Clinically Relevant Mycoses Dermatomycoses

10

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10.1 Definition of Dermatomycoses

The term dermatomycoses comprises superficial fungal infections of the skin and their appendages like the hair follicles and the nail apparatus. These superficial mycoses may be caused by dermatophytes or yeasts and, to a less extend, by moulds. These infections are of high importance in medical disciplines not only for the dermatologist but also for physician and the paediatrician and of course for the patients affected. With regard to the treatment of these fungal infections, the costs of topical antifungals will surpass topical corticosteroids in the healthcare system.

10.2 Superficial Mycoses Caused by Dermatophytes (Dermatophytoses, Ringworm Infection)

Dermatophytoses are caused by different classes of dermatophytes with potency to invade the stratum corneum as well as the hair follicle and the nail apparatus. If caused by anthropophilic species, they produce little to no inflammatory host-mediated immune response resulting in chronic course of infection and missing self resolution. Zoophilic or geophilic species may cause acute, inflammatory mycoses.

Dermatophytoses are of worldwide distribution. Their epidemiology depends from many circumstances, i.e. geographical regions, occupational and social aspects, travel, migration, preventive education and modern conveniences such as antifungal therapy. Awareness given to these infections is of crucial importance reflecting the states of civilization and medical systems. In general the distribution of different dermatophyte species varies in the course of time in different regions.

10.2.1 Etiologic Agents

10.2.1.1 History and New Developments of Classification

The dermatophytes, a group of fungi that infect keratinous tissues, belong to the oldest groups of microorganisms that have been recognized as agents of human disease. The taxonomy of these fungi was initiated in 1841 with studies of Robert Remak and David Gruby [1].

Between 1840 and 1875, five of the main species known today, viz. *Microsporum audoui-*

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nii, *Epidermophyton floccosum*, *Trichophyton schoenleinii*, *T. tonsurans* and *T. mentagrophytes*, had already been described. This was several decades before the discovery of Pasteur's invention of axenic culture [2].

The only ubiquitous modern dermatophyte missing from the list is *Trichophyton rubrum*, which has been hypothesized to have emerged in the twentieth century [3, 4].

After Pasteur's time, culturing of dermatophytes and description of new species have taken off enormously. Species were defined on the basis of combined clinical pictures and morphological characters in vitro. During the following decades, application of new methodological standard led to an explosion of new species and recombined names. Subsequently anamorph nomenclature stabilized by the wide acceptance of *Epidermophyton*, *Microsporum* and *Trichophyton* as the genera covering all dermatophytes.

In the last decades of the twentieth century, the conventional approach to dermatophyte taxonomy combined clinical appearance, cultural characteristics, microscopy and physiology. Because each of these morphologies had it limitations, a novel multilocus phylogenetic taxonomy for the dermatophytes was recently established by the working group of Sybren de Hoog et al. by sequencing for rDNA ITS and partial LSU, the ribosomal 60S protein and fragments of ß-tubulin and translation elongation factor 3 of type and reference strains of members of the onygenalean family *Arthrodermataceae*. The resulting phylogenetic trees reached an acceptable level of stability for dermatophytes and dermatophyte-like fungi. In the newly proposed taxonomy, 7 genera are categorized like the following: *Trichophyton* contains 16 species, *Epidermophyton* 1 species, *Nannizzia* 9 species, *Microsporum* 3 species, *Lophophyton* 1 species, *Arthroderma* 21 species and *Ctenomyces* 1 species. Of these seven genera only *Trichophyton*, *Epidermophyton*, *Microsporum* and *Nannizzia* are clinically relevant with the remaining three genera containing geophilic species (Table 10.1) [5].

10.2.1.2 Classification According to Their Natural Habitat (Ecology)

Reflecting the source of infection dermatophytes may be classified according to their ecology in anthropophilic, zoophilic and geophilic species. Anthropophilic species naturally colonize humans, are being transmitted between humans and usually cause chronic, mild, noninflammatory infections often reaching epidemic proportions. The zoophilic species primarily infect or colonize lower animals and can be transmitted to humans leading to severe inflammation in the host. Geophilic

Table 10.1 Clinical relevant genera of dermatophytes [5]

Trichophyton	*Epidermophyton*	*Microsporum*	*Nannizzia*
T. tonsurans	*E. floccosum*	*M. audouinii*	*N. aenygmaticum*
T. equinum		*M. canis*	*N. duboisii*
T. interdigitale		*M. ferrugineum*	*N. corniculata*
T. mentagrophytes			*N. fulva*
T. simii			*N. gypsea*
T. schoenleinii			*N. incurvata*
T. quinckeanum			*N. nana*
T. erinacei			*N. persicolor*
T. eriotrephon			*N. praecox*
T. benhamiae			
T. concentricum			
T. verrucosum			
T. bullosum			
T. rubrum			
T. soudanense			
T. violaceum			

Table 10.2 Classification of clinically relevant dermatophytes according to their natural habitat (ecology)

Anthropophilic	Zoophilic	Geophilic
Trichophyton rubrum	*Trichophyton mentagrophytes*	*Nannizzia fulva*
Trichophyton interdigitale	*Trichophyton equinum*	*Nannizzia gypsea*
Trichophyton schoenleinii	*Trichophyton erinacei*	*Nannizzia persicolor*
Trichophyton soudanense	*Trichophyton simii*	*Nannizzia praecox*
Trichophyton violaceum	*Trichophyton verrucosum*	
Trichophyton tonsurans	*Trichophyton benhamiae*	
Epidermophyton floccosum	*Trichophyton quinckeanum*	
Microsporum audouinii	*Microsporum canis*	
Microsporum ferrugineum		

species saprophyte in the soil and may have infectious potency in lower animals or humans causing acute, inflammatory mycoses that may quickly resolve (Table 10.2).

10.2.1.3 Sexual States (Anamorph, Teleomorph)

In most dermatophytes no sexual state (=anamorph) is known; therefore the term 'fungi imperfecti' was created in the past. Dermatophytes with known sexual phase (=teleomorph) were formerly categorized into two genera, *Nannizzia* and *Arthroderma*. In truly anthropophilic species, no sexual phases are known, while geophilic species show vigorous mating. Sexual states are generally not isolated from skin, hair or nail cultures, probably because only one mating type initiated the infection.

With regard to the change in the 'Botanical Code of Nomenclature', the dermatophytes are now classified by their phylogenetic relationship, which means in genomic sequencing, species names are not more referred to sexual states [5].

10.2.1.4 Clinically Relevant Species of Dermatophytes (Anthropophilic Source)

Trichophyton rubrum

Initially endemic in Southeast Asia and Africa, by soldiers and slaves brought to America:

- Worldwide distribution
- Main agent of tinea pedis and tinea unguium worldwide
- Causes tinea pedis, tinea cruris, tinea corporis, tinea manuum (infrequent tinea barbae, tinea capitis)
- Follicular granulomatous lesions: Majocchi's granuloma
- Chronic infections

Trichophyton interdigitale (formerly *Trichophyton mentagrophytes* var. *interdigitale*)

- Anthropophilic
- Worldwide distribution
- Tinea pedis (interdigital spaces of the feet)

Trichophyton tonsurans

Initially endemic in Central America and the Caribbean—by Spanish colonists brought to North America:

- North America, Europe (in particular in Great Britain), Africa, rarely in Asia
- Most common agent of tinea capitis in North America and Great Britain
- Causes tinea capitis, tinea corporis, tinea pedis and tinea unguium
- 'Black dot' tinea capitis or kerion formation

Trichophyton soudanense

- Endogenous distribution in West Africa and countries with West African immigration: Europe, Great Britain, the United States, Brazil
- Causes tinea capitis, tinea corporis, tinea unguium [6]

Trichophyton violaceum

- Endogenous distribution in Asia, Africa (East and North Africa), Russia, Europe and South and Central America
- Causes tinea capitis with kerion and favus formation
- Causes tinea corporis, tinea pedis and tinea unguium

Trichophyton schoenleinii

- Eurasia, North Africa, Western Hemisphere
- Causes tinea capitis, tinea corporis, noninflammatory tinea unguium
- Causes favus in humans

Epidermophyton floccosum

- Worldwide distribution
- May reach epidemiological proportions
- No hair invasion
- Noninflammatory tinea
- Causes tinea pedis, tinea cruris, tinea corporis, tinea unguium

Microsporum audouinii

- Endogenous distribution in Africa, more frequently in West African countries
- Sporadic occurrence in Europe (France, Italy, Spain, Portugal, Denmark), Australia
- Causes tinea capitis, tinea corporis and occasionally other dermatophytoses

10.2.1.5 Clinically Relevant Species of Dermatophytes (Zoophilic Source)

Trichophyton mentagrophytes (zoophilic, formerly *Trichophyton mentagrophytes* var. *mentagrophytes*)

- Worldwide distribution
- Infection in humans and lower animals (e.g. rodents)
- Inflammatory tineas with dermatophytid reaction
- Causes tinea corporis, tinea pedis, tinea barbae, tinea capitis, tinea unguium

Trichophyton verrucosum

- Worldwide distribution
- Infections in cattle and individuals in contact with cattle
- Possible occupational infection in farmers
- Highly inflammatory infections with kerion formation
- Causes tinea corporis, tinea faciei, tinea barbae, tinea capitis

Trichophyton benhamiae (formerly *Trichophyton* anamorph of *Arthroderma benhamiae*)

- Transmission mainly by colonized or infected guinea pigs
- First isolated in hedgehogs in Japan
- Steep increase in European countries, source of infection often pets, e.g. guinea pigs
- Highly inflammatory infections with kerion formation and lymph node enlargement and dermatophytid reaction
- Causes tinea corporis, tinea faciei, tinea capitis, tinea genitalis

Trichophyton quinckeanum [7]

- Zoophilic
- Cause of the so-called mice favus
- Causes tinea capitis and tinea corporis, both in children and more frequently in adults
- Middle East, Arab world, Egypt, Iran, Central Asia, European countries (recently increasingly isolated in Germany)
- Source of infection are camels and mice but in Europe more frequently cats

Microsporum canis

- Worldwide distribution
- Highly contagious organism
- Transmission mainly by colonized or infected kittens
- Childhood population mainly affected
- Tinea with kerion formation possible
- Causes tinea corporis, tinea faciei, tinea genitalis, tinea capitis

10.2.2 Dermatophytoses (Tinea of the Glabrous Skin, Ringworm Infection)

10.2.2.1 General Considerations

Diseases caused by dermatophytes—dermatophytoses—are named by the body part designation (in Latin) with the preface *tinea* or ringworm. Beside the glabrous skin appendages like scalp hair follicles and the nail apparatus can be infected. The clinical presentations reflect the

Table 10.3 Dermatophytes (tinea) with regard to the site of infection

Organism	Site of infection
Tinea faciei	Face
Tinea corporis	Glabrous skin (face, trunk, extremities)
Tinea cruris (inguinalis)	Groin
Tinea manus (*pl.* manuum)	Hand
Tinea pedis (*pl.* pedum)	Feet (plantar surface, interdigital spaces)
Tinea barbae	Beard
Tinea capitis	Scalp hair
Tinea unguium	Nail

etiologic agent as source of infection and interaction of the host immune system and may vary from erythematous scaly eruptions to highly inflammatory infections (Table 10.3).

Dematophytes have the ability to produce keratinases and digest keratin in vitro [8].

By this ability the dermatophytes are permitted to sustain itself on the skin, hair or nails. The host immune system plays a significant role limiting the scope of dermatophyte invasion. The cell-mediated immune system in conjunction with the antimicrobial activity of polymorphonuclear leukocytes and serum factors restricts dermatophyte fungi to the stratum corneum [9–11].

When defects in the immune system such as neutropenia occur, locally invasive dermatophyte abscesses may result. In contrast, defects in cell-mediated immunity, such as occurring in HIV infection, predispose to widespread cutaneous infection. In addition to limit the scope and extent of infection, the host immune system mediates the cutaneous eruption and explains the broad variety of clinical features from a given organism.

Another important feature especially of anthropophilic dermatophytes is to sustain chronic infections. Chronic infections are characterized by long-standing, extensive disease with little to no inflammatory response that often involves the palms and soles. In these infections, dermatophyte fungi grow on new-formed keratin as older skin cells are shed. Chronicity means dermatophytic skin invasion proceeds faster than the epidermal turnover. The clinical presentation in long-standing dermatophyte infections yields usually non-inflammatory lesions with only slight scaling and erythema. Several features like sweat, occlusion by tight-fitting shoes, high temperatures and other occupational circumstances are thought to be in close association with chronic dermatophytosis. With regard to additional predisposing circumstances, vascular diseases, metabolic disorders like diabetes, malignancies and genetic disorders like ichthyosis seem to be of possible importance [12].

Infections by zoophilic organisms like *Microsporum canis* or *Trichophyton verrucosum* present as highly inflammatory lesions and are generally short in duration with the possibility of spontaneous resolvement [12].

10.2.2.2 Site of Infection

The clinical presentation of dermatophytosis is beside the etiologic organism mediated by the anatomic site infected. Infections on palms and soles are of chronic course in view of the thickened hyperkeratotic skin. Chronic tinea pedis, tinea cruris and tinea manuum are generally associated with pedal onychomycosis.

Tinea Faciei (Syn. Ringworm of the Face, Tinea Faciale)

Tinea faciei is characterized by erythematous, centrifugally growing, discretely scaly lesions with prominent borders, frequently on the cheeks but also on the eyelids and sometimes in the submandibular region. Mild pruritic (or even non-pruritic), scaly facial lesions with accentuated borders should therefore always prompt a mycologic workup to rule out tinea faciei [13]. Among others, differential diagnostic considerations include impetigo, atopic dermatitis, contact dermatitis, discoid lupus erythematodes and herpes zoster. In children, zoophilic dermatophytes—zoophilic strains of *T. mentagrophytes* as well as *M. canis* and *Trichophyton benhamiae*—are the primary pathogens in tinea faciei. Steroid-modified tinea faciei so-called tinea incognita is possible [14].

