Fungal Resistance, Biofilm, and Its Impact In the Management of Nail Infection
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Dr. Aly has disclosed no relevant financial relationships with any commercial interests.
Learning Objectives

1) Recognize dermatophytoma (biofilm) in order to customize the approach to more specific treatment

2) Explain how biofilm research (an under-recognized condition) could lead to finding new targets for antifungal therapy

3) Emphasize the role of KOH and culture in identifying infection between dermatophytes and non-dermatophytes

4) Discuss latest topical treatments available
Onychomycosis (cont)
Genetic Susceptibility

- The conclusion was that certain patients may inherit susceptibility to *Trichophyton rubrum* infection in an autosomal-dominant pattern.

Onychomycosis: Potential Pathogens

- Dermatophyte fungi
  - *Trichophyton rubrum*
  - *Epidermophyton floccosum*
  - *Trichophyton mentagrophytes*

- Yeasts
  - *Candida albicans*
  - other species

- Nondermatophyte molds
  - *Scopulariopsis brevicaulis*
  - *Aspergillus spp*
  - *Scytalidium dimidiatum*
  - *Scytalidium hyalinum*
  - *Fusarium spp*
  - *Acremonium spp*
Specimen Collection
The Nail Culture
• 1146 nail clippings comparing PAS with KOH and culture
• PAS was most sensitive (82% sensitivity compared with 53% for culture and 48% for KOH)

PAS = periodic-acid Schiff; KOH = potassium hydroxide.
Scopulariopsis brevicaulis
Non-Dermatophyte (KOH)
Aspergillus Onychomycosis

KOH

INFECTED NAIL
Psoriasis commonly misdiagnosed as onychomycosis

Both diseases may coexist

Symptoms: Pitting, onycholysis, subungual thickening, nail plate alterations

Psoriasis distinguished by sharply defined pitting of nail plate surface
Dermatophytoma

A biofilm is any group of organisms in which cells stick to each other and often adhere to a surface.

The adherent cells produce extracellular polysaccharide matrix, adhering to each other and/or to a surface.

Biofilm infection: Pneumonia, cystic fibrosis, chronic wounds, implants, and catheters

- Affects millions of people – Also, dental plaque

The Role of Biofilms in Onychomycosis (cont)

- Biofilm research could lead to new approaches for antifungal therapies
- Studies are needed to understand the microenvironment of biofilm in dermatophyte infection... biological, chemical, and physical factors involved in this complex relationship
  - To alternate or stop bacterial or fungal ability to synthesize the extracellular polysaccharide
  - Drugs that will penetrate the biofilms to kill the fungi or bacteria in this complex relationship
## Current Treatments

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td>250 mg</td>
<td>Daily for 12 weeks</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg</td>
<td>Daily, 12 weeks, 200 mg bid for 1 week/month, 3 pulses</td>
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<tr>
<td>Fluconazole (not approved by the FDA)</td>
<td>300-450 mg</td>
<td>Weekly for 9 to 12 months</td>
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<tr>
<td>Ciclopirox</td>
<td>8%</td>
<td>Remove lacquer/week, 48 weeks</td>
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<tr>
<td>Effinaconazole</td>
<td>10%</td>
<td>Applied o/d for 48 weeks</td>
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<tr>
<td>Tavaborole</td>
<td>5%</td>
<td>Applied o/d for 48 weeks</td>
</tr>
</tbody>
</table>

Non-Dermatophyte Treatment

- *Aspergillus* species onychomycosis can be treated with oral terbinafine (250 mg/d for 2-3 months) or itraconazole (400 mg/d in 2-3 pulses).

- Onychomycosis caused by *Acremonium* species, *Scopulariopsis brevicaulis*, and *Fusarium* species is more difficult to cure.

- The combination of topical with systemic increases the percentage of cure.

- Onychomycosis caused by *Scytalidium* species does not respond to systemic treatment.

- A case of complete cure of *Scytalidium hyalinum* fingernail onychomycosis using amorolfin nail lacquer was reported.

