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Onychomycosis guideline update

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Self-medication with antimycotic nail polishes plays an important role in Germany due to the numerous OTC drugs available and an increasing number of onychomycosis cases. Older patients in particular are more frequently affected due to slower nail growth and the possible existence of predisposing diseases [1]. But the prevalence is also increasing in children [2]. This makes guideline-based recommendations regarding diagnosis, therapy and prophylaxis of onychomycosis all the more important.

The recently published guideline „Onychomycosis" (AWMF register no.: 013-003, 2022) under the direction of Professor Pietro Nenoff, MD, represents the first update of the diagnosis, therapy and prophylaxis of onychomycosis since 2006 [3]. In addition, current treatment approaches such as laser therapy have been evaluated. Also important are the recommendations included on onychomycosis in children, the treatment of which, in Germany, falls predominantly in the area of off-label use due to the lack of clinical studies involving children. Furthermore, the treatment of athlete's foot (tinea pedis, pedum) receives a particular mention, since onychomycosis often develops from an existing case of athlete's foot and the risk of recurrence after successful therapy increases if it is not treated simultaneously. For prophylaxis, the long-term use of antimycotic nail polish preparations in reduced application frequency is considered, as well as the use of disinfectant shoe sprays with quaternary ammonium compounds (didecyl dimethyl ammonium chloride and polyhexamethylene biguanide HCl) and washing of contaminated laundry at 60 °C.

Nail fungus (onychomycosis) is a chronic fungal infection of the fingernails and/or toenails and leads to slow destruction of the nail plate, as the fungus feeds on the keratin of the nail. The infection is progressive if left untreated and has no self-healing tendency (**Tab. 1**). The pathogens can vary depending on the climatic zones. In temperate climate zones – alongside Germany, other European countries and North America – the pathogens are predominantly dermatophytes. A nail fungus infection that is exclusively caused by dermatophytes is also called tinea unguium. In Germany, the most common dermatophyte causing nail fungus is *Trichophyton rubrum*. Candida onychomycosis is less common and onychomycosis caused by moulds is very rare. If yeast fungi (**Candida** spp.) are positively detected, secondary colonisation without significance as illness should always be considered. When yeasts are detected from fingernails, onychomycosis is more likely than when *Candida* species are cultured from toenail material. Moulds – also called „nondermatophyte moulds" (NDM) – occur more frequently in subtropical and tropical regions. Therefore, the pathogens will not be discussed further here.

Tab. 1. General guideline recommendation for therapy (according to Nenoff P et al. S1 guideline onychomycosis [3])

Guideline recommendation
The infection has no self-healing tendency and can become the starting point for further mycosis lesions of the skin and for bacterial complications, so it should be treated unless there are contraindications.

Diagnosis – treatment of onychomycosis based on clinical picture and pathogen detection

The therapy is based on the clinical picture of the infection and the detection of the pathogen, usually by direct microscopy using a native preparation and cultural detection. Molecular detection, for example by means of polymerase chain reaction (PCR), is not the rule, but is recommended due to its high sensitivity and specificity. The correct collection of material is particularly important for successful diagnosis. Nail chips should, as far as possible, be obtained from the proximal border of the visible nail change (ideally by milling). With regard to the clinical picture of onychomycosis, the guideline distinguishes five forms: distolateral subungual onychomycosis (DSO), proximal subungual onychomycosis (PSO), proximal white subungual onychomycosis (PWO), white superficial onychomycosis (WSO) and total dystrophic onychomycosis (TDO). DSO is the most common form and can be treated locally if the nail matrix is not affected. Further criteria for self-medication are a maximum of 40% of the

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nail surface being affected and a maximum of three out of ten toenails being affected. According to the international consensus conference, less than 50% of the nail should be affected [4].

