Diagnosis of Onychomycosis

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. Future directions for dx include molecular diagnostics
1. Confirm dx before initiating treatment

- Why?
- Simulators of onychomycosis are numerous
- Medications have potential side effects
- 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
- In reality, there are many potential pitfalls with basing therapeutic decisions on clinical diagnosis of onychomycosis
- We save patients unnecessary costs, inconveniences, s.e.
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)

Other Manuscripts Dispute That There is a Cost Savings to Treating Empirically

- Study of 688 pts
- 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
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.

Objectively Dx Onychomycosis Before Rx

**ABSTRACT**
Onychomycosis is a fungal infection of the nail unit, representing the most common nail disorder and accounting for 50% all nail diseases. Unfortunately, many patients are mismanaged, as physicians routinely treat onychomycosis empirically, falsely believing that they can make the diagnosis based on history and clinical inspection alone. We propose and provide evidence for why the diagnosis of onychomycosis should be confirmed by objective methods in each patient before initiating treatment.

![Figure 1](image.png)

Podiatric Training Differs From Derm

• Podiatrists see approx. 5x as many pts with onycho as derm
• Their Rx of onycho often does not include antifungals
• Why? Training, Use Debridement
• Underscores the importance of greater understanding, cooperation b/w specialties
Might Miss a Non-Dermatophyte Mold, Yeast

- In USA & Europe, population based prevalence of onychomycosis is around 5%
- T. rubrum is ≥65% of all (& is >90% of dermatophyte onychomycosis)
- There is a genetic predisposition to infection with dermatophyte
- Yeasts e.g. C. parapsilosis (usually w/paronychia) & molds e.g. Scopulariopsis or Fusarium up to 30%, mixed infection in 5-15%
AAD Position Statement

AAD. Choosing Wisely. Available at: https://www.aad.org/education/choosing-wisely
2. Currently available options for dx: KOH, Culture, PAS

- KOH, quick, inexpensive, operator/quantity of scraping/supply dependent
- Cultures are insensitive, approximately 50% sensitive
- PAS performed on formalin fixed nail plate dependent on quantity of proximal clipping, confirm what your dermpath 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
- I generally perform KOH and if not definitely positive then PAS. I rarely culture unless PAS is equivocal and pt wants Rx.
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. Future directions for dx include molecular diagnostics

• Future diagnostic methods include RT-PCR
• Currently expensive
• Turn around time=a few days
Future of Onychomycosis

• Molecular diagnostics

• More research in children and special populations such as those with chronic nail disease that makes dx of onycho a more frequent & difficult problem

• More effective treatments with fewer potential side effects
Molecular Diagnostics: PCR

- Direct demonstration of dermatophyte DNA in nail
- PCR uses primers targeted against topoisomerase II of T. rubrum, T. interdigitale, E. flocc
Combining all ten studies, 392 of the 2176 psoriasis pts were dx with onychomycosis (prevalence 18.0% compared to combined prevalence of 9.1% in the control groups.

Because of heterogeneity between studies, & low methodological quality no ultimate conclusion can be drawn as no meta analysis could be conducted.

However, when giving an overview of included studies, prevalence of onychomycosis in psoriatic pts seems increased compared to controls even though the ultimate evidence remains lacking.

A hypothesized shift from dermatophytes to yeasts and/or molds could not be confirmed.
Table 2: Prevalence numbers of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage onychomycosis patients, %</th>
<th>Percentage onychomycosis, clinically affected (patients), %</th>
<th>Percentage onychomycosis control, %</th>
<th>Percentage onychomycosis, clinically affected (controls), %</th>
<th>Direct microscopy</th>
<th>Culture</th>
<th>Medium</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toenails</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Gupta et al.     | 12.7                                 | 27.0                                                       | 6.9                                 | 43.8                                                       | KOH              | 1. Sabouraud glucose agar + cycloheximide + chloramphenicol + gentamycin (CCG)  
2. Casamino acids erythrol albumin agar + CCG  
3. Jitman oxglio agar + streptomycin | Significant higher prevalence in psoriasis patients |
| Hammenius et al. | 4.6                                  | U                                                          | 2.4                                 | U                                                          | KOH 10% Parkers ink | 1. Sabouraud agar + gentamycin  
2. Dermatophyte medium + cycloheximide + gentamycin | No significant difference.  
No altered susceptibility |                                                |
| Leibovici et al. | 47.8                                 | U                                                          | 28.4                                | U                                                          | KOH              | Sabouraud glucose agar  
1. +Cycloheximide  
2. +Cycloheximide | Significant higher prevalence in psoriasis patients  
($P = 0.0054$) |                                                |
| Zawinska et al.  | 11.4                                 | U                                                          | 3.3                                 | U                                                          | KOH 20% DMSO 40% | 1. Sabourauds dextrose agar  
2. Sabourauds dextrose agar + cycloheximide + chloramphenicol | Higher prevalence  
(significance unknown) |                                                |
| **Toenails and fingernails** |      |                                                            |                                     |                                                            |                  |                                             |                                             |                                                |
| Larsen et al.    | 21.5                                 | 26.2                                                       | 12.7                                | 34.0                                                       | Calcofluor white | Sabouraud glucose agar  
1. +Chloramphenicol + cycloheximide  
2. +Chloramphenicol | No significant difference  
($P = 0.13$) |                                                |
| Kazar et al.     | 13.1                                 | 28.6                                                       | 7.9                                 | 40.6                                                       | KOH 20%          | 1. Sabourauds dextrose agar on potato agar  
2. acetophenol cotton blue  
3. fermentation test Wickerham | No significant difference |                                                |
| Pawiacyczky et al.| 6.0                                  | 18.8                                                       | –                                   | 39.5                                                       | KOH 20%          | 1. Sabourauds agar  
2. Sabourauds agar + chloramphenicol + cycloheximide | No significant difference |                                                |
| Staberg et al.   | 26.9                                 | 30.8                                                       | 19.5                                | U                                                          | KOH 30%          | Sabourauds dextrose agar  
1. +Chloramphenicol + cycloheximide | Higher prevalence but non-significant |                                                |
| Stander et al.   | 30.4                                 | U                                                          | 19.6                                | U                                                          |                  | Malzagar + antibiotics | No significant difference |                                                |
| Szepes           | 63.1                                 | U                                                          | 66.0                                | +                                                          |                  | Sabourauds dextrose agar  
1. +Penicillin  
2. +Streptomycin | No significant difference |                                                |

