

APPENDIX

Onychomycosis: Recommendations for Diagnosis, Assessment of Treatment Efficacy, and Specialist Referral. The CONSONANCE Consensus Project

AUTHORS

Bianca Maria Piraccini^{1*}, Michela Starace², Adam I. Rubin³, Nilton Gioia Di Chiacchio^{4,5}, Matilde Iorizzo⁶, Dimitris Rigopoulos⁷. A working group of the European Nail Society.

*corresponding author (biancamaria.piraccini@unibo.it)

¹ Dermatology- IRCCS, Policlinico Sant'Orsola, Department of Specialized, Experimental and Diagnostic Medicine, Alma Mater Studiorum, University of Bologna, Bologna, Italy. Email: biancamaria.piraccini@unibo.it

² Dermatology- IRCCS, Policlinico Sant'Orsola, Department of Specialized, Experimental and Diagnostic Medicine, Alma Mater Studiorum, University of Bologna, Bologna, Italy. Email: michela.starace2@unibo.it

³ Hospital of the University of Pennsylvania. Children's Hospital of Philadelphia. Perelman School of Medicine at the University of Pennsylvania. Philadelphia, Pennsylvania, United States of America. Email: Adam.Rubin@uphs.upenn.edu

⁴ Faculdade de Medicina do ABC, Santo Andre, Brasil.

⁵ Hospital do Servidor Público Municipal de São Paulo, São Paulo, Brasil. Email: dichiacchiong@gmail.com

⁶ Private Dermatology Practice, Bellinzona/Lugano, Switzerland. Email: matildeiorizzo@gmail.com

⁷ Department of Dermatology-Venereology, Faculty of Medicine, National and Kapodistrian University of Athens, Andreas Sygros Hospital, Athens, Greece. Email: dimitrisrigopoulos54@gmail.com

CONSONANCE PROJECT

CONSENSUS ON ONYCHOMYCOSIS ASSESSMENT IN NON-SPECIALIZED CLINICAL ENVIRONMENTS

Thank you very much for your interest to participate in the **CONSONANCE project** (CONSENSUS ON ONYCHOMYCOSIS ASSESSMENT IN NON-SPECIALIZED CLINICAL ENVIRONMENTS).

Onychomycosis is the most prevalent nail infective disease, and it's responsible for about 50% of all consultations related with nail disorders. Patients with onychomycosis usually consult their pharmacist, general practitioners or dermatologist non-specialized in nail disorders. However, these healthcare professionals do not usually have the specific knowledge and techniques to properly diagnose and define cure of onychomycosis, i.e. dermoscopes, the possibility to do a KOH microscopy, fungal culture or a PCR. This situation reinforces the need to define the criteria to be used in real life practice for proper diagnosis and treatment efficacy assessment of mild to moderate onychomycosis.

The main objectives of the CONSONANCE project are to reach consensus recommendations on the minimum clinical criteria needed for the diagnosis and assessment of the efficacy of treatments for mild to moderate onychomycosis by healthcare professionals (dermatologists, general practitioners and pharmacists) not specialized in nail diseases in their daily clinical practice and establish recommendations for referral to the nail specialist when deemed necessary.

We would like to highlight that these recommendations are aimed to be useful by non-experts who may not have access to any advanced diagnostic/assessment tools.

When answering this short survey, please keep in mind that there are no correct nor incorrect answers, the objective is to know your point of view.

Once again, thank you for your time and interest!

Let's start!

A. Participant profile

Before starting, we would like to have a quick overview of your background and experience with onychomycosis.

1. In which country do you work?
(list of countries)
2. Where do you mainly practice? (single answer)
 - Public setting
 - Private setting
 - Both, public and private setting
3. How old are you?
_____ years
4. What is your speciality? (single answer)
 - Dermatologist
 - Podiatrist
 - Another speciality. Please specify: _____
5. Do you have a practice specialized in nail diseases? (single answer)
 - Yes
 - No
6. For how long have you been treating nail diseases?
_____ years
7. How many patients do you see on average in 1 month? *Please think about individual patients, no consultations.*
_____ patients
8. What percentage of the patients that you see in 1 month are suffering from nail disease?
_____ % ($\leq 100\%$)
9. What percentage of the patients that you see in 1 month are suffering from onychomycosis?
_____ % ($\leq 100\%$) (% Q9 < % Q8)
10. Please classify your onychomycosis patients according to their type of onychomycosis:
 - _____ % of patients with **Distal lateral subungual onychomycosis** (DLSO)
 - _____ % of patients with **Proximal subungual onychomycosis** (PSO)
 - _____ % of patients with **Superficial white onychomycosis** (SWO)
 - _____ % of patients with **Total dystrophic onychomycosis** (TDO)(all % must sum 100%)

11. From your patients with distal lateral subungual onychomycosis (DLSO), please classify them according to the severity of their disease, when they first came to see you.

