CONTINUING MEDICAL EDUCATION

The Diagnosis and Treatment of Nail Disorders

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SUMMARY

Background: Nail disorders can arise at any age. About half of all nail disorders are of infectious origin, 15% are due to inflammatory or metabolic conditions, and 5% are due to malignancies and pigment disturbances. The differential diagnosis of nail disorders is often an area of uncertainty.

Methods: This review is based on publications and guidelines retrieved by a selective search in PubMed, including Cochrane reviews, meta-analyses, and AWMF guidelines.

Results: Nail disorders are a common reason for dermatologic consultation. They are assessed by clinical inspection, dermatoscopy, diagnostic imaging, microbiological (including mycological) testing, and histopathological examination. Some 10% of the overall population suffers from onychomycosis, with a point prevalence of around 15%. Bacterial infections of the nails are rarer than fungal colonization. High-risk groups for nail disorders include diabetics, dialysis patients, transplant recipients, and cancer patients. Malignant tumors of the nails are often not correctly diagnosed at first. For subungual melanoma, the mean time from the initial symptom to the correct diagnosis is approximately 2 years; this delay is partly responsible for the low 10-year survival rate of only 43%.

Conclusion: Evaluation of the nail organ is an important diagnostic instrument. Aside from onychomycosis, which is a common nail disorder, important differential diagnoses such as malignant diseases, drug side effects, and bacterial infections must be considered.

► Cite this as:
Wollina U, Nenoff P, Haroske G, Haenssle HA: The diagnosis and treatment of nail disorders. Dtsch Arztebl Int 2016; 113: 509–18. DOI: 10.3238/arztebl.2016.0509

The nail primordia at the ends of the fingers and toes come into being from the 8th and 9th weeks of gestation onward; in the 13th week, the nail field and the nail matrix are formed. The latter gives rise to the nail plate from the 14th week onward. By the 20th week, the nail plate already covers the entire nail bed.

At birth, the nail plate extends beyond the tips of the fingers and toes (cf. *eTable* for an overview of mutations with relevance to nail organ development).

The mature nail organ comprises the nail matrix, the nail bed, the nail plate, and the nail fold. The proximal portion of the nail matrix is immediately adjacent to the distal interphalangeal joint and the insertion of the extensor tendon. The latter gives rise to a dense superficial connective-tissue lamina enveloping the nail matrix (e1). The distal portion of the nail matrix is attached to the nail bed. The nail plate covers the distal matrix and nail bed and ends in the free edge of the nail plate. The nail plate is covered proximally by the cuticle; it is held within the nail fold both proximally and laterally. The epithelium that directly covers the nail plate proximal to the cuticle is the eponychium. The horns of the nail plate, which lie under the lateral proximal nail fold, are connected to the bony distal phalanx. The nail bed is distally delimited by the nail isthmus, which is continuous with the hyponychium lying under the free edge of the nail plate. The most distally located structure is the distal groove (1). The isthmus of the nail is completely covered in congenital pterygium inversum unguis (2).

The nail plate consists mainly of parallel keratin filaments, which give it mechanical stability. Aside from minerals and cholesterol, about 7% of the content of the nail is water. The nail bed is essential for horizontal nail growth. The nail plate is 1000 times more permeable to water than the intact skin

Components of the nail

The mature nail organ comprises the nail matrix, the nail bed, the nail plate, and the nail folds.

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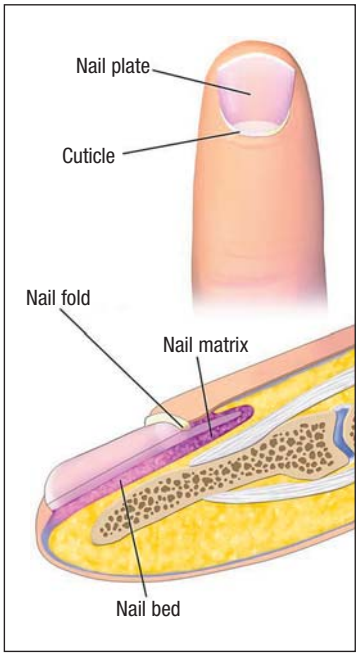

Figure 1: anatomy of the nail organ (modified from Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm "2014.010. ISSN 20018762)

and can also be a site where exogenous substances are deposited, such as medications, drugs of abuse, and arsenic (3). The horizontal growth of the nail depends on an intact connection of the nail plate to the nail bed (e2). Fingernails generally grow faster than toenails (3.5 vs. 1.7 mm/month) (4).

