MANAGING ONYCHOMYCOSIS: NEW APPROACHES

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Conflict of Interests:
Disclosures of Financial Relationships with Industry
• Clinical Research: Grants to University
  - Dusa, Meiji, Valeant, Viamet
• Consultant- Received Honorarium
  - Anacor, Valeant
NO SPEAKER BOARDS OR STOCKHOLDER

OBJECTIVES
• Understand the clinical and laboratory diagnosis of onychomycosis
• Know the differential diagnosis of onychomycosis
• Be familiar with the oral and topical treatment of onychomycosis and which treatment is best for which patient
• Laboratory monitoring: to do or not to do

DIAGNOSIS OF ONYCHOMYCOSIS

PEARLS

HALF OF ABNORMAL NAILS HAVE FUNGUS

THE OTHER HALF DO NOT!
Diagnosis of Onychomycosis

• **LABORATORY DIAGNOSIS**
  - PAS
  - KOH, fungal culture

• **CLINICAL DIAGNOSIS**
  - Clinical signs of onychomycosis

NEW DEVELOPMENTS IN PCR ANALYSIS WILL IMPROVE DIAGNOSIS

- Presence or absence of fungal elements
  - KOH/ calcofluor
  - PAS stain

- Fungal identification
  - Fungal culture
  - PCR analysis

KOH POSITIVE CALCOFLUOR WHITE STAIN

PAS STAIN POSITIVE FOR SEPTATE HYPHAE

What About Diagnosis? Is There a Controversy?

• Empirc treatment with terbinafine for patients with suspected onychomycosis is more cost effective than confirmatory testing with minimal effect on safety
• Confirmatory testing before efinaconazole will reduce costs across a range of disease prevalence

TREAT EMPIRICALLY WITH ORAL TERBINAFINE

Mikaliov A et al JAMA Derm 2015 online Dec 23

If PAS positive for hyphae, diagnosis is confirmed

Yeast cells and spores do not count!
MANAGEMENT BEGINS WITH BEDSIDE DIAGNOSIS

- **LOOK FOR**: Distal onycholysis with subungual debris in toenails
  - Thick nail plate alone not diagnostic!
- **OBSERVE**: Evidence of tinea pedis, presence of dermatophytoma
- **ASK ABOUT**: Present or past history of tinea pedis in patient and family members and risk factors - pedicures, gymnasiums, military history

DISTAL LATERAL SUBUNGUALONYCHOMYCOSIS

DERMATOPHYTOMA - STREAKS AND PATCHES ARE FUNGAL ABSCESSES

LOOK FOR EVIDENCE OF TINEA PEDIS

PEARL...

NO TINEA PEDIS = NO ONYCHOMYCOSIS

TINEA PEDIS MAY NOT BE OBVIOUS!

Look for Collarettes of Scale in T. Rubrum Tinea Pedis
…LOOK HARDER
Look for Collarettes of Scale in Tinea Pedis

ABNORMAL FINGERNAILS- LOOK AT TOENAILS

ABNORMAL FINGERNAILS WITH NORMAL TOENAILS UNLIKELY ONYCHOMYCOSIS

DIFFERENTIAL DIAGNOSIS

LICHEN PLANUS
TUMOR-ONYCHOMATRICOMA
TRACHYONYCHIA
ONYCHOPHYNOSIS
PSORIASIS

DIAGNOSIS OF ONYCHOMYCOSIS
• Half of abnormal nails have onychomycosis
• KOH, PAS and fungal culture diagnostic but expensive
• Bedside diagnosis- look for tinea pedis, distal onycholysis, dermatophytoma
• Abnormal fingernails - look at toenails; onychomycosis more common in toenails.

YELLOW NAIL SYNDROME
TREATMENT OF ONYCHOMYCOSIS

PELARS

CURRENT TREATMENT OF ONYCHOMYCOSIS

ORAL DRUGS
- Terbinafine
- Itraconazole
- Fluconazole*

TOPICAL DRUGS
- 10% efinaconazole solution
- 5% tavaborole solution
- 8% ciclopirox lacquer

* not FDA approved

DEVICES
- Laser
- PDT*

TOPICAL ONYCHOMYCOSIS TREATMENT

SOLUTIONS:
- Efinaconazole 10%
- Tavaborole 5%
- Non-lacquer alcohol based therapies can be delivered on, under and around the nail bed