Treatment of onychomycosis

The guideline defines the following therapeutic goals for the first time:

1. Complete elimination of the pathogen as quickly and safely as possible, defined by a negative control examination (if possible using PCR method*)
   *Fungal detection by means of PCR is reimbursable for privately insured persons according to the German Fee Schedule for Doctors. Those with statutory health insurance must pay for the service themselves.
2. Clinically speaking, largely healthy nails (usually defined as <5–10% residual change at the distal nail edge).
3. Prevention of further transmission or interruption of infection chains

Before starting treatment, the limits of self-medication with a local antimycotic should be considered. Furthermore, comorbidities with regard to possible drug interactions play an important role in the therapy decision, as does the expected compliance of the patient owing to the long therapy duration caused by the slow nail growth.

Mild or moderately pronounced nail infections in which the nail matrix is not affected can be treated locally with antimycotic polishes. In addition to waterproof acrylic polishes with the active ingredients amorolfine or ciclopirox, the guideline recommends a water-soluble polish based on a special HPCH polish technology with the active ingredient ciclopirox (P-3051). In this polish, the antimycotic is bound to a water-soluble biopolymer hydroxypropyl chitosan (HPCH), which enables better transport and release of the active ingredient ciclopirox through its binding to nail keratin.

The chitosan-containing hydrofilm also has an antibacterial effect. The polish is applied once a day. According to the guideline authors, another advantage of this HPCH polish technology is its high biocompatibility with the surrounding (nail) skin, so that application can be made to the residual nail or nail bed, especially after atraumatic nail removal using urea or milling machine. Acrylic-containing polish formulations with the active ingredient amorolfine should not be applied to the skin around the affected nail, according to the information leaflet containing special warnings and precautions for use [5].

Keratolysis with 40% urea preparations under occlusion has become an established method for atraumatic nail removal. The guideline recommends this procedure only as an adjuvant measure before local and systemic antimycotic treatment of onychomycosis to reduce the fungus-infected and hyperkeratotic nail material. „A long-lasting effect and mycological cure cannot be achieved with atraumatic nail removal. Traumatic nail extraction, i.e. the surgical procedure and surgical extraction of fungus-infected nails, which was frequently performed in the past, is now considered obsolete in onychomycosis and should no longer be performed. It is painful, prevents the patient from being able to work, and can lead to irreversible damage to the nail bed with subsequent onychodystrophy. The removal of the mycotically altered parts of the nail by means of milling, for example in a podiatrist's practice, makes sense and has positive effects on the healing process. Milling the nails is particularly recommended in the case of topical monotherapy with antimycotic polishes" [3]. Milling can also reach local cavities that often have a particularly high fungal load, so-called dermatophytomas, which additionally increases the success of the therapy.

Another antifungal agent - efinaconazole - is mentioned in the guideline as part of the listing of the Cochrane meta-analysis. In their paper entitled „Topical and device-based treatments for fungal infections of the toenails", Foley et al [6] evaluated the study evidence of 56 randomised controlled trials (RCTs). As a result, the studies on efinaconazole, which is currently not available on the German market, were rated as providing high-quality evidence with regard to the endpoint of complete healing. Moderate-quality evidence was assigned to the studies of P-3051 (water-soluble ciclopirox 8% nail polish) and tavaborole (not available in Germany, on the market in the USA), and only low-quality evidence was assigned to the studies on complete healing for ciclopirox 8% acrylic nail polish. Studies on acrylic amorolfine polishes are not mentioned in the meta-analysis.

As soon as the nail matrix is infected or a moderate to severe infection is present, oral (systemic) therapy is always recommended, provided there are no contraindications. Antifungal combination therapy with a local antifungal nail polish is recommended due to synergistic effects. Systemic therapy with terbinafine for infections caused by dermatophytes is the drug of choice because of its good fungicidal rather than only fungistatic efficacy. Neither the risk of side effects nor the number of relapses differed between terbinafine and azole antifungals. Other ergosterol inhibitors for systemic therapy are the predominantly fungistatic azoles such as itraconazole and fluconazole. According to the guideline commission, the extent to which itraconazole embedded in SUBA (super bioavailability) polymer represents an alternative to conventional itraconazole still needs to be investigated.

The most important therapeutic recommendations are listed in **Table 2**.

