Antibiotic and Antifungal Therapies in Dermatology

Jón Hjaltalín Ólafsson
Roderick James Hay
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Preface

This book deals with the treatment of skin infections as well as those skin diseases that are treated with antibiotics and antifungals.

Infective skin diseases can often be difficult to diagnose whereas in other instances the treatment is the problem. In addition some diseases that are rare where the reader lives, may be common and easy to diagnose and treat for colleagues living in another part of the world.

The purpose of this book has been to make those who practice dermatology and venereology aware of skin infections and their treatment, including those that may be unfamiliar in everyday practice. A further aim was to present details of treatments for both rare and common infectious skin diseases that included the latest therapeutic advances. We have deliberately avoided discussion of viral skin diseases as well as most parasitic skin diseases, believing that these merit separate attention.

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Common Skin Bacterial Infections

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1.1 Background

1.1.1 Definition

Common skin bacterial infections are very frequent in daily dermatological practice. Superficial pyodermas, characterized by involvement of the epidermis, the upper dermis, and the superficial part of the adnexal structures (hair follicles and nails) [1], include impetigo and impetiginization of dermatoses, folliculitis, furuncles and furunculosis, carbuncle, and suppurative paronychia. Other common skin infections are erythrasma, involving the upper epidermis, primary abscesses, and erysipelas, involving the deep dermis and the hypodermis.

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1.1.2 Bacteriology

Staphylococcus aureus is the main pathogen involved in these infections, group A hemolytic *Streptococcus* being the second in frequency [2].

In contrast with the normal cutaneous flora residing on the superficial epidermal layers and pilotropic adnexa, mainly comprising *Staphylococcus epidermidis* and gram-positive rods such as *corynebacteria* and *Propionibacterium acnes*, *Staphylococcus aureus* is not a permanent part of the normal skin flora but colonizes inflamed skin (psoriasis, atopic dermatitis, cutaneous lymphoma, bullous diseases, erythroderma) [3–5]. *S. aureus* may also colonize the newborn's umbilicus for several weeks after birth.

However, 20–60 % of normal individuals have a persistent or intermittent nasal carriage of *S. aureus*, depending on bacterial adherence and host factors [6]. Other sites of carriage are the perineum, axillary folds, and umbilicus. Nasal carriage is mostly a risk factor for chronic or recurrent furuncles (furunculosis) [7].

Important advances concerning *S. aureus* virulence mechanisms have been made over last decades. For instance Panton-Valentine leukocidin (PVL), carried by methicillin-sensitive or methicillin-resistant *S. aureus*, is responsible for necrosis and apoptosis of neutrophils and is thus frequently involved in the pathogenesis of follicular infections and abscesses [8–10].

It has also been shown that *S. aureus* produces exfoliative toxins responsible for blistering bacterial infections such as bullous impetigo [7] and staphylococcal scalded skin syndrome (SSSS) by cleaving the cell adhesion cadherin desmoglein 1, which plays an important role in the barrier function of the upper epidermal layers [11, 12].

The emergence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) must also be considered today. Since the emergence of MRSA as a nosocomial agent during the 1960s, several clones have spread out of hospitals and health-care facilities: (1) health-care-associated MRSA clones, responsible for infections in patients with risk factors such as recently hospitalized patients, patients with chronic diseases, and drug abusers, and (2) true de novo community producing PVL, responsible for cutaneous or, less frequently, necrotizing pulmonary infections in patients without any risk factors and being now a true public health problem worldwide [13–16].

Group A hemolytic *Streptococcus* (*S. pyogenes A*, *C*, *G*) is present in the mouth in 10 % of the population, periorificial regions but skin carriage in normal individuals is rare. M proteins, pyrogenic and erythrogenic SPE exotoxins and streptolysin are the main virulence factors of the bacteria [17, 18].

The current increasing resistance of *S. pyogenes* to macrolides must be taken in account in some countries but is being better controlled by a lower use of antibiotics [19–21]. However, there is no resistance to penicillin, and clindamycin and pristinamycin (if available) which remain good alternatives in case of allergy to penicillin [22, 23].

1.2 Impetigo

1.2.1 Definition

Impetigo is a contagious primary infection of the skin, involving the stratum corneum, due to *S. aureus*, less frequently *S. pyogenes*, or both. It is particularly common in children and disadvantaged areas. Self-inoculation and small family or communities outbreaks are frequent.

Two types of clinical form are described: (1) crusted impetigo is due to *S. aureus* or *S. pyogenes*, and (2) bullous impetigo is due to the cleavage of very superficial epidermal layers by staphylococcal toxins (exfoliatins) and can be either disseminated (SSSS) or more limited. However, in general practice, both bacteria should be considered when prescribing treatment because bacteriological sampling is often not performed or feasible in general practice unless there is a specific epidemiological context or resistance to classical treatment.

1.2.2 Clinical Presentation

The diagnosis is based on clinical examination. Early lesions are isolated or confluent and polycyclic vesicles or blisters, followed by erosions and yellowish crusts ("honey-colored") (Figs. 1.1 and 1.2).

Typical location in children is around orifices, especially the mouth, but all areas of the skin may be affected. There are usually no systemic symptoms such as fever, although there may be local lymphadenopathy.

Ecthyma, more frequent in patients with poor hygiene, is a necrotic complication of streptococcal impetigo, clinically characterized by deep dermal ulcerations.

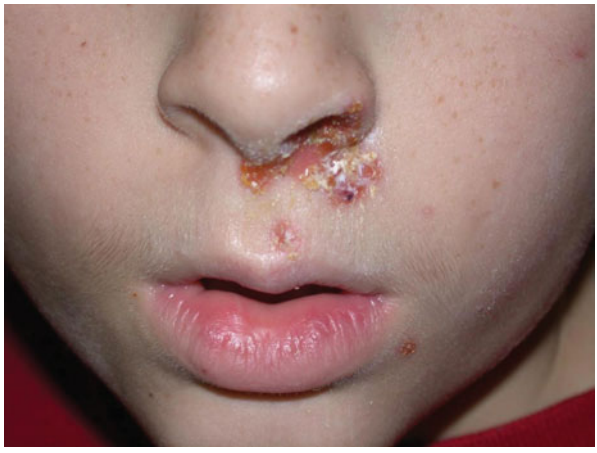

Fig. 1.1 Periorificial crusted impetigo

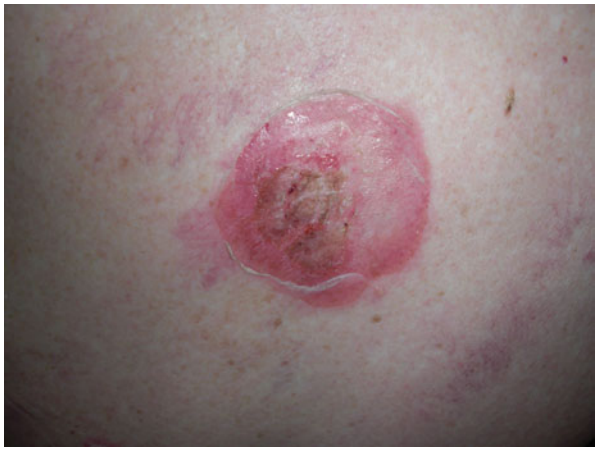

Fig. 1.2 Bullous impetigo

1.2.3 Prognosis

Without treatment, impetigo usually resolves without sequelae within 2 weeks.

Although systemic complications of childhood impetigo are rare today, infectious or post-infectious glomerulonephritis may occur after extensive, chronic, and/or neglected streptococcal or staphylococcal superficial pyodermas in patients with risk factors such as alcoholism, diabetes mellitus, or drug abuse [24]. Furthermore, glomerulonephritis is a major complication of scabies-related streptococcal impetigo in resource-poor countries [25]. In contrast, rheumatic fever does not complicate impetigo except possibly in tropical areas in association with scabies. Other rare complications include sepsis, osteomyelitis, arthritis, endocarditis, lymphangitis, erysipelas, guttate psoriasis, and SSSS [26].

1.2.4 Treatment

Improving personal hygiene with daily showers, washing hands, brushing nails, and frequent change of clothes is important. Washing lesions with soap and water or topical antiseptics (povidone-iodine, chlorhexidine, hexamidine, Dakin's solution) is usually sufficient for very limited lesions. However, topical antibiotics are widely recommended and may be the treatment of choice for impetigo of limited extent (one site and/or five to ten lesions) [27]. Topical fusidic acid and mupirocin have a comparable effectiveness and are as effective as oral flucloxacillin [28, 29]. Furthermore, moisturizing ointments are useful to remove crusts and enhance healing.

With more extensive lesions, systemic antibiotics against both *S. aureus* and *S. pyogenes* are recommended: penicillin M (oxacillin or rather cloxacillin for better oral route bioavailability), amoxicillin-clavulanic acid, first or second generation cephalosporin, fusidic acid, or pristinamycin [30]. Given the emerging resistance of

S. aureus and *S. pyogenes*, macrolides (except erythromycin because of its effect on QT interval [31]) should only be used as a second line where there is intolerance or allergy to beta-lactams [32].

1.3 Folliculitis, Furuncle, Chronic Furunculosis, and Carbuncle

1.3.1 Definition

Folliculitis and furuncles, the most common forms of skin infection, are acute hair follicle infections (infection of the ostium or follicular opening in superficial folliculitis or infection of the entire hair follicle in furuncles), due to *S. aureus* including strains secreting PVL. In the case of superficial folliculitis, other strains of *Staphylococcus*, or other microorganisms such as *Candida albicans*, may be involved. Apart from climatic factors such as humidity or heat, folliculitis and furuncles are more frequent in patients with immunosuppression, diabetes mellitus, long-term antibiotic use, obesity, occlusive clothes, or recurrent shaving, especially in pubic area. Chronic furunculosis is mainly associated with nasal carriage of *S. aureus* [10, 33]. We have recently seen several patients with *Enterobacter aerogenes* folliculitis acquired after spa baths.

Gram-negative folliculitis, especially folliculitis due to *Pseudomonas*, has been described since the late 1970s as case reports or outbreaks in swimming pools, whirlpools, hot tubs, spa, and recently rubber gloves with an incubation period of from 2 to 5 days [34–36].

In patients with acne in whom treatment with tetracyclines has not shown a significant improvement after 3–6 months, a gram-negative infection should be considered and investigated if possible. The gram-negative bacteria include *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Klebsiella*, and *Proteus mirabilis* [37].

1.3.2 Clinical Presentation

- *Folliculitis* is characterized by scattered or extensive follicular pustules surrounded by a macular or papular erythema, mainly located on thighs, buttocks, back, and beard (Fig. 1.3).
- *Pseudofolliculitis* (*pili incarnati*) results from the penetration into the skin of shaved hairs within follicles. This condition [38] affects people with curly hair. Papules and pustules may lead to discomfort and small scars or postinflammatory hyperpigmentation.
- *Furuncle* (*boil*) is the consequence of an acute and sometimes necrotic PVL-positive staphylococcal infection of the entire hair follicle and presents as an

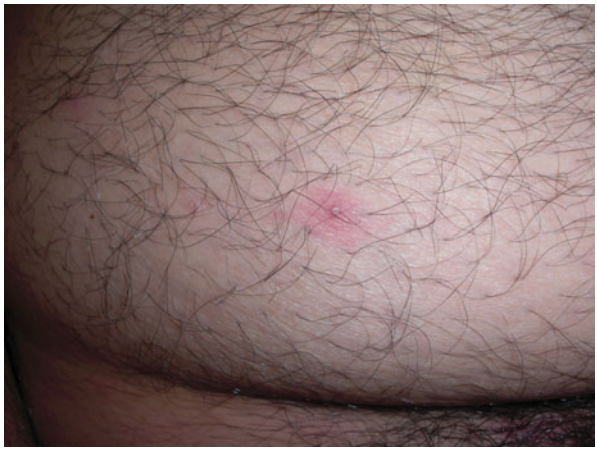

Fig. 1.3 Folliculitis

inflammatory papule then a painful nodule with a central follicular pustule, evolving after a few days leading to spontaneous necrosis and suppuration with discharge of a necrotic core then a permanent scar. Lesions may be single or multiple, involving the face, buttocks, arms, thighs, and anogenital area. There is seldom fever and systemic complications are quite rare. However, with facial furuncles, cavernous sinus thrombosis may constitute a dangerous complication [39].

- *Chronic furunculosis* is the recurrence of furuncles over a number of months and is, favored by obesity, diabetes mellitus, immunodepression, iron deficiency, alcoholism, and malnutrition. However, staphylococcal nasal carriage and exposure to an infected family member are the main risk factors, and antiseptic decontamination is most important in order to avoid recurrences [40–42].
- *Carbuncles* are the aggregation of furuncles and form broad, swollen, painful, and often fluctuant nodules and deep masses with spontaneous multiple drainage tracts. Patients are often febrile may be unwell [43] (Fig. 1.4).

1.3.3 Treatment

1.3.3.1 Superficial Folliculitis

Any external causal agent should be removed or controlled if appropriate. Cleaning with water and soap and/or antiseptics, with a broad antimicrobial activity [44], is effective in most cases. Topical antibiotics such as mupirocin or fusidic acid are usually effective twice a day for 5–7 days with a low rate of resistance but are not always prescribed. Systemic antistaphylococcal antibiotics are recommended in more severe cases defined as extensive, persistent, and/or recurrent lesions, after bacteriological sampling [27, 29, 45].

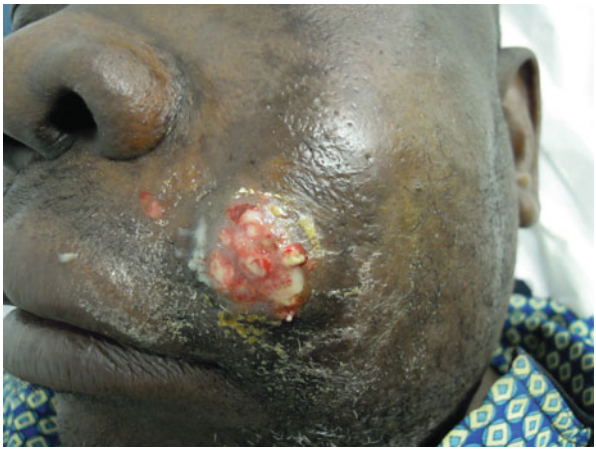

Fig. 1.4 Carbuncle of the face

1.3.3.2 Pseudofolliculitis

In the acute phase, shaving should be stopped for several weeks until improvement, and local treatments such as topic erythromycin or fusidic acid, antiseptics or tretinoin may be useful [46]. Shaving must subsequently be performed with individual adjustment, for example, electric razors preferentially over manual razors for beard folliculitis. Hair should be left 1 mm long. Hair removal with chemical depilatories may be effective, and laser, with or without eflornithine hydrochloride, could provide long-term remission, especially for beard folliculitis in patients with dark skin [46–49].

1.3.3.3 Gram-Negative Folliculitis

Lesions usually cure either spontaneously or with antiseptics such as acetic acid, chlorhexidine, povidone, and potassium permanganate within a few days. Silver sulfadiazine cream may also be useful, but other topical anti-gram-negative antibiotics such as polymyxin are disappointing.

Prevention is based on adequate maintenance of bathing facilities, chlorine level, and disinfecting procedures of public equipments [34].

The best treatment of tetracycline-induced gram-negative folliculitis occurring during the course of acne is isotretinoin [50].

1.3.3.4 Furuncles and Carbuncles

Systemic antistaphylococcal antibiotics such as penicillin M (oxacillin, cloxacillin, flucloxacillin) should be prescribed for 5–7 days [51], associated with topical antibiotics applied on the lesion and the surrounding skin. Occlusive clothes must be

avoided. Hygiene measures should be reinforced (hand washing, nail brushing, repeated showers with soap and/or antiseptics).

In case of recurrences, an underlying condition must be sought (staphylococcal nasal and extranasal carriage in the patient and his household members, diabetes, immunodepression, etc.) and treated (see below). Nasal carriage is found in 60 % of patients with recurrent furunculosis [40].

Carbuncles require the same antibiotics approach as furuncles associated with surgical excision [52].

1.3.3.5 Staphylococcal Carriage

Due to the risk of spreading in the close environment of the patient, staphylococcal carriage must be sought and treated in the patient and his family but is not definitive, with progressive recolonization within 6 months [53, 54]. Prevention of the bacterial spread in the family or close contact persons (sportsmen [55]), especially in case of CA-MRSA, is based on hygiene, no sharing of personal clothes, and regular hand washing. Carriage decontamination procedures, based on antiseptics as chlorhexidine baths or showers associated with prolonged and intermittent topical antibiotics as mupirocin or fusidic acid [41, 56–58], remain unproven and have been mainly studied for MRSA in health-care facilities [42, 59–61].

1.4 Abscesses

1.4.1 Definition and Clinical Presentation

An abscess is a collection of pus. It is not clear in the literature which size of collection can define an abscess, but some consider 2 cm diameter as the lower limit for defining an abscess [62]. The abscess forms a nodule or painful and inflammatory erythematous plaque. After a few days of development, palpation reveals a soft consistency indicating a purulent collection (Fig. 1.5).

Fever is rare, and lymphangitis and satellite nodes may be experienced. The majority of primary or spontaneous abscesses are caused by *S. aureus* producing Panton-Valentine leukocidin [63]. Secondary abscesses (accidental direct inoculation, addiction, septic injections, etc.) are most often due to *S. aureus* but not exclusively. The bacteriological analysis allows the identification of the bacteria. There is worldwide an emergence of *S. aureus* resistant in the community (CA-MRSA) responsible for suppurative infections including abscesses [64, 65].

1.4.2 Treatment

The first treatment is surgery, incision, and drainage [64, 65]. The benefit of antibiotic therapy is low. The Infectious Diseases Society of America (IDSA) recommends systemic antibiotics in the following cases: “critical” location

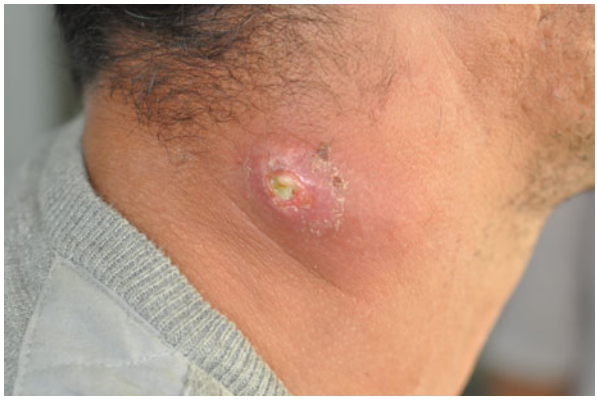

Fig. 1.5 Abscess of the neck

(face for example, etc.), immunosuppression, large volume of the abscess (>5 cm), failure of drainage, extreme age, and the presence of systemic symptoms. In all other cases, antibiotic therapy is not indicated.

1.5 Suppurative Paronychia

1.5.1 Definition

Acute suppurative paronychia is an acute superficial infection or abscesses of the perionychium. Nail biting, finger sucking, aggressive manicuring, and trauma of the nail are the most frequent causes for a portal of entry of the bacteria [66]. *S. aureus* is the most frequent causative agent, followed by *Streptococcus*, *Pseudomonas*, anaerobes, and other microorganisms such as *C. albicans* and herpes. Acrodermatitis continua of Hallopeau is a differential diagnosis [67]. Acute paronychia must be differentiated from chronic paronychia, which is usually nonsuppurative, due to multiple physical external causes and/or *Candida albicans*.

1.5.2 Clinical Presentation

The patient complains of pain and tenderness of the perionychium that appears swollen, purulent, or even fluctuant. The nail coloration and consistency may be altered.

1.5.3 Treatment

If there is no abscess, treatment is based on warm water soaks three times a day and oral antistaphylococcal antibiotics such as amoxicillin-clavulanic acid or clindamycin, also effective on anaerobes, if persistence and after bacteriological

culture. In case of abscess, surgical drainage becomes necessary in the absence of spontaneous evacuation of the pus [66].

1.6 Erythrasma

1.6.1 Definition

Erythrasma is a superficial infection of the skin usually localized in the large folds, especially axillae, due to coryneform bacteria (*Corynebacterium minutissimum*), belonging to the normal skin flora [68]. Warm and humid climate, age, and diabetes mellitus [69] are predisposing factors.

1.6.2 Clinical Presentation

Lesions are large, red or brown sharply marginated and in extensive patches (Fig. 1.6). They may be either asymptomatic or pruritic and complicated by lichenification. Coral-red fluorescence with Wood's light, due to coproporphyrin III, strongly suggests the diagnosis, although it does not necessarily indicate active infection. Systemic septic complications are extremely rare [70]. Main differential diagnoses include pityriasis versicolor, fungal intertriginous infections (dermatophytosis, candidiasis), eczema, and psoriasis. Thus, mycological and bacteriological scraping and/or skin biopsy may be required if there is any doubt, but usually clinical and Wood's light features are typical enough to make the diagnosis.

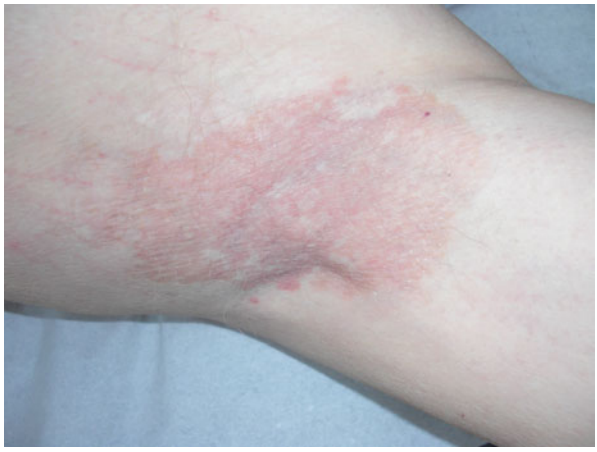

Fig. 1.6 Erythrasma of the axillary fold

1.6.3 Treatment

There is no clear agreement on the best treatment. Both topical (fusidic acid) and systemic antibiotics (erythromycin 14 days, possibly best avoided because of cardiac side effects such as QT interval prolongation [31], clarithromycin single dose) are effective without significant difference [68, 71–73]. Azole antifungal creams are also effective [74]. A photodynamic treatment using red light without any exogenous agent, based on the fact that corynebacteria produce endogenous porphyrins, has been demonstrated in some cases [75].

1.7 Erysipelas

1.7.1 Definition

Erysipelas is an acute superficial dermal infection that usually affects the leg and is commonly caused by streptococci [76]. In contrast with the life-threatening condition necrotizing fasciitis, erysipelas does not involve deep fascia and muscles. However, there is confusion in the literature between erysipelas and cellulitis which is, sensu stricto, an inflammation limited to the subcutaneous tissue but often refers to more severe cases than classical erysipelas [77]. Incidence has increased in the past decades and is now estimated to be 2–2.5/1,000 persons/year [77, 78]. Whereas necrotizing fasciitis often has a multibacterial origin, almost all erysipelas are due to *Streptococcus A* (the most frequent), *C*, and *G*. However, *Streptococcus B* may be involved in perineal cellulitis [79] or in newborns [80]. A small number of bacteria are present in the affected tissue, as shown by needle aspiration, but blood cultures remain negative in most cases [81, 82]. Legs are the main site involved, followed by the face and the upper limb, especially in women treated for breast cancer [83, 84]. In erysipelas of the leg, a portal of entry, i.e., disruption of the cutaneous barrier (leg ulcer, wound, fissurated toe-web intertrigo, chronic dermatomycoses of the foot [85], pressure ulcer), but also lymphedema, are risk factors [86]. In contrast, no association was observed with diabetes, alcohol, or smoking [86, 87]. Furthermore, a previous history of cellulitis is a main risk factor for a subsequent recurrence, which affects up to 29 % of patients. However, recurrent erysipelas shares the same risk factors as single episodes [78, 88–90]. The thigh and the gluteal region are less frequently involved and are favored by metabolic syndrome and previous surgical interventions [91].

1.7.2 Clinical Presentation

The onset of the disease is in general sudden with fever, chills, malaise, and altered general conditions. Locally, erysipelas is characterized by a large erythematous, swollen, well-demarcated, and usually raised lesion [92] (Figs. 1.7 and 1.8).

Locoregional adenopathy is frequent. Superficial blistering secondary to edema, sometimes with superficial hemorrhage, may be observed [93], especially in patients on anticoagulants or in old people with skin atrophy. Local and/or general signs are suggestive of necrotizing fasciitis and must not be ignored because of the risk of a rapid worsening: hemodynamic instability; intensive pain or, in contrast, local anesthesia; muscular pain or functional impairment; deep dermal blisters with no bleeding after incision; livedo or extensive ecchymosis; necrosis; crepitance; or gas effusion [92] (Fig. 1.9). However, in routine practice, intermediate presentations between classical erysipelas and necrotizing fasciitis are frequent, requiring a very close clinical monitoring and sometimes limited surgery [77, 94], (Fig. 1.10). Risk factors for abscesses formation are alcohol abuse and delayed antibiotics initiation [95].

1.7.3 Biological and Imaging Investigations

- No laboratory test is warranted in uncomplicated cases. However, in case of hospitalization and/or in patients with underlying diseases or local signs evocative of intermediate severity cellulitis, the following laboratory tests should be considered [92]: blood count (white blood cells), creatinine, C-reactive protein, and creatine phosphokinase (CK) if there is any doubt about muscle involvement. Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is based on total white cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein and showed very good positive and negative predictive values for the diagnosis of necrotizing fasciitis [96]. Streptococcal serological studies have no value in practical routine management of classical erysipelas, especially as antibody response may be limited by an early use of antibiotics.

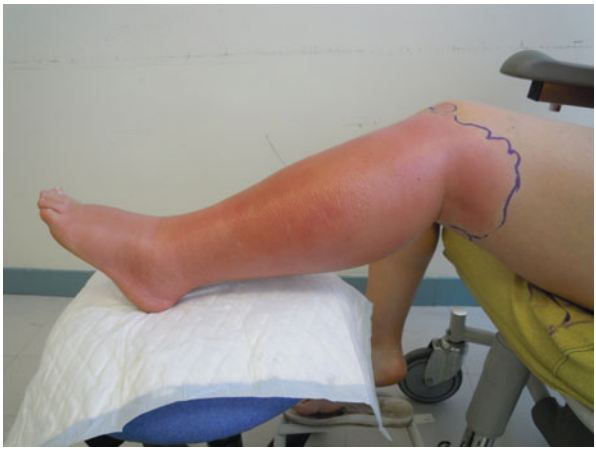

Fig. 1.7 Erysipelas of the leg

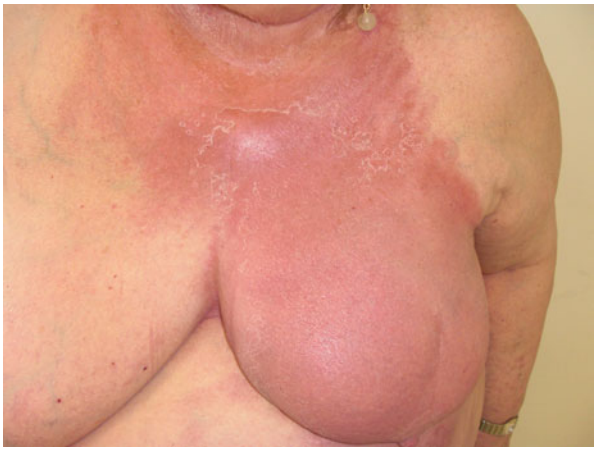

Fig. 1.8 Erysipelas of the breast

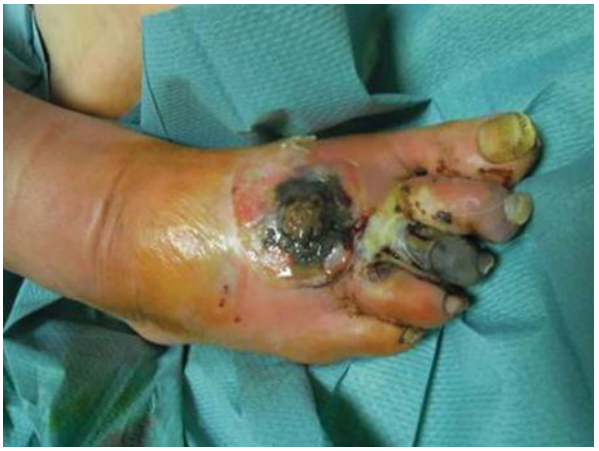

Fig. 1.9 Necrotizing fasciitis

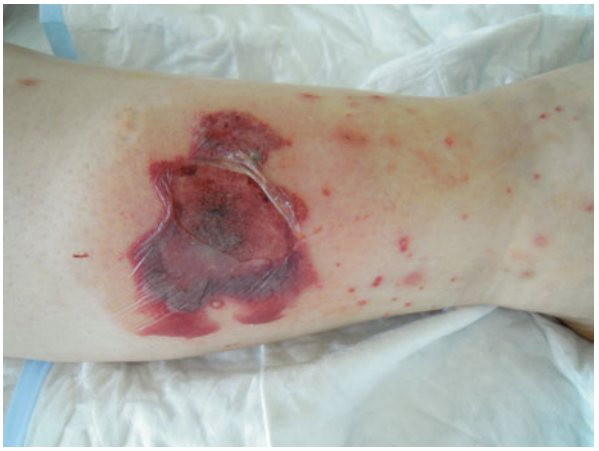

Fig. 1.10 Erysipelas of intermediate severity

- No imaging is necessary in typical cases of classical erysipelas. Similarly, in necrotizing fasciitis, no imaging is warranted before surgery in typical cases. However, in atypical or intermediate cases, imaging may be useful – plain films showing gas, ultrasounds in case of underlying abscesses, and CT scan or MRI if there is any doubt about myositis or fasciitis – but the clinician should always keep in mind that imaging should not lead to any delay in surgical decision and that sometimes only surgical exploration can confirm or not the presence of necrotic tissues [94, 97].
- Bacteriological cultures from superficial swab sampling and fluid-filled bullae, including subcutaneous needle aspiration, are usually negative in common erysipelas but could be performed in immunocompromised patients or in case of failure on empiric treatment in order to investigate another bacteria than *Streptococcus* [81, 92], as previously discussed. Bacteriological sampling of associated wounds or ulcers, representing the portal of entry of *Streptococcus*, leads is of uncertain pathogenic significance, showing frequently gram-negative bacteria or *Staphylococcus* sp. Culture of a skin biopsy is not superior to superficial swabs [92].

1.7.4 Treatment

Hospitalization is necessary if there are local or general signs of severity, as described above [98]. Some underlying conditions such as diabetes mellitus, old age, bad social conditions (homeless people) or immunosuppression, and no possibility of medical reevaluation after 48 h are other criteria that help to determine the need for hospitalization. The best treatment is difficult to define in the absence of large comparative trials [99]. In hospitalized patients, intramuscular or intravenous antibiotics are preferred in severe cases or after failure of ambulatory treatment, whereas oral route remains possible in less severe cases, but the better efficacy of the parenteral route has not been proven [99]. The first-intent treatment in classical erysipelas is antistreptococcal antibiotics. Oral pristinamycin showed its non-inferiority compared to standard intravenous then oral penicillin [76]. However, because of better gastrointestinal tolerance, amoxicillin is usually preferred. In hospitalized patients, even if intravenous penicillin G was previously recommended as first-intent treatment, the currently recommended choice is intravenous amoxicillin 50 mg/kg/day, followed by oral administration after improvement of local signs and disappearance of fever [98]. In case of abscess formation, penicillin M or amoxicillin-clavulanic acid is indicated. In cases of allergy to penicillin, pristinamycin (if available), clindamycin, first generation cephalosporin, or macrolides excluding erythromycin are good choices [76, 98, 100].

The classical recommended duration of the treatment is 10–20 days [98]. Short treatments with levofloxacin (5 days) and tedizolid phosphate (6 days) have been described [101, 102] but are not commonly used in routine practice.

Atypical erysipelas should be treated first with intravenous then oral antistreptococcal and staphylococcal antibiotics such as amoxicillin-clavulanic acid or penicillin M or clindamycin in case of allergy. A surgical treatment may become necessary, especially in case of secondary abscess formation.

There is no indication for anticoagulant therapy for erysipelas. Prophylaxis of deep venous thrombosis should be considered depending on the patient's other risk factors [103]. Venous compression is recommended during the acute phase and the following weeks to reduce the risk lymphedematous sequelae, which is a main risk factor of recurrence. The portal of entry must be treated as appropriate.

1.7.5 Prevention of Recurrent Erysipelas

Patients who experience two or more erysipelas should receive secondary prevention of recurrences. However, although prevention by penicillin has shown some efficacy [90, 104], strong data concerning the best therapeutic scheme are lacking, and recurrences may occur despite the prophylaxis [105, 106]. Intramuscular benzathine-penicillin G 2.4 MU at 14–21-day intervals is a good choice, but oral penicillin V (250 mg twice a day) [104] or amoxicillin (500–1,000 mg a day) is also possible. In cases of allergy, macrolides have been suggested [107], but erythromycin must be avoided (see above). The optimal duration of preventive treatment is unknown. Recently, a duration of 6 months has shown effectiveness against subsequent relapses compared to placebo [104]. However, some patients need prolonged prophylaxis.

Treatment and secondary prevention of portals of entry such as chronic toe-web maceration, fungal intertrigo, and other exacerbating factors, such as lymphedema or venous insufficiency, are of key importance [85, 98, 108, 109].

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Chapter 2
Antibiotics in the Management of Acne

Alison M. Layton

2.1 Antibiotics in Acne

Antibiotics available for the treatment of acne embrace topical and oral therapies. Topical antibiotics represent 46.6 % of the acne topical market and oral antibiotic prescriptions account for 63.2 % of the market for systemic acne treatment [1, 2].

Table 2.1 summarises the randomised controlled studies on topical antibiotics used for acne as monotherapy and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions.

Table 2.2 summarises the randomised controlled studies on topical fixed-dose combination agents used for the treatment of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions.

Table 2.3 summarises the randomised controlled studies on systemic antibiotics used for the treatments of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions.

2.1.1 Topical Antibiotics

Topical antibiotics have been shown to be effective in the treatment of acne, and those used over the last decade include clindamycin, erythromycin and tetracycline [3, 4]. They have been used in concentrations of 1–4 %, in a cream or lotion base. More recently topical 5 % dapsone has been introduced for the use of mild to moderate acne [5]. Topical antibiotics may theoretically impact on non-inflamed

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Table 2.1 Summary of the randomised controlled studies on topical antibiotics used for acne as monotherapy and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions

	Inflamed lesions			Non-inflamed lesion		
	Comparison with other agents			Comparison with other agents		
Agents	Superior to	Equivalent to	Inferior to	Superior to	Equivalent to	Inferior to
Topical clindamycin		Benzoyl peroxide Azelaic acid Oral tetracycline Minocycline	Zineryt®	Topical tetracycline	Oral tetracycline Minocycline	Benzoyl peroxide Zineryt®
Topical tetracycline		Benzoyl peroxide	Topical clindamycin		Benzoyl peroxide	

Table 2.2 Summary of the randomised controlled studies on topical fixed-dose combination agents used for the treatment of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions

	Inflamed lesions			Non-inflamed lesion		
	Comparison with other agents			Comparison with other agents		
Agents	Superior to	Equivalent to	Inferior to	Superior to	Equivalent to	Inferior to
Duac®, clindamycin and benzoyl peroxide	Benzoyl peroxide				Benzoyl peroxide	
Epiduo®, adapalene and benzoyl peroxide	Benzoyl peroxide Adapalene	Duac®		Benzoyl peroxide Adapalene	Duac®	
Zineryt®, Erythromycin and zinc acetate	Topical clindamycin Minocycline	Oral tetracycline		Topical clindamycin Minocycline	Oral tetracycline	

lesions by reducing perifollicular lymphocytes which are involved in comedogenesis [6]; some have a direct anti-inflammatory action as a result of an antioxidant effect on leukocytes [7], but their main mechanism of action is through their ability to significantly reduce numbers and activity of *P. acnes* [8]. At a clinical level, this translates into topical antibiotics being most effective to treat inflammatory acne [9].

2.1.1.1 Topical Antibiotics as Monotherapy

Adequately powered randomised, controlled trials have demonstrated a 55–60 % reduction in mean inflammatory lesion count at 12 weeks but have clarified much less impact on non-inflammatory lesions [10]. The variation in vehicles used in individual products challenges comparisons between individual treatments and studies, but those available to date suggest that there is no overall consistent

Table 2.3 Summary of randomised controlled studies on systemic antibiotics used for the treatments of acne and demonstrates the impact relative to other agents on inflamed and non-inflamed lesions

	Inflamed lesions			Non-inflamed lesion		
	Comparison with other agents			Comparison with other agents		
Agents	Superior to	Equivalent to	Inferior to	Superior to	Equivalent to	Inferior to
Oral tetracycline		Benzoyl peroxide Topical clindamycin Zineryt® Azelaic acid Minocycline[a] Diane®			Benzoyl peroxide Topical clindamycin Zineryt® Azelaic acid Minocycline[a] Diane®	
Minocycline		Benzoyl peroxide Topical clindamycin[a] Oral tetracycline Doxycycline Lymecycline Diane®	Zineryt®		Topical clindamycin Oral tetracycline Doxycycline Lymecycline Diane®	Zineryt®
Doxycycline		Minocycline			Minocycline	
Lymecycline		Minocycline			Minocycline	
Erythromycin		Tetracycline	Erythromycin Stearate		Tetracycline	

[a]Acted quicker but no significant difference at end of trial

difference in clinical outcome from topical clindamycin compared to topical erythromycin in mild to severe acne [11–14]. In contrast to an overall improvement in severity demonstrated with topical clindamycin when compared to topical tetracycline [15, 16]. A detailed analysis of 144 clinical trials of topical antimicrobial therapy rejected over 50 % because of poor trial design [17]. Adequate conclusions could not be drawn from the remaining data because of huge variation in methodology and study design but benzoyl peroxide (BPO) emerged as a successful treatment and was similar in effectiveness to topical erythromycin and clindamycin and confirmed topical tetracycline as the least effective.

A further systematic review examined results from clinical trials using topical erythromycin and clindamycin for inflammatory acne with the implicit aim of establishing whether or not there has been a decrease in efficacy since their introduction of these agents in the mid-1970s. In 50 eligible trials identified, a gradual reduction in the efficacy of topical erythromycin was identified, whilst the efficacy of clindamycin over the same time frame remained stable. The authors postulated that the reduced efficacy of erythromycin probably related to the development of antibiotic-resistant propionibacteria [18].

2.1.2 Combination Therapy

The emergence of antibiotic-resistant *P. acnes* has led to many experts recommending against the use of antibiotics as monotherapy. Guidelines suggest that the use of topical antibiotics alongside BPO should be considered to avoid resistant strains of *P. acnes* emerging at a local level and to reduce the numbers of existing resistant strains already present. The addition of topical agents can also expedite efficacy such that the exposure to the antibiotic is limited.

2.1.2.1 Combining Topical Antibiotics with BPO

BPO is fully active against sensitive and resistant strains of *P. acnes*, and combining topical BPO with topical erythromycin or oral antibiotics results in less resistance both in vitro and in vivo [19]. A number of trials have demonstrated the benefit of combining topical antibiotics with benzoyl peroxide over using individual constituents as monotherapy [20–23].

Two large randomised, double-blind placebo-controlled trials from 2008 demonstrated that clindamycin 1.2 % and BPO 2.5 % gel significantly reduced lesion counts and demonstrated similar tolerability compared with the individual constituents used as monotherapy [24].

A more recent meta-analysis of randomised controlled trials using 5 % BPO and clindamycin versus 2.5 % BPO and clindamycin topical treatments in acne showed that the combination products out-performed the individual constituents in the treatment of inflammatory lesions and the reduction in non-inflammatory lesions [25]. This was most significant with the 2.5 % BPO and clindamycin compared with all other treatments. A further study demonstrated similar efficacy between 2.5 and 5 % BPO in combination with clindamycin but confirmed the 2.5 % BPO/clindamycin combination was better tolerated [26].

In one noncommercial community-based study, BPO monotherapy produced similar clinical efficacy when compared to a combination of BPO and erythromycin although the former caused greater skin irritancy [27].

2.1.2.2 Combining Topical Antibiotics with Zinc

Some topical antibiotics are available in combination with zinc. Whilst zinc itself is not effective in the management of acne [28], two placebo-controlled trials showed that erythromycin 4 % plus zinc 1.2 % was significantly better than placebo at reducing inflamed and non-inflamed lesions [29, 30] and superior to 1 % clindamycin lotion [31].

There is however evidence to suggest that antibiotic-resistant *P. acnes* will emerge when using this combination product over time [32]. One study comparing 1.2 % zinc/4 % erythromycin with oral tetracycline 250 mg twice daily demonstrated no difference in terms of lesion reduction regardless of type [29]. However, a study

comparing this combination product with oral minocycline 50 mg daily demonstrated superiority for the former with respect to reduction of inflamed and non-inflamed lesions [33].

A small single-blind study of patients with mild to moderate acne treated once daily with 1 % clindamycin plus BPO 5 % or erythromycin 4 % plus 1.2 % zinc acetate showed the former had a quicker onset of action and demonstrated significantly greater reduction in lesion count and inflammatory lesions [32].

2.1.2.3 Combining Topical Antibiotics with Retinoids

Topical retinoid and antibiotic combinations are also available and indicated for the treatment of mild to moderate acne.

There are a number of studies that have indicated that combining an antibiotic with a retinoid results in better efficacy and significantly faster clearance when compared to the individual constituent alone [34–37].

The addition of an antibiotic to a topical retinoid may also result in less irritancy [35, 36, 38, 39] although the combination of clindamycin and adapalene in one topical formulation appeared to produce a more irritant effect that when the separate products were used alone [34]. Clindamycin combined with the adapalene results in better efficacy and is associated with less irritation than a combination of clindamycin and tretinoin [40, 41].

The fixed combination products have the advantage of being easier to use but the disadvantage of being more expensive than the individual products they contain.

2.1.2.4 Other Topical Antibiotics Available

Topical 5 % dapsone alone or in combination with 4 % BPO or adapalene 0.1 % has been shown to be effective for mild to moderate acne but was less well tolerated when used in combination with adapalene [42].

2.1.2.5 Topical Versus Oral Antibiotics

Systematic reviews have identified comparative data on the use of oral versus topical antibiotics in acne management [10, 43], and some randomised controlled trials have studied the difference between these different routes of administration [44–46] As outlined previously, one large, randomised, controlled trial in a community care setting showed that topical Benzamycin® and its components given separately (erythromycin and 5 % benzoyl peroxide) were more effective than oral tetracycline and minocycline [27]. However, as oral antibiotics have a delayed onset of activity, shorter studies may introduce bias in favour of the topical agent [47].

Many of these studies were underpowered as well as too short, making it challenging to draw definitive conclusions.

2.1.3 Adverse Effects

2.1.3.1 Topical Agents

The most common side effect of topical antibiotic products for acne relates to primary irritant effects which often subsides with time and can be managed by reducing frequency of application, using emollients and if severe short-term application of a type I potency topical corticosteroid [48, 49]. Some topical therapies have a comparatively lower irritant profile than others. Certain antibiotic/benzoyl peroxide combinations are less irritating than benzoyl peroxide alone [50], possibly explained by the anti-inflammatory action of the antibiotic. Allergic contact dermatitis has been reported with BPO but is rare with other topical agents. From animal studies and much clinical experience, there is no evidence to support the claims that benzoyl peroxide and vitamin A acid induce skin carcinomas, and continued use of these two drugs can be supported [51, 52]. Benzoyl peroxide bleaches clothes and hair, and the patient must be informed of these inconvenient side effects.

One of the main concerns relates to the emergence of antibiotic-resistant strains of bacteria emerging with the use of topical antibiotics; this will be discussed in more detail later.

2.1.3.2 Oral Antibiotics

Oral antibiotics are the most widely prescribed agents in acne and are indicated for severe acne, moderate facial acne not responding to topical therapies and/or extensive truncal acne.

2.1.4 Mechanisms of Action

There are two main mechanisms of action for oral antibiotics; as well as their antibacterial activity, they have anti-inflammatory effects [53–58]. Tetracycline and erythromycin are bacteriostatic, especially in larger doses. In smaller doses oral antibiotics do not reduce the number of organisms, but they do affect their function. The magnitude of reduction of *P. acnes* achieved by oral antibiotics does not correlate well with clinical efficacy [59].

Support for the important role of antibacterial therapy in the management of acne includes the fact that *P. acnes* is integral to the mediation of inflammation in acne, successful treatment with antibiotics is associated with significant reductions in *P. acnes*, and colonisation of the skin with antibiotic-resistant strains of *P. acnes* may be associated with reduced clinical efficacy. Antibiotics can also inhibit various enzyme activities and modulate chemotaxis, lymphocyte function and proinflammatory cytokines, in particular TNF-α, IL-1 and IL-6 expression [56–58].

2.1.5 *Selecting Oral Antibiotics for Acne, Dose and Duration*

A number of publications have proposed how antibiotics should be administered to achieve optimal therapeutic response whilst avoiding antibiotic resistance [60]. Table 2.4 outlines oral antibiotics available and potential adverse effects. Suggestions include restricting the duration of antibiotics, use of combination regimens from the onset of therapy to expedite response and reduce duration of antibiotic exposure, utilisation of benzoyl peroxide either to reduce the emergence of or to treat existing antibiotic-resistant strains of *P. acnes* and avoidance of using chemically dissimilar antibiotics and regular switching of antibiotics.

Table 2.5 summarises these recommendations. The question of how long antibiotics should be given in acne has not been adequately researched in randomised, controlled trials, and recommendations made in publications are not backed by hard evidence. It has been stated that 3 weeks is required before any obvious improvement is noted [61, 62] and that a minimum of 3 months extending to 6 months in conjunction with topical therapy, which should include an anti-resistant agent, is required to achieve maximum benefit [60, 63]. However, one controlled study comparing five antimicrobial regimes for mild to moderate facial acne in the community suggested that maximum improvement was reached at 6 weeks with both oral antibiotics and topical BPO [27].

There is a paucity of randomised, controlled trials examining different dosages of antibiotics in acne. One nonrandomised, controlled study confirmed that patients on oral erythromycin in combination with topical 5 % BPO responded better on 1 g compared to 500 mg daily. The relapse rates within 1 year were also significantly lower in the high-dose group [63].

Table 2.4 Systemic antibiotics in the treatment of acne vulgaris: dosage and adverse effects

Antibiotic tetracyclines	Dosage	Adverse effects
Oxytetracycline	500 mg twice daily half hour pre food and not with milk; makes adherence to medication problematic for some	Common: GI upset
		Rare: onycholysis, photosensitivity, benign intracranial hypertension
Lymecycline (not available in the USA)	300–600 mg daily	As oxytetracycline but tolerated better
Doxycycline	100–200 mg daily	As oxytetracycline
		Photosensitivity (dose dependent)
Minocycline	100–200 mg daily	Rare but serious: headaches and dizziness associated with benign intracranial hypertension, pigmentary changes, autoimmune hepatitis/LE-like syndrome
Erythromycin	500 mg twice daily	Common: GI upset, nausea, diarrhoea
Trimethoprim	200–300 mg twice daily	Maculopapular rash
		Rare: hepatic/renal toxicity/agranulocytosis

Table 2.5 Strategies to avoid antibiotic-resistant propionibacteria emerging

Strategy to avoid propionibacterial resistance emerging	Comments
Avoid inappropriate use of topical and systemic antibiotics	Use oral antibiotics for 6–8 weeks in the first instance and only continue if clinical improvement continues
If extending the duration of oral antibiotics utilises combination therapy	Combine with an agent that reduces the likelihood of promoting antibiotic propionibacterial resistance, e.g. benzoyl peroxide
If repeated courses of antibiotics are required and the initial clinical response was favourable, reuse the same drug	This will avoid multiple resistant strains emerging
Avoid prescribing different oral and topical antibiotics concomitantly	This will avoid multiple resistant strains emerging
Consider using topical retinoids and non-antibiotic antimicrobials wherever possible	These do not promote resistant isolates and when used with antibiotics may achieve more rapid efficacy so reduce the duration of the antibiotic course and the exposure time to the antibiotic
Topical benzoyl peroxide (BPO) can be used for 7 days between antibiotic courses	BPO is fully active against sensitive and resistant strains of *P. acnes* and able to eradicate resistant isolates
Remember to check medical adherence	Poor adherence to antibiotic therapies promotes resistance

Further reports suggest that higher doses of tetracycline [64, 65] and oxytetracycline [66] are more effective in recalcitrant and severe acne. In patients with nonresponding disease, minocycline limited dose-response studies have shown that doubling the dose of minocycline to 200 mg/day is more effective than continuing on an average dose of 100 mg where acne has not responded [67]. Daily doses of doxycycline (100 mg), minocycline (100 mg) and lymecycline (408 mg) are said to be equally effective, provided *P. acnes* is not resistant to doxycycline and lymecycline [68–72]. Subtherapeutic doses of doxycycline have been reported as effective in the treatment of moderate acne via non-antimicrobial mechanisms of action [73].

A correlation between sebum excretion rate and degree of improvement was noted in a retrospective study examining 255 patients treated with oral oxytetracycline, erythromycin and minocycline. Interestingly, this correlation was not noted with trimethoprim. The higher the sebum extraction rate, the less well the patients responded to their systemic therapy. The authors hypothesised that this may relate to a dilutional effect of the antibiotic within the intrafollicular duct and as a result of this suggested that when the sebum excretion rate was greater than 2.5 μg/cm^2, a higher daily dosage of antibiotics might be required (lymecycline 600 mg, doxycycline and minocycline 200 mg) [74]. When prescribing higher doses of antibiotics, patients and physicians should be wary about increased adverse effects [60].

2.1.6 *Adverse Effects*

Cyclines (tetracycline, oxytetracycline, doxycycline, lymecycline, minocycline) have excellent efficacy and are the antibiotics of choice [48, 75–78]. The second-generation cyclines may aid adherence, and of these, lymecycline and doxycycline should be used in preference to minocycline [60].

Macrolide (erythromycin, azithromycin or clindamycin) prescribing for acne has increasingly fallen out of favour due to the emergence of antibiotic-resistant strains of *P. acnes* in line with extensive erythromycin usage in the past [60, 79].

Erythromycin remains the preferred option in female patients who are, or might become, pregnant or are breastfeeding [80] and in children varying from 8 to 12 years (depending on national licences). Tetracyclines are contraindicated in this latter context due to potential musculoskeletal problems and discoloration of dentition.

Clindamycin is highly lipophilic and very effective in acne, but adverse effects including diarrhoea seen in 5–20 % of cases and potential pseudomembranous colitis from overgrowth of *Clostridium difficile* have rightly discouraged prescribers from using it [81, 82].

Oral azithromycin has been reported to be effective for acne in four open and two investigator-blinded trials. Regimens have varied, but intermittent dosing schedules have been advocated (250 mg three times a week) due to the long half-life of 68 h [83, 84]. As azithromycin is commonly used to treat a variety of systemic infections, its use should also be restricted and discouraged in acne. This recommendation also applies to cephalosporins and fluoroquinolones although there are documented cases of acne that have improved with these agents [85]. Exceptions to this rule may include short-term use for extremely refractory disease and/or evidence of Gram-negative folliculitis where other agents are not acceptable.

Trimethoprim (400–600 mg/day) has similar efficacy to tetracycline [85] but does not have a licence for acne and is reserved as a third-line antibiotic for acne or for cases where there is proven resistance to other agents. It has been used successfully in cases that have become refractory to first- or second-line antibiotics over time [86–88]. Trimethoprim may also be used in young patients in whom tetracyclines are contraindicated. However, as trimethoprim is used for treatment of some potentially serious cutaneous and systemic infections, such as those caused by CA-MRSA, it is advisable to limit use to selected cases [88].

Response to systemic antibiotics is variable. Young males with marked seborrhoea and truncal acne respond less well than females with purely facial acne [78]. Patients who require antibiotics should be given 1 g/day of tetracycline or where indicated erythromycin in divided doses [63]. There is no evidence to support the need for this to be four times a day. The major disadvantage of tetracycline is the prerequisite for it to be taken half an hour before food and not with milk to avoid reduced absorption [89]. Second-generation tetracyclines, doxycycline, lymecycline or minocycline, are less likely to be affected by food [89–91] and can be taken once daily, which may enhance patient adherence. The perception that they are more active as a result of their lipophilicity resulting in greater concentration within the pilosebaceous duct is not supported by good evidence.

Table 2.4 outlines dosage regimens for systemic antibiotics recommended for the treatment of acne and considers potential adverse effects.

Many systematic reviews and publications have failed to find any evidence to suggest that there are any clinical benefits between any of the tetracycline antibiotics. In the Western world, minocycline is used very extensively. This may in part have resulted from claims that antibiotic-resistant *P. acnes* is less likely to emerge with minocycline use. However, with the increased use of minocycline, there has been an increased trend of minocycline-resistant *P. acnes* emerging [92–95].

A Cochrane review published in 2003 found no evidence to suggest that minocycline should be prescribed in preference to other tetracyclines [43]. Other reviews have confirmed that minocycline should not be used as first-line therapy [96]. There are many studies examining the efficacy of individual antibiotics against placebo; however, the methodology and quality of these studies are poor, and very few compare one active agent with another. A large randomised, controlled trial conducted in UK community practice demonstrated that oral minocycline and oral tetracycline were of similar efficacy to each other and comparable in terms of efficacy to topical BPO. Hence, given the cost and the increased side effect profile of oral minocycline, minocycline should not be the first choice of oral antibiotic therapy in acne [97].

2.1.7 Combining Oral Antibiotics with Topical Preparations

Oral antibiotics should not be used as monotherapy in acne and should always be combined with topical agents. Combining BPO with antibiotics results in superior efficacy, this may be in part due to the relative lack of activity when used as monotherapy against non-inflammatory lesions. There is also evidence that such combinations prevent, reduce or eliminate bacterial resistance and can achieve significant clinical improvement in patients already colonised with antibiotic-resistant strains of *P. acnes*. Intermittent usage of BPO during extended courses of antibiotics is recommended to eliminate resistant strains [60, 98].

Topical retinoids may also be safely combined with antibiotics and are likely to enhance efficacy by acting on the microcomedo and non-inflammatory lesions [98, 99]. The use of oral and topical antibiotics together does not offer any benefit and may select for multiple different resistant strains if chemically dissimilar preparations are used.

2.2 The Emergence of Antibiotic-Resistant Bacteria as a Consequence of Antibiotic Usage in Acne

2.2.1 The Incidence of Resistance

The issue of antibiotic-resistant *P. acnes* is a global phenomenon with a prevalence increasing from around 20% in 1978 to 62% in 1996. Cross-resistance between erythromycin and clindamycin is frequently observed [100–106]. There is evidence

in the literature to demonstrate a correlation between antibiotic-resistant *P. acnes* and clinical failure when prescribed antibiotics [27, 107, 108]. However, the association between colonisation and antibiotic-resistant strains is complex, and it is important to recognise that even if some specific antibiotic-resistant strain of *P. acnes* is identified microbiologically, it does not necessarily mean that the acne will be clinically resistant to this antibiotic. If the concentration of the antibiotic at the relevant skin site is equal to or greater than the minimal inhibitory concentration (MIC) of the relevant *P. acnes* strain, the patient will be clinically responsive. In addition, many antibiotics with anti-acne properties achieve efficacy via anti-inflammatory mechanisms of action [58] which can offset any problems resulting from antibiotic resistance.

A number of factors have been linked to increased antibiotic resistance in *P. acnes*; notably patient and physician behaviours can influence the development of resistance [109, 110]. Greater numbers of resistant *P. acnes* have been demonstrated on the skin of close contacts of acne patients using antibiotics compared with controls [111]. In addition clinicians working within the field of acne harbour significantly more resistant propionibacteria than clinicians working in an environment unrelated to acne. Given the fact that the resistance is due to a mutant gene [112] it is likely that *P. acnes* resistance is going to last for many years.

Luk et al. recently investigated the prevalence and pattern of antibiotic-resistant *P. acnes* and looked for any associated factors linked to harbouring resistant strains. Fifty-five percent of strains were found to be resistant to one or more antibiotics, and resistance rates were highest to clindamycin and erythromycin. Characteristics associated with antibiotic-resistant *P. acnes* included older age, duration of disease and duration of antibiotic treatment [101].

A health technology assessment conducted between 1998 and 2000 in general practice in the UK identified 18 % of acne patients with tetracycline-resistant strains of *P. acnes*, 47 % with erythromycin-resistant and 41 % with clindamycin-resistant strains [27]. Up to 61 % of patients referred to specialist acne clinics in Leeds, UK, had antibiotic-resistant *P. acnes* [2].

Although resistance is most frequently seen to erythromycin and clindamycin, resistance to more than one antibiotic is seen in 18 % of patients.

Table 2.5 outlines possible reasons to suspect resistance to antibiotic therapies. Antibiotic prescribing policies have been advocated in an attempt to control/reduce the levels of resistance (Table 2.5) [113].

A number of studies have confirmed negative consequences that have resulted from antibiotic usage in acne.

2.2.2 *Impact on Nontargeted Bacteria with Potential Consequences*

When antibiotics are administered for any reason, resistance can occur in both targeted and nontargeted bacteria. The resident flora may have the capacity to retain resistant variants long after the antibiotic has been withdrawn. In addition resistance gene pools are often shared by non-pathogens and pathogens.

Mills and co-workers assessed resistant bacteria in acne patients ($n = 209$) treated with topical erythromycin for a 12-week period in a randomised, double-blind, parallel study. The prevalence of erythromycin-resistant coagulase-negative Staphylococci on the face rose from 87 to 98 %; in addition the density of antibiotic-resistant organisms increased significantly, and the majority of isolates had high-level resistance [114].

Acne patients are frequently treated with multiple courses of antibiotics, and their flora is exposed to significant selective pressure for resistance development. Margolis et al identified that patients treated with antibiotics for acne had a 2.15 times greater risk of developing an upper respiratory tract infection compared with those not treated with antibiotics [115]. Levy et al. demonstrated colonisation of the oropharynx with resistant *S. pyogenes*, in association with antibiotic therapy in patients with acne [116].

2.2.3 *The Developments of Antibiotic-Resistant Strains of* P. acnes *Beyond the Patient in the Community*

Antibiotic use for acne may have consequences for the community. Antibiotic-resistant *P. acnes* are spread primarily by person-to-person contact, and the prevalence of resistant *P. acnes* in household contacts of patients with acne ranged from 41 % in Hungary to 86 % in Spain in one European study [94]. The ability for resistant organisms to move from acne patients to the community has particular importance as *P. acnes* can survive for long periods on inanimate surfaces at room temperature. A significant proportion of acne patients may be colonised by antibiotic-resistant strains before they receive any treatment.

There have also been an increasing number of reports of severe infections due to *P. acnes* including arthritis, endocarditis, endophthalmitis and adenitis. These infections are frequently associated with surgical procedures, predisposing conditions for *P. acnes* infection including malignancy, immunosuppression, trauma, diabetes and steroid therapy. *P. acnes* infections have been associated with a mortality rate of up to 5 % in the context of these clinical situations [117–122].

2.2.4 *Impact of Antibiotic-Resistant* P. acnes *on the Patient*

Resistance may manifest itself in the patient as reduced response or no response to antibiotic therapy and in some cases worsening of disease whilst on therapy.

A systematic review of the literature published in 1998 found a clear correlation between poor therapeutic response and presence of antibiotic-resistant *P. acnes*. It is estimated that harbouring antibiotic-resistant *P. acnes* can result in up to a 20 % nonresponse to therapy, and several studies have confirmed reduced efficacy in this

context [59, 112, 114, 123]. Cunliffe et al. showed a significantly significant association between clinical improvement, reduction in *P. acnes* counts and inhibition of antibiotic drug resistance [124].

2.2.5 *Impact of Antibiotic Therapeutic Efficacy Over Time*

One rigorous meta-analysis of efficacy data indicates that there has been a gradual decrease in the overall efficacy of topical erythromycin between 1977 and 2002 thought to have arisen due to the presence of antibiotic-resistant *P. acnes* [18].

2.3 Strategies for Preventing the Emergence of Antibiotic-Resistant *P. acnes* Over Time

Guidance on acne managements suggests that the duration of exposure to antibiotics should be minimised, and this can be achieved by combining treatment regimens to enhance efficacy and rate of response to treatment. This might be achieved by using a topical retinoid alongside an antimicrobial preparation. Other strategies can be adopted as in Table 2.5 [125].

2.3.1 *BPO as an Anti-resistant Agent*

BPO has the ability to rapidly kill bacteria, including both antibiotic-sensitive and antibiotic-resistant strains of *P. acnes.* There are no reports of antimicrobial resistance to BPO which makes it an ideal therapy for acne as not only does it provide clinical efficacy through a potent bactericidal, anti-inflammatory and some keratolytic/comedolytic action [126], but it also permits an approach that spares the use of antibiotics.

A recent study demonstrated that a BPO cleanser used daily can effectively reduce populations of antibiotic-resistant *P. acnes.* At baseline there were multiple resistances present to including erythromycin, tetracycline, doxycycline, minocycline and clindamycin. Total *P. acnes* counts and counts of each resistant strain decreased by >2logs at 3 weeks [127].

A fixed combination product containing 1.2 % clindamycin and 0.025 % tretinoin demonstrated much better effect on the reduction of total *P. acnes* as well as those demonstrating clindamycin resistance when compared to the impact of 1 % clindamycin alone [128]. This may well have resulted from the tretinoin facilitating higher concentration of antibiotic within the sebaceous follicles and/or resulting in

a change in the microenvironment of the microcomedo leading to less overall *P. acnes.*

A further strategy adopted to minimise the development of antibiotic-resistant *P. acnes* has been to exploit the anti-inflammatory actions whilst avoiding the antimicrobial effects by employing low, sub-antimicrobial doses of antibiotics. Doxycycline has been selected for this purpose as it is the tetracycline found to have the most potent action against matrix metalloproteinases (MMPs). A sub-antimicrobial dose of doxycycline (SDD) 20 mg twice daily downregulates MMPs and proinflammatory cytokines without decreasing microbial counts; this was first demonstrated in periodontal disease [129]. A small ($n=40$) double-blind placebo-controlled study of SDD (20 mg twice daily) in acne was associated with greater reductions in the numbers of comedones ($p<0.01$), inflammatory lesions ($p<0.05$) and total lesions at 6 months [73].

The duration of antibiotics should be limited in an attempt to avoid the emergence of antibiotic-resistant bacteria. In a multicentre, randomised, parallel-group investigator-blinded study of 152 acne patients, researchers demonstrated that the efficacy of antibiotic therapy for acne reached a plateau around 12–16 weeks depending on the antibiotic used. This supports an approach that then switches patients onto alternative maintenance therapy without the use of an antibiotic [130].

2.4 Conclusions

Antibiotics still have an important place in acne management; however, judicious use is advocated to ensure that the patient, close contacts and the wider environment are not compromised. Antibiotic-resistant *P. acnes* will emerge as a result of antibiotic use for acne, and this may result in poor therapeutic response and treatment failures. Strategies should be adopted to minimise risk of antibiotic resistance such that the therapeutic value of antibiotics can be preserved for acne and beyond. Topical antibiotics should be avoided as monotherapy and BPO should be employed as an effective anti-resistant agent in treatment regimens. Fixed-dose combinations should be considered in any acne regimen to achieve more rapid efficacy so avoiding unnecessary exposure to antibiotics.

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Chapter 3
Antimicrobial Treatment of Rosacea

Christos C. Zouboulis, Martin Schaller, and Harald P.M. Gollnick

3.1 Introduction

Rosacea is a common, chronic inflammatory, facial human disorder. It affects primarily the interfollicular skin at the convexities of the central face (the cheeks, nose, chin, and central forehead) and progresses through stages over time [1]. Involvement of the chest and back is rare. Its onset usually occurs between the ages of 30 and 50 years, affecting both genders equally. Although rosacea occurs in all racial and ethnic groups, individuals with skin types 1 and 2 of Celtic and Nordic origin are thought to be particularly prone to the disorder. The highest prevalence has been registered in populations of northern countries, namely, 22 % in Estonia and 10 % in Sweden, whereas the prevalence in Germany is 2.2 % [2–4]. The disease is rather uncommon in individuals with dark skin.

The characteristic clinical signs of rosacea are centrofacial erythema, facial telangiectasias, papules, pustules, nodules, and excessive tissue growth, especially of the nose (Fig. 3.1). They are accompanied by stinging and burning sensations and scaling of the affected skin as well as ocular involvement with chronic recurrent conjunctivitis and eyelid inflammatory changes [5]. Ocular involvement is the most common extracutaneous manifestation and affects 6–50 % of patients with rosacea [6].

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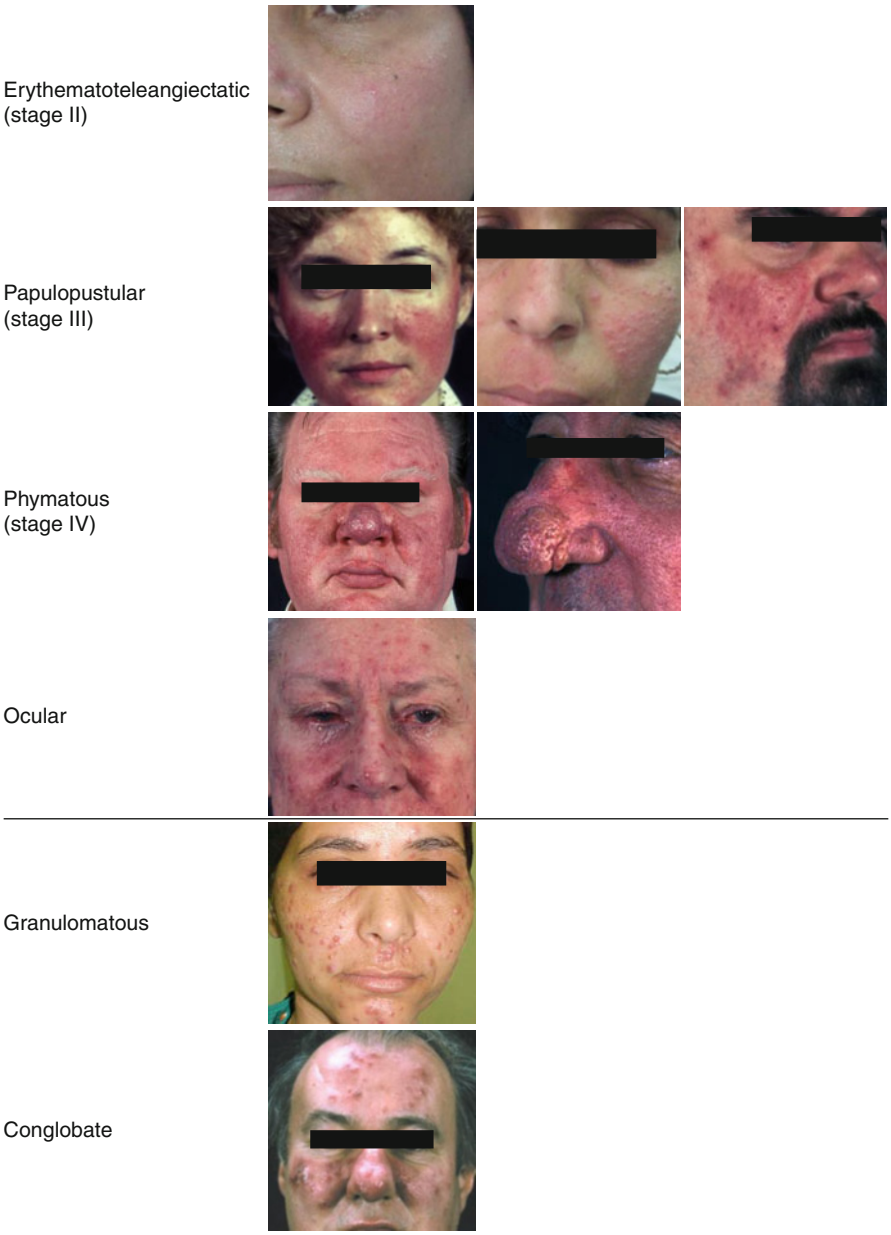

Fig. 3.1 Subtypes and variants of rosacea (Modified from Fimmel et al. [9])

3.2 Classification

The US National Rosacea Society Expert Committee developed a classification system for rosacea in the year 2002 to support the standardization of its diagnosis [7] (Table 3.1).

Table 3.1 Classification of rosacea according to the US National Rosacea Society Expert Committee [7]

Subtype	Descriptive term for rosacea	Clinical signs
1	Erythematotelangiectatic	Flushing and central facial erythema. Additional possible features: edema, stinging and burning sensations, roughness or scaling
2	Papulopustular	Persistent erythema and transient papules or pustules (inflammatory subtype)
3	Phymatous	Thickening skin, irregular surface nodularities, and enlargement of affected areas (the chin, forehead, cheeks, ears, and nose
4	Ocular	Conjunctivitis, keratitis, blepharitis

Erythema in rosacea can be subdivided into (a) erythema alone, (b) erythema with telangiectasias, (c) erythema with edema, and (d) erythema with inflammatory papules and nodules. It is important to differentiate the perilesional erythema of inflammatory lesions from the diffuse facial erythema [8]. Rhinophyma, a rosacea variant with excessive tissue growth of the nose, is almost exclusively seen among males.

Although rosacea is not a life-threatening disease, its progression with papules, pustules, and rhinophyma has a negative impact on the quality of life of a patient. A survey by the US National Rosacea Society in 2006 reported that the disease, in up to 70 % of patients, has adversely affected their self-esteem and their social life [9]. However, rosacea has a small to moderate negative effect on health-related quality of life (HRQoL), which appears to be associated with disease severity and age [10]. The disease affects both genders equally, but men with rosacea are more prone to the development of thickening and distorting skin changes, due to excessive tissue growth and/or granulomatous tissue reaction.

