Objectives

• Discuss the common dermatophytes, yeasts and molds causing fungal infections

• Review signs and symptoms of superficial fungal infections and possible differential diagnosis

• Review topical and systemic anti-fungal medications including general drug interactions and interactions with the Cytochrome P-450 enzyme system

• Review treatment strategies and prevention strategies for fungal infections

Disclosures

• No conflict of interest to declare

• Photographs used for this presentation were taken from the internet.

• No veteran was photographed for this presentation.
The Usual Suspects

Fungus

- Dermatophyte, yeast, mold = Fungus
- Mycosis = Fungal infection
- Superficial mycosis – invasion of keratinized tissue of stratum corneum of skin, hair & nails
- Fungi have nucleus – Bacteria do not
- Fungi (most) are multicellular
- Bacteria are single celled

Fungus

- Organism degrades keratin
- Small breaks in the skin, occlusion and/or maceration allow fungi to germinate and adhere to keratin and epidermis
- Organisms that penetrate the epidermis cause a host response.
- Zoophilic and geophilic species cause more intense inflammatory reactions than anthropophilic species
Fun with Fungus

• Mushrooms are fungus
• Fungus is needed to make bread and beer
• Fungi eat trash
• Several medications are made with fungus:
  • ROSUVASTIN
  • MYCOPHENOLATE
  • PENICILLIN
  • CYCLOSPORIN
  • CEFIXITOREN

AND YOU CAN BUILD WITH IT!

Called Hy-Fi, the building built predominantly of fungus bricks as well as some light reflecting ones. It was designed by New York architect David Benjamin. The shape is three open towers joined together and encased bricks coated with reflective film to bounce sunlight onto fungal root bricks below, to encourage them to grow. The structure’s strange shape is designed to push hot air upwards and draw colder air down to where people can sit and cool down.

Prevalence

• Worldwide approximately 25% of the population has a superficial fungal infection (mycosis)
• In tropical regions prevalence is as high as 40%
• Mycosis ranks fourth of the top ten most commonly reported diseases in the world
• Globally tinea corporis is the most common type of superficial mycosis.
• In the United States [US], tinea capitus is the most common disease seen in children and tinea pedis is the most common disease in adults.
• There are over 51 million outpatient visits for superficial mycosis in the US annually
  — Of those visits, one third were for onychomycosis
  — Most primary care visits for mycosis are seen in older adults.
Common types of Fungus and the Disease [Mycosis] they cause

- Dermatophyte
- Yeast
- Mold
- Pityriasis versicolor
- Paronychia
- Nail infections

Classes of Topical Antifungals

- **Imazoles** – inhibit cytochrome P450 dependent enzymes involved in biosynthesis of ergosterol needed for fungal cell membrane
  - Ketoconazole
  - Clotrimazole
  - Miconazole
- **Allylamines** – inhibit biosynthesis of ergosterol needed for fungal cell membrane at later step than the imazoles
  - Terbinafine
  - Butenafine
  - Naftifine
- **Polyenes** – interferes with cell membrane causing leaks
  - Nystatin
- **Hydroxyopyridones** – interferes with active membrane transport and cell membrane integrity
  - Ciclopriox
  - Rilopirox

The Dermatophytes

- Tinea Pedis/Manus [Manuum]
- Tinea Unguim [onychomycosis]
- Tinea Corporis
- Tinea Cruris
- Tinea Capitis
- Tinea Faciei
- Piedra White
- Piedra Black
Tinea Pedis

- Initial infection usually presents with inflammatory response.
- Chronic tinea pedis may have minimal inflammation.
- More common in males:
  - Communal living in barracks
  - Locker rooms
  - Gyms

Types of Tinea Pedis

- **Moccasin** - Typically presents as dry hyperkeratotic scaling on plantar surface and lateral feet. May or may not itch.
- **Interdigital** - Web spaces are typically affected, usually the 4th and 5th web spaces. These may be dry and cracked or have white macerated skin.
- **Inflammatory** - Severe cases can present with clusters of blisters or pustules on medial foot (instep). May also see circular patches on the dorsal foot similar to tinea corporis.
- **Ulcerative** - Severe form of infection, usually with secondary bacterial infection. More common on severely immunocompromised patients.
Differential diagnosis

- Dyshydrotic Eczema
- Contact Dermatitis
- Psoriasis
- Secondary Syphilis

Tinea Diagnosis

- Clinical presentation
- Potassium Hydroxide [KOH] 10 or 20% - slide must stand for 15-30 minutes to allow degradation of keratin in skin scraping or heated to speed up the degradation. Accuracy can be as low as 30%
- Fungal culture – send to lab, may take weeks for results.