Twenty patients were treated with terbinafine (250 mg/d) for 16 weeks

60% of target nails were cured clinically and mycologically

Two patients showed mild, reversible elevation of liver enzymes

Most nails were infected by Candida parapsilosis

Only two patients were infected with Candida albicans
Non-Dermatophyte Molds

- Clinical studies have shown that terbinafine is more efficacious than itraconazole, although itraconazole has broader antimicrobial coverage for non-dermatophytes.

- Generally, *Aspergillus* species and *Scopulaciopsis* species are more susceptible than other non-dermatophytes.

- For the more difficult-to-treat non-dermatophytes, a combination of oral antifungals with topical agents is recommended.

- Surgical or chemical evulsion or debridement may be the best option in certain cases.

Are Lasers More Effective than Traditional Treatments?

- Evidence-based support for the use of laser is lacking
- Double-blind studies comparing lasers to placebo are lacking
- Laser treatment probably is safe, but its efficacy remains to be proven
- Cost-wise, it is unlikely that laser will be less expensive than the traditional treatments

Bristow IR. *J Foot Ankle Res.* 2014;7:34.
Hepatotoxicity of Antifungals
Estimated Symptomatic Risk

- **Itraconazole** (overall use)
  - 1:500,000+ (De Doncker 1998)
  - No published reports with pulse therapy
- **Terbinafine**
  - 1:45,000 (Canadian monograph)
  - ≥1:25,884 (Hall 1997)
  - 1:120,000 (Hay 1993)
  - Sporadic published case reports
- **Fluconazole** (overall use)
  - 1:500,000+ (pharmacosurveillance)
  - No published reports with intermittent therapy

Poor Prognostic Factors

1. Extent of nail involvement >50%
2. Significant lateral disease
3. Subungual hyperkeratosis
4. White/yellow or orange/brown streaks in the nail (includes dermatophytoma)
5. Total dystrophic onychomycosis (with matrix involvement)
6. Nonresponsive organisms (eg, Scytalidium mold)
7. Patients with immunosuppression
8. Diminished peripheral circulation
9. Chronic plantar tinea pedis

Onychomycosis: Booster Therapy

How to Improve Cure Rate for the Management of Onychomycosis

- Correct diagnosis: Not all dystrophic nails are onychomycotic; KOH, culture, histopathology
- Bioavailability: Oral bioavailability of itraconazole is maximal after a meal
- Poor patient compliance: Drug regimen may be monitored
- Maximizing efficacy of antifungals, longer treatment
- Combination therapy: With oral or topical agent
- Mechanical therapy: Mechanical debridement or partial avulsion of the nail (eg, dermatophytoma [spike])
- Preventing relapses and recurrences
### Alternative Facts

**NailsFungus.org Top 5 Editors’ Choice Award**

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<tbody>
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<td></td>
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<td>76.7%</td>
<td>74.3%</td>
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<td>1. Effectiveness</td>
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<td>★★★★★★</td>
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<td>2. Speed of Results</td>
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<td>Average</td>
<td>Average</td>
<td>Slow</td>
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<tr>
<td>5. Customer Service</td>
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<td>★★★★★</td>
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<tr>
<td>6. Customer Satisfaction</td>
<td>98.1%</td>
<td>79.8%</td>
<td>75.2%</td>
<td>73.3%</td>
<td>61.1%</td>
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<tr>
<td>7. Reorder Rate</td>
<td>Highest</td>
<td>Good</td>
<td>Good</td>
<td>Average</td>
<td>Average</td>
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<tr>
<td>9. Success Rate</td>
<td>97.3%</td>
<td>77.3%</td>
<td>73.2%</td>
<td>75.1%</td>
<td>62.2%</td>
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</tbody>
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Patients (N = 47) with mycologically cured toenail onychomycosis examined for relapse every 3 months for 3 years.

- Patients received either itraconazole or terbinafine therapy.
- Relapse rates for all patients:
  - Month 12: 8.3%
  - Month 24: 19.4%
  - Month 36: 22.2%

- No significant differences in relapse rates between 2 drugs.
- Original pathogen (T. rubrum) caused all cases of relapse.

Recalcitrant Infections

Phase III Studies – Tavaborole 5% solution

1) A

2) A

3) A

The End