- In facial dermatosis with recalcitrant course, a mycology workup should be ruled out (Figs. 10.1 and 10.2).

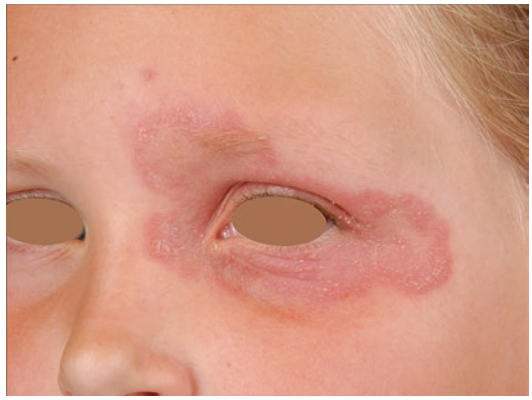

Fig. 10.1 Periorbital tinea due to *Trichophyton benhamiae*

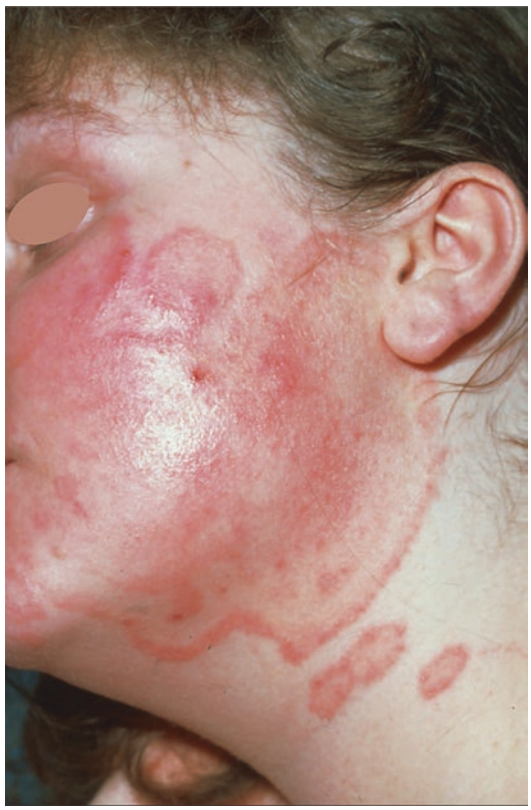

Fig. 10.2 Tinea faciei due to *Trichophyton mentagrophytes*

Tinea Corporis (Ringworm of the Body, Tinea Circinata)

Tinea corporis refers to dermatophytosis of the glabrous skin and may be found on the trunk and the extremities. All dermatophytes, anthropophilic and zoophilic species, are capable of causing tinea corporis with *Trichophyton rubrum* and *Trichophyton mentagrophytes* as main agents. In the USA, Latin America (Mexico) but also Great Britain, the anthropophilic species *T. tonsurans* is the second most common pathogen of tinea corporis after *T. rubrum*. In Africa, *T. violaceum* and *M. audouinii* play a crucial role [15].

In childhood population zoophilic dermatophytes like *Microsporum canis* and *Trichophyton benhamiae* are the most frequently isolated causative fungi. Source of infection are small, domesticated, furry animals that either suffer from dermatophytosis or simply represent asymptomatic carriers of zoophilic dermatophytes [13].

Tinea corporis may present as scaling erythematous lesions with annular figures and accentuated borders. In infections of zoophilic source, highly inflammatory eruptions like vesicular and bullous lesions may develop. The lesions may confluence and tend to centrifugal enlargement. With regard to the etiologic agent and the host immune response, itching and burning may be of subjective complaints. Cutaneous presentations of tinea corporis may mimic other scaling conditions like psoriasis vulgaris, impetigo, atopic dermatitis, contact dermatitis, granuloma annulare, erythema multiforme, pityriasis rosea and T cell lymphoma [12].

Generalized tinea corporis involving at least four different body sites excluding the groins are the criteria for the so-called *T. rubrum* syndrome. This extensive dermatomycosis develops after autoinoculation from a prior existing tinea pedis and tinea unguium. An immunosuppressive treatment—e.g. by glucocorticoids, leflunomide and fumaric acid esters—but also pre-existing immunocompromised diseases like rheumatoid arthritis represent disposing factors for the *T. rubrum* syndrome (Figs. 10.3 and 10.4) [16].

Tinea Inguinalis (Syn. Ringworm of the Groin, Eczema Marginatum, Tinea Cruris)

The term ‘tinea cruris’ (syn. tinea inguinalis) refers to dermatophytosis of the proximal medial aspects of the thighs, perineum and buttocks. Scrotum and penis are generally spared. Tinea cruris is common in males with pre-existing tinea

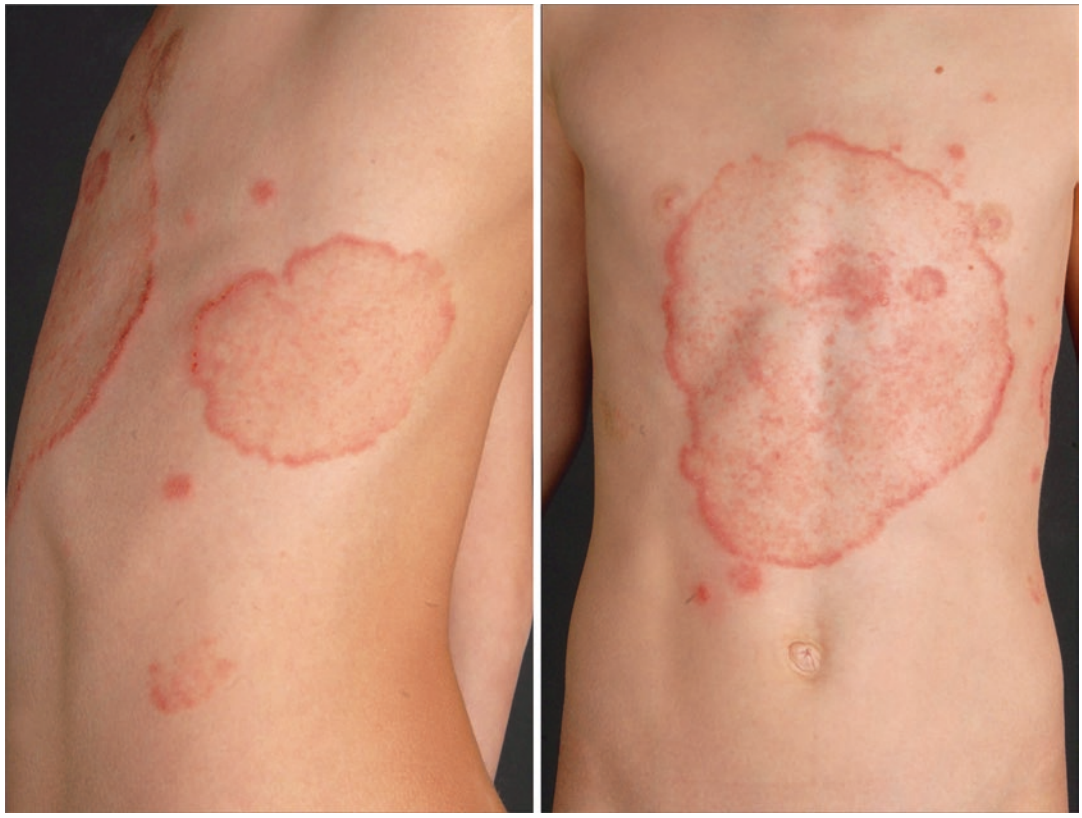

Fig. 10.3 Tinea corporis in a child simulating Lyme disease (migrating erythema)

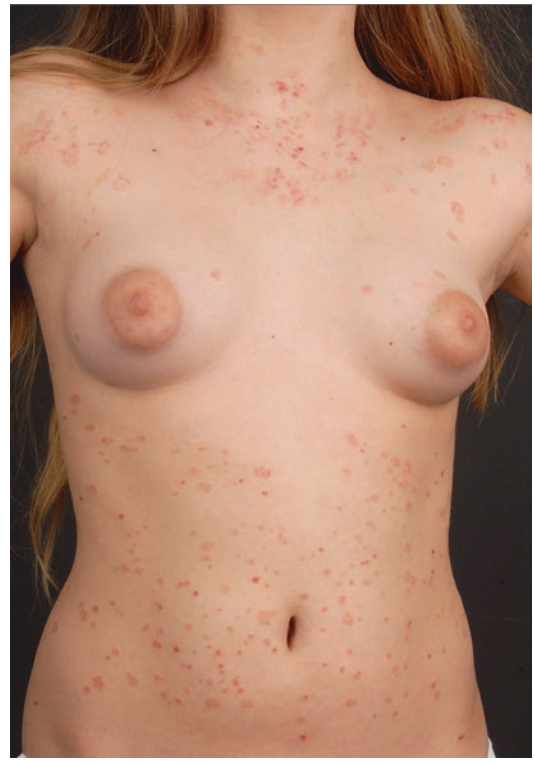

Fig. 10.4 Tinea corporis resembling exanthema due to *Microsporum canis*

pedis and pedal onychomycosis with autoinoculation as source of infection. Additional risk factors are heavy perspiration, tight-fitting clothing, contact sports and environmental factors like high temperatures and humidity [12, 13]. Although *T. rubrum* is a common pathogen, *T. interdigitale* and *E. floccosum* have also been isolated in the inguinal region.

Due to the accentuated borders of the macerated and scaly lesions in tinea inguinalis, the clinical picture corresponds to the so-called eczema marginatum (Hebra), first described in 1860 by Ferdinand Ritter von Hebra (1816–1880), founder of the Vienna School of Dermatology.

Differential diagnosis includes intertrigo, intertriginous candidiasis, erythrasma and inverse psoriasis.

- In infected persons both regions—genital area and feet—should be examined (Fig. 10.5).

Tinea Manus (pl. Manuum) (Syn. Ringworm of the Hand)

Tinea manus (pl. manuum) is referred to as dermatophyte infection of the hand. One or both hands can be infected, but unilateral involvement is most common. Tinea manus is mainly characterized by a dry, mild scaling, hyperkeratotic palm. In some cases the dorsum of the hand, the lateral aspects and the interdigital spaces may reveal scaling erythemas, sometimes with distinct scaling borders. Concurrent fingernail onychomycosis ensures the true diagnosis of fungal infection, whereas in most cases toenail onychomycosis may be the primary cause of this condition. The etiologic organisms of tinea manus are the same as in tinea pedis with *T. rubrum* as the most common agents, with *T. mentagrophytes* (*T. interdigitale*) and *Epidermophyton floccosum* being the others. Differential diagnosis includes eczema, psoriasis and cutaneous T cell lymphoma. Tinea manus yields generally an extremely chronic course and does not respond to topical antimycotic treatment.

Oral Treatment

Terbinafine 250 mg daily for 2–4 weeks
Itraconazole 200 mg daily for 4 weeks
Itraconazole 400 mg daily for 1 week (pulsing)—2 to 3 consecutive months

- In infected persons, feet and nails should be inspected.
- Oral antifungal agents are indicated for cure.
- Underlying fungal nail infection needs treatment (Figs. 10.6 and 10.7).

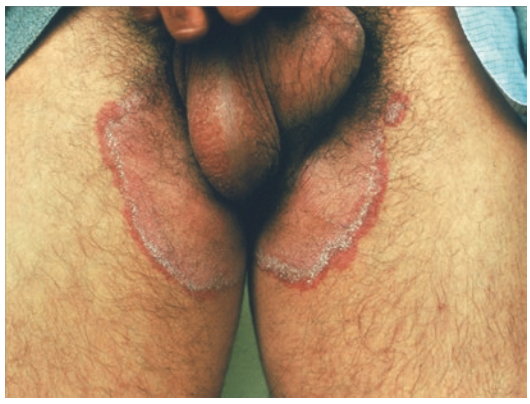

Fig. 10.5 Tinea inguinalis due to *Trichophyton rubrum*

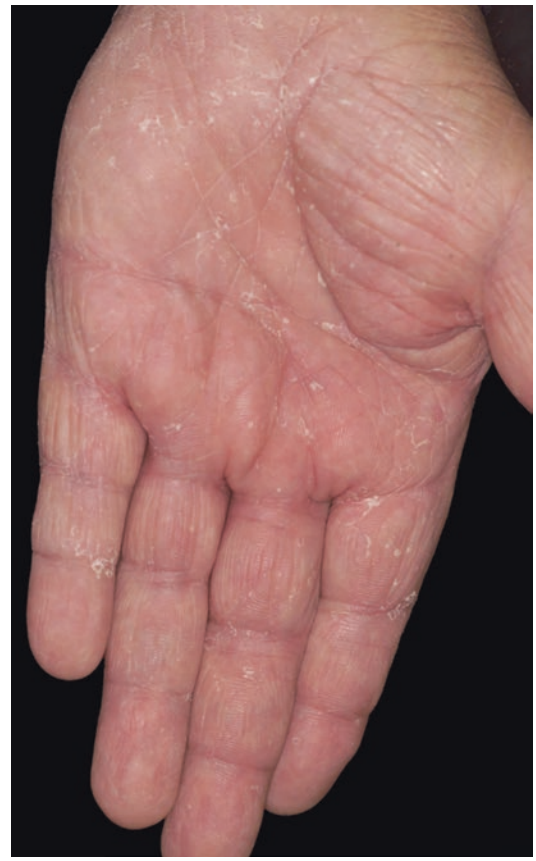

Fig. 10.6 Tinea manus with fine scaling in the creases on the palms

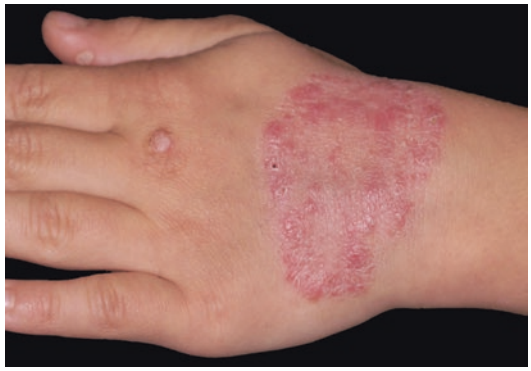

Fig. 10.7 Tinea manus on the dorsum of the hand in a child

Tinea Pedis (pl. Pedum)
(Syn. Foot Ringworm, Athlete's Foot)

Tinea pedis is the most common fungal infection worldwide, affecting 30–70% of the population. It is a disease of civilized humans, with adults and predominately male patients most commonly affected [17].

