



Fungi !

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Agenda

- Classification of fungal infections
- Structure of fungi
- Fungal organisms and infection
- Some available treatments
- New boys on the block
- Your role!



How many?

- Approx. 1,500,000 species
- Less than 100 pathogenic to man
- Which do we usually come across?





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(Dermatophytes)

What are these?

1



2



3



4



5



6





The Diversity of Fungi:

From truffles to toenails to terminal diseases

Relationships with Humans: the good, the bad, and the ugly

-
- Antibiotics derived from fungi (penicillin, cephalosporin)
- Gastronomy
 - Wine, beer; bread; soy sauce, truffles
- Ecological Role: decomposing organic matter;
- Indispensable in nutrient cycling and exchange
- Biocontrol- entomopathogenic fungi
- Other enzymatic processes, e.g. cellulases from *Trichoderma* are used in "biostoning" of denim fabrics to give rise to the soft, whitened fabric--stone-washed denim
- Detrimental to the food chain (plant pathogens)
- Human and associated domestic animal diseases
- Produce Toxins
- Onychomycosis; *Ustilago Maydis* and blue corn



The Pathogenic Fungi

Fungal infections classified on the degree of tissue involvement and mode of entry into the host:

- Superficial- localized to the skin, the hair, and the nails.
- Subcutaneous- infection confined to the dermis, subcutaneous tissue or adjacent structures.
- Systemic- deep infections of the internal organs.

Primary and Opportunistic

- Require the host (host dependent; Pneumocystis, Microsporidia, C. albicans)
- Terminate in host (Aspergillus, Histoplasma)



How do we get infected?

Fungal nail infection has little to do with personal cleanliness.

- Can be as simple as
 - banging a toe or finger;
 - trimming nails too closely;
 - wearing tight shoes .

All enough to weaken the nail and expose the underlying nail bed to infection.

- Toenails are most vulnerable to infection,
 - (spend much of their day dark, warm and moist)



What is the biggest problem for us?



- Patient compliance!
- Why??
- It takes time and repetitive treatment
- Nail growth rate?
- Hallux fully infected?



Increased risk

- Aging is a common risk factor for nail fungus for several reasons, including:
 - Diminished blood circulation
 - More years of exposure to fungi
 - Nails may grow more slowly and thicken with age, making them more susceptible to infection