Methods

This review is based on pertinent articles retrieved by a selective search in PubMed and the Cochrane Library, along with the pertinent guidelines of the Association of Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften,* AWMF).

Learning objectives

This article aims to enable the reader to

- understand the anatomy of the nail organ,
- recognize nail involvement in skin diseases and other medical conditions,
- diagnose the clinical features of the main types of tumor affecting the nail organ, and
- be aware of the main types of infectious disease affecting the nail organ and their treatment.

Nail involvement in inflammatory skin diseases

Nail involvement in psoriasis often points to the diagnosis. It is independent of the severity of skin involvement and can cause functional and cosmetic disturbances and pain (5, e3, e4). Nail symptoms are seen in two-thirds of all patients with psoriatic arthritis and in about 40% of psoriasis patients without arthritis (6, e5) *(Table 1)*.

Psoriatic arthritis can be distinguished from rheumatoid arthritis by the combination of distal arthritis with nail changes.

Case presentation

A 46-year-old man presented with pain in one big toe with isolated yellowish thickening of the nail plate. His family physician had diagnosed gout, but medication to lower the uric acid level had not led to any sustained improvement.

The diagnosis of psoriatic onychopachydermoperiostitis (POPP) syndrome was established—a special type of psoriatic arthritis and an important element in the differential diagnosis of acute gout. An elevated uric acid level is often seen in psoriasis vulgaris because of accelerated cutaneous metabolism.

Nail symptoms are present in up to 66% of patients with severe alopecia areata, with speckling as the main type (e6, e7). Working with wet hands can cause irritative hand eczema, resulting in distal onycholysis and brittle nails (8). Allergic contact eczema with inflammation of the nail folds can be seen in acrylate sensitization due to the use of artificial nail extensions. Severe cases can be associated with destruction of the nail plate and acquired pterygium inversum unguis. Ordinary disinfection of the hands is ineffective in persons who have artificial nail extensions (9).

Nail symptoms in general medical disease

Inspection of the nail organs is part of the routine physical examination in internal medicine *(Table 2)*. It can reveal a number of conditions:

- In the differential diagnosis of rheumatoid vs. psoriatic arthritis, the nails should be inspected for typical psoriatic changes (speckled nails, psoriatic oil spot, psoriatic onychomadesis) (5, e4).
- As many as 60% of persons with chronic renal disease have nail manifestations. The double transverse white lines known as Muehrcke lines are a sign of hypoalbuminemia (< 2.2 g/dL) hin (10).

Nail involvement in inflammatory dermatoses

Nail involvement in psoriasis often points to the diagnosis. It is independent of the severity of skin involvement and can cause functional and cosmetic disturbances and pain.

Nail manifestations of internal diseases

Inspection of the nails is part of the routine physical examination in internal medicine.

- Distal ischemia of the acral skin in scleroderma is a cause of acquired irreversible pterygium inversum unguis (1, e8).
- Hourglass nails are a secondary phenomenon arising from clubbing of the fingers. Clubbing is due either to thickening of the soft-tissue covering of the distal phalanx, as in cor pulmonale, or to distal hypertrophic osteoarthropathy, as in chronic diseases of the lung or intestines, cancer (as a paraneoplastic phenomenon or as a manifestation of metastases), cardiac valvular anomalies, or Graves' disease (1).

Drug-induced nail diseases

Nail symptoms arise in 10–60% of patients undergoing anticancer treatment (11) (Table 3). Chronic paronychia causes pain which restricts fine motor activity (12). Immunosuppressants and chemotherapeutic agents can damage the nail plate, leading to Beau-Reil transverse grooves and onychomadesis (reversible, painless, non-inflammatory proximal detachment of the nail plate) (e8).

Subungual and periungual tumors

Warts due to HPV are the most common type of benign growth affecting the nails. About 10% of all children and adolescents have HPV-induced ungual warts; precise data on the their epidemiology are unavailable. Combination therapy is more successful than monotherapy; for example, cryotherapy plus topical salicylic acid is more effective than salicylic acid alone (risk ratio 1.24) (13). Warts should be treated cautiously in order to avoid permanent iatrogenic nail dystrophy (14).

