Fungal Infections
Pharmacotherapeutics
Advanced Pharmacotherapeutics

Core Concepts Fungal Infections

- MO (microscopic organisms) from the Fungal kingdom, they live in the dead, horny outer layer of the skin. Millions of types, but a mere 3 are problematic for us.
    - The organisms penetrate only the stratum corneum—the surface layer of the skin.
    - infect the skin, hair, and nails
- Dermatophytes (*tinea*) and candida (*candidiasis*) are the main types of infections. Tinea versicolor (*Pityriasis versicolor*) is another type of infection. Fungal infections are OPPORTUNISTIC (meaning they live in certain areas all the time and when an opportunity arises, they make an infection in a different area). They may spread throughout the body after they enter through the opportunistic opening.
- teach the patient about hygiene and ways to avoid transferring fungal infection to others (NP teaching point).
- Factors predisposing to fungal infections
    - Warm, moist, occluded environments
    - Family history
    - Compromised immune system (cancer, HIV/AIDS, steroids)

Fungal Infections of the Skin

- Tinea: epidermal locations feet, body, and mouth
- Tinea versicolor (*Pityriasis versicolor*): interferes with the normal pigmentation of the skin, resulting in small, hypo or hyperpigmented or discolored macules with overlying scales in a patch or plaque. Loves it in warm and humid regions, up to 50% found in tropical areas.
- Candidiasis: typically lives in mouth, throat, gut, vagina, and rectum. No sex or ethnic predilection.

1. Types of Tinea Infections
    a. Location: tinea
        i. capitis: head
        ii. corporis: body
        iii. pedis: foot
        iv. manus: hand
        v. unguium (onychomycosis): nails
        vi. cruris: groin

2. 5 most common fungal types
    a. Trichophyton rubrum
    b. Trichophyton tonsurans

c. Trichophyton mentagrophytes
d. Microsporum canis
e. Epidermophyton floccosum

3. Diagnostic Criteria for Fungal Infections
    a. Symptoms
        i. Pruritic, burning, and stinging of the scalp or skin, possible erythema, and vesicles with inflammatory dermal reactions.
    b. Diagnostic tests
        i. Microscopic evaluation of the stratum corneum with 10% potassium hydroxide (KOH) preparation
            1. Tinea versicolor: grape-like clusters of long hyphae and yeast cells.
                a. Scales and +KOH indicate active dz.
        ii. Fungal culture
        iii. Wood lamp (identifies only Microsporum)
            1. Tinea versicolor: gold-yellow, yellow-green, or coppery-orange fluorescence
4. Tinea Capitis Presentation
    a. Inflamed, scaly, alopecic patches, especially in infants
    b. Multiple round areas w/ diffuse scaling and alopecia, 2ndary to broken hair shafts, leaving residual black stumps
    c. "Gray patch" type with round, scaly plaques of alopecia in which the hair shaft is broken off close to the surface
    d. Tender, pustular nodules
    e. Drug selection
        i. 1ST line: griseofulvin (Grifulvin V) minimum 8 weeks
        ii. 2ND line: terbinafine (Lamisil) or itraconazole (Sporanox) 4 weeks

5. Tinea Corporis
    a. Called "ringworm" when it affects the face, limbs, or trunk but not the groin, hands, or feet
    b. Presentation: ring-shaped lesion with well-demarcated margins, central clearing, and a scaly, erythematous border
    c. Causes: contact with infected animals, human-to-human transmission, and from infected mats in wrestling
    d. Organisms responsible: M. canis, T. rubrum, and T. mentagrophytes
    e. Drug selections
        i. 1ST line: topical azole antifungals for 2 to 4 weeks (1 week past clinical cure), 2 weeks even after rash is gone
        ii. 2ND line: systemic therapy: terbinafine (Lamisil) or fluconazole (Diflucan)

6. Tinea Cruris
    a. Often referred to a "jock itch."

b. A fungal infection of the groin and inguinal folds, tinea cruris spares the scrotum.
c. Causes are T. rubrum or E. floccosum.
d. Symptoms: lesions that are large, erythematous, and macular, with a central clearing; a hallmark is pruritus or a burning sensation.
e. Often fungal infection of the feet is present.
f. Drug Selection
    i. 1ST line: topical azole antifungals for 2 to 4 weeks (1 week past clinical cure), 2 weeks even after rash is gone
    ii. 2ND line: systemic therapy: terbinafine (Lamisil) or fluconazole (Diflucan)