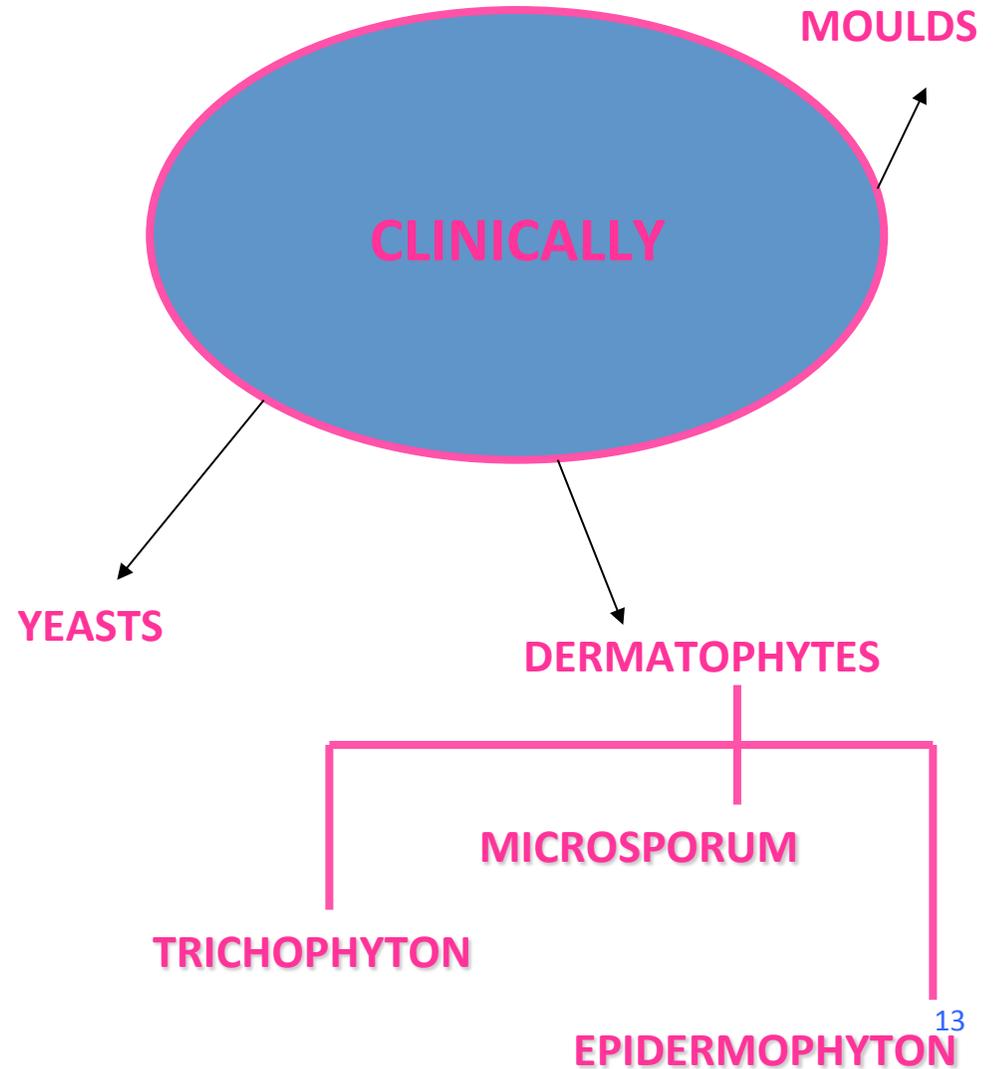
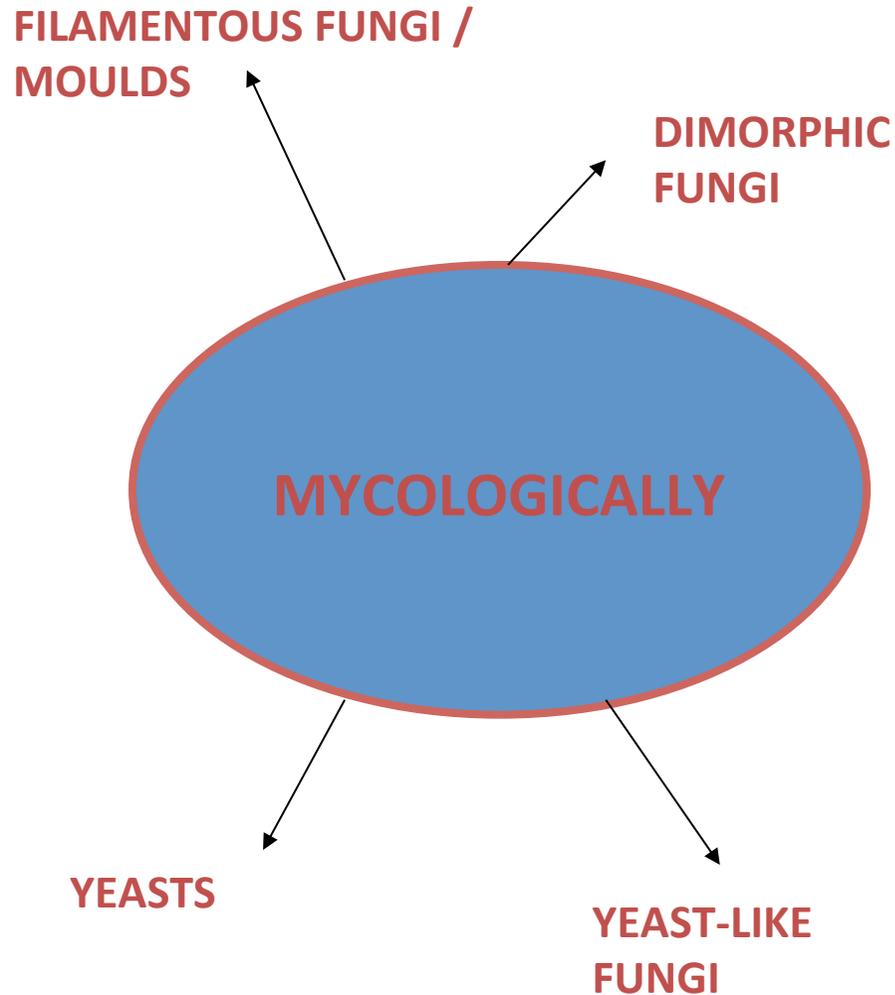


Other factors

- Perspiring heavily
- Working in a humid or moist environment
- Wearing socks and shoes that hinder ventilation and don't absorb perspiration
- Walking barefoot in damp public places, such as swimming pools, gyms and shower rooms
- Presence of Tinea Pedis (*Athlete's foot*)
- Having a minor skin or nail injury, a damaged nail, or another infection
- Having diabetes, circulation problems or a weakened immune system



Fungi





Basic Biology of Filamentous Fungi (moulds)



- The cell wall comprises of chitin.
- Main body of the plant is the Thallus – produces hyphae – forms mycelium.
- Reproduce by formation of spores.
- Produce micro or macroconidia asexually.