Granuloma teleangiectaticum arises as a sequela of trauma or infection. These lesions tend to bleed (15). Fibrokeratoma is an asymptomatic tumor of adulthood that usually arises as a solitary lesion measuring only a few millimeters (16). Koenen tumors are usually multiple, are of variable size, and appear periungually and subungually; half of all cases arise in persons under age 18. Koenen tumors are a major diagnostic criterion for the tuberous sclerosis complex (e9).

Subungual exostoses and mucoid pseudocysts can cause nail deformities. Painful types of nail tumor include glomus tumor, osteoid osteoma, and acquired digital arteriovenous malformation (ADAVM) (15–18).

The most common malignancies affecting the nails are squamous cell carcinoma and Bowen's disease *(Figure 2e, f)*. The clinical manifestations of Bowen's disease with periungual involvement are erythema, hyperkeratosis, fissures, and scaling; subungual involvement leads to onycholysis. Human pamillomavirus of types 16, 31, 33, 56, and 71 has been demonstrated (19). Nodules, hemorrhages, and ulceration are signs of invasive squamous cell carcinoma (e10). These tumors can arise spontaneously, after chronic arsenic exposure, or after organ transplantation (19, 20).

TABLE 1

Nail involvement in selected inflammatory dermatoses

Dermatosis	Frequency of nail involvement (%)	Manifestations
Alopecia areata	7–66	Speckling, trachyonychia, longitudinal grooves, leukonychia
Atopic eczena	25	Shiny nails, transverse grooves, speckling, paronychia
Dyskeratosis follicularis	90	Onychodystrophy, pachyonychia, anonychia
Contact eczema	80 (hands)	Transverse grooves, paronychia, hyperkeratosis or loss of cuticle and eponychium, brittle nails
Lichen ruber	10	Onychoschisis, anonychia, dystrophy
Pityriasis rubra pilaris	80	Pachyonychia, trachyonychia
Psoriasis	50	Speckling, psoriatic oil spot, crumbling nails, pachyonychia
Scleroderma	80	Trachyonychia, paronychia, pterygium inversum, splinter hemorrhages
Systemic lupus erythematosus	20	Red lunule, splinter hemorrhages

Case illustration

A 45-year-old woman presented to a dermatologist with progressive onychomadesis of the left thumbnail.

Subungual and periungual tumors

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Common malignancies of the nails

The most common malignancies affecting the nails are squamous cell carcinoma and Bowen's disease.

TABLE 2

Nail involvement in general medical diseases

Manifestations	Diseases
Beau-Reil lines (transverse grooves)	Raynaud syndrome, pemphigus, infectious diseases, intoxications
Dolichonychia (long, narrow nails)	Marfan syndrome
Yellow nails	Lymphedema, chronic lung disease, chronic cough, pleural effusion
Mees lines (transverse leukonychia)	Chronic renal disease, chronic ischemic heart disease, severe infectious diseases, intoxications (arsenic, thallium, carbon monoxide, other)
Muehrcke lines (transverse double bands)	Chronic renal disease, liver cirrhosis, malnutrition
Koilonychia (spoon nails)	Iron-deficiency anemia, hemochromatosis
Lindsay nails (white proximally, pink-reddish-brown distally, no blanching)	Chronic renal disease with azotemia
Quincke's pulse (alternating flushing and pallor of the nail beds)	Severe, chronic aortic insufficiency
Acquired raquet nails	Hyperparathyroidism
Splinter hemorrhages	Subacute bacterial endocarditis, rheumatoid arthritis, Terry nails (whitish, opaque nail bed without lunule),liver cirrhosis, chronic ischemic heart disease, diabetes mellitus, hyperthyroidism
Triangular lunule and nail dystrophy	Nephrotic syndrome due to LMX1B mutation
Clubbing of the fingers	Chronic obstructive pulmonary disease, lung cancer, asbestosis, chronic bronchitis, congenital heart disease, endocarditis, chronic inflammatory bowel disease
Hourglass nails	Hypertrophic pulmonary osteoarthropathy (lung cancer, bronchiectasis)—associated with clubbing

Mycological cultures were negative. A nail bed biopsy revealed nonspecific inflammatory changes.

Onychodystrophy with destruction of the nail plate in the absence of fungal infection aroused the suspicion of a malignant tumor of the nail organ. A second biopsy performed some time later yielded the diagnosis of an acrolentiginous melanoma. The definitive treatment was a 3D-guided partial amputation of the distal phalanx of the thumb.