7. Tinea Pedis
    a. 3 types
        i. Interdigital: scaling, maceration, and fissures between the toes
        ii. Plantar: diffuse scaling of the soles, usually on the entire plantar surface
        iii. Acute vesicular: vesicles and bullae on the sole of the foot, the great toe, and the instep
        iv. Drug Selection
            1. 1ST line: topical azole antifungals for 2 to 4 weeks (1 week past clinical cure), 2 weeks even after rash is gone
            2. 2ND line: systemic therapy: terbinafine (Lamisil) or fluconazole (Diflucan)

8. Tinea Manuum
    a. Dermatophyte infection of the hand
    b. Always associated with tinea pedis and usually unilateral
    c. Lesions marked by mild, diffuse scaling of palmar skin
    d. Vesicles may be grouped on the palms or fingernails involved

9. Tinea Unguium- Onychomychosis
    a. Fungal infection of the nail; typically, the toenails.
        i. Nails become thick and scaly with subungual debris.
        ii. Onycholysis (nail separation from bed) may occur.
            1. hyperkeratotic substance accumulates underneath the nail and this lifts the nail up.
    b. Organisms causing onychomycosis: dermatophytes, E. floccosum, T. rubrum, T. mentagrophytes, C. albicans, Aspergillus, Fusarium, and Scopulariopsis.
    c. 1ST line: itraconazole (Sporanox) or terbinafine (Lamisil) 12 weeks with food; not recommended for children

10. Tinea versicolor (Pityriasis versicolor):
    a. interferes with the normal pigmentation of the skin, resulting in small, hypo or hyperpigmented or discolored macules with overlying scales in a patch or plaque.

b. Disease recurrence is common
c. Hair loss may occur within the patch or plaque
    i. Thinning on men's forearms, abdomen, neck, and beard regions.
d. Oral and topical antifungals are effective
    i. May impact QOL
    ii. pigmentary changes >> may take weeks or months to clear up.
    iii. Flourishes in warm and humid regions, up to 50% found in tropical areas.

MEDICATIONS USED FOR FUNGAL INFECTIONS

11. Prevention of fungal Infections
    a. Prevention: applying powder containing miconazole (Monistat) or tolnaftate (Tinactin) to areas prone to fungal infections after bathing and blow drying on low temperature
    b. Avoid infection via contaminated soil?? Exposure to animals or people w/ active infection (pets)?? showers and pools?? shared towels or clothing ??

12. Drug Therapy GOT for Fungal Infections
    a. Meds are directed against the offending fungus and site of infection; may be topical or systemic depending on location of lesions
    b. prevent re-infection
        i. contaminated soil? Exposure to animals or people w/ active infection (pets), showers and pools, shared towels, or clothing
    c. Return to work (return to daycare, or/and school) once RX is started; avoid contact sports for 72 hours after RX started. Cover wound also.

13. Topical Azole Antifungals
    a. MOA: work by pairing the synthesis of ergosterol, the main sterol of fungal cell membranes, allowing for increased permeability and leakage of cellular components, resulting in cell death.

    b. INDICATIONS: effective against tinea corporis, tinea cruris, and tinea pedis as well as cutaneous candidiasis.

    c. COMMON DOSAGE: applied once or twice a day for 2 to 4 weeks. Therapy should continue for 1 week after the lesions clear.

14. Topical Allylamine Antifungals
    a. MOA: effective against dermatophyte infections but have limited effectiveness against yeast

    b. COMMON DOSAGE: shorter treatment period with less likelihood of relapse; applied twice daily

c. ADRs: burning and irritation

15. Systemic Azoles and Other Antifungals
    a. INDICATION: Oral antifungals used to treat superficial infections caused by yeasts (Candida, pityriasis versicolor) and dermatophytes (tinea infections) and invasive systemic mycoses
    b. MEDS:
        i. Polyene macrolides
            1. amphotericin B and nystatin
        ii. Azoles with broad-spectrum activity
            1. butoconazole, clotrimazole, ketoconazole, miconazole, terconazole, tioconazole, fluconazole, itraconazole
                a. Absorption of itraconazole is enhanced by food.
                b. Fluconazole is an inhibitor of cytochrome 3A4 (CYP3A4) and CYP2C9. Requires loading dose.
                c. Itraconazole & ketoconazole are inhibitors of CYP3A4.
                d. Fluconazole: has the fewest drug interactions but there is growing resistance
                e. Ketoconazole monitoring: LFTs (AST, ALT, ALK P and bilirubin) before starting and every 3 to 4 months
        iii. Allylamines active against yeast and dermatophytes
            1. naftifine, terbinafine
        iv. Nuclear acid synthesis inhibitors
            1. flucytosine
        v. Griseofulvin
            1. Absorption is enhanced by fat intake at time of ingestion
        vi. ADRs
            1. Azoles & terbinafine (all meds in class) associated w/ hepatotoxicity.
        vii. Drug interactions
            1. CYP3A4 inhibition causes many interactions