Topical Treatment of Onychomycosis

- Preferred by many patients
  - NO systemic side effects
  - No need for laboratory monitoring
- Topical formulations can be applied direct to infection-lacquers and solutions
- Efinaconazole 10% and Tavaborole 5% are both solutions
- Lacquers- ciclopirox and amorolfine not new therapies

EFINACONAZOLE

- Triazole antifungal
  - New molecule
- Broad spectrum antifungal with activity against yeasts, molds and dermatophytes

Efinaconazole Mycologic Cure Week 52

Study P3-01

Study P3-02

Mycologic cure mimics clinical experience
**Mycologic Cure Rates (Pooled Data)**

- Week 48: Efinaconazole 10% Solution: 40%hz, Itraconazole: 50%, Terbinafine: 60%
- Week 52: Efinaconazole 10% Solution: 50%, Itraconazole: 60%, Terbinafine: 70%

Source: package insert terbinafine and itraconazole

**Complete Cure-Lags Behind**

- Week 12: Efinaconazole 10% Solution: 10%, Itraconazole: 20%, Terbinafine: 30%
- Week 24: Efinaconazole 10% Solution: 20%, Itraconazole: 30%, Terbinafine: 40%

**Efinaconazole 10% Solution:** Examples of Complete Cure at Week 52

- Week 24: 5% cure
- Week 52: 0% cure

**Tavaborole Study Design**

- Similar to efinaconazole study design: applied once daily for 48 weeks in mild to moderate disease
- Differences in studies:
  - No upper age limit in tavaborole study
  - Nails were 20-60% involved in tavaborole vs. 20-50% in efinaconazole

**Tavaborole 5% Solution:** Outcome Measures at 52 Weeks

- Complete Cure: Tavaborole 24.4%, Efinaconazole 24.2%, Itraconazole 23.0%
- Mycologic Cure: Tavaborole 35.9%, Efinaconazole 33.5%, Itraconazole 32.5%
**COMPLETE CURE LAGS BEHIND MYCOLOGICAL CURE**

- **Tavaborole Solution: Some Failures are Treatment Successes**
- **Efficacy and safety of tavaborole topical solution.** *JAAD* 73:62–69, 2015

**TAIRILURES: AT STUDY COMPLETION: LESSON LEARNED**

NAIL MAY NEVER BE NORMAL BUT FUNGUS IS **NOT** PRESENT

**FAILURES** AT STUDY COMPLETION: TREAT WITH TOPICAL STEROID SOLUTION TO HELP NAIL ATTACH
ORAL ANTIFUNGAL THERAPY

**TERBINAFINE**

- **Onychomycosis:**
  - **Wk1, Wk2, Wk3, Wk4:** 250 mg/d
  - **Month 1, Month 2, Month 3, Month 4:**
    - **Toenail/Fingernail:**
      - 3 MONTHS DAILY FOR TOENAILS, AND 6 WEEKS FOR FINGERNAILS
      - JAAD 1997; 37:740-45, Drake et al
      - 38% cure rate for 3 months

- **Terbinafine “Pulse” Dosing**
  - Zais and Rebell published 250 mg daily for one week, then 250 mg daily for every other OR third month, until nail is healthy.
    - Arch Dermatol 2004; 140 (6): 691-695
  - Other dosing regimens: 500 mg daily for one week, repeated monthly for 3 months or “pulses”
    - JAAD 2005; 53 (4): 578-584
  - ALCOHOL ANALOGY
  - OFF LABEL THERAPY

- **Itraconazole**
  - **Wk1, Wk2, Wk3, Wk4:** 400 mg/d
  - **Month 1, Month 2, Month 3, Month 4:**
    - **Toenail/Fingernail:**
      - 14% COMPLETE CURE

- **Fluconazole**
  - **Wk1, Wk2, Wk3, Wk4:**
    - 48% complete cure 450 mg/week
    - 46% complete cure 300 mg/week
    - 37% complete cure 150 mg/week
  - NOT FDA APPROVED FOR THIS INDICATION

- **TITRATE DOSAGE BETWEEN 200 MG TO 400 MG WEEKLY**

**NOTES:**

- Once weekly dosing
- Parallels the slow nail growth
- Manages patient expectations
PHASE 3 CLINICAL STUDIES