Basic Biology of Yeasts

- Unicellular
- Reproduce by ‘budding’ .
- *Candida Albicans* (oropharangeal / gastrointestinal commensal) – causes candidiasis, thrush
- Note: Dimorphic fungi can grow as mycelial fungi or as single cell yeast type.



Sources of Fungal infection

- **Animals** – Zoophilic fungi
 - E.g. microsporum canis (cat and dog ringworm)
- **Soil** – Geophilic fungi
- **Humans** – Anthropophilic fungi
 - Spread via infected surfaces and common in the community
- Dermatophytes may originate from any of these sources



Fungi

- Fungi are eukaryotic organisms (cells with organelles & a cell wall)
- Fungi are the major decomposers of organic matter e.g cellulose
- Fungi cause about 70% of all the major crop diseases
- The diverse metabolic pathways of fungi generate many commercial products such as ethanol, organic acids, enzymes, antibiotics BUT some extremely potent toxins that affect human and animal health e.g aflatoxins
- With the advent of transplant surgery and the increase in immunosuppressive conditions, including AIDS, fungi are emerging as a significant group of life-threatening human pathogens



Fungal Structure

- Fungi are eukaryotes that obtain food by absorption.
- Absorptive nutrition means that fungi excrete hydrolytic enzymes to break-down complex organic molecules into simple ones that can be absorbed.
- Fungi may be unicellular (yeasts) or multicellular (most).
- All fungi reproduce by asexual mechanisms BUT most can reproduce by sexual processes as well
- Fungi are **dispersed by means of spores** of almost infinite variety, produced by either an asexual or a sexual process

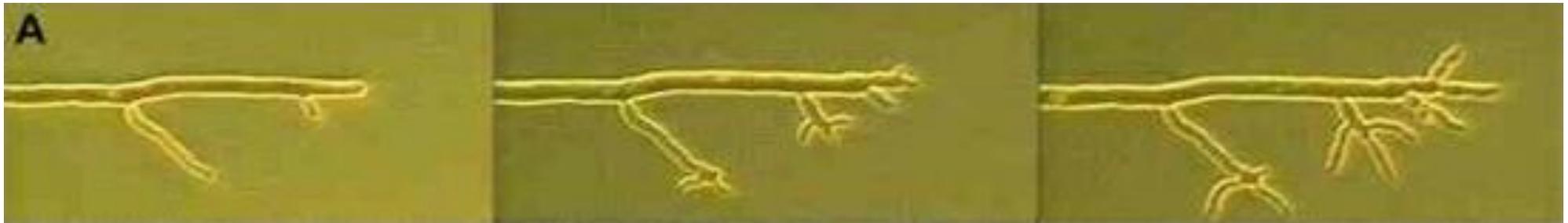


Fungal Structure

- Some species of fungi consist of single cells (yeasts)
- Most species, however, consist of multiple thread-like cells called **hyphae**.
- The hyphae are organised into a network of fibres called a **mycelium** (i.e. the mould that becomes apparent on decaying food)
- Fungi have a cell wall consisting of the polysaccharide **chitin**.



Hyphae





Fungal Structure



- Like human cells, fungal cells contain a nucleus, endoplasmic reticulum, mitochondria, and other organelles.
- BUT most fungal cells possess a rigid cell wall containing polysaccharides such as chitin and glucan, which differ from human & bacterial cell walls.
- The plasma membrane differs from the human in the type of sterol present
 - **Ergosterol**, instead of cholesterol, is the primary component of the cell membrane in fungi.
 - The primary function of ergosterols is to modulate membrane fluidity and initiate growth and increase the size



Fungal Spores

- Many kinds of fungi produce seed-like structures during reproduction that are also called spores.
- The spores of a large number of important fungi are less than 5 μm aerodynamic diameter- hence can enter the lungs.
- They also may contain significant amounts of mycotoxins (secondary metabolites produced by microfungi)
- Diseases associated with inhalation of fungal spores include toxic pneumonitis, hypersensitivity pneumonitis, tremors, chronic fatigue syndrome, kidney failure, and cancer.
- In Britain >20 moulds are known to cause allergic reactions including hayfever & rhinitis



Fungal vs human cells

- Unique cell wall using chitin as the main structural polymer
- Cell membrane contains unique fungal sterols
- Some unique cytoplasmic membrane enzymes in some species
- *NB: these may all be targeted by anti-fungal therapies*