Less frequently the childhood population can be affected, mainly starting at puberty. High humidity in warm climates, sporting, frictions by occlusive shoes, moisture and wet feet are predisposing factors. In addition, the practice of sharing baths, showers, swimming pools and even shoes facilitate the spread of infection.

There are three clinical presentations of tinea pedis. The most common form is the interdigital form with infection of the intertriginous webspace, mainly the fourth to the fifth interspace. The skin involved appears white and macerated; erosions may develop in the course of infection. The infection will extend to other toes and the soles. Hyperhidrosis, pruritus and odour may be accompanying features. Superinfection by bacteria may compete to the infection. The course of this infection usually is chronic and recalcitrant with a high recurrence rate.

In the second form, vesiculobullous lesions may develop from the webspace and extend to the soles and dorsum of the foot. Itch and secondary infection may result in cellulitis with lymphangitis.

The third form is referred to as 'moccasin type' of tinea pedis. In this type the infection involves the sole, heel and sides of the feet according to a moccasin with scaling erythema. The lesions may appear patchy and discrete and are often accompanied by onychomycoses. As symptoms may not be apparent, the chronic course of infection will not be recognized by the herewith affected person.

The 'two foot-one hand' syndrome describes a recalcitrant dermatophyte infection of the soles of both feet and the palm of one hand (mostly the left) with extensive chronic course and accompanying fungal nail infection.

10.2.2.3 Etiologic Agents

Etiologic agents of tinea pedis usually are of anthropophilic source. *Trichophyton rubrum* is the most common causative agent involved in tinea pedis, followed in order of decreasing frequency by *Trichophyton interdigitale* and *Epidermophyton floccosum*. Whereas *T. rubrum* produces noninflammatory tinea of the feet with extended chronic course, highly inflammatory features like vesicles and pustules and fissures may be caused by *T. interdigitale*/*T. mentagrophytes*. Infections can also be mixed and include *Candida* and bacteria, especially in the interdigital type [17].

Cultivation of dermatophytes from normal toe webs corresponds to colonization and may give rise to true infection in the case of stratum corneum barrier disruption.

10.2.2.4 Complications

Interdigital tinea pedis may be the site for secondary infection by gram-negative bacteria or staphylococci resulting in cellulitis. In inflammatory tinea pedis, ID reactions (autoeczematization) with vesiculation and eczematous eruptions on the fingers, palms and toes may develop.

Treatment

- Topical antifungal agents (azoles, allylamine, ciclopirox olamine).
- Oral antifungal agents in moccasin tinea pedis:
  - Terbinafine 250 mg daily for 2–4 weeks
  - Itraconazole 200 mg daily for 4 weeks

  - Itraconazole 400 mg daily for 1 week (pulsing)—2 to 3 consecutive months
- Underlying pedal onychomycosis needs treatment.
- Disinfection of shoes (Figs. 10.8, 10.9 and 10.10).

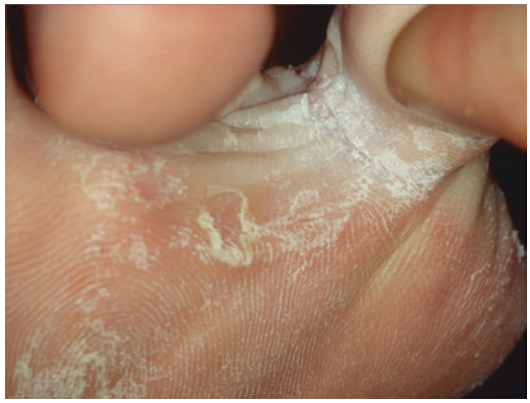

Fig. 10.8 Tinea pedis—interdigital form

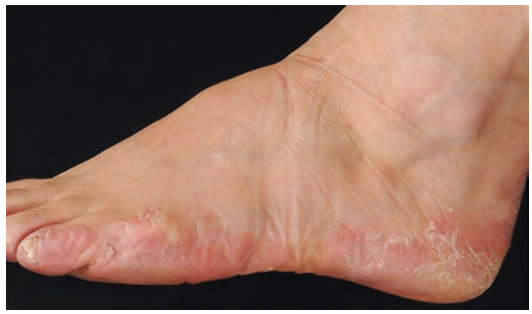

Fig. 10.9 Tinea pedis—moccasin type

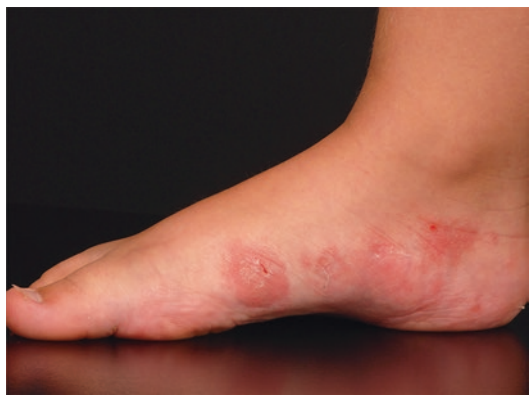

Fig. 10.10 Childhood tinea pedis

Two Feet-One Hand Syndrome

A fungal infection of the left hand and both feet, frequently involving fingernails and toenails, is referred to as 'two feet-one hand syndrome' (TFOHS). Usually *T. rubrum* is the causative pathogen, occasionally *T. mentagrophytes/T. interdigitale* [13, 18].

TFOHS more frequently affects men and is caused by dermatophyte transmission from pre-existing tinea pedis or fungal nail infection to the (left) hand, e.g. by scratching or by pedicure. The non-dominating hand (usually the left) is mostly affected, whereas the dominating or 'working' hand shows a better-developed protective stratum corneum. In general the course of this syndrome is recalcitrant with persistence of the infection over years and the need of long-duration systemic treatment regimen.

Trichophyton rubrum Syndrome

Trichophyton rubrum syndrome (syn. chronic dermatophytosis syndrome, generalized chronically persistent rubrophytia, tinea corporis generalisata, dry-type *T. rubrum* infection) represents a chronic and generalized dermatophytosis. According to the definition, at least four body sites are affected: feet (plantar), hands (palmar), nails as well as one other site. The inguinal region which is a common site of tinea is explicitly excluded. The second diagnostic criterion in *T. rubrum* syndrome includes microscopic fungal detection from all four sites. The third criterion should be the cultural detection of *T. rubrum* from at least three out of four sites.

It is still unclear whether *T. rubrum* syndrome represents a distinct nosologic entity. Treatment with corticosteroids seems to be a predisposing factor. The syndrome is of utmost course and may be refractory even to long-duration treatments [13].

10.2.3 Tinea of the Hair Follicle

10.2.3.1 Tinea Capitis (Syn. Ringworm of the Scalp, Tinea Tonsurans)

Fungal scalp infection (tinea capitis) is defined as infection of the hair follicle by dermatophytes

and presents with a different amount of erythema, scaling and hair loss. Tinea capitis is the most common infection of the scalp in childhood [19].

Both genders may be affected: while in the past boys were thought to be more frequently affected, particularly with respect to *Microsporum canis* infections, this gender difference seems to have disappeared [20].

Currently, even in the USA, there is an even distribution between girls and boys [21].

Etiologic Agents in Europe

The causative organism in tinea capitis may be of zoophilic or anthrophilic source.

In European countries, mainly in Central and Southern Europe, *Microsporum canis* and *Trichophyton benhamiae* are the most common agents, followed by zoophilic strains of *T. mentagrophytes* and *T. verrucosum*. Due to the increase in immigration by people from Africa, the epidemiologic situation with causative agents of tinea capitis has changed dramatically in Europe with a steep swift from zoophilic to anthropophilic dermatophytes. In France (Paris) and Switzerland and in urban areas of Germany (f.e. Munich, Bonn, Würzburg), outbreaks with the anthropophilic fungus *M. audouinii* have been reported [22].

The same holds for the anthropophilic *T. violaceum* brought to Europe (Zürich, Göteburg) by immigrants from Eastern African countries (Eritrea, Ethiopia, Somalia, Kenya, Uganda), whereas *T. soudanense* mainly originates from the western parts of Africa (Nigeria, Mali, Senegal, Angola) [23].

In the USA and the UK, the majority of fungal scalp infections are caused by the anthropophilic *Trichophyton tonsurans*. The main problem with this epidemiological shift to anthropophilic causative agents is the possible transmission by inert items such as reaching epidemiological proportions.

Geophilic dermatophytes with *Nannizzia gypsea* being the clinically most relevant species rarely cause tinea capitis. Present in soil and dust, children may contract them, e.g. while playing outside, with subsequent infection of the skin and occasionally the scalp [13].

Pattern of Hair Involvement

Hair root involvement by dermatophytes may be endothrix, ectothrix or favic. In endothrix infections, seen in *T. tonsurans*, *T. violaceum*, *T. soudanense* and *T. verrucosum*, tinea capitis, arthrospores and mycelia are found inside the hair shaft, without any destruction of the cuticle. In ectothrix infections by *M. canis*, *M. audouinii* and *T. mentagrophytes* (zoophilic type), spores and hyphae aggregate in a cuff-like fashion outside the hair shaft. In favic pattern (mainly caused by *T. schoenleinii*), the infection presents with airspaces within the hair.

Classification According to Clinical Presentation

Tinea capitis can be differentiated according to the *genus* level into *Trichophyton* and *Microsporum* tinea capitis or with relation to the infectious mode of the hair shaft (endothrix vs. ectothrix mode vs. favic pattern). The most common classification describes the clinical picture of tinea capitis with special regard to the different amounts of inflammation varying from a noninflammatory to highly inflammatory state. In general zoophilic strains may cause highly inflammatory infections with purulent discharge and pains with exception to be drawn in attention.

Grey Patch Tinea Capitis

This type is characterized by disc-like alopecic lesions covered by whitish-grey scales. Hairs break off directly above the skin surface resulting in a typical picture of ‘stubble field’ appearance. In some cases, an inflammatory component with erythema may be completely missing responding to noninflammatory-type tinea capitis. Without treatment the lesions show centrifugally growing and recalcitrant chronic course over months. Grey patch tinea capitis is mainly seen in *M. canis*, *M. ferrugineum*, *Nannizzia incurvata* and *T. benhamiae* infections. Favus (caused by *T. schoenleinii*) with so-called scutulum formation may also simulate this type (Figs. 10.11 and 10.12).

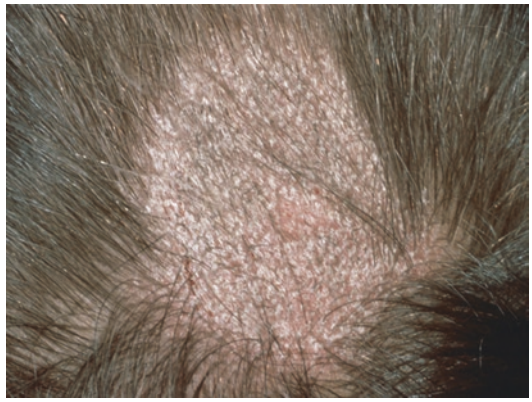

Fig. 10.11 Noninflammatory-type tinea capitis due to *Microsporum canis* ('grey patch' tinea capitis)

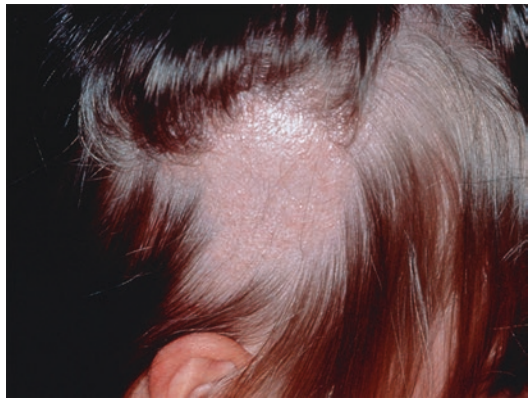

Fig. 10.12 Noninflammatory-type tinea capitis due to *Microsporum canis* resembling alopecia

Moth-Eaten Tinea Capitis

This type presents with distinct scaling small-sized alopecic lesion described as moth-eaten appearance. The clinical picture is the same as in alopecia syphilitica.

Black Dot Tinea Capitis

This clinical manifestation impresses as black (or white or yellow) dots at the scalp following hair shaft breakage representing a noninflammatory type of tinea capitis. This type of infection is mainly caused by dermatophytes of anthropophilic source like *T. tonsurans* (most commonly seen in the Afro-Caribbean population in the USA), *T. mentagrophytes*, *T. soudanense*, *T. violaceum* and *M. audouinii* and is most commonly seen in curling hair type (Fig. 10.13).

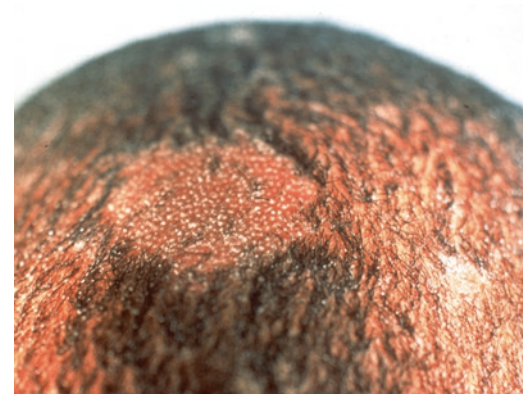

Fig. 10.13 Noninflammatory type tinea capitis due to *Trichophyton tonsurans* ('black dot' tinea capitis)

Pityriasis Capillitii-Type Tinea Capitis

This kind of tinea capitis presents with diffuse scaling of the scalp without signs of inflammation and is mainly caused by *T. tonsurans*, *T. violaceum*, *T. soudanense* and *M. audouinii* (Fig. 10.14).

