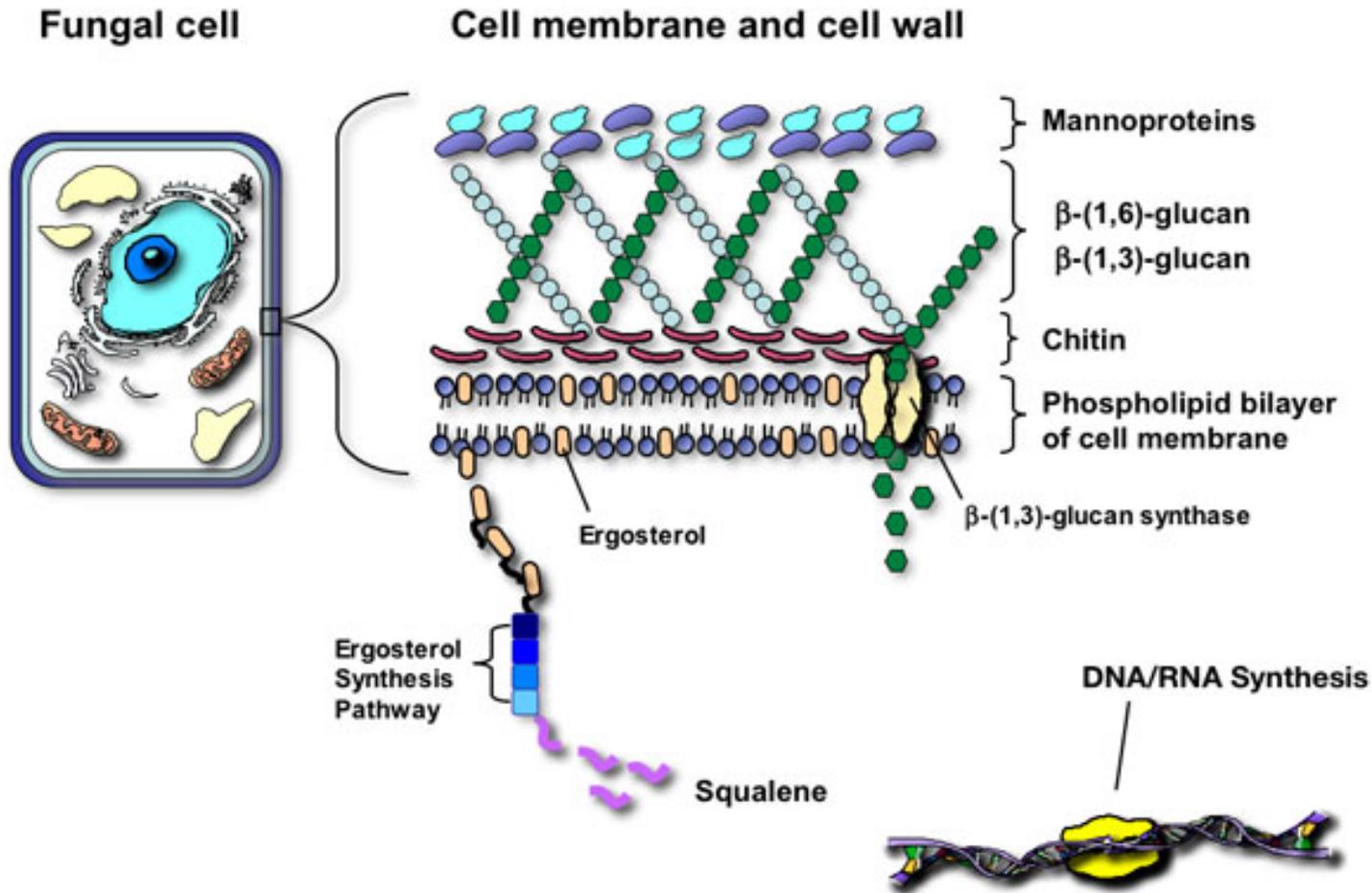
- Fungi are neither plants nor animals
- Classified as their own kingdom (FUNGI)
 - Yeasts - *Candida*
 - Molds –aspergilli
 - Mushrooms
- >70,000 species of fungi identified
- Cell wall is similar to plants but chemically composed of **chitin**.