Subungual melanoma accounts for 2% of all melanomas in persons of European ancestry and up to 20% in persons of Asian ancestry (21). Timely nail biopsy enables the definitive diagnosis. Subungual melanoma cannot be reliably distinguished from longitudinal melanonychia by inspection alone.

Pigmentation of the cuticle and proximal nail fold (the Hutchinson sign) is typical of melanoma, though it is not seen in all cases *(Figure 2a, c)* (22, 23). Dermatoscopy, an optical technique, is useful for the differential diagnosis of nail pigmentation. It reveals individual pigment lines of varying color and intensity *(Figure 2b, c–f)*. The additional information provided by dermatoscopy enables early detection of disease (23).

The Hutchinson sign is often absent in *in situ* or early invasive melanoma *(Figure 2a)* (24). Advanced melanoma is associated with ulcerations, hemorrhages, loss of parallelism of the bands, multiple colors, blurry borders, and marked invasion into the neighboring skin. Thicker tumors are more likely to infiltrate the bone as well (21). Subungual melanomas can also be amelanotic, in which case they are harder to recognize clinically. A biopsy to rule out melanoma is necessary for any patient with nail dystrophy, subungual hyperpigmentation, or persistent "hematomas" of unknown cause. Unfortunately, the mean delay from the onset of symptoms to surgery is 2.2 years. The prognosis of subungual melanoma is, therefore, much

Nail dystrophy of uncertain type

A biopsy to rule out melanoma is necessary for any patient with nail dystrophy, subungual hyperpigmentation, or persistent "hematomas" of unknown cause.

Onychomycosis

Onychomycosis is an infection of the nail apparatus by dermatophytes, yeasts, or molds.

TABLE 3

Drug-induced nail abnormalities

Drug	Nail abnormality
Vitamin A	Dystrophy
Anthracyclines and taxanes	Painful (photo-)onycholysis, subungual abscesses, melanonychia
EGFR inhibitors	Paronychia, unguis incarnatus, granuloma telangiectaticum
D-penicillamine, bucillamine	Yellow nail syndrome
Hydroxyurea	Melanonychia (brownish-black discoloration)
Indinavir, retinoids, chemotherapeutic drugs	Onychomadesis, Beau-Reil lines
mTOR inhibitors	Dystrophy, yellow nail syndrome, distal onycholysis, paronychia
Rituximab	Multiple granulomata teleangiectatica
Tetracyclines, retinoids, clofazimine, zidovudine, quinolones	Photo-onycholysis, discoloration

EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin

worse than that of cutaneous melanoma, with a disease-specific 10-year survival rate of only 43% (25, 26). It is treated with micrographically guided surgery (21, 22).

Infectious diseases of the nails

Onychomycosis is an infection of the nail apparatus by dermatophytes, yeasts, or molds. Tinea unguium (this is the plural form; if only one nail is affected, tinea unguis) is caused exclusively by dermatophytes. Fungal infections of the nails are stigmatizing for the patient, causing difficulties in both personal and professional life (27).

Onychomycoses are found all over the world (28). In Europe and the USA, their population-based prevalence is 4.3%; hospital-based studies reveal a prevalence of 8.9% (29). The prevalence increases with age and is highest in persons over age 65. Men are more commonly affected than women, children markedly less so.

The pathogen most commonly causing onychomycosis is *Trichophyton rubrum*, accounting for about 65% of cases. Molds are found in 13.3% of cases, yeasts in 21.1% (29). In the authors' own retrospective study, the pathogens were dermatophytes in 68% of cases, yeasts in 29%, molds in 3%, and mixed flora in 5–15% (30).

Of all the dermatophytes isolated from patients with onychomycosis, *T. rubrum* is the most common species (ca. 91%), followed by *T. interdigitale* (earlier name: *T. mentagrophytes* var. *interdigitale*) (ca. 7.7%) (30). Rarely isolated organisms include *Epidermophyton floccosum* and *T. tonsurans*. These are anthropophilic dermatophytes, i.e., they cause disease only in humans.

Yeasts are emerging pathogens of onychomycosis that are now being more commonly diagnosed as the causative organisms of onychomycosis. *Candida parapsilosis* is the most common one, followed by *C. guilliermondii*. *C. albicans* causes chronic mucocutaneous candidiasis, which involves the entire nail apparatus (e11).