16. Systemic Allylamine Antifungals
    a. MOA: inhibits squalene epoxidase, a key enzyme in fungal biosynthesis, causing a deficiency of ergosterol causing fungal cell death
    b. COMMON DOSAGES: fingernail onychomycosis: 250 mg/d for 6 weeks; toenail onychomycosis: 250 mg/d for 12 weeks
    c. ADRs: diarrhea, dyspepsia, rash, increase in liver enzymes, and headache
    d. MED Interactions: potentiated by cimetidine (Tagamet) and antagonized by rifampin (Rifadin)

17. Systemic Azole Antifungals

a. MOA: inhibit cytochrome P-450 (CYP) enzymes and fungal 14-a-demethylase, inhibiting synthesis of ergosterol. Systemic therapy is required for tinea capitis and tinea unguium.
b. COMMON DOSAGES: dosage of itraconazole is 200 mg once daily for 12 weeks for toenail infection.
    i. For fingernail infection, the dose is 200 mg twice daily for 1 week, then 3 weeks off, and repeat dosing with 200 mg twice daily for 1 week.

18. Griseofulvin
    a. MOA: deposits in keratin precursor cells increasing new keratin resistance to fungal invasion.
    b. ADRs: nausea, vomiting, diarrhea, headache, or photosensitivity.
    c. MED Interactions: increases levels of warfarin (Coumadin) and decreases levels of barbiturates and cyclosporine (Sandimmune).
        i. It may decrease the efficacy of oral contraceptives and may cause a serious and unpleasant reaction with alcohol.

19. Candidiasis (C. albicans)
    a. Superficial fungal infection of the skin and mucous membranes.
        i. occurs on moist cutaneous sites in people with infection or diabetes, or using systemic and topical corticosteroids, and with immunosuppression.
        ii. invades the epidermis when warm, moist conditions prevail.
        iii. Diagnostic criteria
            1. red, moist papules, or pustules found in the axillae, inframammary areas, groin, and between the fingers and toes.
        iv. Order of treatment
        v. 1ST line: cool soaks with Burow solution, topical azole for 10 days, oral nystatin
        vi. 2NDline: itraconazole (Sporanox) or fluconazole (Diflucan)

20. Tinea Versicolor (Pityriasis Versicolor)
    a. An opportunistic superficial yeast infection
    b. overgrowth of the hyphal form of Pityrosporum ovale; occurs mostly in subtropical and tropical areas
    c. an enzyme oxidizes fatty acids in the skin surface lipids, forming dicarboxylic acids, which inhibit tyrosinase in epidermal melanocytes and cause hypomelanosis
    d. Diagnostic criteria
        i. well-defined skin lesions, round, or oval macules with an overlay of scales forming on the trunk, upper arms, and neck with mild itching; confirmed by positive KOH test
    e. Drug Selection:
        i. 1ST line: selenium sulfide solution 1% or 2.5% topical azole cream or spray for localized lesions
        ii. 2ND 2NDline: itraconazole (Sporanox)

21. Patient Education for Tinea
    a. Teach hygiene and ways to avoid transferring fungal infection to others.
    b. Complete the full course of treatment and do not stop treatment when symptoms subside.
    c. Inform parents and other caregivers that children can attend school while being treated.
    d. Dry areas susceptible to fungus with a hair dryer after bathing.
    e. Use antifungal powder and sprays for prophylaxis.

22. Patient education Azoles
    a. Instruct to take with food.
    b. Discourage alcohol use.
    c. Educate regarding signs of liver toxicity.

23. Complementary and Alternative Medicine
    a. Apple cider vinegar
    b. Plain yogurt
    c. Tea tree oil
    d. Vitamin C

Resources

Various sources are paraphrased and combined to provide most up to date information
Arcangelo. (2020). Pharmacotherapeutics for Advanced Practice – 4th ed.
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FamilyPracticeNotebook.com (various topics)
Up to date (various topics)
Woo, T., & Wynne, A. (2021). Pharmacotherapeutics for Nurse practitioner Prescribers -5th ed.