Ergosterol

- a sterol found in cell membranes of fungi and protozoa
- formed after de-methylation of lanosterol by the enzyme 14α -demethylase

Fungi and protozoa cannot survive without ergosterol; the enzyme (14α -demethylase) that creates it have become important targets for drug discovery

Fungal Cell Wall & Membrane



Antifungals

Five Classes based on mechanism of action

1. Polyenes
2. Azoles
3. Allylamines
4. Echinocandins
5. Other agents (including griseofulvin and flucytosine)

Polyenes:

- bind directly to ergosterol in the fungal cell membrane & weakens it
- causes leakage of K⁺ and Na⁺ ions > cell death
 - Amphotericin B
 - Nystatin
 - Natamycin

Azoles

- inhibit the fungal enzyme 14 α -demethylase which produces ergosterol

Imidazole	Triazole
<u>Clotrimazole</u>	<u>Fluconazole</u>
<u>Econazole</u>	<u>Itraconazole</u>
<u>Ketoconazole</u>	<u>Posaconazole</u>
<u>Miconazole</u>	<u>Voriconazole</u>
	<u>Ravuconazole</u> – <i>in clinical trial</i>

Triazoles - greater affinity for fungal compared with mammalian P450 enzymes > better safety profile

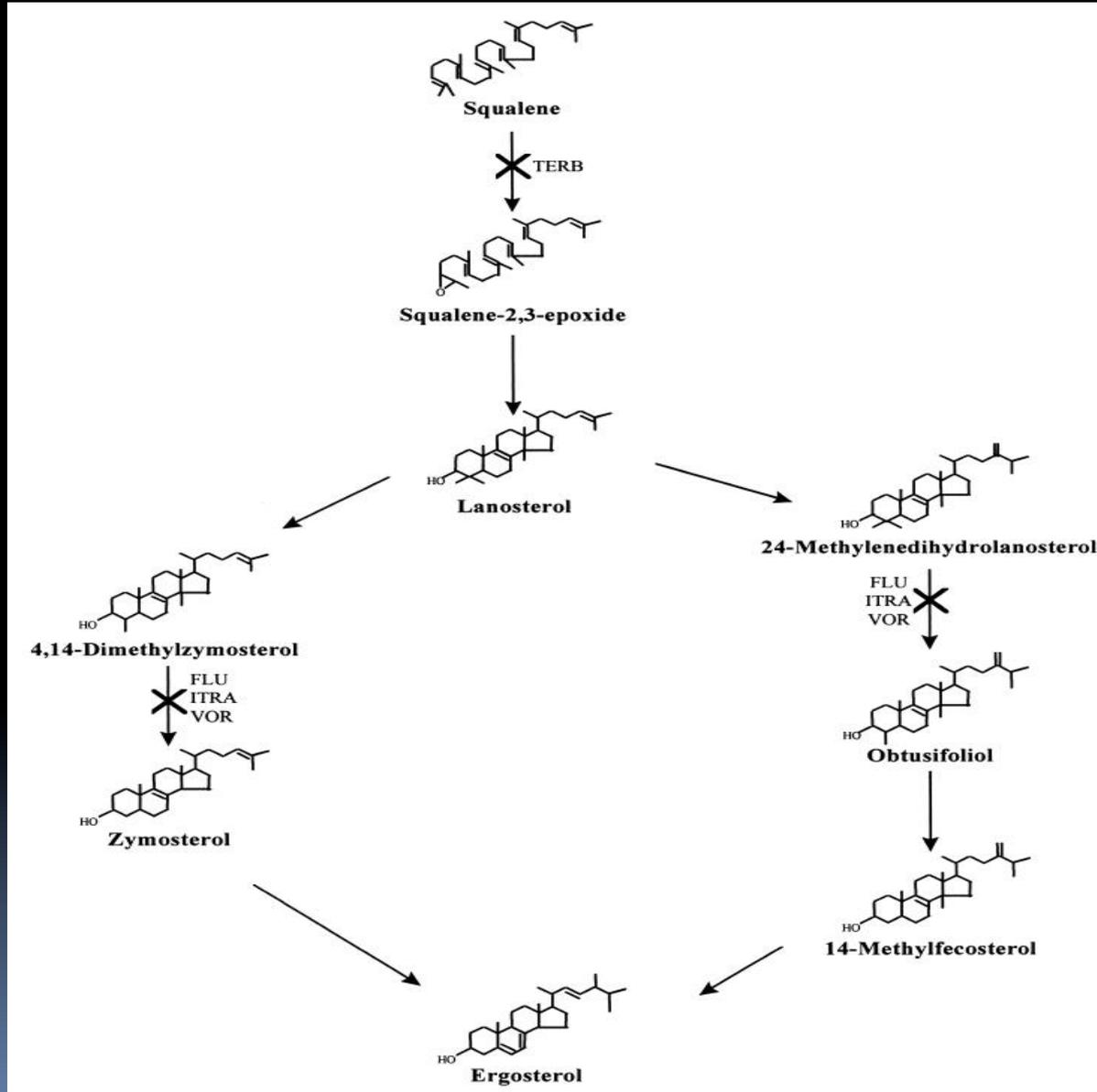
Allylamine

- Terbinafine
- Naftifine
- Inhibits Squalene epoxidase
- Fungal cell death is related primarily to the accumulation of squalene rather than to ergosterol deficiency
- High levels of squalene may increase membrane permeability.

Echinocandins

- Caspofungin
- Micafungin
- Anidulafungin
- inhibit the synthesis of glucan in the cell wall, by inhibition of the enzyme β glucan synthase
- Action is specific to fungal cell walls (*glucan is not found in mammalian cells*) – *less toxicity*

Ergosterol Biosynthetic Pathway



Mechanism of Fungal Cell Resistance

1. Over production of target enzyme
(14 α -demethylase)
2. Altered Drug target
3. Drug pumped out by an efflux pump
4. Prevent entry of drug through cell membrane/cell wall

Mechanism of Fungal Cell Resistance

- contd.

5. Fungal cell has a bypass pathway
6. Inhibition of enzyme that activates drug
7. Fungal cell secretes enzymes to the extracellular medium, which degrade the drug.

Nosocomial Infections



Definition by WHO

An infection acquired in hospital by a patient who was admitted for a reason other than that infection. An infection occurring in a patient in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staff of the facility

Nosocomial Infections (NI)

