Contemporary Management of Onychomycosis

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Pharmacist Objectives

• Summarize the current treatment approach for the treatment of onychomycosis.
• Compare and contrast the new topical antifungals to oral antifungals used for the treatment of onychomycosis.
• List counseling points for the medications used to treat onychomycosis.

Technician Objectives

• Define onychomycosis.
• List names of and routes of administration for medications used to treat onychomycosis.
• Explain to patients how to administer efinaconazole and tavaborole.

Onychomycosis

• Fungal infection of the nails
• Tinea Unguium

The Nails

• Affects the entire nail unit (matrix, bed, plate)
• Made up of protein; a form of modified hair
• Grow at an average rate on 0.1mm/day
• Fingernails require 3-6 months to regrow completely
• Toenails require 12-18 months to regrow completely
Onychomycosis
- Caused by a fungal organism
- Primary or secondary infection
- Chronic condition because of high relapse/recurrence
- Infection transmitted by direct contact with infected host or contact with infected object

Fungi Characteristics
- Eukaryotes (have a nucleus)
- Unicellular (yeasts) or multicellular (molds)
- Live in soil/dead matter
- Symbions and parasites
- Most multicellular fungi grow as hyphae 2-10 mm diameter, several cm in length
- Noticeable when fruiting (mushroom/mold)

Use of Fungi
- Essential role in decomposing organic matter
- Source of food (mushroom)
- Leavening for bread (yeast)
- Fermentation of wine/beer (yeast)
- Production of antibiotics
- Probiotics (yeast)

Classification of Fungi
- Kingdom: fungi
- Phyla: 7
  - Ascomycota: largest, contains:
    - Mushrooms, unicellular yeasts (Saccharomyces, Candida), molds (Aspergillus, Trychophyton)
  - Basidiomycota: most common mushrooms, Cryptococcus

Dermatophytes
- Common labeling for 3 genera of fungi that cause skin infections
  - Microsporum, Epidermophyton, Trichophyton (T. rubrum, T. mentagrophytes)

Microbiology
- Toenail infections
  - Dermatophyte (90%)
  - Other molds
- Fingernail infections
  - Dermatophyte (50%)
  - Candida
**Epidemiology**
- Prevalence is 5-10%
- Represents 50% of all nail problems
- Constitutes 30% of all dermatophyte infections
- Affects all ethnicities

**Risk Factors**
- Older age
- Poor circulation
- Peripheral arterial disease
- Diabetes mellitus
- Tinea pedis
- Psoriasis
- Suboptimal immune function
- Repeated nail trauma
- Inability to cut nails or maintain good foot care
- Inactivity
- Smoking

**Impact**
- Previously thought to be just a cosmetic problem
- Causes pain/disfigurement, affects ADLs/QOL
- Limits mobility of hand
- Compromises peripheral circulation, so poor wound healing
- Can lead to foot ulcers in diabetics

**Signs/Symptoms**
- Thickened/discolored nails (white, black, yellow, green) that separate from nail bed
- Brittle nails
- Painful and inflamed skin surrounding nail
- Foul smell

**Classification**
- Distal subungual
  - Most common; affects nail bed and underside of nail plate
- White superficial
  - 10%; affects superficial layer of nail plate
- Proximal subungual
  - Least common; affects newly formed nail plate
- Candidal
  - Occurs mostly in chronic mucocutaneous candidiasis
  - Generally infects all fingernails

**Diagnosis**
- >50% of fungal-looking nails do not have fungal infection
  - Cannot diagnose onychomycosis by visualization alone
- KOH smear
  - Quick ID of fungi
- Culture
  - Gold standard
  - Delayed ID of organism
Patterns of Infection

Distal Subungual

White Superficial

Proximal Subungual

Candidal

Prevention

• Keep nails short
• File down hypertrophic nails
• Keep foot cool and dry
• Wear properly fitted shoes
• Avoid using same instruments on infected and noninfected nails
• Apply antifungal powder daily
• Use appropriate gloves for work
Treatment

- Goal is complete cure
- Non-pharmacological
  - Buffing/filing nails
  - Surgical/chemical removal of nail plate
  - Laser
- Pharmacological
  - Topical
  - Systemic