Fungal By-Products

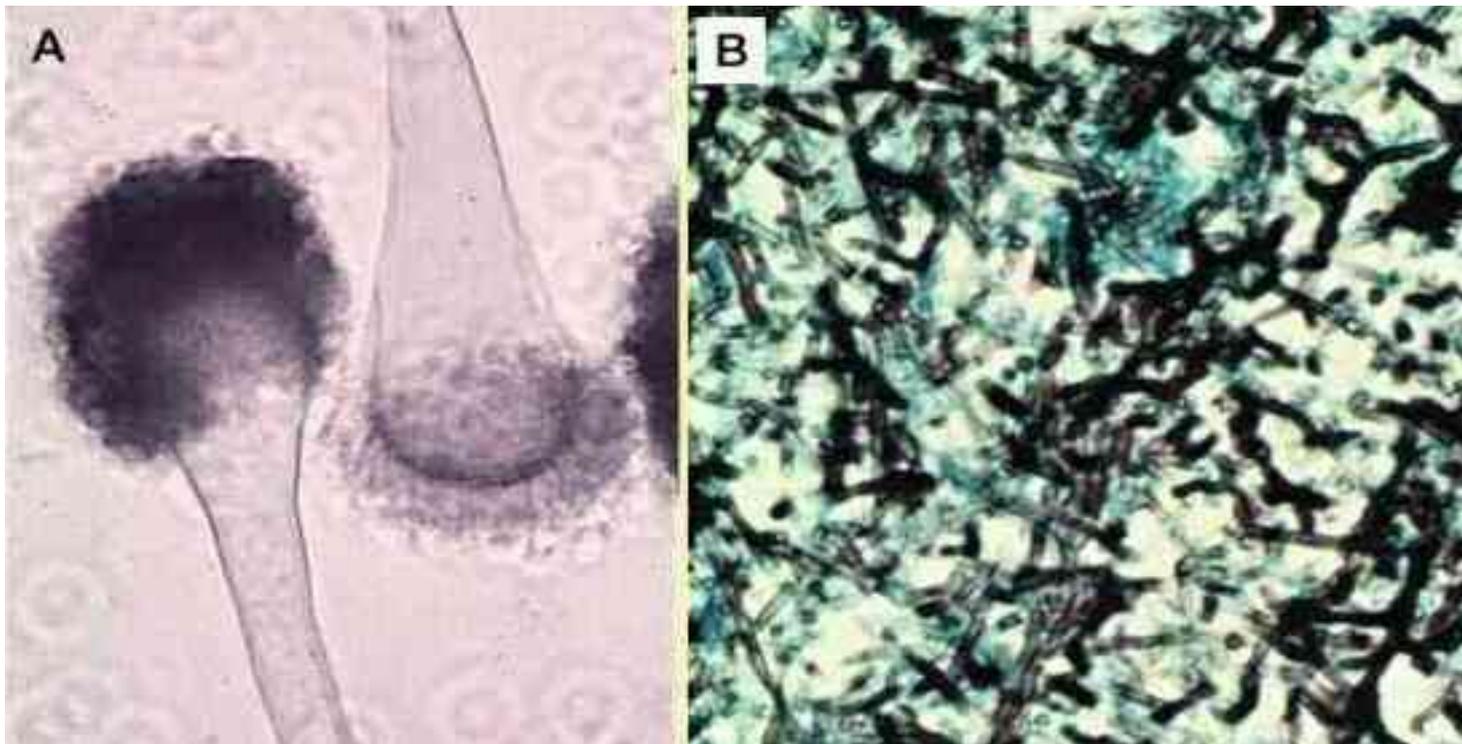
- Fungi produce a wide range of **secondary metabolites** - they play no role in the normal, basic metabolic pathways used for growth and energy production, etc.
- Some of these secondary metabolites have antibiotic properties.
- Others are potent toxins that are dangerous when eaten by humans or other animals e.g. aflatoxins
- Others include pigments inserted into the fungal walls or released into the surrounding environment, or flavour & odour components of toadstools.

Aspergillus fumigatus

Causes Aspergillosis via fungal spores inhaled from decomposing organic matter

(A) Typical sporing heads of the fungus in laboratory culture.

(B) Microscopic section of lung tissue, stained to show hyphae of *Aspergillus* in an air sac. Such a ball of hyphae growing saprotrophically in the lung is termed an **aspergilloma**.





It's not all bad

Yeasts and Fungi have many uses.