- occur worldwide and affect both developed and resource-poor countries
- major causes of death and increased morbidity
- Prevalence survey (WHO)
 - 55 hospitals
 - 14 countries (Europe, Eastern Mediterranean, South-East Asia and Western Pacific)
 - Average 8.7% hospital patients had NI
 - Highest - Eastern Mediterranean (11.8%) and South-East Asia Regions (10%)

Nosocomial Fungal Infections

- Opportunistic organisms
 - *Candida albicans*, *Aspergillus* spp.,
Cryptococcus neoformans, *Cryptosporidium*
- Occur during
 - extended antibiotic treatment
 - Severe immunosuppression
- Environmental contamination
 - airborne organisms (*Aspergillus* spp)
 - originate in dust and soil (hospital construction)



Nosocomial Fungal Infections

- Reduced by maintaining the lowest possible concentration of fungal spores in the ambient air of the institution.
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Prevention of Nosocomial Infections

- Responsibility of all individuals and services providing health care
- Team approach
- Infection control programmes
 - Comprehensive (with surveillance & prevention activities)
 - Staff training.
 - Effective support (national and regional levels)
- WHO manuals online
 - *2.3.4 Role of the hospital pharmacist in the prevention of NI*

MYCOSES

- *Definition:* Fungal infection of animals, including humans.
- The clinical nomenclatures are based
 - (1) site of the infection
 - superficial, cutaneous, subcutaneous, or systemic (deep)
 - (2) route of acquisition of the pathogen
 - exogenous or endogenous
 - (3) type of virulence exhibited by the fungus
 - Primary pathogens, Opportunistic pathogens

MYCOSES

- cause a wide range of diseases in humans
- range from superficial infections of the stratum corneum of the skin to disseminated infection involving the brain, heart, lungs, liver, spleen, and kidneys.
- Affects immunocompetent to immunocompromised patients (HIV, immunosuppressed due to therapy for cancer and organ transplantation, major surgery)

Superficial Mycoses

Include & caused by:

- black piedra (*Piedraia hortae*)
- white piedra (*Trichosporon beigeli*)
- tinea nigra (*Phaeoannellomyces werneckii*).
- pityriasis versicolor (*Malassezia furfur*)
 - involves only the superficial keratin layer.
 - Aka Liver spot
 - hypopigmentation or hyperpigmentation of skin of the neck, shoulders, chest, and back.