Duration of Treatment

- Long (3-12 months)
- Nails have slow growth, reduced blood supply

Topical Antifungals

- Not as effective as oral therapy
- Efficacy limited by their nail plate penetration and ability to maintain a sustained concentration above the MIC for the infecting fungus
- Indicated for:
  - Superficial white onychomycosis
  - Distal subungual affecting <50% of surface area without matrix involvement
  - If few nails are infected
  - Children with thin, fast-growing nails

Traditional Topical Treatments

- Allylamines (naftifine, terbinafine)
- Azoles (miconazole, ketoconazole)
- Ciclopirox
- Organic acids (salicylic acid)
- Nystatin
- Potassium permanganate
- Tolnaftate

Ciclopirox 8% (Penlac)

- Chelates polyvalent cations involved in fungal enzymatic activity, exerting antifungal, antibacterial, and anti-inflammatory effects; fungicidal
- 7% clinical cure rate (32% mycological cure rate) after 6-12 months of treatment

Ciclopirox Continued

- Applied nightly (>8hrs before washing) for up to 48 weeks
- Must clean nail with alcohol weekly
- Must get monthly unattached nail debridement/trimming
- Side effects include rash, erythema, ingrown toenail
- Consider for:
  - Patients with superficial white onychomycosis
  - Infection of nail tip only
  - Patients who can't or won't use oral therapy
Contemporary Topical Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose - Toenails (complete cure rate)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Efinaconazole (Jublia)</td>
<td>10% solution</td>
<td></td>
</tr>
<tr>
<td>Tavaborole (Kerydin)</td>
<td>5% solution</td>
<td></td>
</tr>
</tbody>
</table>

- Apply 1-2 drops to each affected toenail once daily for 48 weeks (17%) for Efinaconazole.
- Apply to each affected toenail once daily for 48 weeks (<10%) for Tavaborole.

- Indicated if ≤50% of toenail involved or pts who can't/won't use oral therapy.
- Mycological cure rates are significantly higher (30-70%) than complete cure rates.
- Have excellent nail penetration.

Efinaconazole (Jublia)

- FDA approved in 2014
- Topical triazole antifungal
  - Inhibits fungal cell membrane synthesis
- Effective against *T. rubrum*, *T. mentagrophytes*, and *Candida*
- Approval based on 2 trials

Tavaborole (Kerydin)

- FDA approved in 2014
- Topical oxaborole antifungal
  - Blocks fungal protein synthesis
- Effective against *T. rubrum*, *T. mentagrophytes*
- Approval based on 2 trials

Efinaconazole, Tavaborole Side Effects

- Efinaconazole
  - Ingrown toenail (2%)
  - Application site dermatitis (1-2%)
- Tavaborole
  - Ingrown toenail (2.5%)
  - Application site exfoliation (2.7%)

Efinaconazole, Tavaborole Patient Counseling

- Compliance with long duration of therapy
- Apply to clean, dry nails
- Efinaconazole:
  - Do not apply within 10 minutes of bathing
  - Drops should be spread with built-in flow-through brush applicator to cover entire nail, cuticle, and skin folds on sides of nail
- Tavaborole:
  - Apply adequate amount to entire nail surface and under tip of nail
  - Wipe away excess solution on surrounding skin
Topical Therapy and Nail Polish

- Ciclopirox – No
- Efinaconazole/tavaborole – Yes
  - Penetration and efficacy not affected
  - Can be applied over nail polish
  - Medication may affect transfer of nail polish color to socks/shoes

Systemic Treatment

- Historical treatment: griseofulvin, ketoconazole
  - Ketoconazole should not be used
    - Linked to serious liver damage, adrenal insufficiency, and harmful drug interactions
- Newer agents have shorter duration of therapy, higher clinical and mycologic cure rates, lower probability of relapse, less side effects, more favorable nail kinetics, less drug interactions
  - Fluconazole, itraconazole, terbinafine
- Indicated for >50% nail involvement or no response after 6 months of topical therapy

Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fingernails Dose</th>
<th>Toenails Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole (Diflucan) (off-label)</td>
<td>150-300mg Qweek X 6 months</td>
<td>150-300mg Qweek X 6-12 months</td>
</tr>
<tr>
<td>Itraconazole (Sporanox)</td>
<td>200mg BID X 1 week/month X 2 months</td>
<td>200mg daily X 12 weeks or 200mg BID X 1 week/month X 3 months (pulse dose off-label)</td>
</tr>
<tr>
<td>Terbinafine (Lamisil)</td>
<td>250mg daily X 6 wks</td>
<td>250mg daily X 3 months</td>
</tr>
</tbody>
</table>