Penicillin

- The antibacterial effect of **penicillin** was discovered by Alexander Fleming in 1929.
- He noted that a fungal colony had grown as a contaminant on an agar plate streaked with the bacterium *Staphylococcus aureus*, and that the bacterial colonies around the fungus were transparent, because their cells were lysing.
- Fleming had devoted much of his career to finding methods for treating wound infections
- He immediately recognised the importance of a fungal metabolite that might be used to control bacteria.
- The substance was named penicillin, because the fungal contaminant was identified as *Penicillium notatum*



- Fleming found that it was effective against many Gram positive bacteria in laboratory conditions, and he even used crude preparations of this substance, from culture filtrates, to control eye infections.
- However, he could not purify this compound because of its instability, and it was not until the period of the Second World War (1939-1945) that two other British scientists, Florey and Chain, working in the USA, managed to produce the antibiotic on an industrial scale for widespread use.
- All three scientists shared the Nobel Prize for this work, which saved literally millions of lives.
- It is still a "front line" antibiotic, in common use for some bacterial infections although the development of penicillin-resistance in several pathogenic bacteria now limits its effectiveness



Fungal Infection

- Fungi can cause a variety of diseases with 3 major divisions: allergies, toxicity reactions, and fungal infections.
- Allergic reactions to fungi are caused by sensitivity to fungal proteins such as inhaled fungal spores.
- Toxicity reactions result from the consumption of fungal toxins in contaminated food or poisonous mushrooms.
 - Fungal allergies and toxic reactions are important concerns in agriculture and other industries where fungal contamination is common.



Mycoses

- 4 groups based on the tissue or body site invaded.

Superficial- affect the hair shaft and the outermost, nonliving layer of the skin e.g tinea nigra (*Exophiala werneckii*) & piedra (*Piedraia hortae*)

- Cutaneous - involve infection of the skin, hair, and nails e.g dermatophyte and candida infections
- Subcutaneous- affect the skin as well as the muscle and connective tissue immediately below the skin e.g mycetoma
- Systemic- involve the blood and internal organs e.g blastomycosis



Dermatophytosis



- Dermatophytosis (tinea or ringworm) of the scalp, glabrous skin, and nails is caused by a closely related group of fungi known as dermatophytes
 - have the ability to utilise keratin as a nutrient source, i.e. they have a unique enzymatic capacity [keratinase].
- The disease process in dermatophytosis is unique for two reasons:
 - no living tissue is invaded the keratinised stratum corneum is simply colonised. Presence of the fungus and its metabolic products usually induces an allergic and inflammatory eczematous response in the host. The type and severity of the host response is often related to the species and strain of dermatophyte causing the infection.
 - the dermatophytes are the only fungi that have evolved a dependency on human or animal infection for the survival and dissemination of their species.



Cutaneous

- 1. Dermatophyte infections are common infections of the skin, hair, and nails. Because of the circular skin patches found in all dermatophytoses, they are often referred to as ringworm, or tinea, infections.
- The infectious fungi belong to one of three Geni
 - *Trichophyton*
 - *Epidermophyton*
 - *Microsporum*
- These fungi originate from infected humans, animals, or soils.
- Transmission is usually from person to person or from animal to person.



Dermatophytes according to Mycology Online (2015)

<http://www.mycology.adelaide.edu.au/Mycoses/Cutaneous/Dermatophytosis/>



<u>Species</u>	<u>Natural habitat</u>	<u>Incidence</u>
<i>Epidermophyton floccosum</i>	Humans	Common
<i>Trichophyton rubrum</i>	Humans	Very Common
<i>Trichophyton interdigitale</i>	Humans	Very Common
<i>Trichophyton tonsurans</i>	Humans	Common
<i>Trichophyton violaceum</i>	Humans	Less Common
<i>Trichophyton concentricum</i>	Humans	Rare*
<i>Trichophyton schoenleinii</i>	Humans	Rare*
<i>Trichophyton soudanense</i>	Humans	Rare*
<i>Microsporum audouinii</i>	Humans	Less Common*
<i>Microsporum ferrugineum</i>	Humans	Less Common*
<i>Trichophyton mentagrophytes</i>	Mice, rodents	Common
<i>Trichophyton equinum</i>	Horses	Rare
<i>Trichophyton erinacei</i>	Hedgehogs	Rare*
<i>Trichophyton verrucosum</i>	Cattle	Rare
<i>Microsporum canis</i>	Cats	Common
<i>Microsporum gypseum</i>	Soil	Common
<i>Microsporum nanum</i>	Soil/Pigs	Rare
<i>Microsporum cookei</i>	Soil	Rare

* Geographically restricted.

