NAILS: TALES, FAILS AND WHAT PREVAILS IN TREATING ONYCHOMYCOYSIS

(AND OTHER BOARD RELEVANT INFORMATION)

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Orlando, Florida
10.18.15
A) Onychodystrophy
B) Onychogryphosis
C) Onychomycosis
D) All the above
E) None of the above
Nail development begins at 8-10 weeks EGA
- Complete by 5th month
- Keratinization ~11 weeks
- No granular layer

Nail plate growth:
- Fingernails 3 mm/month, toenails 1 mm/month
- Faster in summer or winter?
  - Summer!
- Index finger or 5th digit nail grows faster?
  - Index finger!
- Faster growth to middle or lateral edge of each nail?
  - Lateral!
Nail anatomy
Pitting: psoriasis, eczema, aa

Elkonyxis
Nails and systemic disease

- Mee’s lines
- Aka leukonychia striata
  - Arsenic poisoning
  - Trauma
  - Medications
  - Illness
  - Psoriasis flare
Nails and systemic disease

- Muerhrcke’s bands
  - Hypoalbuminemia
  - Chemotherapy
Nails and systemic disease

- Half & half nails
- Aka Lindsay’s nails
  - Chronic renal disease
Nails and systemic disease

- Terry’s nails
  - Liver failure, Cirrhosis
  - Malnutrition
  - Diabetes
  - Cardiovascular disease
Abstract

Yellow nail syndrome (YNS) is a well-defined syndrome with a characteristic appearance, nail changes, and an association with underlying disease. It is often characterized by clubbing, lymphedema, and pleural effusion. The etiology of YNS is not fully understood, but it is thought to be related to a defect in the lymphatic system. The syndrome is more common in older adults and is associated with chronic lung disease, connective tissue disorders, and malignancy.

Case Description and Treatment

A 60-year-old man presented with clubbing and lymphedema in his lower extremities. His chest x-ray showed bilateral pleural effusions. A video-assisted thoracoscopic surgery (VATS) was performed to drain the effusions. Histological examination of the lung tissue revealed a lymphocyte predominant mediastinal lymphoma. The patient was diagnosed with lymphoepithelioma-like carcinoma of the lung.

Discussion

YNS is an intriguing and rare syndrome that can be challenging to diagnose. The presence of clubbing and lymphedema should raise suspicion for YNS, and further evaluation should be performed to rule out underlying disease. Treatment varies depending on the underlying cause, but often involves surgical drainage of pleural effusions and chemotherapy for lymphoma.

Keywords: lung cancer, pleural effusion, lymphedema.
True or False: Onychomycosis = Tinea Unguium?  
- FALSE.

Onychomycosis:
- A fungal disease of the nails (all causes)
  - Dermatophytes, yeasts, molds

Tinea unguium:
- A fungal disease of nail caused by dermatophyte fungi

Onychodystrophy ≠ onychomycosis
Why Onychomycosis?

- Accounts for up to 50% of all nail disorders
- Prevalence; 14-28% of > 60 year-olds
- Variety of subtypes; know them!
- Sequelae
What is the most common cause of onychomycosis?
A) Epidermophyton floccosum
B) Microsporum spp
C) Trichophyton mentagrophytes
D) Trichophyton rubrum

- Account for ~90% of infections
Onychomycosis usual suspects...

- **Dermatophytes**
  - *Trichophyton rubrum*
  - *Trichophyton mentagrophytes*
  - *Trichophyton tonsurans, Microsporum canis, Epidermophyton floccosum*

- **Nondermatophyte molds**
  - *Acremonium spp, Fusarium spp*
  - *Scopulariopsis spp, Sytalidium spp, Aspergillus spp*

- **Yeast**
  - *Candida parapsilosis*
  - *Candida albicans*
  - *Candida spp*
Onychomycosis subtypes

- Distal/lateral subungual onychomycosis (DLSO)
  - Most common; T. rubrum

- Superficial white onychomycosis (SWO)
  - T. mentagrophytes (var. interdigitale)
  - T. rubrum (immunosuppressed)

- Proximal subungual onychomycosis (PSO)
  - Often in immunosuppressed patients
  - T. rubrum
  - T. Megninii

- Candidal onychomycosis
What is the gold standard for diagnosis?