_____ % of patients with **mild-moderate DLSO** (less than 50% of the nail affected)

_____ % of patients with **severe DLSO** (more than 50% of the nail affected, matrix involvement, spikes/dermatophytoma* or nail thickness exceeding 2 mm)

(all % must sum 100%)

**Dermatophytoma:* yellow or white streaks or patches in the subungual space. It is a dense fungal mass encased in a layer of biofilm.

B. Current clinical practice

Now, let's move on to your current clinical practice.

12. On average, in what percentage of your patients treated for onychomycosis **have you used the following therapeutic techniques in the last month?**

_____ % of patients I've prescribed topical anti-fungal treatment

_____ % of patients I've prescribed oral (systemic) fungal treatment

_____ % of patients I've prescribed both topical and oral treatment

_____ % of patients I've done a chemical nail avulsion

_____ % of patients I've done a total surgical nail avulsion

_____ % of patients I've done a partial surgical nail avulsion

_____ % of patients I've done a nail debridement

_____ % of patients I've done a device-based treatment (laser, photodynamic therapy, iontophoresis)

(total can sum > 100%)

13. According to your experience, what is the **degree of sensitivity of the following techniques** for the diagnosis of DLSO?

(one single answer per row).

***Sensitivity of a diagnostic technique:** properly measures the ability of a technique to correctly identify those patients with the disease (true positives).

SENSITIVITY OF DIAGNOSTIC TECHNIQUES	Not sensitive	Low sensitivity	Medium sensitivity	High sensitivity
Evaluation of the clinical aspects of the nail (colour, thickness, detachment)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dermoscopy / Onychoscopy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Microscopy of the nail sample prepared with potassium hydroxide (KOH)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fungal culture	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Histopathology* of a nail clipping with PAS/GMS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PCR (Polymerase chain reaction)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nail unit punch biopsy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

* Histopathology of the nail: microscopic examination of a nail sample.

GMS: Gomori Methenamine Silver.

PAS: Periodic Acid-Schiff.

14. According to your experience, what is the **degree of practicality of the following techniques** for the diagnosis of DLSO?

(one single answer per row).

**Practicality of a diagnostic technique: properly measures the quality of being suitable for what it is designed to be used.*

PRACTICALITY OF DIAGNOSTIC TECHNIQUES	Not practical	Low practicality	Medium practicality	High practicality
Evaluation of the clinical aspects of the nail (colour, thickness, detachment)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dermoscopy /Onychoscopy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Microscopy of the nail sample prepared with potassium hydroxide (KOH)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fungal culture	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Histopathology* of a nail clipping with PAS/GMS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PCR (Polymerase chain reaction)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nail unit punch biopsy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

* Histopathology of the nail: microscopic examination of a nail sample.

** Biopsy of nail sample: examination of a nail sample that has been surgically obtained.

GMS: Gomori Methenamine Silver.

PAS: Periodic Acid-Schiff.

15. When seeing a patient with DLSO, what do you usually do in your current clinical practice? (one single answer per row)

DLSO PRACTICE		Never	Occasionally	Often	Always
Ask for clinical background/ predisposing factors	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Evaluate the clinical aspects of the nail (colour, thickness, detachment)	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dermoscopy /Onychoscopy	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Microscopy of the nail sample prepared with potassium hydroxide (KOH)	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fungal culture	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Histopathology* of a nail clipping with PAS/GMS	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PCR (Polymerase chain reaction)	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nail unit punch biopsy**	At diagnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Follow-up visits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

* Histopathology of the nail: microscopic examination of a nail sample.

** Biopsy of nail sample: examination of a nail sample that has been surgically obtained.

GMS: Gomori Methenamine Silver.

PAS: Periodic Acid-Schiff.

16. When the DLSO diagnosis is confirmed, generally speaking, what treatments and/or techniques do you usually **prescribe in 1st line** according to the severity of the disease? (multiple answers allowed per row & column).

