COMMUNICABLE DISEASES: A GLOBAL PERSPECTIVE EMPHASIZING FUNGI.

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Senior lecturer: School of Pharmacy.
University of Technology, Jamaica
What are these?

Champignons Agaricus

Chanterelle Cantharellus cibarius
FotoosVanRobin from the Netherlands
Objectives:
At the end 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
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
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.
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

- Mannoproteins
- β-(1,6)-glucan
- β-(1,3)-glucan
- Chitin
- Phospholipid bilayer of cell membrane
- Ergosterol
- β-(1,3)-glucan synthase
- Ergosterol Synthesis Pathway
- Squalene
- DNA/RNA Synthesis
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 $14\alpha$-demethylase which produces ergosterol

<table>
<thead>
<tr>
<th>Imidazole</th>
<th>Triazole</th>
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<tbody>
<tr>
<td>Clotrimazole</td>
<td>Fluconazole</td>
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<tr>
<td>Econazole</td>
<td>Itraconazole</td>
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<tr>
<td>Ketoconazole</td>
<td>Posaconazole</td>
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<tr>
<td>Miconazole</td>
<td>Voriconazole</td>
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<td></td>
<td>Ravuconazole – in clinical trial</td>
</tr>
</tbody>
</table>

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 (14α-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.
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
**Definition:** Fungal infection of animals, including humans.

The clinical nomenclatures are based on:

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 (*Phaeoannelomyces 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
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
<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Preparation</th>
<th>Regimen</th>
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</thead>
<tbody>
<tr>
<td><strong>Nonprescription/Topical Vaginal Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butoconazole</td>
<td>2% cream</td>
<td>One applicator × 3 days</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>1% cream</td>
<td>One applicator × 1 day</td>
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<tr>
<td></td>
<td>100 mg tablet</td>
<td>One 100 mg tablet × 7 days</td>
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<tr>
<td></td>
<td>2% cream</td>
<td>One applicator × 1 day</td>
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<tr>
<td></td>
<td>200 mg tablet</td>
<td>One 200 mg tablet × 3 days</td>
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<tr>
<td></td>
<td>10% cream</td>
<td>One applicator × 1 day</td>
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<tr>
<td></td>
<td>500 mg tablet</td>
<td>One 500 mg tablet × 1 day</td>
</tr>
<tr>
<td>Miconazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2% cream</td>
<td>One applicator × 1 day</td>
</tr>
<tr>
<td></td>
<td>100 mg suppository</td>
<td>One 100 mg suppository × 7 days</td>
</tr>
<tr>
<td></td>
<td>200 mg suppository</td>
<td>One 200 mg suppository × 3 days</td>
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<tr>
<td></td>
<td>1,200 mg ovule</td>
<td>One ovule × 1 day</td>
</tr>
<tr>
<td>Ticononazole</td>
<td>2% cream</td>
<td>One applicator × 3 days</td>
</tr>
<tr>
<td></td>
<td>6.5% cream</td>
<td>One applicator × 1 day</td>
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<tr>
<td><strong>Prescription/Topical</strong></td>
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<td></td>
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<tr>
<td>Nystatin</td>
<td>100,000 unit tablet</td>
<td>One tablet × 14 days</td>
</tr>
<tr>
<td>Terconazole</td>
<td>0.4% cream</td>
<td>One applicator × 7 days</td>
</tr>
<tr>
<td></td>
<td>0.8% cream</td>
<td>One applicator × 3 days</td>
</tr>
<tr>
<td><strong>Oral Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>150 mg</td>
<td>One tablet × 1 d</td>
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</tbody>
</table>
Oropharyngeal and Esophageal Candidiasis (OP & EC)

- aka Thrush
- common and localized infection - oral mucosa
- caused mainly by the yeast *Candida albicans*
- 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
<table>
<thead>
<tr>
<th><strong>Therapeutic Options for Mucosal Candidiasis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Episodes of OPC:</strong> Treat for 7–14 Days</td>
</tr>
<tr>
<td>Clotrimazole 10 mg troche: hold 1 troche in mouth for 15–20 minutes for slow dissolution 5 times daily (B-2)</td>
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<tr>
<td>Nystatin 100,000 units/mL suspension: 5 mL swish and swallow 4 times daily (B-2)</td>
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<tr>
<td>Miconazole 50 mg mucoadhesive buccal tablets 50 mg daily (A-1)</td>
</tr>
<tr>
<td>Fluconazole 100 mg tablets: 100–200 mg daily (A-1)</td>
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<tr>
<td>Itraconazole 10 mg/mL solution: 200 mg daily (A-2)</td>
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<tr>
<td>Posaconazole 40 mg/mL suspension: 400 mg daily with a full meal (A-2)</td>
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<tr>
<td>Drug</td>
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<tr>
<td>Fluconazole</td>
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<tr>
<td>Itraconazole</td>
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<td>Voriconazole</td>
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<tr>
<td>Posaconazole</td>
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<tr>
<td>Amphotericin B</td>
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<tr>
<td>Amphotericin B deoxycholate</td>
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<tr>
<td>Caspofungin</td>
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<td>Micafungin</td>
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<td>Anidulafungin</td>
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<td>Drug</td>
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<tr>
<td><strong>Fluconazole</strong></td>
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<tr>
<td><strong>Echinocandin</strong></td>
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<tr>
<td><strong>Amphotericin B deoxycholate</strong></td>
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<td><strong>Posaconazole</strong></td>
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<td><strong>Itraconazole</strong></td>
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<tr>
<td><strong>Voriconazole</strong></td>
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<tr>
<td><strong>Voriconazole and echinocandins</strong></td>
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</table>