- A) Culture
- B) Microscopy
- C) HPE-PAS
- D) PCR
Onychomycosis: current treatment options

- First line therapy
  - Terbinafine (250mg/day x 12 weeks)

- Second line
  - Itraconazole (200-400mg/day x 1 week for 3 months)
  - Fluconazole (300-450 mg/week x 9 months)
  - Posoconazole (200-400mg/day x 6 months)

- Third line
  - Terbinafine + amorolfine
  - Terbinafine + nail debridement
  - Photodynamic therapy

- Topical amorolfine, ciclopiroxolamine, terbinafine
ORAL THERAPY; TERBINIFINE, ITRACONAZOLE, FLUCONAZOLE, POSACONAZOLE, AND OTHERS

Jessica Vincent Hoy, DO
Fungicidal allylamine (inhibits fungal ergosterol)

Standard dosing: 250mg daily x 6 weeks for fingernails, x 12 weeks for toenails
  - Pulse dosing: 250mg daily x 1 week a month for 3 months

A meta-analysis of 18 studies showed a superior mycological cure rate of 76-78% when compared with pulse itraconazole and fluconazole (Gupta, 2004)

After 5 years, 46% of patients remained disease-free vs. 13% treated with itraconazole (Sigurgeirsson, 2002)
How is “mycological cure” characterized?

- Clinical appearance/observation
- Microscopy/KOH
- PAS staining
- Culture
- PCR
Itraconazole

- Fungistatic synthetic triazole
- Dosing: 200mg daily x 6 weeks for fingernails, x12 weeks for toenails
  - Pulse dose: 400mg daily x 1 week for 3 months
  - Pulse therapy advantages: adverse-effect profile, cost-effective and preferred by patients (Gupta, 1998)
- A meta-analysis showed a mycological cure rate for pulse itraconazole of 63-75% (Gupta, 2004)
Fungistatic bis-triazole

Dosed as pulse therapy
- 150 to 450mg once weekly for 6 months (fingernails), 9 months (toenails)

A meta-analysis of 3 studies on fluconazole showed a mycological cure rate of 48-53%

A double-blind RCT showed terbinafine 250mg daily x 12 weeks to be significantly more effective than fluconazole 150mg once weekly for either 12 or 24 weeks (Havu, 2000)
Newer azole (inhibits fungal cell membrane ergosterol synthesis)

Mycological cure rate 48%

A randomized, placebo- and active-controlled, parallel-group, investigator blinded study compared 4 doses of posaconazole with placebo and terbinafine

- At 48 weeks, cure rate was similar for posaconazole 200mg and 400mg for 24 weeks and terbinafine 250mg for 12 weeks

“Use is likely to be limited to second-line treatment in terbinafine-refractory infections, those with non-dermatophyte mold infections or those sensitive to or intolerant of terbinafine” (Elewski, 2011)
The results of the study indicated that surgical avulsion of the toenails in combination with griseofulvin therapy is an effective and practical method of treating onychomycosis of the toenails due to *T. rubrum*.
## Combination therapy

### Table 3 Combined amorolfine/oral antifungal therapy for severe onychomycosis: responses at last reported visit

<table>
<thead>
<tr>
<th>Study</th>
<th>Oral drug and duration of dose</th>
<th>±5% Amorolfin for</th>
<th>Mycological cure (%)</th>
<th>Clinical response (%)</th>
<th>Overall cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaug47</td>
<td>Griseofulvin 12 months</td>
<td>–</td>
<td>50</td>
<td>42</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Griseofulvin 2 months</td>
<td>12 months</td>
<td>63</td>
<td>45</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Terbinafine 3 months</td>
<td>–</td>
<td>66</td>
<td>42†</td>
<td>38*</td>
</tr>
<tr>
<td></td>
<td>Terbinafine 1.5 months</td>
<td>15 months</td>
<td>73</td>
<td>46†</td>
<td>44*</td>
</tr>
<tr>
<td></td>
<td>Terbinafine 3 months</td>
<td>15 months</td>
<td>89</td>
<td>75†</td>
<td>72*</td>
</tr>
<tr>
<td>Lecha49</td>
<td>Itraconazole 3 months</td>
<td>–</td>
<td>&lt;69</td>
<td>90</td>
<td>69‡</td>
</tr>
<tr>
<td></td>
<td>Itraconazole 1.5 months</td>
<td>6 months</td>
<td>≥90</td>
<td>88.1</td>
<td>84‡</td>
</tr>
<tr>
<td></td>
<td>Itraconazole 3 months</td>
<td>6 months</td>
<td>≥90</td>
<td>100</td>
<td>94‡</td>
</tr>
</tbody>
</table>