Complete cure rates 15-50%; Clinical and mycological cure rates >50%

Terbinafine (Lamisil)

- Allylamine
- Inhibits squalene epoxidase, reducing fungal cell membrane in the ergosterol synthesis
- Fungicidal and fungistatic

Itraconazole (Sporanox)

- Triazole
- Inhibits lanosterol 14 alpha-demethylase, thus inhibiting CYP450-dependent ergosterol synthesis
- Fungistatic
- Accumulates, so can give as pulse therapy
- More effective against Candida than terbinafine

Fluconazole (Diflucan)

- Triazole
- Same MOA as itraconazole
- Fungistatic
- Shorter residual concentration results in longer duration of therapy
- Duration of therapy recommended to be until disease nail plate has grown out
- Not FDA-approved for onychomycosis
Systemic Therapy

Side Effects\textsuperscript{9,13}

- GI, rash, increased liver enzymes
- Fluconazole: QT prolongation, PC D
- Itraconazole: increased triglycerides, edema, peripheral neuropathy, PC C (CI for onychomycosis treatment)
- Terbinafine: photosensitivity, sensory changes, BMS, PC B
- Avoid use in lactation

Contraindications\textsuperscript{9,13}

- Fluconazole: pregnancy 1\textsuperscript{st} trimester
- Itraconazole: pregnancy, HF, liver disease
- Terbinafine: CrCl <50ml/min, liver disease, lactation, ANC <1000

Drug Interactions\textsuperscript{9}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substrate of Inhibitor of Fluconazole</th>
<th>Inhibitor of Itraconazole</th>
<th>Inhibitor of Terbinafine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>---</td>
<td>1A2, 2C9, 2C19, 3A4</td>
<td>3A4, PGP</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>3A4</td>
<td></td>
<td>1A2, 2C9, 2C19, 3A4</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>1A2, 2C9, 2C19, 3A4</td>
<td>3A4</td>
<td>2D6</td>
</tr>
</tbody>
</table>

Itraconazole + statins: atorvastatin 20mg QD, avoid simvastatin

Monitoring\textsuperscript{9,13}

- Compliance, efficacy, side effects, drug interactions
- Mycological culture at 3 and 6 months to assess efficacy
- Baseline, periodic liver enzymes
- SCr at baseline
- Terbinafine: CBC if >6 week treatment in immune-deficient patient

Patient Counseling\textsuperscript{9,13}

- S/Sx hepatotoxicity
- Compliance for long duration of therapy
- Itraconazole: take capsules after meals and suspension on an empty stomach

Cost of Treatment for Onychomycosis of Toenail\textsuperscript{14}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment Duration</th>
<th>Approximate Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine (oral)</td>
<td>12 weeks</td>
<td>$10</td>
</tr>
<tr>
<td>Ciclopirox (topical)</td>
<td>48 weeks</td>
<td>$15</td>
</tr>
<tr>
<td>Fluconazole (oral)</td>
<td>52 weeks</td>
<td>$130</td>
</tr>
<tr>
<td>Itraconazole (oral)</td>
<td>12 weeks</td>
<td>$350</td>
</tr>
<tr>
<td>Efinaconazole (topical)</td>
<td>48 weeks</td>
<td>$2500</td>
</tr>
<tr>
<td>Tavaborole (topical)</td>
<td>48 weeks</td>
<td>$4000</td>
</tr>
</tbody>
</table>
2014 British Association of Dermatologists’ Guidelines for the Management of Onychomycosis

Treatment in Adults

- A: Terbinafine, Itraconazole
- B: Fluconazole
- C: Griseofulvin
- D: Combination treatment, ciclopirox, efinaconazole

Treatment in Children (1-12 years)

- A: Terbinafine, Itraconazole
- B: Fluconazole
- C: Griseofulvin

Systemic Therapy Recommendations

- Terbinafine
  - 1st line, especially in DM and if caused by dermatophyte or non-dermatophyte mold
- Itraconazole
  - 2nd line if caused by dermatophyte
  - 1st line if mixed infection or if caused by Candida spp.
- Fluconazole
  - Consider in fingernail infection
  - Consider if fail/intolerant of/have contraindication to 1st/2nd line systemic therapy for toenail infection

Topical Therapy Recommendations

- Usually not considered before systemic therapy
- Consider if patient fails, is intolerant of, or refuses oral therapy
- Ciclopirox
  - Infection of nail tip only
- Efinaconazole
  - Infection of toenails <50% involvement
  - Preferred topical agent based on efficacy and cost
- Tavaborole
  - Infection of toenails <50% involvement

Future of New Topical Therapies?