*Indicates treatment duration of 14–21 days.*
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"
<table>
<thead>
<tr>
<th>Mycoses</th>
<th>Topical\textsuperscript{a,b}</th>
<th>Oral\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea pedis</td>
<td>• Butenafine, daily</td>
<td>Fluconazole 150 mg 1 per week × 1–4 weeks</td>
</tr>
<tr>
<td></td>
<td>• Sertaconazole, twice daily</td>
<td></td>
</tr>
<tr>
<td>Tinea manuum</td>
<td>Ciclopirox, twice daily</td>
<td>Ketoconazole 200 mg daily × 4 weeks</td>
</tr>
<tr>
<td>Tinea cruris</td>
<td>Clotrimazole, twice daily</td>
<td>Itraconazole 200–400 mg/day × 1 week</td>
</tr>
<tr>
<td>Tinea corporis</td>
<td>Econazole, daily</td>
<td>Terbinafine 250 mg/day × 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Haloprogin, twice daily</td>
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<tr>
<td></td>
<td>Ketoconazole cream, daily</td>
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<tr>
<td></td>
<td>Miconazole, twice daily</td>
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<tr>
<td></td>
<td>Naftifine cream, daily; gel, twice daily</td>
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<tr>
<td></td>
<td>Oxiconazole, twice daily</td>
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<td></td>
<td>Sulconazole, twice daily</td>
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<td></td>
<td>Terbinafine, twice daily</td>
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<tr>
<td></td>
<td>Tolnaftate, twice daily</td>
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<tr>
<td></td>
<td>Triacetin cream, solution, 3 times daily</td>
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<tr>
<td></td>
<td>Undecylenic acid, various preparations: apply as directed</td>
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<tr>
<td>Disease</td>
<td>Treatment Options</td>
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<td>-------------------------</td>
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<tr>
<td>Tinea capitis</td>
<td>Shampoo only in conjunction with oral therapy or for treatment of asymptomatic carriers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terbinafine 250 mg/day × 4–8 weeks</td>
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<tr>
<td>Tinea barbae</td>
<td>Ketoconazole 200 mg daily × 4 weeks</td>
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<td></td>
<td>Ketoconazole twice weekly × 4 weeks</td>
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<tr>
<td></td>
<td>Itraconazole 100–200 mg/day × 4–6 weeks</td>
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<tr>
<td></td>
<td>Selenium sulfide daily × 2 weeks</td>
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<tr>
<td></td>
<td>Griseofulvin 500 mg/day × 4–6 weeks</td>
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<tr>
<td>Pityriasis versicolor</td>
<td>Clotrimazole, twice daily</td>
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<td></td>
<td>Ketoconazole</td>
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<td></td>
<td>Econazole, daily</td>
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<td>Miconazole, twice daily</td>
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<td></td>
<td>Itraconazole</td>
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<tr>
<td></td>
<td>Oxiconazole cream only, twice daily</td>
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<td></td>
<td>Itraconazole 200 mg daily × 3–7 days</td>
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<td></td>
<td>Sulconazole, twice daily</td>
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<tr>
<td></td>
<td>Tolnaftate, three times daily</td>
<td></td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>Ciclopirox 8% nail lacquer: apply solution at night for up to 48 weeks</td>
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<tr>
<td></td>
<td>Terbinafine 250 mg/day × 6 weeks (finger), 12 weeks (toe)</td>
<td></td>
</tr>
<tr>
<td>Fingernail</td>
<td>Itraconazole 200 mg twice daily × 1 week per month; repeat for total of two pulses (finger) or three pulses (toe)</td>
<td></td>
</tr>
<tr>
<td>Toenail</td>
<td>Itraconazole 200 mg daily for 6 weeks (finger) or 12 weeks (toe)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole 50 mg daily or 300 mg once weekly for ≥6 months (finger) or 12 months (toe)</td>
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</tbody>
</table>
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
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.
REFERENCES

- Pharmacotherapy: A Pathophysiologic Approach, 9e > Chapter 98. Superficial Fungal Infections
THE END