The Ronald O. Perelman Department of Dermatology

HIGH YIELD NAIL TIPS TO CHANGE YOUR PRACTICE
Evan A. Rieder MD
American Academy of Dermatology
March 2019

Outline
Onychomycosis
- Diagnosis
- Framing
- Monitoring
Conclusions

Diagnosis
Physical findings raise suspicion
Lab evidence is preferred given mimickers

Prevalence of onychomycosis 65 – 95% of patients seeking treatment for onychodystrophy
Other groups demonstrated 75% prevalence based on PAS in patients with clinical diagnosis of onychomycosis from a BCD
Non-BCDs practicing – other physicians, extenders
Patients reluctant to take oral medications

KOH
- Strengths: immediate, high specificity
- Weaknesses: depends on clinician experience / technique; time intensive; no speciation; no info on fungal viability

Image via uptodate
Diagnosis

PAS stain
- Strengths: high sensitivity (82%) vs 48% for KOH stain
- Weaknesses: higher costs, longer wait times, no speciation/ info on fungal viability; requires proximity to dermatopathology lab and may be difficult for technicians

The Ronald O. Perelman Department of Dermatology

Fungal culture
- Strengths: high specificity, fungal speciation & viability
- Weaknesses: low sensitivity (false negative in nearly 1/3 cases), long wait time, often requires repeat sampling, contaminants
- Molds may be true pathogens or contaminants – repeat testing if speciation demonstrates mold

The Ronald O. Perelman Department of Dermatology

Molecular Biology

Polymerase chain reaction (PCR):
- Detects fungal DNA and amplifies across several orders of magnitude
- Strengths: high sensitivity & specificity with quick turnaround, independent of sample quality, can detect multiple simultaneous fungi
- Multiple molecular methods available: conventional PCR, nested PCR, real time PCR

Initial data
- 559 nail specimens subject to PAS, PCR, KOH, and Culture
- Positive results in 54, 40, 27, 21% of specimens respectively

Liz & Cavagnolo 2010

Real-time PCR of 165 nails, 70 of which suspected onychomycosis
Most sensitive even in absence of clinical signs
PPV all excellent, NPV highest for real-time PCR

Gong et al. 2016

Molecular Biology

Since then multiple other groups published PCR data, multiple techniques, labs
Large range of sensitivities, specificities, PPV, NPV
PCR sensitivity better than gold standard* of fungal culture

Bao et al.
Molecular Biology

- PCR decreases false negatives
- Physician sampling matters
- Laboratory matters
- Data matters

<table>
<thead>
<tr>
<th>Pros</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sensitivity</td>
</tr>
<tr>
<td>High specificity</td>
</tr>
<tr>
<td>Easy sampling</td>
</tr>
<tr>
<td>Speciation</td>
</tr>
<tr>
<td>Quick turnaround time</td>
</tr>
<tr>
<td>Better dermatophyte detection</td>
</tr>
<tr>
<td>Lower false negatives</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited and diverse data</td>
</tr>
<tr>
<td>Multiple methods, labs</td>
</tr>
<tr>
<td>Potential false positives</td>
</tr>
<tr>
<td>Direct cost to patients</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of Polymerase Chain Reaction (PCR) and Culture False-Negative Rates

<table>
<thead>
<tr>
<th>Test</th>
<th>Single Samples (n = 187)</th>
<th>Serial Samples (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>44/82 (54)</td>
<td>14/26 (39)</td>
</tr>
<tr>
<td>PCR</td>
<td>14/82 (17)</td>
<td>3/26 (11)</td>
</tr>
</tbody>
</table>

Diagnostic Algorithm

- Rule out other similar presentations
- Clinical appearance of nail dystrophy
- Perform PCR
- PCR positive
- Initiate therapy
- PCR negative
- Alternative treatments

Treatment Modalities

- Topical
- Oral
- Physical measures / Surgery
- Lasers & Light
- Multimodal treatment

### Treatment Modalities

- Patient compliance
- Low cure rates
- High rates of relapse
- Uncertain follow-up time
- Potential adverse events (e.g. hepatotoxicity, drug-drug interactions)
Cure Rates: Orals

<table>
<thead>
<tr>
<th>Medication/Regimen</th>
<th>Complete Cure Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td></td>
</tr>
<tr>
<td>250mg/day x 12wks</td>
<td>38%</td>
</tr>
<tr>
<td>250mg/day x 1wk/mo x 3 pulses</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>250mg/day x 1wk/mo x 4 pulses</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>200mg/day x 12wks</td>
<td>14%</td>
</tr>
<tr>
<td>400mg/day x 1wk/mo x 3 pulses</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td>150mg/wk</td>
<td>37%</td>
</tr>
<tr>
<td>300mg/wk</td>
<td>46%</td>
</tr>
<tr>
<td>450mg/wk</td>
<td>48%</td>
</tr>
</tbody>
</table>

NB: Pulse dosing & fluconazole are not FDA-approved.

The Ronald O. Perelman Department of Dermatology
Adapted from Rosen & Stein Gold 2016

Cure Rates: Topicals

<table>
<thead>
<tr>
<th>Medication</th>
<th>Complete Cure Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopirox 8%</td>
<td></td>
</tr>
<tr>
<td>and 8.5%</td>
<td></td>
</tr>
<tr>
<td>Efinaconazole 10%</td>
<td></td>
</tr>
<tr>
<td>and 17.8%</td>
<td></td>
</tr>
<tr>
<td>Tavaborole 5%</td>
<td></td>
</tr>
<tr>
<td>6.5% and 9.1%</td>
<td></td>
</tr>
<tr>
<td>Amorolfine 5%*</td>
<td></td>
</tr>
<tr>
<td>38% and 48%</td>
<td></td>
</tr>
</tbody>
</table>

*Not approved in US.

Adapted from Rosen and Stein Gold 2016

Terbinafine & Liver

Q4wk LFT monitoring – rates of hepatotoxicity are 1:50,000 – 120,000 CYP2D6 inhibitor

Asymptomatic LFT elevation in 0.2 – 0.5% patients on terbinafine

Liver injury usually 4-6 weeks after initiation of tx:

Idiosyncratic reaction

Reviewed in Kasper 2016

Terbinafine & Liver Transplant

Meta-analysis of 122 studies; 30,000 patients

AST/ALT elevation requiring termination of tx = 0.35%

Asymptomatic AST/ALT elevation not requiring termination = 0.70%

Russo et al; Chelske et al
**Terbinafine & the Liver**

Retrospective study of 4985 patients on terbinafine (n = 4309) or griseofulvin

AST/ALT elevations, anemia, lymphopenia, neutropenia examined

Exclusions:
- Premorbid hepatic and hematologic diseases and abnormalities
- Prior treatment with oral ketoconazole, amphotericin, itraconazole

Conclusions
- Proper diagnosis is important for specification: use PCR
- Set expectations on cure rates
- No need for laboratory monitoring for first line treatment in otherwise healthy patients

**References**


Dermatol 2016; 30; 696.

Stolmear et al 2018

The Ronald O. Perelman Department of Dermatology


Kanzler MH. Reevaluating the need for laboratory testing in the treatment of onychomycosis. JAMA Dermatol 2016; 152: 263.