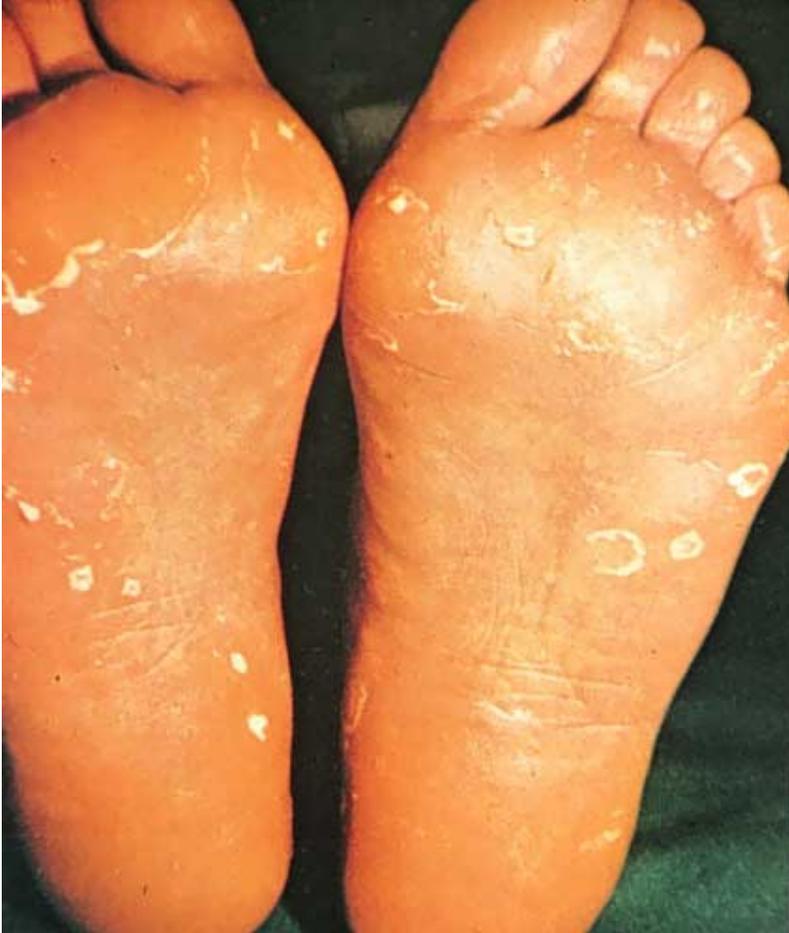


Dermatophyte Infection

- Dermatophyte infections are restricted to the dead tissues of the skin and its appendages (such as nails or hair).
- Minor trauma, prolonged or repeated contact with liquid, and poor skin hygiene promote infections by these fungi.
- Moisture, warmth, and perspiration coupled with patient properties such as specific skin chemistry and genetic predisposition increase the chances of developing a dermatophyte infection.
- Tinea pedis (athlete's foot) often occurs between the toes
- Usually, the infection begins with itching and the development of small fluid-filled blisters.
- The moist skin peels and cracks, allowing secondary bacterial infections to develop. Peeling, cracking, pain, and itching characterise chronic infection.



Tinea Pedis



www.latrobe.edu.au



www.dartmouth.edu



www2.provlab.ab.ca



2. Candidal Infection

- These yeasts are normal inhabitants of the mucous membranes of the nose, mouth, vagina, and anus.
- *Candida albicans* can cause symptoms and disease if the local conditions or the host's weakened immune system allow it to overgrow.
- Susceptibility to *Candida* infections is increased when the skin is weakened by injury, burns, or prolonged exposure to wet environments.
- Warm, moist conditions, as found in the folds of skin in and around the armpits, groin, breasts, in between toes etc
- Rarely *Candida* invades deeper tissues as well as the blood, causing life-threatening systemic candidiasis - more common in immunocompromised



Candida Infection of web of skin between the fingers





Footwear & humidity



- The wearing of footwear is the major contributor to foot infections.
- Plantar surface of foot supplied by a large number of eccrine sweat glands which increase excretion in warm conditions.
- Occlusive footwear creates a warm environment , preventing evaporation and thus hydrating the foot.
- Leyden *et al* (1987) demonstrated this by hydrating the naturally dry region of the forearm. Within 24 hours the normal bacterial population had increased from 10^3 to 10^6 organisms/cm squared. A large increase was in the pathogen *Staphylococcus*
- After 7 days of hydration the results displayed a tripling of the 24 hour bacterial density, including predominance of *Diphtheroids*. The authors stated this population closely resembles that which is found on the foot.



Normal Skin Flora

- Marshall et al (1986) believe that some differences must exist between foot flora and other skin sites. The differences are attributed to anatomical variations already mentioned plus the wearing of occlusive footwear. The authors investigated three sites.
 - 1. sole
 - 2. dorsum
 - 3. 4th toe cleft
- Their results displayed *Micrococci* and *Coryneform* as the most numerous. *Staphylococci* were dominant on the sole and dorsum with *Coryneform* dominant in the 4th toe cleft.
- Pelczar et al (1992) list *Staphylococcus epidermis & aureus*, *Propionibacterium acnes*, *Diphtheroids*, *Pityosporum spp.* and *Candida spp.* as the normal skin flora.



Treatment options?

- Medication
 - Topical solutions / lacquers
 - Tablets
- Chemical nail removal
- Surgery
- Laser / light therapy
- Holistic



How do treatments work?