Onychomycosis in children

Although fungal nail infections in children are atypical, increasing prevalence figures give reason for concern and education about appropriate treatment options. In their systematic review, Vestergaard-Jensen et al. [7] examined the changes in prevalence of onychomycosis in children. Population studies from 1972 to 2014 were evaluated and prevalences ranging from 0% to 7.66% with an overall discrete increase of 0.66% were noted (not statistically significant). The guideline authors also addressed the topic for the first time and included the section „Onychomycosis in children" in the guideline update [3].

Because of the faster nail growth in children, local antifungal therapy can always be considered as a first step. Systemic therapy is recommended in the advanced stage, but is often rejected by the parents or guardians. Adequate education plays an important role here. Modern systemic antimycotics such as terbinafine, fluconazole or itraconazole are not approved for use in children in Germany due to a lack of clinical data (unlike, for example, terbinafine in Austria

Tab. 2. Overview of guideline-based treatment (according to Nenoff P et al. S1 guideline on onychomycosis [3])

Local treatment	**Local treatment with antifungal nail polish is recommended for mild or moderate nail infections (distal subungual onychomycosis, white superficial onychomycosis, max. 40% of the nail surface affected and/or max. 3 of 10 toenails affected).** **Filing or roughening is recommended to reduce the diseased parts of the nail.**		
	Nail polish preparation	*Application frequency*	
	Amorolfine HCl 5% Acrylic nail polish (up to 80% nail surface)	1 x per week	
	Ciclopirox 8% acrylic nail polish	Every 2 days, from 2nd month 2 x per week	
	Ciclopirox 8% nail polish water-soluble + HP chitosan	1 x daily	
	Terbinafine (78.22 mg terbinafine/ml nail polish) water-soluble nail polish + HP chitosan	1 x daily for 4 weeks, then 1 x per week	
Systemic treatment	**For moderate and severe onychomycosis, it is recommended, provided there are no contraindications, to always treat orally (systemically). A combination antimycotic therapy (oral and topical) should be aspired to.**		
	Terbinafine	*Fluconazole*	*Itraconazole*
	250 mg 1 x daily Toenails affected: 12 weeks Only fingernails affected : 6 weeks	150 mg 1 x per week for 3–6 months for onychomycosis of the fingernails and 6–12 months for toenail infection	Interval treatment: 400 mg daily (2 x 2 capsules à 100 mg per day [400 mg]) for 1 week, then three weeks' break = 1 pulse. Three pulses (1 week itraconazole + 3 weeks' break) or 3 months for toenail infection. For fingernail onychomycosis a shorter time, possibly only 2 pulses.
			Continuous administration: Conventional itraconazole Once daily 200 mg (2 hard capsules) for 3 months, shorter if fingernail infection. SUBA-itraconazole For Tinea unguium, 2 capsules à 50 mg (= 100 mg/d) daily for 12 weeks
	Intermittent low-dose terbinafine therapy (off-label use, not supported by studies, „expert opinion") 250 mg terbinafine daily for 3 days, then 250 mg once per week until clinical cure (up to 1 year)		Intermittent low-dose itraconazole therapy (off-label use, not supported by studies, „expert opinion") Loading phase: 2 x 100 mg SUBA-itraconazole (2 x 2 capsules à 50 mg) for 3 days, then maintenance therapy once a week 2 x 100 mg SUBA-itraconazole (= 2 x 2 capsules à 50 mg) until clinical cure (up to 1 year)
Selection of the antimycotic	Dermatophytes: Trichophyton rubrum (most frequent causative agent) Trichophyton interdigitale (second most frequent causative agent)	Topical: Amorolfine or ciclopirox nail polishes Systemic: Terbinafine (T.rubrum + T.interdigitale), fluconazole (T.rubrum), itraconazole (T.rubrum + T.interdigitale)	
	Yeasts: Candida albicans and Candida parapsilosis (often on fingernails)	Topical: Amorolfine or ciclopirox nail polish If necessary, additionally systemic: Fluconazole p.o. (continuous or interval therapy) or itraconazole, in the case of Candida parapsilosis terbinafine is also possible	
	Moulds: Scopulariopsis brevicaulis (common)	Topical: Atraumatic nail removal with 40% urea paste. Amorolfine or ciclopiroxolamine nail polish, if necessary amphotericin B* (as suspension, *off-label use). Often no response to systemic antifungal therapy; exception: Aspergillus spp., Onychocola canadensis (new: Arachnomyces nodosetosus): Terbinafine p.o. works in individual cases	