N, no control group; U, unknown; KOH, potassium hydroxide.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th></th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dermatophyte, n (%)</td>
<td>Yeast, n (%)</td>
<td>Mould, n (%)</td>
<td></td>
<td>Dermatophyte, n (%)</td>
<td>Yeast, n (%)</td>
</tr>
<tr>
<td>Toenails only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta et al.\textsuperscript{15}</td>
<td>45 (84.9)</td>
<td>3 (5.7)</td>
<td>5 (9.4)</td>
<td></td>
<td>41 (87.2)</td>
<td>3 (6.4)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Hamnerius et al.\textsuperscript{18}</td>
<td>No differentiation</td>
<td>No differentiation</td>
<td>No differentiation</td>
<td></td>
<td>No differentiation</td>
<td>No differentiation</td>
<td>No differentiation</td>
</tr>
<tr>
<td>Leibovici et al.\textsuperscript{19}</td>
<td>42 (77.8)</td>
<td>6 (11.1)</td>
<td>6 (11.1)</td>
<td></td>
<td>27 (93.1)</td>
<td>2 (6.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Zawirska et al.\textsuperscript{22}</td>
<td>No differentiation</td>
<td>No differentiation</td>
<td>No differentiation</td>
<td></td>
<td>No differentiation</td>
<td>No differentiation</td>
<td>No differentiation</td>
</tr>
<tr>
<td>Toenails and fingernails</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kacar et al.\textsuperscript{20}</td>
<td>8 (61.5)</td>
<td>3 (23.1)</td>
<td>2 (15.4)</td>
<td>1 (25.0%)</td>
<td>0 (0)</td>
<td>3 (75.0)</td>
<td>Nail psoriasis risk factor for dermatophyte onychomycosis ($P=0.02$)</td>
</tr>
<tr>
<td>Larsen et al.\textsuperscript{11}</td>
<td>8 (36.4)</td>
<td>10 (45.5)</td>
<td>4 (18.2)</td>
<td>12 (50.0%)</td>
<td>7 (29.2)</td>
<td>5 (20.8)</td>
<td>More prevalent yeast in psoriasis patients</td>
</tr>
<tr>
<td>Pawlaczzyk et al.\textsuperscript{21}</td>
<td>19 (65.5)</td>
<td>8 (27.6)</td>
<td>2 (6.9)</td>
<td>1013 (64.2%)</td>
<td>347 (22.0)</td>
<td>148 (9.4)</td>
<td>Dermatophytes frequently seen in nail psoriasis</td>
</tr>
<tr>
<td>Staberg et al.\textsuperscript{22}</td>
<td>10 (47.6)</td>
<td>10 (47.6)</td>
<td>1 (4.8)</td>
<td>4 (50.0)</td>
<td>4 (50.0)</td>
<td>0 (0.0)</td>
<td>Higher prevalence in psoriasis patients with nail involvement</td>
</tr>
<tr>
<td>Stander et al.\textsuperscript{13}</td>
<td>22 (28.9)</td>
<td>48 (62.2)</td>
<td>6 (7.9)</td>
<td>11 (55.0)</td>
<td>7 (35.0)</td>
<td>2 (10.0)</td>
<td>Higher probability of yeast in psoriatic nails</td>
</tr>
<tr>
<td>Szepes et al.\textsuperscript{16}</td>
<td>9 (12.9)</td>
<td>26 (37.1)</td>
<td>35 (50.0)</td>
<td>45 (20.0)</td>
<td>65 (28.9)</td>
<td>115 (51.1)</td>
<td>Rate of dermatophytes is lower while the frequency of yeast was higher</td>
</tr>
</tbody>
</table>

N, number.
Thank You

Molly Hinshaw, MD
Associate Professor, UWHealth Madison, WI
mhinshaw@dermatology.wisc.edu
608-287-2620