In addition to the rhinophyma and granulomatous variants, two other variants of rosacea are seen. The first is a rosacea-like condition triggered by the use of corticosteroids; the second is characterized by severe facial lymphedema (lymphedematous rosacea or morbus Morbihan). Moreover, rosacea fulminans occurs when large and rapidly developing pustular lesions develop occasionally with general symptoms (fever, arthropathy).

3.3 Etiology

Although the precise etiology of rosacea remains unknown, various factors have been suspected of contributing to this condition with the most-cited pathogenic theory centered on inherent abnormalities in cutaneous blood and/or lymphatic vessel homeostasis supported by cranial magnetic resonance tomography studies [1, 5, 9, 11, 12]. A current cohort-based survey of twins led to the separation of genetic susceptibility and the influence of environmental factors affecting rosacea [13]. Approximately half of the contribution to the development of rosacea could be accounted for by genetics and the other half by the environment. Among the environmental factors, the mite *Demodex folliculorum* and ultraviolet (UV) radiation exposure have been considered of major importance [1, 5, 11]. Correlations between rosacea and alcohol, smoking, skin cancer history, cardiac comorbidity, and age could also be assessed.

These findings corroborate Kligman's postulate that rosacea should be viewed as an UV-induced dermatosis [12, 14] and support the general consensus among clinicians, who consider rosacea to be at least a photoaggravated disorder. Pathophysiological processes induced by UV radiation, which are processes similar to those seen in photoaging, contribute to the signs and symptoms of rosacea [15]. The pivotal role of sunlight is supported by the distribution of erythema and telangiectasias on the facial convexities. However, patients without any UV exposure show classical fluctuations of the disease state. UVB irradiation of human skin results in pronounced dermal angiogenesis accompanied by upregulation of the potent angiogenic factor, vascular endothelial growth factor (VEGF), and the downregulation of thrombospondin-1 (TS-1), an endogenous angiogenesis inhibitor [16]. Newly formed and/or widened blood and/or lymphatic vessels facilitate the infiltration of inflammatory cells into the dermal tissue resulting in damage to dermal matrix components.

Flushing or transient erythema is controlled by two vasodilatory mechanisms: humoral substances and neural stimuli [9, 17]. In this context, cytokines, hormones, and neuropeptides probably communicate within the network composed of the endocrine, nervous, and immune systems. The apparent inflammatory reaction in rosacea is likely the result of altered communication and/or reciprocal modulation between them. The major neuropeptides probably involved in rosacea include substance P (SP), vasoactive intestinal polypeptide, and corticotropin-releasing hormone (CRH) [9] (Fig. 3.2). Apart from their pro-inflammatory properties, neuropeptides and neurohormones are also potent downregulators of immunity.

At the cellular level, epidermal Langerhans cells are considered as the main target of UV radiation, since UV light inhibits their antigen-presenting activity and their capacity to stimulate allogeneic type 1 T cells [18]. CD11β+ macrophages and neutrophils infiltrate the epidermis after intense UV radiation. Even at sub-erythema doses, UVB reduces Langerhans cell density, migration, and maturation in the epidermis and regional lymphoid tissue [19]. UVB induces an angiogenic switch in human vessel endothelial cells and keratinocytes by upregulating, among others, the secretion of vascular endothelial growth factor [20–22].

Neurogenic factors [23], increased expression of the antimicrobial and pro-inflammatory peptides cathelicidin and kallikrein 5, their abnormal cleavage products, and the activity of a specific serine protease [24, 25] may be involved. Microorganisms, such as *Demodex folliculorum* and the associated therewith bacterium *Bacillus oleronius*, *Staphylococcus epidermidis*, and others, may therefore contribute significantly to the pathogenesis of rosacea by stimulating the innate immune system [1, 5, 11].

3.4 Treatment

3.4.1 General Measures

In all subtypes of rosacea, provocation factors such as alcohol, hot spices, heat, or cold should be avoided [26, 27]. The patients should pay attention to a consistent UV protection, with the use of both physical sun protective measures such as hats and of mild UV protection lotions with inorganic UV filters, such as titanium

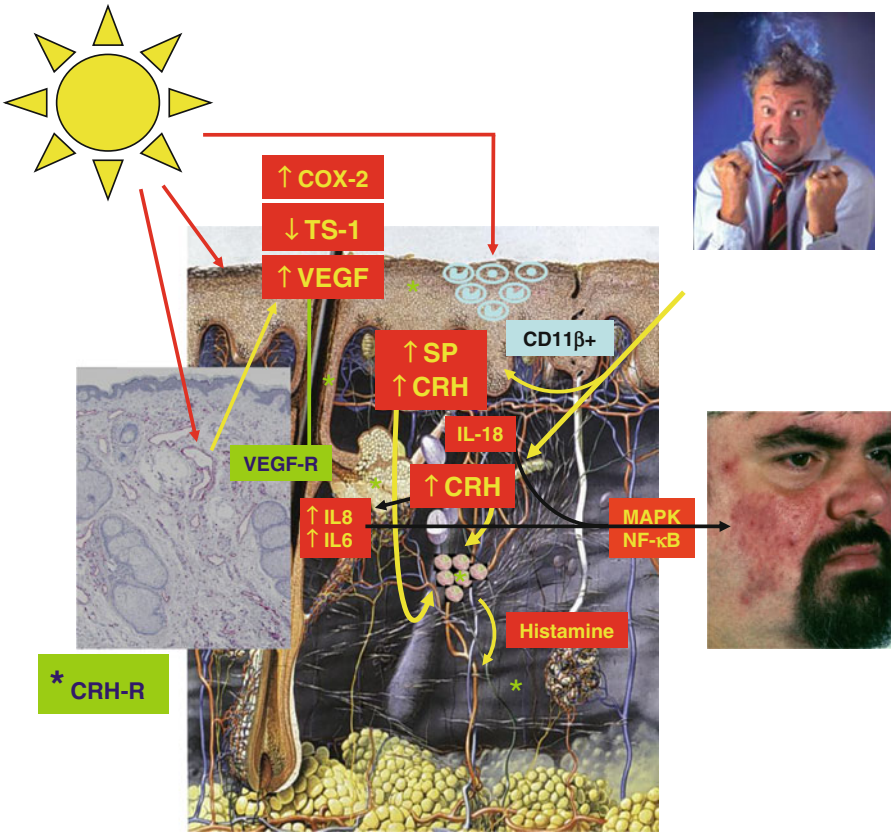

Fig. 3.2 Mechanisms of rosacea pathogenesis. UV irradiation induces pronounced edema in the dermis in conjunction with solar elastosis, slight perivascular lymphocytic infiltrate, and dilated and jagged lymphatic vessels both in the dermis and in the upper subcutis (stained with the selective antibody LYVE-1) presenting strong evidence that rosacea starts as an *actinic lymphatic vasculopathy*. UV irradiation of human skin results in pronounced dermal angiogenesis accompanied by upregulation of vascular endothelial growth factor (VEGF) and downregulation of the endogenous angiogenesis inhibitor thrombospondin-1 (TS-1). Although not expressed by the endothelium, VEGF is present in epithelial cells and in infiltrating cells in rosacea-involved skin. Expression of VEGF receptors (VEGF-R) is observed both by vascular endothelium and infiltrating mononuclear cells. VEGF receptor–ligand binding may contribute to the vascular changes and cellular infiltration that occur in rosacea. The newly formed vessels facilitate the infiltration of inflammatory cells into dermal tissue, resulting in the damage of dermal matrix components. CD11β+ macrophages and neutrophils infiltrate epidermis after intense UV irradiation. In addition, moderate UV irradiation doses can induce an increase of cyclooxygenase-2 (COX-2) expression in keratinocytes to cause a potent induction of the eicosanoid prostaglandin E2. Neurogenic mediators contribute to inflammation and immunosuppression following UV irradiation of the skin. Substance P (SP) induces mast cell degranulation with histamine and leukotriene release, leukocyte–endothelial adhesion, and neutrophil activation. Corticotropin-releasing hormone (CRH) acts as central coordinator for neuroendocrine and behavioral responses to stress and in peripheral organs among others as modulator of local immune and vascular functions. CRH can cause marked increases in vascular permeability in the skin microcirculation through the degranulation of mast cells and mast cell-derived histamine. CRH regulates interleukin (IL)-18 production in human keratinocytes and basal IL-6 and IL-8 secretion in human sebocytes, which regulate MAP kinase (MAPK) and nuclear factor-kB (NF-kB) and may lead to facial erythema. Specificity of the CRH effect was demonstrated by the use of CRH-R antagonist antalarmin and is consistent with accumulated data about the role of CRH in the regulation of local epithelial homeostasis (From Fimmel et al. [9])

dioxide or zinc oxide, which are considered highly suitable for use on the skin. It is advisable to refrain from soaps as well as irritating ingredients in cosmetics (e.g., menthol, camphor, sodium lauryl sulfate, astringents). If necessary, skin lesions should be masked by appropriate covering cosmetics [26]. Systemic drugs provoking blood flow and flushing are to be avoided.

If these general measures are not sufficient due to the severity of the disease, topical or systemic drugs should be added in order to avoid patient's psychological distress.

3.4.2 Drug Therapy

The currently approved drugs and other therapeutic means are listed in Table 3.2. Among them topical azelaic acid (15 % gel; high-quality evidence) and metronidazole (0.75 % gel; moderate-quality evidence) are more effective than placebo [28]. Topical ivermectin (1 % cream) is more effective than placebo (high-quality evidence) and slightly more effective than metronidazole. Brimonidine (0.33 % gel) is more effective than vehicle in reducing erythema in rosacea (high-quality evidence). Cyclosporine A (ophthalmic 0.05 % emulsion) is effective for ocular rosacea (low-quality evidence). Administered orally, tetracycline (moderate-quality evidence) and doxycycline 40 mg/day (high-quality evidence) are more effective compared to placebo. Minocycline 45 is effective for papulopustular rosacea (low-quality evidence). Low-dose isotretinoin appears to be slightly more effective than doxycycline 50–100 mg (high-quality evidence). Laser and light-based therapies are effective for erythema in rosacea (low-quality evidence).

This chapter will focus on the use of antibiotics in the management of rosacea.

3.4.2.1 Topical Antimicrobial Therapy

The registered topical antimicrobial treatments in Europe are metronidazole, azelaic acid, and ivermectin. Their effectiveness on the individual symptoms of rosacea is shown in Table 3.3.

Metronidazole

This antibiotic from the group of nitroimidazoles inhibits nucleic acid synthesis of anaerobic bacteria and protozoa and also exhibits an anti-inflammatory effect. It is approved in Europe as a 0.75 % preparation in cream, gel, and lotion and can also be administered as maintenance therapy over months or even years after successful

Table 3.2 Treatment options for rosacea

	Agents/therapy	Particularly suitable for rosacea
General measures	Avoidance of irritant as well as triggering factors	All subtypes
Topical therapy (registered)	Metronidazole	Papulopustular
	Azelaic acid	Papulopustular
	Brimonidine	Erythematotelangiectatic
	Ivermectin	Papulopustular
Topical therapy (off label)	Retinoids	Papulopustular
	Benzoyl peroxide	Papulopustular
	Cyclosporin A	Ocular
	Calcineurin inhibitors	Steroid-induced rosacea
	Permethrin	Rosacea-like demodex folliculitis
	Benzyl benzoate	Rosacea-like demodex folliculitis
Systemic therapy (registered)	Doxycycline	Papulopustular
	Isotretinoin	Papulopustular
Systemic therapy (off label)	Doxycycline	Ocular
	Tetracyclines	Papulopustular, ocular
	Macrolides (particularly erythromycin and azithromycin)	Papulopustular, ocular
	Metronidazole	Papulopustular, rosacea-like demodex folliculitis
	Isotretinoin	Phymatous, extrafacial, rosacea fulminans, steroid-induced rosacea
	Dapsone	Phymatous, rosacea fulminans
	Beta-blockers (carvedilol)	Erythematotelangiectatic
	Ivermectin	Rosacea-like demodex folliculitis
Physical therapy	LASER	Erythematotelangiectatic, phymatous
Surgical therapy	Dermabrasion, dermashaving	Phymatous

Modified from Yamasaki et al. [24]

Table 3.3 Topical treatment of rosacea and its effect on individual cutaneous symptoms [8, 24]

Compound	Erythema	Papules	Pustules
Metronidazole	–	++	++
Azelaic acid	–	++	+
Ivermectin	–	+++	++
Permethrin	–	++	+

treatment [5, 11, 26, 27]. No risk of the development of resistance exists, because all relevant skin bacteria have primary resistance to metronidazole. In some cases, a type IV allergy to metronidazole has been observed [29].

Azelaic Acid

Azelaic acid exhibits an anti-inflammatory effect and leads to a normalization of keratinocyte differentiation [26]. The active ingredient inhibits the antimicrobial peptides cathelicidin and kallikrein 5 and the activity of a serine protease, which are elevated in the skin of rosacea patients [30]. Azelaic acid is not inferior to metronidazole regarding the reduction of papules and pustules in rosacea. A 15 % azelaic acid gel is approved in Germany for the treatment of rosacea [31].

Ivermectin

Ivermectin is a safe and effective antiparasitic drug. By binding to a chloride ion channel in the peripheral nervous system of parasites, it leads to hyperpolarization followed by paralysis and death [32]. It exhibits not only antiparasitic but also possesses anti-inflammatory properties: it inhibits lipopolysaccharide-induced production of inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-1β) and upregulates the production of the anti-inflammatory cytokine interleukin-10 [33, 34].

Based on the proposed pathogenetic involvement of the mite *Demodex folliculorum* and its associated bacterium *Bacillus oleronius*, a 1 % ivermectin cream was approved in 2014 in the USA und in 2015 in Germany. In a study versus vehicle (12-week observation period), it showed a significant effect in the treatment of inflammatory lesions in papulopustular rosacea, and it was safe and well tolerated [34]. Two 40-week extension studies of those trials were conducted to assess the long-term safety of ivermectin 1 % cream versus azelaic acid 15 % gel, and it was shown to be safe throughout the study with a lower incidence of related adverse events, such as skin dryness or itching, compared to azelaic acid gel.

When comparing 1 % ivermectin cream (once daily) to 0.75 % sodium metronidazole cream, ivermectin reduced the number of inflammatory lesions more effectively and was better tolerated at the 16 weeks observation period [35].

Permethrin and Benzyl Benzoate

Permethrin and benzyl benzoate, which are commonly used for the treatment of scabies, were, according to some case reports, successfully used in rosacea or rosacea-like demodex folliculitis. Permethrin has been applied in a 5 % cream twice daily for 2 weeks occasionally combined with oral ivermectin [36, 37]. In some cases, a longer duration of therapy is necessary.

Permethrin 5 % once a week combined with metronidazole 0.75 % gel daily is highly efficacious and capable to control the life cycle of 8–10 days of *Demodex folliculorum*. Benzyl benzoate (10 %) could significantly reduce mite density of *Demodex folliculorum* [38]. A treatment period of 3 months is recommended.

Antibiotics

Antibiotics such as clindamycin (1 %), erythromycin, and tetracycline can indeed reduce the number of papules, pustules, and nodules of rosacea. However, due to the possible development of resistance when applied topically they are currently not recommended for the topical treatment of rosacea [26, 27]. They lead mostly to reduction of *Staphylococcus aureus* in the interfollicular epidermis and within the acroinfundibulum as a mild trigger of additional inflammation.

3.4.2.2 Systemic Antibiotic Therapy

Systemic treatment of rosacea is indicated in moderate to severe papulopustular rosacea but also in special forms, such as ocular rosacea, phymatous rosacea, conglobate rosacea, and rosacea fulminans. So far, only low-dose doxycycline (40 mg/day) is approved for the treatment of papulopustular rosacea. Other active off-label systemic treatments are other tetracyclines (tetracycline, minocycline), macrolides, metronidazole, and isotretinoin available. In some cases it may be useful to use dapsone, beta-blockers, ivermectin, or short courses of glucocorticosteroids. The effectiveness of systemic compounds on the subtypes of rosacea is shown in Table 3.4.

Tetracyclines (Tetracycline, Doxycycline, Minocycline)

Doxycycline (alternatives: tetracycline or minocycline) is usually the first-choice treatment for reducing severe inflammation with papules and pustules in rosacea [5, 11, 26, 27] (Fig. 3.3). The erythema-reducing effect is based on its anti-inflammatory activity against the papules. The rosacea-associated underlying erythema is not or only slightly affected.

Tetracyclines are bacteriostatic agents, which act by binding to the 30 S subunit of the 70 S ribosome and inhibiting protein synthesis [26]. In addition to their antibiotic

Table 3.4 Systemic treatment of rosacea subtypes [8, 24]

Rosacea subtype	Tetracyclines	Macrolides	Metronidazole	Retinoids	Beta-blockers	Corticosteroids
Erythematotelangiectatic	–	–	–	–	++	–
Papulopustular	++	++	++	++	–	–
Phymatous	+	–	–	+	–	+
Ocular	++	++	++	+	–	–
Fulminans	+	+	+	++	–	++
Steroid-induced	+	+	+	+	–	–
Lymphedematous rosacea (morbus Morbihan)	–	–	–	+	–	+

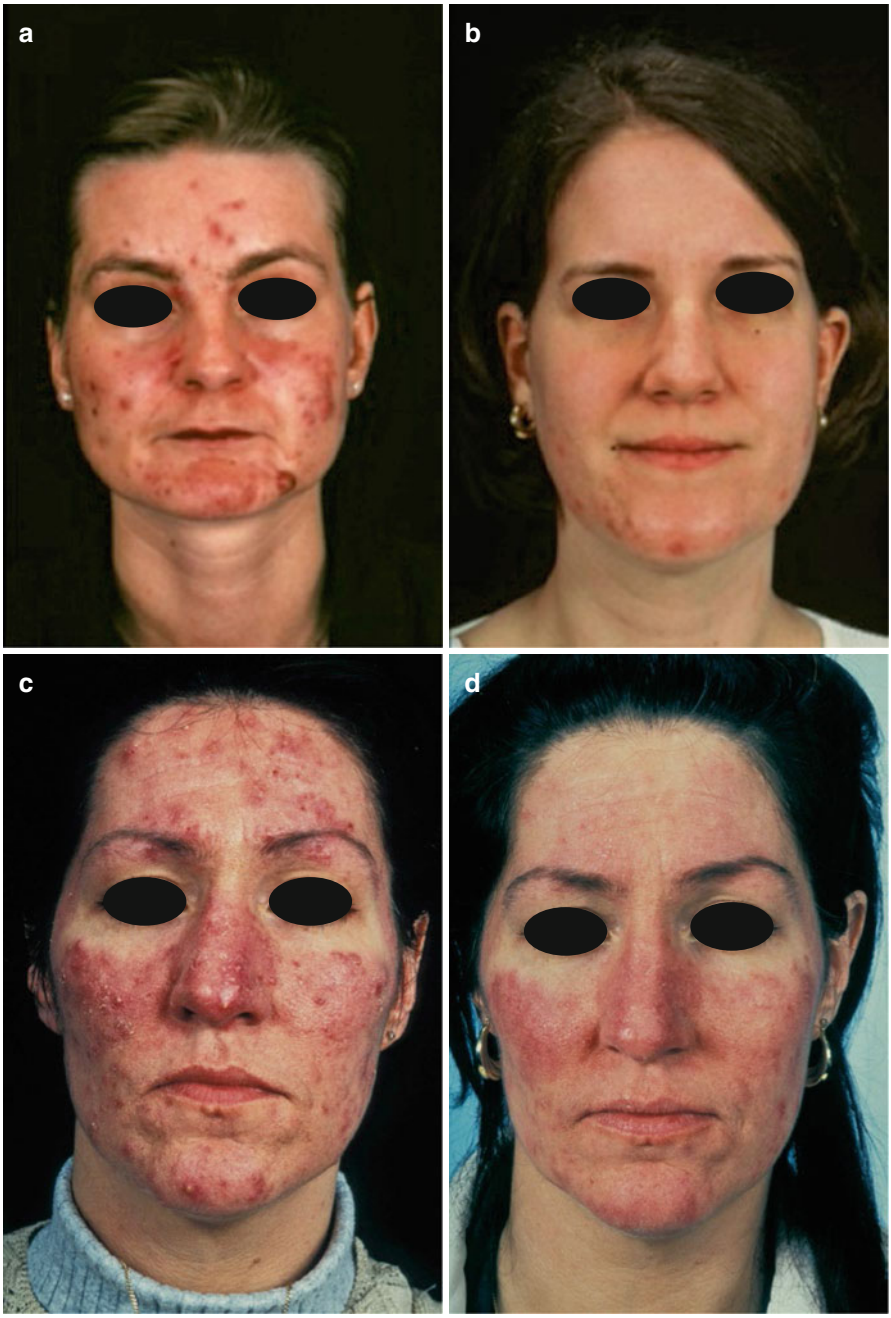

Fig. 3.3 Rosacea papulopustulosa (before, **a**) and after treatment with doxycyclin p.o. over 3 months (**b**)

properties, they exhibit genuine anti-inflammatory effects that may already occur at doses under the minimum bacteriostatic concentration [39]. They inhibit angiogenesis, neutrophil chemotaxis, and metalloproteinases and reduce inflammatory cytokines [40]. In addition, doxycycline reduces the formation of nitric oxide and reactive oxygen species [41], which in turn leads to reduction of vasodilation and dermal defects that play a pathogenetic role in rosacea. Doxycycline with reduction of lesions of 83 % was not inferior to isotretinoin 0.3 mg/kg body weight [42]. Complete remission was diagnosed in 14 % and marked improvement in a further 55 % of patients.

Side effects: Gastrointestinal discomfort, hypersensitivity reaction, phototoxic reaction, vaginal candidiasis, and storage in the bones and teeth. Minocycline can induce hyperpigmentation of the skin, mucous membranes, teeth, and bones. In comparison to doxycycline, drug eruption, neurological and respiratory disorders, eosinophilia, autoimmune signs, and DRESS syndrome (drug rash with eosinophilia and systemic symptoms) are more frequent with minocycline [43]. In the latter, fever, generalized rash, lymphadenopathy, visceral involvement, and blood dyscrasias can occur [44].

Contraindications: Pregnancy (impairment of tooth and bone growth) and lactation, children <8 years of age, hepatic dysfunction, and renal insufficiency. With simultaneous use of oral retinoids, there is a risk of pseudotumor cerebri, a benign increase of intracranial pressure.

Practical information: One hour before to 1 h after, intake of tetracycline dairy products should be avoided, as they can lead to decreased absorption. The concomitant use of antacids leads to decreased absorption. Tetracycline should be taken before and is therefore slightly worse tolerated. The patient should be informed to *use adequate* UV protection. For long-term therapy, low-dose doxycycline with 40 mg/day is preferable due to the better efficacy-risk ratio profile and the lack of development of resistance. Minocycline should not be used as first-line therapy of inflammatory dermatoses [26]. A combination of oral doxycycline and topical therapies (e.g., metronidazole or azelaic acid) is recommended.

Recommended laboratory tests: Complete blood count and liver and renal function tests at regular time periods (e.g., every 4 weeks) for the first 3 months [45].

Dosage: Doxycycline 40–100 mg/day over 3–6 months
Tetracycline 250–1000 mg/day
Minocycline 50–100 mg/day

Macrolides

Alternatives to tetracyclines are the macrolide antibiotics erythromycin, azithromycin, and clarithromycin (orally administrable narrow-spectrum antibiotics) that can be administered during pregnancy and in children under 8 years. In general, those

antibiotics should be used after careful consideration because of the risk of inducing resistance within the microbiome and should generally be reserved for infectious diseases. Among these drugs azithromycin is the preferred option, since it is chemically stable and is better tolerated compared to erythromycin. Azithromycin is rapidly absorbed in the circulation after oral administration and is stored in the intracellular space and released from there slowly. This allows less frequent administration, which can enhance compliance. It also shows an affinity for inflammatory tissue areas and is characterized by less drug interactions compared to other macrolide antibiotics [46, 47]. Azithromycin reduces neutrophil migration, inhibits neutrophil and eosinophil activation, and suppresses the release of reactive oxygen species and the formation of pro-inflammatory cytokines. As a result, it has anti-inflammatory properties [48]. In an open-label study, azithromycin in a tapering dose scheme (500 mg 3×/week in the first month, 250 mg 3×/week in the second month, and subsequently 250 mg 2×/week) was compared with doxycycline (100 mg/day) for the treatment of papulopustular rosacea and found to be equally active [47]. Azithromycin is also active in ocular rosacea, where it produces marked signs of ocular improvement (500 mg 3×/week for 4 weeks [49]).

Side effects: Gastrointestinal discomfort, liver dysfunction (increased transaminases, alkaline phosphatase, bilirubin), hypersensitivity reaction.

Contraindications: Renal impairment (creatinine clearance <30–40 ml/min, substance dependent), severe liver damage, QT prolongation; careful assessment before any use in pregnancy.

Cave: Erythromycin and clarithromycin may interact with other drugs causing inhibition of cytochrome P450.

Dosage: Erythromycin 250–1,000 mg/day
Azithromycin 500 mg 3×/week for 4 weeks

Metronidazole

Metronidazole can also be used systemically in papulopustular rosacea, where it reduces the number of papules and pustules [50]. It has been successfully used for the treatment of conglobate rosacea-like demodex infestation [51].

Side effects: Gastrointestinal discomfort, metallic taste, dark discoloration of the urine, abnormal liver function, blood dyscrasias, superficial *Candida* infections; very rarely – encephalopathy, neuropathy, convulsions.

Contraindications: Severe liver damage, neural diseases, blood disorders, pregnancy (esp. first trimester), alcohol intake (alcohol-related headache).

Recommended laboratory tests: Complete blood count and liver and renal function tests every 4 weeks for the first 3 months.

Dosage: Metronidazole 200 mg 2×/day
(In demodex folliculitis) 250 mg 3×/day for 2 weeks

Ivermectin

Individual cases of successful treatment of refractory or papulopustular rosacea as well as rosacea-like demodex folliculitis with ivermectin and topical permethrin have been reported [36, 37, 52]. When demodex folliculitis is suspected, the diagnosis can be confirmed by histology: in a standardized skin area on the cheek (1 cm^2), healthy subjects exhibit an average of 0.7 mites/cm^2. In patients with papulopustular rosacea, the mite density is at least 5 mites/cm^2. The mite density in patients with erythematotelangiectatic rosacea is not different from that in healthy subjects [53]. Treatment of rosacea with systemic ivermectin should be reserved for exceptional cases (immunocompromised patients, severe demodex folliculitis). The drug is available in France (Stromectol®, Merck & Co., Whitehouse Station, NJ, USA).

Ivermectin is considered to be well tolerated with side effects occurring based on the indication. No serious side effects have occurred in the treatment of rosacea.

Contraindications: Pregnancy, children <5 years.

Dosage: Single dose of 200 μg/kg body weight with a repeat dose after 1 week) in combination with topical permethrin (5 % 2×/day for 2 weeks). Topical permethrin therapy for 3 months may be required.

Other Antimicrobial Drugs for Systemic Treatment of Rosacea

Individual reports exist on the efficacy of other antibiotics such as cotrimoxazole, clindamycin, chloramphenicol, and ampicillin [26]. Due to lack of wide experience, no recommendation can be made for their use in the treatment of rosacea.

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Chapter 4
Venereal Disease I: Syphilis

Erwin Tschachler and George-Sorin Tiplica

4.1 Microbiology of *Treponema pallidum*

Treponema pallidum subspecies *pallidum* is a corkscrew-shaped motile bacterium of 6–15 μm length and 0.1–0.2 μm width [1]. Because it is too thin to be seen by light microscopy, it cannot be identified by Gram staining. However, it can be visualized in smears by dark field microscopy and in both smears and in tissue section by Warthin-Starry stains or immunostaining methods. In vitro culture methods for *T. pallidum* are not available. For propagation it must be inoculated in the tissue of life laboratory animals, most commonly rabbits. Important for therapeutic considerations is the fact that the generation time of *T. pallidum* is longer than 30 h [1]. Recently the genome of *T. pallidum* has been sequenced [2] opening the way for further molecular characterization of this bacterium and its pathogenic potential.

4.1.1 Diagnostic Tests

The approach for confirmation of an infection with *T. pallidum* varies dependently on the clinical disease stage and relies on either the demonstration of the bacterium or assessment of the serologic immune response (Fig. 4.1).

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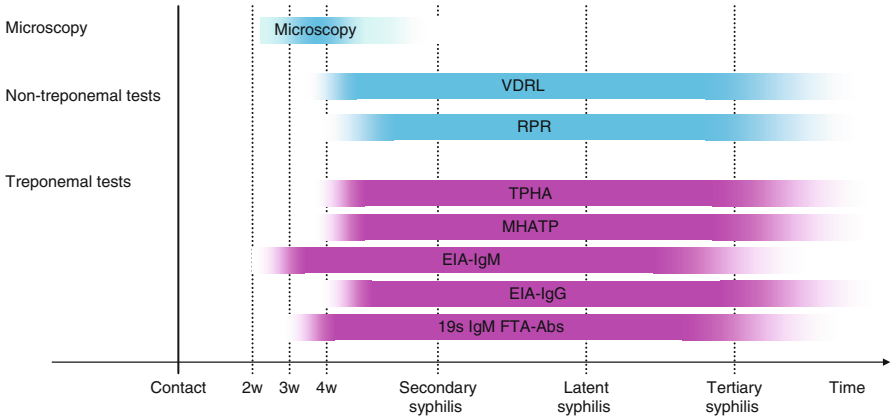

Fig. 4.1 Diagnostic tests for syphilis

4.1.1.1 Microscopy

Dark field and immunofluorescence microscopies are conventionally used to detect bacteria in smears from ulcers in primary syphilis before a serologic response can be monitored. Dark field microscopy needs some experience in preparing the samples and identifying the typical morphology and motility of *T. pallidum*. Slides are best read within minutes after sample preparation. Since specimen from the oral cavity may contain nonpathogenic *treponemes* which are virtually impossible to distinguish from *T. pallidum*, some physicians prefer immunofluorescence tests using specific antisera. An advantage of the latter approach is the fact that the specimen does not need immediate processing and the specificity of the anti-*T. pallidum* sera prevents a mix-up with other *treponemes*.

4.1.1.2 Non-treponemal Serologic Tests

Non-treponemal serologic tests are based on the principle discovered by Wassermann in 1910 that anti-lipid antibodies, reacting with a complexed mixture of cardiolipin, lecithin, and cholesterol, can be detected in the sera of syphilis patients with active disease. Today two variants, i.e., the Venereal Disease Research Laboratory (VDRL) and the Rapid Plasma Reagin (RPR) test, are available. Shortcomings of these tests are that they become reactive only 4–5 weeks after infection and that there are approximately 1 % of biologic false-positive test results [3] frequently associated with infections by other bacterial or viral pathogens, with collagenoses, or with pregnancy. Both VDRL and RPR are assessed in serial dilutions and reported as titers which are used to estimate disease activity and to monitor therapeutic success. Fourfold decrease of VDRL or RPR titers over 6–12 months after therapy is considered a sign of successful therapy.

4.1.1.3 Treponemal Serologic Tests

The specific IgM antibody response against *T. pallidum* can be detected approximately 2 weeks after infection and 2–3 weeks thereafter for IgG antibodies [4]. *T. pallidum* particle agglutination test (TPPA), *T. pallidum* hemagglutination (TPHA), and microhemagglutination assay for *T. pallidum* (MHATP) are all based on the agglutination of particles or erythrocytes coated with *T. pallidum* extracts by the patients' sera. More recently *T. pallidum* enzyme immunoassays (EIA) using detergent extracts of *T. pallidum* or recombinant *T. pallidum* proteins have become available and allow for rapid screenings of large numbers of samples and for detecting also anti-*T. pallidum* IgM antibodies (EIA-IgM). An alternative method which has been used successfully for several decades is the detection of antibodies by indirect fluorescence assays analyzing the reactivity of patients' sera with *T. pallidum* fixed on slides. Since the sera have to be preabsorbed with nonpathogenic *treponemes* to avoid cross-reactivities, the test is referred to as Fluorescent Treponemal Antibody Absorption Assay (FTA-Abs). For the detection of antitreponemal antibodies of the IgM class, the 19S fraction of the sera is isolated by ultracentrifugation and used in a fluorescence assay (19S-IgM-FTA-Abs).

To establish the diagnosis of syphilis and to determine disease activity, the results of both a treponemal and a non-treponemal serologic test are necessary. For cost reasons today, a treponemal test (TPHA, TPPA, MHATP, EIA) followed by one of the non-treponemal (RPR, VDRL) is used in most laboratories.

4.2 Epidemiology

In the developed countries, the incidence of syphilis declined during the late 1980s and 1990s. However, since the turn of the millennium, a steep rise of newly diagnosed cases has been observed in the USA, in Europe, and in China. In Western and Central Europe, this surge was considerably higher in men than in women with a ratio exceeding 20:1 in some countries, mainly due to an increase of infections in men who have sex with men (MSM) [5]. By contrast the numbers of reported cases of syphilis in Eastern Europe have remained more stable although at a higher level and in some countries have a tendency to even decrease [6]. The surge in the MSM population coincided with the availability of highly active anti-HIV drug combinations and suggests a change in the safe sex practice as a consequence of a lessened fear of HIV-1 infection. In contrast to the dramatic increase in some regions, the overall estimates for syphilis incidence worldwide of the WHO have remained stable at about ten million infections occurring annually. The rate for primary and secondary syphilis cases in 2010 was 7.9 $\%_{000}$ in the USA [7] and 4.5 $\%_{000}$ in EU [8].

4.3 Clinical Course

The disease course after infection with *T. pallidum* passes through different stages, i.e., primary, secondary, and tertiary syphilis, separated by periods of latency of different duration. It should be noted that from "studies" [9, 10] which are considered completely unethical by today's standards, in which patients were left untreated but followed up for several decades, it became apparent that about two-thirds of patients went into latency after secondary syphilis and did never enter the stage of tertiary syphilis.

4.3.1 Primary Syphilis

The manifestation of primary syphilis is usually one chancre of a few millimeters up to 2 cm in diameter which most frequently appear at the genital (Fig. 4.2) sites but can also be found at extragenital locations. The time from inoculation to development of the chancres is variable from 2 to 12 weeks. In most cases these chancres are not painful, have a firm base and sharp margins, and are accompanied by indolent regional lymphadenopathies. Without therapy the chancre will heal within 3–6 weeks. Depending on the time elapsed from the contact, the serology might or might not yet be positive. In case of seronegativity, detection of *T. pallidum* either by dark field microscopy or immunofluorescence analysis of smears from the ulcers will help to establish the diagnosis.

4.3.2 Secondary Syphilis

Secondary syphilis is defined as a generalized infection with mucocutaneous lesions and frequently a generalized lymphadenopathy. The mucocutaneous lesions referred to as syphilids, together with a positive syphilis serology, lead up to confirming the diagnosis. However, it should be kept in mind that the mucocutaneous lesions of secondary syphilis display a high variability between individuals. On the skin they may manifest as a typical roseoliform rash (Fig. 4.3) but may also mimic other, noninfectious, skin diseases such as psoriasis, lichen planus, pityriasis rosea, hand eczema, and many others. On the mucous membranes, secondary syphilis can manifest as *condylomata lata* in the perianal/perivulvar regions (Fig. 4.4) and as mucous patches and plaques or opaline patches in the mouth (Fig. 4.5). Inflammation of the tonsils (syphilitic angina) can also occur. Mucocutaneous lesions in this stage are highly infectious. A diffuse or patchy hair loss (Fig. 4.6) is also frequently seen in secondary syphilis. In secondary syphilis, all specific serologic tests are positive, and the unspecific tests (VDRL, RPR) show titers usually above 1:32.

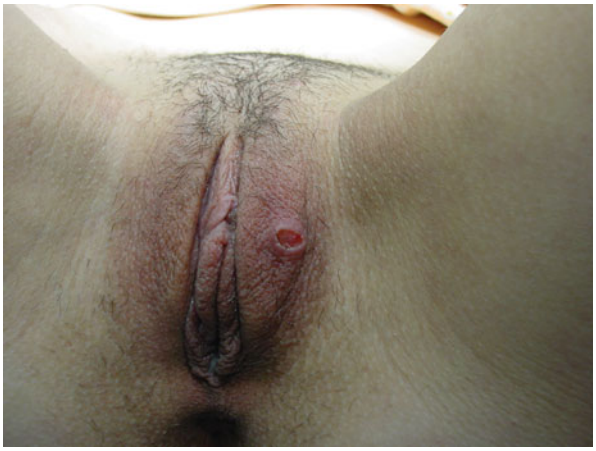

Fig. 4.2 Syphilitic ulcer on the labia majora

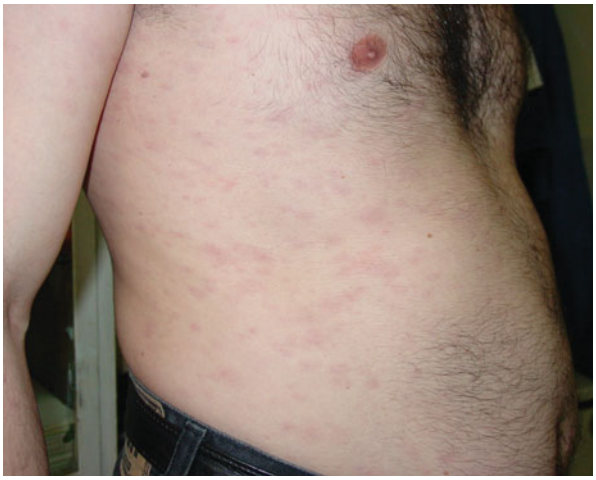

Fig. 4.3 Roseoliform rash of secondary syphilis on the trunk

4.3.3 Therapy of Primary and Secondary Syphilis

Nota bene: There were no major changes in the therapy of syphilis over the past few decades. Penicillin is still the antibiotic of choice to treat all stages of syphilis. In treating syphilis the generation time of >30 h of *T. pallidum* must be considered which means that the plasma and tissue levels of the antibiotics have to remain stable for an extended time period. Benzathine penicillin G fulfills this requirement (Table 4.1).

For both primary and secondary syphilis, the treatment recommended by most guidelines is *2.4 million IU of benzathine penicillin G in a single dose given*

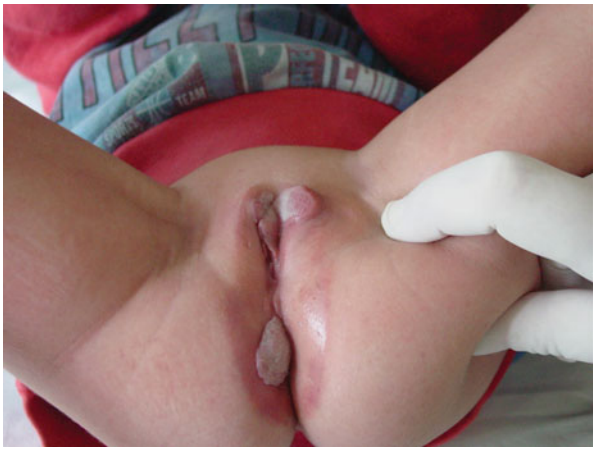

Fig. 4.4 Condylomata lata on the vulva of child (can either arise as manifestation of syphilis acquired due to child abuse or as part of congenital syphilis)

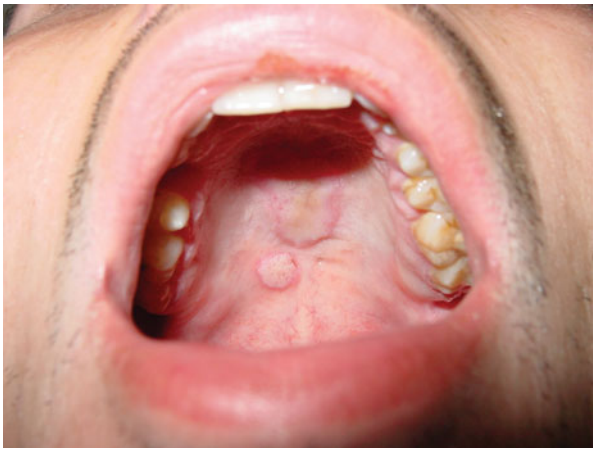

Fig. 4.5 Plaques muqueuses on the hard palate of a male patient

intramuscularly [11, 12]. **Procaine benzylpenicillin** 1.2 million IU by intramuscular injection, daily for ten consecutive days, is recommended by the WHO as an alternative treatment [12]. Nota bene: Based on the data showing that in some cases the plasma concentrations of ethinyl estradiol were decreased in patients receiving penicillin [13], the authors recommend the use of a supplementary method of contraception for the duration of the syphilis therapy.

In patients with penicillin allergy, the possibility of their desensitization [14] and subsequent treatment with benzathine penicillin is recommended. If this is not feasible, the first alternative for nonpregnant, penicillin-allergic patients is either **doxycycline** 100 mg orally twice daily for 14 days or **tetracycline**

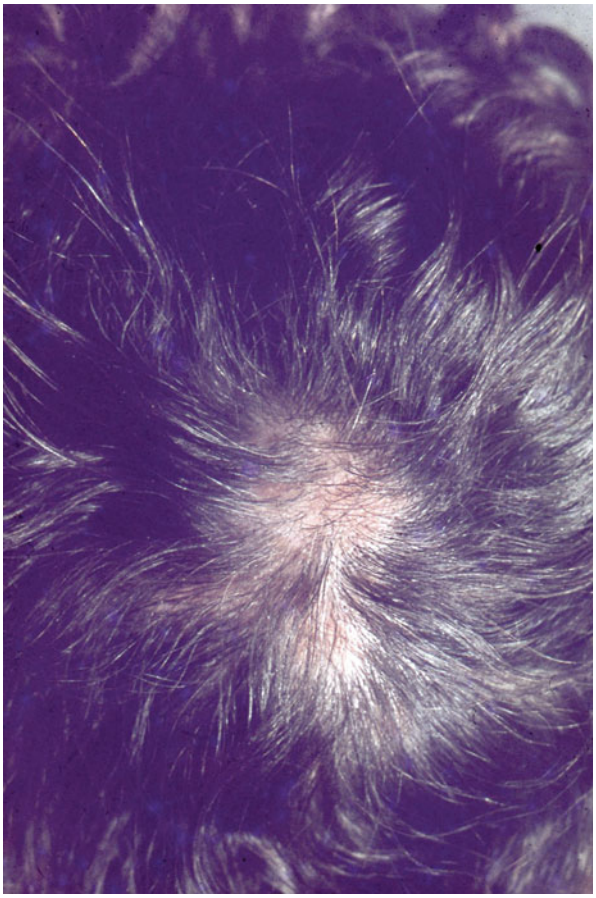

Fig. 4.6 Alopecia syphilitica

500 mg orally four times daily for 14 days. Whereas both regimens are recommended by the WHO guidelines [12], the authors prefer doxycycline since it has to be taken only two times a day by the patients. **Ceftriaxone** (1 g daily either IM or IV for 10–14 days) has also been shown to be effective for primary and secondary syphilis. However, data on the optimal regimen are still missing. **Azithromycin** as a single 2-g oral dose has held some promise but since it has been found that it can cause chromosomal mutations of *T. pallidum* leading to azithromycin resistance and treatment failures [15], its use is not recommended by the authors.

For pregnant patients with penicillin allergy, desensitization [11, 14] and treatment with **benzathine penicillin G** could be considered in some instances. However, it is noteworthy that WHO suggests **erythromycin** 500 mg orally four times daily for 14 days as a possible alternative [12].

Table 4.1 Syphilis therapy – overview

Therapy	Primary, secondary and early latent syphilis	Late latent syphilis, syphilis of unknown duration, late "benign" syphilis and cardiovascular syphilis	Neurosyphilis	Early congenital syphilis	Late congenital syphilis
First option	2.4 Million IU of Benzathin Penicillin G im (single dose)	Benzathine penicillin G in 3 doses of 2.4 million units IM each at 1-week intervals	Benzylpenicillin G 18–24 million IU/day for 10–14 days *followed by* Benzathine penicillin G in 3 doses of 2.4 million units IM each at 1-week intervals	Benzylpenicillin 100000–150000 IU/kg/day, 10 days	Benzylpenicillin 200000–300000 IU/kg/day IV or IM, 10–14 days.
Second option	Procaine benzylpenicillin 1.2 million IU im, 10 days	Procaine benzylpenicillin, 1.2 million IU im 20 days	-	Procaine benzylpenicillin, 50000 IU/kg IM single daily dose, 10 days	-
Penicillin allergy	Doxycycline 100 mg orally twice daily for 14 days	Doxycycline, 100 mg orally, twice daily for 30 days	Doxycycline, 200 mg orally, twice daily for 30 days	Desensitization and treatment with Benzylpenicillin *or* erythromicyn, ceftriaxone	Desensitization and treatment with Benzylpenicillin *or* erythromycin 7.5–12.5 mg/kg orally, 4 times daily for 30 days
Pregnant patients with penicillin allergy	Desensitization and treatment with Benzathin Penicillin *or* erythromycin, 500 mg orally, 4 times daily for 14 days	Desensitization and treatment with Benzathin Penicillin *or* erythromycin, 500 mg orally, 4 times daily for 30 days	-	-	-

4.3.4 Latent Syphilis

If untreated secondary syphilis is followed by a state of latency which is defined as serologic evidence for (untreated) syphilis in the absence of clinical disease signs or symptoms. During latency the serologic response decreases, and the non-treponemal tests ultimately may become negative. CDC defines early latency as the state lacking clinical manifestations within the first year after infection, whereas after 1 year, it is classified as late latency or latent syphilis of unknown duration. By contrast WHO sets the breakpoint between early latency and late latency at 2 years after infection. The transition from early and late latent syphilis is ill defined, in particular, since during the first year, disease relapses may occur. However, the distinction between the two states of latency is relevant for determining the duration and dosing of the antibiotic treatment.

4.3.5 Therapy of Latent Syphilis

In contrast to early latent syphilis which can be interrupted by recurrences of active, infectious disease, in late latent syphilis, the patient is not infectious. The objective to treat latent syphilis is primarily to prevent progression to tertiary syphilis which occurs in approximately one-third of untreated patients.

For early latent syphilis, the treatment is identical to the one for primary and secondary syphilis, i.e., *benzathine penicillin G 2.4 million* units IM in a single dose. Considerations regarding potential alternative regimens and proceeding in penicillin-allergic patients remain the same as discussed above.

For late latent syphilis or syphilis of unknown duration, *benzathine penicillin G 7.2 million units total*, *administered as three doses of 2.4 million units IM each at 1-week interval,* is the treatment of choice [11, 12]. The WHO guidelines [12] suggest intramuscular injections of *procaine benzylpenicillin 1.2 million IU* once daily for 20 consecutive days as first-line alternative. In our opinion for practical reasons, this regimen should only be considered if *benzathine penicillin G is not available*. For nonpregnant patients with penicillin allergy, **doxycycline** 100 mg orally twice daily for 30 days or **tetracycline** 500 mg orally four times daily for 30 days is given as alternative possibility. In case of pregnant patients with penicillin allergy, **erythromycin** 500 mg orally four times daily for 30 days is advocated by the WHO guidelines [12]. Since it might be difficult to motivate patients who do not suffer from any symptoms to take oral medication regularly several times daily for 4 weeks, the authors believe that using the penicillin desensitization protocol [14] and subsequent injection of **benzathine penicillin G** is the preferable mode of treatment.

4.3.6 Tertiary Syphilis

About one-third of patients infected with *Treponema pallidum* progress to clinical manifestations of tertiary syphilis also referred as late syphilis. Clinically late benign syphilis, cardiovascular syphilis, and neurosyphilis are distinguished. However it should be noted that neurosyphilis can occur at any stage of syphilis.

4.3.6.1 Late "Benign" Syphilis

This comprises disease manifestations of tertiary syphilis except for cardiovascular syphilis and neurosyphilis. The characteristic manifestations of benign syphilis are gummata which in the majority of cases affect the skin and mucous membranes and clinically appear as non-tender erythematous nodules and plaques, slowly growing in size and ulcerating. Depending on their location, they can lead to disfiguration and functional impairments. Besides on the skin, gummata can arise at all other organs including the bones and the gastrointestinal tract.

4.3.6.2 Cardiovascular Syphilis

Approximately one-third of patients with tertiary syphilis develop cardiovascular manifestations due to an endarteritis of the vasa vasorum of the larger vessels leading to fibrosis of the affected vessel walls. The most prominent complications are the development of aneurysms and stenosis of coronary arteries.

4.3.6.3 Treatment of Late "Benign" Syphilis and Cardiovascular Syphilis

Antibiotic treatment of late benign and cardiovascular syphilis is identical to the treatment of late latent syphilis, i.e., *benzathine penicillin G 7.2 million IU total*, *administered as three doses of 2.4 million IU IM each at 1-week interval*. It is important to exclude cardiovascular syphilis and neurosyphilis before committing to this treatment. If the respective tests are not feasible or yield equivocal results, the authors prefer to treat the patients according to the protocol for neurosyphilis. Management of cardiovascular syphilis should be carried out in cooperation with a cardiologist. For penicillin-allergic patients, the same considerations as for late latent syphilis, as recommended by the WHO guidelines [12], are valid (see above).

4.3.6.4 Treatment of Neurosyphilis

The regimen recommended for neurosyphilis by both WHO and CDC guidelines is *aqueous crystalline benzylpenicillin* (*aqueous crystalline penicillin G*) *18–24 million IU per day*, *administered as 3–4 million IU IV every 4 h or continuous infusion*, *for 10–14 days*. Since this regimen is shorter than the one for late latent syphilis, the authors prefer to administer *benzathine penicillin G 7.2 million IU total as three doses of 2.4 million units IM each at 1-week interval* after completion of the neurosyphilis treatment regimen. It should be mentioned that although penicillin is the recommended treatment and that in penicillin-allergic patient, the desensitization protocol [14] is the authors' first choice, the WHO guidelines suggest **doxycycline** 200 mg orally twice daily for 30 days or **tetracycline** 500 mg orally four times daily for 30 days as an alternative treatment option for nonpregnant patients [12].

4.3.7 Congenital Syphilis

Although the risk for transplacental infection of the fetus is highest during the active disease of the mother and during early latency, it may occur at any disease stage as well as at any time during pregnancy. Early congenital syphilis refers to newborns who present with clinical symptoms already at birth or during the first 2 years of life. Typical symptoms include persistent rhinitis, fever, skin rashes which can manifest as bullous eruptions at birth or as maculopapular rash later on, as well as hepatosplenomegaly, lymphadenopathy, leukocytosis, and thrombocytopenia. In addition osteochondritis and periostitis may be present. Late congenital syphilis manifests after the second year and is mostly the consequence of the organ damage caused by the active infection during early congenital syphilis and includes scars (perioral "Parrot's lines"), interstitial keratitis of the eye, and malformation of the teeth ("Hutchinson's teeth") and of the skeleton.

Syphilis serology of the newborn is complicated by the fact that maternal antibodies of the IgG class are transferred to the fetus. A demonstration of anti-*T. pallidum*

antibodies of the IgM class in the serum of newborns is considered by many authors as confirmation of active infection of the newborn.

4.3.8 Treatment of Congenital Syphilis

For early congenital syphilis, *aqueous crystalline benzylpenicillin 100,000–150,000 IU/kg/day administered as 50,000 IU/kg/dose IV every 12 h, during the first 7 days of life and every 8 h thereafter for a total of ten consecutive days,* is the treatment of choice. As an alternative, **procaine benzylpenicillin** 50,000 IU/kg by intramuscular injection, as a single daily dose for 10 days, may be given. If penicillin is not an option (e.g., allergy, no availability), other antimicrobial agents (e.g., erythromycin, ceftriaxone) can be prescribed under close serologic and CSF follow-up.

For late congenital syphilis, WHO [12] recommends *aqueous crystalline benzylpenicillin 200,000–300,000 IU/kg/day by intravenous or intramuscular injection, administered as 500,000 IU/kg/dose every 4–6 h for 10–14 days*. Also in this latter scenario, WHO guidelines recommend **erythromycin** 7.5–12.5 mg/kg orally, four times daily for 30 days, as an alternative in penicillin-allergic patients. Tetracyclines of course would be contraindicated in children.

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Chapter 5
Venereal Disease II: *Chlamydia trachomatis* Infection, Gonorrhoea

George-Sorin Tiplica and Erwin Tschachler

5.1 *Chlamydia trachomatis* Infection

The genus *Chlamydia* includes several species of which *C. trachomatis* is of dermato-venereological interest. *C. trachomatis* is a nonmotile, Gram-negative intracellular bacterium responsible for urogenital tract infection (serotypes D–K) and lymphogranuloma venereum (serotypes L1–L3). Infection with *C. trachomatis* is the most common bacterial sexually transmitted infection (STI) in humans [1]. The infection is frequently asymptomatic facilitating disease transmission and the development of complications such as pelvic inflammatory disease, ectopic pregnancy and reactive arthritis.

5.1.1 Microbiology of C. trachomatis

C. trachomatis is a bacterium with DNA, RNA and cell membrane. Its growth is dependent on the metabolism of a host cell, and therefore it is an obligate intracellular pathogen. The infectious particles named elementary bodies are able to survive outside the cells, are metabolically inert and are resistant to antibiotic treatment [2]. When they enter the epithelial cells by endocytosis, they form reticulate bodies which are metabolically active synthesizing their own DNA, RNA and proteins. Reticulate bodies multiply within the endosomes and form inclusion bodies (visible by light

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microscopy) consisting of up to several thousand bacterial cells. However, even at this stage, the bacteria remain dependent on the host cell metabolism. Subsequently bacteria begin to transform again into infectious elementary bodies which within 2–3 days are released into the surroundings through rupture of the infected cells [3].

The distinction between the different strains of *C. trachomatis* is based on the seroreactivities of the major outer membrane proteins (MOMPs) [4]. Based on these reactivities, more than 20 serovars are distinguishable. Infections with strains of different serovars display also different disease manifestations: *Lymphogranuloma venereum* is caused by serotypes L1–L3, whereas A–C cause trachoma and D–K genitourinary diseases.

5.1.2 *Epidemiology of* Chlamydia trachomatis *Infection*

More than 90 million new cases of genital *C. trachomatis* infections occur each year [5], making this infection the leading cause of bacterial STI in developed and developing countries. Genitourinary infections with *Chlamydia* are the most frequently reported STI in Europe. In 2010, 344,491 cases of *Chlamydia* were reported in 24 European Union (EU)/European Economic Area (EEA) Member States with a rate of 186 per 100,000 population [6]. Untreated or repeated *C. trachomatis* infections may cause pelvic inflammatory disease, and, in some cases, these women may become infertile [7]. The general population awareness campaigns and the improved laboratory diagnostic techniques in recent years have contributed to recognition of the high incidence of *C. trachomatis* infection. It is important those activities to be sustained since many *Chlamydia* infections are still going undiagnosed or unreported.

5.1.3 *Venereal Infection with* Chlamydia trachomatis*: Clinical Course*

In women chlamydial infections remain asymptomatic in approximately 70 % of cases [5]. Symptomatic disease presents after an incubation period of 7–14 days generally as nonspecific cervicitis (most of the cases) or urethritis. Chlamydial cervicitis findings include mucopurulent endocervical discharge, intermenstrual vaginal bleeding or post-coital bleeding. Untreated symptomatic *C. trachomatis* infection can result in pelvic inflammatory disease (PID) by invasion of the bacteria into the upper reproductive tract. PID presents with pelvic pain and uterine and adnexal pain on palpation. Infertility and ectopic pregnancy are late complications of PID [8]. Few patients develop perihepatitis manifested as abdominal pain or pleuritic pain. Chlamydial urethritis in women presents with dysuria and/or pyuria. Urinalysis reveals the presence of leucocytes but no bacteria and cultures for bacteria, other than *Chlamydia*, are negative.

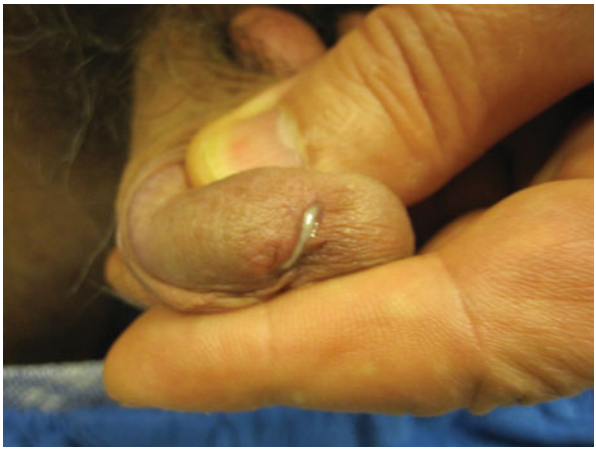

Fig. 5.1 Chlamydial urethritis

In male patients chlamydial infections remain asymptomatic in approximately 50 % of cases [5]. Chlamydial urethritis is the most frequent manifestation, with reduced mucosal or clear discharge seen upon milking the urethra (Fig. 5.1) and dysuria occurring 7–14 days after infection [9]. As in women, urinalysis reveals leucocytes but no bacteria. Untreated chlamydial urethritis can evolve into chlamydial epididymitis presenting with unilateral testicular pain or painful epididymal oedema, or into chronic prostatitis [10]. Reactive arthritis is a rare complication that may occur in untreated patients 1 month after the infection. The classic presentation includes urethritis, arthritis and conjunctivitis. HLA-B27-positive patients with chlamydial infection have a higher risk for developing reactive arthritis [11]. Chlamydial proctitis can occur in men who have sex with men but frequently it remains asymptomatic.

The infection with *C. trachomatis* serotypes L1–L3 causes lymphogranuloma venereum, which is endemic in some areas of Africa, India, Southeast Asia and Central and South America. In Europe and North America, recent outbreaks have been reported in men having sex with men [12]. LGV presents with small genital ulcers accompanied by fever, malaise, myalgia and painful enlarged and purulent inguinal lymph nodes ("bubo"). The symptoms of rectal infections include anorectal pain, discharge, rectal bleeding and lymphorrhoids. Massive enlargement of the perianal lymph nodes (Gerota's nodes) can induce constipation [13].

5.1.4 Diagnostic Tests for C. trachomatis

Nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR), real-time PCR, strand displacement amplification using DNA as a target or transcription amplification using bacterial ribosomal RNA as a target are considered today the methods of choice to detect chlamydial infection. They are superior to either an ELISA test or chlamydial culture both in sensitivity and specificity. For NAAT swab

specimens from the presumed infected location (vagina, urethra, rectum, ocular conjunctiva) or first-catch urine are used as samples [14]. The downsides of NAAT are their high costs which make their use uncommon in developing countries and the fact that they cannot be used to monitor antibiotic resistance [15].

Rapid immunoassays for detecting *Chlamydia* can be used for screening purposes. The test reading is simple (strip colour modification), and the result is available in 30 min [16].

Culturing *C. trachomatis* is expensive and requires more sophisticated laboratory facilities, and the success is dependent on the sample quality. Therefore culture methods are reserved for testing for antibiotic resistance in already confirmed chlamydial infection. Antigen detection in swab specimens from the cervix or urethra by either direct immunofluorescence staining or by ELISA may be used when NAAT is not available [17]. Serological tests are of very limited value since they cannot discriminate between an ongoing and a past infection.

5.1.5 Infection with Chlamydia trachomatis*: Treatment*

C. trachomatis treatment targets the reproductive life cycle of the bacteria. Therefore antibiotics used must have a good intracellular penetration and a half-life ensuring sufficient high bactericidal levels during the entire 48-h life cycle of the bacteria [18]. Tetracyclines and macrolides correspond to these criteria and are used as first-line therapy. Antibiotic resistance is rare.

5.1.5.1 Uncomplicated Genital Chlamydial Infections

For uncomplicated chlamydial cervicitis and urethritis, either **azithromycin** 1 g p.o. (single-dose therapy) or **doxycycline** 100 mg × 2/day, p.o., 7 days, is recommended as equivalent therapies by both the European guideline for the management of *Chlamydia* trachomatis infections (2010, IUSTI-Europe) [19] and the Sexually Transmitted Disease Treatment Guidelines, 2010 (CDC Atlanta) [19–21]. Since 2010 new clinical trials using the NAAT technique for cure rate have suggested a higher microbial clearance of the doxycycline regimen [22, 23]. The authors recommend the doxycycline treatment as a cost-efficient regimen if the patient is sufficiently reliable to take the medication for 1 week.

As with other macrolides, azithromycin should not be given at the same time as haloperidol. If the patient is taking antacids, it is recommended that there is a 2-h interval between the administration of the two drugs. The most frequently reported adverse events were nausea, dyspepsia, abdominal pain, vomiting and diarrhoea.

The most frequently reported adverse events for doxycycline are gastrointestinal and sensitization to UV light. It is recommended that the following medications should not be given at the same time as doxycycline: antacids containing calcium,

aluminium or magnesium, systemic corticosteroids, systemic retinoids, oral contraceptives and penicillins.

Recommendations for therapeutic alternatives include treatment with quinolones: **ofloxacin** 300 mg×2/day, p.o., 7 days, or **levofloxacin** 500 mg o.d., p.o., 7 days. Also macrolides other than azithromycin are alternative therapies: **erythromycin base** 500 mg×4/day, p.o., 7 days, or **erythromycin ethylsuccinate** 800 mg×4/day, p.o., 7 days, or **josamycin** 500–1,000 mg×2/day, p.o., 7 days [19]. However, the longer course of medication and inferior efficacy as compared to azithromycin should be considered. Doxycycline cannot be used in pregnant women and children; therefore azithromycin is recommended [24]. **Amoxicillin** 500 mg×3/day, p.o., 7 days, [20] and **josamycin** have been recommended as alternative treatments for pregnant women.

It is important to note that because of the high frequency of co-infection with *N. gonorrhoeae*, which may remain asymptomatic, it is recommended that *chlamydial proctitis* should be treated with a combination of **ceftriaxone** 500 mg i.m. (single dose)+**doxycycline** 100 mg×2/day, p.o., 7 days (Table 5.1).

For the treatment of *lymphogranuloma venereum,* **doxycycline** 100 mg×2/day, p.o., 21 days, is given [20].

5.1.5.2 Ascending Genital Chlamydial Infections

For chlamydial epididymitis, a treatment regimen targeting *C. trachomatis* and *N. gonorrhoeae* is recommended: **ceftriaxone** 500 mg i.m. (single dose)+**doxycycline** 100 mg×2/day, p.o., 10 days [20] (Table 5.1).

Pelvic inflammatory disease requires a syndromic, empirical approach with broad-spectrum antibiotic therapy directed against *C. trachomatis* and *N. gonorrhoeae* as well as against other Gram-negative and Gram-positive pathogens including *Mycoplasma genitalium*, anaerobes, *Streptococci*, *Staphylococci*, *E. coli* and *H. influenzae*.

In the case of patients with *persistent or recurrent symptoms,* several possibilities must be taken into consideration: reduced adherence to the drug regimen (as low as 25 % adherence in case of doxycycline therapy [25]), reinfection from (new) partner

Table 5.1 Treatment of chlamydial and gonococcal infections – overview

Chlamydial infection – uncomplicated	Chlamydial/ gonococcal proctitis	Chlamydial/ gonococcal epididymitis	Gonococcal infection – uncomplicated	Resistant *N. gonorrhoeae*
Doxycycline 100 mg×2/day, p.o., 7 days	**Ceftriaxone** 500 mg i.m. + **doxycycline** 100 mg×2/day, p.o., 7 days	**Ceftriaxone** 500 mg i.m. + **doxycycline** 100 mg×2/day, p.o., 10 days	**Ceftriaxone** 500 mg i.m. + **azithromycin** 2 g p.o.	**Ceftriaxone** 1 g i.m. (single dose)+ **azithromycin** 2 g p.o. (single dose)
Azithromycin 1 g p.o.				**Gentamicin** 240 mg i.m. (single dose)+ **azithromycin** 2 g p.o. (single dose)

(in up to 14 % of cases [26]) and infection with another pathogen (e.g. *Ureaplasma*, *Mycoplasma genitalium*, herpes virus).

5.2 Gonorrhoea

5.2.1 Microbiology of Neisseria gonorrhoeae

N. gonorrhoeae is a Gram-negative aerobic bacterium that is typically found in pairs (diplococci). Different strains have been described by serotyping, genotyping or antibiotic susceptibility. *N. gonorrhoeae* attaches to the mucosal columnar epithelial cells using filamentous appendages (PilC proteins, Opa proteins) and is incorporated by endocytosis into the epithelial cells or leucocytes. *Gonococci* can replicate inside and outside the cells [27]. Using different complex strategies such as sialylation of antigenic proteins and production of IgA_1 proteases, *N. gonorrhoeae* is able to disseminate and elude host immune defences. *Gonococci* can change their biologic behaviour by genetic exchange mechanisms resulting in modification of their surface markers, thereby escaping the host's immune response or acquiring antibiotic resistance by uptake of β-lactamase plasmids. Transforming DNA is spread by neighbouring *Gonococci* through autolysis or type IV secretion [28].

5.2.2 Gonorrhoea: Epidemiological Data

Gonorrhoea is the second most commonly reported bacterial STI in Europe. In 2010 there were 31.983 cases of gonorrhoea reported by 28 EU/EEA countries (104 cases per 100,000 population), in an increasing trend when compared with 2009 and 2008 [6]. However, due to the differences in national surveillance systems, there are probably many more cases which go undetected. Gonorrhoea is mostly reported in young adults under 25 years of age (43 % of all infections), and currently more than 25 % of the cases are reported in the MSM population [6]. The antimicrobial susceptibility of *N. gonorrhoeae* (monitored by Euro-GASP) has a tendency for rapid change and recently a high prevalence of resistance to ciprofloxacin (63 %) and azithromycin (13 %) [29] as well as a decreased susceptibility to cefixime; an upward trend in the minimum inhibitory concentrations of ceftriaxone has been reported.

5.2.3 Gonorrhoea: Clinical Aspects

In men N. gonorrhoeae mainly infects columnar epithelial cells of the urethra, rectum and pharynx. It most frequently presents as a symptomatic urethritis but it may remain asymptomatic in 10 % of the patients [30]. Gonococcal urethritis occurs after an incubation period of 2–6 days with an abundant purulent urethral discharge (Fig. 5.2).

Patients may report dysuria and painful oedema of the Littre and Tyson glands. If left untreated, the infection can ascend, involving the posterior urethra. Prostatitis, fundibulitis and epididymitis can also occur. Gonococcal proctitis presents with mucopurulent rectal discharge, local pain and tenesmus. It appears mainly following anoreceptive intercourse and increases the risk of HIV infection [31]. Gonococcal pharyngitis is frequently asymptomatic.

Gonorrhoea in women remains asymptomatic in up to 50 % of the cases [30]. The main site of infection is the cervix. Symptomatic gonococcal cervicitis is characterized by mucopurulent and sanguineous discharge and a vaginal burning sensation. Local complications include infection of Bartholin and Skene glands observed as painful swollen nodules. Ascending infection can lead to complications such as pelvic inflammatory disease and perihepatitis (Fitz-Hugh-Curtis syndrome). The pelvic inflammatory disease is increasing the risk for ectopic pregnancy and infertility [8]. Gonococcal urethritis in women can produce dysuria and a mucopurulent discharge. Rectal gonorrhoea evolves as an asymptomatic condition or it can present as proctitis (rectal discharge, pain, tenesmus). The infection of the rectum can occur both by autoinoculation from vaginal secretions and by direct contact. Gonococcal pharyngitis is frequently asymptomatic and constitutes an important source of contamination by unprotected orogenital contact.

Disseminated gonococcal infection is rare (1–3 %) in both men and women [32] and develops as the triad of dermatitis (few haemorrhagic or necrotic vesicles in acral regions), polyarthritis (migratory, painful – Fig. 5.3) and tenosynovitis.

5.2.4 Diagnostic Tests for N. gonorrhoeae

The presence of *N. gonorrhoeae* can be demonstrated in specimens from the affected anatomic sites (e.g. vagina, urethra) or in urine.

Fig. 5.2 Gonococcal urethritis

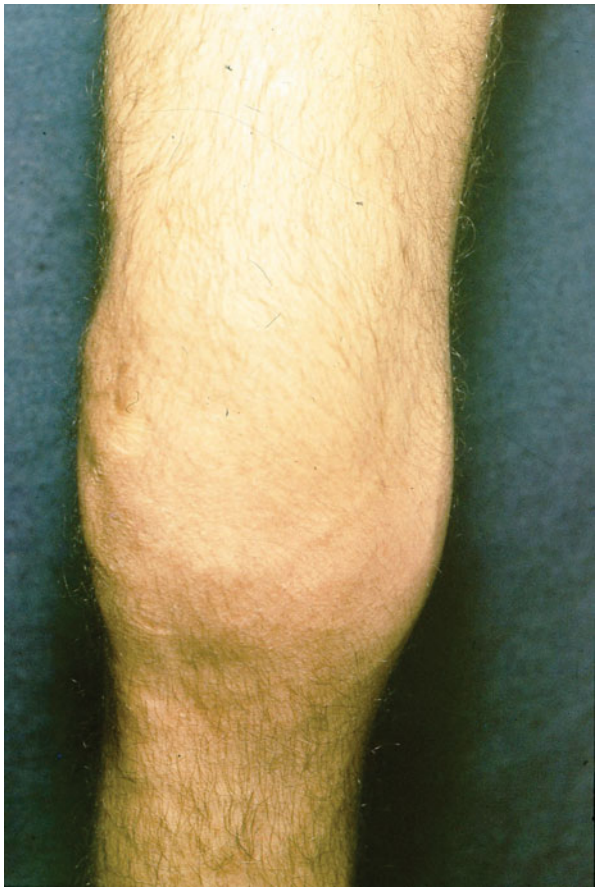

Fig. 5.3 Gonococcal arthritis

Gram staining and light microscopy are cheap and rapid techniques to identify *N. gonorrhoeae* as Gram-negative diplococci inside polymorphonuclear cells (Fig. 5.4). However Gram staining is not recommended for asymptomatic patients and for diagnosing gonorrhoea in women.