Cutaneous Mycoses

Classified as

- dermatophytoses

- *Epidermophyton* - infects only skin and nails
- *Microsporum*, - infect hair and skin
- *Trichophyton* - may infect hair, skin, and nails

- Dermatomycoses

- *Candida* spp

Subcutaneous Mycoses

- Three general types:
 1. **Chromoblastomycosis** – verrucoid lesions of skin
 2. **Mycetoma** – can affect bone, tendon, and skeletal muscle
 3. **Sporotrichosis** - subcutaneous tissue at the point of traumatic inoculation

Deep Mycoses

Caused by:

Primary pathogen

- Can establish infection in a normal host
- Life threatening if exposed to high inoculum or alter host defenses
- e.g. Histoplasmosis
 - Inhalation of *Histoplasma capsulatum*
 - Spread via lymph nodes to spleen, liver, bone marrow, and brain
 - Life threatening

Deep Mycoses

Caused by:

Opportunistic fungal pathogens

- require a compromised host in to establish infection (e.g., cancer, organ transplantation, surgery, and AIDS)
- Invade via respiratory tract, alimentary tract or intravascular devices
- GI & intravascular catheters – major point of entry for deep/visceral candidiasis >> kidneys, liver, spleen, brain, eyes, heart
 - principal risk factors – XS broad spectrum Antibiotics, chemotherapy, corticosteroids



COMMON SUPERFICIAL FUNGAL INFECTIONS

- **Mucocutaneous candidiasis**
 - **Mycoses of the Skin, Hair, and Nails**
- 

Superficial Mycoses

- Among most common fungal infections in the world
- Second most common vaginal infections in North America
- Three forms of **Mucocutaneous candidiasis**
 - Oropharyngeal
 - Esophageal
 - Vulvovaginal disease

Vulvovaginal Candidiasis (VVC)

- *Candida albicans* - major pathogen responsible for VVC. (80% to 92%)
- Non-*C. albicans* candidiasis appears to be increasing.
- Classified as either sporadic or recurrent
 - Depending on episodic frequency

VVC - Risk Factors

- Sexually active
- Oral-genital contact
- Higher-dose oral contraceptive pills
- Diaphragm with spermicide etc
- Antibiotics
- Possibly - Diet (excess refined carbohydrates), douching, and tight-fitting clothing

VVC- Signs & Symptoms

- Intense vulvar itching & soreness,
- Irritation
- Burning on urination, and dyspareunia
- Erythema, fissuring,
- Curdy “cheese”-like discharge
- Lesions, edema

VVC - Treatment

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

Oropharyngeal and Esophageal Candidiasis (OP & EC)

- aka Thrush
- common and localized infection - oral mucosa
- caused mainly by the yeast *Candida albican*
- may extend into the esophagus causing esophageal candidiasis

Oropharyngeal and Esophageal Candidiasis

- *Candida* is a commensal fungus of the oral cavity in up to 65% of healthy individuals.
- Amount of organisms ↑es in immunocompromised persons; e.g. HIV
- Highest in infants younger than 18 months of age and in adults older than 60 years of age

OP & EC - Risk Factors

- Use of steroids and antibiotics
- Dentures
- Xerostomia caused by drugs (e.g., tricyclic antidepressants and phenothiazine)
- Smoking
- HIV infection/AIDS
- Diabetes
- Malignancies (leukemia and head/neck cancer)
- Nutritional deficiencies (e.g., iron, folate, and vitamins B1, B2, B6, B12, and C)

OP & EC - Treatment

- Individualized treatment
- Recurrence is reduced in a well managed HIV+ patient.
- Minimize predisposing factors if possible
 - Antimicrobials
 - Corticosteroids
 - Chemotherapeutics
- Proper oral hygiene important

Therapeutic Options for Mucosal Candidiasis

Initial Episodes of OPC:

Treat for 7–14 Days

Common/Significant Side Effects

Clotrimazole 10 mg troche: hold 1 troche in mouth for 15–20 minutes for slow dissolution 5 times daily (B-2)

