U008 A Practical Approach to the Management of Onychomycosis: Diagnosis

Molly Hinshaw, MD
Assoc. Prof. Dermatology & Dermatopathology
UWHealth
Madison, WI
Key Points

1. Confirm dx before initiating treatment
2. Currently widely available options for dx=KOH, culture, PAS/GMS
3. Confirmation of dx is one piece of data, CPC necessary
4. Emerging technique for dx: molecular diagnostics
1. Confirm dx before initiating treatment

• Why should we confirm dx before we Rx?
• Simulators of onychomycosis are numerous
• Traumatic onychodystrophy, tumors, etc. can all look like onychomycosis
• If test(s) are negative, then no need Rx & we save patients unnecessary $, inconvenience, drug interactions, potential drug s.e.
• Without confirmation of dx then we do not know when to stop Rx
• Recent paper disputes need for dx before treatment based on view that it is more cost effective to make clinical diagnosis, then treat
Based on data from previous literature

Primary Outcomes: Direct Costs Dx & Rx; Cost to Avoid Harm for po Terbinafine

Cost of 12 wks po terbinafine=$10; Rx & Labs(1 lab draw AST&ALT)=$53; 1 drop efinoconazole x 48wks for 1 toe=$2307

Assuming prevalence of 75%, per pt savings of empiric po terbinafine without KOH was $47 and without PAS was $135

KOH and PAS screening before Rx with efinoconazole saved $272 and $406, per pt per nail respectively

Mikailov et al Study was Largely an Update of a 1999 Study

- Study of 688 pts
- 12 wks po terbinafine=$547
- Efinconazole not available
- Estimated costs of treating all based on clinical dx with terbinafine vs objective confirmation of dx then treat only those with confirmed onychomycosis

Results:
- Savings of $159 per pt when dx confirmed before starting treatment
• Overall cost of treating a pt with suspected onychomycosis calculated with and without confirmatory testing for a correct dx (treated as onychomycosis and dx present) and without confirmatory testing for an incorrect diagnosis (treated as onycho but no onycho present)

• Conclusion: Overall cost of an incorrect dx (no confirmatory test used) was $350-$1175 (Canadian). Performing confirmatory tests before Rx costs $320-$930 depending on test, therapy, physician.

• Benefits of confirmatory testing outweigh their cost in Ontario, Canada.
Might Miss a Non-Dermatophyte Mold, Yeast

- In N. America, population based prevalence of onycho=7-14%
- In children <16 population based prevalence=0.2-2.6%
- There is a genetic predisposition to infection with dermatophyte
- 70-90% of onychomycosis due to dermatophyte (90% of that=T. rubrum)
- Yeasts e.g. C. parapsilosis (usually w/paronychia) & molds e.g. Aspergillus, Scopulariopsis or Fusarium, mixed infection in 5-15%
- Mold onychomycosis much more difficult to treat, may not respond
- Open question: do NDM, yeast cause onycho in a healthy nail?
Practice Gap
Dermatologists prescribe oral antifungals for assumed onychomycosis before confirmation of the diagnosis (medical knowledge, system-based practice).

Educational Gap
The educational gap includes the treatment of onychomycosis in dermatology residency training without confirmation of fungal infection (medical knowledge, system-based practice).

Best Practice
Confirmation of onychomycosis is recommended before systemic medications are prescribed because prolonged courses are necessary to treat nail disease. Although more research is needed to reach a consensus of the best and most cost-effective test for onychomycosis diagnosis, confirmation with one of the currently available methods should occur before treatment with an antifungal is initiated.

Existing methods for appropriate dx include KOH, culture of specimens, and histologic sections stained with PAS, GMS. Each test has its own advantages and disadvantages, and there is no current conclusive evidence for one optimal test.

“Don’t prescribe oral antifungal therapy for suspected nail fungus without confirmation of a fungal infection. Approximately half of all patients with suspected nail fungus do not have a fungal infection.”
2. Currently available options for dx: KOH, Culture, PAS

- KOH, quick, inexpensive, operator dependent
- Cultures are insensitive, approx. 50% sensitive
- PAS on formalin fixed nail plate dependent on quantity of proximal clipping, confirm what DP means when they say onychomycosis
- Dermoscopy being used to guide where to take clippings
- Take clipping of as much subungual & as far proximal as is painless
Dermoscopy Assisted Dx Onychomycosis

3 Primary Findings Attributable to Onychomycosis

1. Jagged proximal edge with spikes
2. Longitudinal striations of various colors “aurora borealis pattern”
3. Distal irregular termination aka “ruin appearance” from accumulation of debris

Figure 4: Nail plate dermoscopy showing the vertical pierce after abrasion. Mycological samples from this area were positive.