1 ST TREATMENT LINE	Mild to moderate	Severe					
	< 50% of the nail affected	>50% of the nail affected w/o matrix involvement	Matrix involvement	Spikes/ dermatophytoma*	Nail plate and subungual hyperkeratosis** thickness exceeding 2 mm	More than 3 nails involved	Finger nails also involved
Topical antifungals	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Oral antifungals	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Topical and oral antifungals combined	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nail avulsion (chemical or total/partial surgical)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nail Debridement	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Device-based treatment (laser, photodynamic therapy, iontophoresis ...)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Dermatophytoma: yellow or white streaks or patches in the subungual space. It is a dense fungal mass encased in a layer of biofilm.*

***Hyperkeratosis: Scales under the distal nail*

17. On average, how often do you follow-up your patients diagnosed of DLSO according to the stage of the disease? (single answer per column)

FOLLOW-UP	Mild to moderate	Severe					
	< 50% of the nail affected	>50% of the nail affected	matrix involvement	Spikes/ dermatophytoma*	Nail plate and subungual hyperkeratosis**	More than 3 nails involved	Finger nails also involved
Every month	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Every 3 months	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Every 6 months	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Every year	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Never	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*Dermatophytoma: yellow or white streaks or patches in the subungual space. It is a dense fungal mass encased in a layer of biofilm

**Hyperkeratosis: Scales under the distal nail

18. What is your main criterion to establish cure? (single answer)

- Mycological cure: negative KOH and negative culture
- Clinical cure: 0% nail plate involvement (100% of healthy nail growth)
- Complete cure: mycological cure + clinical cure
- I follow the recommended treatment guidelines in the package insert
- Others, please specify: _____

19. What is your main criterion to establish treatment stop? (single answer)

- Mycological cure: negative KOH and negative culture
- Clinical cure: 0% nail plate involvement (100% of healthy nail growth)
- Complete cure: mycological cure + clinical cure
- I follow the recommended treatment guidelines in the package insert
- Others, please specify: _____

C. Definition of the key recommendations

Considering your expertise in nail disorders, we will now ask you about the key points that need to be taken into consideration by a **non-expert** in order to establish a **DLSO diagnosis suspicion** and **treatment efficacy** evaluation. Please, take into consideration that, usually **they do not have access to specific equipment and diagnosis techniques like dermatoscopes or the possibility to do a KOH microscopy, fungal culture nor a PCR.**

20. Bearing in mind **the limited resources that are available to non-expert Healthcare professionals** for the diagnosis of DLSO, please indicate your opinion about the **necessity to evaluate the following aspects to establish a diagnosis suspicion of DLSO by non-experts** that do not have access to specific equipment and diagnostic tests. *Being 1 totally unnecessary and 9 totally necessary.*

ASPECTS TO EVALUATE	Totally unnecessary								Totally necessary
	1	2	3	4	5	6	7	8	9
Clinical aspects of the nail									
Nail colour: yellow-orange	<input type="checkbox"/>								
Subungual hyperkeratosis (scales under the distal nail)	<input type="checkbox"/>								
Nail detachment (onycholysis)	<input type="checkbox"/>								
Nail surface abnormalities	<input type="checkbox"/>								
Nail crumbling	<input type="checkbox"/>								
Paronychia (periungual inflammation)	<input type="checkbox"/>								
Longitudinal nail fissures	<input type="checkbox"/>								
Nail plate thickening	<input type="checkbox"/>								
Several toenails affected	<input type="checkbox"/>								
Several finger nails affected	<input type="checkbox"/>								
Toenails and finger nails affected	<input type="checkbox"/>								
Others: please specify	<input type="checkbox"/>								

21. Bearing in mind **the limited resources that are available to non-expert Healthcare professionals** for the diagnosis of DLSO, please indicate your opinion about the **necessity to evaluate the following aspects to establish a diagnosis suspicion of DLSO by non-experts** that do not have access to specific equipment and diagnostic tests. *Being 1 totally unnecessary and 9 totally necessary.*

ASPECTS TO EVALUATE	Totally unnecessary								Totally necessary
	1	2	3	4	5	6	7	8	9
Predisposing factors									
Older adult (>65 years)	<input type="checkbox"/>								
Genetic predisposition (similar nail changes in the family members)	<input type="checkbox"/>								
Current tinea pedis diagnosed	<input type="checkbox"/>								
History of repetitive nail trauma	<input type="checkbox"/>								
Frequent attendance to pools, gyms, spas, or any other warm and moist areas.	<input type="checkbox"/>								
Frequent occlusive footwear	<input type="checkbox"/>								
Psoriasis (nail psoriasis / body psoriasis/psoriatic arthritis)	<input type="checkbox"/>								
Peripheral vascular disease	<input type="checkbox"/>								
Diabetes	<input type="checkbox"/>								
Compromised immune function like HIV or oncological therapy	<input type="checkbox"/>								
Others: please specify:	<input type="checkbox"/>								