Terbinafine (Lamisil)

- Interferes with cell membranes.
- Stops fungi from producing ergosterol, an essential component of fungal cell membranes.
- This disrupts the cell membrane and causes holes to appear.

Essential constituents of the fungal cells leak out. This kills the fungi and clears up the infection.



Similar products

- Caneston (clotrimazole)
- Caneston Oral & Duo cream (clotrimazole , flucoazole)
- Daktarin (micanazole)
- Diflucan (fluconazole)
- Nizoral cream (ketoconazole)



Different topical approach

- **MYKORED** (Salicylic acid /Benzoic Acid)
- Changed pH level Inhibits mycelial growth
- Changes structural organization of the mycelium at various levels (wall, mitochondria, vacuole and nucleus)
- Fungal filaments appear empty increasing uptake of acid
- Alcohol base dries environment



When not to treat

- Pregnancy
- Breast feeding
- Decreased kidney function.
- Decreased liver function.
- Psoriasis.
- People with a long-term autoimmune disease affecting connective tissue, called systemic lupus erythematosus (SLE).
- Children (some medicine is not licensed for use with children).

Top 5 USA Nail treatments



ALL DATA AND ANALYSIS PROVIDED BY:
 toenail-fungus.org
 The Nail Fungus Treatment Resource



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 PurNail



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 NailClenZ



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 Curanail



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 NailRx



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 zetaclear

EDITOR RATINGS:

Recommended, Good, Or Fair Buy	Recommended ★ ★ ★	Good ★ ★	Good ★ ★	Fair ★	Fair ★
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PUR NAIL	NAILCLENZ	CURANAIL	NAILRx	ZETACLEAR
\$59.95	\$49.95	\$33.00	\$39.95	\$49.95

Undecylenic Acid, Clotrimazole, Amorolfine, Tea tree/Lav Oil, Tea tree/Almond oil

Dry 5-10 m?



Lamisil At 1% Cream



Chemist Direct	15g £5.99
	Tablets £2.47
Boots	15g £6.25
	Tablets - presc
Amazon	15g £5.00
Trade	15g £4.74 – 6.78
GP	£8.20 presc

Terbinafine hydrochloride based - inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell membrane



Curanail 5% Nail Lacquer Amorolfine Treatment



Amazon: n/a

Boots: £23.99

Chemist Direct: £24.32

Trade: £14.39 - £17.99 (3ml)

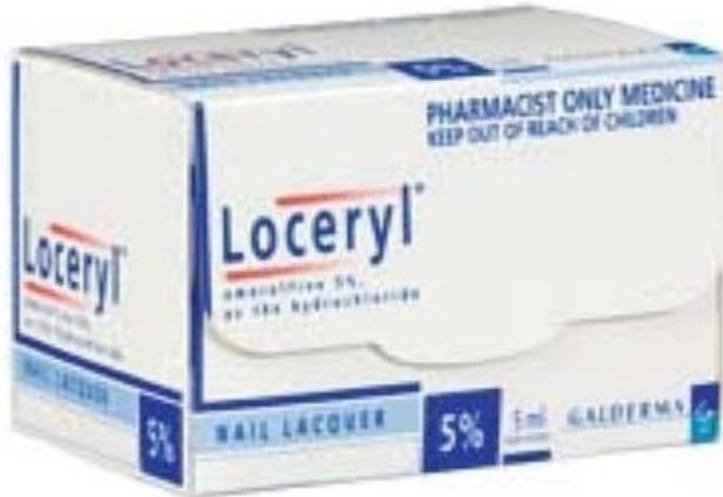
Now known as LOCERYL CURANAIL

Amorolfine hydrochloride based – stops production of ergosterol

Claims to treat MILD fungal infections



Loceryl Lacquer 5ml (POM)



Trade: £23.98- £28.79

Amorolfine hydrochloride based – stops production of ergosterol

Excilor 3.3ml



Boots: £19.99

Amazon: £14.64 - £17.24

Chemist Direct: £18.49 + £3.49
P&P

Trade: £9.87 - £13.07

Acetic acid & alcohol based

Clearzal



Boots: £21.49

Clearzal.co.uk £20.99

Chemist Direct £12.99

Amazon £11.99 – 13.59

Trade £11.04 – 12.78

Application: free edge and sulci only
No lacquer, acids or alcohol.

Clears ALL Fungi, bacteria & viruses ??



Gehwol Med Nail & Skin cream 15ml



Amazon: £6.32 - £7.88

MankyFeet.co.uk: £12.99
(shows improvements in 2 weeks! ??)