Altered taste, mild nausea, vomiting

Nystatin 100,000 units/mL suspension: 5 mL swish and swallow 4 times daily (B-2)

Mild nausea, vomiting, diarrhea

Miconazole 50 mg mucoadhesive buccal tablets 50 mg daily (A-1)

Diarrhea, headache, nausea, dysgeusia, upper abdominal pain, and vomiting

Fluconazole 100 mg tablets:^b 100–200 mg daily (A-1)

GI upset, hepatitis not common

Itraconazole 10 mg/mL solution:^c 200 mg daily (A-2)

GI upset, not common: hepatotoxicity, CHF, pulmonary edema with long-term use^e

Posaconazole 40 mg/mL suspension: 400 mg daily with a full meal (A-2)

GI upset, fever, headache, increased hepatic transaminases not common

Fluconazole-Refractory OPC: Treat for ≥14 Days

<u>Itraconazole</u> 10 mg/mL solution: 200 mg daily (A-3)	See above
<u>Voriconazole</u> 200 mg tablets: 200 mg twice daily (>40 kg), taken on empty stomach (A-3)	GI upset, rash, reversible visual disturbance (altered light perception, photopsia, chromatopsia, photophobia), increased hepatic transaminases, hallucinations, or confusion
<u>Posaconazole</u> 40 mg/mL suspension: 400 mg twice daily × 3 days, then 400 mg daily × 28 days (A-2)	See above
Amphotericin B 100 mg/mL suspension: ^d 1–5 mL swish and swallow 4 times daily (B-2)	Oral: nausea, vomiting, diarrhea with higher dose
Amphotericin B deoxycholate 50 mg injection: 0.3–0.7 mg/kg/day IV daily (B-2)	IV: fever, chills, sweats, nephrotoxicity, electrolyte disturbances, bone marrow suppression
<u>Caspofungin</u> 50 mg IV daily (B-2)	Fever, headache, infusion-related reactions (<5%) (e.g., rash, facial swelling, pruritus, vasodilation), hypokalemia, increased hepatic transaminases, anemia, neutropenia
<u>Micafungin</u> 150 mg IV daily (B-2)	Similar to <u>caspofungin</u>
<u>Anidulafungin</u> 200 mg IV daily (B-2)	Similar to <u>caspofungin</u>

Esophageal Candidiasis:^a Treat for 14–21 Days

Fluconazole 100 mg tablets: 200–400 mg (3–6 mg/kg) daily (A-1) See above

Echinocandin: see above (B-2) See above

Amphotericin B deoxycholate 50 mg injection: 0.3–0.7 mg/kg/day IV daily (B-2) See above

Posaconazole 40 mg/mL suspension: 400 mg twice daily (A-3) See above

Itraconazole 10 mg/mL solution:^c 200 mg daily (A-3) See above

Voriconazole 200 mg tablets: 200 mg twice daily (>40 kg) (A-3) See above

Voriconazole and echinocandins (A-1): generally reserved for refractory cases See above

Dermatophytosis

- Aka Ringworm or Tinea
- Ring-shaped, red, itchy rash on the skin
- Common infection of the skin and nails
- Caused by 40 different species of fungi
- Scientific names:
 - *Trichophyton*,
 - *Microsporum*
 - *Epidermophyton*

Type of Tinea depends on the affected body part.

- Tinea capitis - top of the head, or scalp, & is found mostly in children
- Tinea pedis - feet, aka "athlete's foot"
- Tinea cruris - groin, aka "jock itch"
- Tinea faciei - the face
- Tinea barbae - the beard area
- Tinea manuum - the hands
- Tinea corporis on other body surfaces
- Tinea unguium - Toenails or fingernails aka "onychomycosis"