Tinea Pedis Treatment

- Moccasin – Topical antifungals usually very effective
  - Allylamine antifungals
    - Terbinafine 1% apply twice daily for 2-4 weeks. Use for one full week after symptoms have resolved
    - Butenafine 1% apply twice daily for 2-4 weeks. Use for one full week after symptoms have resolved
  - Imidazole Antifungals
    - Ketoconazole 2% apply twice daily for 4-6 weeks. Use for one full week after symptoms have resolved
    - Luliconazole 1% apply daily for 2 weeks. Use for one full week after symptoms have resolved
    - Clotrimazole 2% apply twice daily for 2-4 weeks. Use for one full week after symptoms have resolved
  - Polyene antifungals such as nystatin are not typically effective for tinea pedis

- Interdigital – requires topical antifungal medication but may need drying agent
  - Phenol 1.5% antiseptic, can dry macerated interdigital areas [Castellani paint]. Apply 1-2 times a day interdigitally
Tinea Pedis Treatment continued

• Inflammatory – Topical antifungals usually clear this mycosis. Severe cases may need oral antifungals
  – terbinafine 250mg po daily for 2 weeks
  – itraconazole 200 mg twice a day for 1 week
  – fluconazole, 150 mg once a week for 4 weeks


• Ulcerative—if secondary bacterial infection and/or cellulitis present will need to treat with antibiotics.

Tinea Pedis Treatment continued

• Cure rates are high, so are rates of re-infection
• Advise patients to:
  – Keep nails short
  – Change socks and shoes daily
  – Rotate shoes and treat with disinfectants/antifungals
  – Discard old sneakers or slippers. Old foot wear can harbor dermatophytes for years
  – Treat tub or shower areas weekly with diluted bleach solution. Leave on surface for 20-30 minutes then rinse off
  – Wear shoes/socks in public gyms

Complications

• Spread of tinea to other areas – hand, groin
• Secondary Bacterial Infections
• Cellulitis
  • Dermatophytid or Id reaction –
    – Systemic reaction to fungal antigens
    – May occur on face and extremities, can be vesicular [small blisters], pustular, or patchy with violaceous hue and scaling, papulosquamous [raised scaling papules], or postular
    – Usually clears rapidly after treatment of the mycosis
Tinea Manus

- Most often seen as one hand two feet syndrome.
- Takes years to develop
- Usually auto-inoculated from scratching feet with dominant hand
- Clears with topical treatment
- Finger nails may involved

Tinea Unguium

- Nail thickening in presence of thick cracked peeling feet or moccasin pattern scaling is highly suggestive of onychomycosis
- Need nail clippings to positively confirm

**Tinea Unguium**

- **Differential Diagnosis**
  - Mold
  - Candida
  - Trauma
  - Lichen planus
  - Psoriasis

- **Diagnosis**
  - Send clipping for PAS testing (periodic acid Schiff)
  - Mycology
    - send nail clipping in dry sterile container
  - Can take weeks to grow dermatophyte/mold etc.
Tinea Unguium Treatment

- Topicals are ineffective against nail dermatophytes. This includes: antifungals, lacquers, Vicks Vapo Rub etc.
- Explain to patient what to expect
- Finger nails will clear faster than toenails
- Oral antifungals can take 6-18 months to clear toe nails
- Recurrence rate is nearly 50% after one year
- Short pulsed NdYAG lasers have been approved in the US to treat fungal nail infections, laser can penetrate nail plate heating up fungal elements destroying them

Tinea Unguium Treatment

- Oral treatment
  - Terbinafine 250 mg/day for 6-8 weeks for fingernails. Check LFT’s prior to starting treatment. For toenails treat for 12-16 weeks. Check LFT’s prior to starting treatment and at 6 weeks.
  - Itraconazole give in pulsed doses 200 mg twice a day for 1 week hold for 3 weeks
    Use for 2 months for fingernails
    Use for 3-4 months for toenails.
  - Fluconazole 150-300 mg once a week for 6-12 months.