Boots: n/a

Trade: £3:91 - £4:50

Clotrimazole based



MYKORED



Boots	n/a
Chemist Direct	n/a
Amazon	50ml £10.79
Trade	50ml £6.66 – 7.30

Liquid – Salicylic acid complex

Cream – Clotrimazole based

(combination of components – no one one active ingredient)

HS 10ml CLASSIKOOL ORGANIC ANTI FUNGAL FUNGUS BACTERIAL NAIL OIL



Amazon: £3.79

eBay: £4.39

Carrier oil + 8 other essential oils
No nasty chemicals or alcohol!

NO Fun-Gus !!



PACT Med light

- Photodynamic Antimicrobial Therapy.
- Uses PACT Nail Fungus Gel
- Activated by exposure to light from the PACT MED light device.

- Canonbury £2995 + VAT
- + gel (£24.99 + VAT)





Evidence?

- Experimental investigations have demonstrated conclusively that both dermatomycetes and yeasts can be effectively killed by photodynamic action
- (and Gram-positive and Gram-negative bacteria and fungi)
- only a very small number of *in vivo* animal and human trials have been published.



PACT treatment protocol

- Heavy de-bridement of each affected nail
- 10 minute gel application of each affected nail
- 9.5 minute light application of each affected nail
- Frequency: 3 complete treatments are needed within 2-3 weeks



Laser



Considerations:

Capital cost

Charge to patients

Evidence

Ease of use (LLLT)

Low level laser therapy becoming more accessible
e.g. Omega

USA costs \$10 -14,000

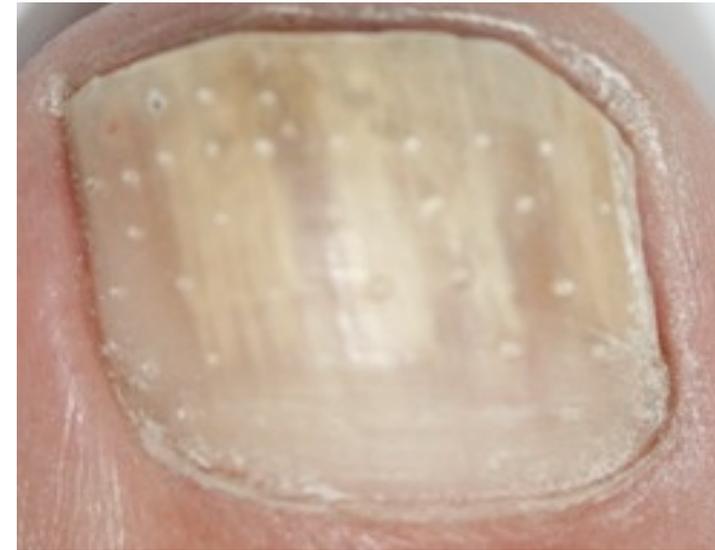
UK?



CLEARANAIL – Controlled Micro Penetration (CMP)



Algeos £1999 + VAT



Used in conjunction with liquid Terbinafine
e.g. Lamisil 1% AT spray





Surgery

- Total nail avulsion
- Does it remove the fungal spores?
- Phenolise the nail matrix?
- Apply anti-fungal agent post surgery?
- Little evidence on effectiveness
- Extreme method!



Holistic therapy



- Apple Cider vinegar soak
- Tea Tree Oil
- Oregano Oil extract
- Others????



Most Popular Toenail Fungus Remedies:

Apple Cider Vinegar **36**

Distilled Vinegar **17**

Tea Tree Oil **14**

Ted's Remedies **14**

Listerine **10**

Hydrogen Peroxide **10**

Iodine **8**

Coconut Oil **8**

Vicks **7**

Garlic **7**

Oregano Oil **7**

Bleach **6**

Lemongrass Essential Oil **5**

Sea Salt **3**

Mouthwash **3**

Urine Therapy **3**

Castor Oil **3**

Dietary Changes **3**

Cayenne **3**



To think about

- Infections of the foot must be treated quickly and efficiently to prevent serious complications from occurring, especially if the host's immune system is compromised.
- The normal flora of the skin has the ability to establish infection of the foot if the barrier of the skin is broken.
- Because the foot is exposed directly to surfaces when ambulating this barrier can easily be disrupted allowing the entry of pathogens.



And you??

- You have a role to play
- NHS Podiatry do not treat fungal infections
- GP's are reluctant to prescribe
- Your professional approach can help- easily!
- Advise, demonstrate, treat
 - Which treatment?
 - Is it fungal? GP – sample (get jar 1st)



Summary

- Fungal spores are all around us
- Patients can more easily be infected than treated
- Wide range of treatments
 - Cost
 - Time
 - Compliance
 - Compromised



The End

- It is up to you how far you want to go
- You can help patients and you can improve your profession
- Questions!