Culture on modified Thayer-Martin agar in a CO_2-enriched environment is used for *N. gonorrhoeae* identification and for testing antibiotic susceptibility. Cultures are performed on swab specimens from the urethral, rectal or pharyngeal areas. A prerequisite for successful culture is the rapid processing of the clinical sample.

Nucleic acid amplification tests (NAATs) for *N. gonorrhoeae* are more rapid and sensitive than cultures [33], but they have a downside in that they cannot be used for the determination of antibiotic susceptibility.

5.2.5 Gonorrhoea: Treatment

Guidelines for gonorrhoea treatment have to be challenged frequently because of the ability of *N. gonorrhoeae* to develop antibiotic resistance. Ceftriaxone has been

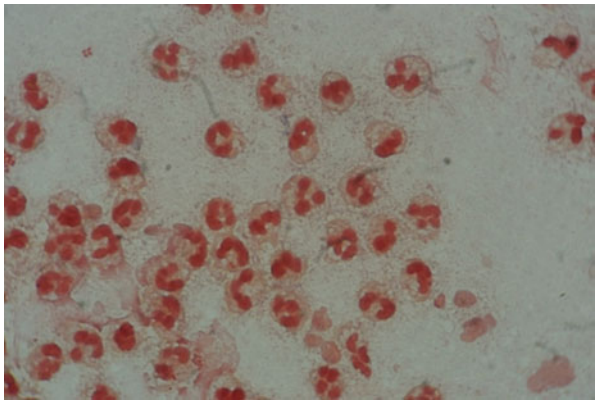

Fig. 5.4 Gram stain of male urethral specimen showing the presence of gram-negative diplococci – 90× oil immersion

the drug of choice for the treatment of gonococcal infection for more than one decade; however, recent studies have revealed that strains of *N. gonorrhoeae* that are also resistant to this antibiotic have been detected in Japan [34], France [35] and Sweden [36]. Other reports have shown a decreasing susceptibility of *N. gonorrhoeae* to ceftriaxone [29]. Therefore recent changes have been added to most treatment guidelines for gonococcal infections [20, 37]. Cefixime [38, 39], azithromycin [39], tetracycline [40] and fluoroquinolones [40] are no longer recommended for anti-gonococcal monotherapy.

The recommendation for treatment of uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx is currently **ceftriaxone** 500 mg intramuscularly (single dose) + **azithromycin** 2 g p.o. (single dose). It should be noted that this regimen has been recommended by IUSTI-Europe in 2012 [37] with double the doses recommended in the CDC STD Treatment Guidelines 2010 [20] due to updated information on antibiotic susceptibility of *N. gonorrhoeae*. **Doxycycline** 100 mg × 2/day p.o., 7 days, may be given as a combination treatment partner to ceftriaxone in proctitis instead of azithromycin [40] or it can be a substitute for azithromycin in other localizations of gonococcal infection (Table 5.1). If ceftriaxone is not available, **cefixime** 400 mg p.o. (single dose) might still represent a suitable alternative [37]. Other cephalosporins do not provide higher efficacy; therefore they cannot be recommended [41]. If allergy to cephalosporins is suspected or if gonococcal resistance to cephalosporin is thought likely, ceftriaxone may be replaced with **spectinomycin** 2 g intramuscularly (single dose) [37].

Ceftriaxone may interact with other drugs used concomitantly by the patient: with aminoglycosides it may increase the risk of nephrotoxicity and ototoxicity; with warfarin it may increase the anticoagulation effect; with diuretics it may induce nephrotoxicity.

Epididymitis in the course of gonorrhoea should include a treatment also effective for *C. trachomatis* since these two infections frequently occur concomitantly. Therefore the combination of **ceftriaxone** 500 mg intramuscularly (single dose) + **doxycycline** 100 mg × 2/day p.o., 10 days, is recommended (Table 5.1).

Infections of the *urethra*, *cervix*, *rectum and pharynx* with extended-spectrum cephalosporin-resistant *N. gonorrhoeae* should be treated with the combination of

ceftriaxone 1 g intramuscularly (single dose) + **azithromycin** 2 g p.o. (single dose). **Gentamicin** 240 mg intramuscularly (single dose) can replace ceftriaxone if therapy is needed in cases of relapse but it is important to be aware of the increased risk for nephrotoxicity.

In patients with *pelvic inflammatory disease,* an empiric broad-spectrum antibiotic therapy is recommended: **ceftriaxone** 500 mg intramuscularly (single dose) + **doxycycline** 100 mg × 2/day p.o., 14 days, + **metronidazole** 400 mg × 2/day p.o., 14 days [42].

Patients with *disseminated gonococcal infection* should be treated in hospital settings under close monitoring with **ceftriaxone** 1 g/day given intramuscularly or intravenously or **spectinomycin** 2 g × 2/day, intramuscularly. After 1 week **cefixime** or **fluoroquinolone** may be introduced (if appropriate) [37] (Table 5.1).

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Chapter 6
Mycobacterial (Skin) Infections

Bernard Naafs, Colette L.M. van Hees, and Jakko van Ingen

6.1 Introduction

Mycobacterium is a genus of the Actinobacteria, belonging to family Mycobacteriaceae. The genus includes pathogens known to cause serious diseases, including tuberculosis (*Mycobacterium tuberculosis*), leprosy (*Mycobacterium leprae*), and Buruli ulcer (*Mycobacterium ulcerans*).

Mycobacteria can be divided into those which are strict pathogens for humans and animals and those which are potentially pathogenic. The first group includes *M. tuberculosis* and *M. leprae*, and the second group comprises the nontuberculous mycobacteria of which *M. marinum* is the most common cause of skin disease (aquarium granuloma) and of which *M. ulcerans* may be considered a specific subgroup [1, 2].

The Greek prefix "myco" means fungus, since mycobacteria have been observed to grow in a mold-like fashion on the surface of liquids when cultured [3]. They are

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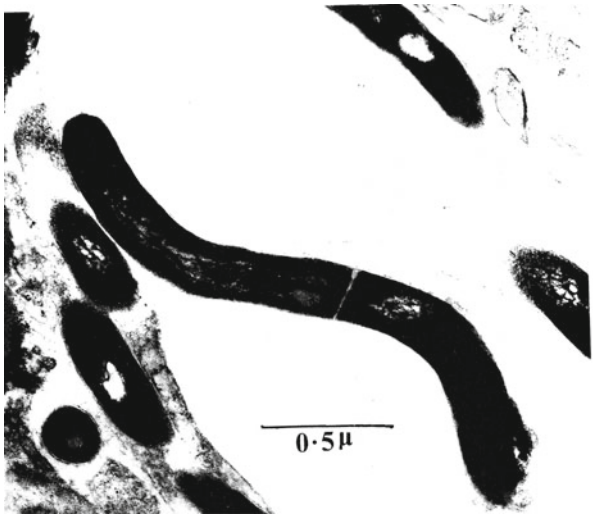

Fig. 6.1 Electron microscopic picture of mycobacteria in macrophage. One dividing bacterium. (Courtesy Dr. John Stanley)

thin, slightly curved to straight nonmotile bacilli, except for *Mycobacterium marinum*, which has been shown to be motile within macrophages. They are between 0.2 and 0.6 μm wide and 1.0 and 10 μm long (Fig. 6.1).

Mycobacteria are aerobic and are characteristically acid-alcohol-fast. Mycobacteria do not contain endospores or capsules and are usually considered Gram neutral. They stain very weakly Gram-positive or not at all (cells referred to as "ghosts") [4]. All *Mycobacterium* species share a characteristic cell wall, thicker than in most other bacteria, which is hydrophobic, waxy, and rich in mycolic acids/mycolates. The cell wall consists of a hydrophobic mycolate layer and a peptidoglycan layer held together by a polysaccharide, arabinogalactan. The cell wall makes a substantial contribution to the hardiness of this genus. The biosynthetic pathways of cell wall components are potential targets for drugs [5].

6.2 Clinical Features and Immunology of Mycobacterial Infections in General [6]

Skin infections caused by mycobacteria usually present as nodules which commonly show crusting, though ulcers and hypo- and hyperpigmentation may be seen. They may be single or multiple due to multiple inoculates or lymphatic spread; nodular lymphangitis is a well-known feature, even in the immunocompetent. In light-skinned people, granulomatous inflammation can be recognized by its so-called apple sauce appearance on diascopy. The clinical appearance does not reveal the causative microorganism; a causative microorganism may not be detected.

Mycobacteria responsible for most cutaneous disease are *M. marinum*, *M. ulcerans*, *M. fortuitum*, *M. chelonae*, *M. avium-intracellulare*, *M. leprae*, and *M. tuberculosis. M. leprae* infects the skin, nerve, and sometimes internal organs. *M. tuberculosis* usually causes internal disease, but skin manifestations may be present. More rarely skin infections are caused by *M. scrofulaceum*, *M. szulgai*, *M. kansasii*, or *M. haemophilum* [6].

Cutaneous mycobacterial disease occurs [6]:

- By inoculation (traumatic or iatrogenic)
- Contiguous with an underlying osteomyelitis or lymphadenitis
- As a manifestation of disseminated disease, which may be acquired through inhalation, ingestion, or trauma

As mycobacteria are intracellular microorganisms, the immunological response of the host is a cell-mediated immune (CMI) reaction, usually resulting in a granulomatous tissue reaction. Immune suppression in HIV-infected patients has caused an increase in the number of mycobacterial skin infections, besides TB, in particular of infections with the *Mycobacterium avium complex*. Antitumor necrosis factor-alpha inhibitors and other immunosuppressive drug treatments have also led to an increase of mycobacterial infections. Another group prone to infection are those with acquired or inherited immune deficiencies (severe combined immunodeficiency (SCID)), such as changes in the interferon-γ receptor 1 (IFN-gR1) and IL-12 receptor. As the interferon-γ and IL-12 pathways are crucial in the development of a CMI response to intracellular microorganisms, widespread involvement can be found [7, 8]. In the Mayo clinics over 30 years, the infections with nontuberculous mycobacteria (NTM) increased threefold [9].

Patients with intrinsic innate immunity against mycobacteria are protected [10]. Here, toll-like receptors play an important role [11]. The involvement of IL-10, Th17, and Tregs in the resulting inflammatory reaction is in discussion [12, 13].

6.3 How Are Mycobacterial Infections Diagnosed? (Table 6.1)

The most important issue is to have a high index of suspicion. One must suspect the possibility of a mycobacterial infection and recognize granulomatous processes. Sometimes there is only crusting but a prolonged history. Histopathology often directs the suspicion. Culture is still the golden standard but may be negative if not prompted by request: Many mycobacteria grow at lower than standard temperatures and often only on selected media. If not specifically requested, no growth will be the result. *M. leprae* cannot be cultured. PCR may be helpful but is regularly negative and may be positive while nonpathogenic. In some cases only clinical suspicion and the response to therapy “confirm” the diagnosis.

Table 6.1 Diagnostic tools in cutaneous mycobacterial infection

1. Clinical suspicion	Ulcerating macules, nodules, or plaques
	Longstanding
	Not particularly painful
	Non-painful lymph node involvement
	History of water contact, travel, trauma, immunosuppressed patient
	Unresponsive to treatment for other conditions, immuno
	Granulomatous aspect
	In leprosy nerve involvement
	In TB systemic disease
	In TB and leprosy contacts
2. Smear or fine needle aspiration for AFB	Ziehl-Neelsen, auramine
3. Biopsy	Histology, AFB (Ziehl-Neelsen, auramine)
4. PCR	Very variable sensitivity and specificity
	Phenotypic susceptibility testing sometimes possible
5. Culture	Appropriate incubation temperature (at 30–32 °C) and media
6. Tuberculin skin test	Latent infection, cross-reactivity
7. Interferon gamma release assays	Latent infection, cross-reactivity (TB, leprosy, several NTM)
8. Response to treatment	

6.3.1 Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. caprae*, *M. microti*, *M. pinnipedii*, *M. orygis*, *M. canettii*, and *M. bovis BCG*), which are acid-fast in the Ziehl-Neelsen stain. They are aerobic (microaerophilic), unencapsulated, and 1–8 μm long by 0.3–0.6 μm wide and do not produce spores or toxins. The reproduction is strictly subject to oxygen pressure; therefore, unlimited *M. tuberculosis* multiplication is observed in the tuberculous cavities, while the multiplication under low oxygen pressure, e.g., in caseous lesions, is reduced [14]. TB is one of the world's deadliest diseases: One third of the world's population is infected with TB. In 2011, nearly nine million people worldwide contracted disease caused by *M. tuberculosis*. Most of these (82 %) live in 1 of 22 high burden countries. TB is a leading killer of people living with HIV [15].

Cutaneous TB was first documented in 1826, when Laennec reported his own "prosector's wart," a lesion that likely represented tuberculosis verrucosa cutis, a variant of TB that results from direct entry of the organism into the skin [16]. However, the causative organism of TB was unknown until Robert Koch discovered

Mycobacterium tuberculosis in 1882. Subsequently, the bacillus was detected in cutaneous lesions [17].

Scrofuloderma and lupus vulgaris are the oldest forms of cutaneous tuberculosis described in the medical literature and were known as the king's evil [18, 19] (see Box 6.1).

Box 6.1: King's Evil
King's evil: Scrofula, or struma, a tuberculous swelling of the lymph glands, once popularly supposed to be curable by the touch of royalty. The custom of touching was first adopted in England by Edward the Confessor and in France by Philip I. In England the practice was attended with great ceremony; and from the time of Henry VII, sufferers were presented with especially touched coins to be worn as amulets or charms. The custom reached its zenith during the Restoration: Charles II is said to have touched more than 90,000 victims between 1660 and 1682. The last royal healer in England was Queen Anne, who touched 200 victims in 1712. In France the ceremony persisted for another century and was even briefly revived by Charles X between 1824 and 1830 (*Encyclopedia Britannica*).
http://www.britannica.com/EBchecked/topic/318668/kings-evil

The range of clinical manifestations of cutaneous tuberculosis provides an example of the varying immune response of the host toward infection with mycobacteria, which is also dependent on previous exposure to other mycobacteria and the route of infection [20, 21].

M. tuberculosis, *M. bovis*, and *M. Bacille Calmette-Guérin* may cause "tuberculosis" involving the skin. Cutaneous tuberculosis can be acquired exogenously or endogenously and present as a multitude of differing clinical morphologies. Cutaneous tuberculosis has become a rare disease in the western hemisphere. The majority of cutaneous tuberculosis cases will be diagnosed in immigrants [6].

6.4 Diagnosis

The clinical diagnosis can be confirmed by smear, biopsy, culture, and/or PCR (Table 6.1). A polymerase chain reaction (PCR) assay has been validated for detecting *M. tuberculosis* and rifampicin resistance in microscopy-negative samples, especially in HIV-infected and drug-resistant tuberculosis (DR-TB) suspects; and a molecular line probe assay has been validated for detecting DR-TB in microscopy-positive samples and culture isolates in DR-TB suspects [22, 23].

6.5 Clinical Manifestations

Cutaneous tuberculosis can be classified according to four categories [6, 24]:

I. Primary infection (in tuberculin-negative persons)
II. Secondary infection (in tuberculin-positive persons)
    A. Exogenous inoculation
    B. Endogenous inoculation by contiguous spread
    C. Endogenous inoculation by hematogenous route
III. Bacille Calmette-Guérin (BCG), *M. bovis* infection
IV. Immunological reactions ("tuberculids")

6.5.1 Primary Infection: Tuberculous Chancre

The lesion starts 2–4 weeks after inoculation, with a smooth papule or nodule which enlarges in the course of several weeks to a plaque which subsequently ulcerates. The ulcer has undermined edges and is painless. Non-tender lymphadenopathy may ensue producing a clinical picture of a lymphocutaneous complex analogous to the Ghon complex seen in the pulmonary infection. This process generally heals spontaneously with atrophic scarring in 3–12 months.

Differential diagnosis: Other causes of ulceration, other mycobacteria (e.g., Buruli), and other chronic conditions like subcutaneous mycoses, cutaneous leishmaniasis, and malignancies. It includes also infections which show sporotrichoid spread, for example, sporotrichosis, cat scratch disease, and tularemia.

6.5.2 Secondary Infection

Secondary infection comprises the vast majority of all cases of cutaneous tuberculosis.

6.5.2.1 Warty Tuberculosis: Tuberculosis Verrucosa Cutis

Warty tuberculosis, known as tuberculosis verrucosa cutis, is the most common type of skin tuberculosis in the East, particularly India [25]. Due to a rapid cell-mediated response, the infection remains localized, and regional lymphadenopathy is not prominent.

The lesion develops from an asymptomatic reddish-brown papule into a verrucous plaque of varying shapes and sizes. The verrucous fissures may become superinfected (Fig. 6.2). The plaque may heal spontaneously in the course of months to years, with atrophic scarring and activity in different parts of the same lesion [26].

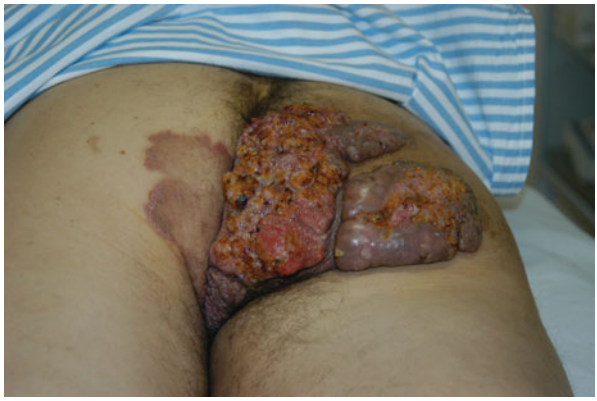

Fig. 6.2 Warty tuberculosis in a 46-year-old man (Courtesy ILSL, Bauru, Brazil)

An identical lesion may be seen among cattle workers. Here the species involved is most commonly *M. bovis*.

Differential diagnosis: Common warts during the initial stage, later hypertrophic lichen planus, and verrucous lesions caused by NTM or by deep mycoses like blastomycosis, sporotrichosis, chromomycosis, lobomycosis, some forms of leishmaniasis, verrucous rupial tertiary syphilis, rupioid psoriasis, and squamous cell carcinoma.

6.5.2.2 Scrofuloderma: Tuberculosis Cutis Colliquativa

Scrofuloderma is the result of contiguous spread from an underlying mycobacterial infection, commonly in lymph nodes or in some cases the bone. It is the most common cause of cervical lymphadenitis in children. Due to suppuration fluctuating nodules develop, which ulcerate. In the course of time, cordlike scars develop. The lesions heal over years with a characteristic pattern of fibrosis, atrophy, and scarring. Recurrence of drainage is common (Fig. 6.3). Other mycobacteria now known to cause scrofuloderma are *M. scrofulaceum*, *M. haemophilum*, and *M. avium-intracellulare* complex, but it is also still seen with *M. tuberculosis*.

Differential diagnosis: Deep mycoses such as sporotrichosis or coccidioidomycosis but also actinomycosis, hidradenitis suppurativa in axillary lesions, granuloma inguinale and lymphogranuloma venereum in inguinal lesions, and chronic bacterial osteomyelitis when localized over the bone.

6.5.2.3 Orificial Tuberculosis: Ulcerative Tuberculosis in the Mucosa

This rare form of cutaneous TB starts with single or multiple nodules which become fluctuant and ulcerate showing draining sinuses. The cause is autoinoculation from active tuberculous foci affecting the mucosa or skin near the oral, genital, or anal orifices. Pain is a cardinal feature [6].

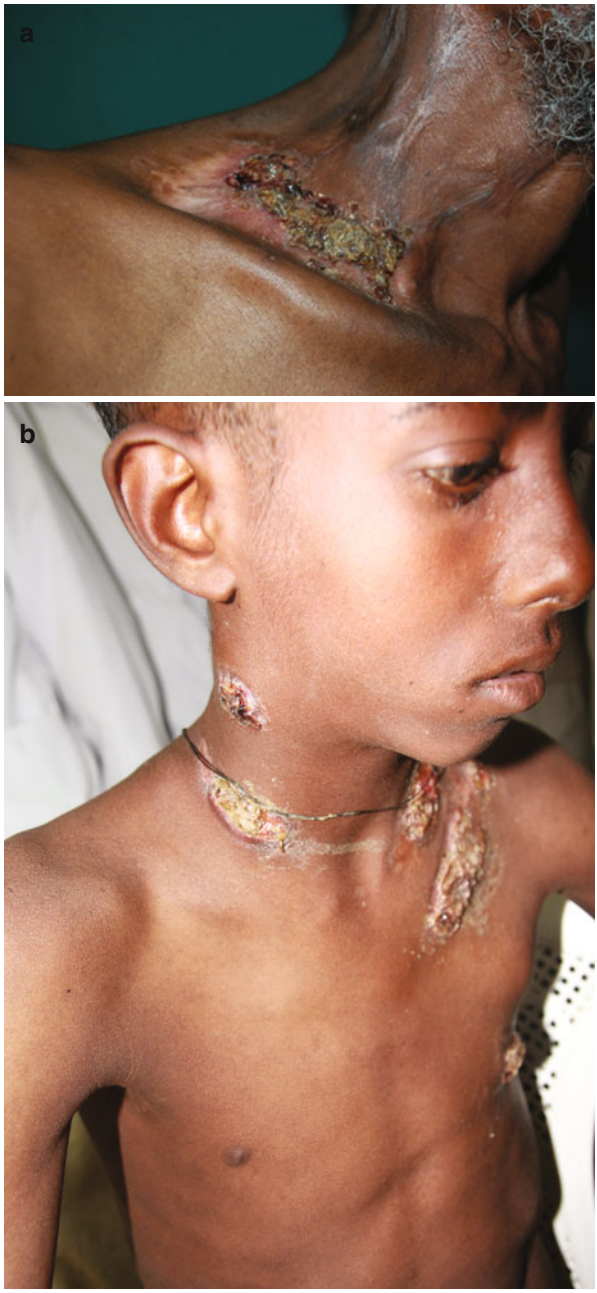

Fig. 6.3 (**a**) Scrofuloderma by *M. tuberculosis* (Courtesy of Dr. Dassoni, Ayder Hospital, Mekelle, Ethiopia). (**b**) Scrofuloderma in a 12-year-old boy. Regional Dermatology Training Center (RDTC), Moshi, Tanzania. The diagnosis was clinically made, but one of the NTM's is possible as cause as well. (Determination was not possible at that time in these institutions)

The primary foci of tuberculosis are the lungs, gastrointestinal tract, and/or genitourinary tract. The affected patient is usually in poor health with long-standing advanced tuberculosis involving multiple internal organs [27].

Differential diagnosis: Leishmaniasis, aphthous ulcers, dental and perianal abscesses, M. Crohn, paracoccidioidomycosis, malignancies, herpes simplex lesions, or ulcerating venereal disease. Painful anal ulcerations may also be seen in cutaneous amebiasis.

6.5.2.4 Lupus Vulgaris

Lupus vulgaris was a common disease in the early twentieth century. Today it is rare in the West and it also occurs less frequently in developing countries. It is due to reactivation of a mycobacterial infection in patients with a moderate to high degree of CMI, hence paucibacillary "tuberculosis."

Reactivation usually stems from cervical adenitis or pulmonary tuberculosis but sometimes from an old, apparently quiescent primary complex. Rarely, it follows primary inoculation or BCG vaccination. Lupus vulgaris lesions have been described around warty tuberculosis and scrofuloderma.

Classic lesions start as brown-red papules which extend to plaques with active, irregular borders and central healing with atrophic, depigmented scarring (Fig. 6.4). Spontaneous involution may occur and new lesions may arise within old scars. Complete healing rarely occurs without treatment. Squamous cell carcinoma may develop in these chronic lupus vulgaris lesions.

Differential diagnosis: Lupoid and recidivans variant of cutaneous leishmaniasis, subcutaneous mycoses, sarcoidosis, chronic discoid lupus erythematosus, and basal cell carcinoma.

6.5.2.5 Tuberculous Gumma: Metastatic Tuberculous Ulcer

The gumma is due to hematogenous dissemination from a primary focus, during periods of decreased immunity. A subcutaneous nodule or fluctuant swelling results in an undermined ulcer with sinus formation, also known as a "metastatic tuberculous abscess" or "metastatic tuberculous ulcer" which may resemble scrofuloderma. It is histologically characterized by massive necrosis [28]. Some of these patients may have an underlying malignancy (lymphoma) [29, 30].

Differential diagnosis: Cold abscess, scrofuloderma, tertiary syphilitic gumma, subcutaneous mycoses, and cutaneous leishmaniasis.

6.5.2.6 Acute Miliary Tuberculosis: Tuberculosis Cutis Miliaris Disseminata

Miliary tuberculosis is the result of hematogenous dissemination of *M. tuberculosis* to the skin and other organs in the absence of CMI reactivity against *M. tuberculosis* antigens. It shows a generalized eruption of small purplish macules and papules (1–5 mm), with vesicles on top which may break, forming crusts. Due to the absence

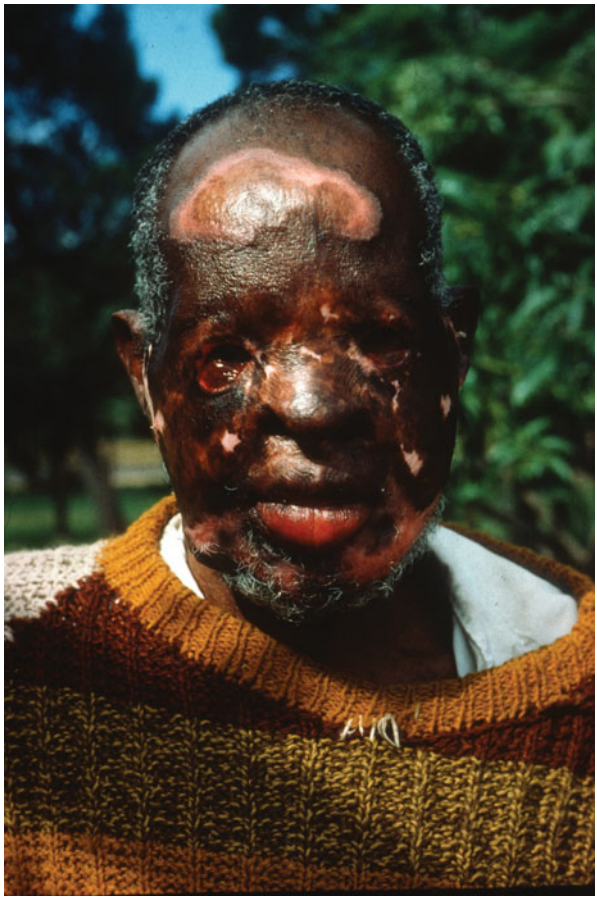

Fig. 6.4 Lupus vulgaris in a 50-year-old Zimbabwean trader

of CMI reactivity, the histopathological picture is that of a nonspecific inflammation with numerous acid-fast bacilli [6, 28]. A patient with miliary tuberculosis usually presents with nonspecific signs, such as low-grade fever, cough, and enlarged lymph nodes, and there may be an enlarged liver, enlarged spleen, inflammation of the pancreas, and multiple organ dysfunction with adrenal insufficiency [31].

Differential diagnosis: The skin eruption is nonspecific, but the patient is ill [6].

*6.5.3 BCG (*M. bovis*, BCG Inoculation)*

BCG vaccination, with an attenuated strain of *M. bovis*, is practiced in many areas of the world. The vaccination provokes a CMI reaction in susceptible persons. This is clinically observed as an infiltrated papule which develops in 10–14 days at the site of inoculation. It enlarges into an ulcerative lesion of approximately 1 cm at

10–12 weeks. It heals which scarring. After approximately 3 months, the tuberculin skin test reverses from negative to positive, except in people with an inherited protective innate immunity. Its protective prophylactic effect varies from less than 10–80 % probably depending on the presence or absence of boosting by environmental microorganisms. But at least it protects against tuberculous meningitis in infants [32].

6.5.4 Immunological Reactions to Tuberculosis Elsewhere: Tuberculids

Tuberculids are generally considered to be a CMI response to dissemination of *M. tuberculosis* or antigenic particles to the skin [33]. Papular necrotic tuberculids would represent the paucibacillary pole of blood-borne disseminated TB, as opposed to the multibacillary picture of acute miliary TB [24]. But because very often *M. tuberculosis* cannot be detected in the skin or elsewhere in the body, antigenic determinants of the host similar to those of *M. tuberculosis* may be the cause [34].

The following are nowadays accepted to be true tuberculids [6]:

1. *Papulonecrotic tuberculid*

   Papulonecrotic tuberculid occurs as crops of symmetric, small, inflammatory papules which have a predilection for acral and dorsal surfaces. Lesions may undergo central ulceration and heal spontaneously within weeks, leaving varioliform scars. Microscopically, a wedge-shaped area of necrosis is seen with underlying vasculitis and granulomatous infiltrate [35]. They may heal with antituberculous treatment but may also resolve spontaneously with a depressed scar with a hyperpigmented border. Some noticed phlyctenular conjunctivitis in children [36].

   The tuberculous etiology is suggested by a positive tuberculin skin test, the demonstration of *M. tuberculosis* DNA in the lesions, and prompt resolution of the condition on antituberculous treatment.

   Differential diagnosis: Prurigo papules, folliculitis, and papular lesions of syphilis. Necrotic lesions should be differentiated from pityriasis lichenoides acuta, necrotizing vasculitis, necrotic insect bite reactions, and self-inflicted injury.
2. *Lichen scrofulosorum*

   Lichen scrofulosorum, also known as "tuberculosis cutis lichenoides," is a rare tuberculid that presents as a lichenoid eruption of minute papules in children and adolescents. The lesions are usually asymptomatic, closely grouped, skin-colored to reddish-brown papules, are often perifollicular, and are mainly found on the trunk (abdomen, chest, back) and proximal parts of the limbs. The eruption is usually associated with a strongly positive tuberculin reaction [37]. PCR has also demonstrated the presence of *M. tuberculosis* DNA in lesions [38].

   Differential diagnosis: Lichen planus, lichenoid drug eruptions, secondary syphilis, and pityriasis lichenoides chronica. Due to the perifollicular distribution

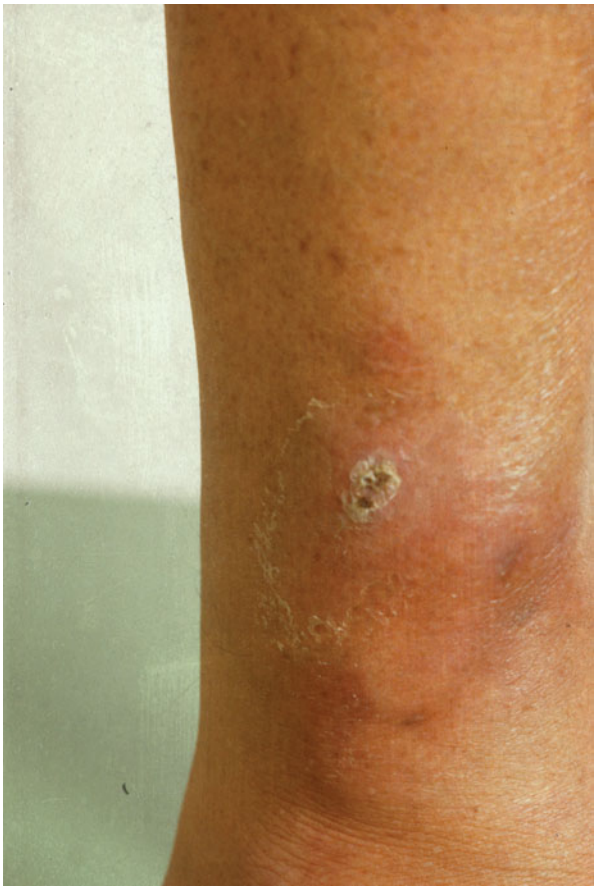

Fig. 6.5 Erythema induratum of Bazin in a 65-year-old Dutch nurse

also keratosis pilaris, lichen nitidus, lichen spinulosus, and pityrosporum folliculitis. Differentiation from the micronodular form of sarcoidosis may be clinically and histopathologically difficult [39].

3. *Nodular vasculitis* (erythema induratum of Bazin)

   Erythema induratum, described by Bazin in 1855, has been considered to be associated with tuberculosis [40, 41]. It can however be induced by numerous triggers including tuberculosis [42]. Erythema induratum presents during early adolescence and perimenopause as recurrent subcutaneous poorly defined erythematous plaques and tender violaceous nodules, sometimes ulcerating, on the calf of the legs of otherwise healthy, often heavy-set, women [43] (Fig. 6.5). At present it is the most prevalent tuberculid in the West. The histopathological picture is that of a nodular vasculitis. *M. tuberculosis* DNA has been demonstrated in lesional biopsies.

   Differential diagnosis: Erythema nodosum, cutaneous polyarteritis nodosa, pancreatic panniculitis, lupus profundus, subcutaneous sarcoid, and cutaneous T-cell lymphoma.

4. *Erythema nodosum*

   Erythema nodosum was frequently associated with tuberculosis in the past, while today it is most frequently caused by streptococcal infections, sarcoidosis, drug reactions, and inflammatory bowel disease. But tuberculosis still should be considered in patients from developing countries.

   Painful erythematous nodules present on the lower legs, especially on the shins. Sometimes the extensor sides of the arms are involved. The histopathological picture is a panniculitis with vessel involvement.

   Differential diagnosis: Panniculitis, polyarteritis nodosa, erythema induratum, nodular lymphangitis, and erythema nodosum leprosum.

6.6 Treatment of Tuberculosis

The first "treatments" of tuberculosis consisted of nutritious food, rest, and "pure" air. TB sanatoria were established from the middle of the nineteenth century onward, and their numbers grew in the early twentieth century. In 1903, Niels Ryberg Finsen was awarded the Nobel Prize for his invention of radiation therapy for skin tuberculosis (lupus vulgaris) [44].

The history of currently used antituberculosis drugs goes back to 1943, when Waksman with his research team from the Rutgers University isolated streptomycin from the actinomycete *Streptomyces griseus*. Streptomycin turned out to be the first drug that decreased mortality due to tuberculosis [45]. The next, not less important step was introduction of para-aminosalicylic acid (PAS) and isoniazid (INH) in the early 1950s – drugs that, similarly to streptomycin, significantly reduced mortality from tuberculosis.

However, drug resistance soon developed to single agents [46]. The synthesis of pyrazinamide [47] in the 1950s and ethambutol in 1962 [48] brought drugs that are used in antituberculosis therapy to this day [49]. At the same time, ethionamide, prothionamide, cycloserine, and thiacetazone were discovered.

Most important in the development of antituberculosis medications was the discovery of the soil bacterium: *Streptomyces mediterranei* in 1959, from which rifamycin was isolated [50]. During further studies, a semisynthetic derivative of the rifamycin antibiotic was synthesized – rifampicin (RMP). This was permanently included in the standard treatment of tuberculosis and many other mycobacterial infections.

Together with the discovery of rifampicin, the increasing problem of drug resistance was observed [51]. Multidrug (MD) treatment was the best way to avoid this. Unfortunately at present MD-resistant (MDR) TB is becoming a huge problem [52]. To date there is even extensively drug-resistant tuberculosis (XDR-TB), which is defined as resistance to at least RMP and INH (the definition of multidrug-resistant tuberculosis (MDR-TB)), in addition to resistance to any fluoroquinolone, and at least one of the three injectable antituberculosis (TB) drugs capreomycin, kanamycin, and amikacin [53]. Inadequate treatment of MDR-TB inevitably results

in high mortality and the development of XDR-TB [54]. About 3.7 % of new tuberculosis (TB) patients in the world have multidrug-resistant strains (MDR-TB). Levels are much higher in those previously treated – about 20 %. The frequency of MDR-TB varies substantially between countries. About 9 % of MDR-TB cases also have resistance to two other classes of drugs or extensively drug-resistant TB (XDR-TB). By March 2013, 84 countries had reported at least one XDR-TB case [55, 56]. TB treatment should be instilled according to local regional or national guidelines. Pulmonary TB is treated using a 6-month course of a combination of antibiotics. The usual course of treatment is two antibiotics (isoniazid and rifampicin) every day for 6 months and two additional antibiotics – pyrazinamide and ethambutol – every day for the first 2 months [57, 58].

Extrapulmonary TB, e.g., cutaneous TB, can be treated using the same combination of antibiotics. However, the treatment may take longer, 12 months.

The US recommendation is 2HREZ/7HR [59]. However, there is good evidence from randomized controlled trials that in tuberculous lymphadenitis [60] and in TB of the spine [61], a 6-month regimen is equivalent to the 9-month regimen.

6.6.1 Leprosy [62]

Leprosy, or Hansen's disease, is a chronic infection caused by *Mycobacterium leprae*. Leprosy takes its name from the Greek words "lepros," a scale, and "lepein," to peel, while the term "Hansen's disease" is named after the physician Gerhard Armauer Hansen who discovered the bacillus in 1873 [63]. It was the first bacterium assigned as a cause to a human disease. This being said, Koch's postulates are not established in leprosy as *M. leprae* cannot be cultured in vitro, and it has not been possible to infect someone willfully with leprosy, although there are some reports of leprosy following trauma or tattooing [64].

It is primarily a disease of peripheral nerves, the skin, and the mucosa, in particular the upper respiratory tract. Skin lesions are usually the first sign noticed. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes. Tissue damage may be caused by primary infiltration by *M. leprae* [65], but most of the damage is secondary to immunological phenomena: reactions [66]. Secondary infections can result in tissue loss causing fingers, toes, and nose to become shortened and deformed, as the bone and cartilage are absorbed.

Frequently leprosy is not in the differential diagnosis, since this subject is often not emphasized in medical curricula. Attention shifted from leprosy to TB and HIV infection in the late twentieth century, and the WHO leprosy program was toned down in the conviction that leprosy was all but eliminated. In 2005 WHO stated that leprosy was eliminated as a worldwide public health problem. Unfortunately this is not the case [67]. To this day worldwide incidence since 4 years remains stable at about 250,000 new patients annually, while the prevalence has also stopped decreasing. Often children are affected and new cases

present late, with permanent disabilities [68]. Due to increased travel, patients are diagnosed everywhere in the Western world, unfortunately often after long doctors' delay. But even in leprosy endemic areas, the diagnosis is often delayed, because leprosy was not in the differential diagnosis [69]. Dermatologists and neurologists are generally poorly trained in leprosy.

6.6.1.1 Diagnosis

Patients may complain of loss of sensation in skin lesions or of their hand or foot. They may have aches and pains in the face or limbs or describe a numb, sleepy, or dead feeling or sensations like "ants running under their skin" in the affected areas.

Skin lesions are usually hypopigmented or erythematous macules or papules and nodules and plaques which are skin colored or slightly red.

Most important for the diagnosis is awareness. Clinically, leprosy is diagnosed when the patient shows two out of three cardinal signs [70]. In endemic countries, one cardinal sign is considered enough [71].

The three cardinal signs of leprosy are:

1. Loss of sensation in a skin lesion
2. Enlarged peripheral nerve
3. Positive skin smears

Loss of sensation is tested with a wisp of cotton wool. The area in the lesion is tested by touch. With closed eyes the patient points to where he is touched. To make sure, the area outside the lesion is tested as well (Fig. 6.6).

Enlarged nerves can be cutaneous nerves, subcutaneous nerves in the vicinity of skin patches, or nerve trunks. At least the posterior auricular nerves, the ulnar, the radiocutaneus, the median, the lateral popliteal, and the tibial posterior nerves should be palpated. Nerve thickness, consistency, and tenderness should be appreciated (Fig. 6.7). Ultrasound is a good alternative [72].

Smears are taken to detect acid-fast bacilli from the earlobes and other cooler areas and from the rim of the lesion in paucibacillary (PB) and central in the lesion in multibacillary (MB) patients. The smear is taken while squeezing the skin, to numb and to diminish the bleeding while incising into the dermis. Only tissue fluid is required. The number of bacilli is counted and graded along a logarithmic scale (BI, bacillary index), and the percentage of solid bacteria, live (viable) bacilli, is estimated (MI, morphological index) [68]. It is important to decolorize shortly with 1 % hydrochloric acid in isopropyl alcohol (as in Fite stain), as opposed to the 3 % solution used for TB, because *M. leprae* is less acid-fast than *M. tuberculosis*. Using the common Ziehl-Neelsen stain (3 % hydrochloric acid) may make the smear negative. Another way to detect bacilli is by PCR or NASBA, which, like the smear, is often negative in PB patients. Smears and molecular techniques can however be very useful in the diagnosis of MB leprosy, in follow-up, and in detection of relapses.

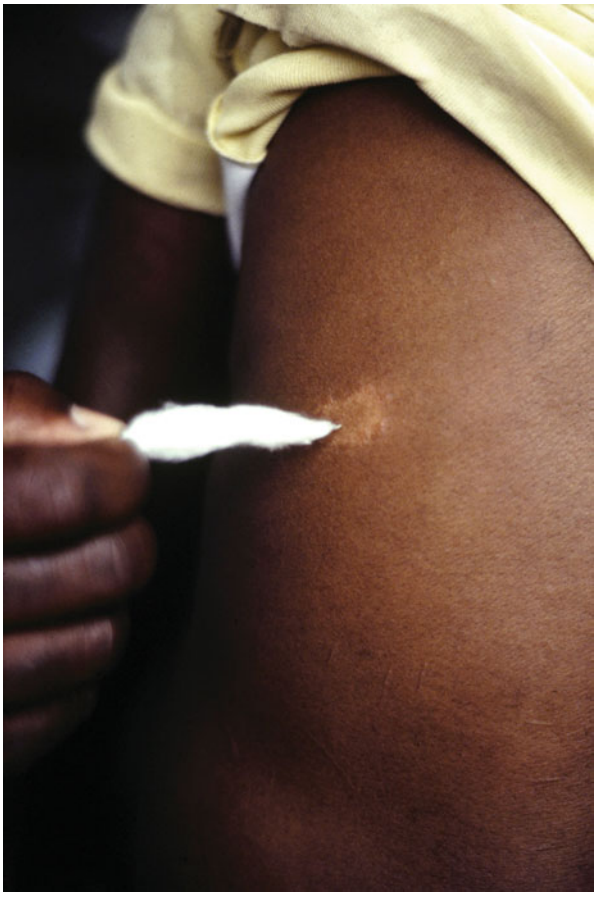

Fig. 6.6 Sensory testing in an 8-year-old Tanzanian boy at the Regional Dermatology Training Center (RDTC), Moshi, Tanzania

Other laboratory investigations are of some help in the diagnosis of leprosy, but none will be diagnostic in all cases. The antibody titer against phenolic glycolipid 1 (PGL-1), a cell wall species-specific glycolipid, is useful in MB leprosy. However, this can be positive in contacts and negative in PB leprosy. It helps to classify leprosy into PB and MB, and it can be used to follow the effect of treatment in MB patients and to detect relapses [73]. The value of the recently introduced "LID" is still not clear.

Lymphocyte transformation tests against different antigenic determinants have been a disappointment up to now. The lepromin test (Mitsuda), an old test, is positive in PB leprosy and negative in MB leprosy. But in healthy people, it can be positive and negative. Thus, it helps only with the classification. Because it is made from biological material, theoretically it may sensitize; therefore, many oppose its use [62].

Histopathology can be very helpful, as can immunopathology, but the latter is still experimental. A problem is that even within lesions, the histopathology of one spot may differ from the other [62].

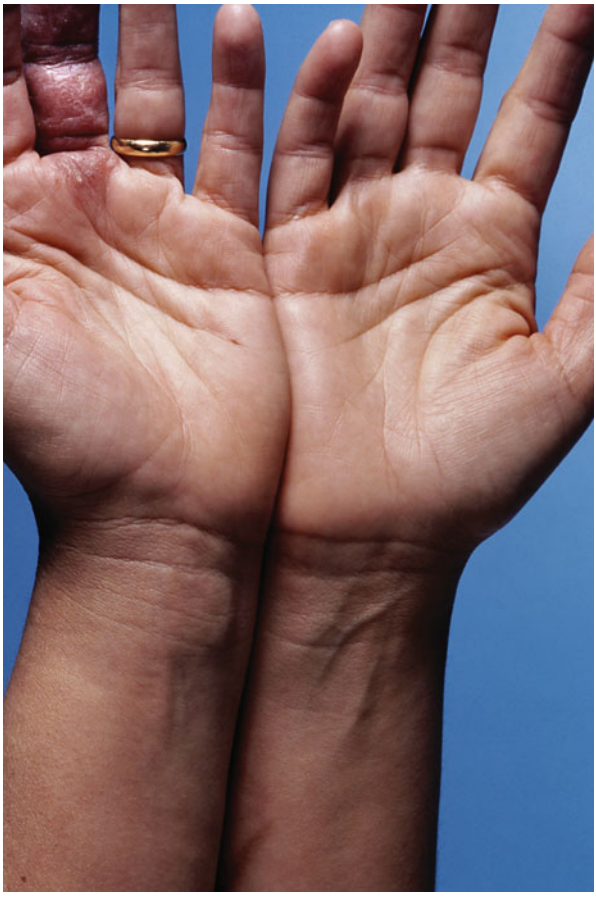

Fig. 6.7 Enlarged median nerve in a Brazilian patient who presented with swelling of the median nerve which was attributed to carpal tunnel syndrome. After unsuccessful surgical and moderately successful treatment with systemic steroids, she developed the skin lesion. Diagnosis: BT leprosy

6.6.1.2 Infection and Classification

Leprosy is highly infectious [74], but the attack rate is low. The major reason for this low attack rate is that most people are genetically unable to supply the mycobacteria in their cells with what they need to survive, because they lack the type of genes the bacterium needs [64, 75].

In order to predict complications and to stratify according to CMI, the Ridley-Jopling scale (Fig. 6.8) is important, with on one side of the spectrum polar tuberculoid (TT) (Fig. 6.9) leprosy with a single well-described lesion or an enlarged nerve and with no bacilli detectible and a high CMI against *M. leprae* antigenic determinants, and on the other side, polar lepromatous (LL) leprosy with nodules and/or plaques (Fig. 6.10), with symmetrically enlarged nerves or even only an infiltrated skin (lepra bonita), and with an absence of CMI against *M. leprae* antigenic determinants and many bacilli. Between the TT and LL leprosy is the borderline group, which comprises the majority of the patients: borderline tuberculoid (BT) (Fig. 6.11a, b) with

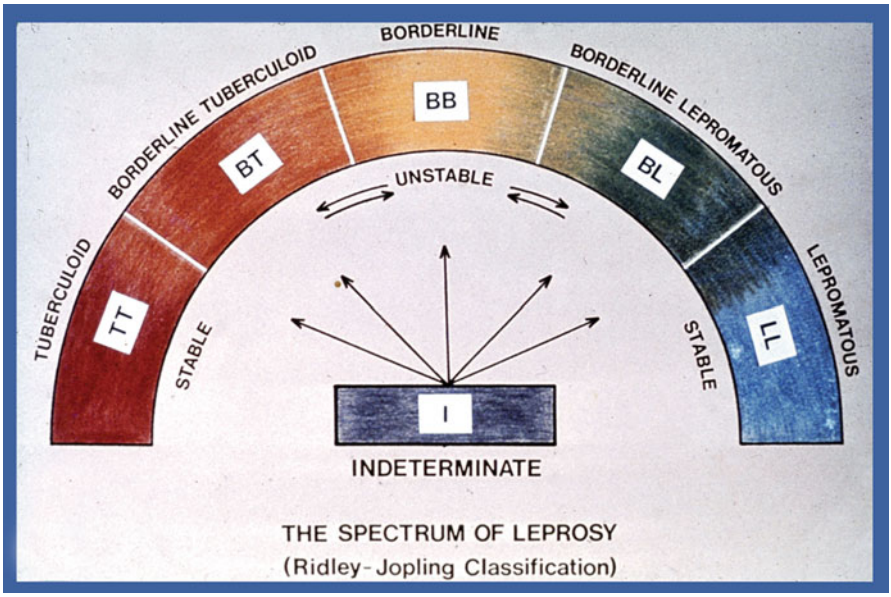

Fig. 6.8 Ridley-Jopling classification of leprosy (Courtesy of Dr. DL Leiker) [76]

predominantly tuberculoid features or borderline lepromatous (BL) (Fig. 6.12a, b) with predominantly lepromatous features. Between those two is a small group of mid-borderline (BB) (Fig. 6.13) patients with typical punched out or dome-shaped lesion [77].

Sometimes it is not possible to classify leprosy. The lesions in those cases are then clinically and histologically indeterminate.

The WHO classified leprosy into just two groups for practical purposes in the field (They count the number of lesions): five or less classified as paucibacillary leprosy (PB leprosy) and more than five as multibacillary leprosy (MB leprosy) [77]. Although this is a very practical approach, several reports have shown that by just counting, up to 30 % of the patients may be wrongly classified as PB and therefore undertreated [78].

6.6.1.3 Treatment

The first treatment known with some effectiveness was chaulmoogra oil, mentioned already in the *Sushruta Samhita* 600 BC. The effect was minimal in different preparations used; however, some success was obtained in PB leprosy [79]. The first effective antibiotic, intravenous sulfone, promin, appeared in 1943 [80]. Soon afterward, a new oral derivate called dapsone (diamino-diphenylsulfone, DDS) became the standard treatment. Upon the appearance of secondary DDS resistance in the 1970s together with the ready availability of rifampin (RMP), the use of combined

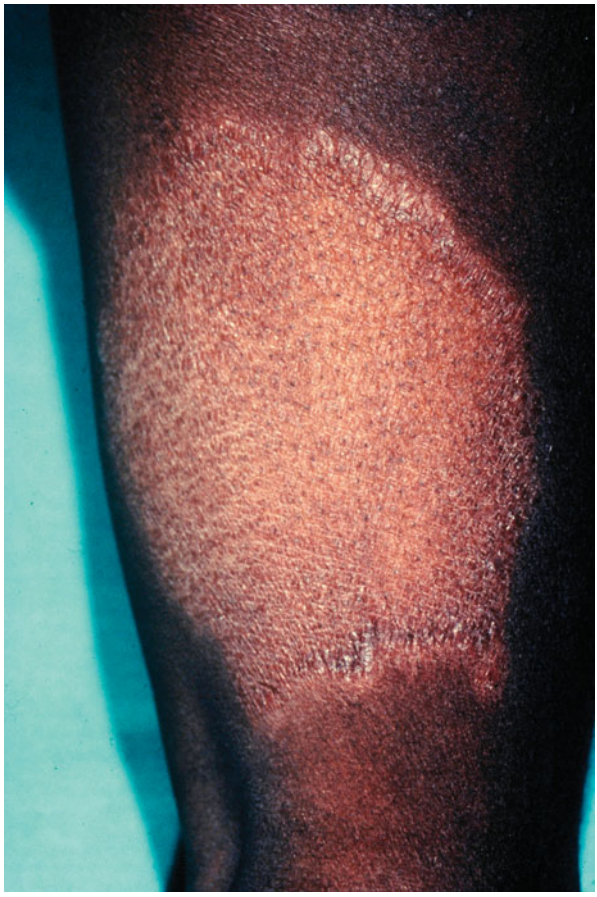

Fig. 6.9 TT leprosy (Courtesy of Dr. DL Leiker)

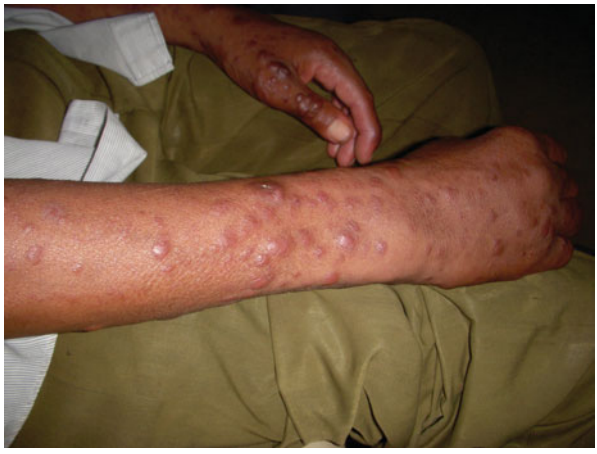

Fig. 6.10 A 20-year-old Tanzanian with LL leprosy (Courtesy of Regional Dermatology Training Center (RDTC), Moshi, Tanzania)

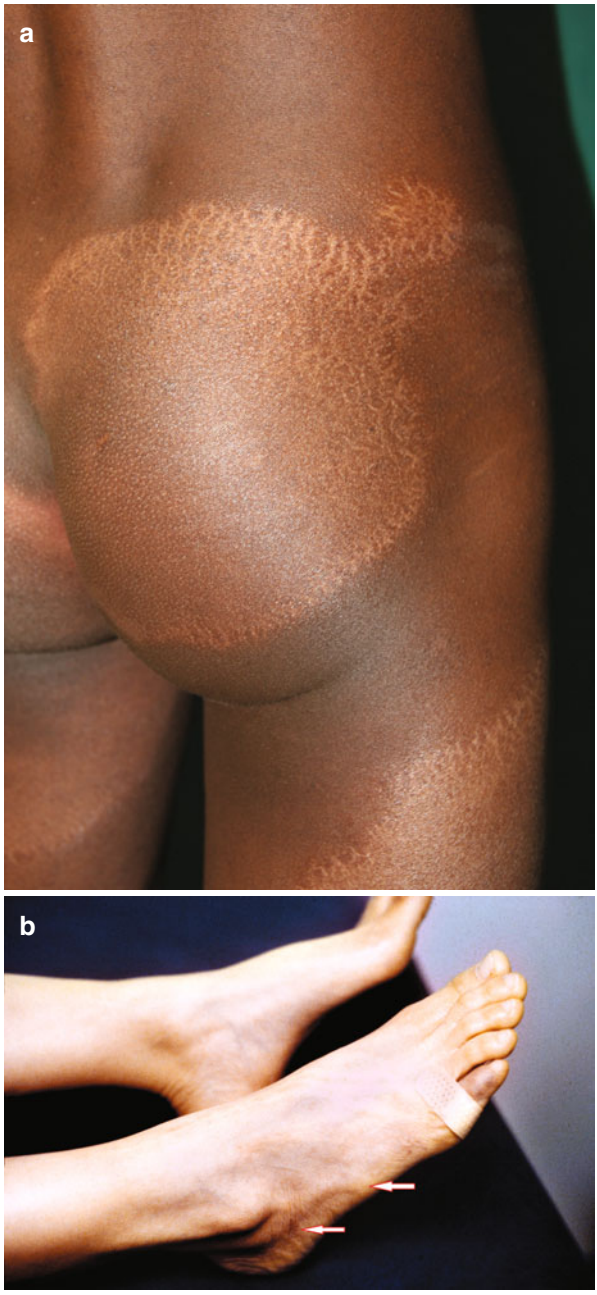

Fig. 6.11 (**a**) BT leprosy (Courtesy of Dr. Workalemahu, Ayder Hospital, Mekelle, Ethiopia). (**b**) BT leprosy showing enlarged sural nerve (*arrows*) in a 40-year-old Chinese woman

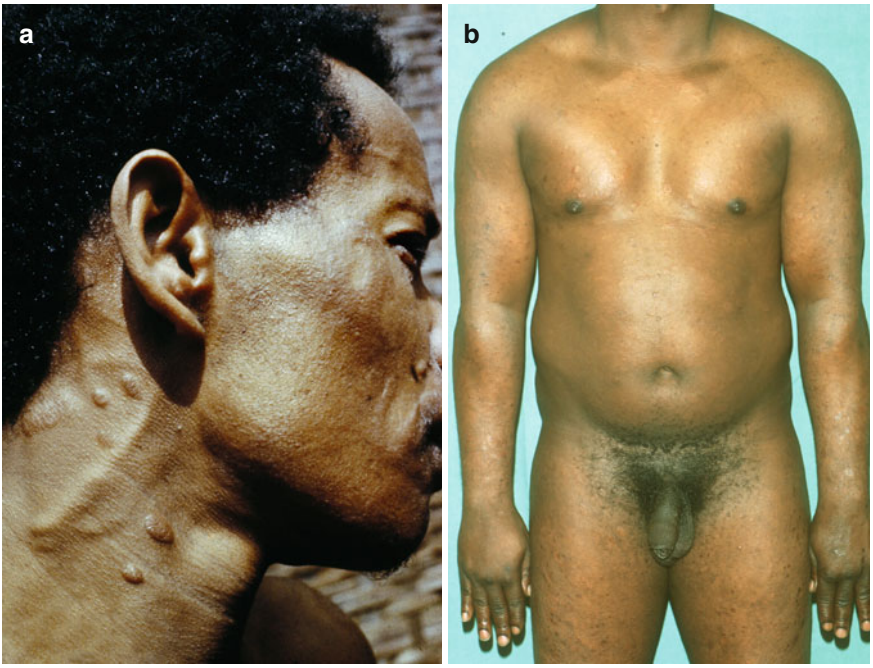

Fig. 6.12 (**a**) BL leprosy, downgrading from BB, enlarged nerve, nodules partly still edematous. (**b**) BL leprosy, small nodules with outside the nodules frequent low BI in smear or biopsy

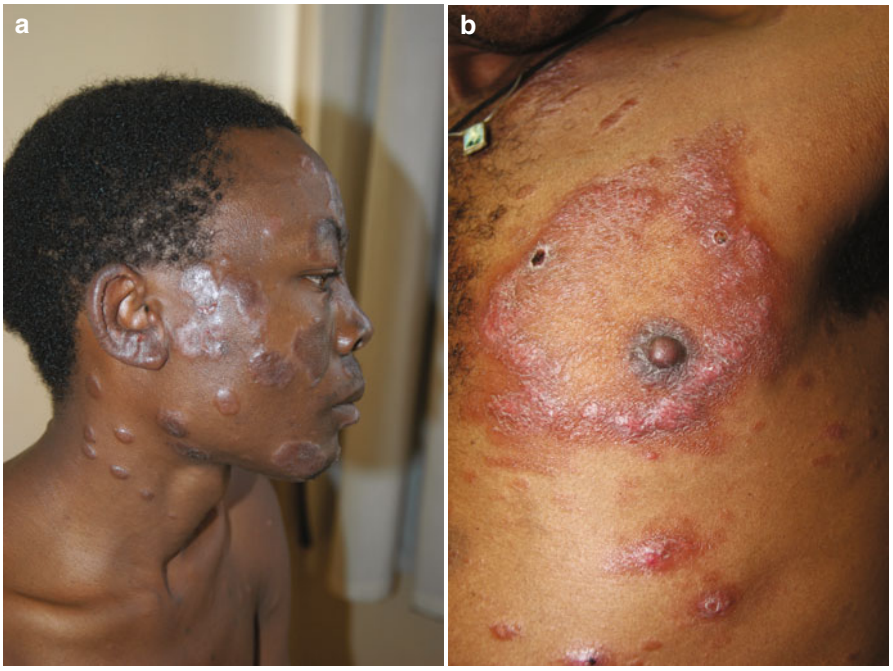

Fig. 6.13 (**a**) BB leprosy, downgrading to BL, nodules become firm showing "immune areas" in the center of the lesions. (**b**) BB leprosy downgraded from BT immune area's, involvement of the palm of the hand is typical. Lesions are still edematous

regimens was recommended [81]. Several treatment combinations, mainly based on previously proven effective tuberculosis therapy, were proposed to combine with DDS, such as rifampin, thioamide drugs, and isoniazid. The latter is however not active against *M. leprae*.

Combined therapy was implemented by several national programs. For instance, in Paraguay and Malta, isoprodian® (175 mg of prothionamide, 50 mg DDS, and 175 mg isoniazid) and RMP were extensively used with only a few reported relapses [82, 83]. It was also used in Ethiopia and Tanzania where many side effects were noticed, gastrointestinal disturbances and particularly liver toxicity. But it was not until 1982 that the WHO's Chemotherapy Study Group recommended the combined use of RMP and DDS with or without clofazimine [81]. WHO-MDT is the current standard treatment and continues to be widely administered.

6.6.1.4 Multidrug Therapy (MDT)

Paucibacillary leprosy: 600 mg rifampicin once monthly under supervision and daily 100 mg dapsone for 6 monthly doses within 9-month time. The dose is for a 60 kg patient.

Multibacillary leprosy: 600 mg rifampicin and 300 mg Lamprene (clofazimine) once monthly under supervision and 100 mg dapsone and 50 mg Lamprene daily. Twelve monthly doses should be given within 18 months for low-BI patients and 24 monthly doses in 36 months for patients with a BI of 4 or more. The doses are for 60 kg patients.

These treatment regimens have proved sturdy; hardly any relapses (4%) are seen. However, be careful with dapsone in Nordic Caucasians who easily develop hemolysis and with Nepalese and Chinese patients who have a greater risk of developing dapsone hypersensitivity syndrome. This is independent of G6PD. Fifty milligram of dapsone is effective in the majority of patients and causes much less anemia. It is probably genetically determined [84].

As alternative for daily treatment and as once-only treatment for single-lesion leprosy, a combination of RMP, ofloxacin, and minocycline was advocated. For BT and LL leprosy, it was given once per month, but it showed to be less effective than WHO-MDT [85].

6.6.1.5 Reactions

Reactions belong to the normal course of a leprosy infection. Treatment can prevent or precipitate them. There are three types of reactions: type I leprosy reaction (T1R), also called reversal reaction (RR); type II leprosy reaction (T2R), also called erythema nodosum leprosum (ENL); and Lucio's phenomenon, a reaction occurring specifically in patients from Mexico.

T1R is a CMI reaction, a type IV Gell and Coombs reaction against *M. leprae* antigenic determinants [86]. Clinically, there is increased inflammation of lesions, which become more visible and erythematous, are raised or enlarged (Fig. 6.14), and even may ulcerate. Nerves may be inflamed, enlarged, and tender, causing diminishing strength, sweating, and sensitivity. There may be acroedema.

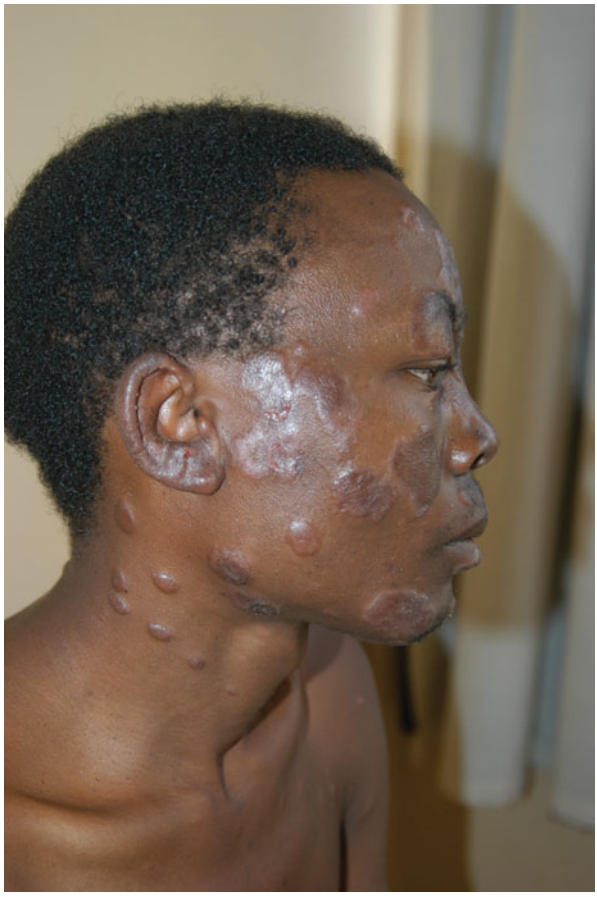

Fig. 6.14 Type 1 leprosy reaction (T1R) in a 25-year-old man (BB-BL leprosy) (Courtesy of RDTC, Moshi, Tanzania)

T2R is an antigen-antibody immune complex reaction in the tissues, particularly in the skin and nerve [87]. The skin shows the characteristic red painful, tender nodules (Fig. 6.15). It is a multi-organ disease; all types of tissues can be inflamed. There may be fever and leukocytosis.

The treatment of T1R primarily consists of corticosteroids, 30–40 mg prednisone starting dose, tapering down, guided by, for instance, graded sensory testing, in 6–12 months, in which the dose needs to be 20 mg at least to be effective. Adequate immune suppression (>0,25 mg/kg) should be given at least for 3 months for BT leprosy to 18 months or even longer for BL leprosy [88]. In some cases dapsone helps to prevent a reaction [89].

T2R treatment is difficult. The reaction is episodic, 95 % of ENL episodes last less than 1 month [90]. Mild reactions can be treated with NSAIDs; arthritis with antimalarials, but severe reactions, needs high dose steroids (60–120 mg) for a short period, diminishing to zero in a month or less. A new attack should be treated the same way [91]. Clofazimine may prevent a T2R or can be used as treatment [92]. Thalidomide as treatment is superior above all and can be used as prophylaxis. But even thalidomide may not be effective in every T2R. The combination of low-dose steroids with

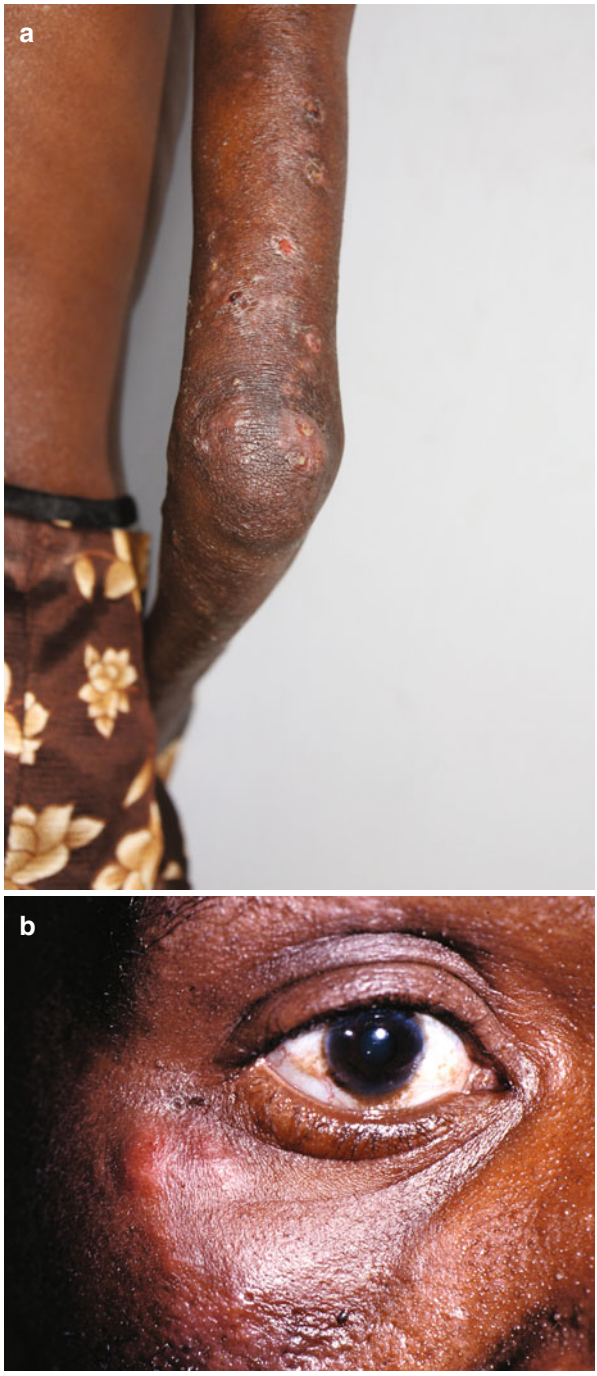

Fig. 6.15 (**a**) Type 2 leprosy reaction (T2R) in a 24-year-old man. (**b**) Type 2 leprosy reaction (T2R) in a 31-year-old woman (Courtesy of RDTC, Moshi, Tanzania)

low-dose thalidomide is counterproductive [93]. When thalidomide is not available, for the prevention of new ENL episodes methotrexate (MTX) could be used [94].

When nerves continue to deteriorate despite proper medical treatment, a nerve release operation needs to be considered. This also can be done for nerves without a reaction that remain tender after treatment.

The Lucio phenomenon presents as an infarction in the skin, when a huge amount of bacilli is blocking the venous return in the small venules. This is only seen in untreated diffuse lepromatous leprosy and may be triggered by sudden cold. The treatment is MDT; RMP is the crucial drug.

The results of nerve damage, loss of sensation, and muscle strength are the sequelae or the stigmata of leprosy. These should be countered with supplying special padded tools, utensils, and shoes. Sometimes in order to increase grip or to improve foot movement, a tendon transfer may be considered, but always with an experienced physiotherapist present.

6.6.1.6 Prevention

Despite many efforts to develop a universal active vaccine, involving DNA techniques, BCG vaccination remains the best prophylactic in many areas. Protection ranges from less than 20 % in some areas to up to 80 % in other, probably depending on the presence and characteristics of environmental microorganism [95]. Treating of contacts with a single 600 mg dose of rifampicin has proven to be effective for a few years, and BCG vaccination may extend this [96].

6.6.2 Buruli Ulcer [97, 98]

Buruli ulcer (BU), also known as the Bairnsdale, Searls, or Daintree ulcer, is an infectious disease caused by *Mycobacterium ulcerans* [97, 98].

The disease was named after the area of the first large epidemic in Uganda (1961), in an area named "Buruli," near Lake Kyoga [99]. *M. ulcerans* grows optimally at 30–32 °C and contains a large plasmid that encodes for enzymes to produce a polyketide-derived macrolide toxin called mycolactone which mediates tissue necrosis, immunosuppression, and apoptosis [97, 100–102].