Table 1. Techniques Used to Diagnose Onychomycosis.

<table>
<thead>
<tr>
<th>Test</th>
<th>Techniques</th>
<th>Fungal Viability</th>
<th>Species Identification</th>
<th>Test Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>Sabourad dextrose agar&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>1-3 weeks</td>
</tr>
<tr>
<td>Microscopy</td>
<td>KOH</td>
<td>No</td>
<td>No</td>
<td>Rapid</td>
</tr>
<tr>
<td></td>
<td>Parker’s blue black ink</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluorescent stain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>PAS</td>
<td>No</td>
<td>No</td>
<td>24 hours</td>
</tr>
<tr>
<td>Molecular Biology</td>
<td>PCR</td>
<td>No</td>
<td>Yes</td>
<td>5 hours to 1 day</td>
</tr>
<tr>
<td></td>
<td>RT-PCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combinations</td>
<td>Microscopy + culture</td>
<td>Yes</td>
<td>Yes</td>
<td>Dependent on the combination used</td>
</tr>
<tr>
<td></td>
<td>Microscopy + histology</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>KONCPA (KOH + PAS)</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

KOH, potassium hydroxide; PAS, periodic acid–Schiff stain; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction.

*With and without cycloheximide.
Cultures Routinely Slow, Insensitive

- Recommended to attempt growth x 4 weeks before calling negative
- Recommended pts are off all antifungals x at least 2 weeks before cx
- Molds, yeast, bacteria may overgrow dermatophyte (false negative)
- Sensitivity at best < 50% (literature, UWHealth)
- In this manuscript, of 5459 submitted nail or skin cx, 20.66% were +
  - Of those 20.66%, 72.69% were + in first 7d, 24% turned + d7-14
  - Only 1.42% (n=16) were positive after 17d incubation period
  - Of those 16, 14 were nails, 4 had been on antifungals, 7 were KOH+
    (no change in Rx)

Cultures

• Reported out as “Dermatophyte” in my institution
• No genus, species
• No sensitivities, no reports of resistance in dermatophytes
• 1 report of total dystrophic onychomycosis caused by Aspergillus resistant to antifungals (32y/o immunocompetent pt w/psoriasis on calcipotriene, infection started proximally, dx made on KOH, cx, & PCR, was sensitive to itra; resistant to posiconazole, vori, terbinafine, econazole, miconazole, butenafine, ampho B)

My Approach

- When my physical exam proves no concern for neoplasm nor other nail disease and pt wants Rx if dx is onychomycosis, then I do KOH
- If KOH is negative then I send nail clippings in formalin to DP for PAS
- I rarely culture unless good clinical for yeast/mold or PAS is equivocal
3. Confirmation of dx is one piece of data. CPC is necessary

- Patients with underlying nail disease are at increased risk of onychomycosis
- Anything that causes nail dystrophy predisposes to onychomycosis
- Confirm using clinical exam that onychomycosis is pts only dx of concern before treating
- Dx of non-dermatophyte onychomycosis requires 1. Clinical presentation c/w onychomycosis; 2. the same non-dermatophyte cultured x 2 out of nail clippings; 3. absence of dermatophyte
- If CPC is poor then must pursue additional evaluation
4. Molecular Diagnostics: PCR

- Direct ID of dermatophyte or non-dermatophyte DNA in nail as opposed to use of morphology as in other methods
- PCR: conventional, nested, real-time
- Vary by DNA extraction methods, targeted DNA & primers.

Development and Evaluation of a Novel Real-Time PCR for Pan-Dermatophyte Detection in Nail Specimens

Jie Gong, Menglong Ran, Xiaowen Wang, Zhe Wan, Ruoyu Li

4. Molecular Diagnostics: PCR

- Dermatophytes ID’d using DNA sequencing due to specific polymorphisms that flank encoded 5.8S ribosomal DNA sequence
- Chitin synthase I (CHSI) gene has been used to ID dermatophytes
- Topoisomerase II (TOP2) used to ID T. rubrum, T. interdigitale, E. flocc
- Able to ID mixed infections using RFLPs, etc.
- Turn around time=hours-1 day
- Currently rarely used; existing methods diagnostic

Key Points

1. Confirm dx before initiating treatment
2. Currently widely available options for dx=KOH, culture, PAS/GMS (I do KOH or PAS routinely)
3. Confirmation of dx is one piece of data, CPC necessary (know how your dermatopathologist signs out nails, confirm pt does not have onychomycosis complicating another diagnosis like SCC or psoriasis)
4. Emerging technique for dx: molecular diagnostics
Thank you!

Molly Hinshaw, MD
Assoc. Prof. Dermatology & Dermatopathology
UWHealth Madison, WI
mhinshaw@dermatology.wisc.edu