NOTE:azole antifungals are CYP3A4 inhibitors, can increase lovastatin and simvastatin levels 10-20 fold, can increase atorvastatin levels 2-4 fold. Pravastatin not metabolized by the CYP3A4 isozyme

Tinea Unguium

- Differential Diagnosis
  - Mold
  - Candida
  - Trauma

- Complications
  - Chronic tinea unguium ➔ chronic tinea pedis ➔ tinea cruvis
  - Secondary bacterial infections
  - In persons with diabetes, chronic venous stasis, lymphedema
    chronic mycosis ➔ cellulitis, recurrent ulcers and poss loss of limb
Tinea Corporis

• Typically presents as erythematous plaques with central clearing and a leading edge of scale.
• Generally spread through direct contact skin to skin, or human to animal contact.
• Self inoculation can occur from tinea infected foot.
• Clothing can harbor the dermatophyte and trap moisture next to skin.

Tinea Corporis - Differential diagnosis

• Cutaneous T Cell Lymphoma
• Granuloma Annulare
• Nummular dermatitis
• Syphillis
• Erythema annulare centrifugum

Tinea Corporis - Treatment

• Topical antifungal creams apply twice a day for 2-4 weeks: Allylamine or Imazole Antifungals
• Generally advise patient to apply for additional week after visible rash clears.
• Launder all clothing and linen in contact with affected area.
• Look for other sources of tinea.
• Combinations of topical steriod and antifungals usually delay cure.
• Offer non-steroidal topicals for relief of itch: Camphor and menthol, pramoxine, mentholated petrolatum.
Tinea Cruis

• Typically presents as erythematous plaques with central clearing and a leading edge of scale in inguinal folds
• More common in men, athletes and the obese
• Can be result of self inoculation by pulling up contaminated clothing or scratching
• Often recurs in warm weather

Tinea Cruis - Differential diagnosis

• Candiasis – note bright red rash with satellite lesions

Inverse psoriasis – note smooth shiny appearance

Tinea Cruis - Treatment

• Topical antifungal creams apply twice a day for 2-4 weeks.
  • Allylamine antifungals or Imazole Antifungals
• Generally advise patient to apply for one more week after visible rash clears
• Look for other sources of tinea
• Treat tinea pedis/unguium
Tinea Cruis - Treatment

- Have patient don socks before putting on undergarments or pants
- Combinations of topical steroid and antifungals usually delay cure
- Wear loose fitting cotton clothing
- Suggest topical moisture barrier products such as zinc oxide. Apply after the antifungal, will help manage moisture and if applied cool can temporarily reduce itch

Tinea Capitus

- More common in children
- In adults, occurs in immunocompromised, elderly living in group communities and in the homeless or near homeless
- Depending on the infecting organism, can have very different clinical presentations
- Usually transmitted human to human
- Animal to human transmission usually causes more severe symptoms. Most common animal
- Most common presentation is alopecia with or without scale

Tinea Capitus

- In United states Trichophyton and Microsporum are most common infecting agents
- Can infect hair shaft causing breakage. Called black dot tinea
- Can infect around the hair shaft causing scaly patches of alopecia. Called gray patch tinea
- Subacute cases can appear as severe seborrheic dermatitis
- Advanced disease can lead to a bacterial boil/purulent plaque/abscess
Tinea Capitus Differential Diagnosis

- Alopecia areata – autoimmune disorder
- Telogen effluvium – occurs as post traumatic stress response ie pregnancy or can be related to protein/vitamin deficiency
- Trichotillomania – compulsive hair pulling
- Syphilis
- Discoid Lupus Erythematosus
- Lichen planopilaris
- Sarcoidosis
- Folliculitis decalvans

Tinea Capitus Treatment

- Treatment almost always requires oral antifungals
- Success of treatment depends on infecting dermatophyte
- Obtain mycology culture
  - Hair which has been pulled out from the roots.
  - Biopsy
  - Brushing off scale from scalp
- Griseofluvan is most effective for treatment for infections caused by Microsporim spp.
- Terbinafine has been noted to be more effective for infections caused by Trichophyton spp.