BU is a public health problem, mainly because of the severe disabilities it causes when diagnosed late and the stigma it carries [103]. Since 1998, WHO has highlighted the growing problem of BU and developed improved treatment and control programs [104].

BU afflicts all age groups but most cases occur in children younger than 15 years of age. There is no gender preference [105]. Most lesions are on the lower extremities, a relatively cooler site which is also prone to traumata.

BU is focally endemic in rural wetlands of tropical countries of Africa, America, Asia, and Australia. BU is most common in West Africa, with highest incidences in

Benin, Ghana, and Côte d'Ivoire [106]. A BU focus in Kenya is confirmed [107]. The disease has been reported in over 30 countries. About 5,000–6,000 cases are reported yearly from only 15 of these countries [106]. A few cases also have been reported in nontropical areas of Australia, Japan, and China. Imported BU has been seen in industrialized countries where BU is not endemic [97].

In the Americas, BU seems most common in French Guyana, with about 200 cases reported since 1970 [108]. The incidence of BU is low in Asia and Oceania. Since 1971, about 400 cases have been reported in Papua New Guinea, whereas in other Asian countries very few cases have been confirmed. In Australia, the main focus is North Queensland, with 92 cases reported over the past 44 years [109].

BU is directly related to environmental factors and thus considered noncontagious [110]. The epidemiology of BU is strongly associated with wetlands, especially with slow-flowing or stagnant water. A plausible mode of transmission is a minor, often unnoticed skin trauma that permits inoculation of *M. ulcerans*. The mode of transmission may be related to the geographic region [111].

M. ulcerans DNA is detectable in some aquatic insects, prompting investigation into biting insects as vectors infecting humans. Portaels et al. reported the first direct isolation of *M. ulcerans* from a water strider, an aquatic insect that however does not bite humans [112]. In Australia, BU may be a zoonosis transmitted by mosquitoes, from indigenous marsupials such as the koala bear and opossum to humans [113]. There may be mammals involved in Africa too [114]. Recently amoebas were implicated as a possible reservoir [115].

6.6.2.1 Clinical Picture

Like in other mycobacterial diseases, exposure of the skin to *M. ulcerans* may lead to one of three outcomes: clearance of the infection, clinical disease soon after infection (primary BU), or subclinical or asymptomatic infection (latent BU) that may later reactivate and produce disease. It is most likely that many individuals exposed to *M. ulcerans* clear the infection and never develop disease [97, 98].

The incubation period of primary BU is estimated to be 2–3 months. Delayed onset of disease, i.e., ≥3 months after leaving an endemic area, may represent activation of latent infection [97, 98]. In contrast, the incubation period may be short (≤15 days), with lesions developing proximal to a bruise or sprain, without clinically detectable damage to the skin. This could be an activation of latent *M. ulcerans* infection caused by local trauma [97].

BU presents with a spectrum of symptoms, which may depend on time of consultation, host immune status, inoculum size, inoculation depth, geographic area, and strain virulence. There can be a striking discrepancy between the complaints and the symptoms as even impressive lesions may be painless. Together with stigma and fear of hospital admittance and surgery, this led as to delayed care-seeking behavior [103]. Delayed care results in more ulcerative forms. The disease develops through two active stages, non-ulcerated and ulcerated lesions (Fig. 6.16) to the third stage, the healed or scarred lesion. There may be mixed forms however, with

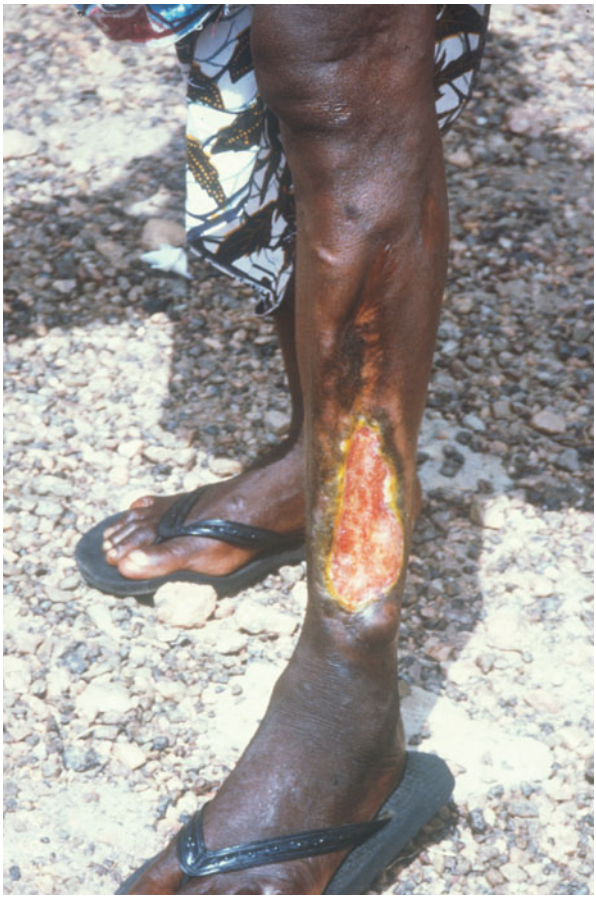

Fig. 6.16 Buruli ulcer (Courtesy of Father George, Ghana)

different stages presenting in the same site or at a different body site. Also disseminated forms occur, through spread by continuity or by lymphohematogenous spread. Bone involvement presents as osteomyelitis and occurs in up to 10 % of patients in Africa [116, 117]. As such, it is important to examine patients thoroughly, looking for new and old lesions. The patient may be unaware of scars from healed BU [97]. HIV seropositivity may be associated with aggressive BU [118].

Non-ulcerative forms often occur in early stages and may heal spontaneously. Non-ulcerative lesions may progress to ulcers after a few weeks to months, bringing patient to the doctor.

Clinical criteria supporting the diagnosis of BU include [97]:

- ≥1 painless ulcers lasting at least several weeks, undermined edges (Fig. 6.17)
- Nodule, plaque or wheal, or depressed scar
- Swelling over a painful joint, suggesting bone involvement
- No fever or regional lymphadenopathy (assumes no bacterial superinfection)

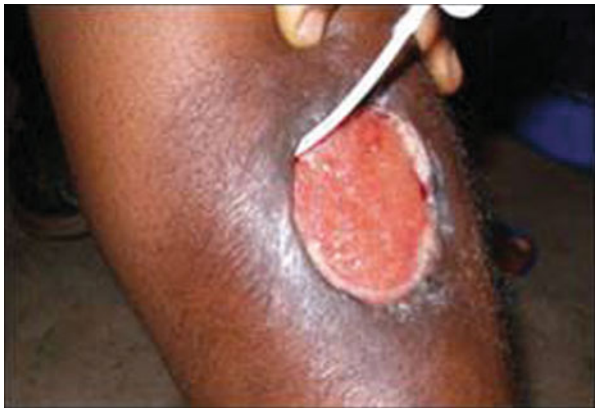

Fig. 6.17 Buruli ulcer with undermined edges (Courtesy of Mr. Vandi, Ivory coast)

- Patient <15 years of age
- Patient lives in, or traveled to, a BU endemic region, particularly West Africa

The disease may also be classified in three categories, according to lesion size, which may be helpful for choosing a treatment regimen:

Category I: single lesion, <5 cm in longest diameter
Category II: single lesion, 5–15 cm in longest diameter
Category III: single lesion, >15 cm in longest diameter, multifocal lesions, lesions at critical sites (eye, breast, genitalia), or bone involvement [87]

6.7 Diagnosis [106]

Many conditions resemble BU. Differential diagnoses include bacterial, deep fungal and parasitic infections, inflammatory lesions, and tumors. For ulcerative and edematous BU, the differential diagnosis includes tropical phagedenic ulcer, leishmaniasis even anthrax, and necrotizing fasciitis [119]. Most of these conditions, unlike BU, are painful, and a phagedenic ulcer emits an unpleasant odor. Painful ulcers may indicate secondary infection.

6.7.1 Collection of Clinical Specimens for Laboratory Testing

For routine assessment of suspected BU, for culture or PCR, ulcers should be swabbed or scraped at the undermined rims. Fine needle aspiration can be used [120]. Lesion biopsies, punch or excisional, are appropriate for suspected imported BU in an industrialized country. If surgery is conducted, specimens should be collected from excised tissues for bacteriological and histopathological analyses.

Curetted bone samples should be cultured to determine the cause. Sampling of at least two sites of each lesion is suggested, which may increase sensitivity over a single sample by up to 25 % [121, 122].

6.7.2 Laboratory Confirmation

Confirmation of BU is important because treatment may involve a moderately toxic antibiotic (streptomycin) and sometimes surgery.

Two out of four laboratory tests should be positive in order to confirm the diagnosis [97].

Lesion swabs or preferably scraping material or material obtained by biopsy may be used for:

1. Direct smear examination for AFB, i.e., Ziehl-Neelsen or auramine stain
2. In vitro culture on mycobacteriological media, at 30–32 °C
3. PCR amplification of insertion sequence 2404 (IS*2404*), which is considered to be specific for *M. ulcerans*
4. The fourth technique, punch biopsy, that allows for histopathologic examination

Laboratory tests vary in sensitivity. Sensitivity is 60–80 % for direct smear examination for AFB, 20–80 % for culture, and >90 % for PCR and histopathology. Direct smear and culture provide about 60 % sensitivity for nodules versus up to 80 % for edematous forms. PCR and histopathology provide >90 % sensitivity for all forms [123].

Histopathology may confirm BU or suggest another diagnosis. Culture can be useful for tracking treatment response [123]. At community level, direct smears are useful, but rapid diagnostic tests are needed. Simple methods for the detection of mycolactone or *M. ulcerans*-specific proteins in lesions or other fluids are under investigation [124].

6.8 Treatment

Historically, BU treatment has consisted mainly of wide excision. Antibiotics were generally considered ineffective, although, already by the 1970s, Meyers indicated that RMP could be used for early lesions [125].

In 2004, supported by data [126], WHO advocated a provisional antibiotic regimen, composed of oral RMP (10 mg/kg) + intramuscular streptomycin (S) (15 mg/kg), given daily for 8 weeks under supervision, with surgery as needed [127].

In 2010, the first randomized trial of RMP+S for “early, limited” BU, defined as lesions of <6 months duration composed of nodules or ulcers <10 cm in diameter, was reported [128]. RMP+S was given daily for 8 weeks or daily for 4 weeks, followed by all-oral RMP + clarithromycin (CLR) daily for 4 weeks, all without surgery. >90 % of the BU patients were cured after 1 year.

The current WHO recommendations for treatment are [129]:

- A combination of specific antibiotics for 8 weeks as first-line treatment for all forms of active disease
- Wound care
- Prevention of disability
- Surgery to remove necrotic tissue, cover large skin defects, and correct deformities

In general, recurrence rates in Category I and II disease after completing an RMP+S-based regimen are low (1–2 %) [97].

Despite the encouraging success of antibiotics for BU [130], extensive disease still requires surgery. However, the point in time at which surgery should be performed in relation to antibiotic treatment is not clear [97]. Twelve weeks of RFM+S for osteomyelitis did not prevent dissemination to other bones, despite one or more surgical procedures [130, 131].

Clearly, management of severe BU, such as length of antibiotic treatment and when to perform surgery, needs further investigation [132]. Physiotherapy, especially for Category III disease, should be instigated to prevent contractures [133].

Small case series describing 4–8 weeks of all-oral regimens for BU, including RMP+CLR in Benin and RMP + moxifloxacin in Australia, are encouraging [134, 135]. The all-oral regimens are less toxic and are relevant in pregnancy, in which streptomycin is contraindicated [136]. Recent investigations showed that RMP lowers CLR serum levels by 65 % and moxifloxacin serum levels by 30 %. The exact clinical relevance of these findings is still to be determined [137, 138].

Sometimes BU worsens during antibiotic treatment, and this may be due to an increased CMI response [139, 140]. Lesions developing after treatment is completed may represent immune responses to subclinical foci of *M. ulcerans*, treatment failures, or reinfections [141]. Sometimes steroids are needed [142].

6.9 Prevention

In tropical rural settings where BU is endemic, protection against contamination of the skin is virtually impossible. Wearing protective clothing, immediate cleansing of any skin injury, and the use of protected water sources in villages may reduce BU [143].

BCG vaccination may protect against BU, estimated 6–12 months after vaccination, and neonatal BCG vaccination may reduce the risk of BU osteomyelitis [144].

M. ulcerans, as an intracellular organism, triggers CMI [145, 146]. BURULIVAC, a collaborative project funded by the European Union under the Seventh Framework Programme, supports efforts to identify vaccine candidates based on DNA engineering and virulence factors, including mycolactone [147]. A mouse model for research has been developed [148].

6.9.1 Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) (synonyms atypical mycobacteria (ATM) and mycobacteria other than tubercle bacilli (MOTT)) are implicated in cutaneous infection [6, 147, 149].

NTM are usually transmitted from environmental sources by ingestion, inhalation, or inoculation [1]. These environmental sources may include aerosols, water (surface water, ponds, streams, municipal waters), soil, dust, food products, and contaminated medical equipment.

6.9.1.1 **Diagnosis** (Table 6.1)

Culture is the golden standard in the diagnosis of NTM. Culture may be negative if the laboratory is not informed of the clinical suspicion because specific conditions are required for culture. Mycobacterial infections usually have some specific features in a skin biopsy, so this may help direct suspicion. The histologic findings of an infection vary by the age of the lesion. Scanning a developed lesion shows a typical granulomatous dermatitis, which forms an extensive inflammatory nodular infiltrate within the dermis. Early lesions may show acute suppurative inflammatory processes with little granuloma formation and sometimes extensive neutrophils. The epidermis may show pseudoepitheliomatous hyperplasia with or without ulceration. Sometimes there are tuberculoid granulomas with varying degrees of abscess formation. The principal infiltrate however is mixed lymphohistiocytic with a few multinucleated giant cells and scattered neutrophils. Acid-fast bacilli may be scarce and are often not found. Molecular techniques are now available but sensitivity and specificity varies. A positive tuberculin test is not specific for tuberculosis but may direct toward NTM as well. To narrow down the possibilities in such cases, interferon gamma release assay (IGRA) may also be performed; however, this is known to cross-react with the NTM *M. kansasii*, *M. marinum*, and *M. szulgai* (and also with *M. leprae*). It is not a standard test in skin disease.

Detection of new species and subspecies of NTM is a constant issue as at the same time it has to be realized how limited the molecular tools are in determining and classifying mycobacteria [150]. This leads to new classifications, for example, of clinical disease which was formerly always attributed to *M. tuberculosis*: Lichen scrofulosorum may also be caused by *M. avium*, papulonecrotic tuberculid reaction by *M. kansasii*, lupus vulgaris by *M. xenopi*, and scrofuloderma by *M. haemophilum*. Pulmonary infections which are attributed to *M. tuberculosis* worldwide are to date also partly attributable to NTM [150].

A natural division occurs between slowly and rapidly growing species. Mycobacteria that form colonies clearly visible to the naked eye within 7 days on subculture are termed rapid growers, while those requiring longer periods are termed slow growers.

The common cutaneous disease-producing rapid-growing species are *M. abscessus*, *M. chelonae*, and *M. fortuitum*. The most common slow growers that cause skin disease are *M. marinum*, *M. avium* complex, *M. haemophilum*, and *M. kansasii* [150].

Mycobacterium marinum Infections [4]

Swimming pool or fish tank granuloma is caused by *M. marinum*, a mycobacterium which causes disease in fresh, brackish, and saltwater fish and occasionally in humans. It is found in aquariums, pools, natural water supplies, and salt water and is among the most common NTM known to cause opportunistic infection in humans. It has an incubation time of 2 weeks to several months.

Clinical Picture

The infection is preceded by trauma, often there is history of cleaning a fish tank or swimming in open water. The initial lesion starts as an inflammatory papule after an incubation period of 2–6 weeks. The papule then gradually enlarges into violaceous nodules or plaques which may ulcerate or show a warty surface. These lesions are painless. They may heal spontaneously in the course of months to years.

M. marinum infections are one of the causes of nodular (also called sporotrichoid after the lymphatic spread of sporotrichosis) lymphangitis where nodules and/or ulcerating lesions are seen along the lymphatic vessels. Deep infections such as tenosynovitis, osteomyelitis, arthritis, and bursitis may occur. They are unusual but more common in immune-deficient patients.

Diagnosis

Diagnosis is based on the clinical picture; the preferential localization in combination with a history of aquatic activity coinciding with skin trauma should give a high index of suspicion (Fig. 6.18). The diagnosis should be confirmed by diagnostic tests. Histopathology can be nonspecific in the early stage of the disease. After 6 months a granulomatous reaction develops. Acid-fast bacilli may be seen; the absence does not rule out a *M. marinum* infection. Cultures can be performed from aspirates or biopsies. Growth is optimal at 30–32 °C and cultures should be maintained for 6 weeks. PCR techniques from biopsy material may provide a diagnosis within days.

Treatment

In superficial cutaneous infections, monotherapy with minocycline, clarithromycin, doxycycline, and trimethoprim-sulfamethoxazole can be effective, but drug resistance varies, and therefore combination therapy of usually two or three drugs is recommended. Ciprofloxacin has shown considerable effectiveness. In cases of severe infection, including those with a sporotrichoid distribution pattern, a combination of RMP and ethambutol (ETM) is the recommended regimen.

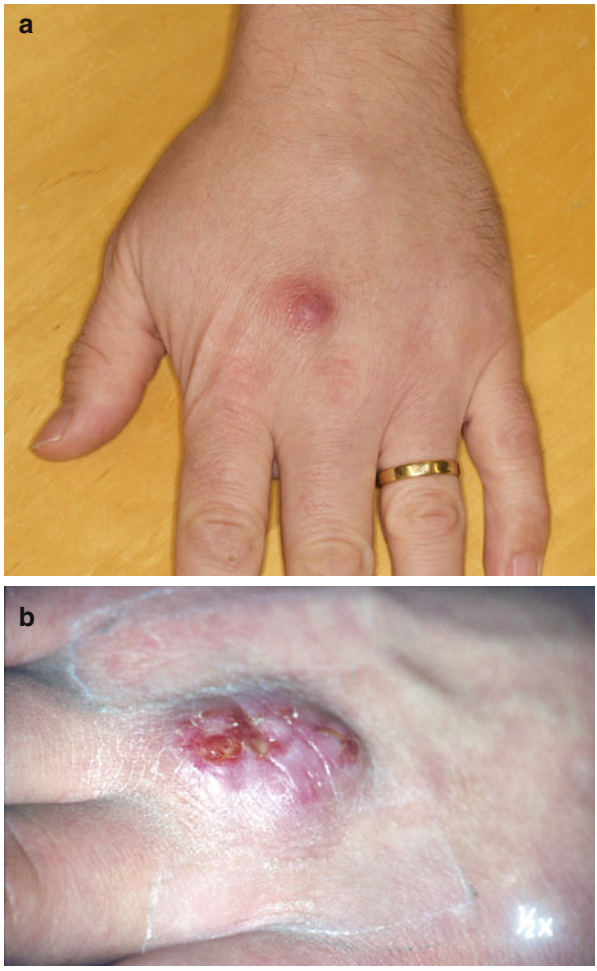

Fig. 6.18 Early *M. marinum* infection

Response to treatment is slow. Treatment is continued until 4 weeks after clinical cure and usually takes 4–9 months. Surgical treatment is not usually recommended. Cryotherapy, X-ray therapy, electrodessication, photodynamic therapy, and local hyperthermic therapy have been reported as effective alternatives. *M. marinum* infection should always be included in the differential diagnosis of patients with poor-healing plaques, nodules, or ulcers on the upper extremities and a history of exposure to aquariums [151].

Mycobacterium kansasii Infections [4]

M. kansasii causes disease in humans throughout the world and is often associated with AIDS. It has been isolated from cattle and swine. However, water is most likely its true habitat. It affects patients of all ages.

Clinical Picture

The most common manifestation is chronic pulmonary disease. Inoculation of the skin is in general through a small wound. Cutaneous lesions include erythematous to violaceous papules and plaques and also pustular, crusted, or verrucous papules or nodules. Lesions can resemble pyogenic abscesses, cellulitis, or sporotrichosis. Cervical lymphadenitis is reported in children.

Treatment

M. kansasii shows good in vitro susceptibility to rifampicin, rifabutin, ethambutol, ethionamide, amikacin, streptomycin, clarithromycin, sulfamethoxazole, and ciprofloxacin. However, when monotherapy is given, drug resistance is common [152, 153]. Therapy usually consists of isoniazid, rifampicin, and ethambutol or rifampicin, ethambutol, and macrolide [154].

Mycobacterium scrofulaceum Infections

M. scrofulaceum was widely distributed in tap water and soil but has become very rare in the last decades. It is included in the "MAIS group" which consists of *M. avium*, *M. intracellulare*, and *M. scrofulaceum. M. scrofulaceum* causes pulmonary infection and it may be the cause of cervical lymphadenitis in children. Cutaneous infection has been described as multiple subcutaneous abscesses and sporotrichoid infection.

Treatment

For childhood cervical lymphadenitis, surgery is the recommended treatment, in which the lesion is excised without chemotherapy. The success rate for this treatment is 95 %. Drugs which are used in treatment include isoniazid, rifampin, and streptomycin [154]. Good results were described with a combination of isoniazid, ethambutol, rifampin, and ofloxacin [155]. Clarithromycin is a good addition [156].

Mycobacterium haemophilum Infections

M. haemophilum causes skin, joint, bone, and pulmonary infections in immunocompromised persons and of submandibular lymphadenitis in children. Most infections occur in patients with AIDS and in transplant recipients. *M. haemophilum* skin infection has been associated with permanent eyebrow makeup and tattoos [157, 158].

Infections with *M. haemophilum* have been reported in a broad geographical range. The natural habitat and route of infection are unknown.

Treatment

Lymphadenitis in children: excision. *M. haemophilum* appears to be susceptible, in vitro, to ciprofloxacin, clarithromycin, rifabutin, and clofazimine but resistant to isoniazid and ethambutol [159]. In vitro observations may not relate to outcome of treatment in vivo and should be interpreted with extreme caution. Susceptibility test assays have not been properly standardized, because of the fastidious nature of *M. haemophilum* and the need to supplement the media [160].

Mycobacterium fortuitum Infections

M. fortuitum has been isolated from water, soil, and dust. Primary cutaneous disease is seen at all ages. It has been implicated in numerous outbreaks of hospital infections.

The clinical manifestations are localized cellulites, frequently with draining abscesses and nodules. Mostly a history of a penetrating injury with possible soil or water contamination is reported [161]. Postoperative infections, in general, develop 3 weeks to 3 months after surgery or trauma.

Treatment

Ciprofloxacin, amikacin, and cefoxitin are considered as first-line drugs. Alternative drugs are doxycycline, imipenem, ethambutol, and co-trimoxazole. A combined regimen, preferably with three drugs, should be used for 2–4 weeks, followed by ciprofloxacin [162] and a companion drug (e.g., clarithromycin despite the bacteria becomes easily resistant to this drug) for 3 months.

Mycobacterium chelonae and M. abscessus Infections

The two closely related species *M. chelonae* and *M. abscessus* (which consists of two subspecies) cause similar diseases worldwide. The skin disease caused by these opportunistic pathogens can be localized, similar nature to *M. fortuitum*, or may present as a disseminated disease with cellulitis and multiple often draining (sub) cutaneous nodular lesions in "immunocompromised" patients.

The localized infection may occur at all ages, typically after a trauma or a surgical incision. Inoculation may also follow tattooing, implicating contaminated water for the dilution of ink, or cosmetic procedures such as dermal filling, where contaminated ice used to cool the skin may be the cause [163, 164].

Treatment

The only clinical trial performed for this infection type applied clarithromycin monotherapy without distinguishing *M. chelonae* from *M. abscessus*; although just one patient failed on treatment with an acquired drug resistance, the use of monotherapy is no longer recommended [154]. Tobramycin and clarithromycin are drugs of choice for *M. chelonae* [160]. In general, cefoxitin and amikacin are active against both subspecies of *M. abscessus* [165, 166]. Clarithromycin is only active against *M. abscessus* subsp. *bolletii*, as *M. abscessus* subsp. *abscessus* possesses an erm gene that induces resistance in vitro and in vivo [160].

Mycobacterium szulgai

The natural habitat of *M. szulgai* is unknown. It has, however, been isolated from snails and tropical fish. The predominant localization of infections is pulmonary. Cases of skin infection even after minor trauma have been reported: cellulitis, inflamed tender nodules leading to draining abscesses.

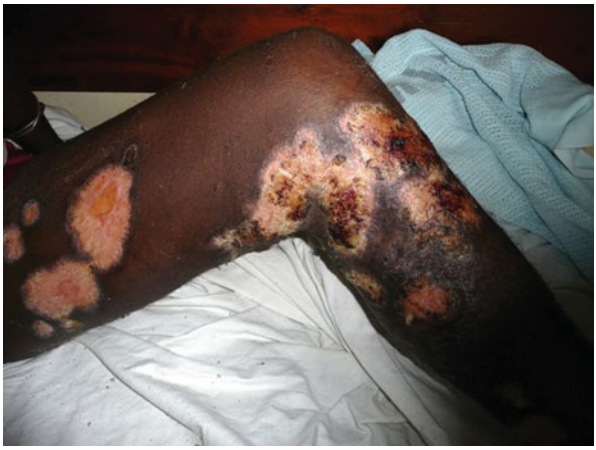

Fig. 6.19 An infection with a NTM (Courtesy of Ayder Hospital, Mekelle, Ethiopia)

Treatment

Triple-drug therapy with rifampicin, ethambutol, and clarithromycin guided by sensitivity testing [167]. It is recommended to use multiple drugs to reduce development of resistance. The treatment may take up to 1 year.

Mycobacterium avium-intracellulare Complex Infections

This group of mycobacterial species (*Mycobacterium avium-intracellulare* complex (MAC)), with several closely related species, occurs worldwide in nature. It is the most common group of NTM infections associated with AIDS in the West. The infection is caused by two closely related and difficult to distinguish bacteria, *M. avium* and *M. intracellulare*. These two bacteria can be found in drinking water, dirt, and household dust. MAC may be isolated in more than 30 % of fecal samples. It primarily causes opportunistic infections in the immunosuppressed, *M. intracellulare* tends to cause lung disease, and *M. avium* causes lung disease and lymphadenitis in children and disseminated disease in the immunocompromised. Symptoms of disseminated *M. avium-intracellulare* infection include fever, night sweats, weight loss, abdominal pain, fatigue, and diarrhea [168].

Skin involvement occurs in the course of disseminated disease, rarely by inoculation. Depending on the degree of immune suppression, widespread skin involvement may present as papules; nodules; plaques, with possible abscess formation; and ulcers (Fig. 6.19). Lymph node involvement can occur.

Treatment

In general, MAC infection is treated with two or three antimicrobials for at least 12 months. Commonly used first-line drugs include macrolides (clarithromycin or azithromycin), ethambutol, and rifamycins (rifampicin, rifabutin). Aminoglycosides, such as streptomycin and amikacin, are also used as additional agents as is ciprofloxacin [169] although supportive evidence for the latter is absent.

Lymphadenitis in Children: Surgery

Treatment of cutaneous atypical mycobacterial infections depends upon the infecting organism, the severity of the infection, and host immunity. In most cases a course of antibiotics is necessary. These include rifampicin, ethambutol, isoniazid, minocycline, ciprofloxacin, clarithromycin, azithromycin, and co-trimoxazole. Treatment of cutaneous localized disease is generally continued until 1 month after clinical cure, for pulmonary and generalized infection even longer: 18–24 months.

Usually treatment consists of a combination of drugs [170, 171].

There are some points to consider when treating atypical mycobacterial infections:

- *M. marinum* bacteria are resistant to isoniazid. Treatment with other antibiotics should be continued for at least 4 weeks after resolution of the skin lesions.
- *M. kansasii* should be treated for at least 18 months.
- *M. chelonae* is best treated by clarithromycin in combination with another agent. Related *M. abscessus* requires intravenous drugs including amikacin and cefoxitin. Sometimes surgical excision is the best approach for both species.
- AIDS patients on HIV protease inhibitors cannot be treated with RMP because RMP significantly increases the breakdown of these drugs. Rifabutin is a suitable alternative.

Treatment

For treatment of cutaneous infections by NTM, it is preferable to select the drugs based on the antimicrobial susceptibility profile. In vitro susceptibility testing is useful for rapidly growing mycobacteria (RPM) but not for slow-growing NTM MAC, *M. haemophilum*, and *M. szulgai* as in vitro results in this group do not correlate with in vivo response to treatment [160]. Empiric therapy is sometimes necessary in case of strong suspicion with negative culture and no identification by means of PCR (Table 6.1).

Duration of treatment is not fixed and is based on clinical judgment and will require in general 6–9 months [149].

For the treatment of rapid growers, it is important to follow the results of in vitro tests. For slow growers that is not the case since in vivo and in vitro results often are not related.

6.10 Drugs Commonly Used in Mycobacterial Infection

6.10.1 Rifampicin and Rifamycin

Rifampin and related rifamycins are the most important drugs for the treatment of mycobacterial infections. The rifamycins are a group of antibiotics that are synthesized either naturally by the bacterium *Amycolatopsis mediterranei* (old name *Streptomyces mediterranei*) or artificially. Rifamycins are particularly effective against mycobacteria and are therefore used in the treatment of tuberculosis, leprosy, Buruli ulcer, and many NTM infections.

The antibacterial activity of rifamycins relies on the inhibition of bacterial DNA-dependent RNA synthesis [171]. This is due to the high affinity of rifamycins to prokaryotic RNA polymerase. Rifampicin and its analogs kill actively multiplying extracellular organisms, intracellular mycobacteria, and semidormant mycobacteria in the tissues.

The addition of rifampicin to treatment regimens for tuberculosis can shorten treatment duration for active disease from 12 to 6 months and for latent infection from 9 months to 2–3 months. In leprosy a single 600 mg dose kills 99 % of all live bacilli, but sadly not the metabolic inactive persisters.

Because of their potencies and sterilizing activities, rifamycins are the cornerstone of modern therapy for most mycobacterial infections and are extremely effective in the treatment of latent infections [172, 173].

6.10.1.1 Dosages

Daily regimen: 10 mg/kg (up to 600 mg/day) orally or IV once a day. For TB there is a discussion, one may consider even about four times this dose, and this could help against persisters [160].

Intermittent regimen: 10 mg/kg (up to 600 mg/dose) orally or IV two or three times a week.

For children 10–20 mg/kg.

6.10.1.2 Adverse Effects

Via lever enzymes P450, CYP, 1A2, 2C9, 2C19, and 3A4, it influences concomitant treatments. Its toxicity is predominantly hepatic and allergic [174]. Hepatic toxicity is dose related and has been observed mainly in patients with underlying liver disease, which then can be fatal.

The “allergic” effects are usually associated with intermittent or prolonged therapy. These allergic effects may be minor (cutaneous, gastrointestinal, or an influenza-like syndrome) or major (hemolytic anemia, shock, or acute renal failure) [175]. Well known is the leprosy flu syndrome due to intermittent rifampicin with less than 3 weeks interval [176], and this can be fatal.

There may be some orange discoloration of urine, tears, and sweat.

6.10.2 Ethionamide

Ethionamide (2-ethylthioisonicotinamide) is an antibiotic used in the treatment of tuberculosis. It was discovered in 1956 [177].

Ethionamide, a prodrug, is activated by the enzyme EthA, a monooxygenase in *Mycobacterium tuberculosis*, and binds nicotinamide adenine dinucleotide to form an adduct which inhibits the 2-trans-enoyl-acyl carrier protein reductase (InhA) in the

same way as isoniazid [178]. Expression of the EthA gene is controlled by EthR, a transcriptional repressor. It is understood that improving EthA expression will increase the efficacy of ethionamide and so EthR inhibitors are of great interest to co-drug developers [179]. The action may be through disruption of mycolic acid [180].

It is a thioamide and used in regimens to treat multidrug-resistant and extensively drug-resistant tuberculosis. It has been proposed for use in combination with gatifloxacin [181].

Dosages: 500 mg to 1 g orally (15–20 mg/kg) in 1 or divided doses per day. Maximum dose: 1 g orally per day. Children: 10–20 mg/kg orally in 2 or 3 divided doses per day or 15 mg/kg orally once per day after meals [171].

6.10.2.1 Adverse Effects

The most common side effects of ethionamide are gastrointestinal. These appear to be dose dependent, with approximately 50 % of patients unable to tolerate 1 g as a single dose. Effects may be minimized by decreasing dosage, by changing the time of drug administration, or by the concurrent administration of an antiemetic agent.

Psychotic disturbances (including mental depression) and postural hypotension have been reported. Concurrent administration of pyridoxine has been recommended to prevent or relieve neurotoxic or pellagra-like effects.

Transient increases in serum bilirubin, SGOT, and SGPT; hepatitis (with or without jaundice) can be seen.

Hypersensitivity reactions including rash, photosensitivity, thrombocytopenia, and purpura have been reported. Hypoglycemia, hypothyroidism, gynecomastia, impotence, and acne also have occurred [182]. The management of patients with diabetes mellitus may become more difficult in those receiving ethionamide.

6.10.3 Ethambutol

Ethambutol is a bacteriostatic antimycobacterial drug prescribed to treat tuberculosis. It is usually given in combination with other tuberculosis drugs, such as isoniazid, rifampicin, and pyrazinamide.

Ethambutol is bacteriostatic against actively growing TB bacilli. It works by obstructing the formation of cell wall. Mycolic acids attach to the 5′-hydroxyl groups of D-arabinose residues of arabinogalactan and form mycolyl-arabinogalactan-peptidoglycan complex in the cell wall. It disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase. Disruption of the arabinogalactan synthesis inhibits the formation of this complex and leads to increased permeability of the cell wall [183].

Dosages: Adult 15 mg/kg once a day. Treating relapses: for 2 months 25 mg/kg once a day, followed by 15 mg/kg again. Children the same. For MAIC: 900 mg once a day.

6.10.3.1 Adverse Effects

Ethambutol may induce a decrease in vision due to optic neuritis. This effect is dose related and is generally reversible when administration of the drug is discontinued in time. Irreversible blindness has been reported.

Other reactions are gastrointestinal, allergic skin reactions, and infrequently polyneuritis [184].

6.10.4 Fluoroquinolones

Ofloxacin and moxifloxacin are broad-spectrum fluoroquinolones that are active against both Gram-positive and Gram-negative bacteria but also against mycobacteria: *M. tuberculosis*, *M. leprae*, and several NTM [185, 186].

Fluoroquinolones interfere with DNA replication by inhibiting an enzyme complex called DNA gyrase. This can also affect mammalian cell replication. Some congeners of this drug family display high activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases and are toxic to cultured mammalian cells and in vivo tumor models [187].

Although a quinolone is highly toxic to mammalian cells in culture, its mechanism of cytotoxic action is not known. There is debate as to whether or not this DNA damage is to be considered one of the mechanisms of action concerning the severe and non-abating adverse reactions experienced by some patients following fluoroquinolone therapy.

Dosages: MAI 400 mg orally every 12 h. Tuberculosis: 300–400 mg orally or IV every 12 h. Leprosy: 400 mg OD. For children with leprosy 200 mg OD. Basically the drug is contraindicated for children.

6.10.4.1 Adverse Effects

Quinolones have few direct adverse effects, most notably nausea, headache, dizziness, and confusion. Less common but more serious adverse events include prolongation of the QT interval, phototoxicity, liver enzyme abnormalities, arthropathy, and cartilage and tendon abnormalities, the latter particularly in children [188]. Moxifloxacin is contraindicated in patients with myasthenia gravis.

6.10.5 Isoniazid (INH)

Isoniazid also known as isonicotinylhydrazine (INH) is an organic compound that is the first-line medication in prevention and treatment of tuberculosis. The compound was first synthesized in the early twentieth century, but its activity against

tuberculosis was first reported in the early 1950s. With the introduction of INH, a cure for tuberculosis was for the first time considered conceivable.

INH is available in tablet, syrup, and injectable forms (given intramuscularly or intravenously). It is available worldwide, is inexpensive, and is generally well tolerated.

It is a prodrug and must be activated by a bacterial catalase-peroxidase enzyme that in *M. tuberculosis* is called KatG. KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall [189].

INH is bactericidal to rapidly dividing mycobacteria but is bacteriostatic if the mycobacteria are slow growing [190, 191].

Dosage: Adults 300 mg OD; children 5–6 mg/kg OD.

6.10.5.1 Adverse Effects

INH inhibits the P450 system. Severe and sometimes fatal hepatitis may occur within the first 3 months of treatment and many months after treatment. Risk is related to age and increased with daily alcohol consumption. The N-acetylhydrazine metabolite is believed to be responsible for this hepatotoxic effect. The rate of acetylation is genetically determined. Approximately 50 % of Blacks and Caucasians are slow inactivators; the majority of Inuit and Asians are rapid. The half-life in fast acetylators is 1–2 h, while in slow acetylators, it is 2–5 h. Elimination depends on renal function, but the half-life may be prolonged in liver disease. The rate of acetylation has not shown to alter the effectiveness, but there is an increased risk of toxicity. Hepatitis is 250 times more common in slow acetylators.

It may give pellagra-like symptoms, CNS and peripheral neuropathy, gastoenteral and skin problems. Pyridoxine (vit B6) should counteract most. LE is described [192].

6.10.6 Pyrazinamide

Since the discovery of pyrazinamide in 1952 [47], and its routine use to treat TB, the duration of treatment required to achieve acceptable relapse rates has been reduced from 9 to 12 months to the current 6 months [193], although its bactericidal activity is inferior to that of INH and rifampin. It is largely bacteriostatic but can be bactericidal.

Pyrazinamide is a prodrug. It diffuses into *M. tuberculosis*, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid. Under acidic conditions, the pyrazinoic acid slowly leaks out and converts to the protonated conjugate acid, which is thought to diffuse easily back into the bacilli and

accumulates. Thus, more pyrazinoic acid accumulates inside the bacillus at acid pH than at neutral pH [194].

Pyrazinoic acid was thought to inhibit the enzyme fatty acid synthase (FAS) I, which is required by the bacterium to synthesize fatty acids [195]. It was also suggested that the accumulation of pyrazinoic acid disrupts membrane potential and interferes with energy production, necessary for survival of *M. tuberculosis* at an acidic site of infection. Further studies reproduced the results of FAS I inhibition as the putative mechanism [196]. This study was followed by an in vitro assay of tuberculous FAS I enzyme that tested the activity with pyrazinamide, pyrazinoic acid, and several classes of pyrazinamide analogs. Pyrazinamide and its analogs inhibited the activity of purified FAS I [197]. Pyrazinoic acid binds to the ribosomal protein S1 (RpsA) and inhibits trans-translation. This may explain the ability of the drug to kill dormant mycobacteria [198].

Dosage: 15–30 mg/kg (up to 2 g) orally OD. Children non-HIV: daily therapy, 15–30 mg/kg/dose (maximum, 2 g/dose) OD. HIV: 20–40 mg/kg/dose once daily (maximum, 2 g/day).

6.10.6.1 Adverse Effects

Dermatologic side effects are rare and include rash, urticaria, pruritus, skin pigmentation, desquamation, and photosensitivity. Gastrointestinal side effects include nausea, vomiting, and anorexia. Renal side effects include dysuria and interstitial nephritis. Hepatotoxicity (1%) appears to be dose related and may appear at any time during therapy [199].

6.10.7 Para-Aminosalicylate Sodium (PAS)

The 4-aminosalicylic acid is commonly known as PAS. Since the 1940s it was used for inflammatory bowel diseases (IBDs), where it showed to have great potency in ulcerative colitis and Crohn's disease, both by some thought to be related to mycobacteria.

PAS was introduced for use in tuberculosis in 1948. It was the second antibiotic found to be effective after streptomycin. PAS formed part of the standard treatment for tuberculosis prior to the introduction of rifampicin and pyrazinamide. Its potency is less than that of the current five first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin), but it is still useful in the treatment of multidrug-resistant tuberculosis.

It is thought to inhibit folic acid biosynthesis and uptake of iron [200]. Mutations in the thyA gene encoding the enzyme thymidylate may lead to resistance. Induction of the folate biosynthesis pathway has been identified in PAS-resistant *M. tuberculosis*, suggesting that PAS may act as a folate antagonist [201].

Dosage: The dose when treating tuberculosis is 150 mg/kg/day divided into two to four daily doses; the usual adult dose is therefore approximately 2–4 g four times a day.

6.10.7.1 Adverse Effect

A joke in the past was that under the windows of a TB ward plants did not grow and that this was due to the terrible taste of PAS. Common side effects are nausea, vomiting, diarrhea, and abdominal pain. Goiter with or without myxedema has been described. Other side effects are fever, skin eruptions, infectious mononucleosis-like syndrome, leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, jaundice, hepatitis, encephalopathy, Loffler syndrome, and vasculitis [202].

6.10.8 Streptomycin

Streptomycin was the first antibiotic remedy for tuberculosis. It is derived from the actinobacterium *Streptomyces griseus*. Streptomycin is bactericidal. Streptomycin cannot be given orally but must be administered by regular deep intramuscular injections.

Streptomycin is a protein synthesis inhibitor. It binds to the small S12 rRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formylmethionyl-tRNA to the 30S subunit [203]. This leads to codon misreading, inhibition of protein synthesis, and ultimately death of microbial cells through mechanisms that are still not understood. Human ribosomes differ from bacterial ribosomes structurally and remain intact. At low concentrations, however, streptomycin only inhibits growth of the bacteria by inducing prokaryotic ribosomes to misread mRNA [204].

Dosage: Adults and children, 15 mg/kg daily or two or three times weekly. Patients over 60 years may not be able to tolerate more than 500–750 mg daily. In Buruli ulcer: adults, 1,000 mg daily; children, 20 kg/300 mg; 30 kg/500 mg; 40 kg/740 mg. No patient should be given more than 90 doses of streptomycin (according to weight) in their whole lifetime.

6.10.8.1 Adverse Effects

Fever and rashes result from persistent use. The vestibular portion of cranial nerve VIII (the vestibulocochlear nerve) can be affected, resulting in tinnitus, vertigo, and ataxia. Other side effects are nephrotoxicity, fetal auditory toxicity, and neuromuscular paralysis.

6.10.9 Cotrimoxazole

Trimethoprim/sulfamethoxazole or co-trimoxazole is a sulfonamide antibiotic used in the treatment of a variety of bacterial infections. It consists of one part trimethoprim to five parts sulfamethoxazole.

Opinions differ as to whether co-trimoxazole is a bactericidal or a bacteriostatic agent.

The synergy between trimethoprim and sulfamethoxazole was first described in a series of in vitro and in vivo experiments published in the late 1960s [205]. Trimethoprim and sulfamethoxazole have a greater effect when given together than when given separately, because they inhibit successive steps in the folate synthesis pathway.

Sulfamethoxazole acts as a false-substrate inhibitor of dihydropteroate synthetase. Sulfonamides such as are analogs of p-aminobenzoic acid (PABA) and thus are competitive inhibitors of the enzyme, inhibiting the production of dihydropteroic acid.

Trimethoprim acts by interfering with the action of bacterial dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid.

Folic acid is an essential precursor in the de novo synthesis of the DNA/RNA nucleosides thymidine and uridine. Bacteria have to take up folic acid, from the host – if that is not possible, they are dependent on their own de novo synthesis – inhibition of the enzyme starves the bacteria of the two bases.

Dosage: Adults and children over 12 years 960 mg bd orally. Children ≥6–12 years 480 mg bd orally.

6.10.9.1 Adverse Effects

It has been associated frequently with mild allergic reactions and regular with serious adverse effects, including Stevens-Johnson syndrome, myelosuppression, mydriasis, agranulocytosis, and severe liver damage (cholestatic hepatosis, hepatitis, necrosis, and fulminant liver failure).

Due to displacement of bilirubin from albumin, there is an increased risk of kernicterus in the fetus during the last 6 weeks of pregnancy. Renal impairment, up to acute renal failure, and anuria have also been reported. These side effects may be fatal.

Folic acid and folinic acid were found equally effective in reducing the adverse effects of trimethoprim/sulfamethoxazole. The trophoblasts in the early fetus are sensitive to changes in the folate cycle. A recent study has found a doubling in the risk of miscarriage in women exposed to trimethoprim in early pregnancy [206].

Cotrimoxazole is a major cause of severe blistering drug reactions in the HIV-infected patient: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).

6.10.10 Cycloserine

Cycloserine is an antibiotic effective against mycobacteria. It is produced by *Streptomyces garyphalus*. For the treatment of tuberculosis, it is only used as a second-line drug.

Cycloserine is an analog of the amino acid D-alanine. It interferes with an early step in bacterial cell wall synthesis in the cytoplasm by competitive inhibition of two enzymes, L-alanine racemase, which forms D-alanine from L-alanine, and D-alanylalanine synthetase, which incorporates D-alanine into the pentapeptide necessary for peptidoglycan formation and bacterial cell wall synthesis [207].

Dosage: 500 mg to 1 g orally per day, in one or two divided doses (10–15 mg/kg/day). Children: 10–15 mg/kg/day in two divided doses. Maximum dose: 1 g/day.

6.10.10.1 Adverse Effects

Most adverse reactions occurring involve the nervous system or are manifestations of drug hypersensitivity. Sudden development of congestive heart failure in patients has been reported.

6.10.11 Minocycline

Minocycline is a broad-spectrum tetracycline; it has a broader spectrum than the other members of the group. It is to date frequently used in mycobacterial infections.

It is a bacteriostatic antibiotic, classified as a long-acting type. Minocycline is the most lipid soluble of the tetracycline-class antibiotics. Minocycline is metabolized by the liver.

Minocycline passes directly through the lipid bilayer or passively diffuses through porin channels in the bacterial membrane. Tetracyclines like minocycline bind to the 30S ribosomal subunit, preventing the binding of tRNA to the mRNA-ribosome complex and interfering with protein synthesis [208].

Dosage: In NTM infections up to 100 mg BD is given. In leprosy 100 mg daily or 100 mg once a month.

6.10.11.1 Adverse Effects

Minocycline inhibits cytochromes P450 as do all tetracyclines; therefore, there are many drug interactions. Because it penetrates into the prostate and brain easily, it also has the greatest number of central nervous system (CNS)-related side effects of all the tetracyclines, such as vertigo and dreams. A common side effect is diarrhea.

In children up to age 9, minocycline may cause permanent staining of the teeth. Uncommon side effects (with prolonged therapy) include skin discoloration and autoimmune disorders that are not seen with other drugs in the class. Photosensitivity, which was expected, is hardly seen.

6.10.12 Doxycycline

Doxycycline, like minocycline, is lipophilic and can pass through the lipid bilayer of bacteria. Doxycycline reversibly binds to the 30S ribosomal subunits and possibly the 50S ribosomal subunit(s), blocking the binding of aminoacyl tRNA to the mRNA and inhibiting bacterial protein synthesis [208]. It is a more bioactive medication than the other tetracycline antibiotics, including minocycline. Conversely, minocycline is a broader spectrum drug than doxycycline and is used against a wider variety of bacteria. It can be considered against some RGM (*M. abscessus*), but most are resistant.

6.10.12.1 Adverse Effects

Doxycycline inhibits cytochromes P450 as do all tetracyclines; therefore, there are many drug interactions. Diarrhea is regularly seen, photosensitivity and dizziness hardly.

6.10.13 Dapsone

4,4'-Diaminodiphenylsulfone (DDS) was the magic drug for leprosy. It was for the first time synthetized by Fromm and Wittmann in 1908. It was used as an antibiotic first for streptococcal udder infections in cattle. For human it was for the high doses used too toxic. It was Faget in 1941, who first used the derivative promin for leprosy, and it was already used for tuberculosis.

As antibacterial, like all sulfonamides, dapsone inhibits bacterial synthesis of dihydrofolic acid, via competition with para-aminobenzoate for the active site of dihydropteroate synthetase [209].

Dosage: For adults 100 mg once a day (1 mg/kg), but sometimes because of hemolysis 50 mg. Children: 0.5–1 mg/kg.

6.10.13.1 Adverse Effects

The most prominent side effects of this drug are dose-related hemolysis (which may lead to hemolytic anemia) and methemoglobinemia. About 20 % of Nordic Caucasian and Celtic patients treated with dapsone suffer hemolysis, and this side

effect is slightly more common in those with glucose-6-phosphate dehydrogenase deficiency. Abnormalities in white blood cell formation, including aplastic anemia, are rare, yet are the cause of the majority of deaths attributable to dapsone therapy.

Toxic hepatitis has been reported. Jaundice may also occur as part of the dapsone reaction or dapsone syndrome. Dapsone is metabolized by the cytochrome P450 system. Dapsone metabolites produced by the cytochrome P450 2C19 isozyme are associated with the methemoglobinemia side effect of the drug.

Other adverse effects include nausea, headache, rash, insomnia, psychosis, and peripheral neuropathy.

Dapsone syndrome: The patient is ill and may have a rash, fever, jaundice, and eosinophilia; these symptoms will occur within the first 6 weeks of therapy or not at all and may be ameliorated by corticosteroid therapy.

6.10.14 Clofazimine

Clofazimine is a fat-soluble riminophenazine dye used in combination with rifampicin and dapsone as multidrug therapy (MDT) for the treatment of leprosy. It has been used for other mycobacterial infections in combination with other antimycobacterial drugs particularly to treat *Mycobacterium avium* infections in AIDS patients and *M. avium* ssp. *paratuberculosis* infection in Crohn's disease patients and in Melkersson-Rosenthal syndrome patients.

Clofazimine, initially known as B663, was first synthesized in 1954 in Dublin as an antituberculosis drug. The drug proved ineffective against tuberculosis, but in 1959 Chang identified its effectiveness against leprosy what later was confirmed by Brown and Hoogerzeil [210, 211].

Clofazimine works by binding to the guanine bases of bacterial DNA, thereby blocking the template function of the DNA and inhibiting bacterial proliferation. It also increases activity of bacterial phospholipase A2, leading to release and accumulation of lysophospholipids, which are toxic and inhibit bacterial proliferation [212].

Clofazimine also acts as FIASMA (functional inhibitor of acid sphingomyelinase) [213]. It may also bind to bacterial potassium transporters, thereby inhibiting their function.

Dosage: For leprosy for adults, 300 mg once a month and 50 mg once daily. For T2R sometimes 300 mg a day is given for a short time. For other mycobacteria 100–200 mg daily. Children according to weight.

6.10.14.1 Adverse Effects

Darkening of the skin is the major side effect. The fat becomes yellowish. There are a few toxic effects: Abdominal symptoms are dose dependent and usually not severe, but they may rarely be fatal. Rare reports have included splenic infarction, bowel obstruction, and gastrointestinal bleeding.

6.10.15 Azithromycin

Azithromycin is a subclass of macrolide antibiotics. It is derived from erythromycin, with a methyl-substituted nitrogen atom incorporated into the lactone ring, thus making the lactone ring 15-membered. It works against quite a number of mycobacteria, particularly the MAC. *M. abscessus* has developed resistance to azithromycin dihydrate to varying degrees.

Azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome and thus inhibits translation of mRNA [214].

Dosage: 600 mg orally OD for an adult. Children: 10–12 mg/kg (maximum, 500 mg/dose) orally OD. Some double the dose for severe infections.

6.10.15.1 Adverse Effects

The most frequent reported adverse effects for azithromycin have been nausea, diarrhea, and abdominal pain. Azithromycin can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. It can prolong the QT interval. On the double dose, the side effects are more prominent. Allergic reactions are not common [214].

6.10.16 Amikacin

Amikacin is an aminoglycoside antibiotic. It can be used to treat non-tubercular mycobacterial infections and tuberculosis (if caused by sensitive strains) when first-line drugs fail to control the infection.

It works by binding to the bacterial 30S ribosomal subunit, causing misreading of mRNA and leaving the bacterium unable to synthesize proteins vital to its growth.

Dosage: May be administered once or twice a day but must be given by the intravenous, via nebulization, or intramuscular route. There is no oral form available as amikacin is not absorbed orally.

6.10.16.1 Adverse Effects

Adverse effects of amikacin are similar to that of other aminoglycosides. Kidney damage and hearing loss are the most important effects. In people with kidney failure, dosage must be adjusted according to the creatinine clearance, usually by reducing the dosing frequency [215].

6.10.16.2 Future Developments

The greatest problem at this moment in the treatment of mycobacterial infections is multidrug resistance [216]. Some patients do not respond to treatment and have to receive drugs that are still under research. Some are already approved, like thioridazine [217] and linezolid [218], but also there are new classes of drugs like benzothiazinones, diarylquinolines (bedaquiline), and other compounds such as delamanid and SQ109 [218].

Another problem is the drug interactions resulting into low serum levels of the drugs affecting dosing [219].

In this context, the identification of TREM1 signaling is interesting and promising, providing a new angle for activation of monocytic cells by *M. tuberculosis* antigenic determinants. Potentially, *M. tuberculosis*-derived molecules target this pathway, in synergy with TLRs, to activate innate and adaptive immune responses. Thus, vaccination as treatment may become possible [220].

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Chapter 7
The Antifungal Drugs Used in Skin Disease

Bárður Sigurgeirsson and Roderick J. Hay

7.1 Introduction

The medical treatment of fungal infections affecting the skin has changed considerably over the past 200 years from the application of crude astringent or emollient dressings to the current use of active and specific antifungal agents. Indeed in the early part of the nineteenth century, there was still a debate over the need to treat fungal infections, such as favus, at all, some arguing that the infection "exerted a salutary influence on the constitution" and therefore required no treatment, whereas others believed that it always interfered with "the moral and intellectual faculties" of children affected by it [1] and should be treated. There were a wide variety of different options although popular choices including bathing affected areas in sulfurous or alkaline waters. The later treatments devised were equally controversial. For instance, in the *Dermatophyte* infection, favus, the use of depilatory plasters was much advocated [1]. The plaster might contain, among other ingredients, copper bicarbonate and pitch (tar), both of which are now recognized to have antifungal properties. The plaster was applied to the affected scalp and left in place for 2–3 days before being rapidly removed and then replaced by another such plaster; such treatment was widely practiced although acknowledged to be very distressing to the patient. A more humane approach used a depilatory ointment containing astringents such as potassium bicarbonate in hog's lard applied every 10–15 min to the scalp for varying periods. This resulted in inflammation and subsequent shedding of the affected hairs without the trauma of physical removal.

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The introduction of early precursors of the modern approach to the development of antibiotics through the work of the new chemical and dyeing industries in the late nineteenth century provided a number of different chemicals, some of which had an antifungal effect. They included gentian violet, brilliant green, and magenta. With the passage of time, some of these became viable additions to a list of antifungal treatments available. These included brilliant green [2], gentian violet [3], and magenta paint, the last of which, when combined with resorcinol, was known as Castellani's paint after Aldo Castellani [4]. Gentian violet, while less effective in *Dermatophyte* infections, had a therapeutic effect in *Candida* infections.

A further advance was the combination of salicylic acid with benzoic acid, the former providing a means of descaling fungal infected skin and the other in inhibiting growth of the organisms. Benzoic acid compound was introduced as an antifungal treatment for superficial mycoses and is known as Whitfield's ointment. It is still available for use today [5]. It contains a mixture of 3 % salicylic acid and 6 % benzoic acid. After 1945 developments in treatment focused on antifungals with specific antifungal activity. The first of these, mainly used for superficial infections, were derivatives of undecylenic acid [6] such as zinc undecenoate which inhibits the growth of *Dermatophytes* or thiocarbamates, tolnaftate [7], and tolciclate [8] which were the first inhibitors of squalene epoxidase which plays a key role in the biosynthesis of ergosterol in the fungal cell membrane. Another early specific antifungal was haloprogin, an acetylenic compound, which was thought to inhibit oxygen uptake; haloprogin had a broader spectrum of activity, affecting yeasts as well as *Dermatophyte* fungi. With the discovery of the antifungal activity of a novel antibiotic, nystatin, [9] in 1950, a new family of antifungal agents, the polyenes, also derived from microorganisms, *Streptomyces* species, such as *S. nodosus*, evolved. These include the topically active compounds nystatin and natamycin [10] as well as amphotericin B [11] which when stabilized with bile salts lasts provided an intravenous means of treatment. Other polyene drugs, such as hamycin, were not developed further for human use. Nystatin is still used in the treatment of superficial mycoses, and amphotericin B, although usually nowadays given in a lipid-associated form, remains a first-line drug in the management of systemic mycoses. In 1958 griseofulvin, a compound synthesized of the mold fungus *Penicillium griseofulvum*, was found to be active orally in the treatment of dermatophytosis in humans [12], and its rapid development led to the rapid elimination of tinea capitis in much of Europe and the United States. It was only active orally although many attempts have been made to produce a topically active version; yet none have been commercially viable. The drug works through inhibition of the formation of microtubules in the fungal cell.

The early 1970s saw the introduction of the first azole antifungals whose mode of action was on the formation of the fungal cell membrane at the step of inhibition of 14 α demethylase. The first products miconazole [13] and econazole [14] have been followed by other imidazoles and then by a subbranch of this group called triazoles. Ketoconazole was the first of these compounds to be found to have activity after oral absorption [15] although early formulations of clotrimazole in the

form of troches produced low serum levels. Ketoconazole was succeeded by fluconazole and then by newer triazoles such as itraconazole [16], posaconazole [17], and voriconazole [18], all of which are absorbed after oral administration. Another family of antifungal agents, the allylamines, was developed which had both topical, terbinafine, butenafine, and naftifine, and oral activities, terbinafine [19]. These are all potent inhibitors of squalene epoxidase. Ciclopirox olamine, a hydroxypyridone antifungal which disrupts the cell membrane structure [20], and the morpholine derivatives amorolfine which inhibits two stages of the formation of ergosterol, Δ14 reductase and Δ7-D8 isomerase activity, were to later additions.

Other recent developments have been the introduction of the echinocandins such as caspofungin, anidulafungin, and micafungin, all available as intravenous compounds used in the treatment of *Candida* and other systemic infections [21]. They act by inhibition of the formation of the fungal cell wall through interaction with 1,3 β-glucan synthase. They are not used in dermatology. The triazole antifungals have also expanded, although at the time of writing no new drugs have been licensed: albaconazole, isavuconazole, ravuconazole, terconazole, and pramiconazole [22–24]. A further topical thiazole agent, abafungin [25], has also been assessed in clinical trials, mainly against *Dermatophyte*s, but has not yet been licensed.

Much work has also been performed to try to alter the way in which antifungals are absorbed, penetrate, or achieve optimal bioactivity. These include the formulation of amphotericin B with lipids such as liposomes (AmBisome) or lipid microstrands (Abelcet), as a means of reducing toxicity [26]. The reformulation of azoles such as itraconazole to overcome variations in absorption, e.g., Lozanoc [27], has also been attempted. In the case of the topical agents for treatment of cutaneous mycoses, there has been considerable interest in developing other methods of treatment that improve nail penetration. Some of these compounds are available such as amorolfine [28] nail lacquer which is one of the first agents to be presented in the form of a Transungual Delivery System, or TUDS, designed to enhance penetration, in this case by allowing the drugs to concentrate in a stable base before penetration through the nail plate; others such as oxaborole and some of the terbinafine penetration enhancers (see Chapter 10) are in development.

Under specific sections, other approaches to therapy including lasers and photodynamic therapy will be discussed.

In the current day, the treatment of fungal infections is now comparatively straightforward, and in uncomplicated infections, cure rates are around 80 % [29]. The treatment results are less satisfactory in certain forms of superficial fungal infection, namely, onychomycosis, mycoses in the presence of immunodeficiency, infection due to uncommon organisms such as *Fusarium* or *Neoscytalidium* species, and very widespread infections such as extensive tinea corporis. There is now a wide selection of antifungal agents which can be used in both topical and oral formulations [30–33]. All these are effective in a substantial majority of patients, provided they are used regularly and as instructed.

7.2 Topical Applications

A great variety of topical applications have been used for the treatment of ringworm infections [32]. Allergic contact dermatitis is rare. Irritant effects may occur with any of them, especially on raw skin and in fissures between the toes. However benzoic acid compound ointment (Whitfield's ointment), full strength, is particularly an irritant and is not used on tender skin sites, such as the scrotum or the groins. Magenta paint (Castellani's paint) is still used in some cases of inflammatory tinea pedis, particularly when bacterial infection coexists, although potassium permanganate followed by a topical antifungal is preferred. Other cream or powder preparations that can be purchased without prescription include tolnaftate or zinc undecenoate.

Imidazole preparations for topical use, such as clotrimazole, econazole, and ketoconazole, are now well established as effective treatments in ringworm infections with an extremely low incidence of adverse reactions; other drugs in this group, miconazole, isoconazole, tioconazole, and sulconazole, are equally effective. Newer preparations such as sertaconazole, luliconazole [34], and isoconazole [35] are available in some countries. Generally they are used in cream, solution, or spray formulations at a concentration of 1 %. Most are used twice daily for 2–4 weeks although bifonazole is licensed for once-daily use.

The major topical alternative is the topical formulation of terbinafine. Terbinafine applied topically has been shown to produce responses in some *Dermatophyte* infections in very short periods of application, e.g., 1–7 days. There is also a topical formulation of terbinafine which is designed for use in infections of the sole of the foot.

Ciclopirox, amorolfine, and bifonazole are available as topical treatments in some but not all countries. The first two agents are available as specially formulated topical nail treatments and the latter as both a cream formulation and as combined treatment in a urea based for nail ablation.

The most recent Cochrane review of topical treatments for foot infections indicates little difference in efficacy between these different azole compounds and alternatives.

7.3 Oral Antifungals

7.3.1 Griseofulvin

This is a metabolic product derived from several species of *Penicillium*, which was first isolated from *P. griseofulvum*. Its activity, which is fungistatic, is largely restricted to *Dermatophyte* infections. It has little activity against yeasts and other mold fungi. The mode of action appears to be in part, through inhibition of the formation of intracellular microtubules; as a result it inhibits nucleic acid synthesis,

arresting cell division and inhibiting fungal cell wall synthesis [36–38]. Resistance to griseofulvin among *Dermatophytes* is rare. The smaller particle size microcrystalline preparations of griseofulvin are better absorbed than those with larger particles, and the micronized form is now the standard preparation. Unlike itraconazole, griseofulvin is not firmly bound to keratin.

The usual human regimen is 10 mg/kg/day (1,000–2,000 mg daily) given in tablet form, or solution form for children; the latter is no longer available in many countries. Treatment duration varies between 2 and 4 weeks for tinea corporis to over 1 year for onychomycosis of toenails. In tinea capitis, a single dose of 1–2 g griseofulvin has been reported to be effective in some patients with tinea capitis. Drug interaction with phenobarbital and coumarin anticoagulants occurs. Headaches and nausea are common complaints with griseofulvin; however, serious side effects have been extremely rare. There are a few reports of apparent precipitation or exacerbation of systemic lupus erythematosus (SLE) and porphyrias by griseofulvin. Occasionally, urticarial rashes are seen, and light-sensitivity eruptions (distinct from lupus erythematosus and porphyria) have occasionally been reported.

The use of griseofulvin has largely been superseded in many countries by terbinafine or itraconazole, except in tinea capitis.

7.3.2 Terbinafine

Discovered in 1983, it is closely related to naftifine [19, 39]. Terbinafine was licensed in Europe in 1991 and in 1996 in the United States. It is an allylamine that inhibits the enzyme squalene epoxidase (Fig. 7.1) and thus depletes the fungal cell wall of ergosterol, a key sterol component in the plasma membrane of the fungal cell [40, 41]. A deficiency of ergosterol results in a fungistatic effect similar to that seen with the azole antifungal compounds. Since the biosynthetic pathway of ergosterol is disrupted, squalene accumulates in the intracellular space, which is believed to exert a further toxic effect on susceptible fungal cells, thereby exerting fungicidal activity [42].

The two main antifungal allylamine compounds in clinical use are naftifine and terbinafine. Both are active in vitro against *Dermatophytes* in addition to other fungi. Terbinafine is a broad-spectrum antimycotic drug that exhibits the best activity against *Dermatophytes*, reasonable activity against most *Aspergillus* species and *Scopulariopsis brevicaulis*, but poorer response against yeasts including most *Candida* species [43–46]. It is both fungicidal and fungistatic (Fig. 7.1). Terbinafine is quickly absorbed after oral intake, is 99 % bound to plasma proteins, and accumulates in the skin and adipose tissue, from where it is slowly released [47].

Terbinafine can be given topically or orally. When given orally, it is rapidly laid down in the stratum corneum, and it persists in the nails at high concentrations for several months. These may exceed the minimum inhibitory concentration 80 days after the end of therapy. Terbinafine is given orally in a dosage of 250 mg/day. It has

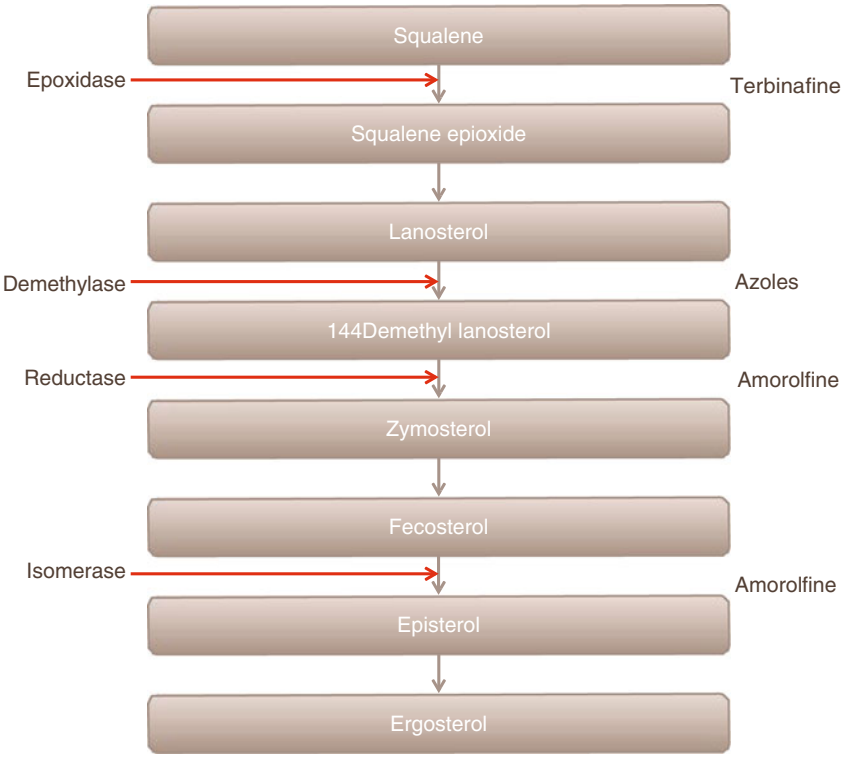

Fig. 7.1 Mechanism of action of antifungal drugs. *Red arrows* indicate the enzyme that is blocked by the corresponding drug

produced rapid and long-lasting remissions in both nail disease and persistent tinea pedis as well as tinea corporis. A smaller tablet form of 125 mg is available in some countries for treatment of children.

Safety Terbinafine is an unusual cause of significant drug-to-drug interactions [39], probably because terbinafine does not interact with the mammalian cytochrome P-450 enzyme system. In vitro studies have shown that terbinafine inhibits the CYP2D6 liver enzyme and may be of importance for patients taking tricyclic antidepressants, SSRI antidepressants, MAO inhibitors, and beta-blockers. Terbinafine can increase serum levels of imipramine and nortriptyline [48, 49].

The need for monitoring of liver function tests in patients taking terbinafine has been debated. In the US clinical trials, asymptomatic liver enzyme abnormalities have occurred in 3.3 % of patients receiving terbinafine versus 1.4 % of patients receiving placebo [50]. Signs of hepatobiliary dysfunction were seen in 1:45,000 patients [50]. The SPC (Summary of Product Characteristics) now recommends monitoring in patients with and without preexisting liver disease (pretreatment and after 4–6 weeks of treatment) [48] since hepatitis can occur without preexisting liver disease.

Terbinafine is generally well tolerated, but that does not mean that adverse events do not occur [51]. In a large uncontrolled post marketing surveillance study of 25,884 patients, adverse events were reported in 10.4 %, mainly from the gastrointestinal system (4.9 %) and skin (2.3 %) [51]. The most common reactions in the skin are eczema, pruritus, urticaria, and rash [51]. Serious adverse events (SAEs) occur, but are rare [52]. In a register-based study (the National Adverse Reaction Database) from Denmark, SAEs during a 10-year period were studied [53].

Terbinafine use as measured by DDD rose steadily in the period studied, from 929,000 DDD in 1998 to 3,132,000 DDD in 2007. During this period 263 patients reportedly experienced an adverse event due to terbinafine. One third of the reports noted skin reactions, subacute cutaneous lupus erythematosus ($n=4$), erythema multiforme ($n=8$), exfoliative dermatitis ($n=8$), Stevens-Johnson syndrome ($n=2$), and toxic epidermal necrolysis (TEN) ($n=2$) [53]. Taste disturbances were seen in ten patients. Hepatobiliary disorders ($n=7$) and increases in liver enzymes ($n=22$) together accounted for 15 % of the reports. Gastrointestinal disorders ($n=17$) and general disorders ($n=17$) each accounted for 9 % [53]. One case of death was reported during the period studied: an 86-year-old man died of pancytopenia on receiving treatment for fungal skin infection [53].

One study estimated the frequency of erythema multiforme to be 15 per 110,000 patients treated with terbinafine [54]. So it must be remembered that although terbinafine is perceived as a relatively safe medication, serious adverse events occur although they are rare.