Pustular Tinea Capitis

Fungal infections of the hair root may present as scattered pustules covering the scalp; in addition hair loss may be visible. *T. violaceum*, *T. soudanense* and *T. mentagrophytes* have to be considered as causative agents (Fig. 10.15).

Kerion (Tinea Capitis Profunda)

The most severe form of tinea capitis is characterized by an abscess-like deep infection of the scalp and accompanying nuchal or cervical lymphadenopathy. The hairs in the surrounding of the charging mass may be epilated without difficulty. This highly inflammatory condition may cause pain and febrile temperature. According to the course of infection, it will result in permanent scaling due to hair loss. This type of infection is mainly caused by zoophilic dermatophytes like *T. mentagrophytes*, *T. verrucosum* but also *T. benhamiae* (Fig. 10.16).

Favus

Tinea capitis of favus type has disappeared in Europe but may still be found in Turkey, Iran and Northern African countries. Causative agent is *T. schoenleinii*.

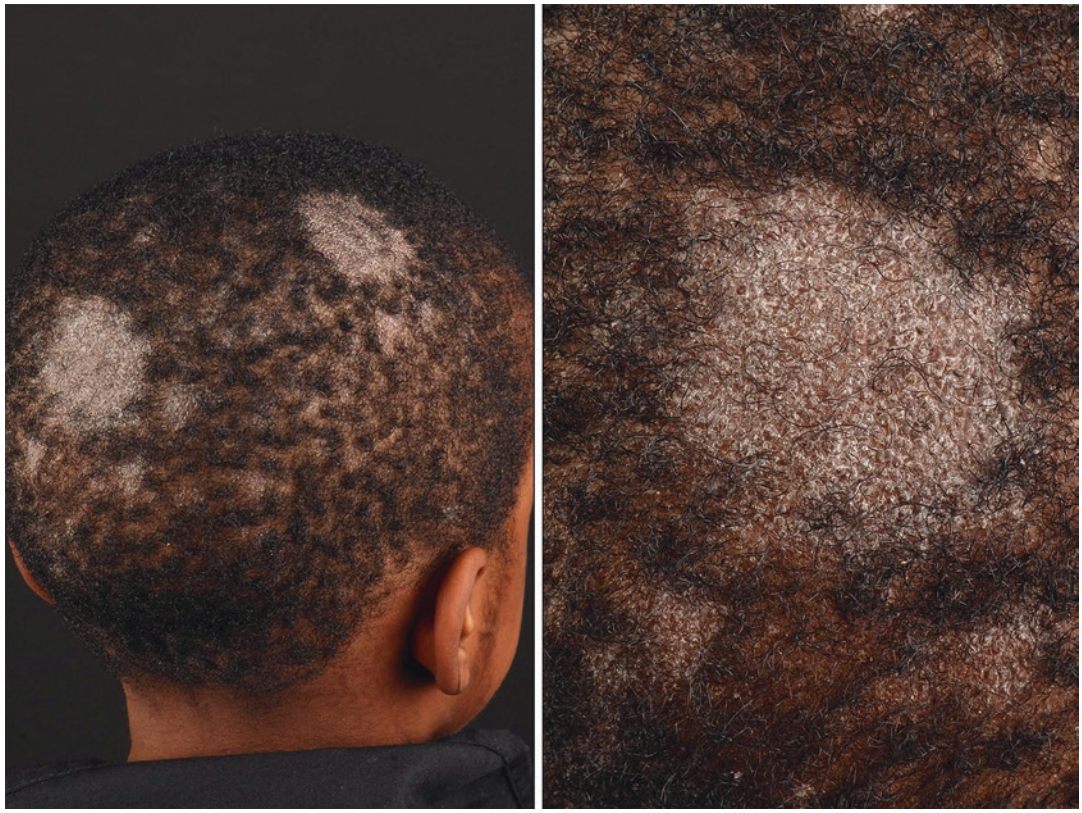

Fig. 10.14 Pityriasis capillitii-type tinea capitis due to *Trichophyton soudanense*

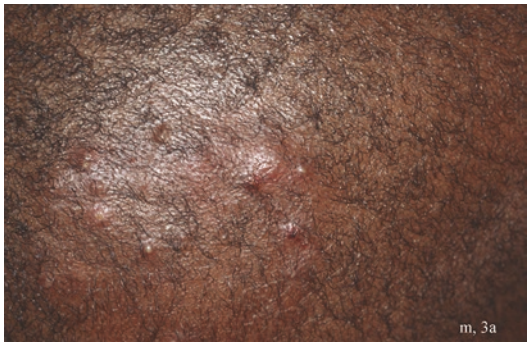

Fig. 10.15 Pustular tinea capitis due to *Trichophyton soudanense*

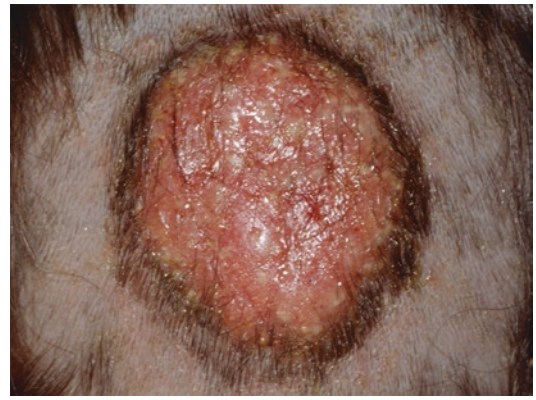

Fig. 10.16 Tinea capitis profunda (kerion-type) due to *Nannizzia gypsea*

Tinea Capitis in Adults

Even though childhood population is usually affected by tinea capitis, mycotic scalp infection may be seen in adults and elderly. The infection manifests as a different amount of erythema, scaling and hair loss and may simulate disorders like discoid lupus erythematosus, psoriasis or other forms of hair loss. The true nature of the condition may be proofed by histology. The infection may be caused by *M. canis*, *T. schoenleinii* or *M. audouinii* and even by *T. rubrum* as result of autoinoculation (Fig. 10.17) [13].

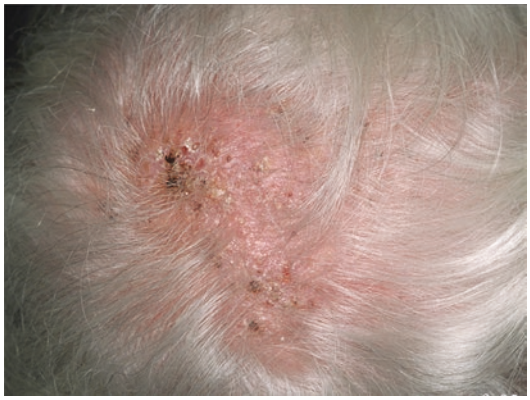

Fig. 10.17 Tinea capitis microsporica in an elderly

Differential Diagnoses of Tinea Capitis

There is a broad range of disorders of the scalp to be drawn in attention:

- Scaling disorders like psoriasis capitis, pityriasis capillitii, pityriasis amiantacea (formerly tinea amiantacea) and seborrheic dermatitis of the scalp
- Bacterial infections like bacterial abscesses, impetigo, pyodermas (furuncle, carbuncle)
- Different forms of hair loss like alopecia areata, scarring alopecia
- Autoimmune disorders like discoid lupus erythematosus, lichen planopilaris
- Other disorders like erosive pustular dermatitis of the scalp, sterile eosinophilic pustulosis (Ofuji), folliculitis decalvans, dissecting cellulitis, folliculitis et perifolliculitis capitis abscedens et suffodiens (Hoffmann), acne keloidalis nuchae
- Syphilis II (alopecia syphilitica)

The correct diagnosis is a challenge with regard to microbiological investigations and histology.

Carrier State (=Asymptomatic Tinea Capitis)

The cultural isolation of dermatophytes from a scalp without any signs of infection is termed carrier state. The situation with scalp contamination by dermatophytes, mainly *T. tonsurans* and *M. audouinii*, has been observed in children and adults. The causative role of pathogen carriers is of suggestive nature—given the fact that contamination by dermatophytes is an invisible source of transmission or gives rise for true infection [24, 25].

Treatment

General Considerations

Tinea capitis needs to be treated with an oral agent because the antifungal needs to penetrate into the hair follicle. Topical antifungal agents used as sole therapy are therefore ineffective [26].

Treatment needs to be continued until mycological cure is proved as microscopically documented by a fungus-free hair root and the inability of the causative organism to grow on culture. Treatment duration in general depends on the causative agent and the thereby administered oral antifungal and the clinical response of the patient. Fully hair regrowth is a matter of time and needs patience. Scarring alopecia may be a task for aesthetic/plastic surgery [27].

Systemic Treatment

Oral antifungal agents are the primary interventions for treating tinea capitis (e.g. griseofulvin, terbinafine, ketoconazole [not yet available in Europe, black box warning of the FDA due to hepatotoxicity and QT prolongation and drug interactions], fluconazole and itraconazole). Griseofulvin and terbinafine should be considered as first-line choice. Terbinafine is most effective for *Trichophyton* infections, whereas griseofulvin is the drug of choice in *Microsporum canis* infections. Itraconazole and fluconazole are alternative treatments [28]. Oral ketoconazole has been withdrawn from use in the UK and Europe since 2013 [29].

The problem with systemic treatment in childhood population is that not all medication for tinea capitis are available in paediatric formulation (f.e. suspension) and most agents are not licensed in this age group (Table 10.4).

The use of systemic antibiotics or corticosteroids has to be considered in special cases but seems to be of no advantage.

Topical Treatment

In addition to systemic treatment, topically antifungal agents like antifungal shampoos containing azoles (ketoconazole 2% shampoo) or 2.5% selenium disulphide at least twice weekly and

Table 10.4 Systemic treatment of tinea capitis in childhood

Griseofulvin Tablets, suspension	15–20–25 mg/kg BW daily (fatty meals) 6–8–12 weeks
Terbinafine (not licensed/ off-label use) Tablets (USA: oral granules for suspension)	62.5 mg daily (<20 kg BW) 125 mg daily (>20–40 kg BW) 250 mg daily (>40 kg BW) *Trichophyton* TC: 2–4 weeks (kerion 8–12 weeks) *Microsporum* TC: 6–12 weeks
Itraconazole (not licensed in tinea capitis/off-label use) Capsules (50 mg, 100 mg) Suspension (10 mg/ml)	Capsules: 5 mg/kg BW daily (with food—postprandial) Suspension: 3 mg/kg BW (fasting state) 50 mg daily (<20 kg BW) 100 mg daily (>20 kg BW) 2–4–6 weeks
Fluconazole (not licensed in tinea capitis/off-label use) Capsules (50 mg, 100 mg) Suspension (50 mg/10 ml)	5–6 mg/kg BW daily 8 mg/kg BW once weekly 3–6–12 weeks

daily application of antifungal therapy should be recommended until cure is achieved.

Surveillance Control

To prevent the spread of infection, screening of the infected person's family members and primary contacts should be obligatory. With regard to 'carrier state', all family members and other persons exposed to the affected individual should be treated with an antifungal shampoo. Clothing and hair care items used by the affected should not be shared by other persons. Haircutting procedures are strongly prohibited in infected persons.

There is evidence that infectious organisms like *M. canis* and *T. tonsurans* may be spread by contaminated fomites like toys, furniture and telephones with need for disinfection. A proven or reliable method to sterilize fomites has not been established.

In infections of zoophilic source, identification and treatment of the infected animal are of special concern.

After initiation of oral treatment regimens, children should be allowed to return to the kindergarden or school, only if *M. audouinii* infections quarantine is strictly followed [29].

10.2.3.2 Tinea Barbae (Syn. Ringworm of the Beard)

Ringworm of the beard and moustache areas of the face is a disease of the adult male and is mainly caused by zoophilic dermatophytes, *Trichophyton verrucosum* and *Trichophyton mentagrophytes* [30]. Patients affected are commonly farm workers with the infection retrieved by cattle ringworm. Ringworm of the beard may manifest as scaly, reddish, circular lesions up to highly inflammatory pustular folliculitis presenting features of a kerion with exudation and crusting. Hairs within the affected lesions are loose and easily considerably enlarged and painful. The lesions may persist over some months and settle spontaneously. Treatment of tinea barbae involves the use of oral terbinafine supplied by topical antimycotic preparations. Control of surveillance by the veterinarian is mandatory. Vaccines against *T. verrucosum* in cattle are available in many countries (Fig. 10.18).