*Combined clinical response and negative mycology at 18 months.
†Unpublished data.
‡Global cure assessment at 6 months.
TOPICALS FORONYCHOMYCOSES;
CICLOPIROX, AMOROLFINE NAIL
LACQUER, EFICONTACONAZOLE (JUBLIA),
TAVABOROLE (KERIDIN), AND OTHERS

Kylee Crittenden, DO
Topical treatment

- Adverse effects are site specific.
- No need for laboratory monitoring or concern about systemic adverse effects.
- Efficacy affected by ability to penetrate nail unit.
Ciclopirox lacquer, 8%

- Approved by FDA for onychomycosis in 1999
- Binds trivalent cations and blocks enzymatic co-factors; interferes with active membrane transport; disruption of cell membrane integrity, and inhibition of enzymes required for respiratory processes
- Requires frequent nail debridement
- 29-36% mycologic cure; 5.5% to 8.5% complete cure from once daily application
- Promising results of combination of ciclopirox and itraconazole for 3 months\(^3\). Needs further investigation.

(Baran, R. et al 2000)
Acts primarily by inhibiting ergosterol biosynthesis

Fungistatic and fungicidal

Used in combinations therapy with systemics; griseofulvin, terbinafine, itraconazole or fluconazole, against a number of dermatophytes implicated in superficial infections\(^5\).

(Polak A. 1993)
Triazole antifungal; blocks ergosterol biosynthesis, presumably through inhibition of sterol 14α-demethylase, leading to degenerative changes

First topical triazole to become available for dermatologic use

No debridement of nails is required

Applied daily x 48 weeks

In trials, yielded a mycologic cure of about 50% and complete cure of about 15% to 18%

(Tatsumi, et al. 2013)
- Broad-spectrum oxaborole antifungal agent with low molecular weight, permitting nail plate penetration
- Inhibits aminoacyl-tRNA synthetase; inhibits fungal protein synthesis
- Applied daily x 48 weeks
- Mycologic cure rate of 16%; complete cure rate of 6.5% vs. 5% cure rate for vehicle alone

*(Elewski, et al. 2014)*
### Topical Treatment Regimens

<table>
<thead>
<tr>
<th>Topical agent</th>
<th>Length of treatment in trials</th>
<th>Complete cure rate from once daily application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopirox 8%</td>
<td>Apply daily, up to 48 weeks</td>
<td>5.5% to 8.5%</td>
</tr>
<tr>
<td>Efinaconazole</td>
<td>Phase III clinical trials studied daily application for 48 weeks</td>
<td>15% to 18%</td>
</tr>
<tr>
<td>Tavaborole</td>
<td>Phase III clinical trial (data available on first of two recently completed) studied daily application for 52 weeks</td>
<td>6.5%</td>
</tr>
</tbody>
</table>
OTHER TREATMENT OPTIONS FOR ONYCHOMYCOSIS

Rich Winkelmann, DO
Laser for onychomycosis

- **Pros:**
  - Minimal systemic side effects
  - No laboratory monitoring or black box warning

- **Cons:**
  - Expensive
  - Poor efficacy
  - Research is lacking in highly variable
    - Small case studies, limited # pts, significant COI
Nd:YAG Laser

- 37 patients
- One to three sessions four to six weeks apart
- **Cure rate**
  - 51% (complete cure)
  - 19% (significant improvement)
  - 11% (moderate improvement)

- Treatment on days 1, 14, 42, and 120
- **Clinical cure rate:**
  - Mild cases: 65% (3 mm of nail clearance), 26% (4 mm of nail clearance)
  - Moderate to severe cases: 63% (3 mm of nail clearance)
- **Mycotic cure rate:**
  - 50-65% (mild to moderate cases)
  - 35% (severe cases)

m mentholated ointment


Derby R¹, Rohal P, Jackson C, Beutler A, Olsen C.

Abstract

BACKGROUND: current medication treatments for onychomycosis have less than full cure-rate efficacy and have the potential for adverse side effects. Vicks VapoRub (The Proctor & Gamble Company, Cincinnati, OH) has been advocated in the lay literature as an effective treatment for onychomycosis. This pilot study tested Vicks VapoRub as a safe, cost-effective alternative for treating toenail onychomycosis.

METHODS: eighteen participants were recruited to use Vicks VapoRub as treatment for onychomycosis. Participants were followed at intervals of 4, 8, 12, 24, 36, and 48 weeks; digital photographs were obtained during initial and follow-up visits. Primary outcome measures were mycological cure at 48 weeks and clinical cure through subjective assessment of appearance and quantifiable change in the area of affected nail by digital photography analysis. Patient satisfaction was a secondary outcome, measured using a single-item questionnaire scored by a 5-point Likert scale.