<table>
<thead>
<tr>
<th>COMPLETE CURE</th>
<th>MYCOLOGIC CURE</th>
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<tbody>
<tr>
<td>Terbinafine</td>
<td>38%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>14%</td>
</tr>
<tr>
<td>Meltrex itra</td>
<td>22%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>37-48%*</td>
</tr>
<tr>
<td><strong>Fluconazole not FDA approved for onychomycosis</strong></td>
<td>47%-62%*</td>
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**Data Per Package label**

**NOT ALL PATIENTS ARE CURED**

Complete cure = normal nail, myc cure

Nails With High Failure Rates: Oral Plus Topical May be Helpful

**WHAT ABOUT SEVERE INFECTIONS?**

- Should we use oral antifungal agents such as terbinafine when "severe" infections are present?
- Or in diabetics?

**NOT NECESSARILY**

BASELINE

FAILED ORAL TERBINAFINE
CULTURED T. RUBRUM
DERMATOPHYTOMA PRESENT
SO NOT ELIGIBLE FOR TOPICAL STUDY

DIABETICS AND NON-DIABETICS DID THE SAME

BASELINE

TOPICAL EFIRACONAZOLE
UNDER AND AROUND THE NAIL
After three months, the treatment eventually went on to complete cure.

**Use Topical and Oral Drugs Concomitantly to Enhance Cures with Dermatophytomas**

Eventually became cured with continued treatment after 5 months of therapy.

**When Are Oral Antifungals Needed?**

- Immunocompromised patients
  - Includes those on biologics for psoriasis
- Matrix involvement
- Both fingernails and toenails infected
- Most patients with psoriasis who also have onychomycosis (almost 30%)

**Treatment of Onychomycosis Pearls**

- Topical solutions can be applied on, under and around infected nails
- Topical antifungals do not cure every patient
- Oral antifungal drugs do not cure every patient
- Oral plus topical antifungal may be effective
- Mycological cured nails that are close to clinically cured may benefit from topical steroid solutions
- Intermittent dosing may be safer than daily

**Other Considerations: Common Comorbidities that Prevent Normal Nails**

- Psoriasis
  - High prevalence (about 30%) of onychomycosis with psoriatic toe nails
- Nail tumors and structural abnormalities
  - Onychomatricoma
  - Pincer nails
  - Yellow nail syndrome
  - Prior nail trauma
  - Onychogryphosis

**Laboratory Monitoring Pearls**
Laboratory Monitoring: To Do or Not to Do?

- Hepatic risk for Terbinafine: 1:50K to 120K
  - idiopathic
- Trend away from routine monitoring
  - Isotretinoin
  - Spironolactone
  - Terbinafine

Mikailov A JAMA Derm 2015
Kander MK JAMA Derm 2015 online Dec 23

Laboratory Monitoring Controversy

- Baseline hepatic panel and CBC for terbinafine, itraconazole and fluconazole: is this needed?
  - Trend is away from routine monitoring
  - Liver injury is very rare
  - Most common cause of drug induced hepatitis is trimethoprim-sulfamethoxazole
  - Pulse dosing likely safer- alcohol analogy

Kander MK JAMA Derm 2015 online Dec 23

Reevaluating the Need for Laboratory Testing in Onychomycosis Treatment

- 3 cases of liver injury from short term exposure (less than 2 weeks) have been reported in the Drug-Induced Liver Injury database- pulse dosing safer? Alcohol analogy
- Trend away from periodic monitoring as long as no history of pre-existing liver disease
- Other drugs which are trending away from periodic monitoring include isotretinoin and spironolactone

JAMA DERM Kander MH; online Dec 23 2015

Oral Antifungal Therapy: Cost Considerations

- Terbinafine is the least expensive oral antifungal drug followed by fluconazole then itraconazole
- The cost of oral antifungal therapy is less than topical antifungal therapy
- The most expensive drug is the one that does not work so choose your therapy carefully

Which nail has onychomycosis?

Onychomycosis Diagnosis and Treatment: KEY POINTS

- Diagnosis: PAS, KOH and fungal culture
- Bedside diagnosis: tinea pedis, distal onycholysis, dermatophytomas on toenails
- Topical efinaconazole and tavaborole solutions offer options to patients
- Laboratory monitoring - may not be necessary
- Oral therapy is significantly less costly than topical therapy
THE END