10.2.3.3 Tinea of the Genitoinguinal Region (Tinea Genitalis)

Pubogenital tinea or tinea genitalis represents a rare type of dermatophytosis which, however, is increasingly observed [31]. The mons pubis is affected but also the outer regions to the penis shaft and the labia together with the groins. The infection may manifest from superficial erythrosquamous type to deep trichophytosis of kerion type with accompanying painful enlargement of the regional lymph nodes. Causative agents were mainly zoophilic dermatophytes (*M. canis*, *T. mentagrophytes*, *T. benhamiae*, *T. verrucosum*) with anthropophilic dermatophytes like *T. rubrum* being exceptionally observed by autoinoculation from undetected tinea unguium. Beside infected pets as the main source of infection, shaving procedures of the genital area seem to be

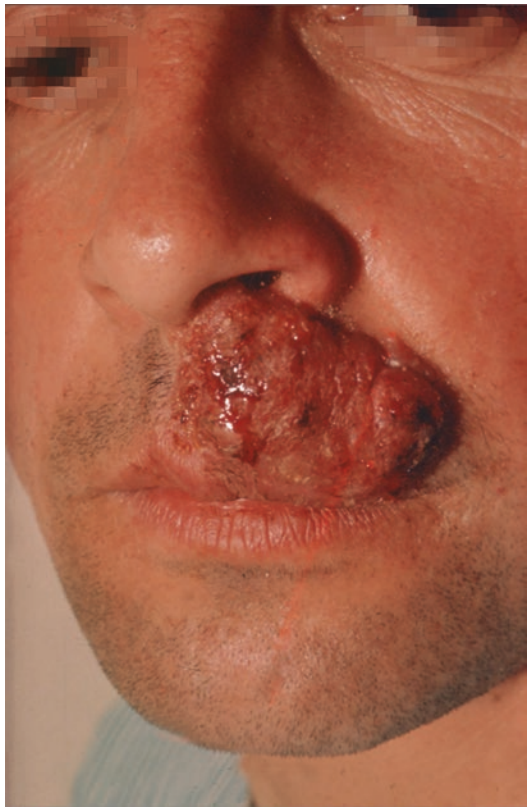

Fig. 10.18 Tinea barbae due to *Trichophyton verrucosum* in a farm worker

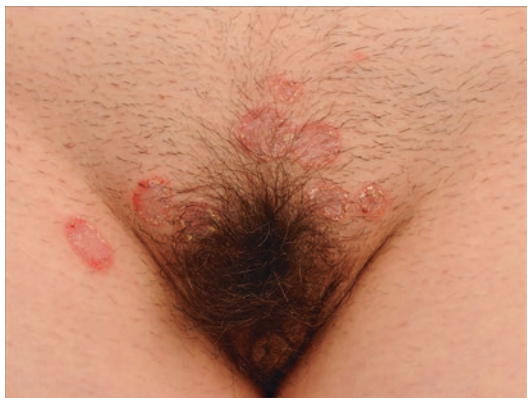

Fig. 10.19 Tinea genitalis with scaling and sharp marginated erythematous lesions due to *Microsporum canis*

the disposing factors explaining traumatic inoculation of infective agents. The infection needs systemic treatment with regard to the infectious organism (Figs. 10.19 and 10.20).

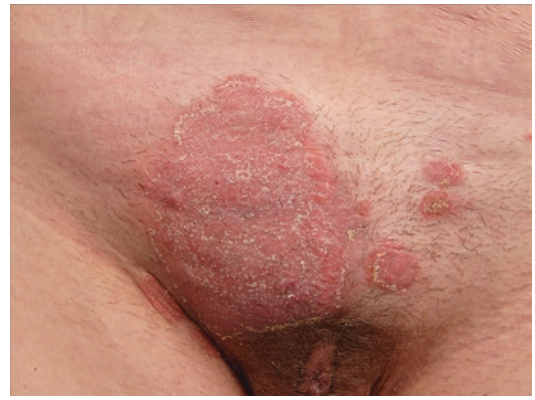

Fig. 10.20 Tinea genitalis due to *Trichophyton mentagrophytes*

10.2.4 Tinea Unguium (Onychomycosis)

Tinea unguium refers to dermatophyte infection of either fingernails or toenails. *Onychomycosis* is a broader term that includes nail infection by nondermatophytic moulds (NDM) and yeasts.

10.2.4.1 General Considerations

Fungal nail infections account for about one-third of all dermatophytoses and 50% of all nail disorders [32]. Fungal nail infection is of worldwide distribution with an estimated prevalence of 2–8%. According to the Foot Check Study, 23% of the European population suffers from pedal fungal infection with 12.4% prevalence in Germany [33].

The incidence of onychomycosis is inevitably going to rise, as industrialized societies are getting older.

In general toenails are more frequently infected than fingernails. In addition fungal nail infection is more prevalent in men and in individuals with other nail problems.

Tinea unguium is associated with tinea pedis in up to one-third of cases [34].

Many risk factors have been identified [35–37]:

Increasing age (approximately 20% of the population aged over 60 years and up to 50% of subjects aged over 70 years are reported to have onychomycosis)

Peripheral vascular disease
Periphery neuropathy
Occlusive footwear
Repeated nail trauma
Distorted nail surfaces
Slow nail growth
Foot deformities
Diabetes
Psoriasis vulgaris and psoriasis unguium
Immunosuppressive conditions (f.e. HIV infection)

Genetic predisposition (autosomal dominant pattern of inheritance in onychomycosis caused by *T. rubrum*)

10.2.4.2 Spread of Infection

Fungal nail infection is caused by interhuman transmission due to contact with exfoliated infected material, i.e. scalings or contaminated footwear or bathing units. All of the different morphological forms of dermatophytes have the potential to cause human infection, with the nonvegetative arthrospores (produced by fragmentation of hyphae) to be most suitable for the growth of dermatophytes in the nail-plate [38, 39].

10.2.4.3 Etiologic Agents in Onychomycosis

About 90% of fungal nail disease is caused by dermatophytes with the main organism *Trichophyton rubrum* and *Trichophyton interdigitale* (formerly *Trichophyton mentagrophytes*). Five to 10 percent of all onychomycosis are estimated to be caused by *Candida* species and about 2–11% by nondermatophyte moulds (NDM).

10.2.4.4 Classification According to Clinical Presentation [13]

Distal and Lateral Subungual Onychomycosis (DLSOM)

Fungal nail infections predominantly start at the distal free edge of the toenails as distal subungual onychomycosis. In the course of time, the pathogen slowly migrates from the hyponychium at the bottom side of the nail-plate proximally towards the matrix, resulting finally in DLOM. The nail appears thickened and hyperkeratotic with yellowish-brown discoloration. As time progresses, onycholysis sets in. Yellow streak represent dermatophytoma and point towards fungal matrix involvement. The most common causative agent is *T. rubrum* (Figs. 10.21 and 10.22).

Proximal Subungual Onychomycosis (PSOM)

Proximal subungual onychomycosis is quite rare. In this case the pathogen progresses from the proximal nail wall due to underlying tinea pedis onto the cuticle and later on onto the eponychium (the epithelium at the bottom side of the proximal nail wall). PSOM is a sign of immunodeficiency and may be seen in HIV-positive and AIDS patients. The association between PSOM and HIV is particularly striking in countries with high HIV prevalence, e.g. Sub-Saharan Africa. *T. rubrum* is usually the infectious organism of this kind of infection (Fig. 10.23).

White Superficial Onychomycosis (WSOM)

White superficial onychomycoses (leukonychia trichophytica) refer to a superficial dermatophyte infection of the nail-plate, mostly caused by *T. rubrum* but also *T. interdigitale*. In this infection a flat, bright white, plaque-like layer covers the nail-plate, sometimes affecting the entire nail surface.

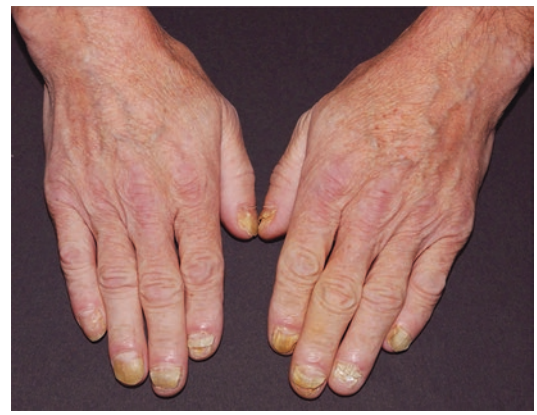

Fig. 10.21 Distal subungual onychomycosis presenting onycholysis due to *Trichophyton rubrum*

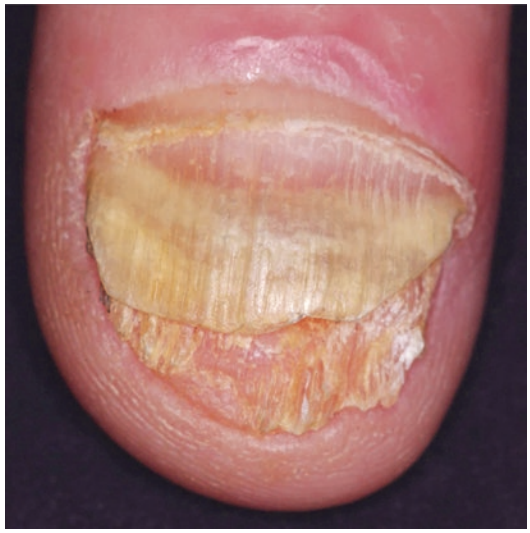

Fig. 10.22 Distal subungual onychomycosis presenting onycholysis due to *Trichophyton rubrum*

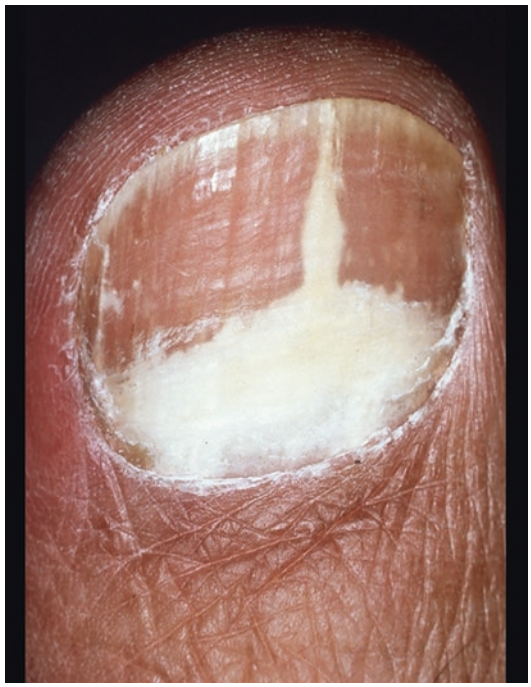

Fig. 10.23 Proximal subungual onychomycosis due to *Trichophyton rubrum*

Proximal white subungual onychomycosis (PWSOM) represents a special variant with white discoloration underneath the proximal part of the nail-plate and may be caused by *T. rubrum*, *T. schoenleinii* and *Epidermophyton floccosum.* Another special variant is black superficial onychomycosis caused by mould *Hendersonula toruloidea* (now renamed according current taxonomy as *Nattrassia mangiferae*).

Endonychial Onychomycosis (EOM)

Endonychial onychomycosis is a variant of nail infection with no subungual hyperkeratosis and no onycholysis. The nails are hyperkeratotically thickened and show white discoloration. This form of onychomycosis is caused by *T. soudanense* and is likely to be encountered in Africa.

Total Dystrophic Onychomycosis (TDOM)

Total dystrophic onychomycosis represents the most severe variant of onychomycosis and may be the final result of long-standing fungal nail infections. H. Grimmer coined the term ‘glacier nail’ in the 1960s. In this form the entire nail is mycotic and subsequently pushed upward by subungual hyperkeratoses, resulting in onycholysis. Yellow streaks, which mean longitudinal streaks medially or laterally frequently reaching the nail matrix, are characteristics for this type of onychomycosis [40].

In chronic mucocutaneous candidiasis, fingernails may become yeast-infected and appear as TDOM (Figs. 10.24 and 10.25) (Table 10.5) [41].

10.2.4.5 Onychomycosis by Nondermatophyte Moulds (NDM)

Nondermatophyte moulds account for about 5–11% of cases of onychomycoses [34].

Unlike dermatophytosis, these mould infections are not contagious and will not respond to the standard treatments for dermatophyte or *Candida* onychomycosis.

Causative Organisms

Various filamentous fungi other than dermatophytes have been isolated from abnormal nails [35, 42, 43].

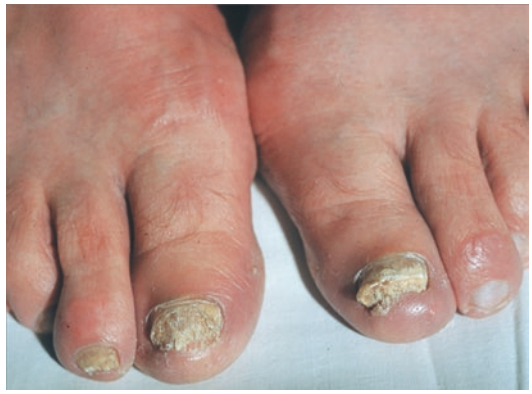

Fig. 10.24 Total dystrophic onychomycosis as result of long-standing nail infection

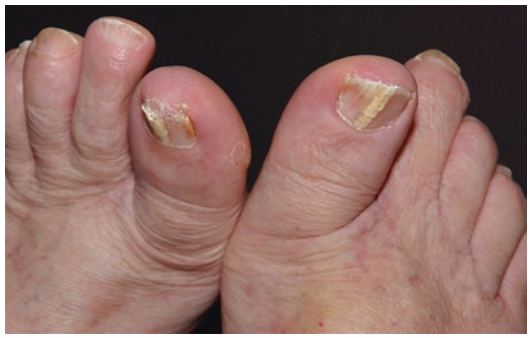

Fig. 10.25 Onychomycosis presenting yellow streaks

Table 10.5 Classification according to clinical presentation

Distal and lateral subungual OM	DLSO
Superficial white OM	SWO
Proximal subungual OM	PSO
Endonyx OM	EO
Total dystrophic OM	TDO
Mixed pattern OM	

Often these are casual, transient contaminants, and direct microscopic examination of nail clippings and scrapings is negative. However, environmental moulds that are found in soil or plant material are capable of causing nail infection. These moulds, with exception of *Neoscytalidium* species, are not keratinolytic, and they are generally considered to be secondary invaders rather than primary pathogens of the nail-plate [34].

The most common causative organism of NDM nail infection is *Scopulariopsis brevicaulis*, a ubiquitous soil fungus. Other causes of nail infections are *Neoscytalidium dimidiatum* (formerly called *Scytalidium dimidiatum* or *Hendersonula toruloidea*—causes black nail and skin infections in patients from tropics), *Sarocladium* (formerly *Acremonium*) species, *Aspergillus* species, *Fusarium* species and *Onychocola Canadensis* [44].