RESULTS: fifteen of the 18 participants (83%) showed a positive treatment effect; 5 (27.8%) had a mycological and clinical cure at 48 weeks; 10 (55.6%) had partial clearance, and 3 (16.7%) showed no change. All 18 participants rated their satisfaction with the nail appearance at the end of the study as "satisfied" (n = 9) or "very satisfied" (n = 9).

CONCLUSIONS: Vicks VapoRub seems to have a positive clinical effect in the treatment onychomycosis.
n = 154 patients

- Soak and debride affected nails, then apply solution every two weeks for three to four visits; patients may also apply at home

- Clinical cure rate - n/a

- Mycotic cure rate after 3 months:
  - 50-65% (mild to moderate cases)
  - 35% (severe cases)

Rehder et al, Foot Ankle Spec, 2008
Argeratina pichinchensis (snakeroot extract)

- Applied every third day for the first month, twice per week for the second month, then once per week for the third month
- Clinical cure rate – 71%
- Mycotic cure rate – 59%
- Study of 110 patients; effectiveness was similar to that in the ciclopirox control group

Onychomycosis; other treatment options

- Salicylic acid
  No current literature
- Tea tree oil
- Hydrogen peroxide
- Vinegar soaks
- Oil of Bitter Orange
- Bleach soaks
Comparison of two topical preparations for the treatment of onychomycosis: Melaleuca alternifolia (tea tree) oil and clotrimazole.

Buck DS¹, Nidorf DM, Addino JG.

Abstract

BACKGROUND: The prevalence of onychomycosis, the most frequent cause of nail disease, ranges from 2% to 13%. Standard treatments include debridement, topical medications, and systemic therapies. This study assesses the efficacy and tolerability of topical application of 1% clotrimazole solution compared with that of 100% Melaleuca alternifolia (tea tree) oil for the treatment of toenail onychomycosis.

METHODS: A double-blind, multicenter, randomized controlled trial was performed at two primary care health and residency training centers and one private podiatrist's office. The participants included 117 patients with distal subungual onychomycosis proven by culture. Patients received twice-daily application of either 1% clotrimazole (CL) solution or 100% tea tree (TT) oil for 6 months. Debridement and clinical assessment were performed at 0, 1, 3, and 6 months. Cultures were obtained at 0 and 6 months. Each patient's subjective assessment was also obtained 3 months after the conclusion of therapy.

RESULTS: The baseline characteristics of the treatment groups did not differ significantly. After 6 months of therapy, the two treatment groups were comparable based on culture cure (CL = 11%, TT = 18%) and clinical assessment documenting partial or full resolution (CL = 61%, TT = 60%). Three months later, about one half of each group reported continued improvement or resolution (CL = 55%; TT = 56%).

CONCLUSIONS: All current therapies have high recurrence rates. Oral therapy has the added disadvantages of high cost and potentially serious adverse effects. Topical therapy, including the two preparations presented in this paper, provide improvement in nail appearance and symptomatology. The use of a topical preparation in conjunction with debridement is an appropriate initial treatment strategy.
Vinegar Soak for Toenail Fungus

If your toenails are thick, crumbling and yellow, white or black in color, you may have a fungal infection on the nails, according to MayoClinic.com. Soaking the foot in vinegar is an old home remedy to reduce nail fungus. Its antifungal properties may help vinegar cure your toenails. If your doctor approves, you can try vinegar to help reduce fungus.
Oil of bitter orange: new topical antifungal agent.
Ramadan W, Mourad B, Ibrahim S, Sonbol F.

Abstract

BACKGROUND: Superficial dermatophyte infection is one of the most resistant to therapy.

METHODS AND PATIENTS: Sixty patients participated in this study; comparable numbers of patients with tinea corporis, cruris, and pedis times daily; group 2 was treated with 20% OBO in alcohol three times examinations were performed before therapy and every week until a

RESULTS: In group 1, 80% of patients were cured in 1 to 2 weeks at weeks and 20% in 3 to 4 weeks. In group 3, 25% of patients did not c in 1 to 2 weeks, and 6.7% in 2 to 3 weeks. Oil of bitter orange produc

CONCLUSIONS: An in vitro study showed that OBO (natural product dermatophyte species. It is a promising, cheap, and available topical
Bleach for Toenail Fungus

By R. Drysdale | Fungal

Perhaps you have heard of people using bleach as a home remedy that used to be more popular. Now medications and commercial home remedies are more popular. Bleaching requires twenty to thirty minutes.