Molds, also called non-dermatophyte molds (NDM), are also being increasingly diagnosed as the causative organisms of onychomycosis (31). *Scopulariopsis brevicaulis* causes onychomycosis of the big toenails. *Fusarium spp.* is considered an emerging pathogen (28). Further mold pathogens include *Onychocola canadensis* (e12), *Aspergillus fumigatus, Acremonium spp., Chrysosporium pannorum, Neoscytalidium dimidiatum* (earlier name: *Hendersonula toruloidea*), *Arthrographis kalrae, Chaetomium globosum* as well as *T. interdigitale*, and *Chaetomium globosum* (31, 32, e13).

These infections can be transmitted within the family, e.g., in the home bathtub, either horizontally (from one spouse to the other) or vertically (across generations). Further sources of infection include swimming pools, bathhouses, saunas, sporting facilities, etc. Predisposing factors include prior nail trauma, advanced age (slower nail growth, poorer limb circulation), vascular diseases, lymph

Common dermatophytes

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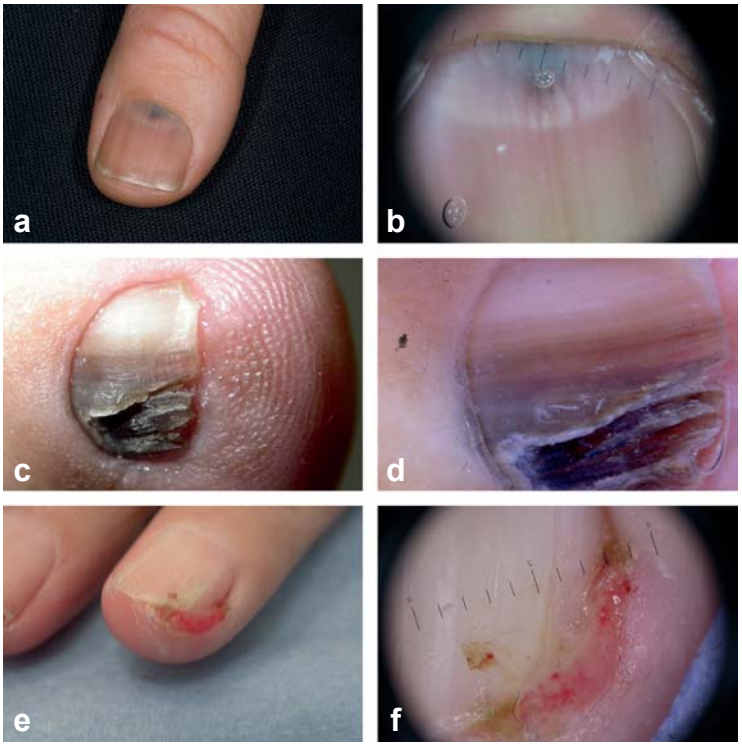

Figure 2: the clinical and dermatoscopic features of common nail disorders

a) and b): early subungual acrolentiginous melanoma.
a) Clinical image of subungual blue discoloration in the area of the lunula.
b) Dermatoscopy showing unstructured blueish-gray lunular pigmentation with incipient longitudinal pigment striae in the nail plate.
c) and d): subungual invasive melanoma.
c) Black pigmentation under the nail and also within the partially destroyed nail plate. Incipient Hutchinson phenomenon on the proximal nail fold and cuticle.
d) Dermatoscopy showing longitudinal bands of varying widths and colors.
e) and (f): Bowen's disease of the nail bed.
e) Clinical appearance resembling that of a chronic paronychia.
f) Dermatoscopy showing partial destruction of the distal nail groove and hyponychium, together with the characteristic "dots along lines" pattern (red dots along dilated vessels)

edema, diabetes mellitus, immune compromise, tinea pedis, psoriasis vulgaris, psoriasis unguium, and hyperhidrosis. Older persons often have multiple risk factors. Candida onychomycoses often affect immunosuppressed persons (33).

There is an autosomal dominant genetic predisposition to distal subungual onychomycosis due to *T. rubrum* (e14).

Onychomycosis is present in only about half of all pathological changes of the nails that visually suggest a fungal infection (e14). The differential diagnosis includes non-infectious nail diseases such as psoriasis unguium, lichen ruber, yellow nail syndrome, and tumors.