Mould infections of nails are most prevalent in older individuals, with men more commonly affected than women and toenails more frequently involved than fingernails. Similarly to dermatophyte onychomycosis, risk factors include increasing age, local trauma and immunosuppressive conditions such as diabetes mellitus or HIV infection [34].

NDM usually occur as secondary invaders in nails that have been previously been diseased or traumatized. This may account for the fact that these infections often affect only one nail [42].

Mould infections of nails have few specific clinical features and may present with onycholysis and hyperkeratosis like dermatophytic nail infection or with painful paronychia.

Suspicion of NDM onychomycosis [42]:

- Only one nail affected.
- Brown or black stained nails and subungual material.
- Previous antifungal treatment has failed on several occasions.
- Direct microscopic examination has been positive, but no dermatophyte has been isolated.
- No sign of associated skin infection (with exception of *Neoscytalidium dimidiatum*) (Figs. 10.26 and 10.27).

10.2.4.6 *Candida* Nail Infection

Candida infection accounts for 5–10% of all cases of onychomycosis [35].

Among the various species implicated, *C. albicans* and *C. parapsilosis* and *C. guilliermondii* are the most common causative agents.

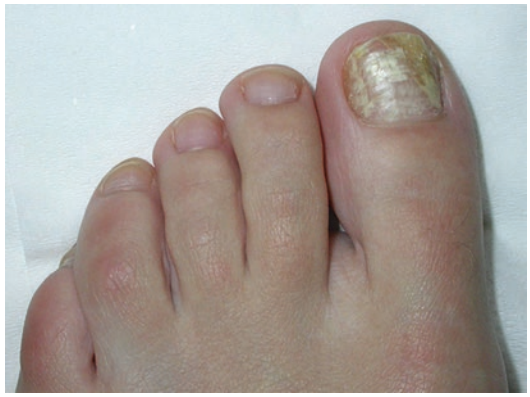

Fig. 10.26 Onychomycosis of the great toenail due to *Scopulariopsis brevicaulis*

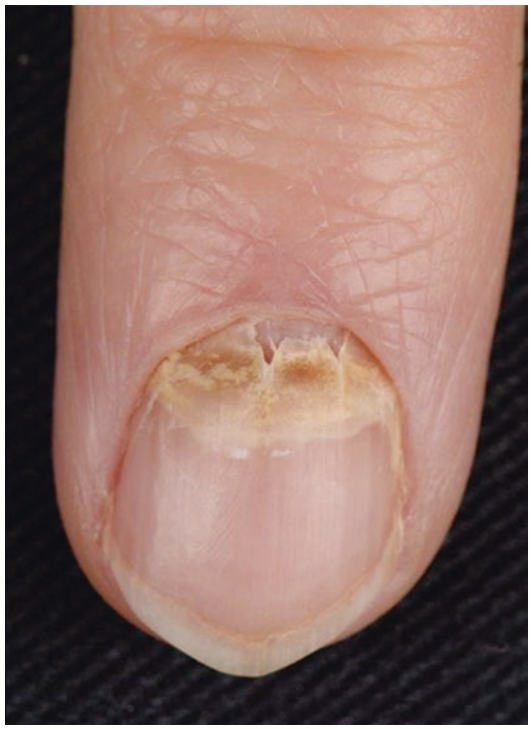

Fig. 10.27 Onychomycosis due to *Fusarium solani* presenting with proximal onycholysis

There are three forms of infection recognized: infection of the nail folds (or *Candida* paronychia), distal nail infection and total dystrophic onychomycosis.

Nail and nail fold infections with *Candida* (*Candida* paronychia) are more common in women than in men, with fingernails more commonly infected than toenails. These infections often occur in individuals whose occupations necessitate repeated immersion of the hands in water. The fingers mainly affected are the thumbs and middle fingers of the dominant hand. *Candida* paronychia usually starts in the proximal nail fold with erythematous and painful swelling followed by nail-plate involvement. The nail becomes more opaque with white, green or black discoloration and transverse or longitudinal furrowing or pitting. In the course of time, the nail-plate becomes friable and may become detached from the nail bed. Pressure on and movement of the nail are painful. Bacterial superinfection is common [34].

Distal *Candida* nail infection presents as onycholysis and subungual hyperkeratosis and must be distinguished from dermatophytosis. The fingernails are nearly always involved. Nearly all patients with this condition suffer from Raynaud's phenomenon or some other underlying vascular problem [45].

Total dystrophic onychomycosis caused by *Candida* is mainly seen in patients with chronic mucocutaneous candidiasis (CMCC) with gross thickening and hyperkeratosis of the nail-plate [34].

Nail and *Candida*:

- Women mostly infected
- Fingernails mainly infected
- Colonization more like than true infection
- Predisposing circumstances like repeated immersion
- Food allergy discussed (Figs. 10.28, 10.29 and 10.30)

10.2.4.7 Differential Diagnosis of Fungal Nail Disease

Many non-infectious conditions can produce nail changes that mimic onychomycosis

- Nail dystrophies following repetitive trauma
- Onychogryphosis
- Onycholysis
- Psoriasis
- Nail lichen
- Subungual malignant melanoma
- Yellow nail syndrome
- Darier's disease
- Ichthyotic conditions (f.e. KID syndrome, etc.)

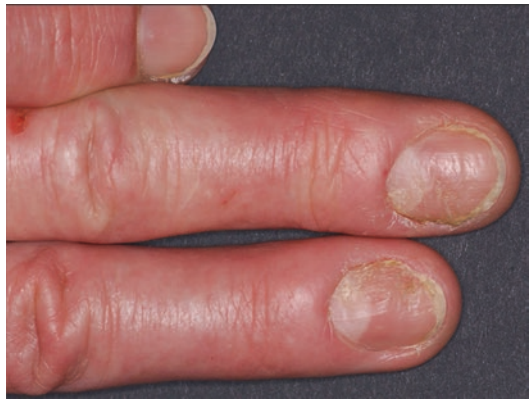

Fig. 10.28 *Candida* paronychia

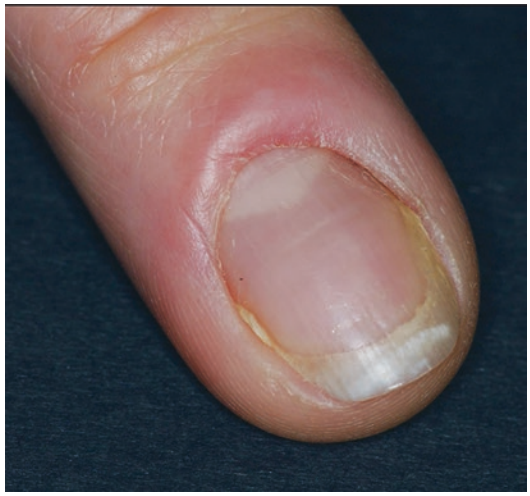

Fig. 10.29 *Candida* onycholysis

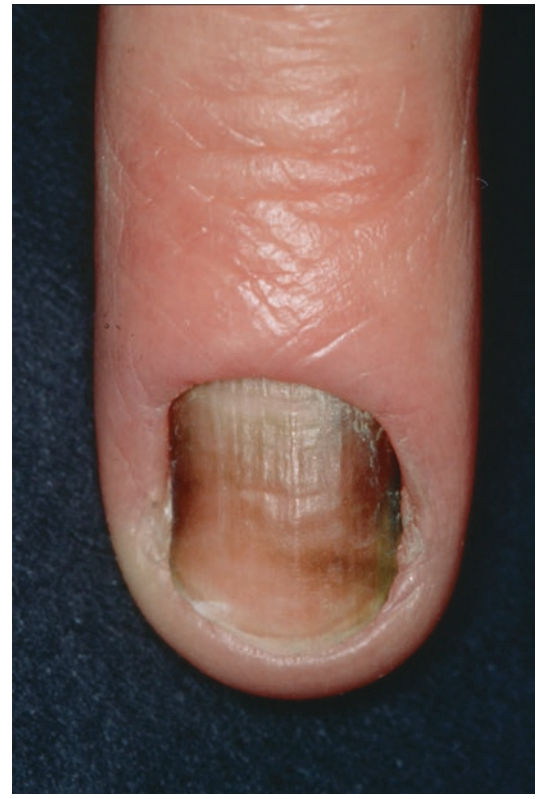

Fig. 10.30 *Candida* onychomycosis with *Candida* paronychia

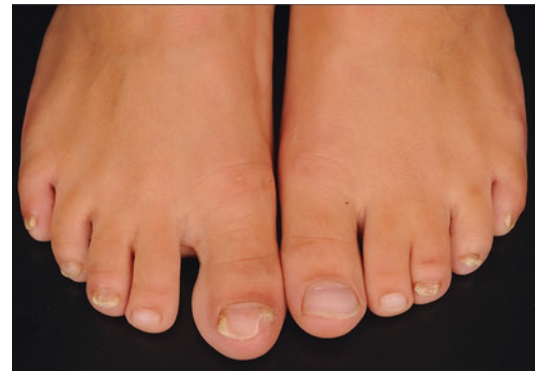

Fig. 10.31 Childhood onychomycosis in a 9-year-old boy

10.2.4.8 Childhood Onychomycosis

There has been a recent increase in childhood onychomycosis. The prevalence of childhood onychomycosis is between 0% and 2.6% [46].

Most cases of onychomycosis show pre-existing tinea pedis and a family history of pedal fungal infections, which means the infections have been transmitted by infected family members like the parents or grandparents. Physical activities like soccer and wearing of occlusive footwear are facilitative. Beside genetically determined predisposure for fungal nail infection, trisomy 21 is well known in children affected. The clinical picture of childhood onychomycosis resembles the same features as in adult infections with distal and lateral subungual onychomycosis being the most common picture, in addition to the infectious agents being the same (Fig. 10.31).

10.2.4.9 Onychomycosis in Athletes

Specific aspects of athletics such as repetitive nail injuries, increased sweating and increased exposure to infectious dermatophytes lead to a higher prevalence on fungal nail infection [47].

The key predisposing factors in sports persons are the intensity involved with sport (f.e. runners) and the sudden starting and stopping nature of specific activities as well as water sports and communal bathing.

10.2.4.10 Onychomycosis in Patients with Diabetes

Diabetics are almost three times more likely to develop onychomycosis than nondiabetics [48]. Approximately 34% of all diabetics have onychomycosis related to underlying risk factors like obesity, peripheral vascular disease and neuropathy and foot deformities. As in the general population in diabetic patients, *T. rubrum*, followed by *T. interdigitale* (formerly *T. mentagrophytes*), are the most common causative agents [49].

The types and frequency pattern of dermatophyte species in diabetic patients were similar to those in the immunocompetent group.

10.2.4.11 Diagnosis of Fungal Nail Infection

See Sect. 10.4, Diagnostic procedures.

10.2.4.12 Treatment

Onychomycosis can have a significant impact on the quality of life of patients by discomfort, difficulty in wearing footwear and walking, cosmetic embarrassment and lowered self-esteem [50–52].

Infected nails may serve as a reservoir of fungi with a potential for spread to the feet, hands and groin and to other family members. Another sequelae can be the disruption of the integrity of the skin leading to bacterial infections like cellulitis [53]. In the view of these aspects, treatment of fungal nail infection should be strongly considered.

With few exceptions in general, systemic therapy is compulsory to cure fungal nail infection, supported by topical treatment. The decision about other methods like surgical nail removal or nail avulsion by urea has to be drawn in attention in individual cases, which means in single nail onychomycosis. Laser treatment or photodynamic therapy (PDT) needs more experience and may be an option in the future.

Fungal-free nails are the goal of antifungal therapy in onychomycosis.

Topical treatment

- The efficacy of topically applied antifungal drugs is limited because the hard keratin and compact structure of the dorsal nail-plate act as a barrier against diffusion into and through the nail-plate. The concentration of topically administered drugs can drop by 1000 times from the outer to inner surface [54].
- The hydrophilic nature of the nail-plate also precludes absorption of lipophilic molecules with high molecular weight. These circumstances explain the limited role of monotherapy with topical antifungals with restriction to SWO and early DLSO [34].
- Terbinafine (topical formulation) [55]
- Amorolfine (morpholine) 5% lacquer—fungicidal against *C. albicans* and *T. mentagrophytes*
- Ciclopirox olamine (hydroxypyridone derivate) 8% lacquer—antifungal activity against *T. rubrum*, *S. brevicaulis* and *Candida* spp.
- Ciclopirox olamine and amorolfine are available in alcohol-based nail lacquers.
- Another ciclopirox olamine-containing nail lacquer has been available now for several years. Here, unlike the above-mentioned alcohol-based preparation, a film-forming agent is used as lacquer base. By binding to nail keratin, the water-soluble biopolymer hydroxypropyl chitosan (HPCS) allows for a better transport and release of ciclopirox olamine. The lacquer is applied once daily [56].

For successful application of antimycotic nail lacquer, onychomycosis should affect only up to 40% of the nail surface (an infestation level of <50% according to an international consensus conference) or a maximum of three out of ten affected toenails. The SPC for amorolfine-containing nail lacquer, however, lists onychomycosis with an involvement of <80% as indication.

Systemic Therapy

The main systemic drugs approved and widely used for the treatment of onychomycosis are the allylamine terbinafine and the triazole itraconazole. Griseofulvin is much less commonly used now given the higher efficacy and safety as well as compliance rates of the other systemic agents. Fluconazole represents a third-line therapy with restricted limitations, and in some countries, f.e. in the UK, it is not licensed for the treatment of onychomycosis [34].

Mainly with toenail onychomycosis, the rate of treatment failure with standard antifungal drugs is in the range of 25–40%, and this failure has been attributed to many aspects like poor patient compliance, low bioavailability, lack of drug penetration into the nail, drug resistance and poor nail growth [57].

New second-generation triazoles (f.e. voriconazole, posaconazole, ravuconazole, albaconazole, pramiconazole) recently are under development and may be of choice in refractory cases of onychomycosis.