Treatment of Mycoses of the Skin, Hair, and Nails

	Topical ^{a,b}	Oral ^c
Tinea pedis	<ul style="list-style-type: none"> • <u>Butenafine</u>, daily • <u>Sertaconazole</u>, twice daily 	<u>Fluconazole</u> 150 mg 1 per week × 1–4 weeks
Tinea manuum	<u>Ciclopirox</u> , twice daily	<u>Ketoconazole</u> 200 mg daily × 4 weeks
Tinea cruris	<u>Clotrimazole</u> , twice daily	<u>Itraconazole</u> 200–400 mg/day × 1 week
Tinea corporis	<u>Econazole</u> , daily	<u>Terbinafine</u> 250 mg/day × 2 weeks
	Haloprogin, twice daily	
	<u>Ketoconazole</u> cream, daily	
	<u>Miconazole</u> , twice daily	
	<u>Naftifine</u> cream, daily; gel, twice daily	
	<u>Oxiconazole</u> , twice daily	
	<u>Sulconazole</u> , twice daily	
	<u>Terbinafine</u> , twice daily	
	<u>Tolnaftate</u> , twice daily	
	<u>Triacetin</u> cream, solution, 3 times daily	
	Undecylenic acid, various preparations: apply as directed	

Table 98-8 Treatment of Mycoses of the Skin, Hair, and Nails

Treatment of Mycoses of the Skin, Hair, and Nails

Tinea capitis	Shampoo only in conjunction with oral therapy or for treatment of asymptomatic carriers	<u>Terbinafine</u> 250 mg/day × 4–8 weeks
Tinea barbae		<u>Ketoconazole</u> 200 mg daily × 4 weeks
	<u>Ketoconazole</u> twice weekly × 4 weeks	<u>Itraconazole</u> 100–200 mg/day × 4–6 weeks
	<u>Selenium sulfide</u> daily × 2 weeks	<u>Griseofulvin</u> 500 mg/day × 4–6 weeks
Pityriasis versicolor	<u>Clotrimazole</u> , twice daily	<u>Ketoconazole</u>
	<u>Econazole</u> , daily	
	Haloprogin, twice daily	<u>Fluconazole</u>
	<u>Ketoconazole</u> , daily	
	<u>Miconazole</u> , twice daily	<u>Itraconazole</u> 200 mg daily × 3–7 days
	<u>Oxiconazole</u> cream only, twice daily	
	<u>Sulconazole</u> , twice daily	
	<u>Tolnaftate</u> , three times daily	
Onychomycosis	<u>Ciclopirox</u> 8% nail lacquer: apply solution at night for up to 48 weeks	<u>Terbinafine</u> 250 mg/day × 6 weeks (finger), 12 weeks (toe)
Fingernail		<u>Itraconazole</u> 200 mg twice daily × 1 week per month; repeat for total of two pulses (finger) or three pulses (toe)
Toenail		<u>Itraconazole</u> 200 mg daily for 6 weeks (finger) or 12 weeks (toe)
		<u>Fluconazole</u> 50 mg daily or 300 mg once weekly for ≥6 months (finger) or 12 months (toe)

Patient Advice

- Recommend liver function test (LFT) before starting terbinafine & three months after.
- Continue to using cream/ung. until 2 weeks after infection seems to have gone
- Antifungal shampoo – use on second lather; allow on scalp at least 5 minutes before rinsing.

Patient Advice

- Do not share clothing or towels
- Avoid tight-fitting clothing; Cotton preferred
- Change your socks and underwear at least once a day.
- With athlete's foot, put socks on before underwear so the infection does not spread to groin.
- Always dry body completely after bathing.
- Keep pubic hair low

SUMMARY

- Poorer developing countries face triple burden
 - Communicable disease
 - Non-communicable disease
 - Socio-behavioural illness
- Significant emphasis on communicable disease is still necessary

SUMMARY

- Fungal infection (mycoses)
 - Few are reportable communicable diseases
 - They are significant communicable diseases
- Mycoses cause a wide range of diseases in humans
 - Superficial to deep/visceral infections
- The range of patients at risk for invasive fungal infections continues to expand

SUMMARY

- Nosocomial Fungal infection can be reduced by maintaining the lowest possible concentration of fungal spores in the ambient air of the institution.
- Ergosterol is essential to cell membrane of fungi & their survival
- 14α -demethylase is a target for antifungals

SUMMARY

- Superficial mycosis is the most common fungal infection in the world.
 - Some can spread by human to human contact
- 5 classes of Antifungals based on MOA
 1. Polyenes
 2. Azoles
 3. Allylamines
 4. Echinocandins
 5. Other agents (including griseofulvin and flucytosine)
- Wholesome patient advice from pharmacist is necessary for full elimination of mycoses

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