7.3.3 Itraconazole

This is an orally absorbed triazole. It has similar activity to the imidazole and ketoconazole, but with less risk of hepatotoxicity. Its mode of action is through the inhibition of the cytochrome P-450-dependent demethylation stage in the formation of ergosterol on the fungal cell membrane (Fig. 7.1) [55]. It is active in vitro as a fungistatic drug against all the main superficial fungal pathogens including *Candida albicans*, as well as a wide range of fungi that cause deep infections such as *Histoplasma capsulatum*. Itraconazole is well absorbed orally, and because of its highly lipophilic character, it is accumulated in the tissue at a higher level than in the plasma [56]. Itraconazole rapidly penetrates to the outer stratum corneum and is also found in sebum. It is strongly bound to keratin-containing tissues and, in the nail, for instance, may persist long after cessation of therapy.

It has been shown that after 3 months of 200 mg/day itraconazole, levels in the toenail persist for up to 6 months [57]. This feature allows a range of different dose regimens. These have evolved so that the initial treatments first described involving 100 mg/day itraconazole have been superseded by higher or intermittent (pulsed) therapy. It is active against a wide range of *Dermatophytes* and is effective in regimens of 100 mg for 15 days in tinea cruris and tinea corporis or 30 days in tinea pedis. The currently preferred regimen uses 400 mg/day, given as two daily doses of

200 mg. In tinea corporis, 1 week of therapy is sufficient and in tinea pedis, 2 weeks. For onychomycosis, a regimen of 400 mg/day for 1 week every month for 3 months is usually given. Occasionally, longer periods of treatment are needed. Although it is not licensed yet in many countries for the treatment of tinea capitis in children, it is effective in this indication.

The bioavailability of the drug is increased if it is taken with a fatty meal, but can be decreased in patients taking drugs that impair gastric acidity, such as histamine-2 blockers and antacids [58].

Safety Itraconazole is embryotoxic and teratogenic in rats [31] and should not be used during pregnancy [59]. Women of childbearing potential taking itraconazole should use contraceptives. A very small amount of itraconazole is excreted in human milk [59], and therefore itraconazole should not be given to breastfeeding women.

Itraconazole is generally well tolerated. The incidence of side effects is 7 % with short-term treatment, but rises to 12.5 % with longer duration of therapy [31, 60, 61]. The most common side effects are headache and gastrointestinal symptoms such as nausea, dyspepsia, abdominal pain, diarrhea, and flatulence [52]. Dermatological symptoms such as rash, pruritus, and urticaria and acute generalized exanthematous pustulosis and toxic epidermal necrolysis are less common [52].

Elevated liver function tests have been described in 0.3–5 % of cases [31, 59]. Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have been described [59]. Liver function monitoring is recommended in patients receiving treatment with itraconazole of over one month duration [59]. Itraconazole may be associated with congestive heart failure [62, 63]. High-dose itraconazole (400 mg/day) causes a significant decrease in serum LDL-cholesterol and a significant increase in HDL-cholesterol [64].

Absorption of itraconazole from capsules is impaired when gastric acidity is reduced in patients with reduced gastric acidity; it is advisable to administer the drug with an acidic beverage and/or a high-fat meal [59].

Itraconazole is metabolized in the liver by CYP3A4 enzyme system and therefore has a long list of potential drug interactions (Table 7.1). The interacting drugs are categorized as follows: *contraindicated* (2 weeks washout), *not recommended* (2 weeks washout), or *use with caution* (careful monitoring required) (see Table 7.2).

7.3.4 Ketoconazole

This orally active imidazole is a broad-spectrum antifungal agent. It was the first broad-spectrum oral antifungal drug. In ringworm infections requiring systemic treatment, it offers an alternative agent and is given in a 200–400 mg/day regimen with food (for adults). It works well on *Dermatophytes* and *Candida*, but the effect on molds is poor [15]. Hepatitis is a proven complication, occurring in 1 in 10,000 patients. Because of this, ketoconazole is not used in Europe and the United States for superficial infections. At high doses, ketoconazole may also inhibit androgen biosynthesis.

Table 7.1 Drug interactions

Type of drug interaction	Terbinafine	Itraconazole	Fluconazole
Decreased absorption of antifungal drug (mainly itraconazole capsules)		Antacids	
		H2-receptor antagonists	
		Proton pump inhibitors	
		Didanosine	
Antifungal drug	Rifampin	Rifampin	Rifampin
Decreased		Rifabutin	
		Phenytoin	
		Isoniazid	
		Carbamazepine	
		Nevirapine	
	Phenobarbital	Phenobarbital	
		Statins	
Increased concentration of coadministered drug	Warfarin	Warfarin	Warfarin
		Phenytoin	Phenytoin
	Nortriptyline		Nortriptyline
	Imipramine	H1 antagonist	H1 antagonist
	Nicotinamide		
	Desipramine	Cyclosporine	Cyclosporine
		Tacrolimus	Tacrolimus
		Sulfonylureas	Sulfonylureas
		Terfenadine	Terfenadine
		Astemizole	Astemizole
		Rifabutin	Rifabutin
		Midazolam	Midazolam
		Triazolam	Triazolam
		Alprazolam	Alprazolam
		Calcium channel antagonists	Calcium channel antagonists
		Quinidine	Quinidine Statins Zidovudine Theophylline
		Statins Zidovudine Pimozide Digoxin	Diazepam Amitriptyline Losartan Irbesartan
		Fluoxetine Corticosteroids	Cyclophosphamide Methadone Sulfamethoxazole
		Vinca alkaloids Indinavir Saquinavir Buspirone Busulfan Sildenafil Dofetilide Cisapride Protease inhibitors	

(continued)

Table 7.1 (continued)

Type of drug interaction	Terbinafine	Itraconazole	Fluconazole
Drugs increasing level of antimycotic	Cimetidine		Hydrochlorothiazide and possibly other thiazide diuretics
Drugs that may be decreased in activity		Oral contraceptives Antipyrine	Oral contraceptives

Drug interactions of antifungal drugs. Adapted from Brodell, Dismukes [76] Lamisil SPC [48], Sporanox SPC [59]. This list may not be complete. Readers are advised to check the manufacturers' prescribing information to see whether additional contraindications for drug use have been introduced

Table 7.2 Itraconazole drug interactions

Drug class	Contraindicated	Not recommended	Use with caution
Alpha-blockers		Tamsulosin	
Analgesics	Levacetylmethadol (levomethadyl), methadone	Fentanyl	Alfentanil, buprenorphine IV and sublingual, oxycodone
Antiarrhythmics	Disopyramide, dofetilide, dronedarone, quinidine		Digoxin
Antibacterials		Rifabutin	
Anticoagulants and antiplatelet drugs		Rivaroxaban	Coumarins, cilostazol, dabigatran
Anticonvulsants		Carbamazepine	
Antidiabetics			Repaglinide, saxagliptin
Anthelmintics and antiprotozoals	Halofantrine		Praziquantel
Antihistamines	Astemizole, mizolastine, terfenadine		Ebastine
Antimigraine drugs	Ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)		Eletriptan
Antineoplastics	Irinotecan	Dasatinib, nilotinib, trabectedin	Bortezomib, busulfan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids
Antipsychotics, anxiolytics, and hypnotics	Lurasidone, oral midazolam, pimozide, sertindole, triazolam		Alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone

Table 7.2 (continued)

Drug class	Contraindicated	Not recommended	Use with caution
Antivirals			Maraviroc, indinavir, ritonavir[b], saquinavir
Beta-blockers			Nadolol
Calcium channel blockers	Bepridil, felodipine, lercanidipine, nisoldipine		Other dihydropyridines, including verapamil
Cardiovascular drugs, miscellaneous	Ivabradine, ranolazine	Aliskiren	
Diuretics	Eplerenone		
Gastrointestinal drugs	Cisapride		Aprepitant, domperidone
Immunosuppressants		Everolimus	Budesonide, ciclesonide, cyclosporine, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid regulating drugs	Lovastatin, simvastatin		Atorvastatin
Respiratory drugs		Salmeterol	
SSRIs, tricyclics, and related antidepressants			Reboxetine
Urological drugs		Vardenafil	Fesoterodine, imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Others	Colchicine, in subjects with renal or hepatic impairment	Colchicine	Alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

Drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding coadministration with itraconazole. Based on SPC for itraconazole [59]. This list may not be complete. Readers are advised to check the manufacturers' prescribing information to see whether additional contraindications for drug use have been introduced

7.3.5 Fluconazole

Fluconazole is an orally active bis-triazole antifungal used for the treatment of *Dermatophyte* and *Candida* infections as well as systemic mycoses. Being an azole it inhibits the same step as other azoles in the ergosterol biosynthesis (Fig. 7.1) [65].

This leads to ergosterol depletion and fungistatic action [66]. This antifungal is dependent on the CYP450 system. Fluconazole interacts with the cytochrome system

more weakly than itraconazole, but despite this there is potential for drug-drug interactions (Table 7.1) [67]. Although the MIC for fluconazole is high, it works well against most fungi that cause dermatomycoses [68]; in vitro drug sensitivities are a poorer predictor of antifungal efficacy with this drug. In contrast with many other azoles and terbinafine, fluconazole does not bind strongly to the plasma proteins. It is mostly eliminated unchanged and has a long half-life, which allows once weekly dosing. It is metabolically stable and excreted in urine (91 %) and feces (2 %) [69].

Because of this the dose needs to be adjusted depending on creatinine clearance [70]. It is given either as a continuous regimen of 100–200 mg daily or intermittently at 150 mg/week for 2–3 weeks for tinea corporis and tinea cruris and somewhat longer for dry-type tinea pedis. It is also reported to be effective given in weekly doses in onychomycosis. There are fewer interactions than with itraconazole, but, like the latter, side effects are rare and mainly confined to gastrointestinal discomfort.

However, drug resistance in *Candida* species, particularly *C. krusei* and *C. glabrata*, has been described. There is *C. albicans* resistance in patients particularly in those with HIV/AIDS.

Safety Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor, and these concomitant drugs that are metabolized through these enzymes should be avoided or closely monitored (Table 7.1). It should not be coadministered with oral hypoglycemic agents, phenytoin, cyclosporine, rifampin, theophylline, or terfenadine (Table 7.1).

Fluconazole is well tolerated in general. Adverse drug reactions reported include mostly mild gastrointestinal disturbances, skin rashes, headache, and diarrhea [68, 71, 72]. In a meta-analysis, pooled risks for discontinuation of treatment due to any adverse event were 1.98 % (95 % CI, 0.05–3.92) with fluconazole 150 mg/week and 5.76 % (95 % CI, 2.42–9.10) for fluconazole 300–450 mg/week [73]. The risk for discontinuation because of elevated liver function tests was 0.4–0.9 %, depending on the dose [73]. Due to limited data and long treatment period, liver function test monitoring may be indicated, but this matter is controversial [74].

7.3.6 Other Antifungal Drugs

There is little data at present on the use of posaconazole, although this is active in onychomycosis, and voriconazole in dermatophytosis. Both drugs have a similar mode of action to itraconazole and voriconazole and are mainly used for the treatment or prophylaxis of systemic mycoses. Voriconazole has a slightly higher incidence rate of reported liver adverse reactions than posaconazole and is also associated with the development of photosensitivity and rapidly growing skin cancers, mainly nonmelanoma but melanomas have been reported. Other newer azole antifungal agents such as ravuconazole, albaconazole, and pramiconazole are not marketed for the treatment of superficial mycoses at the time of writing.

The echinocandins have not been used in superficial or mucosal fungal infections apart from *Candida* esophagitis. All are given intravenously. Renovate (VT-1161) is a potent and selective orally available inhibitor of fungal CYP51. It blocks the production of ergosterol. It has been demonstrated to be effective against *Candida* and *Dermatophytes* and is currently in phase II trial [75].

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Chapter 8
Fungal Infections of the Skin

Roderick J. Hay

8.1 Introduction

The fungi are recognized causes of disease in all regions of the world [1]. The most common of these infections are superficial mycoses, and these include diseases such as dermatophytosis or ringworm and candidosis. However, disabling, and potentially fatal, deep, or systemic fungal infections can also occur although many are geographically restricted to specific environments; others are opportunistic infections that develop in the ill and immunosuppressed. Fungi are eukaryotes which have a similar structure to that of mammalian cells although they also have a polysaccharide-based cell wall. Fungi grow in one of two different ways [2]. In some growth forms, known as yeasts, single cells reproduce by a process of bud formation that gives rise to single daughter cells. Other morphological forms, the mycelial or mold fungi, grow as chains of cells which appear as strands of cells, hyphae. These mycelial cells generally do not separate. Other fungi, the dimorphic fungi, exist as either yeasts or mycelia at different stages of their life cycles, a process that is often temperature dependant. In order to survive, fungi propagate by forming specialized reproductive structures or spores (conidia). These vary in morphology according to growth conditions, the most elaborate being produced only under conditions of laboratory culture. However, they may also form vegetative conidia called arthrospores which are usually located within a hyphal chain in vivo. These are thick walled cells that are able to resist periods of desiccation and poor nutrition. Arthrospores are formed by dermatophytes in vivo, for instance, in epidermis or nail, and their formation may affect the ability of antifungal drugs to destroy cells. Other superficial fungi have different structural adaptations. For

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instance, *Malassezia* species on the skin are also equipped with a thick cell wall which is grooved on the inside. Again it is thought to enable the organism to survive on the skin surface, and after treatment these cell walls are often retained even though the cell cytoplasm has been destroyed by an antifungal drug.

Fungi can cause human disease in a number of different ways, through the production of toxins or mycotoxins, through sensitizing antigens (allergens), or by the invasion of tissue. Invasive diseases caused by fungi are known collectively as the mycoses: the superficial, subcutaneous, or systemic mycoses. The superficial mycoses have been ranked as the fourth most common of all human diseases, largely because they are common at all age groups, in all climates and are often chronic unless treated. The distribution of superficial mycoses is affected by a number of factors [3] such as the presence of the organisms in the environment, host immunity, frequency, and route of exposure.

8.2 Superficial Mycoses

Superficial infections caused by fungi are common globally [3]. In addition the distribution of some is dependent on local climatic conditions or the existence of endemic foci of specific species seen, for instance, in tinea imbricata or tinea capitis. The main superficial infections are dermatophytosis or ringworm, superficial candidosis, and pityriasis (tinea) versicolor. However, other conditions such as foot or hand infections caused by *Neoscytalidium dimidiatum* as well as the hair shaft infections, white and black piedra, and tinea nigra are also seen.

8.3 Dermatophytosis (Ringworm)

The dermatophyte or ringworm fungi are frequent causes of superficial infection [2]. These mold fungi can invade the epidermis but their growth remains confined to the stratum corneum, the hair shaft, or the nail plate. There are three pathogenic genera of dermatophyte in humans: *Trichophyton*, *Microsporum*, and *Epidermophyton*. These organisms normally cause exogenous infections that originate from a source external to the patient. Human infections originate from one of three different sources—other humans, animals, or soil, known, respectively, as anthropophilic, zoophilic, or geophilic.

8.3.1 Epidemiology

In most countries dermatophytoses are common [3–6]. The main types of infection seen are tinea pedis, tinea corporis, tinea cruris, and tinea capitis. Tinea pedis is very common and in temperate climates may affect some 15 % of the population; it is

less common in many parts of the tropics. Occlusion of the feet with shoes or socks predisposes to infection, although a higher proportion of the populace may have asymptomatic infections of the skin plantar skin. In communities where there is heavy industry, such as mining or petroleum refining, the incidence of foot infections may be much higher, because of the ease of spread between workers who use industrial foot wear, such as heavy boots, and communal showering facilities. There are a number of different organisms which can cause web space infections of the foot, known as athlete's foot, ranging from dermatophytes to *Candida* or *Neoscytalidium* species and Gram-negative bacteria, and erythrasma, a Gram-positive bacterial infection. Populations of microorganisms on the feet, particularly those affecting the interdigital spaces, may vary over time and one may replace another to cause infection [7, 8]; the term "dermatophytosis complex" has been coined to describe this phenomenon where the dermatophytes are replaced, usually with Gram-negative bacteria such as *Pseudomonas* species. Dermatophyte infections of the feet may occur at all ages but usually start in childhood at 5–6 years of age reaching a peak in early adult life.

Tinea corporis or dermatophytosis of the trunk is usually a sporadically occurring condition as the opportunities for spread of infection are less. Often the infection originates from an animal with which the patient has contact. The most common sources are domestic pets such as cats or dogs which can be infected with *Microsporum canis*. However, other sources of infection are rodents, horses, cattle, and other mammals. Infection with fungi of animal origin (zoophilic infection) depends on exposure to an appropriate and infected animal source. In other areas tinea corporis is usually an anthropophilic infection arising from contact with other infected humans, e.g., tinea imbricata due to *T. concentricum* or tinea corporis due to *T. rubrum*. Some are occupationally transmissible. For instance, sportsmen and sportswomen who come into close physical contact such as wrestlers are susceptible to transmitted dermatophytes such as *T. tonsurans* [9], although usually an infected site is the site of contact, e.g., the face or neck area.

The epidemiology and clinical features of onychomycosis and tinea capitis are discussed in separate chapters (Chaps. 9 and 10).

8.3.2 Pathogenesis

The fungi invade the skin after adhering to stratum corneum cells and producing keratinases or proteases such as subtilisins [10, 11]. Factors which encourage fungal invasion include increased environmental humidity and CO_2 content, both of which may occur in a tropical environment and in the presence of occlusion, e.g., by shoes. Less is known about those factors which determine human susceptibility, although generally it is thought that most individuals are susceptible to infection. Recently susceptibility to deep dermatophyte infections has been linked to mutations of the CARD 9 gene but as yet how susceptibility in normal populations is regulated remains a mystery [12]. The presence of antimicrobial peptides

such as defensins in human epidermis plays a role in prevention of dermatophyte invasion [10]. In addition, patients with persistent dermatophytosis affecting the palms and soles are significantly more likely to have an atopic background, with a personal or family history of eczema and asthma, than others. Resistance is largely mediated via nonspecific factors such as an increase in epidermal turnover and epidermally derived peptides or by the specific activation of T cell-mediated immunity. Patients with the acquired immune deficiency syndrome (AIDS), for instance, although not apparently showing an increased incidence of infection, may have clinically atypical and extensive lesions [13]. However, even patients with an intact immune system often have a poor immunological response to dermatophyte fungi, possibly through modulation in the expression of immune responses by dermatophyte products.

8.3.3 Clinical Features

By convention, the normal term for dermatophytosis is tinea, followed by the Latin for the appropriate part of the body affected (tinea capitis, head; tinea cruris, groin, etc.).

8.3.3.1 Tinea Corporis

This presents with a scaly and itchy rash affecting the trunk or proximal limbs [2]. The typical lesion is a circular scaling patch with some central clearance. However, in many lesions the main abnormalities, scaling or papule/pustule formation, are seen at the edge of the lesion where an intact or broken rim can just be made out. In zoophilic infection, the lesions can be raised, indurated, and very inflamed. Pustules are sometimes seen. Tinea corporis lesions may be very large and affect a wide area on the back and chest, and, in pigmented skin, postinflammatory hyperpigmentation may mark the outline of the infected area even where there is little inflammation. In patients with HIV/AIDS, the normal pattern of symptoms and signs may be altered considerably, with extensive or follicular forms being seen in some patients. The common causes of tinea corporis are *Trichophyton rubrum* and *Microsporum canis*. Generally *M. canis* is more inflammatory and circumscribed, whereas *T. rubrum* infections may be very extensive and cover large areas, often with little inflammation (Fig. 8.1). The outline of the lesion in *T. rubrum* infections may be difficult to trace, although parts of the outer rim of the lesions can be distinguished as described above.

Tinea imbricata is a specific type of tinea corporis caused by the fungus *Trichophyton concentricum*. It is endemic in remote and humid tropical areas in the West Pacific and parts of Malaysia, India, Brazil (Amazonas), and Mexico [14]. Lesions are characterized by the development of multiple concentric rings of scales which may cover a large area of the body from childhood (Fig. 8.2).

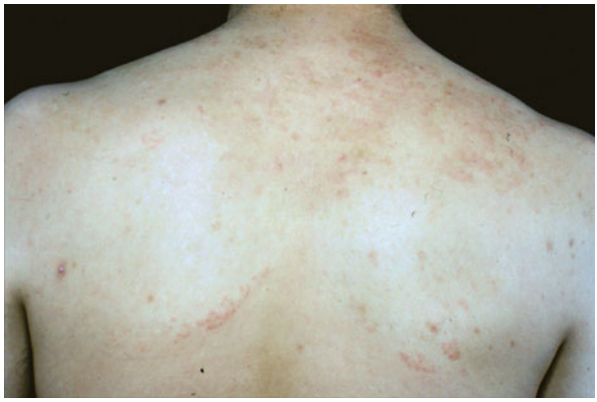

Fig. 8.1 Diffuse tinea corporis caused by *Trichophyton rubrum*

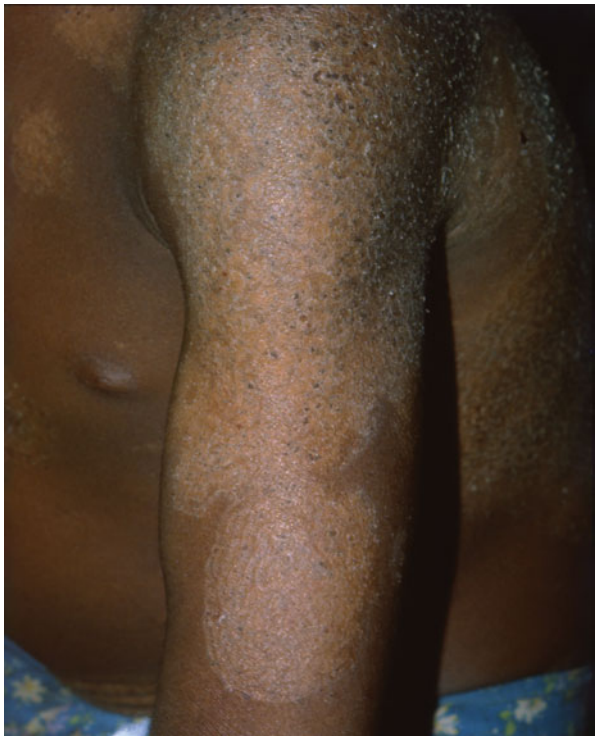

Fig. 8.2 Tinea imbricata

8.3.3.2 Tinea Cruris

Dermatophytosis affecting the groin—tinea cruris—is a sporadic infection which may be common in most humid or tropical countries. It is almost always caused by anthropophilic species of dermatophytes, mainly *Trichophyton rubrum* and *Epidermophyton floccosum*. Sometimes these infections may become common in

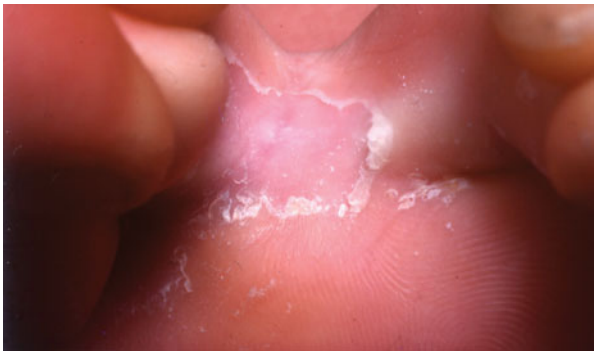

Fig. 8.3 Interdigital tinea pedis caused by *Trichophyton rubrum*

certain groups such as soldiers or prisoners. The usual lesion is an itchy rash with a raised border extending from the groin down the upper thigh and on occasions into the natal cleft. In women and men, it may extend around the waist area affecting the buttocks and upper thighs. In *T. rubrum* infections, other areas, particularly the soles or interdigital spaces on the feet, are often involved at the same time.

8.3.3.3 Tinea Pedis

Dermatophytosis affecting the feet is very common in most temperate climates; and although less common in tropical countries, it nonetheless occurs anywhere where shoes are worn. The most common sites of infection are the interdigital spaces or the soles [15, 16]. The main symptom of interdigital infection is itching. The skin is usually cracked and the main areas affected are the third and fourth interdigital spaces (Fig. 8.3). The web spaces may also appear macerated, and, if there are severe erosive changes, particularly if there is greenish discoloration of the area, Gram-negative bacteria such as *Pseudomonas* species may be implicated [7] as secondary invaders. This is the dermatophytosis complex type of infection, and these patients often have painful rather than itchy feet. Both *Candida* and erythrasma, *Corynebacterium minutissimum*, may cause maceration and whitening of the interdigital skin. *Neoscytalidium* and, less commonly *Fusarium*, species mimic dermatophytosis in the interdigital space usually presenting with itching and cracking of the skin. When *T. mentagrophytes* affects the interdigital spaces, it may cause more severe itching and the formation of vesicles or bullae (Fig. 8.4). These more inflammatory infections may also trigger an "id" reaction where the patients develop vesicular eczema (pompholyx) on the feet and the hands, the changes being more prominent on the foot where the infection started. These are immunologically mediated reactions to the presence of the dermatophyte infection, and the secondary lesions do not contain dermatophyte hyphae.

When the infection is located on the soles, plantar tinea pedis, the main signs are scaling which often presents in tiny circular patches. Usually there is little inflammation and itching may be minimal. The infection generally becomes

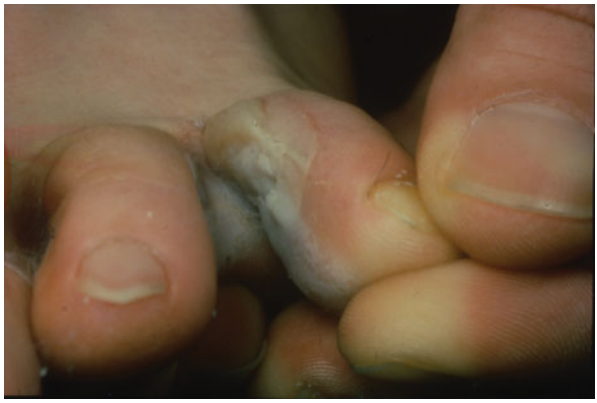

Fig. 8.4 Vesicular tinea pedis caused by *Trichophyton mentagrophytes*

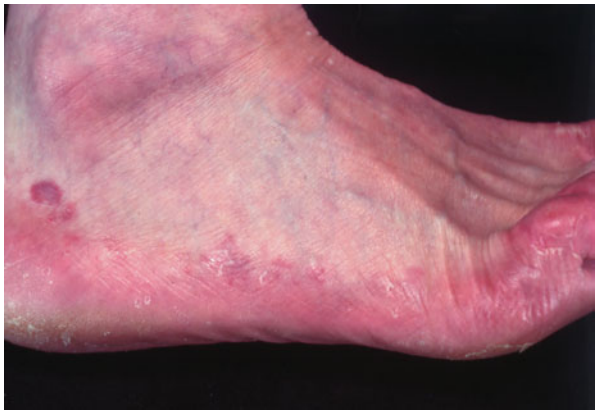

Fig. 8.5 Moccasin tinea pedis caused by *Trichophyton rubrum*

apparent when it spreads to involve the lateral borders of the feet, "moccasin-type infection" (Fig. 8.5). Here the scaling is easily seen on the lateral margins of the foot and may spread to involve the dorsal surface of the feet. This pattern is typical of *T. rubrum* infection but it can also be caused by *Neoscytalidium* species. Once again when *T. mentagrophytes* affects the soles, it may lead to the formation of bullae.

8.3.3.4 Other Sites of Infection

Dermatophyte infections can affect the palms of the hands, tinea manuum, rather in the same way as they do the soles. Often only one hand is affected and the scaling remains confined to the palmar surface, although with extensive infection, it can affect the dorsum of the hands. *Trichophyton rubrum* is the usual cause.

Dermatophytosis of the face or tinea faciei is often difficult to diagnose as the changes may be subtle with little inflammation [16]. However, generally at least

part of the outline of the infection can be seen. Some patients with tinea faciei complain of increased itching and sensitivity to sun exposure.

When the infection involves the beard area, tinea barbae, deep pustule formation and itching accompany the infection although the outline of the ring is often seen. In very severe cattle ringworm infection, caused by *T. verrucosum*, the infection in the beard area may be painful and very extensive.

8.3.4 Laboratory Diagnosis

Clinical diagnosis of dermatophytosis is not completely reliable, and ideally the presence of infection should be confirmed by demonstrating the organisms in skin scrapings taken from lesions [2]. Scrapings are generally best removed with a blunt scalpel from the edge of lesions or by using the reverse side of a scalpel blade. For diagnosis they are mounted in 5–10 % potassium hydroxide and are then microscopically examined. The organisms are seen in scrapings as chains of cells forming hyphae. In addition, they can be cultured on mycological media such as Sabouraud's agar, and their gross and microscopic morphology is used to distinguish the different species. At present molecular techniques play little part in the diagnosis of dermatophytosis of the skin [17].

8.3.5 Management of Dermatophyte Infections

The treatment of dermatophyte infections is now comparatively simple, and cure rates range from 80 to 90 %. There is a wide range of antifungal agents which can be used in both topical and oral formulations [18–20]. All these are effective in a substantial majority of patients, provided that they are used regularly and as instructed. In assessing therapeutic response, there has been a trend to favor the use of complete clinical cure as a primary end point for clinical trials; secondary end points are a complete mycological cure or combined mycological and clinical cure or clinical improvement [20, 21]. These assessments have an impact on the interpretation of studies as the older studies often used complete clinical cure or 90 % improvement as primary end points. In some forms of dermatophytosis such as interdigital tinea pedis or onychomycosis (see Chap. 10), complete clinical recovery is often not achieved during the time period of the study as the timing of improvements in the pathological changes lags behind that for disappearance of the organism.

The approach currently adopted to treatment of dermatophytosis affecting the skin is to use topical treatments for well-circumscribed infections or infections of limited extent and oral treatments for extensive infections or those affecting hair or nails where, despite many attempts to design new topical applications with a high degree of penetration to the infected site, there has yet to be a breakthrough in local

Table 8.1 Topical antifungal agents used in dermatophyte infections

Compound	Formulations	Other features
Benzoic acid compound (Whitfield's ointment)	Ointment	Cheap
Undecenoates—various brands available	Ointment, powder	Cheap
Tolnaftate	Cream, powder, lotion	Cheap
Miconazole, clotrimazole, econazole, sulconazole[a], ketoconazole, bifonazole[a]	Cream, powder, lotion, spray, shampoo (ketoconazole)	Broad spectrum including antibacterial(not ketoconazole)
Terbinafine, naftifine[a], butenafine	Cream	Very rapid expensive
Cyclopyroxolamine[a]	Cream, lotion	Broad spectrum

[a]Availability varies in different countries

therapy. A further issue of importance in the management of dermatophytosis is compliance with treatment as many patients find repeated applications time consuming and difficult, and there is a high rate of noncompliance with longer topical treatment regimens [22]. For this reason some antifungals have been assessed in trials for once rather than the more usual twice-daily application. It is difficult to comment, therefore, on their relative effectiveness as a function of the frequency of application, as many of those licensed for twice-daily use have not been formally studied in once-daily treatment regimens and may be similarly effective.

8.3.5.1 **Topical Applications** (Table 8.1)

A great variety of topical applications have been used for the treatment of ringworm infections [19, 23–41]. They have the advantage of being relatively free from adverse effects. Allergic contact dermatitis is rare. Irritant effects may occur with any of them, especially on raw skin and in fissures between the toes, but generally are not common. However, benzoic acid compound ointment (Whitfield's ointment), full strength, is particularly irritant and is not used on tender skin sites, such as the scrotum or the groin area. Magenta paint (Castellani's paint) is still used in some cases of inflammatory tinea pedis, particularly when bacterial infection coexists, although potassium permanganate followed by a topical antifungal is preferred for exudative or weeping foot lesions. Other cream or powder preparations that can be purchased without prescription include tolnaftate or zinc undecenoate. Haloprogin is another antifungal which, although it is not extensively used, is an effective topical treatment.

Imidazole preparations for topical use, such as clotrimazole, miconazole, econazole, and ketoconazole, are now well established as effective treatments in ringworm infections with an extremely low incidence of adverse reactions; other drugs in this group, isoconazole, tioconazole, and sulconazole, are equally effective. Newer preparations such as sertaconazole [28, 37], luliconazole [20], and isoconazole [23] are available in some countries. Generally the azole antifungals are available in

cream, solution, or spray formulations at a concentration of 1 %. Most are used twice daily for 2–4 weeks although some, such as bifonazole, are licensed for once-daily use. The most recent Cochrane review of topical treatments for foot infections indicates little difference in efficacy between these different azole compounds.

The major alternative treatment is the topical formulation of terbinafine [22]. Terbinafine applied locally in dermatophytosis has been shown to produce responses in some dermatophyte infections, e.g., interdigital tinea pedis, after very short periods of application, e.g., 1–7 days. Also 1 week of topical terbinafine was found to be more effective than 4 weeks of clotrimazole in tinea pedis. There is also a topical formulation of terbinafine which is designed for use in infections of the foot and across the sole in a film-forming solution which is used as a single application only [41]. The solution is applied and left to dry for 3–4 min. Other allylamines such as naftifine [33] and butenafine [34] are also effective. Ciclopirox is available in some countries as a topical application for use in dermatophytosis [26].

There has been considerable recent work on developing new formulations of topically active antifungal drugs to improve efficacy. The single application terbinafine film-forming solution was discussed above but other approaches to new formulations include both gels and sprays. Work has also been carried out to assess whether application of a co-treatment with 40 % urea would enhance clinical efficacy [36]. Few of these approaches have been adopted into clinical practice.

8.3.5.2 Oral Antifungals

The mode of action, pharmacology, and adverse events related to the oral antifungal medications are discussed in Chapter. This section is concerned with the specific use of these drugs in dermatophyte infections.

Terbinafine Terbinafine is a member of the allylamine antifungal group, which acts by the inhibition of squalene epoxidase in the formation of the fungal cell membrane. When given orally, it is rapidly laid down in the stratum corneum, and it persists in nails at high concentrations for several months. These may exceed the minimum inhibitory concentration for a long period after the end of therapy. Terbinafine is given orally in a dosage of 250 mg/day for dermatophytosis. It has produced rapid and long-lasting remissions in dry-type tinea pedis and tinea cruris, as well as tinea corporis. A smaller tablet form of 125 mg is available in some countries for treatment of children.

Itraconazole This is an orally absorbed triazole. It has similar activity to the imidazole, ketoconazole, but without the heightened risk of hepatotoxicity. Its mode of action is through the inhibition of the cytochrome P-450-dependent demethylation stage in the formation of ergosterol on the fungal cell membrane. It is active against a wide range of dermatophytes and is effective in regimens of 100 mg for 15 days

in tinea cruris and corporis or 30 days in dry-type tinea pedis. The currently preferred regimen uses 400 mg/day, given as two daily doses of 200 mg. In tinea corporis, 1 week of therapy at this dosage is sufficient and in dry-type tinea pedis 2 weeks. Occasionally, longer periods of treatment are needed.

Griseofulvin [13] This is a metabolic product derived from species of *Penicillium*, which was first isolated from *P. griseofulvum*. Its activity, which is fungistatic, is largely restricted to dermatophyte infections. The usual human regimen is 10 mg/kg/day given in tablet form. There is a solution form for children although this is no longer available in many countries. Treatment duration varies between 2 and 4 weeks for tinea corporis or cruris. The use of griseofulvin has largely been superseded in many countries by terbinafine or itraconazole, except in tinea capitis (Chap. 9).

Ketoconazole This orally active imidazole is a broad-spectrum antifungal agent. In ringworm infections requiring systemic treatment, it offers an alternative agent and is given in a 200–400 mg/day regimen with food (for adults). Hepatitis is a proven complication, occurring in approximately 1 in 10,000 patients. Because of this, ketoconazole is not used in Europe and the USA for superficial infections.

Fluconazole Fluconazole is an orally active triazole antifungal used for the treatment of dermatophyte and *Candida* infections as well as systemic mycoses. It can also be given as daily treatment of 100 mg 2–4 weeks in dermatophyte infections of the skin. It can also be used in a regimen of 150 mg/week for 2–3 weeks for tinea corporis and tinea cruris and somewhat longer for dry-type tinea pedis. There are fewer interactions than with itraconazole but, like the latter, side effects are rare and mainly confined to gastrointestinal discomfort.

There is little data at present on the use of posaconazole and voriconazole in dermatophytosis affecting the skin. New oral drugs such as pramiconazole, ravuconazole, and albaconazole have been tested by clinical trial in specific dermatophyte infections but at present have not been marketed for these indications.

8.3.6 Treatments in Practice

The different clinical forms of dermatophyte infection require different approaches to treatment. Generally, topical therapies are used for localized or mild infections and oral antifungals for the more extensive infections [23]. The oral azoles, such as fluconazole or itraconazole and terbinafine, are now the preferred oral treatments for extensive or severe dermatophytosis rather than griseofulvin; they are also used in severe steroid-treated dermatophyte infections which often develop follicular or pustular changes (Fig. 8.6).

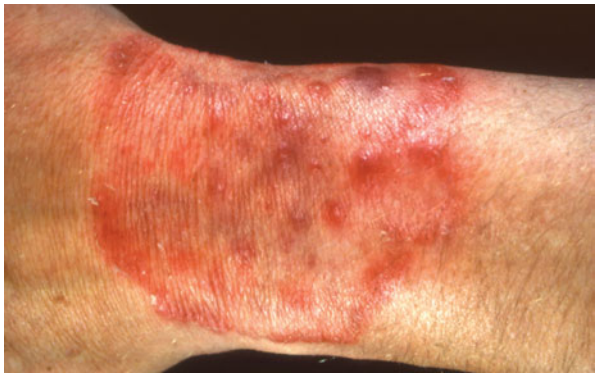

Fig. 8.6 Steroid-treated tinea corporis

8.3.6.1 Tinea Corporis

Localized or nonextensive tinea corporis responds to topical therapy applied twice daily, usually for about a month. Topical terbinafine often works in a shorter time (e.g., 2 weeks) than topically applied azoles. But because of the difficulty in accurately locating the extent of infection in more widespread infections of recent onset, oral terbinafine or itraconazole will generally be preferred, and these clear the condition in 2–3 weeks, depending on the dosage used. With griseofulvin, longer periods of treatment are effective. In tinea imbricata, the most appropriate duration of the treatment regimen is not clear although 2 weeks of terbinafine has been found to be effective.

There is a form of persistent tinea infection usually caused by *T. rubrum* at sites in the groin or the trunk which, while responding initially to treatment with either terbinafine or itraconazole, relapses quickly. Different treatment regimens have been tried including combinations of azole or allylamine oral medications plus topical azoles or allylamines. At present there is no effective remedy in these cases. In contrast tinea infections of the skin in immunosuppressed patient including those with HIV/AIDS usually respond to treatment although it is often necessary to double the normal dose.

8.3.6.2 Tinea Barbae

Tinea barbae or infections of the beard usually respond satisfactorily to itraconazole or terbinafine, sometimes in combination with topical therapy over a period of 4–6 weeks. Long-term follow-up is recommended, as late recurrences occur.

8.3.6.3 Tinea Facei

In localized cases, promptly diagnosed, topical therapy works well, especially with terbinafine or one of the imidazoles. When steroid therapy has modified the underlying infection, oral terbinafine or itraconazole is generally preferred. Most cases will clear in 3 or 4 weeks, certainly in 6 weeks, but long-standing infections may occasionally need longer periods of treatment.

8.3.6.4 Tinea Pedis

For very mild toe cleft changes, one of the topical antifungal preparations is generally used. With toe cleft changes that are more than trivial, a cream is preferred to a powder and any of the preparations discussed previously can be used for minor forms of tinea pedis. Imidazole preparations are cheap and are usually effective in up to 30 days, but topical terbinafine can be used for a period of 7 days; most antifungals are given twice daily, exceptions include bifonazole which is a once-daily treatment. The film-forming solution of terbinafine is applied once across the soles of the fee and is effective for both dry-type sole and interdigital infections. If the toe clefts are very inflamed and secondary bacterial infection is likely, potassium permanganate tablets dissolved in water used as a soak in a basin for 15–20 min twice daily can ease secondary infection. If there is any evidence of serious bacterial infection, swabs should be taken to confirm the identity of the organism. With dermatophytosis complicated by Gram-negative bacterial infection, both infections should be treated. Many topical antiseptic preparations such as povidone or hydrogen peroxide (Crystacide) products are active against the bacteria, while topical formulations of imidazoles or terbinafine can be used for the fungal infection. None of the topical antifungals has activity against Gram-negative bacteria, although most azoles, apart from ketoconazole, have moderate efficacy against Gram-positive bacteria such as *Staph aureus*. If there is clinical evidence of cellulitis, patients should receive a systemic antibacterial antibiotic.

In dry-type tinea pedis, which is usually caused by *T. rubrum*, terbinafine or itraconazole are the preferred treatments. Speed of recovery is faster and relapse rates less than with griseofulvin. Treatments using terbinafine 250 mg/day for 2 weeks or itraconazole 400 mg/day for 1–2 weeks are usually given.

8.3.6.5 Tinea Cruris

Topical therapy is usually effective within 2–4 weeks. Tolnaftate, terbinafine, and the imidazoles are well tolerated in the flexural areas, and if the diagnosis is in doubt, terbinafine and the imidazoles have the advantage of being effective topically against *Candida* as well. Where the condition has resisted topical treatment, or has spread more widely to the pubic area, the natal cleft, or the buttocks, and where topical steroids have been used, systemic treatment is advisable. Oral terbinafine or itraconazole usually produces remission in 1–2 weeks. Some patients relapse even after this therapy and a longer course of therapy may be necessary.

8.3.6.6 Tinea Manuum

Ringworm infections of the palm are not easy to clear, and oral therapy is always needed. Itraconazole and terbinafine are both effective in this condition. Most cases clear with 2–4 weeks of treatment although it may be advisable to review the results a few months after the end of treatment.

8.3.7 Prevention

Prevention of dermatophytosis is not practicable except in situations where there is a high risk of spread to other individuals. Infected individuals using gyms or public swimming paths should be encouraged to seek treatment.

8.4 Superficial Candidosis

Superficial infections due to *Candida* species are common [42] and include oral and vaginal as well as skin infections. The principal pathogen is *C. albicans*, although other species such as *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glabrata* may also cause human infections. The disease is seen worldwide, although some clinical varieties such as interdigital candidosis are more common in warm climates.

8.4.1 Epidemiology

Candida albicans is a normal commensal of the mouth, gastrointestinal tract, and vagina. Carriage rates vary but 15–60 % of normal individuals have commensal carriage in the mouth. Somewhat lower percentages have colonization of the gastrointestinal tract or vagina [43]. Colonization does not usually affect the skin. Candidosis of the skin is seen in association with diabetes mellitus (groins) and obesity (interdigital). But not all patients have a predisposing risk factor, and women with vaginal candidosis usually have no underlying heath problem. Oral candidosis is a common problem in immunocompromised patients including those with HIV/AIDS not receiving antiretrovirals [44].

Survival of the organisms in these sites depends on a variety of factors, including their ability to adhere to mucosal cells and compete with commensal bacteria. Factors which disturb this balance favor either elimination or growth and subsequent invasion by the organism. For instance, use of antibiotics eliminates other members of the commensal flora of the mouth and bowel and allows *Candida* to invade. Depression of either T lymphocyte or neutrophil-mediated immunity allows the organisms to grow and invade following inhibition of normal control mechanisms [42]. As with dermatophytes, antimicrobial peptide products expressed in the epidermis are inhibitory to *Candida* species. By contrast, in most skin infections, a key element in invasion appears to be occlusion which encourages infection, rather than any defect of host immunity.

8.4.2 Clinical Features

The main clinical forms of superficial disease are oropharyngeal, vaginal, and cutaneous candidosis. In addition, chronic mucocutaneous candidiasis is a rare chronic skin and mucosal infection of predisposed patients. Systemic candidosis is a potentially life-threatening infection generally confined to compromised patients; it occasionally presents with skin signs.

8.4.2.1 Oral Candidosis [45, 46]

There are different clinical forms which depend partially on the underlying predisposing factors.

1. Acute pseudomembranous candidosis. This presents with one or more patches of creamy or white pseudomembrane on an erythematous base. The infection is sore and taste may be altered. The common sites affected are the buccal epithelium on the cheeks, the gums, or the palate. In immunocompromised patients, the dorsum of the tongue may be affected; extension to the pharynx or the esophagus may occur, and stricture is a complication of persistent or relapsing infection.
2. Acute erythematous candidosis ("antibiotic sore tongue"). There are soreness and atrophic erythematous mucous membranes, particularly on the dorsum of the tongue. It may follow pseudomembranous candidosis. It is especially associated with antibacterial antibiotic therapy, but is also seen in HIV-positive subjects and patients taking inhaled steroids.
3. Chronic pseudomembranous candidosis. This does not differ clinically from the acute pseudomembranous variety but, as the name suggests, lesions are persistent. It is mainly seen in immunocompromised patients.
4. Chronic erythematous candidosis (denture sore mouth). Erythema and soreness in the epithelium in the denture-bearing area are common and most are caused by candidosis. It is likely that other factors such as chronic irritation and bacterial colonization have a role in the pathogenesis of this condition. It is most common on the palate and gums. AIDS patients with erythematous candidosis usually have chronic infections.
5. Chronic plaque-like candidosis (chronic hyperplastic candidiasis; *Candida* leukoplakia). This presents with chronic irregular white plaques that occur in the mouth, commonly on the cheek or the tongue. Symptoms are mild. Unlike the pseudomembrane of oral thrush, this plaque cannot be easily removed. Smokers appear to be particularly prone to develop this form of oral candidosis and true leukoplakia can develop in the area affected.
6. Chronic nodular candidosis. This is a rare form, which produces a white and cobbled appearance. It is most often seen in patients with chronic mucocutaneous candidosis.

Other forms of oral candidosis include angular cheilitis which presents with soreness at the angles of the mouth extending outward in the folds of the facial skin. In atopics *Staph aureus* can cause a similar appearing syndrome. *Candida* can also secondarily infect other oral conditions such as ulcerative lichen planus, leukokeratosis, and white-sponge nevus.

8.4.2.2 *Candida* Intertrigo

This occurs with infection of the skin surface in body fold areas, due to *Candida* species usually *C. albicans* [42]. It is often a primary event although it may also be secondary to adjacent infection; for instance, the skin of the groin may be involved secondary to vaginal infection when there is spread of infection to the vulva and the perineum. In this case a prominent red rash in the groin and on the upper surface of the thighs may appear, together with satellite pustules and papules outside the ring margin of the infection. The same can occur in other sites such as beneath the breasts and around the umbilicus. In some cases, there is no underlying skin abnormality, although groin candidosis in males and females is more common in diabetic subjects. Eczema or psoriasis of the skin flexures may also be accompanied by secondary candidosis, and again the presence of satellite pustules is an important diagnostic clue.

8.4.2.3 Interdigital Candidosis

Infection of the finger- or toe-web spaces by *Candida* is more common in hot climates or in patients with long-standing interdigital disease, and it may also form part of the dermatophytosis complex discussed previously as a secondary infection following interdigital dermatophytosis. It is a common type of fungal foot infection in military groups in the tropics. Lesions are white with soggy-looking skin which is superficially eroded. Lesions between the fingers are mainly seen in women and a relationship between repeated washing and cooking has been suggested; it is also more common in those who are overweight. Here the interdigital skin becomes macerated and fissured.

8.4.2.4 *Candida* Infection and Nappy Dermatitis

Nappy rash in infants is a form of irritant eczema which is often secondarily infected with, among other organisms, *C. albicans*. The presence of yeasts may be suspected by the appearance of satellite pustules, and this can be confirmed by culturing the organisms from swabs of the area.

8.4.2.5 Vulvovaginal Candidosis

This condition affects around 75 % of women of childbearing age at least once and presents with itching and soreness and with a thick, creamy white discharge. In many patients there is erythema of the vaginal mucosa together with the discharge, but on occasions the only sign is erythema. Most women with vulvovaginal candidosis have no evidence of any underlying disease. The rash may extend onto the perineum and into the groins. The perianal area is often affected. In extensive cases, satellite pustules may be seen peripherally.

Candida vulvovaginitis may become recurrent, and in around 4 % of women with the infection, it becomes a chronic or chronically relapsing condition. In chronic cases, the vaginal mucosa is often glazed and atrophic. There may be considerable vaginal soreness or irritation as well as pain during intercourse.

It is important in patients with chronic symptoms to evaluate the presence of *Candida* during repeated episodes, to establish that recurrence of signs of disease is associated with recurrence of *Candida* as other causes of vaginosis or *Chlamydia* infection may be causing the symptoms.

8.4.2.6 *Candida* Balanitis

The skin of the glans penis may develop a *Candida* infection usually when the sexual partner has a symptomatic infection. In mild cases, transient tiny sore papules or pustules develop on the glans penis a few hours after intercourse and rupture, leaving a peeling edge. In more severe and chronic cases, the inflammatory erythematous changes become persistent over the glans and the prepuce. There may be associated involvement of the groins.

8.4.2.7 Chronic Mucocutaneous Candidosis [47, 48]

The rare syndrome of chronic mucocutaneous candidosis (CMC) usually presents in childhood or infancy with oral, nail, and cutaneous candidosis which recurs despite treatment. Other chronic skin infections such as warts (papillomaviruses) and dermatophytosis may also develop. Some forms also present in adult life.

The oral lesions are usually of the chronic pseudomembranous or plaque types. But in addition the skin may be covered with hyperkeratotic plaques particularly where the infection has spread to the face or scalp. The fingernail changes involve the nail plates, nail folds, and periungual skin, all of which may be severely damaged.

A large number of immunological abnormalities have been described in association with this condition, but with few exceptions, these have been found to change with time and therapy. In most cases infection forms part of the autoimmune poly-

endocrinopathy, candidosis, and ectodermal dystrophy syndrome with associated hypoadrenalism, or hypoparathyroidism; the common defect is a mutation in the autoimmune regulator (AIRE) genes [47]. A second variety occurs with autoimmune thyroid disease [48] and is associated with mutations in the STAT1 gene. Extensive immunological investigation of children with CMC is not necessary unless they have very severe or recurrent infections or a history suggestive of abnormal responses to other infections, such as chickenpox or severe staphylococcal boils. Here it is worth excluding functional leukocyte abnormalities, such as chronic granulomatous disease, although such patients usually have a history of internal infection. With the exception of bronchiectasis, most patients with CMC do not have internal disease, although the most severely affected patients may later develop systemic infections such as tuberculosis. All cases should be screened for endocrinopathy, and if this is negative on first testing, it should be repeated if necessary annually, as the *Candida* infection often predates endocrine dysfunction.

8.4.3 Laboratory Diagnosis

The diagnosis of superficial candidosis can be confirmed by direct microscopy (see dermatophytosis) of skin scrapings or swabs [42]. Both yeasts and hyphae can be seen. *Candida* species can be distinguished by culture and by assimilation and fermentation reactions. Although molecular diagnostic tests have been developed, few are available commercially.

8.4.4 Treatment in Practice

Candida infections of the skin respond well to a range of antifungals available in cream, powder, or solution forms [42, 49, 50]. Antifungal agents not discussed under dermatophytosis are the topical forms of the polyene antifungal drugs such as nystatin, amphotericin B, and natamycin [51]. These are available in different countries although the topical polyene most widely found is nystatin which is produced in cream form but also as lozenges for oral infection and as a vaginal tablet.

Other useful antifungals for candidosis are azole drugs (econazole, clotrimazole, ketoconazole, miconazole). Generally superficial infections due to *Candida* of the skin and mucous membranes respond well to these treatments.

The most commonly used oral treatments for candidosis are the two triazoles, fluconazole [52], and itraconazole [53]. The usual daily doses are itraconazole 100–200 mg and fluconazole 100–400 mg. A formulation of itraconazole in cyclodextrin solution is better absorbed in severely immunocompromised patients where there is wide individual variation in absorption of the drug. Resistance to fluconazole is an emerging issue which has been reported in HIV/AIDS or CMC patients receiving long-term therapy. Within an infected area such as the mouth, there may be both sensitive and resistant strains of *Candida* isolated showing that there is heterogeneity

of the population in an infection [54]. Characteristically patients at risk from drug resistance are those with persistent infection requiring long-term suppressive treatment and who are immunosuppressed. Primary drug resistance to fluconazole has been recorded with some *C. albicans* species and with *C. krusei*, *C. dubliniensis*, and *C. glabrata*. However, *Candida* resistance is less common in patients under treatment for candidosis who are receiving highly active antiretroviral (HAART) therapy [55]. Other azoles active against *Candida* species include voriconazole and posaconazole [56, 57]. Both have been used for severe oropharyngeal and esophageal infection in the seriously ill. In addition caspofungin and anidulomycin, intravenous fungal cell wall inhibitors [58], are other anti-*Candida* agents used in systemic or esophageal infections.

Flucytosine is an oral agent that is absorbed from the gut and is relatively safe and active against those sensitive strains of *Candida* [42]. Resistance may develop during treatment, and this drug is now only occasionally used for candidosis as a sole treatment.

8.4.4.1 Oral Candidosis

In infants, suspensions of nystatin, amphotericin, or miconazole gel for 2–3 times a day are usually effective in treating oral candidosis. A mucoadhesive oral form of miconazole is also effective as treatment [59]. In adult patients with dentures, removal of these combined with careful cleansing at night is important in ensuring success [60]. Amphotericin or nystatin lozenges, oral nystatin suspension or miconazole oral gel, or mucoadhesive tablets are effective treatments in non-immunocompromised patients. The duration of the treatment varies with the patients underlying condition: 10–14 days may be enough in acute cases in the immunologically normal. For treatment of chronic infections, such as those with hyperplastic or chronic erythematous candidosis, the responses to topical therapy are poor, and orally absorbed drugs such as fluconazole (100–200 mg/day) or itraconazole (100–200 mg/day) are more effective. Voriconazole and posaconazole are alternatives.

Oral candidosis in patients with HIV/AIDS, not receiving antiretrovirals, or CMC, usually fails to respond to topical polyene or azole therapy. Fluconazole and itraconazole are the drugs of choice. If possible, therapy should be given in short courses, because of the risk of resistance with continuous therapy. Treatment is continued until there is clinical recovery. The solution formulation of itraconazole is an alternative to the capsule form, and a new and more consistently absorbed itraconazole formulation (SubaCap) is available in some countries. Posaconazole and voriconazole are alternative treatments.

8.4.4.2 Genital Candidosis

Acute vulvovaginitis can be treated with a single-dose topical preparation (pessary, ovule), such as clotrimazole, econazole, or isoconazole. Longer courses of treatment with azoles (e.g., 14 days), as well as the polyenes, such as nystatin, can also be used. Single-dose oral treatment with fluconazole 150 mg is widely available

without prescription and is convenient; an alternative single does treatment is itraconazole 600 mg [61]. There is no completely dependable method of curing recurrent vaginal candidosis [62], although solutions includes using long-term suppressive treatment in pulses with itraconazole and fluconazole both being used.

Candida balanitis usually responds to topical antifungals applied several times a day, but if there is a source of infection in the sexual partner, this should be treated appropriately.

8.4.4.3 Flexural Candidosis

Candida intertrigo requires topical therapy (azole or polyene creams) given for 2 weeks, but treatment may be continued for longer periods. Drying the infected site is also important. For instance, in some patients with moist *Candida* intertrigo, potassium permanganate soaks are effective. In finger- or toe-web infections, topical antifungal therapy is appropriate.

8.4.4.4 Rashes in the Napkin or Nappy Area

Rashes in the napkin area in infants should be investigated for *Candida*, and, if present, this can be treated topically with an antifungal often combined with hydrocortisone. The antifungal should be combined with a general regimen for napkin or diaper dermatitis, with frequent napkin changes.

8.4.4.5 Paronychia and Onychomycosis

Candida paronychia respond to prolonged topical therapy with frequent applications of polyenes, imidazoles, or antiseptics such as 4% thymol in chloroform. Lotions are probably preferable to creams as they are easier to apply to the nail-fold area. There have been few studies of either itraconazole or fluconazole although they are effective in many cases of paronychia. Antifungal treatment should be followed by general measures, such as adequate drying of the hands. Other factors such as irritant or allergic contact dermatitis may play a part in the continuing inflammation. In many cases the addition of a topical corticosteroid is a logical approach.

8.4.4.6 Chronic Mucocutaneous Candidosis

Treatment of this condition depends on antifungal chemotherapy although attempts have been made to restore T-cell function by the use of different measures such as transfer factor, or grafting compatible lymphocytes from blood or marrow, and nonspecific measures such as restoration of normal iron stores when these are low.

Systemic anti-*Candida* therapy with fluconazole, itraconazole, or posaconazole is usually necessary, and treatment may have to be prolonged and repeated.

When the patient is in clinical remission, maintenance therapy should be avoided if possible because of the risk of antifungal resistance. But controlling infection is advisable as many patients develop deeper lesions in the pharynx and esophagus which may lead to the formation of strictures. Intermittent therapy with oral antifungals such as fluconazole is the usual approach. Nonabsorbed oral medications such as miconazole gel and nystatin are also worth trying although these are often less effective than the absorbed oral drugs. There is sometimes a role for alternative medicines such as posaconazole or intravenous caspofungin, an echinocandin cell wall antagonist. Endocrine deficiencies should be treated, although such treatment by itself has no clinical effect on the candidosis. Endocrine screening tests should be repeated, even if initially negative, as patients with endocrinopathy may develop endocrine disease years after the first appearance of candidosis. Where indicated, parents should be given genetic counseling. The possibility of coexisting dermatophytosis should not be forgotten, but it usually responds satisfactorily to oral treatment with itraconazole or terbinafine.

8.5 *Neoscytalidium* Infections

Neoscytalidium dimidiatum, a plant pathogen found in the tropics and subtropics, and *N. hyalinum*, which has only been isolated from humans, cause infections of the skin which mimic the dry-type infections caused by *Trichophyton rubrum* [63, 64]. These infections have mainly been reported in immigrants from tropical areas to temperate countries, although infection in the tropics may be more common than previously believed. Studies from Nigeria, for instance, have suggested that this is a common infection in both dermatological outpatients and industrial groups such as mine workers. Infections have been reported from West and East Africa, India and Pakistan, Thailand, Hong Kong, and several countries in Latin America.

The infection presents with scaling of soles and palms (Fig. 8.7) and cracking between the toe webs. Nail dystrophy is common and onycholysis without significant thickening is often seen; some patients have nail-fold swelling. The clinical features of *N. dimidiatum* and *N. hyalinum* infections are indistinguishable.

It is important to recognize these infections because they are common in some areas and do not respond to most antifungal drugs. The laboratory diagnosis is similar to that used in dermatophytosis—skin scrapings and culture. The appearance of these fungi in skin scrapings is characteristic as they are sinuous and irregular. They cannot be cultured on media containing cycloheximide.

Treatment of these infections is difficult as they do not respond in a predictable way to topical or oral antifungal drugs. Responses of skin infection in individual patients have been recorded with a number of compounds such as Whitfield's ointment, econazole, or terbinafine, although relapse is common.

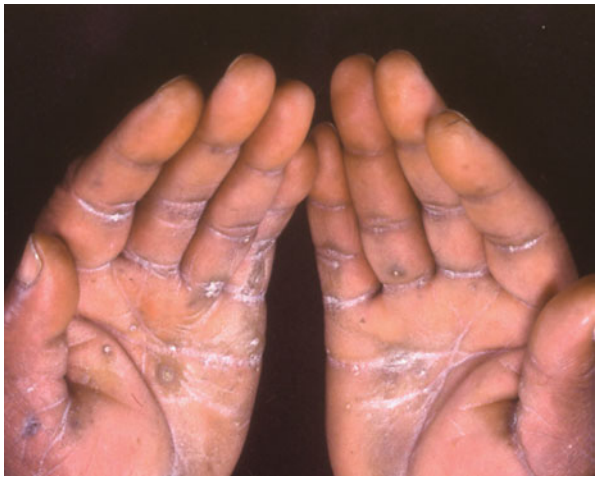

Fig. 8.7 *Neoscytalidium hyalinum* infection of the palms

8.6 Malassezia Yeast Infections

The *Malassezia* (lipophilic) yeasts are skin-surface commensals which have also been associated with certain human diseases, the most common of which are pityriasis versicolor, *Malassezia* folliculitis and seborrhoeic dermatitis, and dandruff [65, 66]. In addition these organisms rarely cause systemic infections, usually in prematurely born infants receiving intravenous lipid infusions. There are a number of *Malassezia* species, of which the main ones are *M. sympodialis*, *M. globosa*, *M. restricta*, *M. slooffiae*, *M. furfur*, *and M. obtusa* which are oval or round yeasts and their distribution on the skin surface differs. *M globosa* and *M sympodialis* are the most common and most widely distributed of these yeasts. The formation of short stubby hyphae by round yeasts on the skin surface is a feature of the development of pityriasis versicolor.

8.6.1 Pityriasis Versicolor

The pathogenesis of pityriasis versicolor is still poorly understood. The disease occurs in young adults and older individuals but is less common in childhood. Most cases are caused by *M. globosa*. Pityriasis versicolor is a common disease in otherwise healthy patients. However, it has also been associated with Cushing's syndrome and immunosuppression associated with organ transplantation, but not with HIV/AIDS. The infection is very common in the tropics, and incidence rates of over 70 % have been reported in some studies. Generally this disease is associated with warm climates and sun exposure. Studies of the immunology of pityriasis versicolor suggest that one potential reason for persistence of the infection is inhibition of the induced immune responses due to a lipid associated with *Malassezia* species.

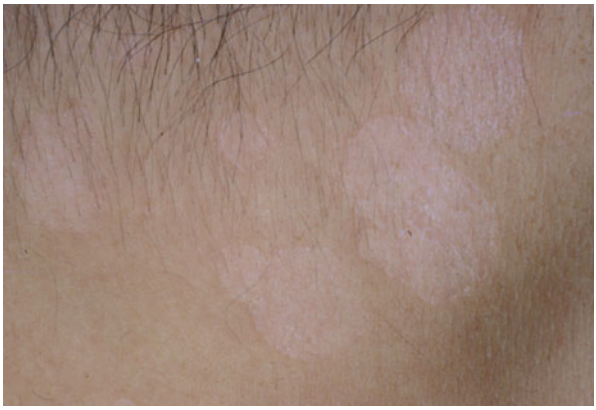

Fig. 8.8 Pityriasis versicolor

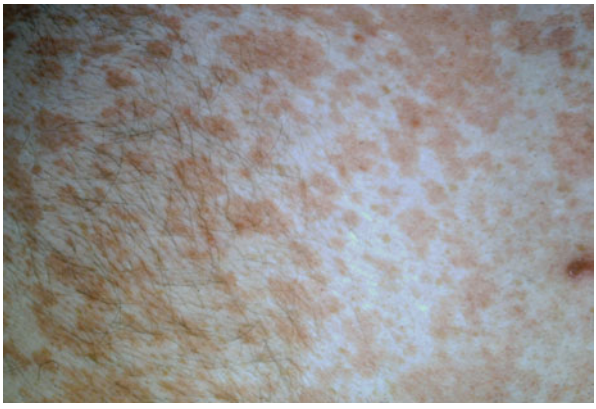

Fig. 8.9 Pityriasis versicolor (erythematous type)

8.6.1.1 Clinical Features

The rash consists of multiple hypo- or hyperpigmented, occasionally red, macules which are distributed across the upper trunk and back which coalesce with time (Fig. 8.8). The lesions are asymptomatic or mildly itchy and scaly. The hypopigmented lesions may be confused with vitiligo, but the presence of scaling and partial loss of pigment is, however, typical of pityriasis versicolor. In some individuals, there is more erythema and the lesions may resemble those of seborrhoeic dermatitis (see below) (Fig. 8.9); in these cases the infection is often recalcitrant and difficult to treat adequately, whereas usually treatment is straightforward and effective. Rare forms of pityriasis versicolor include atrophic, or anetoderma-like, lesions and an atypical variety which presents with scaly patches that are irregularly distributed around the waist area or upper part of the limbs.

Lesions can also be highlighted by shining a wood's light on the area. They fluoresce with a yellowish light, although this is generally a weak response and complete darkness and a powerful light source are necessary. Scrapings taken from the lesions

will show the characteristic organisms, which consist of clusters of round yeasts closely associated with short stubby hyphae. These are normally viewed in 10% potassium hydroxide-treated mounts, as with dermatophytosis. This infection is usually caused by *Malassezia globosa* but neither cultural nor molecular diagnostic methods are necessary for diagnosis.

8.6.2 Malassezia *Folliculitis*

A second condition associated with *Malassezia* yeasts is an itchy folliculitis on the back and upper trunk which often appears after sun exposure usually in teenagers or young adults; it is more prevalent in males. Lesions are itchy papules and pustules which are often widely scattered on the shoulders and back. The condition has to be distinguished from acne as it does not respond to the same range of treatments. But itching is prominent and there are no comedones.

8.6.3 Seborrhoeic Dermatitis

A third common condition associated with *Malassezia* species is seborrhoeic dermatitis. While this cannot be considered an infection because there is no tissue invasion, there is strong and growing evidence that in this condition, *Malassezia* species such as *M. globosa* or *M. restricta* produce breakdown products including oleic acid or immune signaling molecules such as indolocarbazole or malassezin, which play a role in triggering inflammation in the skin which results in the rash of seborrhoeic dermatitis [67]. It is still not clear why this is common in patients with Parkinsonism or with HIV/AIDS. However, a key part of treatment is the use of antifungal drugs active against *Malassezia*.

The characteristic distribution of seborrhoeic dermatitis includes scaling affecting the scalp either diffusely or in patches, scaling and erythema of the eyebrows, nasolabial folds, external ears, and presternal panel of the anterior chest. Other affected areas include additional sites on the face and the axillae or groins. The rash is covered with greasy scales and may be very itchy. Isolated scaling of the scalp without other signs of disease, dandruff, is thought to be a mild variant of seborrhoeic dermatitis.

One other condition associated with *Malassezia* and which may improve with the use of antifungal agents is a head and neck eczema seen in atopic patients which usually presents in early adult life.

8.6.4 Treatment in Practice

One of the main features of the treatment of pityriasis versicolor is that a wide range of different antifungal drugs is effective in the short term against this infection [49, 68–70]. Usually assessments have been made at between 2 weeks to 1 month post

therapy and cure rates of over 85 % are achievable. Some drugs which are not known to have antifungal properties but which may affect the environment, which supports *Malassezia* such as adapalene, have also been used [71]. Topically applied azole antifungals such as miconazole, clotrimazole, ketoconazole, and sertaconazole work well in pityriasis versicolor, and there is no difference in results achieved by different antifungal compound [72]; generally imidazole creams are used. Topically applied allylamines such as terbinafine 1 % cream, naftifine, or butenafine are also effective in pityriasis versicolor. Likewise topical ciclopirox is effective. The usual time to recovery with all treatments is 2–3 weeks. The main problem with the use of topical antifungals is the practical difficulty in applying creams to a wide and ill-defined surface area. An alternative solution is to use a formulation which can be spread easily across a wide surface area ketoconazole shampoo which, by virtue of its composition, is easier to apply or an alternative formulation in mousse form, ketomousse [73]. Ketoconazole shampoo is left on the skin after lathering the preparation into the skin for at least 5 min before showering. Ketoconazole shampoo has not been formally evaluated in pityriasis versicolor, but two or three applications of the shampoo over a week appear to clear most infections.

A second approach is the application of 2.5 % selenium sulfide in a detergent base (Selsun® shampoo) [74]. It is applied to all the affected areas and left overnight. In many cases, it is necessary to apply the material regularly (e.g., every other night over 2 weeks). It is irritant and it also stains clothes and bedding. Alternatives include 20 % sodium hyposulphite solution and 50:50 propylene glycol in water. The latter has also been used intermittently as long-term suppressive therapy to prevent relapse.

Oral itraconazole is also very effective in cases of pityriasis versicolor, mainly for extensive or recalcitrant cases [72]. This approach has the advantage of simplicity and convenience for the patient. Itraconazole is active against pityriasis versicolor in a total dosage of 800–1,000 mg usually given over 5 days; a single dose of itraconazole at 400 mg has also been used but long-term results are not known. Fluconazole can also be used [66]. Ketoconazole is also effective although now little used.

On a practical point, patients should be warned that depigmentation may take several months, as otherwise they will often report treatment failure, even when the organisms have been destroyed, simply because the hypo- or hyperpigmentation persists for several months.

The other common clinical problem is relapse and in certain patients relapse can be rapid; also there are some patients who regularly develop pityriasis versicolor when exposed to climatic conditions which are suitable for the development of this infection. There are no studies of methods of managing these apart from the long-term use of propylene glycol. However, one method of approaching the latter problem where patients reacquire pityriasis versicolor when revisiting an overseas climate is to give treatment once weekly during their overseas stay with ketoconazole shampoo or an equivalent.

The best treatment for *Malassezia* folliculitis is itraconazole given orally at a dose of 100 mg daily for 2–3 weeks rather than topical treatment, to which this infection seldom responds [75].

In seborrhoeic dermatitis, there have been a few studies of the efficacy of azole antifungals. In a systematic review [76] on the subject, there was evidence that medications containing ketoconazole applied topically either to the scalp or facial skin were effective. Likewise there are also studies with bifonazole and selenium sulfide that demonstrate efficacy [76]. In practice other azoles appear to be effective and in extensive cases oral itraconazole can be used usually for 10–14 days to induce a remission. Relapses are managed with a topical azole containing cream or shampoo. Alternatives includes topical corticosteroids or topical tacrolimus. The practical problem with this condition is that it relapses often on a regular basis and patients should be made aware of this.