Terbinafine is presently the only oral fungicidal antimycotic. It is detected in the nail within 1 week of starting therapy and persists for 6 months after the completion of treatment, as it has a long half-life [58]. Terbinafine has broad and potent fungicidal effects against dermatophytes, particularly *T. rubrum* and *T. interdigitale*, but has lower fungistatic activity against *Candida* species than the azoles [59]. The most common side effects are gastrointestinal, such as nausea, diarrhoea or taste disturbance, and dermatological events [60]. Serious side effects like hepatic toxicity are rare and occur mainly in patients with pre-existing liver disease; therefore systemic terbinafine is not recommended in those patients [61].

The efficacy and safety of terbinafine for the treatment of onychomycosis have been widely studied with different dosage—schedules with continuous dosing being superior to pulsing regimens (Table 10.6).

Itraconazole is active against a broad range of fungi including yeasts, dermatophytes and some nondermatophyte moulds. Like terbinafine it penetrates the nail quickly and is detectable in the nail as early as 7 days after starting therapy and persists in the nails for up to 6–9 months after treatment discontinuation [58]. The most common side effects including headache and gastrointestinal upset and asymptomatic liver function abnormalities are observed in 1.9–3% of patients [62]. Itraconazole can be administered in continuous or pulsing dosing regimens (Table 10.6).

Table 10.6 Systemic treatment of onychomycosis

Terbinafine	250 mg daily 6 weeks in fingernail infection 12–16 weeks in toenail infection
Itraconazole	*Continuous schedule* 200 mg daily for 12 weeks *Pulsing schedule* 400 mg daily for 1 week per month 2 pulses in fingernail infection 3 pulses (or more) in toenail infection
Fluconazole	150–450 mg per week 3 months in fingernail infection At least 6 (-10) months in toenail infection

Onychomycoses is associated with high recurrence rates (40–70%) [63]. The term 'recurrence' suggests both relapse and reinfection: in treatment relapse, infection is not completely cured and returns and in reinfection cure of fungal nail disease is followed by a new infection by the same or a different organism. Nail thickness (>2 mm), slow outgrowth, severe onycholysis and dermatophytoma are considered the most common reasons for recurrence and should raise attention to the outcome of antifungal therapy.

- Oral antimycotic agents are indicated for cure [64].
- Management requires correct mycological identification.
- Risk-to-benefit ratio of onychomycosis treatment should be assessed.
- Terbinafine is drug of choice in tinea unguium.
- Triazoles (itraconazole, fluconazole) in candidal and NDM onychomycosis.

10.2.5 Tinea Incognita (Steroid-Modified Tinea)

In tinea incognita (=tinea atypica), i.e. unrecognized tinea, cutaneous dermatophytosis is not considered as differential diagnosis. By definition, tinea incognita is a dermatophyte infection

that has lost its typical clinical appearance due to the unjustified use of topical corticosteroids or calcineurin inhibitors [65].

Groin, lower legs, the face and the hands are mostly affected, with clinical lesions of dermatophyte infections being misdiagnosed as eczema, psoriasis and facial dermatoses. Due to the use of corticosteroids, typical aspects of the dermatophytosis are modified, i.e., the raised margin is diminished, scaling is lost and inflammation may be reduced to few nondescript nodules of bruise-like brownish discoloration. In the course of time due to chronic steroid treatment atrophy, telangiectasia in the axillae and groins striae may develop. The history of tinea incognita is characteristic—whereas discontinuation causes relapses, the patient continues the use of steroids, despite cure may not be achieved [66].

Special features of tinea incognita are Majocchi's granuloma, *Malassezia* folliculitis (formerly called *Pityrosporum* folliculitis) and Ofuji's syndrome. Majocchi's granuloma is defined to a deep-seated dermatophytosis, mainly as granulomatous folliculitis, following trauma, such as shaving as well as long-standing natural or therapeutic occlusion or topical steroid treatment. Treatment requires recognition; KOH testings have to be done to prove the nature of infection. In general systemic antifungals have to be administered (f.e. itraconazole or terbinafine for a three to four weeks duration), accompanied by topical treatment regimen.

Clues for diagnosis of tinea incognita:

- Long-standing treatment by corticosteroids with regular relapse after treatment discontinuation
- Misleading clinical features due to corticosteroid modification [67]
- Face, groin and hands mostly affected (Fig. 10.32)

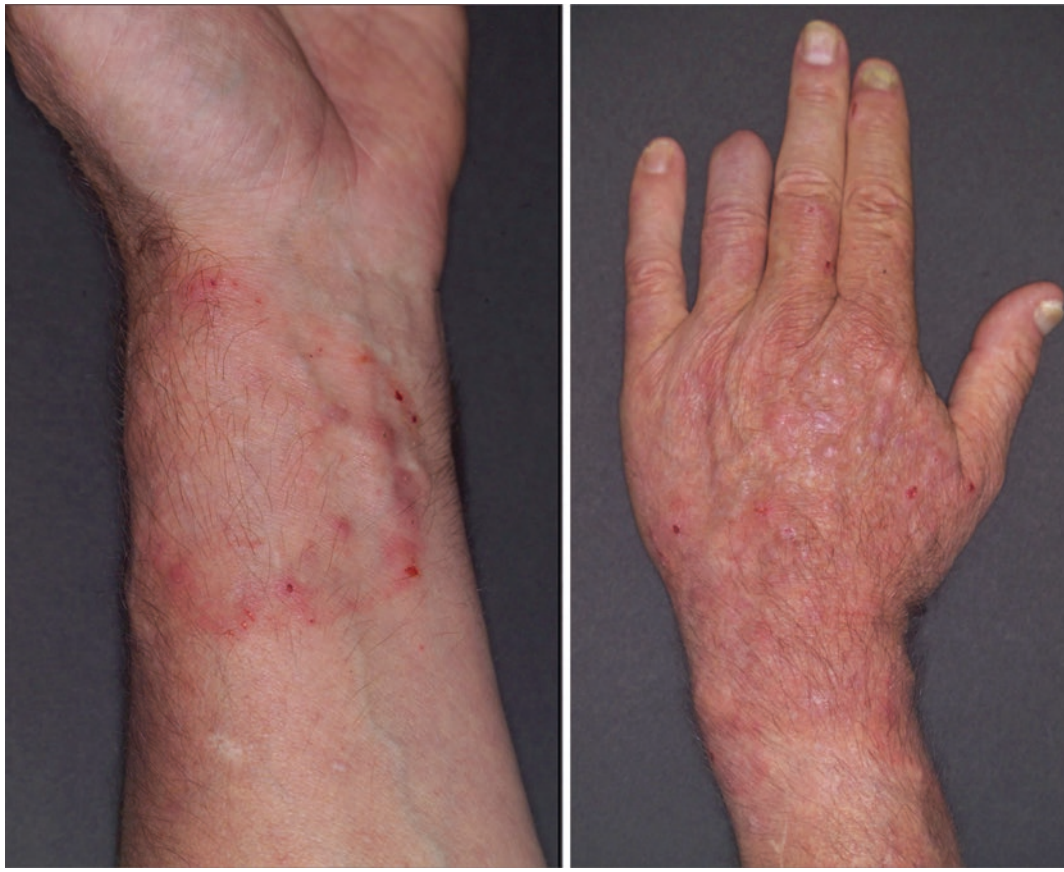

Fig. 10.32 Tinea incognita due to *Trichophyton rubrum* following autoinoculation by fungal infection of the toenails

10.3 Yeast Infections

10.3.1 Etiologic Agents

Yeasts are unicellular fungi that are reproduced by the process of budding in which daughter cells are produced from parents by outpouching of the cell membrane and wall, migration of cytoplasma into the new structure that formed and then separation from the parent cell [45].

The most frequently isolated causative agents in superficial infections are *Candida* species, *Cryptococcus neoformans* and the lipophilic yeasts of the genus *Malassezia*. In addition to *Candida albicans*, the genus *Candida* includes over 100 species, some of which (*C. stellatoidea*, *C. africana*, *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*, *C. krusei*, *C. kefyr* (formerly *C. pseudotropicalis*), *C. zeylanoides*, *C. glabrata*, etc.) occasionally cause human disease.

10.3.2 Superficial Candidiasis

Candidiasis is an infection most commonly caused by the yeast *Candida albicans* or other species of *Candida*. Most common are superficial infections of the mucous membranes and skin, giving entrance to invasive infections by dissemination. Humans carry yeast fungi in the gastrointestinal tract, from the mouth to rectum as part of the normal commensal flora. The vagina may also be colonized by yeasts without any signs of infection. By contrast, *Candida* species are not permanent members of the normal flora of the skin but can transiently colonize some areas like fingers and body folds. In given predisposition colonization can proceed to true infection.

10.3.2.1 Skin Infections by *Candida* Species

Cutaneous candidiasis predominantly affects intertriginous areas, i.e. groins, abdominal skin folds, inframammary skin but also interdigital spaces. Skin infections caused by yeasts are typically characterized by erythematous (bright red to purple-red), erosive, dry, scaly, sometimes macerated lesions. It often has an irregular edge and satellite papules and pustules that develop beyond the margin. Where the webspaces of the toes or the fingers are affected, marked maceration with a thick white horny layer is usually prominent. In interdigital candidiasis of the toe webs, Gram-negative bacteria are often co-pathogens beside *Candida*. Non-intertriginous areas characteristically display erythemato-squamous lesions with collaret-like scaling. Soreness and burning itch are usual [13, 45].

The development of superficial candidiasis in general needs predisposing factors to manifest. Obese subjects as well as diabetics, immunosuppression, serious illness, the age group of the elderly and early infants are predisposed for these infections. With regard to immunosuppression, interdigital mycoses by *C. albicans* may be indicative of full-blown AIDS in areas with high HIV prevalence, e.g. in sub-Saharan Africa. Differential diagnosis of candidiasis includes tinea (dermatophytosis), contact dermatitis, seborrheic dermatitis, bacterial infections and inverse psoriasis. *Candida* may also contaminate any of these conditions and lead to secondary infection.

Diaper Candidiasis (Napkin candidiasis)

Candida albicans is commonly isolated from the moist skin of the buttocks and genitalia of the infant but is more prevalent where the skin is infected by nappy rash [68]. This special form of cutaneous candidiasis is marked by maceration and erosion, yet also whitish patches and desquamation. In addition fringed irregular borders and satellite lesions are indicative for the infection. Wet and warm surroundings are a predisposing factor, aggravated by urine acting as irritant. Similar lesions can be found in elderly, bedridden and incontinent patients [69].

In recalcitrant cases with *Candida* infection, acrodermatitis enteropathica (zinc deficiency syndrome) should be drawn in attention.

Nodular or granulomatous candidiasis of the napkin area (syn. granuloma gluteale infantum) is a syndrome that represents a peculiar reaction to *Candida* infection. This kind of napkin eruption is characterized by the development of bluish or brownish nodules. Beside *Candida* topical steroids are probably an important etiological factor. The true nature of this condition has not yet been elucidated [70, 71].

Treatment

With regard to treatment, underlying localized and general predisposing and susceptibility factors should be considered. In skin infections drying and ventilation are of highest importance. In many cases topical therapy alone is sufficient, but considerations should always be given to the reduction of the *Candida* reservoir in the mouth and the gut, not at least with respect to prophylactic reasons [72].

The polyene antibiotics (f.e. nystatin) and the group of imidazoles (clotrimazole, miconazole, econazole, ketoconazole, flutrimazole, etc.) are highly effective against *Candida* spp. and most other yeast pathogens. Development of resistance against these groups is *up to now not* observed.

- Mind localized and general predisposing factors.
- Topical steroids may modify the inflammatory changes.
- Topical antimycotic treatment (azoles, nystatin) alone usually sufficient.
- With recurrent infections oral therapy with a polyene or triazole should be considered (Figs. 10.33, 10.34 and 10.35).

10.3.2.2 Mucocutaneous Candidiasis

- Oral candidiasis—see Chap. 4
- Genital candidiasis
  - *Candida* vulvovaginitis—see Chap. 4
  - *Candida* balanitis (balanoposthitis candidomycetica)

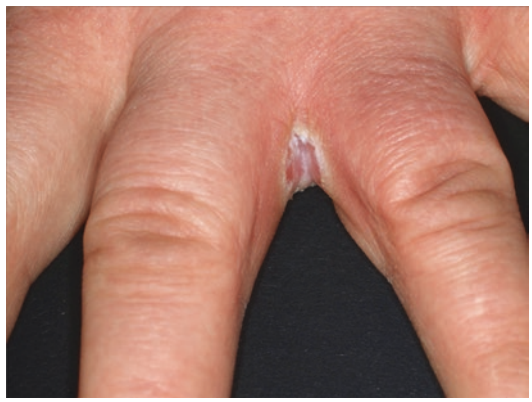

Fig. 10.33 Candidal infections of interdigital spaces (‘erosio interdigitalis blastomycetica’) arising from prolonged water exposure of the hands

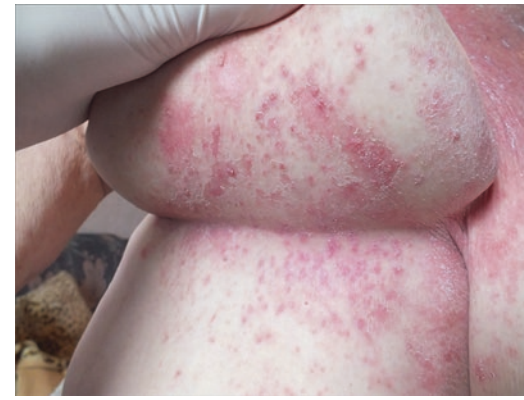

Fig. 10.34 Intertriginous candidiasis (‘*Candida* intertrigo’) in the inframammary folds

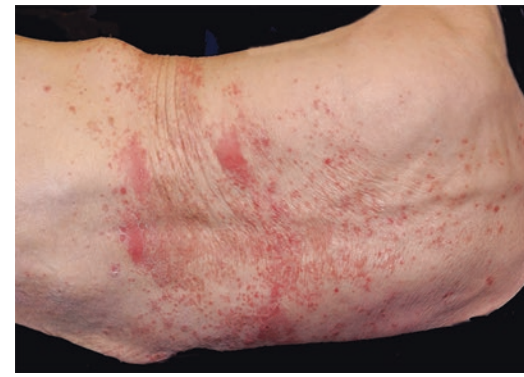

Fig. 10.35 Cutaneous widespread candidiasis in a bedridden elderly

The skin of the glans penis, especially in the uncircumcised, may sometimes be colonized by *Candida* asymptomatically [73]. When *Candida* balanitis develops, it presents with transient tiny papules and white pustules or vesicles and rupture, leaving a peeling edge. Soreness, itching and irritation may be of subjective complaints. Exacerbation of the condition after intercourse is common. In more severe and chronic cases, the inflammatory changes become persistent over the glans and the prepuce. When *Candida* balanitis develops, usually either abundant vaginal *Candida* carriage (symptomless) or frank vulvovaginitis in the sexual partner may be found. It is worth considering diabetes where persistent lesions spread beyond the genitalia. Concerning the situation with a contracted prepuce (phimosis), the need of circumcision has to be drawn in attention.