Toenails are affected much more often by onychomycosis than fingernails because of trauma (shoes) and underlying vascular diseases. Onychomycosis most commonly appears in the form of distal and/or lateral subungual onychomycosis. The pathogens invade the distal/lateral portion of the nail bed, leading to subungual hyperkeratosis, discoloration (dyschromia), and onycholysis *(Figure 3)*.

In white superficial onychomycosis (leukonychia trichophytica), a rarer condition, the fungal pathogens invade from the surface of the nail plate. This condition exclusively affects toenails. The most common pathogen is *T. rubrum*; *T. interdigitale* is rare. The mold *Fusarium spp.* is a further cause.

In proximal subungual onychomycosis, the infection proceeds from the cuticle (particularly in immunosuppressed patients). The maximal variant of fungal disease of the nail is total dystrophic onychomycosis. In endonyx onychomycosis—caused in the tropics by *T. soudanense*—the nail plate is thickened. Candida onychomycosis is generally associated with paronychia (inflammation of the nail fold) (34).

Diagnostic evaluation

Onychomycosis has broad differential diagnosis and cannot be diagnosed on clinical grounds alone *(Figure 3)*. Mere inspection has the highest false-positive rate of any diagnostic method. Rather, the diagnosis should be based on mycological laboratory tests—either a potassium hydroxide preparation or an optical fluorescence preparation, along with growth of the pathogenic fungus in culture—in treatment-naive patients (the diagnostic gold standard). The histologic demonstration of fungi causing nail infections by means of the periodic acid Schiff (PAS) reaction after a punch biopsy of the nails, or nail clippings, is likewise highly sensitive. Neither the native preparation nor the histologically examined specimen enables determination of the genus or species of the responsible fungus; culture alone enables identification down to the species level (e15, e16). There are also newer molecular-biological methods such as the polymerase chain reaction (PCR) for the direct demonstration of dermatophyte DNA in nail specimens. A PCR enzyme immunoassay (EIA) with primers specifically directed against the topoisomerase II gene can directly detect the dermatophytes *T. rubrum, T. interdigitale,* and *Epidermophyton floccosum* in clinical material (35). Used as a complement to

Non-infectious causes of nail disease

Onychomycosis is present in only about half of all pathological changes of the nails that visually suggest a fungal infection. The differential diagnosis includes a variety of non-infectious nail diseases.

The diagnosis of onychomycosis

Onychomycosis should not be diagnosed on clinical grounds alone. The diagnosis should be based on mycological laboratory tests, including the demonstration of the fungal pathogen by culture of a specimen taken from the treatment-naive patient.

conventional fungal culture, the direct demonstration of pathogenic fungi in nail tissue by PCR, multiple-fungus PCR for the simultaneous identification of (for example) 20 relevant types of fungus, or real-time PCR for the detection of dermatophyte DNA enable much faster, highly sensitive, and very specific diagnosis (33). *In vitro* sensitivity testing, although a routine part of the work-up of bacterial infections, is not commonly done for fungi.

A limited onychomycosis that does not involve the matrix often responds to topical treatment alone. On the other hand, matrix involvement—often recognizable from the so-called yellow streaks—should be treated with a systemic antimycotic drug, generally in combination with a topical one. The decision on the optimal type of treatment is also based on the number of affected fingernails or toenails, the extent of nail involvement, multimorbidity, drug interactions, and the identified pathogen *(Table 4)*. For topical use, water-soluble ciclopiroxolamine nail varnish is more effective than amorolfin (36).

Confirmed dermatophyte infections should be treated with terbinafin, fluconazole, or itraconazole, while confirmed *Candida spp.* infections are preferably treated with fluconazole. Either continuous or intermittent therapy is possible, depending on the preparation; terbinafin yields the highest response rate (37). Persons with liver disease should only be given systemic antimycotic drugs for strict indications. The recurrence rate of fungal nail infections within 36 months of the end of treatment ranges from 20% to 50% (e17).

Onychomycosis due to molds generally does not respond to systemic antimycotic treatment. In infections with *Aspergillus* species and *Scopulariopsis brevicaulis*, a trial of oral terbinafin may be successful. There remains the option of atraumatic nail removal with 40% urea (34). The utility of laser treatment for onychomycosis is debated (38–40).