Tinea Capitus Treatment

- Griseofluvan 6.25mg – 12.5mg/kg/day for 8 weeks for treatment for infections caused by Microsporim spp.
- Terbinafine 3.125mg – 6.25mg/kg/day for 4 weeks for infections caused by Trichophyton spp.
- Ketoconazole shampoo 2% used daily or every other day, leave on for 10-15 minutes if possible then rinse off. May help with superficial crusts and itch
- Advise patients to treat combs and brushes as well as launder hats, caps scarfs and bed linens
- Avoid picking or scratching scalp
A Few Words about Griseofulvin

- Usual dose: Microsize 500mg/day or Ultramicrosize 375mg/day. Usual treatment course is 4-6 weeks.
- Difference between microsize and ultramicrosize is absorption; when taken with fatty meal there is minimal difference in absorption.
- Not recommended for persons with significant liver disease or porphyria.
- Assess renal and hepatic function if using for over 6 weeks.
- Usual dose and vomiting if taken with alcohol.
- Interferes with absorption of some oral contraceptives and warfarin.
- Rash & urticaria are most common side effects. Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. Discontinue if any rash occurs.
- Category X for pregnant woman and not recommended for lactating women.
- Men should avoid fathering a child for 6 months after completing treatment. Women should avoid getting pregnant for at least a month after the treatment has finished.

A Few Words about Terbinafine

- Usual dose: 250mg daily. Usual treatment course is 4-6 weeks.
- Not recommended for persons with significant liver disease.
- Assess LFT's and CBC prior to starting treatment and repeat if dosing for longer than 6 weeks.
- Discourage alcohol consumption while on this medication.
- Potentially interferes with metabolism of warfarin, tricyclic antidepressants, beta-blockers, comedetin oral contraceptives and medications that suppress the immune system:
  - azathioprine (Imuran)
  - cyclosporine (Neoral, Sandimmune)
  - methotrexate (Rheumatrex)
  - sirolimus (Rapamune) and tacrolimus (Prograf)
  - rifampin (Rifadin, Rimactane)
  - selegiline (Eldepryl)
- Category B for pregnant woman, is not recommended for lactating women.

Tinea Faciei

- Most common on glaborous skin (non-hair bearing).
- When occurs in male beard area is called tinea barbae.
- Often transmitted from pets or farm animals.
- Presents as annular lesions with leading ring of erythema and scale.
Tinea Faciei – Differential Diagnosis

- Discoid Lupus Erythematosus
- Seborrheic Dermatitis
- Rosacea
- Contact Dermatitis
- Polymorphous light eruption

Tinea Faciei - Treatment

- Topical antifungal creams apply twice a day for 2-4 weeks: Allylamine or Imazole Antifungals
- Apply topical cream 1 to 2 inches beyond the lesion
- Advise patient to apply for one week after visible rash clears
- Avoid combinations of topical steroid and antifungals
Peidra

• Peidra is Spanish for Stone
• Fungal infection of hair shaft
• Types
  – White Peidra more common in South America, Japan, Middle East, Asia, Africa and southern US. Fungus is found on foliage, rotting wood, infected animals such as horses, monkeys or dogs.