Treatment

- Topical antimycotic treatment (azoles, nystatin) usually satisfactory.
- Rule out susceptibility factors (phimosis, diabetes, etc.).
- Screening of the sexual partner (s) and appropriate treatment.
- Exclude differential diagnoses, like psoriasis inversa, balanitis simplex, herpes genitalis, balanitis plasmacellularis Zoon (Fig. 10.36).

10.3.2.3 *Candida* and the Nail

See Sect. 10.2.4.6.

10.3.3 Pityriasis Versicolor

Pityriasis versicolor is a mild chronic infection of the skin caused by *Malassezia* spp. (formerly *Pityrosporum ovale sive orbiculare*). The condition is characterized by discrete discoloured or depigmented areas mainly on the upper trunk, back, chest, shoulders and upper arms.

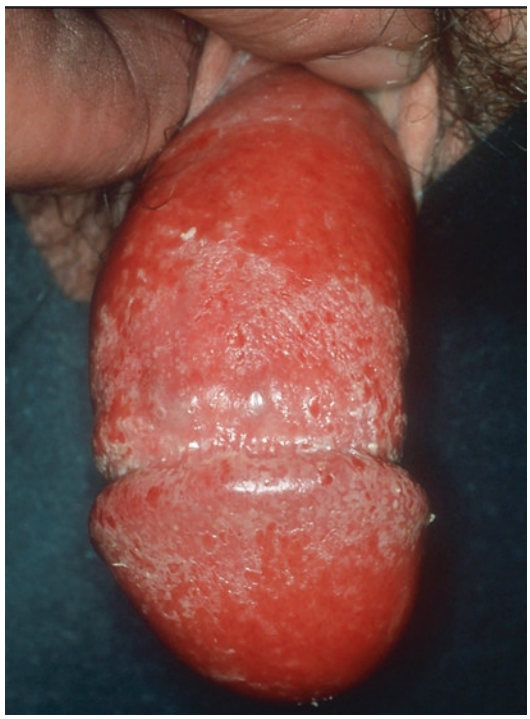

Fig. 10.36 *Candida* balanitis

The disease typically starts with brownish-red, macular, coalescing, apparently non-scaly lesions and is defined as 'pityriasis versicolor rubra'. In the course of time, the lesions spread in a map-like fashion without sharp demarcation. Except in children and dark-skinned people in tropical countries, pityriasis versicolor never affects the face. By tangential scraping the skin with a wooden scapula or scalpel bran-like scaling may be evoked (shaving phenomenon).

'Pityriasis versicolor alba' presents the white pseudochromatic variant of pityriasis versicolor. This depigmentation is caused by dicarboxylic acids, such as azelaic acid produced by *Malassezia* spp., which may competitively inhibit tyrosinase and perhaps have a direct cytotoxic effect on hyperactive melanocytes [74].

10.3.3.1 Skin and *Malassezia*

The lipophilic yeast fungus *Malassezia* spp. is the only fungal genus or species which is part of the physiological human microbiome, beside in other warm-blooded animals [75].

Today, at least 14 different *Malassezia* species are known, of which 8 have been isolated from human skin. Most of them can only be identified using molecular biological techniques. In pityriasis versicolor, *M. globosa* is predominantly found in 62.5% of patients, followed by *M. sympodialis* [76, 77].

Colonization by these species is particularly dense in the scalp, upper trunk and flexures. Pityriasis versicolor appears to represent a shift in the balance between host and resident flora in which mycelial forms develop [45]. Multiple factors contribute to the change and include genetically determined host susceptibility factors, climate and immune competence [78, 79].

Likewise *Malassezia* folliculitis and seborrheic dermatitis are conditions contributed to Malassezia yeasts. Whereas in seborrheic dermatitis or scaling of the scalp, dandruff, *Malassezia* yeasts are found in large quantities in the scales of patients, in *Malassezia* folliculitis yeasts may be found by means of histology within the body of the follicles. Lesions are itchy papules and pustules diffusely scattered on the shoulders and back [45].

Beside these conditions *Malassezia* allergens should be considered as the trigger of 'Head-Neck'-type atopic dermatitis [76, 80].

10.3.3.2 Treatment

The topical azole antifungals but also the allylamine terbinafine and the hydroxypyridone antifungal agent ciclopirox olamine work well, with ketoconazole, selenium sulphide or zinc pyrithione shampoos being available for washings. Alternatively, itraconazole is effective in a total dose of 800–1000 mg (given over 7 days, e.g. 100 mg twice daily for 1 week) but may be subject to extensive disease. Repigmentation may take several months and should not be interpreted as treatment failure. In some patients who are unresponsive to conventional treatments with frequent relapsing episodes, narrow-band UV-B phototherapy may be effective [45, 81, 82].

- Scalp, upper trunk and the flexures are colonized by *Malassezia* spp.
- Topical and oral azoles first-line drugs in pityriasis versicolor.
- Repigmentation takes several months (Figs. 10.37, 10.38 and 10.39).

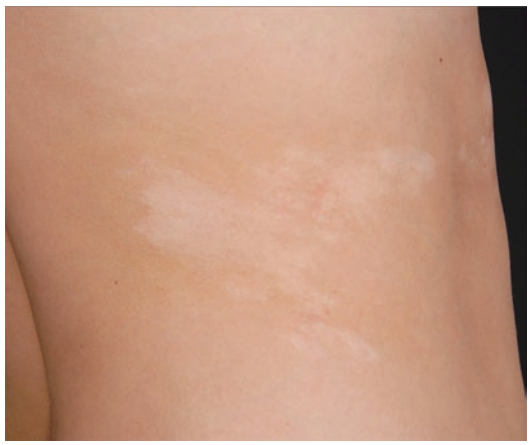

Fig. 10.37 Pityriasis versicolor presenting finely scaling hypopigmented lesions

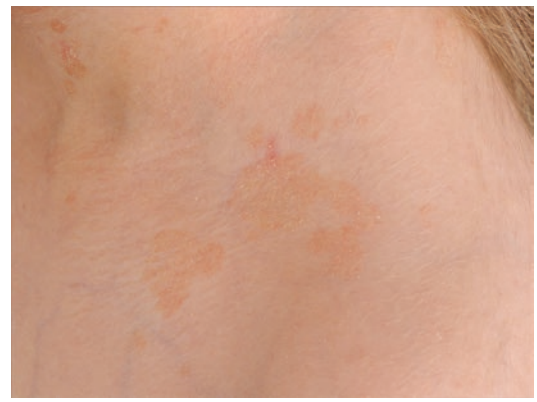

Fig. 10.38 Pityriasis versicolor on the neck in a child

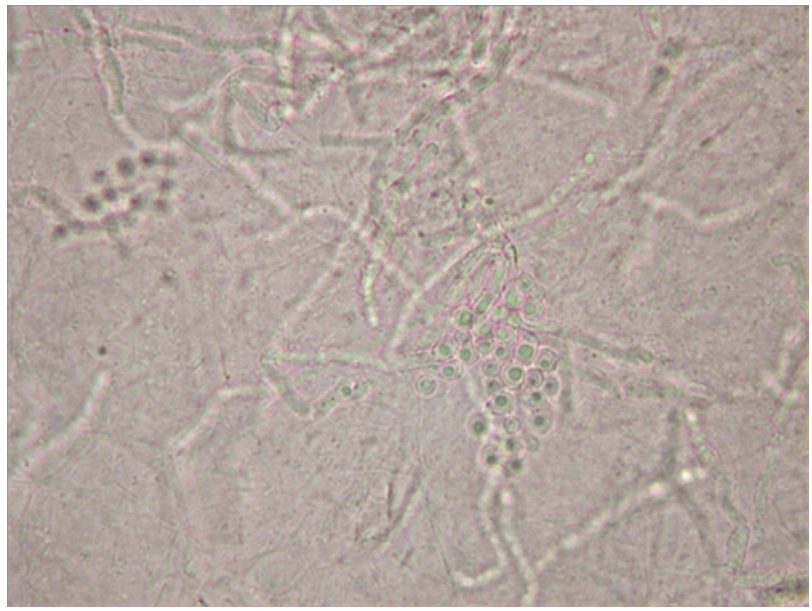

Fig. 10.39 Microscopic examination of KOH-treated skin scrapings: *Malassezia* yeasts (spherical yeasts and short hyphae =pseudomycelia)

10.4 Diagnostic Procedures

Diagnostic procedures in fungal infections comprise sampling of material, microscopy, cultivation proceedings and molecular methods (PCR) for detection of fungal pathogens. In general topical antimycotic treatment may be started if microscopic findings are positive.

10.4.1 Diagnostic Sampling

Apart from skin scrapings, samples include hair roots in cases of suspected tinea capitis and nail clippings in cases of suspected onychomycosis. Skin scrapings should be taken by a scalpel or curette from the lesional border, whereas hair roots may be collected by epilation tweezers. Additional methods like the hairbrush technique (in scaling tinea capitis or for screening exams among family members) or swab sampling (in purulent infections) are other techniques for diagnostic sampling.

10.4.2 Microscopic Preparations

The KOH (potassium hydroxide) examination using 20% KOH represents the simplest method to detect fungi in skin scales, nails and hair roots microscopically. Tetraethylammonium hydroxide (TEAH) may be used alternatively for immediate determination of fungal elements mainly in nail clippings. The diagnostic sensitivity may be partially insufficient, especially in onychomycosis. The most sensitive method of microscopic detection of fungi in skin scales, nail clippings, hair roots, hair as well as Scotch tape preparations is fluorescent staining with optical brighteners (diaminostilbene). These substances bind to chitin, the main cell wall component of fungi. Currently available stains are Blankophor® or Calcofluor® test solutions that are prepared with 20% KOH. Using fluorescent microscopy, spores, yeast cells, hyphal fragments and arthrospores (=disintegrating mycelium) may be differentiated [13].

10.4.3 Cultural Dermatophyte Detection

As fungi are heterotrophic microorganisms, culture media contain organic nutrients required for growth and reproduction, among them a carbon source (glucose), a nitrogen source (peptone, meat extract), water, vitamins and antibiotics.

Every sample should be inoculated onto two culture media, one of them containing cycloheximide (Actidion®) to suppress mould growth. Cultures should be incubated at a temperature of 26–32 °C, optimally at 28 °C, for 3–4 weeks and visually checked for fungal growth twice weekly. For slow-growing dermatophytes (*T. verrucosum* or *T. violaceum*), the incubation period should be extended to 5–6 weeks.

The selective dermatophyte agar according to Taplin is a selective but at the same time also differentiation medium because the addition of cycloheximide allows for selective growth of dermatophytes on this cultural medium. Dermatophytes produce alkaline metabolites that alkalize the initially acidic cultural medium, causing the indicator phenol red to turn from yellow to red, thus signalling dermatophyte growth.

The differentiation of dermatophytes, yeasts and moulds is predicated on macroscopic (upper and bottom side of colonies as well as pigmentation) and microscopic characteristics (formation of macro- and microconidia) as well as biochemical properties. Quite frequently, cultural detection fails (sensitivity roughly 70% in onychomycosis) because of pretreatment with topical or systemic antifungals. Thus, vital fungi are already inhibited in vivo, preventing them from growing in vitro [13].

10.4.4 Molecular Detection of Dermatophytes [13]

Nucleic acid amplification techniques (NAAT) are more and more used for direct examination of dermatophytes in clinical samples, e.g. *T. rubrum* and *T. interdigitale*. NAAT are also used

as culture confirmation tests for identification of rare dermatophytes like *T. verrucosum*. Today, singleplex and multiplex quantitative real-time PCR (qRT-PCR) assays for the detection of the most common dermatophytes including rare dermatophyte species like *T. verrucosum* in clinical specimens are available.

Ohst et al. from Germany developed a modular singleplex quantitative real-time PCR (qRT-PCR) assay for the detection of the most common dermatophytes in clinical specimens [83]. This qRT-PCR assay is based on single-tube reactions with TaqMan probes. *T. rubrum* (75.6%) and *T. interdigitale* (16.9%) were the most frequently detected dermatophytes. Some less common dermatophytes, among them *M. canis*, *Epidermophyton floccosum*, *T. benhamiae* and *T. verrucosum*, were detected, too. It was concluded that the qRT-PCR assay allows a specific and sensitive detection of relevant dermatophytes at low cost in a short time.

A dermatophyte-specific single-tube real-time PCR assay based on internal transcribed sequences was developed for rapid detection and identification of 11 species within the 3 dermatophyte genera *Trichophyton*, *Microsporum* and *Epidermophyton* in nail, skin and hair samples within a few hours [84].

Sequencing of the ITS region of the rDNA is used for culture confirmation of rare dermatophytes [85, 86].

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