

Non-dermatophytes as agents of onychomycosis

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Features of saprotrophic / opportunistic infectious agents

General pathogenesis

Acquiring the fungus is seldom the limiting factor (the load varies)

Local or general (temporary?) debilitating factors may be required

Problems of laboratory diagnosis

Same species also occur as air-borne contaminants

Same species also occur as saprotrophic colonizers

Selective Dermatophyte media give false negative results

Criteria of pathogenesis

No Dermatophyte, or other known disease mechanism, is present

The non-Dermatophyte fungus is present in repeated, well-taken samples

Growth of fungus is confirmed by microscopy (ideally histology)

A disease mechanism (e.g. keratin-attacking enzymes) can plausibly be assumed

Specific eradication of fungus results in clinical cure.

What we know

Long-term growth of these fungi in nails is well documented
(=colonisation or infection, NOT contamination!)

About 10 repeatedly nail-pathogenic genera are recognized

Treatment may differ from Dermatophyte treatment and may be
more difficult

A majority of cases could be cured by careful diagnosis and
antifungal treatments

Typical clinical features and outcomes for some fungi.

What we don't know

Recognition of causative infections from colonization in many individual cases

Targeting sufficient clinical effort in the right cases

Effective diagnosis and treatment practices (including non-fungal causes)

Cell-level ecology and immunology of the fungi in the nails

Specific pathogeneses of rare agents

Candida (= mitosporic Ascomycetes with yeast morphology)

C. albicans, *C. guilliermondii*, *C. tropicalis*... - *C. parapsilosis* is often a milder colonizer.

The most common causes of fingernail onychomycosis. Spain: 60% of true onychomycoses (cured by antifungals) were *Candida*! (Vélez 1997: Mycopathol 137:1). Includes cases secondary to paronychia

Possible symptoms (incl.)

Chronic proximal paronychia

Hyperkeratosis of whole nail plate

Distal + lateral onycholysis

Yeast - search for a reason

Often secondary to local irritation of nail folds (Culture-dependent roles of sexes > high rates in females!)

Peripheral vascular disease (Raynaud) or Cushing's syndrome

Various debilitating factors (HIV, diabetes, hepatic diseases, trauma...)

Specific genetic predispositions (CMCC, about 10 types)

Yeast: Treatment outlines

Underlying paronychia? > isolation of irritant, steroids!
(+ antifungals?)

Control other debilitating factors

Itraconazole or Fluconazole (+topical lacquer?)

CMCC prophylaxis: consider resistance problems

Scytalidium dimidiatum (other mitosporic stage: *Nattractasia*)

Common environmental mould in tropical climate. Rare in the north

Colombia: Comprises 30% of non-dermatophyte onychomycosis

Primary skin and nail pathogen (e.g. foot sole infections common)

Nail: Lateral and distal onychomycosis, extensive onycholysis,
finger paronychia

Drug resistant, difficult to treat. Amorolfine lacquer??

Scopulariopsis (meiosporic stages: *Microascus*)

S. brevicaulis, *S. candida*, *S. acremonium*, *S. brumptii* ...

The most common mould genus in European nails (c. 1-5% of onychomycoses). Old age promotes.

Alpha-keratinolytic enzymes slow but sufficient to primary pathogenesis. Strains of varying activity! (Filipello Marchisio 2000: Mycoses 43:281)

Nail symptoms vary, often proximal subungual onychomycosis of big toe nail. Pathogenesis often difficult to ascertain.

Occur independently from Dermatophytes and traumas but may also follow them. Predisposing factors not solved.

About 70% cured by Itraconazole or Terbinafine for up to 1 year, often combined with local treatments.

Note: The related *Pseudallescheria boydii* is documented as primary nail pathogen in horses (white line disease). Sometimes present in human nails. Significance?

Aspergillus (meiosporic stages *Eurotium*, *Neosartorya* etc.)

A. flavus, *A. fumigatus*, *A. terreus*, *A. versicolor*...

Second most common cause of mould onychomycosis

Typically chalky deep white nail, rapid involvement of lamina,
painful perionyx without pus

Sensitive to Terbinafine (1 week monthly pulses for 3 mths), usually
easy to treat. Also Itraconazole may work.

Fusarium (meiosporic stages *Nectria*, *Gibberella* etc.)

F. solani, *F. oxysporum*, *F. proliferatum*...

Present in the North but more common in South?

(Colombia: 50% of non-dermatophytic onychomycosis)

Occurs also in fingernails

Often proximal subungual leuconychia + (sub)acute paronychia

Drug resistant. Difficult to treat. Only 40% cured by intensive combination therapy (e.g. Itra pulses for 6 mths, combined with siclopirox lacquer).

F. oxysporum may be more Itra sensitive than the others?

Onychocola canadensis (meiosporic stage: *Arachnomyces*)

More than 30 nail cases published in temperate climate.

Rare cases of skin infection

Single nail cases met in the Nordic countries (slow growth!)

Mainly distal lateral subungual onychomycosis (+ white superficial)

Soil contact (+ old age?) may promote

Drug resistant, difficult to treat. Itraconazole??

Other genera include:

Alternaria

About 10 cases published.

Nail often brownish. Soil contact promotes?

Some cases have responded to Itraconazole pulse therapy

Chaetomium

About 10 cases published

Some cases have responded to Itraconazole pulse therapy (6 mths)

Acremonium

About 70% curable by intensive combined therapy (Terbinafine better than Itra?)

Trichosporon

Basidiomycetous yeasts. High nail incidence in Korea? Common but poorly studied in the Nordic countries.

Thinking algorithm (suspected onychomycosis)

Other reasons than fungi? > Treat accordingly

Dermatophyte present? > treat as tinea

Does the Non-Dermatophyte really GROW there?

Ask Lab / Profuse? / Microscopy / Histology / REPEATS!

> IF NOT

> Contaminant

> IF YES

> Colonization or infection

> Handle as presumptive mycosis

(Well-documented colonization

is not a priori separable from infection!)

Does the growth cause disease??

Host factors?

Yeast in fingernails? Household or washing occupation?

> Consider primary irritation of nail folds

Genetic, age-specific or temporary deviations?

> Nail defence against fungi may be altered

Haematological etc. patient?

> Consider the risk of dissemination

Antifungal treatment?

Check typical response of the fungus (moulds often Itra or Terbi S)

Ensure motivation for a long-term project, schedule treatment and follow-ups

More evidence of etiology is provided by the response

Future: Biological studies

Various parts and types of (diseased) nail as microbial niches

Other components than keratin as microbial nutrients

Revealing subtle genetic / immunological / age-dependent predispositions

Initiation and development of disease

Future: Diagnostics:

Ideal: 3D Histological sections, illustrating molecular identification AND enzymatic activity AND drug sensitivity.

Short-term: Rapid, cheap, repeatable molecular identification of all pathogens

Rapid, cheap tests for strain-specific features (pathogenicity, resistance)?

Old and new test limitations (sampling procedures, contamination...)

How and when to combine and repeat tests? Influence of price.

Future: Treatment:

Accumulation of treatment data on rare organisms

Effective systemic treatment for all species

Low-cost topical preventive or disease-limiting treatments?

Future: Public health:

Active search for early disease stages in mid-age population

Public information: Treat your nails early > Keep cute and Save money!