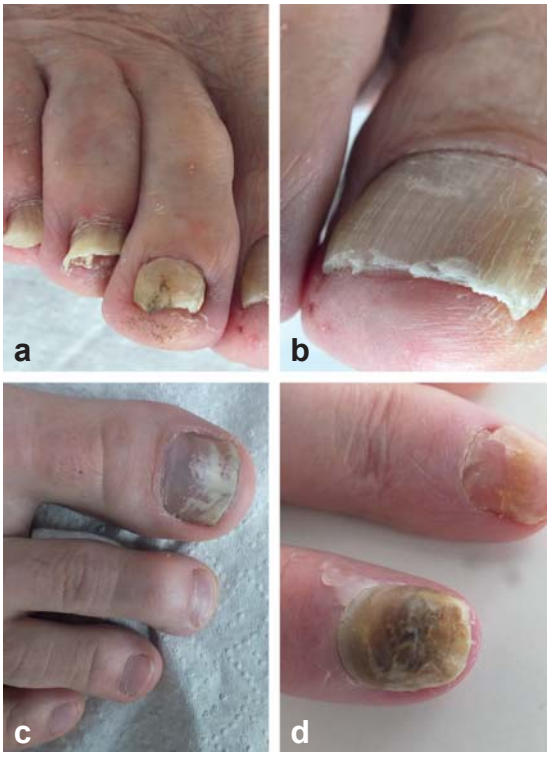

Figure 3: Onychomycoses

a) Distal-lateral subungual onychomycosis due to *T. rubrum* in a 79-year-old man

b) Onychomycosis of the big toenail in the same patient, with lateral white streaks. There is visible subungual hyperkeratosis of the markedly thickened nail plate, which is no longer transparent and manifests a yellowish-brown discoloration

c) White superficial onychomycosis (leuconychia trichophytica) in a 41-year-old man

d) Total dystrophic onychomycosis of the fingernails due to *C. albicans* and *Aspergillus niger* in an 88-year-old man

Bacterial infections of the nails

Bacterial infections of the nails often arise out of acute or chronic paronychia, from which *Staphylococcus aureus* bacteria or streptococci can spread under the nail. Subungual bacterial infection can also be caused by *Pseudomonas aeruginosa*. Risk factors include repetitive minor trauma, working in damp conditions, onychotillomania (compulsive nail-picking or nail-tearing), psoriasis, thumb-sucking, diabetes mellitus, and immunosuppression. The greenish nail discoloration characteristic of *Pseudomonas* infection is probably caused by the diffusion of pyocyanin into the nail tissue, or else by bacterial invasion of the nail plate (e18).

Artificial fingernails are more heavily colonized than natural ones by both bacteria (mainly Gram-negative bacilli) and fungi (mainly *Candida spp.*) (e19, e20).

There have not been any controlled clinical trials on the treatment of bacterial nail infections. There have been reports of the successful topical treatment of fingernail infections due to *Pseudomonas*

Onychomycosis and molds

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The state of the evidence

There have not been any controlled clinical trials on the treatment of bacterial nail infections.

TABLE 4

The treatment of onychomycosis (usual duration: 6 weeks for fingernail involvement, 12 weeks for toenail involvement)*

Treatment	Indication	Active agent	Dosing schedule and cure rate (culture)	Level of evidence
Atraumatic nail extraction	Prior to specific treatment	20–40% urea with occlusion	Daily Cure rate unknown	III
Antifungal nail varnish	Monotherapy only if <50% of the nail surface is affected and no more than 3 nails are affected, without matrix involvement	Ciclopiroxolamine	Daily for 48 weeks, 58.3%	Ia
		Amorolfin	1 × / week for 48 weeks, 26.7%	Ia
Systemic antifungal treatment	Involvement of >50% of the nail surface or of >3 nails, or if there is proximal subungual onychomycosis	Terbinafin	250 mg qd for 6–12 weeks, 76%	Ia
		Itraconazole	200 mg bid for 1 week, then pause for 3 weeks and repeat	Ia
			6–12 weeks (pulse therapy), 63%	Ia
			200 mg qd for 6–12 weeks (continuous treatment), 69%	Ia
		Fluconazole	150–300 mg 1 ×/ week for 3–12 months, 48%	Ia
Laser therapy	Currently debated	Various kinds of laser	–	IV

*modified from (40)

aeruginosa and other Gram-negative bacteria with nadifloxacin (e18, e21). 0.1% octenidine also appears to be effective (e19).

Ciprofloxacin is used for the systemic antibiotic treatment of *Pseudomonas* infections of the nails.