- May become preferred first line topical agents when <50% nail is infected
- May be a useful adjunct to systemic therapies as dual therapy
- May be useful to prevent recurrence after treatment with systemic therapy
Summary

- Types of onychomycosis
- Treatment options
- Duration of treatment
- Monitoring parameters
- Counseling points

References

14. Prices found at GoodRx.com, accessed 5/24/16.

Questions

• FT is a 65 year old white male with DM, HTN, CAD.
• Meds: metformin 1g BID, atorvastatin 40mg QD, aspirin 81mg QD, lisinopril 20mg QD, metoprolol XL 50mg QD, and nicotine patch 14mg QD.
• He presents to the pharmacy with a prescription for a medication to treat his distal subungual onychomycosis of the big toenail, which has about 40% involvement.

Case Questions

• Which of the following medications would be an appropriate treatment for FT’s onychomycosis?
  - Itraconazole, fluconazole, terbinafine PO, efinaconazole, tavaborole, ciclopirox
• If FT were treated with itraconazole, would he require any other medication changes?
• If FT were treated with itraconazole, what would be the dose/duration?
• What counseling points should be discussed with FT regarding itraconazole?

Case Questions Continued

• Would terbinafine or fluconazole be a better choice for FT? Why?
• If FT desired topical therapy, what do you think would be the best option?
Other Questions

• What are the most common fungal organisms that cause onychomycosis?
• How is onychomycosis usually diagnosed?
• What are the 4 most common types of onychomycosis?
• Why does onychomycosis require a long duration of treatment?

Pharmacist CE Question 1

• Which of the following medications requires dose adjustment, but does not need to be avoided for patients on itraconazole (Sporanox) for the treatment of onychomycosis?
  – Atorvastatin (Lipitor)
  – Rosuvastatin (Crestor)
  – Simvastatin (Zocor)
  – Pravastatin (Pravachol)

Pharmacist CE Question 2

• GH is a 50 year old patient who is diagnosed with proximal subungual onychomycosis of her toenails, with 90% involvement. Which of the following would be the best treatment option for GH?
  – Tavabarole (Kerydin)
  – Terbinafine (Lamisil) PO
  – Ciclopirox (Penlac)
  – Efinaconazole (Jublia)

Pharmacist CE Question 3

• Which of the following is an appropriate counseling point for a patient being started on efinaconazole (Jublia)?
  – Apply immediately after bathing
  – Apply to nail only; avoid applying to skin folds near nail
  – Apply 1-2 drops to cover entire nail with included nail brush
  – Wash medication off nails before bedtime

Pharmacist CE Question 4

• Which of the following represents guideline-based recommended first line treatment options for onychomycosis?
  – Efinaconazole, terbinafine PO
  – Itraconazole, fluconazole
  – Fluconazole, terbinafine PO
  – Itraconazole, terbinafine PO

Technician CE Question 1

• Which of the following best defines onychomycosis?
  – Fungal infection of the toe or fingernails
  – Bacterial infection of the toe or fingernails
  – Viral infection of the toe or fingernails
  – Parasitic infection of the toe or fingernails
Technician CE Question 2

• Which of the following medications is recommended for the outpatient treatment of onychomycosis?
  – Nystatin topical
  – Terbinafine PO
  – Amoxicillin PO
  – Triamcinolone topical

Technician CE Question 3

• Which of the following is an appropriate counseling point for a patient being started on efinaconazole (Jublia)?
  – Apply immediately after bathing
  – Apply to nail only; avoid applying to skin folds near nail
  – Apply 1-2 drops to cover entire nail with included nail brush
  – Wash medication off nails before bedtime

Technician CE Question 4

• What is the route of administration for tavabarole (Kerydin)?
  – Oral
  – Subcutaneous
  – Topical patch
  – Topical solution