22. Considering that DLSO can be quite often mistaken with other nail diseases. Indicate your degree of agreement with the following statements related with **mild to moderate DLSO differential diagnosis suspicion**. Being 1 "Totally disagree" and 9 "Totally agree"

STATEMENTS FOR DLSO DIFFERENTIAL DIAGNOSIS SUSPICION	Totally disagree								Totally agree
In case of DLSO, ...	1	2	3	4	5	6	7	8	9
... the nail colour is solid white	<input type="checkbox"/>								
... the nail colour is yellow/orange	<input type="checkbox"/>								
... the nail colour is salmon pink	<input type="checkbox"/>								
... the nail colour is green	<input type="checkbox"/>								
... there is subungual hyperkeratosis (scales under the distal nail)	<input type="checkbox"/>								
... subungual scales are white-yellow-orange in colour	<input type="checkbox"/>								
... there is periungual inflammation	<input type="checkbox"/>								
... the nail plate is detached	<input type="checkbox"/>								
... the nail plate is thicker and opaque	<input type="checkbox"/>								
... abnormalities are observed on the nail plate surface	<input type="checkbox"/>								
... the nail shows one or several brown-black lines	<input type="checkbox"/>								
... longitudinal fissures are observed on the nail plate	<input type="checkbox"/>								
... the distal margin presents fissuring	<input type="checkbox"/>								
... the patient reports pain	<input type="checkbox"/>								
... only 1 nail is commonly affected	<input type="checkbox"/>								
... all toe nails are commonly affected	<input type="checkbox"/>								
... finger nails can also be affected	<input type="checkbox"/>								

23. How often do you consider that Healthcare professionals non-experts in nail diseases should assess the **treatment efficacy for mild to moderate DLSO**? (one single answer)

- Every month
- Every 3 months
- Every 6 months
- Every year
- Follow-up not needed

24. How relevant are the following **clinical signs** to be assessed to confirm **the effectiveness of a treatment for mild to moderate DLSO in the context of non-experts' real-life practice?**

CLINICAL SIGNS OF DLSO TREATMENT EFFECTIVENESS	Not relevant								Extremely relevant
	1	2	3	4	5	6	7	8	9
The nail colour is normal	<input type="checkbox"/>								
There is no nail detachment (onycholysis)	<input type="checkbox"/>								
The scales under the nails are reduced/absent	<input type="checkbox"/>								
The nail plate is normal	<input type="checkbox"/>								
Periungual inflammation is absent	<input type="checkbox"/>								
All the treated nails are changing in the same way	<input type="checkbox"/>								

25. How relevant are the following **outcomes** to confirm **the effectiveness of a treatment for mild to moderate DLSO in the context of non-experts' real-life practice?**

OUTCOMES OF DLSO TREATMENT EFFECTIVENESS	Less relevant								Most relevant
	1	2	3	4	5	6	7	8	9
The newly grown nail plate is normal	<input type="checkbox"/>								
Normal nail plate appearance	<input type="checkbox"/>								
Satisfied patient with the appearance of the nail plate	<input type="checkbox"/>								

26. When do you consider that a patient with suspicion of **DLSO needs to be referred to a nail specialist?**
Indicate your degree of agreement with the following statements being 1 “Totally disagree” and 9 “Totally agree” (multiple answers)

REFERRAL TO SPECIALIST	Totally disagree								Totally agree
	1	2	3	4	5	6	7	8	9
When the patient presents mild to moderate DLSO	<input type="checkbox"/>								
When patient presents severe DLSO	<input type="checkbox"/>								
In presence of a dermatophytoma (yellow or white streaks or patches in the subungual space. It is a dense fungal mass encased in a layer of biofilm)	<input type="checkbox"/>								
When the nail matrix is involved	<input type="checkbox"/>								
When subungual hyperkeratosis (scales under the distal nail) is thicker than 2mm	<input type="checkbox"/>								
When the topical treatment is not showing efficacy	<input type="checkbox"/>								
When the need for oral treatment is considered	<input type="checkbox"/>								
When the oral treatment is not showing efficacy	<input type="checkbox"/>								
When the fungal infection seems to progress despite oral treatment	<input type="checkbox"/>								
When other treatments in addition to topical and oral are needed, like nail avulsion	<input type="checkbox"/>								
When several/all nails are involved	<input type="checkbox"/>								
When the patient suffers from concurrent nail or skin psoriasis	<input type="checkbox"/>								
When the patient suffers from other nail diseases	<input type="checkbox"/>								
When the patient presents severe comorbidities (uncontrolled diabetes, immunodepression, peripheral vascular disease, ...) or polypharmacy	<input type="checkbox"/>								