Nail infections due to *Staphylococcus aureus* and Gram-negative bacteria, such as *Klebsiella spp.*, are treated according to the sensitivities and resistances revealed by the antibiogram.

Conflict of interest statement
Dr. Nenoff owns Pfizer stock. He has served as a paid consultant for Galderma and has received lecture honoraria from Hermal, Galderma, and MSD.

Prof. Wollina, Dr. Haenssle, and Prof. Haroske state that they have no conflict of interest.

Manuscript received on 8 January 2016, revised version accepted on 25. April 2016.

Translated from the original German by Ethan Taub, M.D.

Artificial fingernails

Artificial fingernails are more heavily colonized than natural ones by both bacteria (mainly Gramnegative bacilli) and fungi (mainly *Candida spp.*).

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Supplementary material
For eReferences please refer to:
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Question 1

The end product of the nail organ is the nail plate. What structure is essential for horizontal nail growth?

a) the nail root
b) the lateral nail fold
c) the nail bed
d) the hyponychium
e) the horns of the nail plate

Question 2

What manifestation is of greatest help in the differential diagnosis of rheumatoid arthritis from psoriatic arthritis?

a) the combination of distal arthritis with nail changes
b) the combination of nail plate discoloration with nail fragility
c) the combination of scalp dandruff with onycholysis
d) the combination of melanonychia with pterygium inversum unguis
e) the combination of work with damp hands and brittle nails

Question 3

Hypoalbuminemia should be ruled out if which of the following manifestations is present?

a) splinter hemorrhages of the nail plate
b) Muehrcke lines
c) Beau-Reil lines
d) brittle nails
e) hourglass nails

Question 4

What kind of cancer is common among persons with nail disorders?

a) fibrokeratoma
b) Koenen tumor
c) squamous cell carcinoma
d) granuloma teleangiectaticum
e) hyperkeratosis

Question 5

What change causes hourglass nails?

a) shortening of the distal phalanx
b) a disturbance of the nail matrix
c) hypertrophy of the distal phalanx or of the subcutaneous soft tissue
d) thinning of the nail plate
e) onychomycosis

Question 6

Dermatoscopy, an optical technique, is particularly useful in the differential diagnosis of what type of nail abnormality?

a) nail pigmentation
b) onychorrhexis
c) speckling
d) trachyonychia
e) tender nail plate

Question 7

What type of fungus is the most common cause of onychomycosis in Germany and elsewhere in Europe?

a) Trichophyton rubrum
b) Trichophyton interdigitale
c) Epidermophyton floccosum
d) Candida albicans
e) Trichophyton tonsurans

Question 8

What diagnostic method is most likely to yield a false positive diagnosis of onychomycosis?

a) a potassium hydroxide preparation
b) fungal culture
c) nail histology
d) visual inspection
e) dermatoscopy

Question 9

What nail change is a sign of chronic renal disease with azotemia?

a) Lindsay's nails
b) Beau-Reil lines
c) Muehrcke lines
d) yellow nails
e) hourglass nails

Question 10

What nail change is due to excessive vitamin A intake?

a) distal onycholysis
b) dystrophy
c) subungual abscesses
d) melanonychia
e) paronychia

Supplementary material to:

The Diagnosis and Treatment of Nail Disorders

by Uwe Wollina, Pietro Nenoff, Gunter Haroske, and Holger A. Haenssle

Dtsch Arztebl Int 2016; 113: 509–18. DOI: 10.3238/arztebl.2016.0509

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eTABLE

A selection of identified mutations that affect the nail organ

Mutation	Consequence
Frizzled6	Nail dystrophy
Frizzled agonist R-spondin 4 (RSPO4)	Anonychia
FZD6	Severe isolated autosomal recessive nail dysplasia
Keratin 16 and keratin 6a	Pachyonychia congenita type 1
Keratin 17 and keratin 6b	Pachyonychia congenita type 2
KRT74, KRT85, or HOXC13	Pure ectodermal hair and nail dysplasia (PHNED) (nails: koilonychia, micronychia, distal onycholysis)
LMX1B	Nail-patella syndrome
MSX1	Witkop syndrome (hypodontia-nail dysplasia syndrome with koilonychia or anonychia)
MSX2-noggin	Polydactyly
TP63	Acrodermato-ungual-lacrimal-tooth (ADULT) syndrome; ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC or Hay-Wells syndrome)
WNT10A	Odonto-onychodermal dysplasia (OODD)