8.7 Rarer Superficial Infections

White piedra is a chronic infection of the hair shafts caused by a yeast, *Trichosporon beigelii*. This disease can be seen in temperate and tropical areas. It is generally sporadic and rare and the infection is mainly seen in genital hair. It may also affect the axilla and scalp [77]. The lesions are soft yellowish nodules around the hair shaft but it is usually asymptomatic. Black piedra caused by *Piedraia hortae* is a rare asymptomatic infection confined to the tropics [78]. Here, scalp hairs are surrounded by a dense black concretion containing spores, forming a small nodule. Both infection are best treated with topical imidazole solution or creams for 2–3 weeks.

Tinea nigra is an infection of palmar or plantar skin caused by a black yeast, *Phaeoannellomyces werneckii*. It is mainly seen in the tropics but can present in Europe and the USA. The main differential diagnosis is an acral melanoma as it presents as a flat pigmented mark on the hands or feet. If the lesion is scraped with a glass slide or scalpel, it can be shown to be scaly. Lesions are usually solitary. The presence of pigmented hyphae in skin scrapings is typical. Tinea nigra responds to a variety of treatments including Whitfield's ointment and azole creams. Topical butenafine has also been used with success.

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Chapter 9
Fungal Infections of the Hair

Roderick J. Hay

9.1 Common Fungal Infection of the Hair Shaft: Tinea Capitis

Tinea capitis or scalp ringworm is an infection of the scalp hair caused by dermatophyte fungi. Only certain species appear to have the physiological capacity to invade hair shafts, and one, *Trichophyton schoenleinii*, invades to cause the disease known as favus but does not survive for long within the hair shaft keratin. Conversely, dermatophytes causing tinea capitis can also invade the skin of other sites, mainly the body or the face [1, 2]. Other dermatophyte infections are discussed in Chap. 8

9.2 Introduction

Scalp ringworm has been known for centuries and is well described in the older dermatological literature although often confused with other causes of scalp scaling. Topical treatments, such as mercurials, tars and, later, dyes were used extensively as treatments along with physical methods of epilation. Favus which is a clinically distinct form of infection with crusts and a sharp odour was also recognised for centuries because of its clinical appearances. Control of scalp ringworm was part of a major public health movement in Europe and the USA in the early and middle

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parts of the twentieth century [2]. Children with tinea capitis were often segregated or excluded from school, and adjunctive treatments such as scalp shaving prior to application of topical medications were frequently used, thereby contributing to the stigma. In the UK, for instance, schools or hospital wards originally attached to the Poor Law workhouses were often converted into hospital or clinical treatment facilities and used for specific purposes such as treatment of ringworm which was associated with poverty compounding the stigma that went with it. The newly discovered radiation was employed as a means of depilation using machines specifically designed for the purpose, and many hundreds of children were treated. The long-term consequences of this treatment included radiodermatitis and dysplastic skin lesions or nonmelanoma skin cancer. By the middle of twentieth century, there was also recognition that tinea capitis could reach epidemic proportions, and outbreaks of infection were recorded by community medical officers and also in the dermatological literature.

A massive change in the distribution of tinea capitis followed the introduction of griseofulvin as in a few years a combination of organised treatment regimens, surveillance in schools through the school nursing services and the treatment of contacts resulted in the virtual disappearance of endemic tinea capitis from Europe and the USA by the 1970s [2, 3]. In the succeeding years, tinea capitis was a largely sporadically occurring disease with most new cases attributable to infection from pets or domestic or farm animals. *Microsporum canis* dominated the clinical pattern. The picture is changing again in the USA, parts of Europe and in Latin America with the spread of *Trichophyton tonsurans* originally described by Sabouraud as known to have been present in Europe [3–7]. The source of the most recent outbreak of *Trichophyton tonsurans* infection is not completely understood, but it may well have entered the southern USA with migrants from Mexico and Central America where the infection had remained endemic at a low level. However, the new outbreak of infection travelling through the USA in schools has crossed the Atlantic and is now prevalent in European schools as well as spreading to South America and Africa. The major focus of infection is children with black hair type. With the difficulties and costs inherent in mass treatment and school surveillance, tinea capitis remained an endemic disease in many resource poor countries throughout this period (Figs. 9.1, 9.2, 9.3 and 9.4).

9.3 Epidemiology

Tinea capitis is a disease of childhood although adults may be affected occasionally. Although it is usually seen in children from 2 years old to puberty, it may occur in those younger and even within the first 6 months of life [2]. Infection is usually derived from either a human (anthropophilic) or animal source (zoophilic). Infection in younger children is mainly due to anthropophilic infection. There has been little

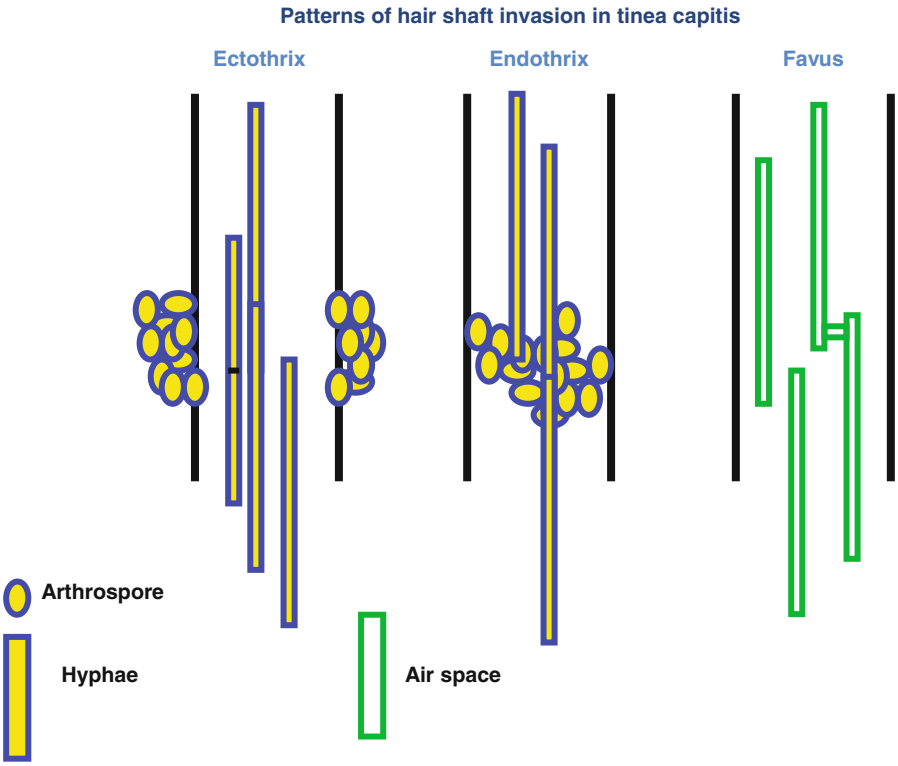

Fig. 9.1 Tinea capitis – patterns of hair shaft invasion

research on susceptibility to this infection although recently polymorphisms within certain genes such as those involved in leucocyte activation and migration, extracellular matrix integrity and remodelling, epidermal maintenance and wound repair, and cutaneous permeability have been associated with increased susceptibility to tinea capitis caused by *Trichophyton tonsurans* in children [8]. Apart from this, there is little information on the basis for susceptibility although infection is clearly associated with the presence of other infected children, and classroom or household spread is a likely factor in transmission. In addition, other sources of exposure may be involved, and sharing the same barber/hairdresser is also associated with increased risk of infection presumably through direct contamination via instruments. The data on gender risk is confusing as some studies have shown increased susceptibility in male children and others with no difference between the two genders.

African-type hair is also more associated with certain infections such as *T. tonsurans* although carriage, e.g. isolation in culture of colonies of organisms from the scalp without clinical signs of infection is seen equally across ethnic groups [9].

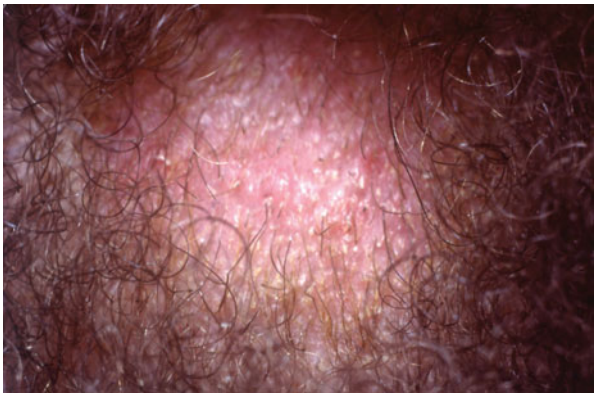

Fig. 9.2 Tinea capitis – ectothrix infection caused by *Microsporum canis*

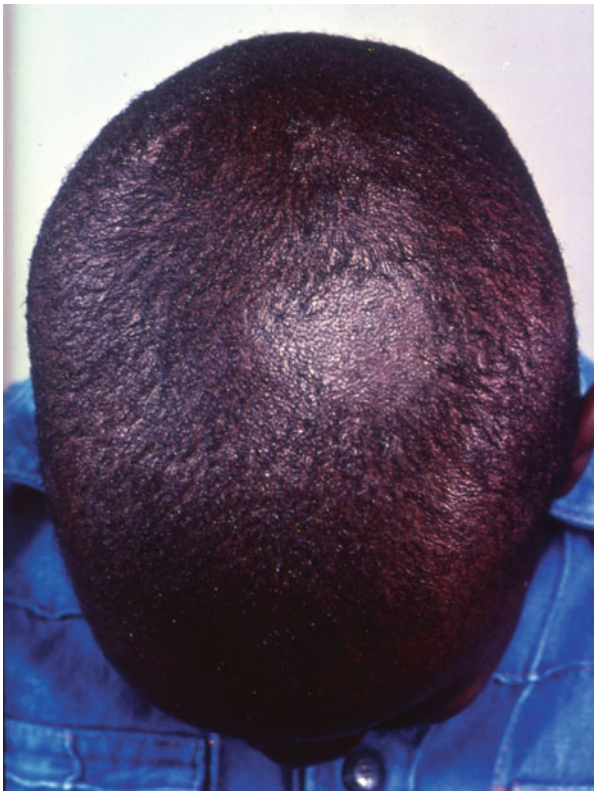

Fig. 9.3 Tinea capitis – endothrix infection caused by *Trichophyton yaoundei (*now reclassified as a variant of *T. violaceum)*

Infection caused by those fungi originating from animals is associated with exposure to the animal although this may not be direct as arthrospores may remain viable in farm building or fences over many months. The main human and animal organisms involved are seen in Table 9.1.

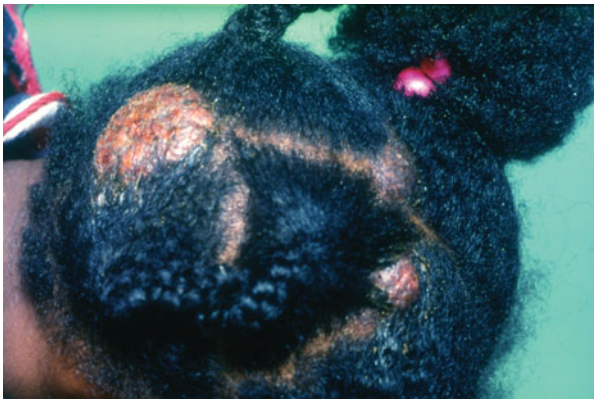

Fig. 9.4 Kerion caused by *Trichophyton tonsurans*

Table 9.1 Common causes of tinea capitis and their distribution

Organisms	Type of infection	Geographic area
Zoophilic		
Microsporum canis	Ectothrix	Global
Trichophyton verrucosum	Endothrix	Europe mainly
Anthropophilic		
Trichophyton tonsurans	Endothrix	USA, Canada, Caribbean, UK, Europe, West and East Africa, Brazil, Mexico
T. violaceum	Endothrix	East Africa, Middle East, Indian subcontinent
M. audouinii	Endothrix	Europe, West Africa
T. schoenleinii	Favus	Rare – Ethiopia, southern and north Africa, Middle East

9.4 Geographic Distribution (Table 9.1)

The worldwide distribution of dermatophytes causing scalp ringworm is determined by (a) the presence of suitable hosts, in the case of animal infection, and (b) geographic location of patients in anthropophilic cases.

Transmission is fairly simple to explain in the case of zoophilic infection as infection occurs where there is a suitable infected animal host [1, 2]. There are underlying variations where there are pockets of hyperendemic infection, for instance, associated occasionally with breeding establishments for cats or dogs where there has been a high incidence of infection. The slow elimination of *T. verrucosum* in cattle in Europe through control measures such as immunisation has resulted in a decline in the case numbers of this infection due to this organism. Although there have been regional changes in the major causes of tinea capitis due to anthropophilic infections, their exact distribution is subject to variation with time where there is movement of populations. The most obvious example is *T. tonsurans* which until the early 1970s was endemic at a low level in many parts of the world,

and it appeared from time to time as cause of sporadic infection. As described above, there has been spread of infection through the USA and Canada particularly in children with black hair type [10]. The infection has more recently spread to the Caribbean islands and also to Europe mainly in inner city areas. In London, for instance, it is currently the dominant cause of tinea capitis [11]. Further, there has been spread to both West and East Africa as well as to South America and Brazil. Other infections have remained more stable such as *T. violaceum* in East Africa and the Indian subcontinent although there is some evidence to suggest that where *T. tonsurans* is introduced into a new area, it may replace the local endemic cause of tinea capitis. In many areas, scalp infection is subject to local changes and, for instance, it may become endemic in a particular school but not in other areas.

Favus, while once common in Europe and the USA, has largely disappeared although it may still be seen in some populations, e.g. Ethiopia. The reason for this change is not clear. But as it is known to result in scarring alopecia and it is clinically distinct, it is likely that patients will present for treatment at an earlier stage. In many countries where it is endemic, there are distinct local words to describe favus different to those used for other types of tinea capitis.

9.5 Pathogenesis

In experimental infection in animals, infection of hair can generally only be initiated if the scalp epidermis is abraded, i.e. there is some form of local epidermal damage. However, in human infection, it is not clear if trauma plays any role in establishing infection. If it is the case, the trauma is likely to be minor as it is seldom recorded by patients. From animal models, it is known that specific dermatophyte genes are switched on in the early phases of hair infection [12–14]. These include protease genes such as subtilisins in *M. canis*, but others such as sulphur transporters appear to be involved. Invading fungal hyphae expand to form a modified structure or hair penetration organ on the cortex of the hair shaft, and beneath the site of this structure, there is a microscopic evidence of loss of keratin. Hyphae penetrate the scalp hair cortex and can proliferate within the central core of the hair shaft. Depending on the organism, arthrospores, which become the future propagules of infection, are formed either within the hair matrix (endothrix) or on the outer surface of the hair (ectothrix). The effect of fungal proliferation is to induce fracture of the hair shaft which is generally closer to the scalp epidermis in the endothrix infection. Clinically in these infection, the hair may break at scalp level leaving clinical appearances often referred to as a black dot or black dot ringworm. Ectothrix infection leads to hair shaft fractures 1–5 mm above the scalp surface.

Immunity to hair infection in experimentally infected animals occurs 2–3 weeks after the onset of infection [12]. However, in naturally acquired infections in both animals such as cats and humans, effective immunity may be delayed. The inflammation caused by the development of an immune response is variable but may result in the development of a severely infiltrated patch of scalp leading to the

formation of massive granulation tissue and infiltration of leucocytes leading to the formation of pustules – a kerion. This is more likely to occur with zoophilic infection in humans, but anthropophilic infections may also lead to severe inflammation in some cases. In the majority of cases of anthropophilic, the inflammation is mild, and in some cases barely visible, the reason for this is not clear although the existence of T cell immunological modification as described with other dermatophyte infections although likely remain unproven [12]. However, the result of this apparent lack of inflammatory response is that naturally occurring infections, again particularly those caused by anthropophilic fungi, are often slow to heal and may last for months without clinical change.

9.6 Clinical Features

The classical features of dermatophyte infection in the scalp result from a combination of hair loss or alopecia and inflammation presenting with scaling and erythema, with or without surrounding infiltration of the scalp [15]. Generally as described above, zoophilic infection leads to more prominent inflammatory changes with marked erythema, itching, hair loss and scaling. These changes are distributed in well-circumscribed patches across the scalp although in some cases the area involved is greater than 10 cm in size. On close inspection, the hair shafts, where the hair has broken, appear slightly swollen and greyish in colour.

In endothrix infection, the same changes occur, but the range of clinical variation is more extensive. In some children, the infection may only present with scaling of the scalp which is then difficult to distinguish from eczema or seborrhoeic dermatitis [15, 16]. The presence of erythema is also variable. Kerion may occur but is less frequent than in ectothrix infections. Hair shafts usually fracture closer to the scalp than in ectothrix infections and may give the appearance of a swollen hair shaft within the follicle – black dot ringworm. Sometimes, one or more patterns dominate, and these have been described as black dot type, seborrhoeic dermatitis-like or grey scale forms of infection. However, these terms are simply describing the main clinical features seen in each case.

In most patients, resolution is not accompanied by any scarring. This is not always the case with kerion as there may be destruction of hair follicles. Even so, there is a surprising degree of recovery in children as the scarred area contracts over succeeding months to leave a smaller area of hair loss. In elderly patients, a pseudopelade reaction has been rarely associated with adult-type tinea capitis, but it is not clear whether this is a reaction to the dermatophyte or whether these patients have pseudopelade with secondary fungal scalp infection.

The clinical appearance of favus is distinct again as here the invading fungus only survives for a short period in the scalp hair and degenerates leaving air channels in the hair shaft which may be weakened but not broken. The second distinctive change is that there is a massive influx of neutrophils at the opening of the hair follicle with keratin debris resulting in the formation of an inflammatory crust which appears as

a grey-coloured mass over the affected area, the scutulum. This has a stale odour. The inflammatory infiltrate also affects the upper dermis and follicle areas, and there is considerable scarring alopecia after the infection leading to permanent hair loss. Infection may also persist for years and, in some cases, into adult life.

In adults, infection of the scalp is rare [17]. However, it has been recorded although it appears to be commoner in females. The inflammatory changes are often minimal, and scaling with patches of hair loss are the usual presentations. There are some reports that suggest that this is also more likely to occur in HIV-positive individuals.

In addition to tinea capitis, patients with scalp infection may also have other lesions of dermatophytosis caused by the same organism usually on the face or upper trunk. Similar changes may be found in their contacts.

9.7 Carriage

Carriage is the term used to describe the presence of the organism in culture from the scalp in individuals who have no signs of infection [16, 17]. It is usually assumed that this occurs because of contamination of scalps by arthrospores shed from other infected patients in the vicinity, e.g. children in the same class. Longitudinal studies have shown that many of those designated as carriers may lose the positive cultures if the scalp is resampled after 6 months suggesting that this is a form of temporary carriage. However, the validity of this definition has been questioned particularly for *T. tonsurans* infections where careful examinations of apparently unaffected children may reveal that a small number of hairs are affected raising the possibility that hair shaft infection occurs but is of a very limited extent in some individuals. The importance of this observation is that if a carriage occurs without hair shaft invasion, then use of topically applied shampoos such as ketoconazole will be effective in preventing subsequent invasion. However, if there is invasion, then oral antifungal therapy is the only viable option for treatment. Ultimately, it is important to examine the siblings or contacts of infected patients very carefully to ensure that there is not a limited infection without significant symptoms.

9.8 Differential Diagnosis

The differential diagnosis of tinea capitis includes other scalp conditions prevalent in children with hair loss. These include seborrhoeic dermatitis or dandruff, eczema, psoriasis, discoid lupus erythematosus and lichen planus. The clinical diagnosis is not easy, and some of these conditions can be confused with tinea capitis which serves to re-enforce the importance of confirming the diagnosis by laboratory methods [18].

9.9 Laboratory Investigations

Treatment of tinea capitis should wherever possible be based on an accurate diagnosis confirmed by laboratory investigation [18, 19].

9.9.1 Wood's Light

Hairs infected with the majority of *Microsporum* species that cause tinea capitis fluoresce with a greenish colour under filtered ultraviolet light or Wood's light. This is important not just as a direct diagnostic clue, but it also serves as a good method to identify infected hair which can then be removed gently for laboratory tests. As usual with this method, it is important to ensure adequate darkness before using the light as the fluorescence may be faint. *Microsporum canis* causes fluorescence as *M. audouinii* does, but it is fainter with *M. gypseum.* The crusts in favus appear yellowish. *Trichophyton* species in hair infections do not produce fluorescence.

9.9.2 Direct Microscopy

This is a very useful diagnostic procedure as direct microscopy of plucked hairs can show the presence of organism and the site of formation of arthrospores in scalp hairs, and it also provides a partial diagnosis on which to base treatment; identification of an endothrix infection on microscopy in many cities in the USA and Europe suggest that the infection is most likely to be due to *T. tonsurans*. It is important to use 5–10% potassium hydroxide solution and to examine the specimen after 10–15 min of incubation. If the examination is delayed, it may be more difficult to discern the relationship between arthrospores and the shaft of the hair and to distinguish between endo- and ectothrix infections. It is not usually necessary to use a fluorescent whitener, such as calcofluor.

Hair samples are taken by gently scraping the scalp of the lesion with a blunt scalpel or the reverse side of the scalpel blade. The samples needed for diagnosis should contain hair rather than skin scales. Removing scalp hair in children is always difficult particularly with a kerion as they may find this painful. Using Wood's light may help as if the infection fluoresces the hair shaft illuminated can be removed simply without exerting pressure. However, if it remains difficult, a moistened swab may be a better approach as this will generally pick up infected hair. A useful alternative is a disposable tooth brush which will both remove loose hair and also can be used to inoculate a culture plate directly. The brush comes with a case, and it can be labelled and sent directly to the laboratory.

9.10 Culture

Cultural examination is carried out as with other dermatophytes on the Sabouraud dextrose agar containing antibiotics such as penicillin and streptomycin as well as cycloheximide.

The organisms generally take 2 weeks to grow sufficiently for identification although *T. verrucosum* may be slower. Dermatophytes are identified using conventional laboratory criteria.

At present, there are no commercially available systems for the diagnosis of scalp infections using molecular tools although there are a number of investigational studies of these methods, and they will become more important over the next few years [20].

9.11 Treatment

Complete treatment of tinea capitis has three main objectives: the treatment of the patient, where appropriate, screening of contacts and prevention of spread of the infection [19]. This involves assessment of the infection and initiation of the correct therapy and in the case of family's careful examination of siblings to check whether they have concurrent infection. It is the best practise in anthropophilic infections to use standard diagnostic tools such as culture and examination of scalp brushes to prove the presence of carriage or infection in family members. If a zoophilic infection is suspected, animal contacts and other children in the household should be screened for similar infection, as they may have been exposed to the same source. Laboratory-confirmed contacts, whether carriers or infected cases, should be treated. Hence, it is important as part of the clinical assessment of the patient with tinea to identify the likely cause as this will show whether the infection is anthropophilic or zoophilic. A second reason for pursuing laboratory confirmation is that it will also help the physician select the optimum antifungal.

9.12 Topical Antifungals

These have no role in the management of tinea capitis. Very little is known about the penetration of topically applied agents applied to hair, and there are no antifungal formulations that have been designed to achieve high hair shaft levels. It is unlikely that any formulation can produce growth inhibition or achieve fungicidal activity. One study compared miconazole with Whitfield's ointment showed that patients receiving topical treatment showed some improvement including some negative cultures and only during therapy, but these were not as great as that expected with oral antifungals, and the patients relapsed subsequently [21].

Topical antifungals are often used as adjunct to oral therapy to reduce the frequency of positive cultures from hair during the early stages of therapy and thereby reduce the risk of dissemination to other children [22]. The antifungals used for this have mainly been shampoo formulations such as selenium sulphide and ketoconazole shampoos.

9.13 Oral Treatments

9.13.1 Griseofulvin

The oldest effective treatment for tinea capitis is griseofulvin given in a dose of 10–15 mg/kg daily, generally for a treatment period of 6–8 weeks [19, 22]. Griseofulvin is fungistatic in vitro against the fungi that cause tinea capitis, and its mode of action is through the inhibition of the formation of intracellular microtubules.

Griseofulvin was one of the earliest antifungal drugs to be introduced, and there are therefore few comparative clinical trials against placebo. However, for most organisms that cause tinea capitis, it is clinically and mycologically effective although there are some patients with infections such as those caused by *T. tonsurans* infections who require longer courses of treatment, e.g. 12 weeks or who may fail to respond. Often, a higher dosage of 20 mg/kg/day is recommended for *T. tonsurans* infections. Clinical trials comparing terbinafine with griseofulvin show equal efficacy in *Microsporum* and *Trichophyton* infections, but responses for *Trichophyton* species appear to be faster [23, 24].

Higher doses of griseofulvin given as single treatments may also be effective as part of a mass drug administration (MDA) for community-based treatments of against certain endothrix infections, e.g. *T. violaceum* [25]. Dosage regimens vary, but 1,000 mg given as a single dose or 500 mg as a stat dose followed by a repeat dose after 2 weeks have been two such regimens employed to reduce population frequency of infection. However, these dosage regimens are not recommended for routine use.

There are both tablet and oral solution formulations of griseofulvin. However, in Europe, the liquid paediatric formulation of griseofulvin is difficult to obtain in many countries. Alternative formulations can be imported, or some pharmacies suspend crushed tablets of griseofulvin in a suitable liquid base.

9.13.2 Terbinafine

Terbinafine is an allylamine drug with broad-spectrum in vitro antifungal activity, including all the dermatophytes that cause tinea capitis in vitro. For tinea capitis, terbinafine is available in a 250 mg tablet form. In some countries, a paediatric tablet is available in 125 mg. The normal daily dose is 250 mg for adults. In children,

the treatment regimen used is based on weight: <20 kg 62.5 mg/day, 20–40 kg 125 mg/day and >40 kg 250 mg/day.

Terbinafine is effective against a range of fungi that cause tinea capitis, and there are a number of studies comparing terbinafine with griseofulvin [23, 24, 26–28]. The recommended treatment period for most infections is usually 4 weeks. Studies have shown that in infections caused by *T. tonsurans*, 4 weeks of treatment is required although shorter periods are sometimes effective. In a study of *T. violaceum* infection, there was no difference in mycological cure rates at follow-up when 1 week of treatment was compared with 2 or 4 weeks therapy [27]. A meta-analysis of studies comparing terbinafine with griseofulvin showed that terbinafine was as effective at treatment durations of up to 2–4 weeks for *Trichophyton* infections compared with griseofulvin for 6–8 weeks [28]. However, the responses of *Microsporum* species were slower than those of *Trichophyton*, and in some patients, there appears to be no response [29–31]. A suggested solution is the use of higher doses of terbinafine, and for *Microsporum* infections, doubling the normal daily dose is therefore generally advised. Unfortunately, the choice of drug cannot be guided by in vitro sensitivity treating as isolates of *Microsporum* are not significantly less sensitive to terbinafine in vitro than those of *Trichophyton* [31].

In some countries, a paediatric terbinafine tablet 125 mg is available. Otherwise, for smaller children, it is necessary to break the 250 mg tablets, which may be scored (depending on source). Other formulations of terbinafine have been developed including a solution but these are not generally available.

9.13.3 Itraconazole

Itraconazole is an orally active triazole antifungal which is fungistatic in vitro against the main causes of tinea capitis. Itraconazole comes in three main formulations: a capsule containing pelleted itraconazole (Sporanox), an oral solution containing itraconazole in cyclodextrin and a newer solid formulation with better absorption (Subacap or Lozanoc). The latter has not been tested specifically for tinea capitis. The currently available cyclodextrin solution is not approved for paediatric use in dermatophytosis.

For tinea capitis, itraconazole is generally given in doses of 3–5 mg/kg daily [32–35]. The regimens used have varied between 3 and 5 mg/kg daily for 4–6 weeks. Efficacy rates have varied from over 80 to 40 % in one study. There is no evidence that *Microsporum* and *Trichophyton* species causing tinea capitis differ in their responses to itraconazole. A pulsed regimen using intermittent treatment with 5 mg/kg/day for 1 week in every 3 weeks has been evaluated in a small number of children. Usually two to three pulses were found to be necessary for most infections [35].

The pelleted capsule formulation is difficult to use in children on a dose per weight basis as it involves opening and dividing the contents of capsules.

9.13.4 Fluconazole

Fluconazole is an orally active triazole antifungal, and there are both capsule and liquid formulations. The drug is active against a range of fungi including those dermatophytes that cause tinea capitis. The recorded doses that have been used in tinea capitis have ranged from 1.5 to 6 mg/kg daily and up to 8 mg/kg weekly [36–38]. Fluconazole appears to be equally effective against a range of different organisms in tinea capitis including both *Trichophyton* and *Microsporum* species. It also appears to be as effective as griseofulvin [39, 40]. The oral solution may be particularly helpful in young children.

9.13.5 Other Azoles

The other azoles in current usage such as posaconazole or voriconazole have not been used in tinea capitis.

9.14 Treatment in Practice

The generally recommended treatment for tinea capitis due to *Trichophyton* species is terbinafine which is given for a 1 month period as the initial treatment of choice. For *Microsporum* infections, there remains a choice which is largely determined by drug availability of griseofulvin for 6–8 weeks; itraconazole or terbinafine at double normal doses are alternatives, and these are also given for 6–8 weeks. Generally children are also treated with a topical agent to reduce the risk of spread in the early phase of oral treatment. Ketoconazole shampoo, twice or three times weekly for the first 2 weeks of oral therapy, is often used.

9.15 Treatment of Carriers

Topically applied ketoconazole and selenium sulphide in shampoos reduce the frequency of positive cultures form both infected children and those carrying the organism without clinical evidence of infection [41–43]. Topical antifungals are recommended for carriers defined as asymptomatic children with positive brush cultures. If scalp brushes produce very heavy growth of fungus, it is likely that the children have a true but asymptomatic infection, and these should be treated as infected patients by using the appropriate oral antifungal.

9.16 Schools

While infected children pose a potential risk to those who are not infected, the method by which the organisms spread from head to head is not known, e.g. aerosol and direct contact. Exclusion from school is not recommended in most countries. Recent work suggests that treating whole classes where there is a risk of infection with ketoconazole shampoo to prevent infection is not effective.

9.17 Kerion

In kerions the same treatment regimens as those used for children with other forms of tinea capitis are used. But it is often necessary to continue antifungal therapy for longer periods, e.g. 12–16 weeks. Few clinical trials have addressed the issue of the use of systemic corticosteroids in kerions, and advice is based on anecdotal experience. However, one trial which examined the value of oral corticosteroids found that they made no difference to clinical and mycological response rates [44].

Removal of surface crusts is often helpful as it relieves itching and secondary infection. It can be painful; therefore, the procedure is best carried out after soaking the crusts with lukewarm water or saline applied topically in the form of moistened dressings. The softened crusts can then be gently teased away. Secondary bacterial infection, usually due to *Staph. aureus,* should be treated with antibiotics such as flucloxacillin; however, pustules in the lesions of kerion are more often a response to the fungus rather than bacteria. The application of an antifungal cream with anti-Gram-positive bacterial activity such as miconazole, clotrimazole or econazole may allow the scalp to heal and prevent formation of new crusts.

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Chapter 10
Onychomycosis

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10.1 Introduction

Onychomycosis is a chronic fungal infection of the nail and may involve the nail bed, the nail plate, and the matrix. It is difficult to treat and relapses, and reinfections are common. The diagnosis can be made only when both positive laboratory and clinical criteria are present [1]. It can be caused by dermatophytes, yeasts, or non-dermatophyte molds. Tinea unguium is sometimes used as a synonym, but strictly speaking, the term is reserved to a dermatophyte infection of the nail unit.

Despite several treatment advantages during the post-griseofulvin era, onychomycosis is still a challenging disorder to treat. The diagnosis, with several differential diagnoses that can mimic onychomycosis, can also be difficult to make.

10.2 History

A German medical student, Georg Meissner (November 19, 1829–March 30, 1905), first described onychomycosis in 1853 [2]. Meissner later became famous for discovering the tactile instrument of the skin (Meissner's corpuscle).

Onychomycosis was rare at the start of the twentieth century but its incidence has increased dramatically during the last century. Dr. Sabouraud, considered by many to be the father of modern mycology, noted in 1910 in his classic monograph that out of 500 patients with superficial fungal infections, only one patient (0.2 %) had onychomycosis [3]. This is in great contrast to recent laboratory series where more than 50 % of the subjects with fungal infections had onychomycosis [4].

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It is hard to imagine that the first case of tinea pedis was described only 125 years ago by an Italian dermatologist Celso Pellizzari [5]. Most of the early reports on onychomycosis are from Europe [6]. The first reported case of tinea pedis in the United States was noted in Birmingham, Alabama, in the 1920s [7]. Returning World War I troops may have transported *Trichophyton rubrum* to the United States [7]. The first case of toenail onychomycosis presented in the United States is in 1937 when Montgomery presented a 28-year-old woman with onychomycosis before the Manhattan Dermatologic Society on December 14, 1937 [8]. However, "mycotic conditions of the nails" were described much earlier in the United States, and Guy and Jacob in 1923 recognized hyperhidrosis as a risk factor for onychomycosis and tinea pedis [9]. They also understood that "injury is a definite factor; mycotic conditions of the nails, especially, often date from injury" [9]. In a personal case series in 1927, White reported on 1013 patients diagnosed with "fungus diseases of the skin" between 1910 and 1925 [10]. Only three patients were diagnosed in 1910 and 147 in 1925. Out of 1013 patients, 23 (2.3 %) had onychomycosis and 341 (33.7 %) tinea pedis [10].

The increase in the prevalence onychomycosis parallels that of tinea pedis and the spread of the dermatophyte *Trichophyton rubrum* into the Western world [11]. *Trichophyton rubrum* is today the major cause of onychomycosis worldwide [12]. The change in the frequency of onychomycosis and *Trichophyton rubrum* is illustrated in Fig. 10.1.

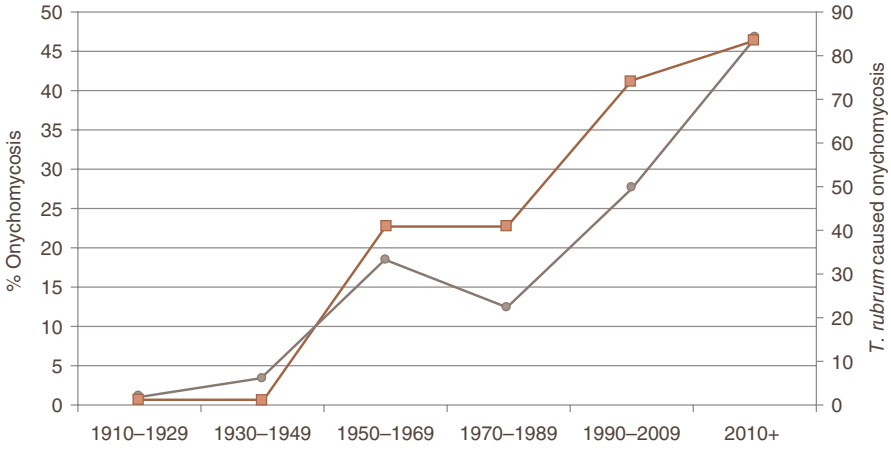


Fig. 10.1 Changes in frequency of onychomycosis and *T. rubrum* over time based on data from the whole world [12]. The figure shows proportion of onychomycosis compared to all other superficial mycosis (*gray line*) and the proportion of fungal nail infections caused by *Trichophyton rubrum* (*orange line*) (based on studies published in the literature (Sigurgeirsson data on file))

Trichophyton rubrum originated from West Africa and the Eastern world. The indigenous populations of this area developed neither tinea pedis nor onychomycosis, probably because they mainly walk barefoot [13]. When the colonialists and soldiers arrived, wearing boots that caused hyperhidrosis and maceration of the feet, it was easy for *Trichophyton rubrum* to find a new home. During the late eighteenth and early nineteenth century, there was increased urbanization and travel. The great wars (World War I and II and the Vietnam War) may have contributed further in the spread of *T. rubrum* (Fig. 10.1). Modern lifestyle with leisure travel and the "health boom" with frequent use of gyms and shared bathing facilities have helped further with the dramatic increase of onychomycosis seen during the past 100 years (Fig. 10.1).

10.3 Epidemiology

Onychomycosis is the most frequent nail disease and accounts for up to 50 % of nail diseases [14, 15]. Nail changes in general are common, and in a sample of 15,000 patients, abnormal-appearing nails were observed in 2505 persons (16.7 %) [15] (Fig. 10.2). Between 1.5 and 16 % of patients presenting to a dermatologist have onychomycosis [16].

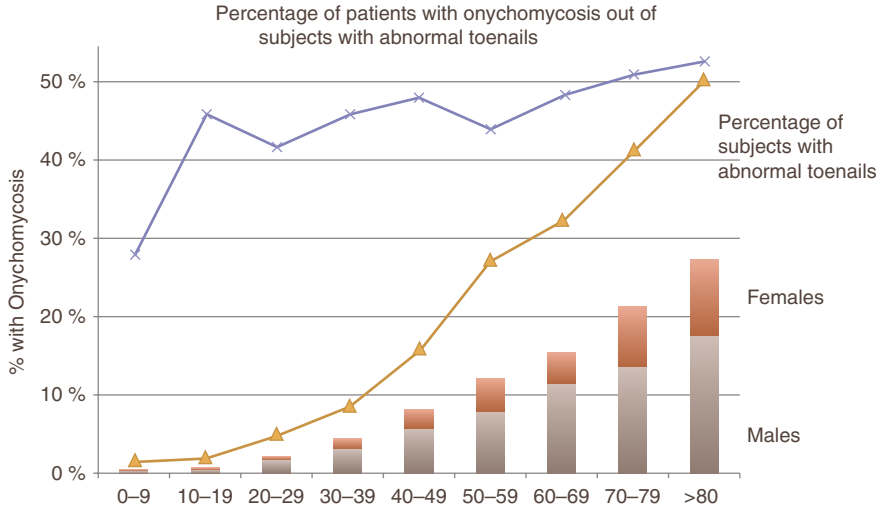


Fig. 10.2 Onychomycosis and nail changes according to age. This figure demonstrates that onychomycosis increases with age and is more common in males at all age groups. The prevalence of abnormal toenails also increases with age. The prevalence of onychomycosis in patients with abnormal toenails is fairly constant, 40–50 % in all age groups except the youngest children (Produced with data on 15,000 subjects from Gupta and colleagues [15])

Table 10.1 Onychomycosis worldwide. Estimated prevalence is based on world population [18] and worldwide prevalence from a recent review [12]

Continent	Population in 2013 (billions)	Estimated prevalence (%)	Estimated with onychomycosis (millions)
Asia	4.30	1 %	43
Africa	1.11	0.5 %	6
Europe	0.74	4 %	30
North America	0.56	4 %	23
South America	0.41	4 %	16
Oceania	0.04	4 %	1.5
Total	*7.2*		*120*

It has been estimated that over 50 million people are currently suffering from onychomycosis [17], but this may be an underestimation. Based on the published epidemiological data, the prevalence of onychomycosis in Europe and North America is estimated to be around 4 % [12]. The prevalence in Central Africa is very low, but studies indicate that it is higher in North Africa and probably in South Africa. We have estimated the prevalence in Africa to be 0.5 %.

Not much is known about the prevalence of onychomycosis in China and India, where prevalence studies are not available. It is likely that the prevalence of onychomycosis is the same in urban China and India as in the rest of Asia, where prevalence similar to that in Europe and North America [12]. The prevalence is probably lower in rural locations. A conservative estimate of a prevalence of 1 % for Asia is therefore used.

Based on available epidemiological data [12], it is likely that at least 120 million people worldwide have onychomycosis (Table 10.1).

The onychomycosis treatment market was valued at $2.1 billion in 2010 and is forecasted to grow at a compound annual growth rate of 7 % over the next 7 years, to reach $3.4 billion by 2017 [17].

10.3.1 Prevalence

In a recent review on the prevalence of onychomycosis, only 11 population-based studies could be located [12]. Two of the studies were from Central Africa where the prevalence was very low, nonexistent in one study, and 0.56 % in another [13, 19]. The remaining nine studies [20–28] were from North America and Europe with prevalence ranging from 0.6 to 8.4 %, but with a mean prevalence of 4.3 % (95 % confidence interval (CI), 1.9–6.8 %). Based on this data, it is likely that the prevalence of onychomycosis in the general population is between 2 and 8 % in Western populations [12]. This is in harmony with a recent literature review by Gupta and colleges which found the prevalence of dermatophyte onychomycosis to be 3.22 %

Table 10.2 Worldwide prevalence of onychomycosis [12]. The population-based studies give the most reliable estimate of prevalence. The methodology used in different studies is not always comparable, as some studies used clinical signs, while others used mycology to ascertain the diagnosis

	Population % (95 % CI)	Hospital based (95 % CI)
Europe and the United States	4.3 (1.9–6.8)	8.9 (4.3–13.6)
North America	N/A	9 (3.6–14.3)
Europe	6.4 (2.8–9.9)[a]	8.9 (1.4–16.4)
Africa (central)	<0.6	N/A
South America	N/A	18.8 (0.0–43.1)
Asia	N/A	12.1 (0.0–25.6)
Australia	N/A	N/A

N/A Not available
[a]Based on five European studies that used mycology to ascertain the diagnosis

(95 % CI, 3.07–3.38 %) in the general population [29]. If yeasts and molds were included, the prevalence was 3.94 % [29].

There are studies that have shown a higher prevalence, but these have not been done on the general population, but rather used in hospital or clinic population or patients recruited from waiting rooms (hospital-based studies). The subjects in such studies are not matched for other predisposing factors or comorbidities such as diabetes, psoriasis, immunosuppression, poor peripheral circulation, and several other disorders that are associated with a higher prevalence of onychomycosis. As a result, onychomycosis will be higher in this unmatched population compared to the general population. Also older individuals are more likely to seek medical attention and to have a higher prevalence of onychomycosis than younger individuals, which also can lead to an overestimate of prevalence [12]. One such study is the Achilles study, which showed a prevalence of 26.9 % [30]. When hospital-based studies were compared with population-based studies, the prevalence was generally higher [12]. Twenty such studies could be located in the literature with a mean prevalence for all studies ($n=20$) of 10.9 % (95 % CI, 7.1–14.2) (Table 10.2) [12]. As pointed out before, hospital-based studies probably overestimate the prevalence, but they show that there is a considerable geographical variation.

10.3.2 Toenails Versus Fingernails

Only two population-based prevalence studies have reported the ratio between finger and toenail onychomycosis, and both showed that onychomycosis is 6–16 times more common in toenails [23, 26].

In eight hospital-based prevalence studies, there was information on the ratio between toenail infection and fingernail infection. In seven out of eight studies,

Table 10.3 Epidemiology of onychomycosis

General population	Prevalence on average 4 % (2–8 %)
Patient population (from clinics)	Prevalence on average 9 %
Geography	More common in South America. Very rare in Central Africa
Children	Does exist, but rare (<0.5 %)
Age	Increases with age (Fig. 10.2)
Gender	More common in males
Toenails vs. fingernails	Ten times more common in toenails
Sports	More common in those who engage in sports activities, particularly fast sports that can cause nail trauma
Living conditions	More common in "close quarter living" including the home
Other superficial fungal infections	Particularly tinea pedis carries high risk
Diseases	Increased in patients with diabetes, psoriasis, immunosuppressive disorders (incl. HIV), peripheral vascular disease, and possibly other chronic disorders

onychomycosis was more common in toenails with an average toenail/fingernail ratio of 10.6 (95 % CI, 0.0–22.6).

The evidence suggests that onychomycosis is about ten times more common in toenails (Table 10.3) [12].

10.3.3 Prevalence in Children

Although onychomycosis is rare in children, the prevalence may be increasing. In a study from Iceland, the annual incidence was low, but increased from 1.65 per 100 000 children in 1982–1985 to 21.30 per 100 000 children in 1996–2000 [31]. Gupta and colleagues examined children from dermatology offices and found a prevalence of 0.44 % when children who presented with onychomycosis were included, but 0.16 % when they were excluded [32]. The prevalence may be higher in boys (Table 10.4). The risk of onychomycosis increases with the child's age (Table 10.5) [31, 38]. Although very rare, onychomycosis is not unknown in infants [31, 39, 40]. A recent meta-analysis of published studies showed a prevalence of 0.14 % (95 % CI, 0.11–0.18 %) [29].

10.3.4 Predisposing (Risk) Factors

Several factors have been shown to increase the risk of onychomycosis (Table 10.6). Consideration of these factors is important when selecting the appropriate treatment or potential prophylaxis for onychomycosis.

Table 10.4 Studies on prevalence of onychomycosis in children

Author	Year	Country	Sample size	Age	Prevalence % (n)	Comment
Mahgoub [33]	1968	Sudan	8443	7–12	0.1 (7)	From schools
Roy [34]	1972	India	440	5–12	0.2 (1)	From schools
Philpot [35]	1989	The United Kingdom	494	5–10	0.2 (19)	From schools
Gupta [32]	1997	North America	2500	0–17	0.16 (4)	From waiting rooms
Gunduz [36]	2006	Turkey	23,235	7–14	0.18 (41)	From schools. More common in boys (OR = 5.85)
Leibovici [37]	2009	Israel	1148	5–14	0.87 (10)	From schools. Boy/girl =2.2

Table 10.5 Number of cases positive for the growth of a dermatophyte according to age in 148 children with onychomycosis

Age (years)	Number of samples	Number of samples positive for the growth of a dermatophyte	% of samples positive
0–4	81	8	9.9
5–9	121	42	34.7
10–14	162	57	35.2
15–17	129	41	31.8

(Modified from Sigurgeirsson with permission [31])

10.3.4.1 Age

Numerous studies have shown that onychomycosis increases with age (Fig. 10.2) [26, 41–44]. In a population-based study, the odds ratio (RO) of having onychomycosis was 2.74 (95 % CI, 2.19–3.42) for those aged 50 or older [42]. The association of onychomycosis with age has been demonstrated in several studies [23, 26, 45, 46]. A recent literature review showed the prevalence of dermatophyte onychomycosis in the elderly to be three times higher than the general population [29]. Laboratory- or clinic-based series typically show a different pattern, as patient-seeking behavior affects the patient population. In these series, prevalence increases with age until the highest age groups, where a decline in prevalence is seen, as the oldest patients are less likely to seek help for their problem [4]. There are numerous reasons for higher prevalence in older individuals such as chronic illness, diabetes, repeated nail damage, poor foot hygiene, longer cumulative exposure to pathogenic fungi, poor peripheral circulation, inability to cut toenails, altered immune status, inactivity, larger nail surface, and slower nail growth [47].

Table 10.6 Predisposing (risk) factors for onychomycosis

Group	Risk factor	Comment
Subject characteristics	Age	Prevalence increases with age
	Sex	More common in males
	Genetics/family history	May lie in families
	Smoking	
Systemic disorders	Diabetes	
	Peripheral vascular disease	
	Immunosuppression	Includes both conditions such as HIV and use of immunosuppressive medications
	Autoimmune disorders	
	Renal disease	
	Other	Atopy, urticaria and angioedema, cancer, rheumatoid disorders, and gastrointestinal disorders may also be risk factors for onychomycosis
Environmental factors	Close quarter living	This includes infected family members
	Sports activities	
	Occlusive footwear	
	Nail trauma	
	Use of communal bating facilities	
	Occupation	
	Climate	Individuals who walk barefoot have lower risk
Local factors	Tinea pedis	
	Concurrent nail diseases	
	Repeated trauma	
	Feet hyperhidrosis	
	Dry crackled skin	

10.3.4.2 Gender

Out of seven population-based studies reporting gender, onychomycosis is more common or equal in males in six studies (Fig. 10.2). In a recent meta-analysis on population-based prevalence studies [12], the mean male/female ratio was 1.6 (95% CI, 0.9–2.3), but on average 1.4 (95% CI, 1.0–1.9) in hospital based. Studies from Africa did not include information about sex. Onychomycosis was more common in males (male/female >1) in North America (1.9; 95% CI, 1.2–2.6) and Europe (1.5; 95% CI, 0.3–2.7). There was only one study from Asia that included information on gender. In South America, onychomycosis is more common in females (0.8; 95% CI, 0.2–1.3). This may be because of the warm and humid climate and a greater tendency of fingernail candida onychomycosis. Many studies have shown more fingernail onychomycosis is more common in women [48, 49]. In most of these cases, the fingernail onychomycosis is caused by *Candida*.

Other explanations for the gender difference may be difference in hormone levels that might affect the ability to inhibit dermatophyte growth [41, 50].

Laboratory- or clinic-based patient series often show different results, but such series are based on the patients seeking help for onychomycosis and are thus affected by patient-seeking behavior. Gender ratio from population-based studies is most likely to mimic the true situation in the population.

10.3.4.3 Diabetes Mellitus

Several studies have shown increased prevalence in patients with diabetes mellitus [51–59]. It is known that hyperglycemia and insulin resistance change cellular immunity, causing increased risk of infections [53]. It is possible that the prevalence of candida onychomycosis is higher among diabetic patients [53]. Data from the literature suggest that onychomycosis is 2–3 times more common in patients with diabetes compared to controls (Table 10.7). This has been confirmed by a recent literature review that showed a prevalence of 8.75 % (95 % CI, 7.48–10.21) for dermatophyte onychomycosis, 3.97 % (95 % CI, 3.09–5.09) for onychomycosis caused by yeasts, and 1.68 % (95 % CI, 1.07–2.64) caused by molds [29].

Studies on prevalence of onychomycosis that do not include controls do indicate that between 20 and 80 % of diabetics are affected [53, 60–62]. It is also possible that patients with diabetes show poorer responses to treatment [63].

Table 10.7 Studies on prevalence of onychomycosis in patients with diabetes

Author	Year	Country	Sample size	Diabetic patients (%)	Controls (%)	Ratio	Comment
Buxton [51]	1996	The United Kingdom	100	12	11	1.1	Patients with well-controlled insulin-dependent diabetes compared to a control group of 100 non-diabetics matched for age, sex, occupation, and sporting activity
Gupta [57]	1998	Canada	550	n/a	n/a	2.8	Diabetics attending diabetes and dermatology clinics. After controlling for age and sex, the risk odds ratio for diabetic subjects to have toenail onychomycosis was 2.77 times compared with normal individuals (95 % CI, 2.15–3.57)

(continued)

Tabel 10.7 (continued)

Author	Year	Country	Sample size	Diabetic patients (%)	Controls (%)	Ratio	Comment
Dogra [58]	2002	India	400	17	6.8	2.5	The prevalence of onychomycosis in diabetics was compared with that in a nondiabetic control group
Piérard [59]	2005	Belgium	380	65	51.5	1.3	Diabetic patients and matching controls consulting a dermatology division because of toenails showing discoloration, thickening, and dystrophy
Al Mutairi [52]	2010	Kuwait	460	18.7	5.7	3.3	This study included 460 consecutive diabetic patients and the same number of nondiabetic age-matched subjects attending dermatology clinics in Kuwait

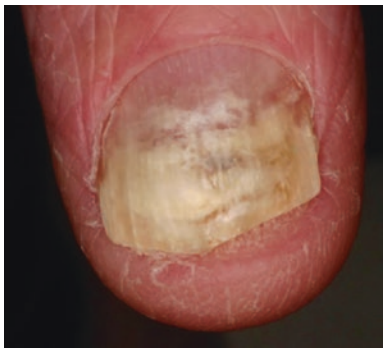


Photo 10.1 A 65-year-old male with psoriasis and onychomycosis. Nail changes in two fingernails and both big toenails. As the signs and symptoms of onychomycosis and psoriatic nail disease can be identical, it can be difficult to predict how well the patient will respond to antifungal treatment

10.3.4.4 Psoriasis

Nail changes in patients with psoriasis are common, but the reported prevalence varies from 15 to 80 % with a much higher lifetime incidence [64]. Another problem is that onycholysis, discoloration, and hyperkeratosis are seen both in patients with onychomycosis and psoriasis (Photo 10.1). As in patients with diabetes mellitus,

early studies did not show increased risk of onychomycosis in patients with psoriasis [65, 66]. Henseler and Tausch showed that patients with psoriasis had lower risk of tinea of the skin [67].

Gupta found that psoriatics had 56 % greater odds of developing onychomycosis compared to non-psoriatics of the same age and sex and that 47 % of psoriasis patients had abnormal-appearing nails compared to 16 % of non-psoriatics [68]. Sigurgeirsson and Steingrímsson examined several putative predisposing factors in 3999 randomly selected subjects and found an odds ratio of 2.4 in psoriatics (95 % CI, 1.6–3.7) [42]. As can be seen in Table 10.8, although many of the studies showed higher prevalence in psoriatics compared to controls, only two showed a significant difference. Zisova and colleagues evaluated 228 patients with psoriasis and nail changes [75]. Positive mycological cultures were obtained from 62 % of these patients.

A recent meta-analysis was unsuccessful because of the heterogeneity of the data: however, when all studies were combined, a combined prevalence of 18 % was found in psoriatics compared to 9.1 % in controls [64]. Therefore, this evidence together with the population-based study of Sigurgeirsson and Steingrímsson [42] leans toward a higher prevalence of onychomycosis among patients with psoriasis, although this issue is far from resolved. It is probably right to regard all nail changes in psoriatics as suspicious and to have a low threshold for taking samples for mycology. A recent literature review showed a prevalence of 10.22 % (95 % CI, 8.61–12.09) for dermatophyte onychomycosis in patients with psoriasis [29].

10.3.4.5 Renal Disease

It has been shown that several chronic disorders increase the risk of onychomycosis [42]. There have been no controlled studies on patient with renal disease. Virgili and colleagues investigated 73 renal transplant recipients and found that the prevalence of onychomycosis and tinea pedis was similar to that found in the normal immunocompetent population [76]. Similarly Güleç and colleagues did not find higher prevalence of dermatophytosis in a case–control study [77]. Udayakumar examined cutaneous manifestations in patients with chronic renal failure on hemodialysis and found that 30 % of the patients had a fungal infection (of any kind) [78]. In the Turkish study, onychomycosis was diagnosed in 26.6 % of hemodialysis patients, but diabetes mellitus was present in 68.9 % of patients with onychomycosis, which may explain the seemingly increased prevalence in this group [79]. In an Egyptian study, 100 patients with chronic renal failure under regular hemodialysis were examined as well as 100 healthy control subjects of matched age and sex [79]. Nail changes were much more common in the hemodialysis patients, but there was not an increased risk of onychomycosis [79]. The medical records of 401 patients followed up in a transplant center in Turkey were used in a retrospective analysis. Skin infections were found in 55 % of the patients and 64 % of these were of fungal in nature. The prevalence of onychomycosis was 5.7 % [80]. In another study of 302 kidney transplant patients and a control group which included 302 healthy individuals [81], onychomycosis was significantly

Table 10.8 Studies on prevalence of onychomycosis in patients with psoriasis

Author	Year	Country	Sample size (patients with psoriasis)	Psoriatic patients (%)	Controls (%)	Significant difference	Comment
Gupta [68]	1997	Canada and the United States	561	12.7	6.9	Y	Patients with psoriasis. If nails were abnormal, samples were taken. 922 matching controls were included. Patients were recruited from dermatology offices
Ständer [69]	2001	Germany	250	9.8	10.8	N	A collective of 250 psoriatic patients compared to a group of 102 non-psoriatic persons. *Candida* was more commonly isolated from psoriatic nails
Larsen [70]	2003	Denmark	79	21.5	12.7	N	Seventy-nine inpatients with psoriasis compared to 142 inpatients with other skin diseases. Abnormal nails sampled
Hamnerius [71]	2004	Sweden	239	4.6	2.7	N	Consecutive psoriasis outpatients attending a department of dermatology were examined and samples taken. Matching controls from patients without psoriasis
Kaçar [72]	2007	Turkey	168	13.1	7.9	N	Over a period of one year, 168 patients with psoriasis and 164 non-psoriatic controls were recruited. Samples were taken from abnormal nails

Table 10.8 (continued)

Author	Year	Country	Sample size (patients with psoriasis)	Psoriatic patients (%)	Controls (%)	Significant difference	Comment
Leibovici [73]	2008	Israel	113	47.6	28.4	Y	A prospective study of toenail onychomycosis, among 113 psoriatic and 106 healthy non-psoriatic subjects, selected from the normal population in the Jerusalem area in the period 2003–2005. Samples taken from affected nails
Kavaliausk [74]	2010	Lithuania	30	23.3	23.6	N	The study included 559 patients examined for fungal infection of nails using direct microscopy and culture tests. Of these, 30 patients had psoriasis

more common in the transplant patients (7.6 %) compared with controls (2.3 %) $p = 0.002$ [81]. In another study on patients with chronic renal failure on hemodialysis, 31 % of the patients had onychomycosis, but no control group was included [82]. In a similar study, 39 % of the patients had onychomycosis [83]. It must be concluded that the data is inconclusive although a recent pooled estimate from the literature showed a mean prevalence of 11.93 % (95 % CI, 7.11–19.35) of dermatophyte onychomycosis in patients on dialysis [29].

10.3.4.6 HIV

HIV is a common disorder and is one of the leading causes of death in young adults [84]. As the disease progresses, the risk of fungal infections, such as onychomycosis, increases [85–87]. Signs and symptoms of onychomycosis can improve after combined antiretroviral therapy [88, 89] which suggests that the risk of onychomycosis is related to immunosuppression. Nail symptoms in general are more common in patients with HIV, 68 % with HIV compared to 34 % of controls [90]. In this study, the following symptoms were significantly more frequent in the HIV group: clubbing (5.8 %), transverse lines (7.1 %), onychoschizia (7.1 %), leukonychia (14.3 %), and longitudinal melanonychia (14.8 %) [90]. Proximal subungual

onychomycosis, which is normally rare, is relatively common in patients with HIV [91, 92]. There are only two studies on the prevalence of onychomycosis in HIV-infected individuals that have used age- and sex-matched controls. Both studies showed that the prevalence of onychomycosis is higher in HIV-infected individuals [87, 90]. In studies that did not include controls, the prevalence of onychomycosis ranged from 6 to 55 % (Table 10.9). A pooled estimate from the literature showed a prevalence of 10.4 % (95 % CI, 8.02–13.38) in HIV-positive patients [29].

Table 10.9 Studies on prevalence of onychomycosis in patients with HIV

Author	Year	Country	Sample size (patients with HIV)	HIV patient Onychomycosis prevalence (%)	Controls (%)	Comment
Korting [93]	1993	Germany	138	42*	N/A	Skin scrapings from the toe clefts, soles, and nail plates of 138 HIV-infected patients at various stages were examined for the presence of dermatophytes using both microscopy and culture
Ravnborg [91]	1998	Denmark	22	55	N/A	HIV-positive patients with nail changes referred to the dermatological outpatient clinic because of skin diseases
Cribier [90]	1998	France	153	30	103	Prospective controlled study at a primary care university hospital. Nail changes were recorded by a standardized clinical examination (curvature, nail plate, color, onychomycosis). In case of clinical diagnosis of onychomycosis, mycological culture was performed
Gupta [94]	2000	Canada and Brazil	500	23	N/A	HIV-positive individuals were evaluated at five clinics: four in Ontario, Canada, and one in Sao Paulo, Brazil. The subjects were asked questions to determine the epidemiology of onychomycosis in HIV-positive individuals. The feet were examined and nail material was obtained for mycological examination
Kaviarasan [95]	2002	India	185	6	N/A	The present study was to note the prevalence and clinical variations in dermatophytosis in HIV-infected patients

Table 10.9 (continued)

Author	Year	Country	Sample size (patients with HIV)	HIV patient Onychomycosis prevalence (%)	Controls (%)	Comment
Freytes [96]	2007	Puerto Rico	95	18	N/A	Ninety-five HIV-positive adults in San Juan, Puerto Rico
Surjushe [97]	2007	India	250	20	N/A	To study the epidemiology and clinical manifestations of onychomycosis in HIV-infected individuals and to identify the various causative fungi microbiologically. Only patients with a clinical suspicion of onychomycosis ($n=60$). Fungi found in 49
Rodwell [87]	2008	The United States	105	35	19	Patients were recruited from a HIV testing site, general dermatology clinics, HIV clinic, and methadone clinic at San Francisco General Hospital, from the community, and from free clinics in San Francisco City Center. Very few women
Moreno Coutiño [85]	2011	Mexico	280	20	N/A	Retrospective review of 280 adult HIV-infected patients and searched for data of onychomycosis diagnosis and its presentation
Cambuim [98]	2011	Brazil	100	32	N/A	Samples were taken from 100 patients that attend a Brazilian hospital for HIV
Jimenez Gonzalez [99]	2013	Mexico	300	17	N/A	HIV-infected patients diagnosed clinically with onychomycosis from 2008 to 2010. Samples were collected from 300 (84% men) patients

10.3.4.7 Peripheral Vascular Disease

Onychomycosis has been reported to be more prevalent in patients with peripheral arterial disease (PAD) and chronic venous insufficiency (CVI) [100]. This may partly be explained because of a higher prevalence of diabetes in these groups. Fukunaga and colleagues investigated 86 patients aged ≥50 years old who visited the outpatient or inpatient dermatology clinic [101]. Of these, 44 had mycological evidence of onychomycosis. Multiple logistic analyses identified PAD and measured ankle

brachial pressure as a strong risk factor for onychomycosis (OR, 9.85; 95 % CI, 1.37–70.72). Ozakan and colleagues examined 33 patients with bilateral onychomycosis in toenails and 37 control subjects, who had healthy nails with ultrasound [102]. Patients with onychomycosis had a higher frequency of venous insufficiency than the control group (42.4 % and 10.8 %, respectively; $p = 0.003$), but no significant difference in frequency of PAD was found [102]. In 78 cases caused by molds, PAD was identified as a predisposing factor in 15 % of cases [103]. In a study where 42 patients with onychomycosis and 39 healthy controls were examined with a Doppler examination, venous insufficiency was detected more frequently in patients with onychomycosis (36 % vs. 15 %) [104]. In another study where 36 patients with venous leg ulcers were examined, 61 % of the patients had nail changes, and the overall frequency of onychomycosis was 36 % [105]. Gupta and colleagues examined 254 patients attending a vascular clinic [106]. Over half of the patients had nail changes and the overall prevalence of onychomycosis was 22.4 % [106]. Factors associated with onychomycosis included smoking (OR 1.9, $p = 0.02$) and peripheral arterial disease (OR 4.8, $p = 0.02$) [106]. Vascular disease was found to be a predisposing factor for onychomycosis in the Achilles project where 15.8 % and 17.4 % in study I and II, respectively, had PAD [30]. Judging from the evidence presented, it seems that both peripheral arterial disease and venous insufficiency predispose to the development of onychomycosis. Possibly impaired perfusion of the lower extremities may result in suboptimal oxygenation and reduced metabolic exchange of nutrients and other substances in the foot. This may result in the instigation and progression of onychomycosis, also hindering nail growth, delaying the clearance of infection, and exposing the subject to reinfection [100].

10.3.4.8 Genetic Factors

Onychomycosis seems to be more common in some families. This can be explained by intrafamilial transmission [107, 108] and/or genetic susceptibility. It has been demonstrated that HLA-DR6 confers protection against the development of onychomycosis in a Mexican Mestizo population [109]. This is also suggested by low prevalence of *T. rubrum* infection in people marrying into infected families [110]. Further evidence is provided in studies of children with onychomycosis showing that in almost half of cases parents were also affected [32]. Zaias suggested an autosomal dominant pattern of inheritance for *T. rubrum* onychomycosis in families from Italy and France [111]. In a Chinese study of 545 patients with onychomycosis, 82.5 % of the patients with a *T. rubrum* onychomycosis infection had an infected family member [63].

10.3.4.9 Sports

Several studies that have investigated the epidemiology of onychomycosis indicate that sports may be a risk factor for onychomycosis and tinea pedis [112–114]. Onychomycosis is probably more common because tinea pedis (athlete's foot) is more common in athletes [115–117]. This may be because of exposure of the feet

to infected surfaces [118] and the microclimate caused by increased perspiration inside closed shoes. Hyperhydration and maceration of the skin involved in swimming may also play a role. In a study from Iceland, 40 % of the visitors to a large public swimming pool were suspected to have onychomycosis, and mycological proof was found in 28 % [119]. Trauma to the toenails involved with intensive sports can also be of importance. In the Achilles project, over 100 000 subjects were screened [114]. As sports activities are more common in younger individuals, the group not engaged in sports was older and had higher frequency of other risk factors such as diabetes. After adjusting for these factors, it was demonstrated that fungal foot disease was significantly more common in those who were sports active [114]. In a Polish study of patients with onychomycosis presenting to a dermatologist, over 50 % were exposed to fungal infections in swimming pools or common bathrooms [120]. In a population-based study from Iceland where 2500 randomly selected individuals were examined, the odds ratio for onychomycosis in regular swimmers was 2.57 (95 % CI, 2.00–3.30) [42].

10.3.4.10 Other

Shemer and colleagues evaluated 68 patients suffering from nail changes and paronychia, which appeared after removal of artificial nails and found a positive culture in 96 % of the cases [121]. *Candida* was the most common species.

Autoimmune disorders may carry an increased risk of onychomycosis. One study found prevalence of onychomycosis in autoimmune patients to be 10.2 % (95 % CI, 6.5 %, 15.9 %) compared to 6.7 % (95 % CI, 3.8 %, 11.6 %) in non-autoimmune patients ($p > 0.05$, 2 sided) [122]. Of immunobullous patients, mainly presenting with pemphigus and who were mostly on immunosuppressive medication, 24 % had onychomycosis [$p = 0.013$; OR, 4.39 (95 % CI, 1.27, 14.89)] [122]. Other studies have shown the same trend [123, 124]. Autoimmune patients may be more prone to proximal white subungual onychomycosis, probably because of immunosuppression [125, 126]. Dermatophytosis is more common in patients with rheumatoid arthritis compared to controls [127].

Not washing the feet daily is associated with an increased risk of onychomycosis [128].

Both tinea pedis and unguium were high in worshippers in mosques, probably because they are required to remove their shoes during prayers [129]. In another study, regular visitors in mosques were compared to non-Muslims [130]. The prevalence of onychomycosis and tinea pedis was 85 % in the Muslim worshippers compared to 41 % in the control group [130].

Abnormal or damaged nails due to trauma or disease are more susceptible to onychomycosis [131].

There is an indication that climate or working conditions requiring the use of closed shoes or boots involve a risk of tinea pedis and onychomycosis [132]. The prevalence of onychomycosis is low in areas where people do not wear shoes [13, 133]. It is postulated that the closed shoes create a hot and humid microclimate that facilitates the development of fungal infections.

Hereditary palmoplantar keratoses also are associated with onychomycosis [134].

Immunodeficiency can play a major role in the development of onychomycosis. A high frequency of tinea pedis and unguium has been found in patients with Kaposi sarcoma [135]. Also increased risk in patients with autoimmune disorders is probably related to immunosuppression. The results of immunosuppression are clearly seen in patients with mucocutaneous candidiasis [136, 137]. Other immunodeficiencies with a higher risk of onychomycosis include patients with organ transplantation [77, 81, 138] and Cushing's syndrome [122] and lymphoma [139].

In a case–control study, the authors examined 141 patients with inflammatory bowel disease (IBD) and compared them to 100 control individuals without IBD. The prevalence of onychomycosis was 15 % in patients with IBD compared to 6 % in subjects without IBD ($p<0.05$). It was noted that the subjects with IBD with onychomycosis had lower counts of leukocytes ($p=0.04$) during azathioprine therapy [140].

10.3.4.11 Tinea Pedis

Tinea pedis is a strong predisposing factor for onychomycosis [141]. In a study from Mexico, 76.5 % of patients with onychomycosis had plantar tinea pedis and 61.7 % interdigital involvement [142]. One study demonstrated that dermatophytes may be isolated from normal-appearing toenails and are associated with concurrent tinea pedis [143]. If patients with tinea pedis can harbor a fungus in their nails for a period of time before they develop clinical onychomycosis and if topical treatment is an option for the tinea, it is logical to combine it with the topical lacquer, even if all the toenails are normal. Since tinea pedis is a risk factor for onychomycosis, increased risk of tinea pedis also includes increased risk for onychomycosis. The risk factors for tinea pedis and onychomycosis include hyperhidrosis [144], dry pedal skin [141], sports activities [145], and occupation to name a few.

10.3.4.12 Living in Close Quarters

In a recent paper, Gazes and colleagues reviewed studies on the living environment of the patients with onychomycosis [146]. It can be argued that the home is the ultimate "close quarter living." People walk on the same floors, share a bathroom, may share shoes and nail clippers, and often have close bodily contact, which sets the stage for intrafamilial transmission of fungi. El Fekih et al. found that family history of mycosis was a predisposing factor for foot fungal infection [147]. In a study on tinea pedis, it was found that 86 % had a family history of tinea pedis [148]. In a study on onychomycosis, the odds ratio of having onychomycosis was 2.6 if the parents had onychomycosis, 3.5 if a child had onychomycosis, and 2.5 if the spouse had onychomycosis [42]. Based on this data, it is likely that both genetics and close living conditions predispose for onychomycosis.

A military life results in similar closeness as described in the home and has been associated with tinea pedis [149] and onychomycosis. In one study, soldiers were

examined before and 6 months after duty [150]. Fungal infections before duty were found in 16.4 %, but in 32.3 % of the soldiers after duty [150].

The joint prevalence of tinea pedis and onychomycosis was 66 % in members of the Japanese self-defense forces [151]. The prevalence was higher in long-serving members.

The prevalence of onychomycosis in nursing homes is high [146]. However, the inhabitants of nursing homes are elderly people, which as a group are already predisposed to onychomycosis. As no controlled studies exist, it is difficult to say how strong risk factor "nursing home inhabitancy" really is.

In a study on foot infections in teenagers from Peru, 72 % of those who were infected used a shared shower on a regular basis [152].

Based on the evidenced presented and the review of Gaza [146], it must be concluded that "close quarter living" is a risk factor for onychomycosis. The most important of which is other infected individuals at home.