Control Toenail Fungus

Get info on an Rx medication for Toenail Fungus Today. Read More

Toenail Fungus Trouble and a Unique Cure

Published: February 1, 2007  
Publication: Bottom Line Natural Healing  
Source: Mark A. Stengler, NMD  
Print:

When is the last time you looked at your toenails? If it has been a while, you may be in for an unpleasant surprise—in fungal form. Toenail fungus, also called onychomycosis, is a common condition that turns nails a yellow or brown color. In some cases, the nail thickens or splits and may fall off. Sufferers may experience pain around the nail and notice a foul smell. The infection is typically caused by any one of several types of fungi that feed on keratin, the protein surface of the nail. Occasionally, different yeasts and molds may cause the infection.

By age 70, almost half of Americans have had at least one affected toe. While the infection can occur in fingernails, it most often affects toenails because feet are confined to the dark, warm environment of shoes, where fungi can thrive. The nails of...
How is “complete cure” defined?
- 0% involvement of target nail(s)  PLUS
- Mycological cure (Culture & KOH)
<table>
<thead>
<tr>
<th>Therapy &amp; Dose</th>
<th>Mycological cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole 400mg daily x 3 months + Amorolfinex 6 mo</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Itraconazole 400mg daily x 1.5 months + Amorolfinex 6 mo</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Terbinafine 250mg daily x 3 months + Amorolfinex x 15 mo</td>
<td>~89%</td>
</tr>
<tr>
<td>Terbinafine 250mg daily x 3 months</td>
<td>~77%</td>
</tr>
<tr>
<td>Terbinafine 250mg daily x 1.5 months + Amorolfinex x 15 mo</td>
<td>~73%</td>
</tr>
<tr>
<td>Itraconazole 400mg daily x 1 week for 3 months</td>
<td>~69%</td>
</tr>
<tr>
<td>Ageratina (snakeroot extract) applied q3rd night</td>
<td>~59%</td>
</tr>
<tr>
<td>Nd-YAG laser 1-3 sessions, 4-6 weeks apart</td>
<td>~61%</td>
</tr>
<tr>
<td>Efinaconazole 10% solution applied daily x 12 months</td>
<td>~50%</td>
</tr>
<tr>
<td>Cyanoacrylate, undecylenic acid, hydroquinone applied every 2 weeks x 3-4 visits</td>
<td>~50%</td>
</tr>
<tr>
<td>Griseofulvin 1g daily x 12 months</td>
<td>~50%</td>
</tr>
<tr>
<td>Fluconazole 450mg weekly x 9 months</td>
<td>~51%</td>
</tr>
<tr>
<td>Posaconazole 200mg daily x 6 months</td>
<td>~48%</td>
</tr>
<tr>
<td>Ciclopirox 8% lotion applied daily x 9 months</td>
<td>~33%</td>
</tr>
<tr>
<td>Mentholated ointment (Vicks) applied daily x 12 months</td>
<td>~28%</td>
</tr>
<tr>
<td>Tavaborole 5% solution applied daily x 12 months</td>
<td>~16%</td>
</tr>
</tbody>
</table>
The concept of the onychodermis (specialized nail mesenchyme): an embryological assessment and a comparative analysis with the hair follicle.


Frizzled6 deficiency disrupts the differentiation process of nail development.


Incomplete development of the nail of the hallux in the newborn.

Milano A1, Cutrona M, Laforgia N, Bonifazi E.

Abstract

Between March and October 2008, the nails of 541 (252 females, 289 males) consecutively born neonates with an average age of 3.2 days were examined in the Neonatology Unit. Of these newborns with nail disorders, 36 were re-examined after a period that ranged from seven days to six months. The most frequent nail alteration was the incomplete development of the hallux nail, which was triangular - sometimes trapezoidal - shaped. This alteration, which had been previously reported in literature as congenital hypertrophy of the lateral folds of the hallux, spontaneously regressed within one to three months in the infants re-examined. There was no associated inflammation or onychocryptosis at any time. The apparent hypertrophy of the nail folds seemed to be secondary to the lack of pressure of the nail lamina.

Conclusions

- Onychomycosis..
  - Easy to diagnose
  - Easy to treat
  - Difficult to cure (without a lot of work)
- Many oral, topical and alternative options exist
- Tailor treatment to patient needs
References


References


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- OhioHealth – O’Bleness residents
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