  – Black Peidra more common in tropics. Fungus found in plant oil, fungus also found in soil and stagnant water

Peidra

• White Peidra – usually found facial hair, axillary hair and pubic hair
• Black Peidra- usually found on scalp hair

Peidra - Treatment

• Hair clipping or full removal is most effective, especially for pubic infestation
• Black Peidra is difficult to clear, typically oral terbinafine is needed in conjunction with topical antifungal shampoos
• White Peidra can be treated with topicals such as midazoles, ciclopirox, 2% selenium sulfide, chlorhexidine solution, Castellani paint, zinc pyrithione, and amphotericin B lotion.
Molds

- Infections of nails, nail matrix and nail fold (paronychia)
- Can appear as streaks of brown or green with pitting of nail plate
- Usually caused by excessive moisture
- Often indistinguishable from tinea unguium
- Usually are co-infecting organisms
- Chromoblastomycosis - mold infection of skin and subcutaneous tissue. Often caused by thorns or splinters

Treatment for Mold Infections

- Keep nails as short as possible
- Minimize prolonged exposure to water, if unavoidable should use protective gloves
- For mold under nails, soaking affected digits in 1/4 strength acetic acid BID is helpful
- Oral itraconazole or terbinafine
- Short pulsed NdYAG laser

Paronychia

- Warm compresses 3-4 times a day
- Topical mupirocin 2% 3-4 times a day after soaking
- May require short course of antibiotics. Cephalosporin, clindamycin and amoxicillin-clavulanate are all appropriate.
- If an abscess develops, an I&D may be needed
- Need to r/o herpetic whitlow
Yeast

- **Candida** – Found in oral washings from 50% of healthy people and in 90-100% normal adult stool.
- **Malassezia** (formerly known as *Pityrosporum*)
  - Requires fat to grow, seen most commonly in heavy sebaceous gland distributions such as central face, upper body, axilla and inguinal areas.
  - Grows rapidly in warm environments.

**Pityriasis Versicolor**

- Caused by Malassezia species.
- Previously called Tinea Versicolor.
- More common in young adult males.
- Present on 90-100% of the population as normal flora.
- Density of the flora is related to age, regional sebaceous glands & genital secretions.
- Overgrowth and conversion to hypheal state is caused by heat and moisture.
- Linked to seborrheic dermatitis and folliculitis.


**Pityriasis Versicolor – Differential Diagnosis**

- Pityriasis rosea
- Pityriasis alba
- Vitiligo
- Seborrheic dermatitis
- Tinea corporis
Pityriasis Versicolor - Treatment

- No treatment is needed as this is essentially a cosmetic problem.
- Use of antifungal shampoo as body wash daily for 2-3 weeks. Lather up and leave on for 10-15 minutes then rinse off. Use 1-2 times weekly for prophylaxis. Most effective if entire body is treated not just visibly affected areas.
- Topical antifungal cream – Hydroxypyridones (ciclopriox; rilopirox) and the allylamines (terbinafine; naftifine) are most effective. Apply twice a day for 2-3 weeks.
- For wide spread involvement, may need systemic therapy with oral azole antifungal. The FDA has limited the use of oral ketoconazole as of 7/26/13. Is no longer indicated for treatment of candida or dermatophyte infections of skin or nails.
- Inform patients that the discoloration may take weeks to months to resolve.
- Recurrence is very common, especially in warm weather.

*Candiasis*

- Usually caused by candida albicans.
- Cutaneous infection is usually opportunistic.
  - Infants
  - Obese persons
  - Immunocompromised
    - Diabetes
    - HIV/AIDS
    - Hepatitis
    - Long-term steroid therapy
  - Prolonged antibiotic therapy
- Appears as itchy papules/pustules within area of erythema. Often have papules or pustules at periphery (satellite lesions).

Candiasis - Differential Diagnosis

- Inverse psoriasis
- Tinea
- Seborrheic dermatitis
- Atopic dermatitis
- Intertrigo

*http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm*
Candiasis-Treatment

- Keep affected areas clean and dry
- Control perspiration if possible
  - Cool environment
  - Use topical products with zinc or dimethicone
- Topical antifungal twice a day for one week beyond resolution of the rash
  - polyene (ie nystatin)
  - azole
  - allyamine
- Silver impregnated clothing can reduce bacterial and fungal organisms
- Avoid combinations of topical steroid and antifungals

Thank You
References Provided in the On-Line Presentation

Any Questions?

References