10.4 Anatomy of the Nail Unit

Knowledge of the terminology and anatomy is important for understanding nail diseases and for scientific work within this field. The nail plate can be considered a translucent window to the underlying structures, mainly the nail bed. This can change in disease states where the nail often becomes thick and non-translucent. The nail bed is highly vascular giving the nail a pink color. The color of the nail

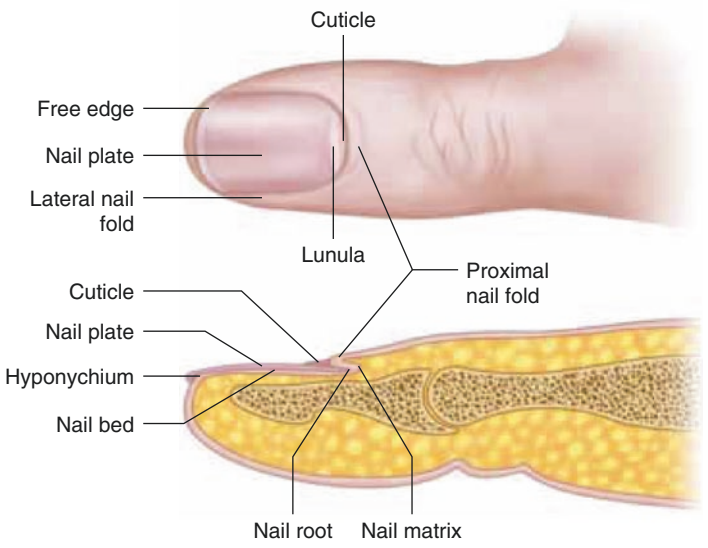


Fig. 10.3 Anatomy of the nail unit

changes in many disease states and can give important clues to the diagnosis of nail diseases. The nail is attached to the nail bed, which holds it in place with the nail folds and matrix. The most important structures can be seen in Fig. 10.3. The nail plate consists of tightly packed cells that have lost their nuclei. The nail plate is continuously formed by the matrix and continues to grow throughout life. The nail matrix is sometimes called the "nail root" for obvious reasons. The matrix is often divided into two parts. The ventral matrix is also called the nail bed and starts at the distal end of the lunula. It is limited distally by the hyponychium. The dorsal matrix lies under or is a part of the ventral part of the proximal nail fold. The lunula (from Latin: half-moon) is the more lightly colored part of the proximal nail plate which often looks like a half-moon. It is best seen on the thumbs and great toenails. The lunula determines the shape of the nail. The lateral nail folds are the folded part of the skin that helps to hold the nail in place. The proximal or posterior nail fold has a similar function and is continuous with the cuticle, but on the ventral surface, it becomes the dorsal part of the matrix. The cuticle (eponychium) is a thin translucent layer of the epidermis extending from the proximal nail fold and adheres to the nail plate. The hyponychium is the area beneath the free edge of the nail. The distal area of the nail bed has a different color. This 1–2 mm band is called the onychodermal band and is light in color in fair-skinned individuals, but darker in people with darker skin. This band is the first defense against microorganisms, and if it is disrupted, fungal invasion is easier. The distal groove is a landmark that delineates the subungual structures from the pulp.

10.5 Clinical Patterns

Most authors classify the clinical patterns of onychomycosis according to the site of initial fungal invasion [153]. It was Zaias who came up with the first classification of three different clinical forms [153], but it has subsequently been extended by Baran and others [154]. Sites of invasion associated with different clinical patterns are shown in Fig. 10.4.

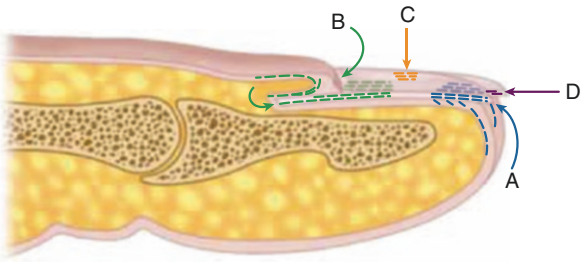


Fig. 10.4 Sites of invasion and types of onychomycosis. (*A*) *DLSO* distal and lateral subungual onychomycosis, (*B*) *PSWO* proximal white subungual onychomycosis, (*C*) *SWO* superficial white onychomycosis, (*D*) *EO* endonyx onychomycosis (Reproduced from Baran with permission [155])

10.5.1 Distal and Lateral Subungual Onychomycosis (DLSO)

This is the most common form and the fungus invades via the distal subungual area and/or the lateral nail groove. After the onychodermal band is disrupted, the fungus has easy access to the distal subungual area. In other cases, the fungus makes entry by invading under the lateral nail folds. The first step is often an infection of the horny layer of either the feet (tinea pedis) or hand (tinea manuum) [154]. The first signs of infections can be subtle and can be any of the following: onycholysis, yellow-brown discoloration, and hyperkeratosis of the nail bed (Photo 10.2). With time, an inflammatory reaction occurs in the nail bed and hyponychium with subsequent increased hyperkeratosis. Later the infection progresses proximally and in the end involves the whole nail apparatus. *Trichophyton rubrum* is the most common cause of this kind of infection.

10.5.2 Superficial Onychomycosis (SO)

The white form, superficial white onychomycosis (SWO), is the most common (Photo 10.3). In this form, the fungus invades via the nail plate. The infection can progress to involve the nail bed, but is often confined to the nail plate where it causes small superficial chalky white patches (Photo 10.3) which may later coalesce and even involve the whole or a large part of the nail. This form can occur with other

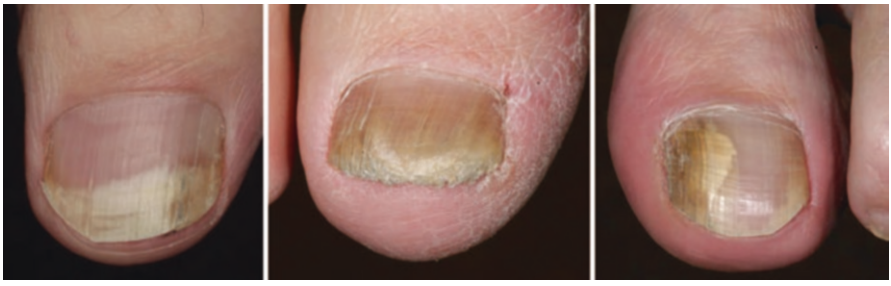


Photo 10.2 Distal and lateral subungual onychomycosis (*DLSO*). The fungus invades the subungual space at the distal or lateral edges. Onycholysis, yellow-brown or whitish discoloration, and hyperkeratosis of the nail bed can be seen

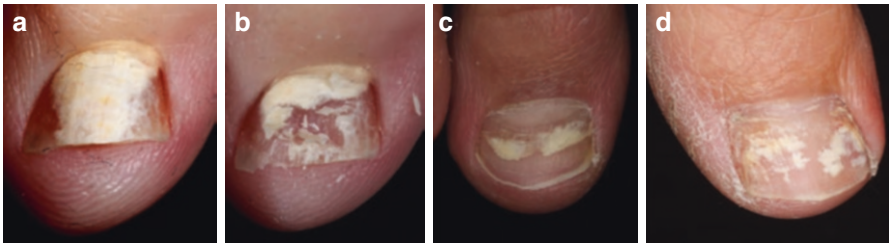


Photo 10.3 Superficial white onychomycosis. As the infection is between the nail plate layers, the white pigment can easily be removed with a curette (before **a**, after **b**)

forms. This form is typically cased by *Trichophyton mentagrophytes* but can also be caused by *Trichophyton rubrum* and molds. Similarly, some fungi can cause black pigment and then the term superficial black onychomycosis is used (SBO).

10.5.3 Proximal Subungual Onychomycosis (PSO)

This form is rare and was initially thought to be more common in HIV-infected or immunosuppressed individuals. In this form, the fungus enters via the proximal nail fold (Photo 10.4). Usually a white discoloration is seen, but here the fungus has left the nail plate intact as opposed to SWO. Proximal onychomycosis secondary to paronychia has also been described.

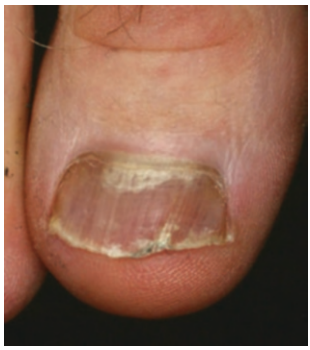
10.5.4 Endonyx Onychomycosis

Not all authors include this form. It is thought that the organism directly invades the nail plate distally and there is no inflammation of the nail plate. As with SWO, the nail is chalky white and lamellar splitting is often seen. It is probably only seen with fungi that have the ability to invade the hair shaft such as *Trichophyton soudanense*. It is thought that many patients have tinea capitis and get infected by scratching the scalp.

10.5.5 Totally Dystrophic Onychomycosis (TDO)

TDO is not considered a form by itself, but rather an end stage of the other forms when the whole nail unit is involved and the nail plate has been eroded (Photo 10.5).

Photo 10.4 Proximal onychomycosis. The patient also has mild DLSO which makes this a mixed form



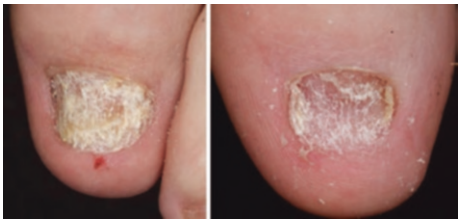


Photo 10.5 Total dystrophic onychomycosis. This is the most advanced form of onychomycosis. In most cases, the nail plate is damaged or sometime has eroded away leaving a hyperkeratotic nail bed. Nail plate fragments are often seen

10.5.6 Other Forms

Mixed forms exist, that is, that more than one form is found in the same nail, such as DLSO and SWO. Some authors consider paronychia associated with fungi a separate form.

10.6 Diagnosis

The diagnosis of onychomycosis is based on clinical suspicion and laboratory confirmation. As there are several other nail disorders that can mimic onychomycosis, a laboratory confirmation is of paramount importance. Dependence on culture of an organism alone is not sufficient for the diagnosis of onychomycosis – a fungus isolated from a normal nail does not demonstrate infection. The reverse is also true – an abnormal nail without mycological confirmation is insufficient to make an accurate diagnosis of onychomycosis [1].

10.6.1 Differential Diagnosis

Nail changes are common, but the prevalence of onychomycosis is only 50 % or less among patients with nail changes (Fig. 10.2) [14, 15]. The diagnosis of onychomycosis can only be made after mycological confirmation, and other diagnoses must always be considered and excluded (Photo 10.6).

(Table 10.10). Some patients have more than one disease and might have been more easily infected because a concurrent disease such as psoriasis has damaged the nail. When it is considered that the nail apparatus can only display a rather limited collection of reaction patterns, it is not surprising that clinical signs and symptoms of different nail diseases can be similar [16].

10.6.1.1 Psoriasis

Psoriatic nail disease is common and some of the signs are similar, such as discoloration, onycholysis, and hyperkeratosis. Patients with psoriatic nail changes should therefore be sampled to exclude a fungal infection. Psoriatic nail disease and onychomycosis can coexist in the same nail.

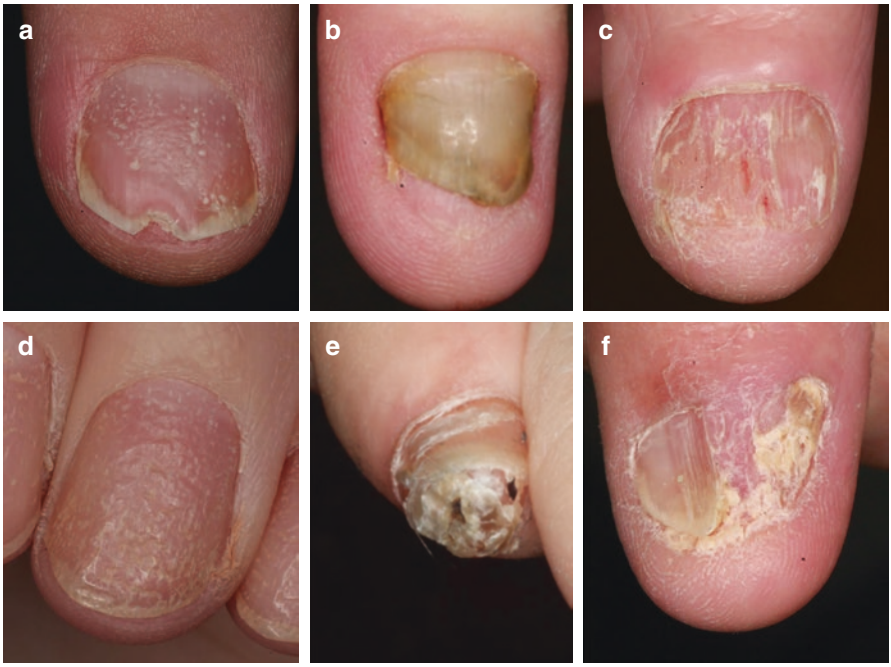


Photo 10.6 Several other dermatologic disorders can mimic onychomycosis. The diagnosis must always be ascertained with a laboratory confirmation. (**a**) Psoriasis, (**b**) yellow nail syndrome, (**c**) lichen planus, (**d**) alopecia areata, (**e**) trauma, and (**f**) tumors (in this case melanoma and psoriasis)

10.6.1.2 Lichen Planus (LP)

This is another inflammatory dermatosis that can cause nail changes that mimic onychomycosis. LP is usually limited to the hands and can occur without associated skin involvement [156]. Longitudinal grooves, longitudinal fissures, and progressive thinning of the nail plate are characteristic lesions of lichen planus of the nail [157].

10.6.1.3 Trauma

Repeated microtrauma, which is common in sports-related activities, can lead to nonspecific nail changes that are indistinguishable from onychomycosis, such as nail plate thickening, hyperkeratosis, and onycholysis. Trauma caused by the friction of the toes against the shoe is a very common cause of injury that mimics a nail onychomycosis. Morton's toe is a condition of a shortened first metatarsal in relation to the second metatarsal [158]. This promotes an anterior position of the second metatarsal-phalangeal joint in relation to the hallux and causes repeated trauma to the second toe and nail changes that can mimic onychomycosis. Nail changes due to this condition are not an uncommon cause of consultation. A secondary infection should always be ruled out with a mycological examination.

Table 10.10 Onychomycosis. Differential diagnoses

	Cause of nail abnormality
Dermatologic disorders	Psoriasis
	Lichen planus
	Lichen striatus
	Alopecia areata
	Chromic dermatitis
	Autoimmune bullous diseases
	Onycholysis
	Reiter's syndrome
	Psoriasiforme Nail changes seen in actual Pustulosis)
	Pityriasis rubra pilaris
Infections	Viral warts
	Chronic paronychia
	Bacterial (i.e., *Pseudomonas*)
	Scabies
	Herpes simplex
Tumors	Melanoma
	Squamous cell carcinoma and Bowen's disease
	Subungual exostosis
	Fibroma
	Keratoacanthoma
	Myxoid cysts
	Other tumors
Systemic	Yellow nail syndrome
	Cancer
	Iron deficiency
	Connective tissue disorders
	Bazex syndrome
	Changes in thyroid metabolism
	Raynaud's disease
Physical causes	Trauma
	Burns
	Foreign body implantation
	Cosmetic manipulation
Genodermatoses	Darier's disease
	Epidermolysis bullosa
	Congenital pachyonychia
Drugs	Cytotoxics
	Retinoids
	Antibiotics (tetracyclines, fluoroquinolones)
	Psoralens
Chemicals	Alkalis and mineral oils
	Household products such as detergents
	Occupational exposure
	Acids

Modified from Allevato [157] and Baran [16]. List may not be complete

10.6.1.4 Yellow Nail Syndrome (YNS)

In this syndrome, which is associated with chronic disorders of the upper reparatory tract, the nails become thickened and acquire a yellowish color [159]. The cause and pathophysiology are not known. The nails grow slowly and the transverse curvature is increased. Anatomic and/or functional abnormalities have been proposed as the underlying cause [159]. Patients with YNS should be screened for respiratory disorders. Vitamin E and itraconazole (promotes increased nail growth) are the mainstay of treatment.

10.6.1.5 Tumors of the Nail Unit

This is one of the most important differential diagnoses as both benign and malignant tumors can cause nail changes. Bowen's disease and squamous cell carcinoma can originate from the periungual skin or the nail bed causing hyperkeratosis, onychomycosis, pain, and bleeding. Melanoma is rare, but has an unfavorable prognosis, probably because of a delay in diagnosis and the rapid development of metastases from this location [157]. Benign tumors such as a myxoid cyst, fibroma, and keratoacanthoma are not uncommon.

10.6.1.6 Onycholysis

There are many different causes for onycholysis, one of them being onychomycosis. Infections (bacterial and fungal), systemic conditions, and dermatological disorders can cause onycholysis, but the most common cause is external irritation, wet work, and allergens. An idiopathic form also exists.

10.6.2 Laboratory Diagnosis

The clinical pattern can offer a clue to the type of organism involved, but the final diagnosis rests on a laboratory diagnosis. The mycological diagnosis consists of two steps: (a) microscopy where fungal elements are demonstrated with the aid of KOH or calcofluor white and (b) demonstration of the organism by culture [160, 161]. Other methods are histology and molecular diagnosis.

10.6.2.1 Sampling

A correct mycological diagnosis depends on several factors, such as an experienced laboratory and an adequate sample. Distal samples and nail clippings often result in false-negative results. The sampling technology depends on the type of onychomycosis involved. In patients with distal and lateral subungual onychomycosis, the sample is taken from the nail bed and the ventral nail plate. It is important to take the

sample as proximally as possible, as this increases the chance of a positive culture. In the most distal part of the infection, the fungus often has low viability, and the chance of a positive culture is therefore lower [162]. The sample is taken by removing the overlying nail plate with a clipper and then curetting the nail bed. It is also possible to use a very small curette and insert it under the nail plate and dig as proximal as possible. In patients with superficial white onychomycosis, a white patch is located and the nail shaved with a scalpel of a sharp curette as the fungal elements are located in between the nail plate layers. In patients with proximal subungual onychomycosis, the overlying nail plate must be removed with a sharp curette or a punch biopsy knife and the sample taken from the underlying area. In the case of the superficial white variant, a similar technique as is described with SWO can be used. In patients with endonyx onychomycosis, clippings are used. See Table 10.11. It is best to collect the sample onto a black paper and seal it with tape and place it in a small sealable plastic bag, before it is sent to the laboratory. Commercial especially designed sampling envelops, such as the Dermapak® (www.dermapak.com), exist.

Correct interpretation of the results is important. If the results are negative and the clinical suspicion of onychomycosis is high, the sample should be repeated. There are several factors that can cause false-negative results (Table 10.12). Many patients use over-the-counter antifungal drugs, and even though the topical drug cannot cure the infection, a small amount of an antifungal drug in the sample can prevent the fungus from growing. Soap and detergents can have the same effect. It must be remembered that bacteria and molds grow much faster than dermatophytes, and if the sample is contaminated, there will be an overgrowth of contaminants. The nail should therefore be wiped clean with an alcohol pad and allowed to air-dry before the sample is taken. This reduces the risk of bacterial contamination.

Table 10.11 Location for sample collection depending on type of onychomycosis

Distal and lateral subungual onychomycosis (DLSO)	Take sample from the nail bed. Ventral side of the nail plate can also be helpful. Try to take sample as proximally as possible
Superficial onychomycosis	Scrape the affected surface area with a curette or shave it with a scalpel
Proximal onychomycosis	The overlying nail plate must be removed with a sharp curette or a sharp punch biopsy knife, and the sample must be taken from the underlying nail bed with a curette
Endonyx onychomycosis	Nail clippings
Candida onychomycosis	Take sample close to the lateral and proximal nail folds

Table 10.12 Reasons for false-negative results on culture

Sample too small
Wrong type of sample (clippings rather than material from nail bed and ventral nail plate)
Sample taken at wrong location (to distal-proximal is better in DLSO). See Table 10.11
Low viability of fungi (long-standing infection, particularly if factors described above apply)
Use of topical antifungals
Nail not wiped clean with alcohol (overgrowth of contaminants)
Soap or detergent remains on the nail

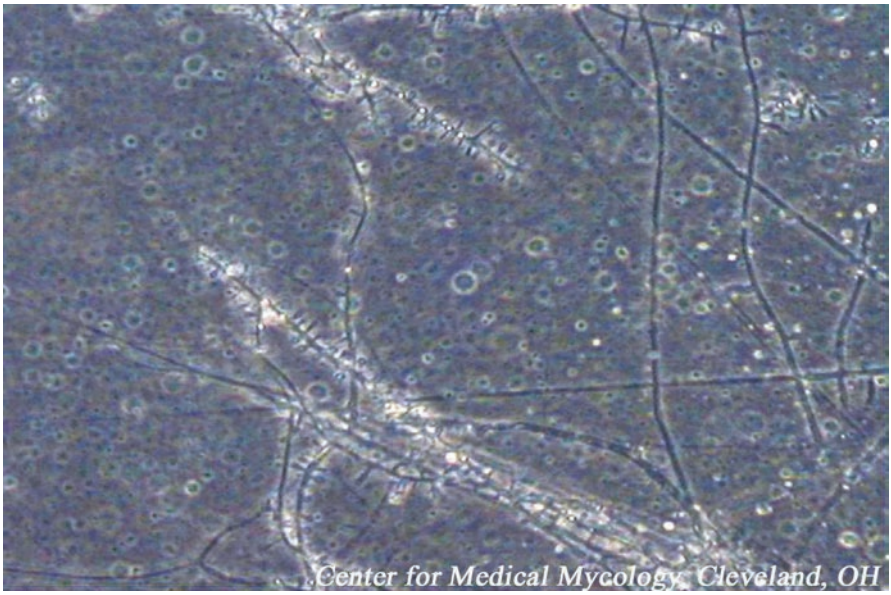


Photo 10.7 Subungual nail scrapings in KOH solution. Microscopy can be done in the office. In this sample, septate hyphae can be seen, which confirm the diagnosis of dermatophyte onychomycosis (Courtesy of Dr. Ghannoum, Center for Medical Mycology, Cleveland, OH)

10.6.2.2 Microscopy

Microscopy can be used in the office to confirm the presence of fungal elements. A part of the sample is put on a glass slide with a small amount of 20–30 % KOH and a cover slide (Photo 10.7). The sample is then heated gently to speed up the process of dissolving the keratin, which aids with visualization of the fungal elements. It has been shown that adding "Parker Superchrome Blue-Black" fountain pen ink to the KOH facilitates the identification of the fungi [163]. Fluorescent stains, such as Calcofluor white, can be used to further increase the sensitivity of the microscopy, but requires a fluorescent microscope [164]. The sample is now examined for the presence of septate hyphae, which are indicative of dermatophytosis. To best identify the hyphae, the microscope diaphragm is closed until a dark background is seen, which helps to bring out the hyphae because the light refracts. It is best to start with low-power magnification and increase the magnification when hyphae are suspected. Hyphae must be differentiated from artifacts such as sock fibers [165].

10.6.2.3 Culture

Culture techniques on solid media usually involve plating the sample on Sabouraud's dextrose agar with or without cycloheximide. Cycloheximide is generally added to inhibit the growth of non-dermatophyte molds and other fungi and is used to select for dermatophytes in culture. Bacteria grow much faster than fungi, and if there is just

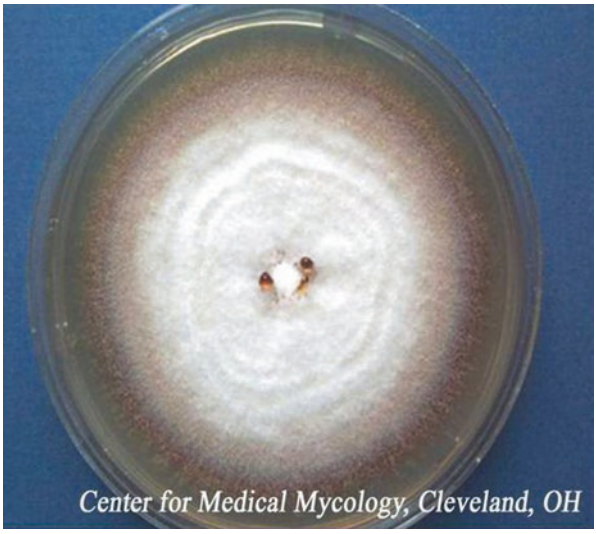


Photo 10.8 This agar plate shows growth of *Trichophyton rubrum*. Note the reddish hue which is typical for *Trichophyton rubrum* (Courtesy of Dr. Ghannoum, Center for Medical Mycology, Cleveland, OH)

a slight bacterial contamination, the bacteria will overgrow the fungal pathogen, making the diagnosis difficult. Chloramphenicol and gentamicin or other antibiotics are therefore included in primary culture plates to inhibit bacterial growth. The sample is then incubated at 30 ° C for up to 5 weeks, but the results can be available as early as after 2 weeks. The plates are examined at weekly intervals. Positive cultures are identified by gross colony characteristics (Photo 10.8) and microscopic morphology.

The most common dermatophyte species causing onychomycosis *is Trichophyton rubrum* followed by *Trichophyton mentagrophytes var. interdigitale*, *Trichophyton tonsurans*, and *Epidermophyton floccosum*. Fungi other than dermatophytes are also isolated from abnormal nails, which include non-dermatophyte molds and yeasts (Table 10.13).

In a recent worldwide meta-analysis of published studies, *Trichophyton rubrum* was the single most common fungus and was cultured on average in 44.9 % of the cases (95 % CI, 33.8–56.0) [12]. Molds were found on average in 13.3 % (95 % CI, 4.6–22.1) and yeasts in 21.1 % (95 % CI, 11.0–31.3). Dermatophytes were most commonly found in North America (82.1 % of the cases).

It is not always simple to determine the importance of yeasts and molds in particular, as they can easily appear as contaminants both from the patient and the laboratory. To establish the role of molds and yeasts as pathogens, some authors suggest that repeated samples should be taken and should show the same fungus before treatment is initiated (see discussion on Sect. 10.8.5 – selection of antifungal drugs based on mycology).

Aspergillus is the most common mold isolated from patients with onychomycosis, but *Scopulariopsis brevicaulis* and *Neoscytalidium* spp. are also frequently isolated.

10.6.2.4 Polymerase Chain Reaction (PCR)

DNA-based diagnosis is not considered as a standard in the diagnosis of onychomycosis. The PCR methodology has several advantages such as rapid results and higher sensitivity, but the cost is higher. As this method is very sensitive, the problem of the

Table 10.13 Most common fungi isolated from patients with onychomycosis. Modified from Baran [155]

Type	Most common organisms isolated
Distal and lateral subungual onychomycosis	Dermatophytes (*T. rubrum*, *T. mentagrophytes*) *Candida albicans* *Fusarium* spp. *Neoscytalidium* spp. *Scopulariopsis brevicaulis*
Superficial onychomycosis (white or black):	*T. mentagrophytes*, *T. rubrum*, *Fusarium*, *Acremonium Neoscytalidium*, *T. rubrum*, *Fusarium*
Endonyx onychomycosis	*T. soudanense*, *T. violaceum*
Proximal subungual onychomycosis	*T. rubrum*

"innocent fungal bystander" has not been solved. The future diagnosis of onychomycosis may lie in this technology.

10.6.2.5 Histology (PAS and GMS)

Routine histological examination of nail clippings with standard hematoxylin- and eosin-stained sections is insufficiently sensitive for the diagnosis of onychomycosis. It has been documented in many studies that the periodic acid-Schiff (PAS) stain is a sensitive method superior to culture and potassium hydroxide preparation for the diagnosis of onychomycosis (Photo 10.9) [166–169]. Recently good efficacy has been showed using Gomori methenamine silver (GMS) stain. The problem with this method is that it cannot accurately determine the type of fungus, unless combined with traditional culture.

10.7 Complications

Onychomycosis can lead to several complications (Table 10.14). Onychomycosis can be quite painful. In one study, 33 % of the patients experienced pain, 51 % discomfort in walking, and 13 % limitations in work and other activities [170]. Other studies have shown similar results [171, 172]. Patients with onychomycosis frequently experience low self-esteem and embarrassment and are therefore less willing to participate in social and leisure activities [170, 173]. Using quality of life (QOL) instruments, it has been shown that the patients feel better after successful treatment, and the self-esteem is higher [173]. A large number of the patients have a problem wearing shoes (82 %) and have difficulties in cutting their nails (75–85 %) [174]. The risk of infections, particularly cellulitis of the leg, is higher in patients with onychomycosis [175, 176]. As both tinea pedis and onychomycosis represent risk factors that are the most amenable to treatment, careful screening and treatment of foot dermatomycoses can help eliminate these specific risk factors for bacterial cellulitis of the leg, especially in patients with other risk factors, such as history of this disease, chronic venous insufficiency, or being overweight.

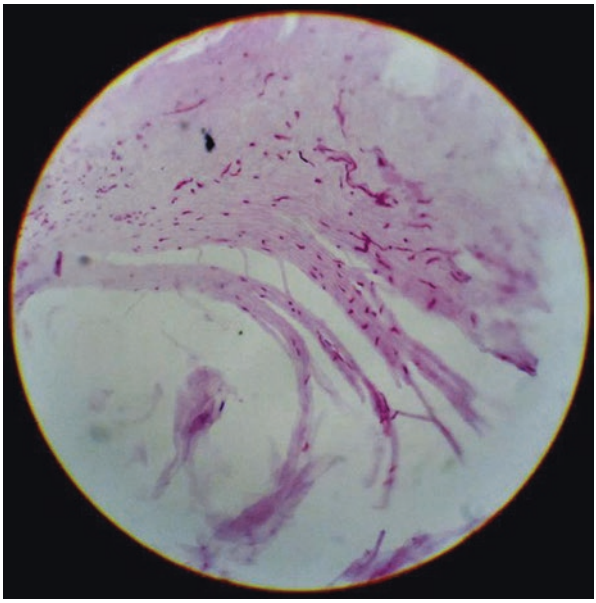


Photo 10.9 PAS staining. Abundant short slender hyphae seen as intensely stained dots and threadlike structures on HPE-PAS in distal lateral subungual onychomycosis (original magnification, ×400) (Courtesy of Jeelani and colleagues [166])

Table 10.14 Complications of onychomycosis

Type of complication	Characteristics	Result
Social	Low self-esteem, embarrassment	Avoidance of social events and activities
Pain	Difficulty in walking, cannot wear shoes	Decreased mobility, particularly in the elderly
Bacterial infections	Increased bacterial infections, bacterial paronychia, and cellulitis of the leg	Considerable increase in morbidity and mortality
Fungal infections	Infected nail can serve as a "fungal reservoir"	Can lead to tinea pedis, corporis, faciei, cruris, and capitis. Can infect others
Loss of the nail plate	Decreased counterpressure leads to elevation of the nail bed. Difficulty in picking up objects	Pain. Occupational and leisure problems
Decreased elasticity and thickening of the nail plate	Bleeding into the matrix. Difficult to cut nails	Pain. Ecchymosis. Increased cost because of pedicure. Secondary infections because of trauma
Allergic disorders	Asthma, urticaria, atopic dermatitis, rhinitis	Increased morbidity
Reactive disorders	Erythema multiforme, erythema nodosum	Increased morbidity
Dermatophytid	"Hand eczema like" pruritic eruption of the fingers and palms	Increased morbidity. Can lead to unnecessary investigations and treatment

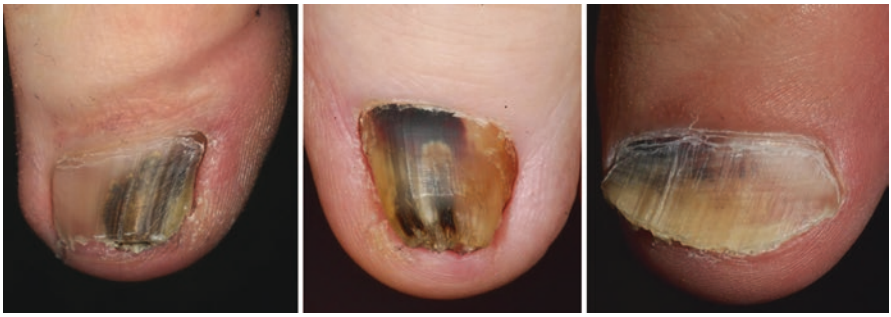


Photo 10.10 Onychomycosis with nail ecchymosis

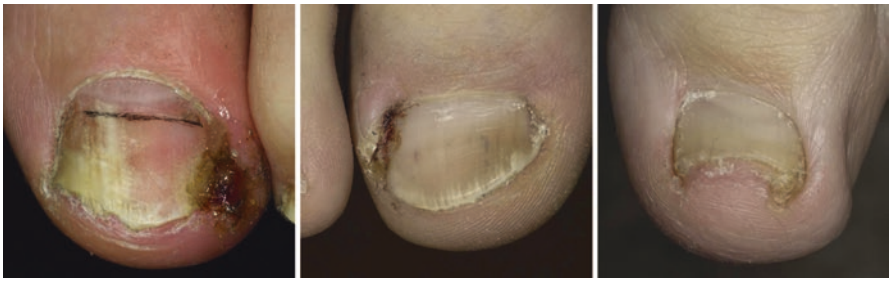


Photo 10.11 Ingrown toenails (onychocryptosis) can be very painful and are not an uncommon complication of onychomycosis. It is often seen when a healthy nail is growing back after successful treatment

When the nails are infected with a fungus, the nails often lose their elasticity and therefore do not absorb trauma as well as normal nails. This often leads to a bleeding into the matrix (ecchymosis), which can be painful (Photo 10.10). It is also possible that these patients are more difficult to treat as it can be difficult for the drug to penetrate through a layer of coagulated blood.

Onychomycotic toenails have a tendency to grow into the surrounding lateral nail folds, which is very painful and easily results in an ingrown toenail or onychocryptosis (Photo 10.11). It is not uncommon that this happens in patients with long-standing onychomycosis when normal toenails are growing back [177–179]. It is estimated that up to 20 % of the patients experience this side effect [178].

The infected nail can serve as a "fungal reservoir," and if not adequately treated, it can lead to repeated superficial fungal infections, such as tinea pedis, inguinalis, corporis, faciei, and capitis.

Asthma has been reported in patients with onychomycosis. In several cases, the asthma resolved after successful treatment with antifungal drugs [180]. The association of tinea and asthma, chronic urticaria, rhinitis, and worsening of atopic dermatitis has been demonstrated in several studies [181–190]. Reactivity to dermatophytes was demonstrated both with a positive skin test (both immediate type I reaction and delayed type IV reaction) and by measuring specific IgE to dermatophytes [190].

Erythema multiforme has also been described in patients with dermatophyte infections [191–193]. Erythema nodosum has also been described [194].

The id reaction is a secondary inflammatory reaction that develops from a remote localized immunological insult such as onychomycosis or tinea. Such reaction is often called dermatophytid, to distinguish it from id reactions with different etiology. The dermatophytid reaction results in erythematous vesicles usually seen on the lateral aspects of the fingers and the palms and is typically pruritic. Later the skin becomes dry and fissured as in chronic hand eczema. This reaction is thought to be an allergic reaction to dermatophytes. Clinically the dermatophytid reaction cannot be distinguished from hand eczema. The dermatophytid reaction resolves when the underlying fungal infection is treated.

Partial or complete loss of the nail plate is often a result of onychomycosis. The patients may also try to "cut away" the discolored infected part of the nail plate. This leads to loss of counterpressure effect of the nail plate, and upward forces then lift the distal nail bed, which can be painful and cause problems when a healthy nail grows back as a result of successful treatment [195].

10.8 Therapy

The goal of the treatment is eradication of the fungus and restoration of a normal nail. This may not always be possible as the nail may not have been normal when it was infected and even possibly been infected because it was not normal. The ultimate goal, complete cure (100 % normal nail, negative culture, and microscopy), may therefore not always be achievable. A multidisciplinary expert group concluded that the criteria for cure should be relaxed and allow minimal residual nail changes (Table 10.15) [1]. The most common efficacy criteria used in clinical studies are listed in Table 10.16.

Table 10.15 Definitions of cure. A multidisciplinary expert group has proposed relaxation of the stringent criteria used for complete cure. Reproduced from Scher with permission [1]

Criteria for cure:
A. 100 % absence of clinical signs of onychomycosis (mycology not required)
Or
B. Negative mycological laboratory results with one or more of the following clinical signs
(i) Distal subungual hyperkeratosis or onycholysis leaving less than 10 % of the nail plate affected
(ii) Nail plate thickening that does not improve with treatment because of comorbid condition
Criteria for noncure:
A. Presence of positive mycological results
Or
B. Any one of the four clinical signs, even in the presence of negative mycological results
(i) Residual major changes (> 10 %) of the nail plate compatible with dermatophyte infection
(ii) Lateral onycholysis with debris in an otherwise clear nail plate
(iii) White/yellow or orange-brown patches or streaks in or beneath the nail
(iv) Hyperkeratoses on the lateral nail plate/nail fold edge

Table 10.16 End points commonly used in clinical studies

End point	Microscopy	Culture	Nail involvement
Clinical cure	Not considered	Not considered	0 %
Mycological cure	Negative	Negative	Not considered
Complete cure	Negative	Negative	0 %
Effective treatment[a]	Negative	Negative	≤10 %

[a]Some studies use different terminology for this parameter

When treating onychomycosis, there are several factors that must be considered. The identity of the organism is important. Other factors to consider are fingernail vs. toenail infection or both. The general health of the patient is also important with the potential for adverse events and drug interactions. Is the patient likely to be compliant, and is there a particular dosage schedule that is more likely to be successful such as weekly doses compared to daily doses? Is there risk of drug-drug interactions? The risk or predisposing factors are also important as they can tell us if the patient is likely to be reinfected after therapy has been stopped. What drugs are available in that particular area? Prognostic factors can indicate at start of treatment if the patient is likely to respond poorly to treatment. Finally, there is a cost that may be an issue for many patients. The dosage for common topical and systematic drugs is shown in Table 10.17.

10.8.1 Topical Therapy

Although it is logical to treat onychomycosis with a topical drug, such treatment has not been very successful in the past. This is sad since topical treatment avoids many of the problems that are associated with oral treatment, such as drug interactions and side effects. Even though it has been shown that the topical drugs are effective against the fungi that cause onychomycosis, the problem has been to get them through the nail plate and into the subungual area. The topical drugs that are on the market at the time of writing are not very effective. They have their greatest potential in patients with very mild onychomycosis and in children. According to guidelines developed at an international consensus conference, onychomycosis is treated topically when the degree of involvement of the distal portion of the nail is under 50 % percent and no involvement of the matrix exists [196]. Topical therapy is also indicated in patients who cannot tolerate an oral drug because of drug interactions, side effects, or fear of taking an oral drug.

There are several new drugs in development which may have greater potential than the drugs currently on the market [197]. It has been demonstrated that the use of amorolfine every other week can reduce the risk of reinfections [198]; thus in patients prone to onychomycosis infections, a topical drug can be used to prevent a new infection in high-risk patients. A summary of possible indications for topical treatment can be seen in Table 10.18.

Table 10.17 Dosage schedules for antifungal drugs

Drug	Mode of administration	Fingernails	Toenails
Terbinafine	Oral	250 mg/day for 6 weeks	250 mg/day for 12 weeks
Itraconazole, continuous	Oral	200 mg/day for 6 weeks	200 mg/day for 12 weeks
Itraconazole, pulse	Oral	200 mg *x*2/day 1 week on and 3 weeks off. 2 pulses	200 mg *x*2/day 1 week on and 3 weeks off. 3 pulses
Fluconazole	Oral	150 mg once weekly until the abnormal nail has grown out. Typically 3–6 months[a,b]	150 mg once weekly until the abnormal nail has grown out. Typically 9–12 months[a, b]
Amorolfine 5 % nail lacquer	Topical	Once or twice weekly for 6–12 months or until cure	Once or twice weekly for 12 months or until cure
Ciclopirox 8 % nail lacquer	Topical	Once daily 6–12 months or until cure	Once daily for 12 months or until cure
Efinaconazole 10 % topical solution	Topical	Indication is toenail onychomycosis. Although not tested in clinical trials, the drug is likely to work on fingernails	Once daily for 12 months

[a]Not registered for onychomycosis in all countries
[b]If no response a dose of 300–450 mg weekly can be tried

There are reports of several topical therapies that may be effective for the treatment of onychomycosis such as tioconazole 28 % solution [199], bifonazole 1 % cream and 40 % urea [200], urea with propylene glycol and lactic acid [201], partial nail avulsion followed by topical miconazole [202], clotrimazole solution 1 % [203], *Melaleuca alternifolia* 100 % (tea tree) oil [203, 204], butenafine 2 % with 20 % urea cream [205], and sequential therapy with RV4104A ointment, ciclopiroxolamine cream, plus ciclopirox film-forming solution [206].

The conventional drug formulations, such as sprays, creams, and powders that are on the market, are not of much use in the treatment of onychomycosis, as they are not formulated for this purpose. They are easily washed or rubbed off and therefore do not stay long enough in contact with the nail to promote diffusion across the nail barrier.

The topical drug must reach the subungual space to be effective, and the main obstacle is the nail plate, where the keratin presents high resistance to drug penetration. Delivery systems, mostly in the form of nail lacquers, have been produced. The active drug is dissolved in a volatile solvent, and when the solution is painted on the nail plate, the solvent evaporates leaving a higher concentration of the drug in contact with the nail plate in film depot. The stage is now set for a gradual release of the drug into the nail plate although the drug is not applied daily. It has been hypothesized that the available topical therapies display low efficacy because the delivery systems utilized cannot achieve adequate concentrations of the active ingredients in the nail bed to eradicate the fungus. There are several systems

Table 10.18 Selection of therapy of onychomycosis

Topical therapy	Systemic therapy	Combination therapy	Surgery or chemical avulsion	Booster therapy
Less than 50 % involvement	>50 % involvement	History of previous treatment failure	Dermatophytoma or streaks	Positive culture at 6 months
Without matrix involvement	Matrix involvement	Mycology indicates that a combination could be useful	Thick hyperkeratotic nails	History of previous treatment failure
Four or fewer nails involved	Many nails involved	Negative local prognostic factors, such as thick nail plate, dermatophytoma	Edge involvement	Poor response to oral treatment
In children, even though other criteria are not fulfilled	Mycology indicates that an oral drug must be used	Negative systemic prognostic factors	Poor response to oral treatment (full nail avulsion)	Mycology indicates that treatment will be difficult
Prophylaxis in high-risk patients	No response after 9 months of topical therapy			
Mild superficial onychomycosis that does not extend to nail folds	Negative local prognostic factors, such as thick nail plate, dermatophytoma			
Palliative therapy in patients that cannot take oral drugs	Negative systemic prognostic factors			

in development such as a carrier-based dosage form of the drug in a lipid-based drug carrier to ferry it across the nail plate [207]. Systems that provide sustained release of the drug and facilitate diffusion across the nail barrier have been called “transungual drug delivery system” or TUDDS [155]. The commercial products of amorolfine and ciclopirox both use such systems.

Several new classes of antifungal agents have been specifically designed to penetrate the nail. One of these agents is tavaborole (AN2690). Physical techniques to disrupt the nail plate, such as debridement, microporation, and the use of lasers, electric currents (iontophoresis), and ultrasound, have also been used to enhance drug penetration. Chemical enhancers are also being investigated, but, according to available clinical data, do not support increased efficacy [208]. The dosage of antifungal drugs is shown in Table 10.17. The efficacy of topical drugs that are currently on the market and those who are pending market approval is shown in Table 10.19.

Table 10.19 Cure rates of topical drugs

Topical drug	Complete cure	Mycological cure	Reference
Amorolfine	1 % (5/522)	15.7 % (82/522)	Elewski [208]
Amorolfine	12.7 %	46.5 %	Paul [206]
Ciclopirox (study 1)	5.5 % (6/110)	29 % (30/105)	Gupta [209]
Ciclopirox (study 2)	8.4 %(10/118)	36 % (41/115)	Gupta [209]
Efinaconazole (study 1)	17.8 %	55 % (nr)	Elewski [210]
Efinaconazole (study 2)	15.2 %	53 % (nr)	Elewski [210]
Tavaborole (study 301)	6.5 %	31.1 % (nr)	Anacor Pharmaceuticals [211]
Tavaborole (study 302)	9.1 %	35.9 % (nr)	Anacor Pharmaceuticals [211]
Terbinafine nail solution 48 weeks (vehicle-controlled study)	2.2 % (6/271)	18.8 % (51/271)	Elewski [208]
Terbinafine nail solution 48 weeks (comparator-controlled study)	1.2 % (6/507)	16.2 % (82/507)	Elewski [208]

10.8.1.1 Amorolfine

Amorolfine belongs to the morpholine class of antifungal drugs and has been shown to be highly active against yeasts, dermatophytes, and molds responsible for onychomycosis [212–215]. Amorolfine inhibits two steps in the pathway of ergosterol biosynthesis, the 14α-reductase and the isomerase (figure 7.8, chapter 7), which play an important role building the fungal cell membrane and inhibit growth. Amorolfine is active both in vitro and in vivo against dermatophytes, yeasts, and molds responsible for superficial fungal infections [216]. A concentration of 5 % lacquer shows better efficacy than a 2 % lacquer [216].

Pharmacokinetic studies show good penetration into the subungual area [217, 218]. When a 5 % solution is painted on the nail after evaporation of the solvent, the amorolfine concentration at the nail surface is 27 %. The concentration of amorolfine is highest in the upper layers of the nail plates and decreases in the lower layers by a factor of 100 [218]. The concentration in the nail bed was sufficient to inhibit fungi most commonly causing onychomycosis. A study by Franz also demonstrated that amorolfine reaches the nail bed in sufficient concentration to inhibit the growth of fungi [219]. Despite this and excellent antifungal activity, the in vitro property of amorolfine is not mirrored by high cure rates in vivo. This can possibly be explained by a recent in vivo study where concentrations of amorolfine were 80 % lower 25 days after starting treatment with twice-weekly 5 % amorolfine compared with 15 days after starting treatment [220]. The authors explain this by the fact that at day 15 the samples were taken 12–20 h after application, but the at day 25, samples were taken 84–92 h later. This is not in agreement with previously published data [219]. This may be explained by the fact that the previous studies were done in vitro and therefore cannot account for all the environmental interactions occurring in vivo.

Both the finger and toenails are continuously touching tissues and objects during real life, with a consequent loss of medication, which may be negligible in the short run, i.e., during the first day after the application, but can become important after repeated applications and as time passes [220]. Based on this, it might be advisable to use amorolfine more frequently than once or twice weekly, i.e., every other day. However, this needs to be confirmed in future studies.

Unfortunately most studies on the efficacy of amorolfine were performed over 20 years ago and do not use the golden standard "complete cure" as an end point and do not report on the intent-to-treat population.

Amorolfine 2 % and 5 % lacquer were compared in 157 patients [221, 222]. In 57 or 36 % of patients, there was a protocol violation and they were excluded from the study. At 9 months, 38 % of the patients treated with 5 % amorolfine lacquer were cured. The definition of cure was defined as "based on the clinical response and mycological finding." The mean infected area went from 40 % to 30 %.

Reinel and Clarke compared 5 % amorolfine applied once weekly versus twice weekly in 554 patients [216, 222]. They defined "cure" as an overall clinical cure and negative mycological culture where "clinical cure" was defined as all patient's nails were cured or if there were only residual signs of infection ($\leq$10 % of nail still affected). At 9 months, 3 months after stopping treatment, 45.6 % of the once-weekly treated and 51.8 % of the twice-weekly treated patients were cured. The dropout from this study was high and 221 patients were excluded from the efficacy analysis.

In 2011 amorolfine (n=507) was compared to topical terbinafine [208]. The duration of treatment was 48 weeks and the efficacy was evaluated at week 52. Only five patients (1 %) achieved complete cure, 82 mycological cure (16.2 %), and eight clinical cure (1.6 %).

Amorolfine twice weekly for 36 weeks was the comparator in a recent study [206]. The primary efficacy end point was at 48 weeks. The complete cure rates were 12.7 %, clinical cure 16.9 %, and mycological cure at week 48. The cure rates for amorolfine and other topical drugs are shown in Table 10.19.

The two latter studies used more stringent criteria for cure. The cure rates of amorolfine are low in these studies. It is likely that less stringent end points and high dropout explain the high cure rates reported in the early studies with amorolfine. Clinical experience suggests that treatment with amorolfine sometimes needs to be longer than 1 year, and many clinicians treat until the patients are cured if the patient is showing continuous improvement during treatment.

Recently it was demonstrated that treatment with amorolfine every 2 weeks might be effective to prevent recurrences in patients already cured with an oral antifungal drug [198]. After 3 years, significantly fewer patients in the amorolfine treatment group had experienced a recurrence.

10.8.1.2 Ciclopirox

Ciclopirox has the chemical formula of $C_{12}H_{17}NO_2$ and a molecular weight of 207.27. It does not block one of the steps involved in sterol biosynthesis, as most antifungal drugs do. Ciclopirox is a chelating agent that affects $Fe3^{+}$ and results in

the inhibition of the metal-dependent mitochondrial enzymes that are responsible for the degradation of peroxides within the fungal cell.

It is formulated in an 8 % lacquer, but after application to the nail, the solvents evaporate and the concentration of ciclopirox in the remaining film increases to 34.8 % [16]. Three studies on cow horn slices, pigskin, and human toenails have shown that the lacquer formulation penetrates the nail and produces sufficient antifungal concentrations of ciclopirox under the nail plate [223].

Ciclopirox shows broad antifungal activity against dermatophytes, yeasts, and non-dermatophyte molds [223].

Seebacher reported on a multicenter study with 1239 patients with 5401 infected nails treated with ciclopirox lacquer once daily [224], and "cure" was reported in half of the patients. In two identical registration studies, the primary efficacy variable was "treatment success," defined as simultaneous negative KOH and culture, and ≤10 % area involvement of the target nail plate. Only 6.5 % in study I and 12 % in study II achieved this goal. Mycological cure rates were higher, 29 and 36 %, respectively. Treatment cure was defined as negative KOH and negative culture and physician's global evaluation score of "cleared". This is equivalent to what is usually called "complete cure". The respective cure rates were 5.5 % and 8.5 %, respectively (Table 10.19). There are several open-label studies that have assessed the efficacy of ciclopirox over a period of 6–12 months [225]. Mycological cure rates varied between 50 and 70 %, but clinical cure rates were not always available. Many of these studies used less frequent application than the recommended daily application.

Recently a water-soluble nail lacquer (P-3051, 8 % ciclopirox), based on hydroxypropyl chitosan, has been developed. This formulation showed better penetration and higher predicted efficacy when compared to amorolfine lacquer in healthy subjects [220].

This new water-soluble biopolymer form of ciclopirox lacquer was compared with the reference marketed product [226]. Patients were treated with a daily application for 48 weeks and the primary study end point was complete cure at 60 weeks. Both the new form and reference product were significantly better than placebo with complete cure rates of 12.7 and 5.8 %, respectively.

In a recent open non-comparative study, 36 patients were treated with ciclopirox daily application. At 9 months, eight of 36 patients (22 %) had complete cure (clinical and mycological) of the toenails [227].

Safety of ciclopirox seems to be excellent although slight erythema and burning/tingling sensation have been described [228].

10.8.1.3 Efinaconazole

Efinaconazole is a new triazole antifungal drug currently under development as a topical treatment for onychomycosis and has been approved for the treatment of onychomycosis in some countries. It has shown promising results in two identical phase 3 studies [210]. Like other azoles, it inhibits sterol 14α-demethylase in the ergosterol biosynthesis pathway [229]. The lack of ergosterol affects the fungal cell wall and this growth.

Two identical vehicle-controlled studies on efficacy of efinaconazole in 1655 patients with 20 %–50 % neil involvement [210]. The lacquer was applied once daily for 48 weeks, with a follow-up 4 weeks later. The primary efficacy variable was complete cure at week 52, defined as 0 % clinical involvement of target toenail and negative potassium hydroxide examination and fungal culture. The efinaconazole groups had greater complete cure rates than vehicle patients, 17.8 and 15.2 % in studies 1 and 2, respectively (Table 10.19). The mycological cure rates were 55.2 and 53.4 %. Efinaconazole was well tolerated in general, with only 2 % local site reactions, which were similar to vehicle treatment.

10.8.1.4 Tavaborole

In addition, several new classes of antifungal agents that have been specifically designed to penetrate the nail are in development for onychomycosis. Tavaborole (AN2690) is the first of the new benzoxaborole class of antifungals [230]. These are novel boron-containing small molecules designed to penetrate nails and have a broad-spectrum antifungal activity and a low MIC [231]. Tavaborole inhibits an essential fungal enzyme, leucyl transfer RNA synthetase that is required for protein synthesis. Anacor Pharmaceuticals recently released the results of two phase three trials and has applied for registration of tavaborole [211]. Complete cure was seen in 6.5 and 9.1 % of the patients in studies 301 and 302, respectively (Table 10.19). Similarly 26.1 and 27.5 % of the patients had clear or almost clear nail at 48 weeks.

10.8.1.5 Terbinafine

It is already known that terbinafine is an effective molecule against most fungi that cause onychomycosis. It is very effective if given orally and should work well in a topical form if it can reach the nail bed in sufficient concentrations. A phase 2 study that was presented at the 2008 Annual Meeting of the American Podiatric Medical Association showed that terbinafine nail solution was superior to ciclopirox [232]. However, the result from a large phase 3 program (Table 10.19) was disappointing [208]. Many of the patients included in this study may have been too severe, the end points too stringent, and the follow-up too short [208]. Novel approaches being investigated in onychomycosis include the use of ultra-deformable lipid vesicles to facilitate delivery of terbinafine to the nail bed. TDT 067 (1.5 % terbinafine in Transfersome®) is an agent in the ultra-deformable lipid vesicles that is in development [207]. MIC against dermatophytes for TDT 067 is lower compared to "naked" terbinafine [207]. Phase 2 data has shown promising results [233] and a phase 3 program has been started.

10.8.1.6 Luliconazole

Luliconazole is an imidazole which is *fungicidal* for *T. rubrum* at its MIC levels through the inhibition of sterol 14α-demethylase and resulting ergosterol synthesis but is *fungistatic* at below MIC levels through inhibition of extracellular protease secretion [234]. In both in vitro and in vivo studies, luliconazole has demonstrated potent and broad-spectrum activity against dermatophytes and non-dermatophyte molds.

Luliconazole solution, 10%, has been shown to readily penetrate healthy human toenails in vitro, in part due to luliconazole' low binding affinity for keratin.

Currently, a randomized, double-blind, phase 2 study is being conducted to determine the efficacy and safety of luliconazole solution, 10%, in patients with toenail onychomycosis.

10.8.2 Systemic Therapy

In general the cure rates are higher when systemic therapy is used (Fig. 10.5). The problems associated with systemic therapy are drug-drug interactions and side effects. The characteristics of the main oral antifungal drugs used to treat onychomycosis can be seen in Table 10.20. An example of a successful treatment with an oral antifungal drug can be seen in Photo 10.12.

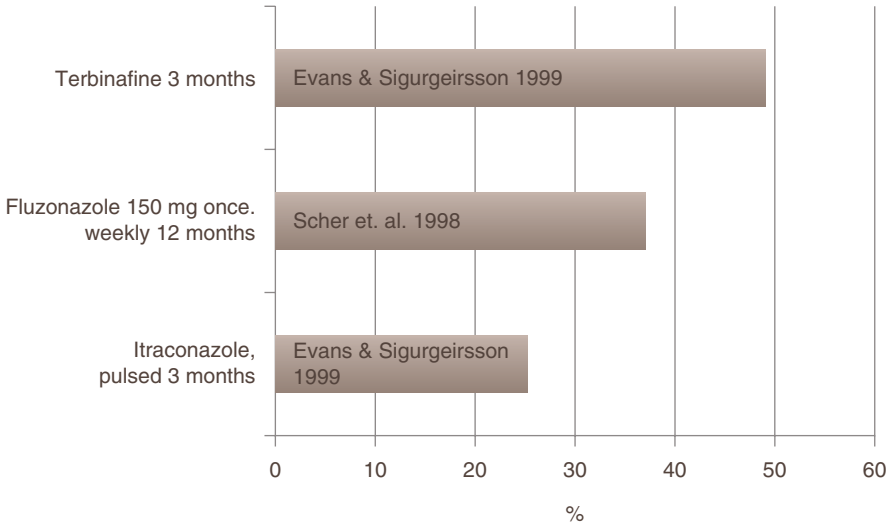


Fig. 10.5 Complete cure rates of oral antifungal drugs (Produced with data from Evans and Sigurgeirsson [235, 236] and Scher [237])

Table 10.20 Characteristics of oral antifungal drugs

	Terbinafine	Itraconazole	Fluconazole
Chemistry	Allylamine	Triazole	Bis-triazole
Solubility	Lipophilic	Lipophilic	Hydrophilic
Protein binding	99 %	99 %	11 %
Tissue affinity	Strong	Strong	Weak
Keratin adherence	High	High	Low
Renal excretion	>70 %	>1 %	65 %
$T_{½}$ plasma	17 h	17–25 h	22–30 h
Metabolism in the liver	Extensive	Extensive	Virtually none
Cytochrome p450 dependent	No	Yes	Yes
Intake restriction	None	Requires acid pH	None
MIC_{90} (μg/ml) dermatophytes	0.001–0.01	0.1	20–200
In nails after drug withdrawal	1–3 months	6–9 months	1–5 months

Modified from Tosti [238] and Baran [195]

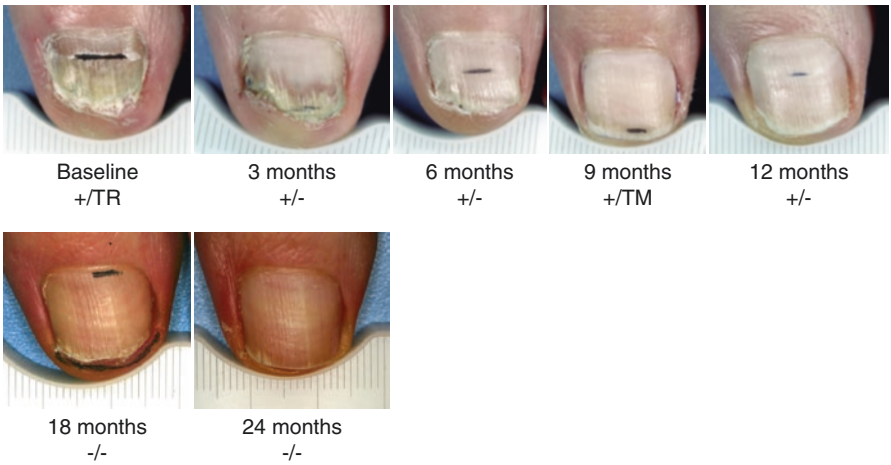


Photo 10.12 Successful treatment with terbinafine. A healthy 50-year-old female with a 4-year history of onychomycosis. She was treated with 250 mg of terbinafine daily for 3 months. Microscopy was positive and culture showed *Trichophyton rubrum* (TR). Microscopy remained positive for 1 year. It is not clear whether *Trichophyton mentagrophytes* (TM) grown at 9 months was an innocent bystander or if she had a double infection from the start. Mycology at 18 and 24 months was negative. Result of microscopy is shown above the slash and casfune below

10.8.2.1 Griseofulvin

See chapter 7. Griseofulvin is the first oral antifungal drug used to treat onychomycosis, but is rarely used anymore because of poor cure rates, lengthy treatment, and adverse events. It is effective against dermatophytes, but has no activity on molds or yeasts. It administered daily for months until the nail grows out, which means at

least 9–18 months of treatment. The dose is 1000–2000 mg daily. The pharmacokinetics has not been studied in details, but the drug reaches the nail via the matrix. Cure rates are low, and in a study by Faergemann and colleagues, the complete cure rate was only 2 % after 12 months of therapy [239]. Other studies have shown more reasonable cure rates with mycological and clinical cure rates around 30 % for toenails but around 70 % for fingernail infections [240]. However, the mycological cure rates dropped after treatment was stopped at 2 years [240]. The most common adverse events are headache and gastrointestinal symptoms and rash. This drug has been compared with terbinafine [239, 241, 242] and itraconazole [243, 244]. Based on these studies, the necessity of long treatment and side effects on the use of this drug for the treatment of onychomycosis cannot be recommended anymore.

10.8.2.2 Ketoconazole

See chapter 7. Ketoconazole was the first broad-spectrum antifungal drug and, although effective, should not be used for the treatment of onychomycosis because the safety profile is not acceptable. If ketoconazole is used for onychomycosis, the standard dosage is 200 mg daily. But higher doses can be tried, up to 600 mg. Side effects increase with higher dosage and include gastrointestinal symptoms. The risk of hepatitis and the availability of safer drugs are what limit the use of this drug in the treatment of onychomycosis. Treatment of onychomycosis with ketoconazole cannot be recommended.

10.8.2.3 Itraconazole

Pharmacology See chapter 7. It has been demonstrated that itraconazole appears in the distal part of the nail within 1 week of starting therapy [245, 246]. This suggests that itraconazole does not only enter the nail plate through the nail matrix but also from the nail bed. The concentration of itraconazole was above the MIC both for dermatophytes and *Candida* species from the first month of treatment to the third or sixth month, in fingernails or toenails, respectively, after therapy was stopped [247].

When intermittent itraconazole is given, higher peak drug concentration in plasma is seen compared to continuous itraconazole although the total drug exposure is lower. Lower concentrations are also seen in the nails. Despite this, the concentration is well above 100 ng/g [247] (well above the MIC for most fungi that cause onychomycosis) for at least 6 months. In contrast with continuous treatment, a steady state is not reached in the nails with intermittent treatment, even with four pulses, as concentrations were always slightly higher after each successive pulse [247, 248]. This is probably not important as cure rates are not lower with the intermittent schedule, indicating that itraconazole nail concentrations remain within the therapeutic range [248]. The half-life in the nail is long and itraconazole can be found in the nails for several months after the treatment was stopped.

Safety See chapter 7

Efficacy The efficacy of itraconazole has been thoroughly studied in several open and randomized controlled trials [177, 235, 236, 244, 248–275]. In a meta-analysis of 1131 patients that participated in seven studies on treatment with continuous itraconazole in the treatment of toenail onychomycosis, mycological efficacy was 59 % (95 % CI, 54–64 %) [276]. Similarly in the same analysis on 318 patients in six studies, the mycological cure rates for intermittent itraconazole were 63 % (95 % CI, 56–70 %) [276]. In a double- blind randomized study, the mycological, clinical, and complete cure rates of treatment with intermittent itraconazole (three pulses) were 38, 32, and 23 %, respectively [235, 236]. In a study with a similar design, mycological cultures gave negative results after treatment in 79 patients given terbinafine (92 %) and 56 given itraconazole (67 %) [253].

10.8.2.4 Terbinafine

Pharmacology See chapter 7.

Terbinafine can be detected in the nails within 1 week of starting therapy [277], probably via diffusion into the nail plate [278]. After standard treatment with terbinafine for 3 months, the concentration remained well above the MICs [279] and MFCs for dermatophytes [280], from the second to the 36th week after treatment was initiated [281]. This explains why a relatively short treatment of 12 weeks is effective for onychomycosis of the toenails.

Safety See chapter X.

Efficacy The efficacy of terbinafine has been thoroughly studied in several open and randomized controlled trials [235, 236, 239, 241, 250, 253, 255, 256, 282–293] and reviews [276, 294]. In a large randomized trial, the mycological, clinical, and complete cure rates were 75.7, 53.6, and 45.8 %, respectively [235, 236] (Fig. 10.5). In a meta-analysis of 18 randomized trials that included 993 patients, the pooled mycological cure rate was 76 % (95 % CI, 73–79 %) [276]. The corresponding value for clinical cure was 15 trials, 1199 patients, and clinical cure of 66 % (95 % CI, 61–72 %) [276]. A meta-analysis of eight studies comparing intermittent itraconazole with continuous terbinafine suggests that terbinafine is more likely to lead to mycological cure with odds ratio of 2.3 (95 % CI, 1.7 to 3.0; $p \leq 0.0001$) [295].

Terbinafine was compared with itraconazole in four trials [235, 236, 253, 274, 296] and these studies were pooled in a review study [294]. A statistically significant advantage in favor of terbinafine was observed for negative culture and microscopy at the end of the trials (RR = 1.64; 95 % CI, 1.48–1.81) [294]. In the L.I.ON. study where terbinafine was compared with intermittent itraconazole, the cure rate was approximately double for terbinafine, with mycological cure rates of 76 % vs. 38 % at 72 weeks [235, 236]. In another study, terbinafine was compared with continuous itraconazole. Similarly, the mycological cure rates were 81 % vs. 63 % [253].

Terbinafine has been compared to griseofulvin and produced a significantly higher rate of negative microscopy and culture than griseofulvin (RR = 1.31; 95 % CI, 1.10–1.56) [294]. Faergemann compared terbinafine 250 mg/day for 16 weeks with 500 mg/day griseofulvin for 52 week [239]. Terbinafine was significantly more effective than griseofulvin, with 42 % being completely cured and 84 % mycologically cured compared with only 2 % with total cure and 45 % with mycological cure in the griseofulvin-treated group [239].

Not many studies have compared terbinafine with fluconazole in a head to head trial. In the study of Havu, 12 weeks of terbinafine were compared with fluconazole 150 mg once a week for 12 or 24 weeks. The mycological cure rates at the end of study were 89, 51, and 49 %, respectively [297].

10.8.2.5 Fluconazole

Pharmacology See chapter 7.

The concentration in the nails increases with the length of treatment and correlates with the dosage [298]. The fluconazole concentration seems to be higher in toenails than fingernails [299]. The retention of fluconazole's effective concentration in the nails is not as long as that for itraconazole and terbinafine [298, 300, 301]. Therefore the duration of treatment with fluconazole is longer. Fluconazole is active against dermatophytes and *Candida* [302, 303]. The general recommendation is that fluconazole is given until the diseased nail has grown out, which means 6–12 month for toenails and up to 6 months for fingernails. Fluconazole has been associated with rare cases of serious hepatic toxicity and should not be given to patients with hepatic dysfunction. As fluconazole is mainly excreted through the kidneys, the dose must be modified in patients with renal failure.

Efficacy The efficacy of fluconazole is not as thoroughly studied as is the case with terbinafine and itraconazole [304]. Three placebo-controlled studies have evaluated different weekly dosages of fluconazole between 150 and 450 mg [237, 305, 306]. All studies demonstrated the superiority of fluconazole over placebo. In the study of Scher, 362 patients with toenail onychomycosis were studied. The mycological cure at the end of therapy was 47, 59, and 62 % with 150, 200, and 450 mg/per week, respectively [237]. The corresponding clinical cure rates were 28, 29, and 36 %. Drake studied 349 patients with fingernail onychomycosis where the mycological cure rates for the same dosages were 89, 95, and 100 % at the end of therapy [306]. The corresponding clinical cure rates were 76, 85, and 90 %. In the study of Ling, almost all of the 384 patients had toenail onychomycosis caused by *T. rubrum* [305]. All patients were treated with fluconazole 450 mg/week for 4, 6, or 9 months. The mycological cure rates at the end of therapy were 36, 38, and 59 %, respectively. The corresponding clinical cure rates were 10, 10, and 26 %. In a non-controlled study, three different doses of fluconazole, 100, 150, and 300 mg/weekly, in combination with topical ketoconazole 1 % cream were tested in 121 patients [307]. The cure rates were similar for all groups, 42–48 %, but the patients in the 100 mg

group needed the longest treatment. Comparative studies indicate that fluconazole is less effective than both terbinafine and itraconazole. The study of Arca is a small randomized, open-label study on 50 patients with dermatophyte onychomycosis. At the end of follow-up, the clinical cure rates were 81.3, 77.8, and 37.5 %, in patients treated with terbinafine, itraconazole, or fluconazole [250]. In another study in 137 patients from Finland, the clinical cure rates were 67, 21, and 32 % in patients treated with terbinafine for 12 weeks, fluconazole for 12 weeks, and fluconazole for 24 weeks, respectively [297]. Finally Gupta treated 59 patients with onychomycosis caused by the non-dermatophyte mold *Scopulariopsis brevicaulis* [308]. Patients were treated with griseofulvin, ketoconazole, itraconazole, or terbinafine. Clinical cure was seen in only 3/12 patients treated with griseofulvin, 8/12 with fluconazole, 10/12 with ketoconazole, 11/12 with terbinafine, and 12/12 with itraconazole.

In a recent review by Gupta, all the above mentioned studies with an open-label study [309] were pooled in an attempt to determine the optimal regimen for fluconazole [310]. In this review, there was no evidence of significantly increased efficacy resulting from higher doses of fluconazole, even when the weekly dose was tripled from 150 to 450 mg [310]. Adverse events were more common with higher doses. The evidence therefore does not support the use of fluconazole dose higher than 150 mg weekly [310]. The duration of fluconazole treatment had a significant impact on efficacy, with durations of more than 6 months producing higher mycological and clinical cure rates than durations of 6 months or less [310].

Safety See chapter 7.

10.8.2.6 Drugs on the Horizon

Albaconazole

Albaconazole is a new broad-spectrum azole antifungal that has in vitro activity against yeasts and a broad range of filamentous fungi and dermatophytes, including organisms that are most commonly associated with onychomycosis. Albaconazole has a long half-life, which allows for a once-weekly dosage [311]. As albaconazole is still in development, much less is known about its pharmacokinetics in the nails and plasma, compared to other oral antifungals. Once-weekly albaconazole resulted in plasma accumulation of albaconazole and 6-hydroxyalbaconazole. Plasma and toenail albaconazole exposure increased with dose, and albaconazole remained detectable in toenails, with significant mean concentrations 16–18 weeks after stopping treatment [311]. In a recent phase II study, 54 % of the patients treated with 400 mg albaconazole once weekly for 36 weeks reached a mycological cure and clear or almost clear nail at week 52 [311]. At this stage, the optimal dose for albaconazole in the treatment of onychomycosis is not known. No important safety concerns were seen in this study.