HP-Chitosan: Biopolymer Hydroxypropyl chitosan (HPCH); SUBA: Super-bioavailability-Polymer

Tab. 3. Guideline recommendation for local and systemic therapy in childhood (according to Nenoff P et al. S1 guideline onychomycosis)

Local and systemic therapy in childhood	**Topical therapy is recommended for initial onychomycosis in childhood.** **For advanced onychomycosis in childhood, systemic therapy is recommended.**		
	Terbinafine (off-label use)	*Fluconazole (off-label use)*	*Itraconazole (off-Label use)*
	62.5 mg/day for a bw of <20 kg or 125 mg/day for >20–40 kg bw or 250 mg/day for >40 kg bw. Continuous administration for 12 weeks.	3–5 mg/kg bw (up to max. 50 mg/d) until healthy nail outgrowth	5 mg/kg bw once daily. Capsules with the main meal, the solution one hour after the meal at the earliest on an empty stomach. Practical procedure: 50 mg daily for bw <20 kg or 100 mg daily for >20 kg bw. Under 10 kg bw strictly body weight-adapted.
	Intermittent low-dose therapy (not supported by studies; „Expert opinion") Loading phase: Terbinafine dosed according to body weight (see above) daily for 3 days, then one dose per week until clinical cure (up to 1 year).	Intermittent therapy 6 mg/kg bw once a week for 3–6 months for onychomycosis of the fingernails and 6–12 months for toenail infection. Until clinical cure (up to 1 year).	Intermittent low-dose therapy (not supported by studies. Expert opinion) SUBA-itraconazole: Children 7–12 years 2 x 50 mg for 3 days (loading phase), then once a week 2 x 50 mg SUBA-itraconazole. In children <7 years: 50 mg daily for 3 days (loading phase), then application once a week 50 mg. Until healthy nail growth.

and Switzerland, where it is approved for use in children). Especially for terbinafine, there has been good experience regarding the weight-adapted therapy of onychomycosis in children. Griseofulvin was approved for treating children, but since 2018 has no longer been on the market in Germany and could only be ordered via the international pharmacy. However, this antimycotic is not recommended for treating onychomycosis in children due to lower efficacy, high relapse rate, and frequent side effects.

The most important therapeutic recommendations of the guideline on onychomycosis in children are summarised in **Table 3**.

Prophylaxis after treatment of onychomycosis

According to the guidelines, a prophylactic further treatment of the nail with antimycotic nail polishes in reduced application frequency after successful onychomycosis therapy can be considered in individual cases. This recommendation is not evidence-based due to lack of clinical studies. The treatment of existing athlete's foot with antimycotic sprays, solutions or creams is recommended and presumably also has a prophylactic effect to reduce the recurrence risk of onychomycosis.

Another prophylactic measure is shoe disinfection. Fungal elements can survive in shoes for up to six months or longer [9]. According to the guideline, a dosage spray with an aqueous solution that does not contain propellant gas or alcohol, does not attack the colour of the shoes and is highly effective due to two quaternary ammonium compounds (didecyldimethylammonium chloride and polyhexamethylene biguanide HCl) is particularly suitable. Laundry that has direct contact with the mycosis, for example socks and towels, should be washed at 60 °C [9].

The complete guideline contents (register number 013 - 003) are available on the AWMF portal (https://www.awmf.org/leitlinien/detail/ll/013-003.html)

All information is given to the best of our knowledge and belief, but no liability is accepted in individual cases, especially for dosage recommendations, which must be checked individually and updated.

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