Posaconazole

Posaconazole is another new azole that is effective against most fungi that cause onychomycosis [312]. Its use in the treatment of onychomycosis is limited [313]. It is detected in the toenails as early as 2 weeks, and levels continued to increase, even after discontinuation of treatment, whereas plasma levels decreased shortly after the drug was stopped [314]. The maximum concentration was found in 36–42 weeks [314]. It is assumed that posaconazole reaches the nail plate via diffusion from the nail bed, similar to other oral antifungals.

VT-1161

VT-1161 is a potent and selective orally available inhibitor of fungal CYP51 [315]. This could mean a more favorable side effect profile compared to drugs of the azole class. VT-1161 blocks the production of ergosterol, an essential component of the fungal cell membrane. VT-1161 is a potent, highly selective, and orally administered inhibitor of fungal CYP51, a metalloenzyme important in fungal cell wall synthesis. In preclinical studies, VT-1161 has demonstrated broad-spectrum activity against dermatophytes, including the most common species that cause onychomycosis, and against *Candida* species, including azole-resistant strains. This drug is now being investigated in a phase 2 trial. The treatment arms comprise low- or high-dose VT-1161 given once daily during a 14-day loading-dose phase followed by once-weekly administration for additional 10 or 22 weeks. Judging from the available data, this drug has great potential.

10.8.3 Dosage of Oral Antifungal Drugs

The dosage for antifungal drugs is summarized in Table 10.17.

10.8.3.1 Terbinafine Dosing

If no contraindications exist, terbinafine is usually the first choice in the treatment of dermatophyte onychomycosis, because of the best efficacy, acceptable side effect profile, and low risk of drug-drug interactions.

According to the SPC in most countries, liver function tests should be checked before treatment and 6 weeks after start of treatment in adults and children. In some countries, only pretreatment serum transaminase (ALT and AST) tests are advised, and additional tests only done if symptoms occur (see below).

Treatment with terbinafine should be discontinued if biochemical or clinical evidence of hepatic injury develops. Patients should be asked to report immediately

any symptoms of liver disease, such as nausea, anorexia, fatigue, vomiting, abdominal pain or jaundice, dark urine, or pale stools.

In patients with renal impairment (creatinine clearance <50 mL/min), the use of terbinafine has not been adequately studied and, therefore, is not generally recommended. Since it has not been adequately studied in patients with impaired renal function, great care should be taken, and monitoring should be done when these patients are treated with terbinafine.

Regarding pharmacology, pharmacokinetics, and side effects, see chapter on the respective drugs (Chpater 7).

The usual adult standard dosage of terbinafine for the treatment of onychomycosis of the fingernail and toenail is 250 mg/day for 6 and 12 weeks, respectively (Table 10.17) [316].

There is no need for dosage adjustment in the elderly [317]. Dosage may need to be changed in patients taking certain drugs such as cimetidine (Table 7.7 Chapter 7). Patients should be evaluated 6 months after treatment was initiated, as some patients may benefit from extended and/or repeated booster courses of terbinafine therapy at that time [249]. Extension of a standard course calls for repeated LFTs.

Terbinafine is excreted in breast milk, and therefore breastfeeding mothers should not receive treatment with terbinafine during the breastfeeding period [316].

Fetal toxicity and fertility studies in animals indicate no adverse effects of terbinafine on pregnancy or on the health of the newborn child, but there is no clinical experience with terbinafine in pregnant women [316]. The use of terbinafine for onychomycosis during pregnancy is therefore not recommended.

10.8.3.2 Itraconazole Dosing

Most authors recommend monitoring of liver function parameters during treatment, especially when prolonged itraconazole administration is required, even in asymptomatic patients lacking apparent risk factors of hepatic injury [318–320]. Itraconazole should not be prescribed in patients with elevated liver function tests, in patients with active hepatic disease, or in patients that have a history of elevated LFTs [320]. Itraconazole is a potent suppressor of CYP3A4 that opens up a possibility of a wide range of drug-drug interactions (Table 7.1 and 7.2, chapter 7).

Itraconazole can be given continuously 200 mg daily or intermittently 200 mg twice daily for 1 week out of every 4 weeks (pulse therapy) [320]. The efficacy seems to be comparable for intermittent and continuous therapy, and intermittent therapy involves less drug exposure. Consequently, most doctors prefer intermittent therapy. The standard pulsed regimen dosage is 200 mg b.id./day for 6 weeks or two pulses for fingernail onychomycosis and 200 mg b.i.d./day for 12 weeks or three pulses for toenail onychomycosis [320]. If continuous itraconazole is given, the standard dose for adults is 200 mg/day for 3 months for toenail onychomycosis, but 6 weeks for fingernail disease.

10.8.3.3 Fluconazole Dosage

Fluconazole is an alternative in the treatment of onychomycosis. The once-weekly dosage can be an advantage in some patients, but long treatment duration and lower efficacy are a disadvantage. Fluconazole must therefore be considered a third alternative, after terbinafine and itraconazole. The recommended dose is 150 mg weekly until the nail has grown out. This means treatment for at least 6–9 months or longer for toenail onychomycosis. Fluconazole is not registered for the treatment of onychomycosis in all countries. As fluconazole inhibits both CYP3A4 and CYP2C9, there is potential for drug-drug interactions (Table 7.1, Chapter 7). As with itraconazole, it is prudent to check liver function before initiating therapy and during treatment. In therapy-resistant cases, the weekly dose can be doubled (300 mg).

10.8.4 Treatment of Onychomycosis in Children

Trichophyton rubrum is the most common pathogen that causes onychomycosis in children although other pathogens have been reported. The most common differential diagnosis in children is psoriasis, atopic dermatitis, seborrheic dermatitis, alopecia areata, lichen planus, and congenital nail dystrophies [321]. It is important to exclude a concomitant infection at other locations, as topical treatment is usually not sufficient in such cases. When children are infected, other family members should also be checked for infection.

Dosage for antifungal drugs in children is summarized in Table 10.21.

Success of topical treatment is higher in children compared to adults and it is often reasonable to try such treatment first. Before treating children with a systemic drug, it is important to carefully consider if the benefits of treatment outweigh the potential risks of side effects. The dose for topical drugs in children is the same as in adults (Table 10.17).

Terbinafine is registered for use in children over 2 years of age (>12 kg) in many countries. The dose is 62.5 mg o.d. for children less than 20 kg in weight, 125 mg

Table 10.21 Dosage of oral antifungal drugs in children

Drug	Dose
Fluconazole	3–6 mg/kg (4.5 mg) weekly until the nails are normal
Itraconazole	>50 kg: 200 mg b.i.d. 7/28 days, 2–3 pulses (toenails 3, fingernails 2)
	40–50 kg: 200 mg b.i.d. 7/28 days 2–3 pulses (toenails 3, fingernails 2)
	20–40[a] kg: 100 mg o.d. 7/28 days 2–3 pulses (toenails 3, fingernails 2)
	<20 kg: 5 mg/kg o.d. 7/28 days, 2–3 pulses (toenails 3, fingernails 2)[b]
Terbinafine	>40 kg: 250 mg daily for 6–12 weeks (toenails 12 weeks, fingernails 6 weeks)
	20–40 kg: 125 mg daily for 6–12 weeks (toenails 12 weeks, fingernails 6 weeks)
	<20 kg: 62.5 mg daily for 6–12 weeks (toenails 12 weeks, fingernails 6 weeks)

[a]Some authors treat the 35–40 kg children with 100mg alternating with 200mg.
[b]5 mg/kg can be used to calculate dose for all children.

for children 20–40 kg, and for children over 40 kg, the adult dose of 250 mg is given [316, 321, 322]. The length of the treatment is the same as in adults.

Limited data is available on the use of itraconazole in the pediatric population. If itraconazole is used in children, the pulse regimen is recommended since it involves less drug exposure. As for adults, two pulses are given for fingernails and three pulses for toenails. In children itraconazole can be given as capsules or as an oral solution (does not exist in all countries). The following dosage schedules are for guidance only, and the SPC should be consulted before initiating treatment: in children more than 50 kg, 200 mg b.i.d.; 40–50 kg, 100 mg b.i.d.; 20–40 kg, 100 mg o.d., and less than 20 kg, 5 mg/kg o.d. [16, 323].

If fluconazole is used, the dose is 3–6 mg/kg given once weekly until the nails are normal, which requires 12–16 weeks for fingernails and 18–26 weeks or more for toenails [16]. The following dose equivalency scheme has been proposed for fluconazole, based on the product monograph: 3 mg/kg (pediatric patients) equivalent to 100 mg (adults), 6 mg/kg (pediatric patients) equivalent to 200 mg (adults), and 12 mg/kg (pediatric patients) equivalent to 400 mg (adults) [323]. The equivalence of the standard adult pulsed dose is therefore 4.5 mg/kg weekly.

It is prudent to do a blood test, with blood count and chemistry profile (including liver function tests), before treatment and after 6 weeks. If treatment is longer than 3 months (as in the case of fluconazole), blood tests should be repeated every 2 months.

10.8.5 Selection of Antifungal Drugs Based on Mycology

The choice of a therapeutic agent should always be based on the results of mycology.

10.8.5.1 Dermatophytes

If a dermatophyte is cultured and there is an indication for an oral drug, terbinafine is the first choice of treatment, if no contraindications exist followed by itraconazole and fluconazole.

10.8.5.2 Molds

Non-dermatophyte molds are often thought to be contaminants and can often be considered innocent bystanders that do not influence the clinical outcome [324]. English developed criteria for diagnosis of non-dermatophyte mold onychomycosis [325]: isolation of the same mold from three consecutive nail samples, at least five inocula on the same culture, and finally the presence of hyphae in the KOH preparation. Many authors feel that these criteria are too stringent, and the author of this text feels that the presence of a mold in two consecutive samples is sufficient if other criteria apply (Table 10.22).

Table 10.22 Criteria for diagnosis of mold and yeast infections

If a dermatophyte is isolated, it is taken to be the pathogen without further supporting evidence[a]
If a mold or yeast is isolated, it is only considered of significance if the appropriate fungal elements – mycelium, arthrospores, or yeast cells – are seen on direct microscopy
For a diagnosis of mold infection, no dermatophyte must have been isolated and at least 5/20 inocula must have yielded the mold
Isolation of the same mold or yeast from 2–3 consecutive samples

Modified from English [325]

[a]May be more difficult to treat if combined with a mold

In mild cases of SWO that does not extend to the proximal or lateral nail folds, it may be sufficient to treat with nail abrasion followed with a topical lacquer. If there is no clinical response in 6 months, the treatment should be supplemented with an oral antifungal. Chemical avulsion can also be used. There are reports of successful oral monotherapy with both terbinafine and itraconazole [326, 327]. The MIC of oral antifungal drugs is quite variable and the outcome often unpredictable [328]. Intermittent treatment with oral terbinafine 500 mg/day for 1 week per month for 3 months has been successful, particularly in patients with *Aspergillus* spp. infections [329], but the safety of this regimen has not been thoroughly studied. Fluconazole has also been reported to be effective in a patient with *Fusarium* infection [330].

10.8.5.3 Yeasts

Even though the nail plate is not often invaded by *Candida*, extensive onycholysis is often associated with *Candida* [331, 332]. In these cases, avoidance of contact irritants, exposure to nail cosmetics, strong soaps and foods, especially citruses, or physical trauma and wet work is important. In these cases, there is often secondary invasion of *Pseudomonas*, and the nails then have a greenish discoloration. The onycholytic part of the nail must be removed and the nail bed treated with a daily application of a topical antifungal [332].

In true *Candida* onychomycosis, the fungus has invaded the nail plate with subsequent dystrophy as a result. These cases must be treated orally with itraconazole or fluconazole. Terbinafine is not effective. If there is onycholysis, it must be managed as described above. Recalcitrant cases should be treated with a combination of an oral, topical, and surgical approach.

If there is chronic *Candida* paronychia, irritants, as described above, must be avoided. The nail folds are usually inflamed so a topical steroid in addition to a topical antifungal drug will help to reduce the inflammatory response.

As with molds, a culture of *Candida* does not necessarily mean a diagnosis of *Candia* onychomycosis. One investigator could not establish any significant difference in the frequency of *Candida* spp. or other yeasts isolated from clinically healthy and diseased nails [333]. When a *Candida* species other than *C. albicans* is a primary pathogen, it must grow out in culture as a single organism (no other concomitant pathogen) on repeated isolations, and direct microscopy must show

yeast pseudomycelia [334]. In the case of *Candida albicans*, a single isolation is sufficient if other criteria are met [334]. PAS staining can also be helpful in distinguishing between primary and secondary *Candida* infections. In primary infections, the nail plate and nail bed are directly involved.

10.8.6 Combination Therapy

Combination therapy, where a combination of a topical and oral drug is given, is not new [335]. There has been a growing interest in combination therapy to improve the therapeutic outcome. Combination therapy may be associated with a wider antifungal spectrum, possibly synergism in some cases, especially with drugs with different mechanism of action. This may result in a more rapid recovery and higher cure rates.

The different modes of drug administration allow for complementary drug penetration into areas of infected tissue where each drug alone does not accumulate in effective concentrations; oral drugs rapidly suffuse and accumulate in the nail bed, while topical therapies effectively penetrate the nail plate and may be effective in preventing reinfection of the nail itself [336].

It is not necessary to use combination treatment in all patients. The ideal candidate is a patient suspected of being difficult to treat (Table 10.18) because one or more negative prognostic factors are present (Table 10.24). This kind of treatment can also be considered in patients with fungi that respond poorly to treatment or with a mixed infection.

10.8.6.1 Efficacy

The first combination treatment was with griseofulvin and a topical drug [337, 338]. Hay and colleagues combined griseofulvin with tioconazole and found that 69 % of nails treated with this combination achieved clinical and mycological remission compared with 41 % of nails receiving oral griseofulvin and placebo solution.

Combinations with an oral drug and amorolfine have been thoroughly studied [198, 339–345]. Amorolfine and griseofulvin have been combined, and after 6 months of treatment, the number of nails cured in the combination group was approximately doubled than seen in the griseofulvin group [339].

In an open study, Baran and colleagues studied 147 patients randomized to one of three treatment arms: terbinafine was given orally for 6 or 12 weeks and amorolfine nail lacquer was applied weekly for 15 months. A control group received terbinafine alone for 12 weeks. The global cure rates were markedly higher in the 12 weeks of terbinafine combination group, 72.3 % compared to 37.5 % in patients treated with terbinafine alone [345]. A similar study was done in patients with matrix involvement. These patients are considered more difficult to treat [342]. This study confirmed the superiority of the combination with an overall response

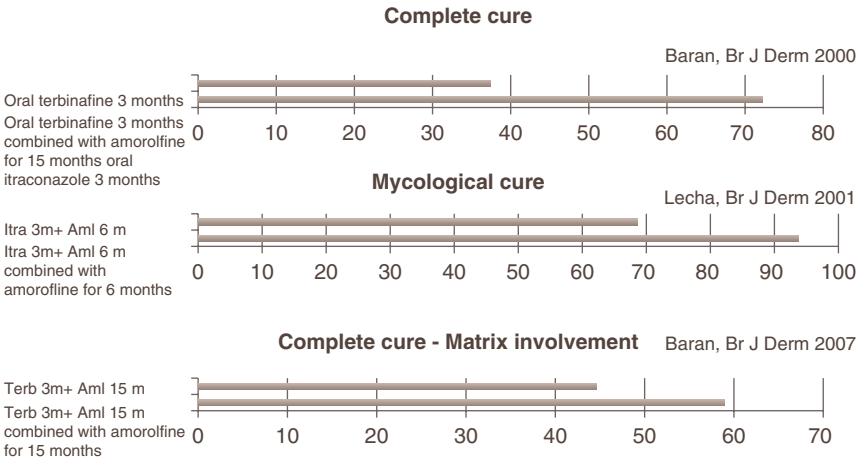


Fig. 10.6 Cure rates for combination treatment compared to monotherapy with the same oral agent

(mycological cure and less than 10 % residual changes in the nail) of 59.2 % in the combination group compared to 45 % in the terbinafine alone group [342]. Lecha [344] confirmed the value of combining amorolfine with itraconazole. See Fig. 10.6.

Eighty patients with onychomycosis were randomly assigned to receive either oral terbinafine 250 mg/day for 16 weeks or a combination of oral terbinafine 250 mg/day for 16 weeks and topical ciclopirox nail lacquer once daily for 9 months. At the end of study, mycological cure rates were 22/34 (64.7 %) for the terbinafine-only group and 30/34 (88.2 %) for the combination therapy group [346]. No significant difference was noted in the complete cure rates. Gupta and colleagues treated patients with severe onychomycosis (>60 % involvement) [347]. Mycological cure rates were 70.4 % in the combination group compared to 56 % in the terbinafine alone group [347]. The combination of fluconazole and amorolfine has only been studied in one study [348]. The patients were treated with fluconazole 150 mg once weekly until less than one third of the nail was affected. At this time, fluconazole was discontinued and treatment with amorolfine (sequential treatment) initiated and continued until cure. Out of 23 patients, there were only four treatment failures (83 % cure) [348].

Not all studies have been able to demonstrate superiority of combination treatment [341, 343].

10.8.6.2 Dosage

The oral drug is given in a standard dosage for 12 weeks combined with a topical drug. When the topical and systemic drug is given together from the start, it is called "parallel combination treatment" [336]. The other scenario includes patients who have started an oral treatment, but the response is at some stage suboptimal. Adding

a topical drug is one option to enhance the treatment response. This kind of treatment is often called “sequential combination treatment” [336]. The oral drug is given in a standard dose for 3 months and then a topical added and used until cure.

10.8.6.3 Conclusion

Although there are few controlled studies and not all studies have been able to demonstrate added efficacy of combination, it is likely that combination of a topical drug and oral drug increases the efficacy compared to an oral drug alone. Most of the studies have used terbinafine and amorolfine, but combining other oral drugs with a topical drug is likely to be of value. If there is no contraindication of using terbinafine and amorolfine, it is probably the combination of choice today. Other combinations are a clear alternative. Efinaconazole is a new topical that seems to have better efficacy compared to the topical drugs that are currently on the market. It will be interesting to see the efficacy of this drug in combination with terbinafine.

10.8.7 Surgery

It sounds logical if the infected part of a nail is removed; it will facilitate the penetration of the drug into infected areas. This kind of treatment is rarely used on its own, but rather combined with an oral or topical drug and sometimes both. Another indication is a painful toenail or when an oral drug is contraindicated. Surgical treatment can be used to remove part of the nail without local anesthesia (debridement) or the whole the nail plate (avulsion), usually with local anesthesia. In many cases, a partial avulsion is sufficient, i.e., when the infection is limited to only a part of the nail. It can also be used in patients with negative local prognostic factors such as a dermatophytoma, edge involvement, thick hyperkeratotic nail, or streaks. A partial surgical avulsion can often be done without local anesthesia using a nail clipper (Photo 10.13). Some podiatrists and dermatologists use a CO_2 laser to ablate the nail plate and then a curette to remove the subungual debris. Podiatrists use a rotating device or drill.

10.8.8 Chemical Avulsion

Chemical avulsion with 40 % urea is another alternative. The author has used this method with success in children and adults. The formulation is shown in Table 10.23. The skin surrounding the nail must be protected with an adhesive dressing. The urea ointment is then applied to the nail and it is covered for up to a week [155]. This formulation spares the normal nail. The application can be repeated as needed. After the application of the urea ointment, the diseased nail can easily be curetted away. This method should be combined with a topical or oral drug.

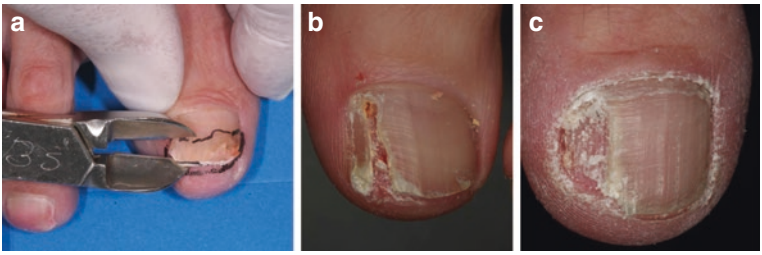


Photo 10.13 Surgical treatment can be used to remove part of the nail without local anesthesia by using a nail clipper (**a**). In the example above, a spike (**b**) has been removed and in the latter patient, a dermatophytoma (**c**). A nail clipper and a curette were used. Local anesthesia is not needed

Table 10.23 Urea ointment formulation

Constituent	Percentage
Urea	40 %
White beeswax (or paraffin)	5 %
Anhydrous lanolin	20 %
White petrolatum	25 %
Silica gel type H	10 %

From Baran [155]

10.8.9 Treatment with Devices

This is a rapidly developing field, but most of the therapeutic modalities discussed here must be regarded as investigational therapies. Some devices, such as iontophoresis, are used to increase the diffusion of the drug through the nail plate [349, 350]. Photodynamic therapy has successfully been used to treat onychomycosis [351–354]. This technique is based on the phototoxicity of target cells or microorganisms and involves an interaction between a photosensitizing agent, a light source, and molecular oxygen [350, 354].

Carbon dioxide laser has been used with some success to treat onychomycosis [355], but is probably not of much use if not combined with an antifungal drug. The Food and Drug Administration (FDA) has approved several laser systems that at least temporary increase the amount of healthy nail in patients with onychomycosis [350]. It is believed that the effect on the fungus is mediated by heat or by disintegration of fungal structures and production of both ATP and toxic levels of reactive oxygen species, thus disrupting the mitochondrial membrane potential [356]. Although many laser systems are on the market, there is still lack of efficacy data. Most studies are small and do not always fulfill the stringent criteria that are used in modern clinical research. Case reports that indicate successful treatment exist [357]. Most studies have only managed to show increase in the amount of clear nail, but studies with sufficiently long follow-up are currently lacking [356]. A recent non-industry-sponsored randomized controlled trial of patients with onychomycosis treated with Nd: YAG laser failed to show efficacy [358]. In this trial, patients were treated with Nd: YAG spaced 2 weeks apart compared to no treatment in 27 patients

($n=125$ affected nails) with clinical and mycological diagnosis of onychomycosis. At 3 months, 33 % of patients treated with laser achieved a negative mycological culture compared with 20 % of the control group ($p=0.49$) and had more proximal nail plate clearance compared with control subjects (0.44 vs. 0.15 mm, $p=0.18$). This difference is not significant. At 12 months, there was no difference in nail plate clearance between laser and control subjects.

There are no studies that compare the efficacy of laser systems with oral drugs. The advantage of laser treatment is that there are no drug side effects or drug-drug interactions and compliance is usually not a problem since the procedure is performed at the clinic.

10.8.10 Why Does the Treatment Fail?: Prognostic Factors

It would be of importance if patients that likely to fail a standard course of treatment could be identified early and their treatment could be tailored accordingly. Examining known prognostic factors at baseline can help clinicians to identify these patients before initiating treatment (Table 10.24). Prognostic factors can, therefore, help determine the choice of therapeutic agent (oral, topical, combination, surgery, later prophylactic treatment, and type of oral drug), length of treatment, and duration of follow-up [359].

Table 10.24 Prognostic factors

Local factors	Lateral edge disease
	Extensive onycholysis
	Dermatophytoma or spikes
	Thick nail plate
	Extensive hyperkeratosis
	Matrix involvement
	Slow nail growth
	Other nail diseases
	Traumatically damaged nails
	Thick hyperkeratotic nails
Patient factors	Poor circulation. Peripheral vascular disease, diabetes
	Reduced absorption
	History of a previous episode of onychomycosis
	Immunosuppression
	Sex
	Age
	Poor drug compliance
Mycology	Mixed infections, bacterial, viral
	Difficult-to-treat organism such as *Candida* and some molds
	Antifungal drug resistance
Positive culture at 6 months	Patients with a positive culture at this time point have a poor prognosis and a booster dose should be considered
Severity index	The higher the score, the poorer the prognosis

10.8.10.1 Nail Involvement

The percentage of onychomycosis is often considered to be an important prognostic factor and used to select the type of treatment used and as part of inclusion criteria in clinical studies [228]. It is common to classify the infection into mild ≤25 %, moderate 26–74 %, and severe ≥75 % of the nail involved. Although it is the general perception that the less the nail involvement, the better the response to treatment, it has been difficult to prove this in clinical studies. In a study on 496 patients treated with terbinafine or intermittent itraconazole, cure rates were not correlated with nail involvement (OR, 1.003; 95 % CI, 0.995–1.010) we just have to be consistent in the use of CI or confidence interval and OR [360]. In a study on topical terbinafine, the cure rates were higher in patients with <40 % involvement [208]. This factor may be of greater importance when topical drugs are used.

10.8.10.2 Lateral Edge Involvement

Baran and de Doncker were the first to show that patients with lateral edge involvement have a poor prognosis [361]. This has been confirmed in a study by Sigurgeirsson where patients with lateral edge involvement responded poorly to treatment (OR, 3.468; 95 % CI, 1.300–9.250) [359]). This is probably caused by formation of onycholytic or hyperkeratotic pockets or canals that form at the lateral edges and that it is difficult for the drug to penetrate into this space (Photo 10.14).

10.8.10.3 Sex

At least one study has demonstrated that male patients are more difficult to treat. The reason for this is not clear. It is known that in most countries, the prevalence of onychomycosis is higher in male populations [24, 26], but few studies have compared cure rates between the genders. It is possible that men more frequently suffer nail trauma and that men may seek help for more advanced disease. Compliance may also be an issue.

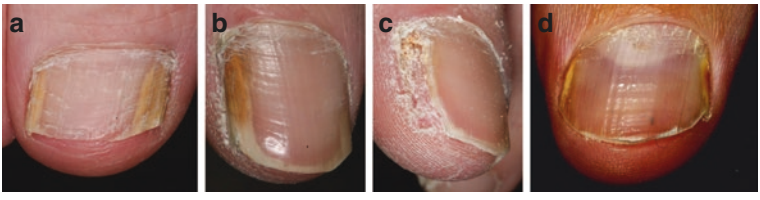


Photo 10.14 Lateral edge involvement. Plates (**a**–**d**) are typical examples. As these patients are considered difficult to treat, the infected part has been removed in patient (**b**). The result is shown in plate (**c**). This patient is expected to respond well to a standard course of an oral antifungal drug

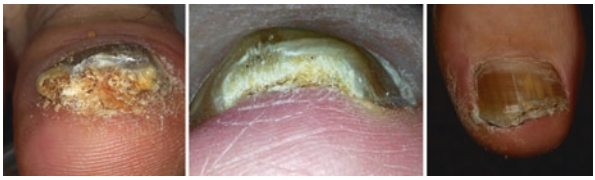
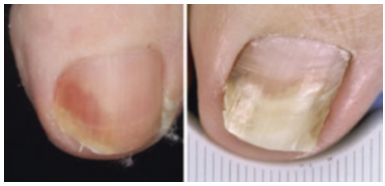


Photo 10.15 Thick nails. It has often been suggested in the literature that thick nails are difficult to treat, but statistical support has been missing. It is logical that it can be difficult to treat patients with thick nail plate or subungual hyperkeratosis, as it is likely that it is more difficult for the drug to reach sufficient concentration in thick hyperkeratotic nails

Photo 10.16 Onycholysis. Hard evidence statistical proof is lacking for the relevance of onycholysis, but frequently cited in the literature that this is a negative prognostic factor. This is supported by clinical experience. It is logical that a topical or systemic drug cannot penetrate a layer of air



10.8.10.4 Nail Thickness

It is logical that it can be difficult to treat patients with thick nail plate or subungual hyperkeratosis, as it is likely that it is more difficult for the drug to reach sufficient concentration in thick hyperkeratotic nails (Photo 10.15). This has often been suggested in the literature, but statistical support is missing [132, 362]. In a recent study, patients with thick toenails were less likely to reach cure, but the results did not quite reach statistical significance [359].

10.8.10.5 Extensive Onycholysis

Extensive onycholysis may prevent a topical drug to reach the nail bed (Photo 10.16). This may also result in reduced delivery of the oral antifungal agent from the nail bed to the adjacent ventral nail plate [16] Possible treatment strategies include extensive trimming back of the diseased nail plate or supplemental therapy as described in the section on lateral onychomycosis. Patients appear to respond better to oral antifungal therapy when there is minimal onycholysis and absence of lateral onychomycosis.

10.8.10.6 Age

Younger patients respond better to therapy [63]. In a study where 24 patients between 18 and 64 years of age were treated with intermittent therapy, itraconazole was orally administered for 4 months and age was the only parameter that was correlated with the cure rate [363]. In another study, patients over 65 years of age were far less likely to be cured compared to patients between 18 and 40 years (OR = 3.702; 95 % CI, 1.407–9.743) [359].

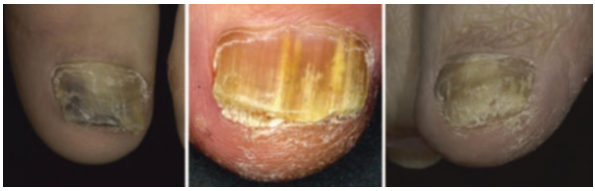


Photo 10.17 Matrix involvement. Patients with matrix involvement are more difficult to treat

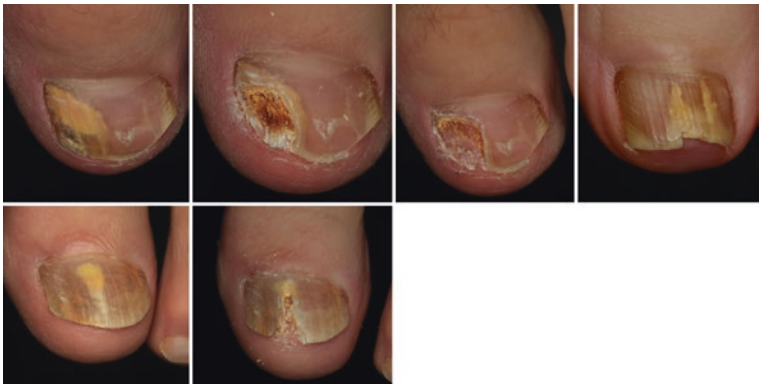


Photo 10.18 Dermatophytoma and spikes affect cure rates negatively. Removing the dermatophytoma/spikes will increase cure rates

10.8.10.7 Matrix Involvement

Extension of the infection into the matrix is often mentioned as a negative prognostic factor, and many dermatologists believe [345] that these patients are more difficult to treat (Photo 10.17). It is not completely understood why patients with matrix involvement are more difficult to treat compared with those without matrix infection. It is possible that involvement of the nail matrix affects nail growth or other physical characteristics of the nail. Matrix involvement is common, and in a study on 199 patients with onychomycosis, 134 (67 %) had matrix involvement [359]. When factors predictive for cure were examined, the odds ratio for these patients not reaching cure was 2.591 (95 % CI, 1.261–5.322) [359].

10.8.10.8 Dermatophytoma or Spikes

Roberts and Evans first described this entity [364]. It consists of a hyperkeratotic mass with a densely packed clump of dermatophyte hyphae which are thick walled and somewhat abnormal looking [364]. Clinically either a dense white or yellow area clearly demarcated from the surrounded infection (Photo 10.18). Roberts and Evans suggested that antifungal drug penetration into such lesions does not achieve adequate concentrations and that, in order for antifungal drugs to prove effective,

surgical removal was necessary. In a small study designed to examine prognostic factors, the authors were unable to confirm dermatophytoma as a poor prognostic indicator, but the numbers may have been too small [365]. In a study of 199 patients treated with terbinafine, dermatophytoma clearly had a negative effect on the probability of cure (OR =3.453; 95 % CI, 1.170–10.192) [359]. The negative impact of dermatophytoma on cure is now generally accepted [132, 196, 366, 367]. The general recommendation is to remove a dermatophytoma surgically before treatment is initiated.

10.8.10.9 Organism

In one study, patients with onychomycosis caused by *T. rubrum* had higher cure rates [63]. Patients infected with *Candida* respond poorly to terbinafine, better to azoles. Molds are filamentous fungi that are commonly found in nature as saprophytes and plant pathogens. Because these molds are not keratolytic, unlike dermatophytes, they only live on unkeratinized intercellular material or must take advantage of previous keratin destruction by dermatophytes, trauma, or another nail disease. This explains why the prevalence of molds is relatively low. Molds causing onychomycosis include *Scopulariopsis brevicaulis*, *Aspergillus* species, *Fusarium* species, *Neoscytalidium* species, and *Onychocola canadensis*. Molds, when they are the real cause of onychomycosis, rather than a secondary pathogen, can be difficult to treat.

10.8.10.10 Nail Growth Rate

The general perception is that nails that have a faster rate of growth are likely to respond better compared to slow-growing nails [368]. This is supported from the clinical observation that patients exhibiting faster outgrowth show a better response to treatment [369]. This was also supported in a recent study (OR = 1.549; 95 % CI, 1.103–2.176) [359]. This is logical as the infected part is likely to be shed earlier in patients with fast-growing nails. However, a study by Yu and colleagues examined 49 patients with onychomycosis, but could not find a link between cure rates and nail growth [370]. Zheng and colleagues showed that cure rates are higher in patients with fast-growing nails [63].

10.8.10.11 History of More Than One Episode of Onychomycosis

Patients with a history of a prior infection are less likely to be cured [359]. This could be explained by a subgroup of patients who could not be cured by the previous standard treatment course and are hence unlikely to be cured with another standard treatment course. This may also be a marker for a patient group with strong onychomycosis tendency.

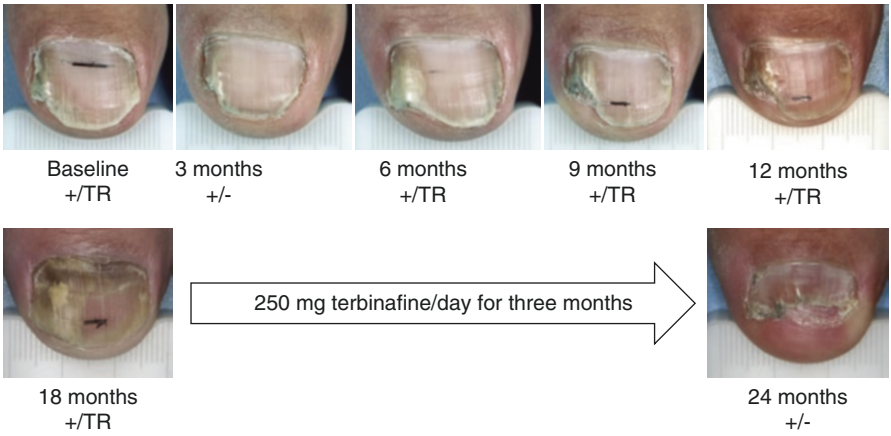


Photo 10.19 A 49-year-old healthy male with a history of onychomycosis for 8 years. Treated with terbinafine 250 mg/day for 3 months. Culture was positive for *Trichophyton rubrum* at 6 months which is a negative prognostic sign. The nail continued to deteriorate until the patient was retreated at 18 months. TR = trubram. (microscopy/calture)

10.8.10.12 Positive Culture 12 or 24 Weeks After Starting Therapy

Positive culture at 12 or 24 weeks after start of therapy is associated with treatment failure [359, 360]. The association at 24 weeks is stronger. Positive culture at 12 and 24 weeks could be used to evaluate the chance of cure of onychomycosis in patients treated with oral antifungal agents. This may help to identify difficult-to-treat patients for whom a more tailored treatment approach would be indicated (Photo 10.19).

10.8.10.13 Other

Patients with diabetes mellitus or hyperhidrosis, as well as with positive family history, or basic nail diseases such as trauma and paronychia, had a lower recovery rate, and the curative effects were not satisfactory. Zheng suggested that the treatment duration should be prolonged in order to increase the curative effects and decrease the recurrence under such conditions as the following: old patients above 60 years, patients with slow-growing-speed newborn nails, patients with thumb and big toe injury and ingrown nail, patients with diabetes mellitus and hyperhidrosis, patients with nail trauma before or during the treatment, patients with PSO or TDO manifestation, patients with onychomycosis caused by *Candida* or *Aspergillus*, and patients with nails of abnormal color, coarse surface, or abnormal thickness [63].

Table 10.25 Severity indices

	Parameter	Points given		
		OSI index	B-H index	SCIO index
Local	Type of onychomycosis	n.c	n.c	1–3
	Nail involvement (%)	1–5	n.c.	n.c
	Location	n.c.	n.c	1–3
	Involvement from the distal edge	1–4	1–3	1–3
	Edge involvement	n.c.	n.c.	n.c.
	Matrix involvement	5[a]	3	n.c.
	Dermatophytoma	10	n.c.	n.c.
	Subungual hyperkeratosis >2 mm	10[b]	1–3	1–3
	Onycholysis	n.c.	1–2	n.c.
	Paronychia with melanonychia	n.c.	3	n.c.
	Melanonychia w/o paronychia	n.c.	3–4	n.c.
Systemic	Age	n.c.	1–3	1–3
	Immunosuppression	n.c.	4	n.c.
	Peripheral vascular disease	n.c.	2	n.c.
	Diabetes	n.c.	1	n.c.
Organism	*Neoscytalidium* spp.	n.c.	4	n.c.
	Other mold and fungi	n.c.	2	n.c.
	Yeasts	n.c.	1	n.c.
Calculation		Add points	Add points	Formula

OSI Onychomycosis severity index [367], *B-H index* Baran-Hay's severity index [195], *SCIO* Scoring clinical index for onychomycosis [371]
n.c. not considered, *w/o* without
SCIO index formula= $\mathrm{SCIO} = \left[\left(d/3 \right)^{3-f} \left(f + h\left(3-f\right) \right) \left(1\right) \left(a+3\right)/3 \right]^{1-\left[\left(2-f\right)\left(3-f\right)/2 \right]}$
[a,b]Both parameters cannot be used in the same calculation

10.8.11 Grading Onychomycosis

Some patients are more difficult to treat than others, but it is not always easy to predict how the patients are going to respond to the treatment. In attempt to weigh in several prognostic factors, severity indexes have been developed (Table 10.25). The SCIO index was developed in Russia [371]. This index takes into account the clinical form, nail involvement, degree of hyperkeratosis, location, and age of the patient. The index has a range from 1 to 30 and higher index indicates more severe onychomycosis. The author suggests six different treatment modalities based on the index. The main drawback with this index is that it is a little bit complicated to calculate and this index has there never gained any popularity. An calculator index is now available online which should facilitate the use of this index (http://www.onychoindex.com).

The Baran-Hay's severity index evaluates ten different factors: extent of involvement, nail plate thickening, streaks, onycholysis, location, presence of paronychia,

Table 10.26 Onychomycosis Severity Index (*OSI*)

Area of involvement		Proximity of disease to the matrix		Presence of dermatophytoma or subungual hyperkeratosis >2 mm	
Affected nail, %	No. of points	Amount of involvement from distal edge	No. of points	Present	No. of points
0	0	<1/4	1	No	0
1–10	1	1/4–1/2	2	Yes	10
11–25	2	>1/2–3/4	3		
26–50	3	>3/4	4		
51–75	4	Matrix involvement	5		
76–100	5				

The Onychomycosis Severity Index is calculated as follows: the score for area of involvement is multiplied by the score for the proximity of disease to the matrix, and ten points are added for the presence of a dermatophytoma or subungual hyperkeratosis of greater than 2 mm. A cumulative score of 0 indicates cured; 1 through 5, mild onychomycosis; 6 through 15, moderate onychomycosis; and 16 through 35, severe onychomycosis. Table is based on the work of Carney and colleagues [367] (Reproduced with permission from the authors)

melanonychia, age of the patients, presence of concomitant predisposing disorders, and type of causative organism [195]. The advantage of this index is that it considers both local and systemic factors, but it has not gained popularity among busy clinicians.

The latest index is a result of a consensus conference that was convened to develop an objective, reproducible numeric grading system describing the extent and involvement of distal subungual onychomycosis [367]. This index gives 1–5 points, based on nail involvement and amount of involvement from the distal edge and finally ten extra points for a dermatophytoma or more than 2 mm subungual hyperkeratosis [367]. The authors call this index "The Onychomycosis Severity Index" (OSI). Mild nail involvement is classified as a score of five or less; moderate, 6 through 15; and severe, 16 through 35. The advantage of the OSI is that it is simple and easy to use (Table 10.26), but this disadvantage is that it does not evaluate systemic factors or the type of organism involved. Also the OSI does not give points for edge involvement, which many authors consider to have a considerable predictive value. It is likely that severity indices still need improvement. The use of a severity index in clinical trials provides an objective measurement of disease severity and will make results from different trials more comparable. In the clinical setting, the use of a severity index will aid in the therapeutic decision-making process.

10.8.12 Recurrence

The treatment of onychomycosis is not always successful (Table 10.27). Despite several effective therapeutic agents, recurrence of onychomycosis after successful treatment is not uncommon. Every clinician who treats patients with onychomycosis has met patients that have a long history of repeated infections. Recurrence is

Table 10.27 Why does the treatment of onychomycosis fail?

Patient factors	Dietary mistakes, i.e., low gastric acidity when itraconazole is used
	Poor compliance
Wrong diagnosis	More than one nail disease, i.e., psoriasis
	Laboratory diagnosis not done
	All pathogens not detected
New infection	Reinfection (Table 10.28)
Treatment to short	Relapse
Bad local prognostic factors	See Table 10.24
Unfavorable mycology	Molds or yeasts. Presence of arthroconidia with thicker cell walls
Poor host response	Immunosuppression because of treatment or disease

Table 10.28 Measures for preventing reinfections

Contributing factor	Recommendation
Shoes	Treat shoes with terbinafine powder. Do not share shoes
Tinea pedis	Treat with a topical antifungal
Socks	Wash socks on 60 ° C. Do not share
Public showers, gyms, etc.	Use flip-flops. Rinse floors frequently
Nail clippers	Do not share. Disinfect regularly
High-risk individuals (see Table 10.6)	Prophylactic lacquer Consider combining with a topical antifungal such as terbinafine weekly
Infected family members	Recommend treatment
High-risk patients	Prophylaxis

sometimes divided into relapse and reinfection (Fig. 10.7). Relapse is defined as reappearance of the same episode of disease, whatever time has elapsed, but reinfection is defined a new episode of the same disease caused by a new infection [372]. Relapse indicates that the original infection was not adequately treated and at least theoretically could be prevented if adequate treatment was given. Sigurgeirsson and colleagues followed up 151 patients treated with terbinafine or itraconazole for 5 years. At the end of the observation period, mycological and clinical recurrence rates were significantly higher in itraconazole- vs. terbinafine-treated patients (53 % vs. 23 % and 48 % vs. 21 %, respectively) [249]. Most of the recurrences occurred during the first 3 years (Fig. 10.8). Recent meta-analysis also suggests that itraconazole therapy is more likely to produce mycological recurrence compared with terbinafine therapy [373]. It is not plausible that itraconazole-treated patients have a greater tendency to get reinfected, so the difference between the two drugs must be explained with different relapse rates. It is tempting to speculate that the fungicidal activity of terbinafine enables it to kill the fungus more rapidly at low concentrations and that this may account for the lower relapse rate after treatment with that drug. Itraconazole is fungistatic and may not always kill the fungus, even though a negative mycological result is produced.

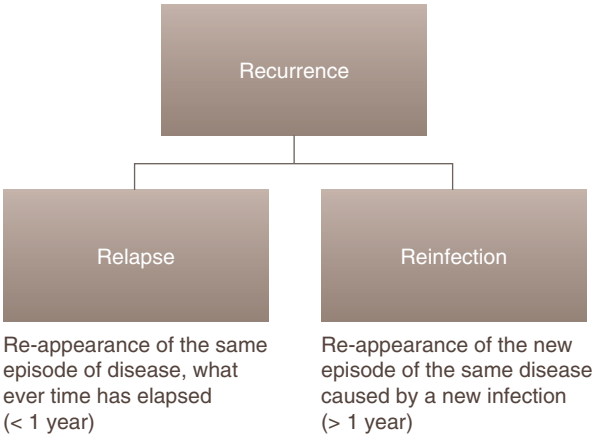


Fig. 10.7 Recurrence, relapse, and reinfection (Source from Shuster and Baran [372])

Several other studies have shown that recurrences are common (Fig. 10.9) [374–376]. Some authors claim that the recurrences are more common than demonstrated in the literature and can be as high as 50 % [377].

10.8.12.1 Preventing Reinfections

It is important to identify individuals who are at increased risk of reinfections. The same factors that predispose to a reinfection increase the risk for onychomycosis in general (Table 10.6). The clinician should be particularly alerted if several such factors coexist in a single patient.

The most obvious predisposing factor is tinea pedis [42]. It is therefore important to teach the patients to recognize and promptly treat tinea pedis. If the patient has one or more risk factors, prophylactic treatment can be considered. A lacquer can be used for prophylaxis and is applied to all toenails twice every month [198]. Many authors also suggest concomitant use of a topical antifungal powder in socks. The feet should be kept cool and dry to decrease the risk of tinea pedis and subsequent onychomycosis. If other family members are infected, it is recommended that they are treated as well to reduce the risk of cross infection. It has been demonstrated that footwear can be an important reservoir of infection and theoretically can reinfect a patient that has been successfully treated with and antifungal drug [378–380]. It is therefore logical to recommend that shoes are sanitized to minimize the risk of potential reinfection. It has recently been demonstrated that ozone gas is effective in sanitizing footwear, but devices for this are not commercially available [381]. Using ultraviolet C is another possibility and devices for this are commercially available [380]. The simplest method is probably to use terbinafine spray or powder [382]. A recent study demonstrated the successful treatment with terbinafine of insoles colonized by *T. rubrum*-infected

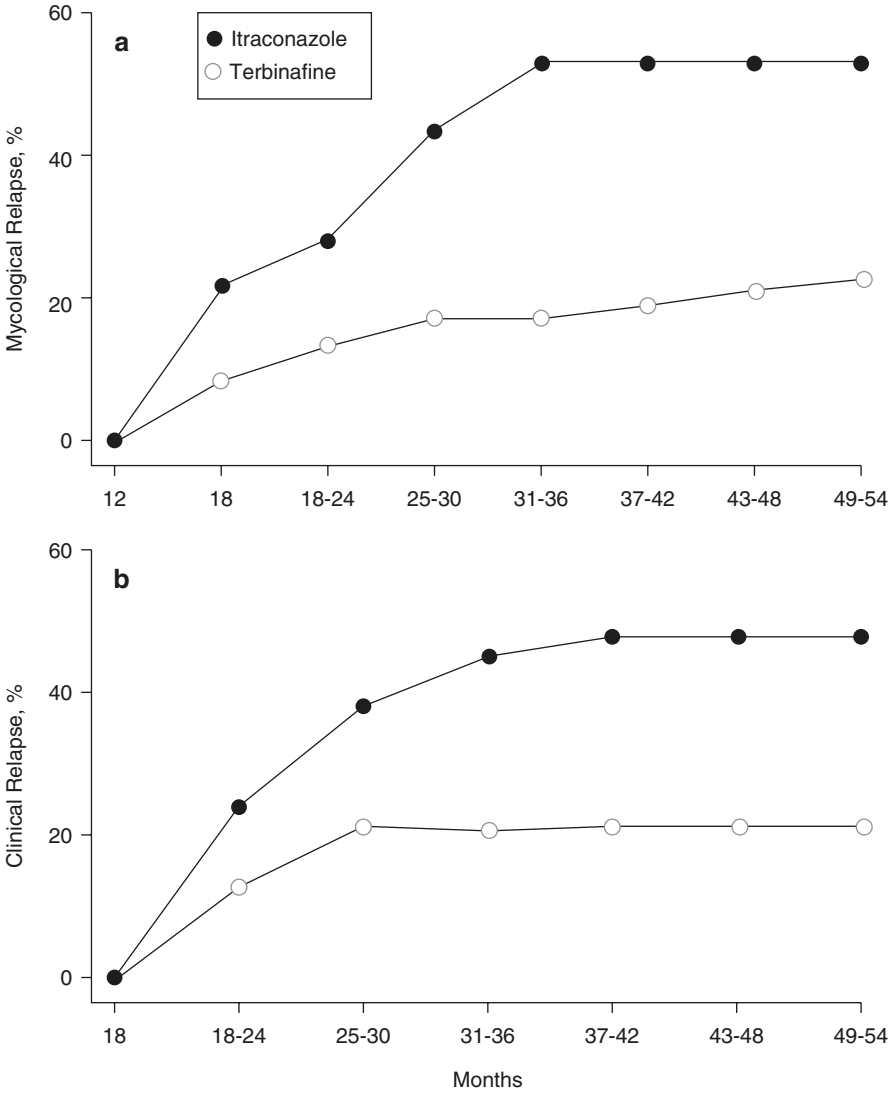


Fig. 10.8 Mycological (**a**) and clinical (**b**) recurrence rates (Modified from Sigurgeirsson [249] with permission)

skin scales [382]. Terbinafine 1 % spray solution and powder showed good efficacy; the dermatophyte could no longer be cultured 48 h after a single application of terbinafine [382].

Socks may be another source of reinfection [379]. It has been demonstrated in a "clothes basket simulation" that about 10 % of the infectious material is transferred from contaminated textiles to sterile textiles during storage indicating a high infec-

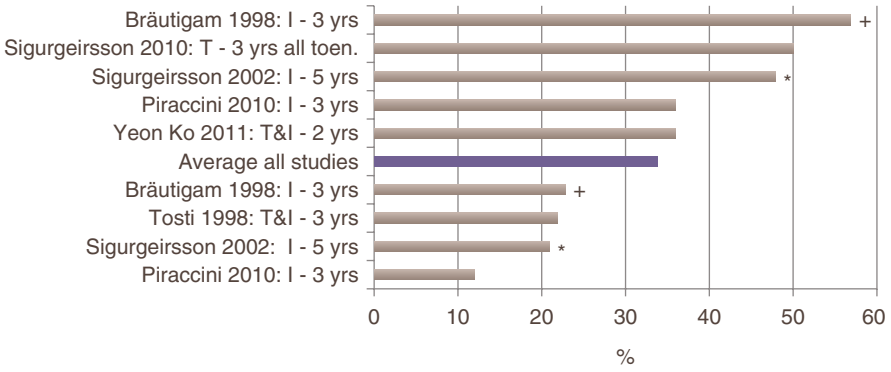


Fig. 10.9 Recurrence rates. *T* terbinafine, *I* itraconazole, *Yrs* years from initiation of therapy randomized controlled study

tion risk during storage [383]. Domestic laundering at 40 ° C does not kill fungi and therefore has a potential for textile cross-contamination [384]. Contravening current trends for energy saving and environmental protection, laundering requires high-temperature laundering at 60 °C to eradicate the fungal pathogens [384].

Locker rooms and public baths are a frequent source of infection. In a study where randomly selected visitors in a large swimming pool were examined, over 40 % had a clinical suspicion of onychomycosis, and mycological confirmation was established in every fourth visitor [119]. In this study, mycological proof of onychomycosis was found in 26 % of men and 15 % of women. When locker rooms were examined, fungal contamination on the floors was more frequent in the male locker rooms suggesting a bidirectional interaction between floor contamination and dermatophyte infections [118]. If this is the case, the incidence of infection might be reduced by the adoption of intensified cleaning and individual measures that prevent dermatophyte shedding or adherence to the feet [118]. In the same study, efficacy of cleaning was confirmed, where all early morning samples are taken before the early morning rush hour, but two were negative [118]. It must be assumed that jobs that necessitate the use of common showers carry the same risk of reinfection. Ingordo et al. [385] monitored the prevalence and contraction risk factors for skin fungus in Navy Cadets resident at an Italian military school. Only two cases, or 0.2 % of the population, had positive mycological examination results for onychomycosis. However, it was noted that all individuals not infected wore sandals while showering, creating a barrier between the infected foot and floors, possibly reducing the overall spread of fungal infection [385].

Patients visiting public baths, swimming pools, and other sports facilities should be advised to use flip-flops or other protective footwear in all common areas [377, 386].

Patients should be instructed to disinfect nail clippers at regular intervals. Such instruments should not be shared [377, 386]. See summary in Table 10.28.

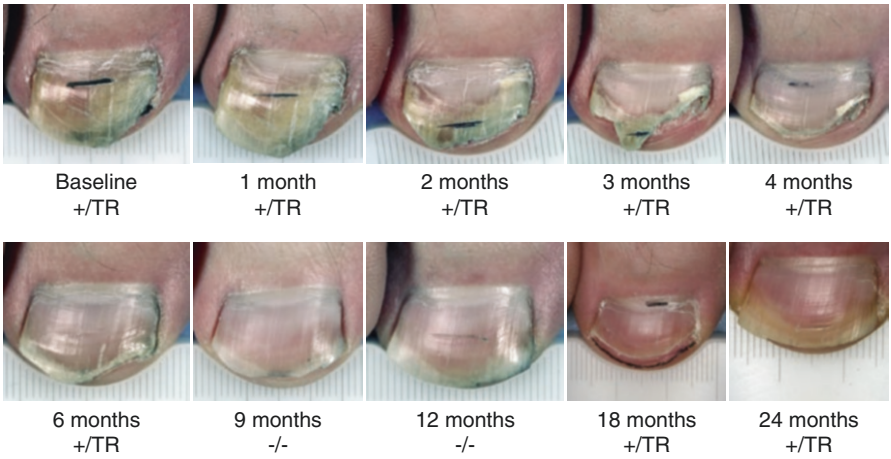


Photo 10.20 A 34-year-old healthy male. Microscopy and culture were positive at baseline. Treated with terbinafine 250 mg/day for 3 months. Clinical and mycological cure at 9 and 12 months. Mycological recurrence at 18 months with clinical and mycological recurrence at 24 months. Culture was positive at 6 months, which is a negative prognostic sign. TR = turbrum (microscopy/calture)

10.8.12.2 Preventing Relapses

Much less is known what factors determine the risk of a relapse. By definition, these patients have not been adequately treated in the first place leading to incomplete eradication of the fungal pathogen. This can happen even if the clinical signs have subsided (Photo 10.20). The following clinical signs, even in the presence of negative mycological results, are suggestive of noncure: (i) residual major changes (>10 %) of the nail plate compatible with dermatophyte infection, (ii) white/yellow or orange-brown patches or streaks in or beneath the nail, (iii) lateral onycholysis with debris in an otherwise clear nail plate, and (iv) hyperkeratoses on the lateral nail plate/nail fold edge [1]. The presence of a positive culture at 24 weeks indicates low probability of cure [359, 360], and this can be used as an indication that a booster treatment is needed.

It has been noted that patients treated with terbinafine are less likely to experience a recurrence (Fig. 10.8) compared to patients treated with itraconazole [249, 373]. The only logical explanation for the differences between these groups is that the itraconazole-treated patients experience more relapses. This might be because terbinafine is a fungicidal drug [249]. It is therefore better to choose treatment with a fungicidal drug, at least in patients with negative prognostic factors.

Patients with negative prognostic factors are probably more likely to relapse. Presumably all the prognostic factors listed in Table 10.24 can increase the risk of relapse. Care should therefore be taken to identify these factors before treatment is initiated. Poor compliance increases the risk of relapse.

Consider an additional pulse or “booster” therapy with a systemic agent to decrease the chance of relapse. This has been suggested at month 6 after a traditional

Table 10.29 Stepwise approach to improve cure rates

Confirm the diagnosis with mycology or another objective test. Only half of all nail changes are of fungal in nature
Choose your drug based on mycological culture, patient characteristics, and local factors
Examine nail characteristics. Look for dermatophytoma, thick nails, edge involvement, etc. (Table 10.24). Surgical intervention if negative local prognostic factors exist. Consider using a severity index to aid with decision-making
Combination treatment if negative prognostic factors exist (Table 10.24)
Look for systemic conditions that have a negative prognostic value (Table 10.24), and if they exist, consider combination therapy, booster therapy, or extended therapy
Follow-up visit at 6 months with mycological sampling. In case of a positive culture, give additional booster with an antifungal drug
Educate the patient to prevent reinfections (Table 10.28)
Consider prophylactic treatment if predisposing factors exist (Table 10.6)

3-month systemic course for difficult-to-treat toenail disease [290, 359, 386–389]. It is not clear how long this additional therapy has to be. In a study, patients with clinical signs of onychomycosis after 18 months after a standard course with an oral antifungal were offered treatment with terbinafine in an open manner [249]. Around 90 % of these patients were mycologically cured at the end of follow-up at 5 years. The average treatment extension needed was 4.3 months with a range of 2–11 months [249]. Although the evidence is not strong and further studies are needed, it is likely that patients that need an extension of treatment need at least additional 3 months of treatment.

10.8.12.3 Stepwise Approach to Improving the Efficacy of Onychomycosis Treatment

Although treatment efficacy has improved in the post-griseofulvin era, there is still room for further improvement. There are new drugs on the horizon, both oral and topical, but it is not clear if improved cure rates will follow. There are however several strategies that can be used to improve cure rates using available current therapy (Table 10.29).

The first thing is to always confirm the diagnosis by using an objective test such as microscopy, culture, histology, or PCR.

Choose your drug or drug combination based on the results of mycological tests.

If negative local prognostic factors exist (Table 10.24), such as a dermatophytoma, thick nails, lateral edge involvement, or extensive onycholysis, use surgery or chemical avulsion to correct the abnormality. It may be helpful to use a severity index to aid with and ensure consistent decision-making.

Consider combination therapy and an additional booster at 6 months in patients with negative prognostic factors (Table 10.24).

Schedule a follow-up visit at 6 months with mycology. If the culture is positive at 6 months, consider a booster with an oral antifungal drug for 3 months [290, 389].

When cure is reached, educate the patient to prevent reinfections (Table 10.28). If the patient has one or more risk factors, consider prophylactic therapy with a topical drug (lacquer and/or cream) after cure has been reached.

Constantly scan the literature for new information.

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Chapter 11
Cutaneous Leishmaniasis

Colette L.M. van Hees and Ben Naafs

11.1 Introduction

Leishmaniasis (L) is an infectious disease caused by a protozoan parasite: *Leishmania*, which was identified as the cause of the disease early in the twentieth century. The infection is transmitted by female sandflies. It is a widespread disease which is endemic in the "Old World" (Europe, Middle East, Africa, Central Asia, and India) and in the "New World" (Central and South America).

Leishmaniasis may present as visceral (VL, also known as kala-azar, meaning "black fever" in Hindi), cutaneous (CL) or mucocutaneous (MCL) disease depending on the species of *Leishmania*. Disease progression and severity is determined by parasite species, host genetics and immune factors. There are 1.5–2 million new infections each year, of which approximately two-thirds represent cutaneous forms (Fig. 11.1). Leishmaniasis currently affects more than 12 million people in nearly 100 countries (WHO). The estimated annual global mortality due predominantly to VL is 20,000–40,000 [1]. The size of the population at risk is about 350 million [2, 3].

Many species of *Leishmania* may infect humans (Table 11.1). However the majority of the parasites reside in zoonotic reservoirs, for example, *Leishmania* (*L.*) *infantum* in dogs and *L. major* in rodents. Humans dwelling close to these reservoirs become infected relatively easily and may become an anthroponotic reservoir.

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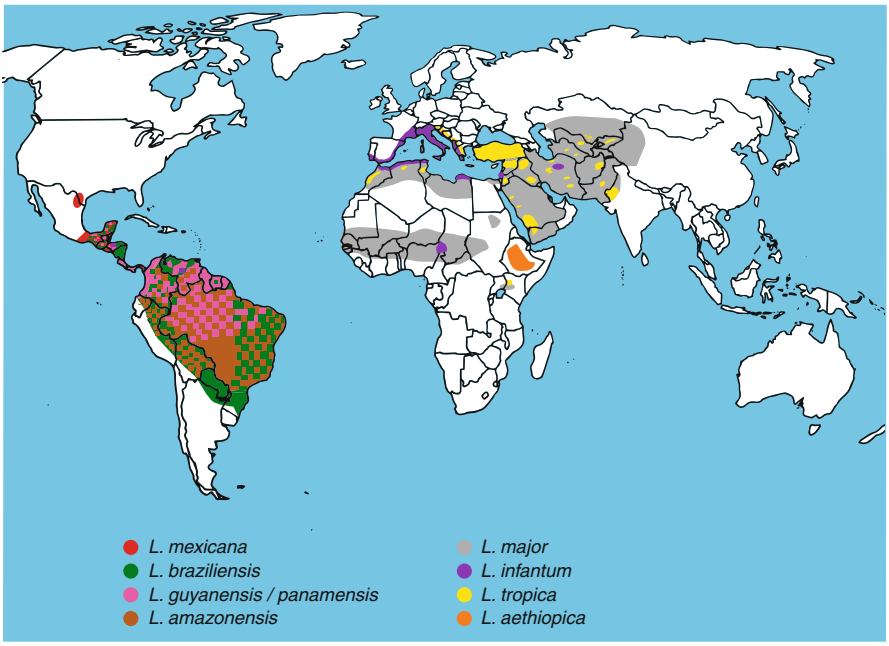

Fig. 11.1 The main causative species of CL and their approximate global distribution. Adapted from A. Magill [211]

Examples of human reservoirs are cutaneous leishmaniasis (CL) caused by *L. tropica*, anergic diffuse cutaneous leishmaniasis (ADCL) due to *L. aethiopica* and VL caused by *L. donovani*.

Box 11.1: Different Types of Leishmaniasis: Abbreviations
CL: Cutaneous Leishmaniasis
ML: Mucosal Leishmaniasis
VL: Visceral Leishmaniasis (Kala-azar)
LCL: Localised Cutaneous Leishmaniasis
MCL: Mucocutaneous Leishmaniasis
DCL: Disseminated Leishmaniasis
ADCL: Anergic Diffuse Cutaneous Leishmaniasis
PKDL: Post-Kala-Azar Dermal Leishmaniasis

11.2 Infection

The sandfly vector becomes infected during blood meals on infected hosts when it ingests macrophages infected with amastigotes. In the sandfly's midgut, the parasites differentiate into promastigotes. The procyclic stage promastigotes express

Table 11.1 Species of *Leishmania* which may infect humans and their clinical manifestation

	Old World leishmaniasis	New World leishmaniasis	
Subgenus	*Leishmania*	*Leishmania*	*Viannia*
Cutaneous	*L. major* *L. tropica* *L. aethiopica* *L. infantum*	*L. mexicana* *L. amazonensis* *L. venezuelensis*	*L. braziliensis* *L. guyanensis* *L. panamensis* *L. peruviana* *L. shawi* *L. naiffi* *L. lainsoni* *L. lindenbergi*
Anergic diffuse cutaneous	*L. aethiopica*	*L. amazonensis*	
Recidivans cutaneous	*L. tropica*		
Mucocutaneous	*L. aethiopica*		*L. braziliensis* *L. guyanensis* *L. panamensis*
Mucosal	*L. aethiopica* (*L. major*) (*L. tropica*)		*L. braziliensis* *L. panamensis* *L. guyanensis*
Visceral or viscerotropic	*L. infantum* *L. donovani*	*L. infantum/chagasi*	
Post-kala-azar dermal leishmaniasis	*L. donovani* *L. infantum*	*L. infantum/chagasi*	

species-specific lipophosphoglycan (LPG) on their surface. LPG protects them from proteolytic digestive enzymes and facilitates their attachment to the insect gut epithelium where the promastigotes divide [4, 5]. Non-infective dividing procyclics differentiate into infective non-dividing metacyclic promastigotes and migrate to the proboscis. Characteristics of the intravectorial cycle (which may be supra- and peripyloric) are used to define the subgenus group (*Leishmania* (midgut) or *Viannia* (hindgut)) [6, 7]. Transmission of infective metacyclic *Leishmania* promastigotes to a mammalian host may occur after the bite of an infected female sandfly of the species *Phlebotomus* (Old World) or *Lutzomyia* (New World) (Table 11.2) [208]. The sandfly injects the promastigotes into the skin during a blood meal after which they are phagocytised quickly by macrophages and transform into amastigotes. Amastigotes multiply in infected macrophages or dendritic cells in various tissues, depending on the species of *Leishmania* and host factors. *Leishmania* is an obligate intracellular parasite in mammals. The varying organ specificities together with the host's immunity are responsible for the diverse clinical manifestations of the various forms of leishmaniasis.

In vector-borne leishmaniasis, three types of transmission cycle are observed in human infections:

1. A primarily zoonotic reservoir of wild animals which is isolated from human residence. Humans become infected only as trespassers (e.g. sloths in *L. guyanensis*, *L. panamensis*, etc.)

2. A primarily zoonotic reservoir of (peri)-domestic animals close to human residence (e.g. dogs in *L. infantum*)
3. A primarily human reservoir (e.g. *L. tropica and L. donovani*)

Table 11.2 Main relevant *L.* species, sandfly species, global distribution, clinical manifestations, transmission route and mammalian host

Species of leishmania	Sandfly species	Geographical distribution	Clinical disease in humans	Main transmission route	Main mammalian hosts
L. major	*Phlebotomus papatasi*, *duboscqi*, *salehi*	Central and West Asia, North Africa, Sahel, Central and West Arica	CL (oriental sore, "wet")	Z rural	Great gerbil, fat sand rat
L. tropica	*Phlebotomus sergenti*	Central and West Africa, North Africa	CL (oriental sore, "dry")	A urban	Human, rock hyrax
L. aethiopica	*Phlebotomus longipes*, *pedifer*	Ethiopia, Kenya	CL, ADCL, LR	Z rural	Rock hyrax
L. donovani	*Phlebotomus argentipes*, *orientalis*, *martini*	Indian subcontinent, East Africa	VL (kala-azar), PKDL	A epidemic	Human
L. infantum	*Phlebotomus ariasi*, *perniciosus*	Mediterranean basin, Central and West Africa	VL (often HIV coinfection), CL	Z peridomestic	Domestic dog
L. infantum (*chagasi*)	*Lutzomyia longipalpis*	Central and South America	VL, CL (mostly children)	Z peridomestic	Domestic dog, fox
L. mexicana	*Lutzomyia olmeca olmeca*	Central America	CL (chiclero's ulcer)	Z sylvatic (wild)	Forest rodents
L. amazonensis	*Lutzomyia flaviscutella*	South America	CL, ADCL	Z sylvatic (wild)	Forest rodents
L. (*V.*) *braziliensis*	*Lutzomyia wellcomei*, *complexus*, *verrucarum*	Central and South America	CL, MCL (espundia)	Z sylvatic (wild)	Forest rodents
L. (*V.*) *peruviana*	*Lutzomyia peruensis*, *verrucarum*	Peru	CL (uta)	Z?	Dog?
L. (*V.*) *guyanensis*	*Lutzomyia umbratilis*	South America	CL, often metastatic (pian bois)	Z sylvatic (wild)	Sloth, anteater
L. (*V.*) *panamensis*	*Lutzomyia trapidoi*	Central America	CL	Z sylvatic (wild)	Sloth

Adapted from Bates [208]
L leishmania, *V Vianna*, *CL* cutaneous leishmaniasis, *VL* visceral leishmaniasis, *MCL* mucocutaneous leishmaniasis, *ADCL* anergic diffuse cutaneous leishmaniasis, *LR* leishmania recidivans, *PKDL* post-kala-azar derma leishmaniasis, *Z* zoonotic, *A* anthroponotic

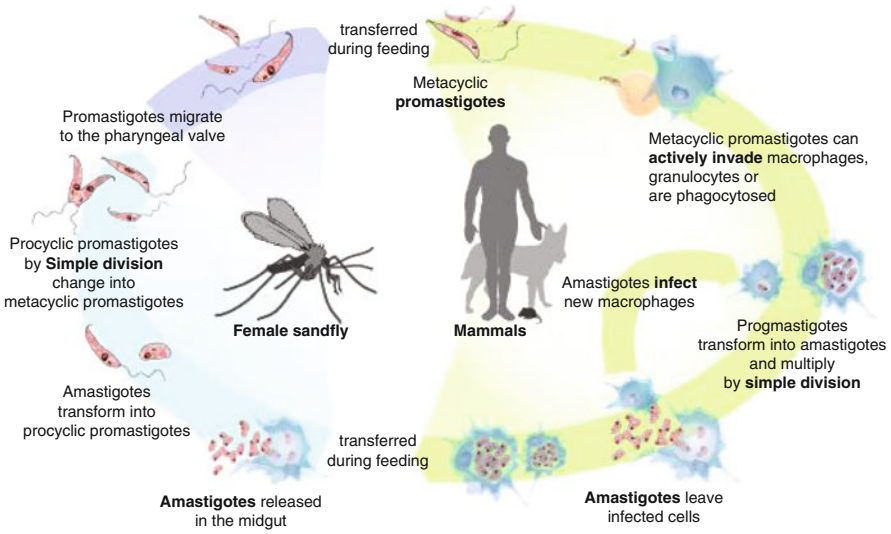

Fig. 11.2 Life cycle of *Leishmania* (Reproduced from Wikimedia Commons)

Human to animal transmission appears to be negligible. Transmission independent of the sandfly vector is rare and accounts for congenitally acquired leishmaniasis, or infection through needle-sharing or prick or cut accidents, and transfusion-acquired cases (Fig. 11.2).

11.3 Immunology

Each form of leishmaniasis has distinct clinical features. The individual features are relevant in order to design effective therapeutic interventions and to establish a prognosis. The bite of an infected sandfly may lead to no infection, subclinical or asymptomatic infection, self-healing lesions, localised cutaneous leishmaniasis (LCL), mucosal leishmaniasis (ML), mucocutaneous leishmaniasis (MCL), disseminated cutaneous leishmaniasis (DCL), anergic diffuse cutaneous leishmaniasis (ADCL) and visceral leishmaniasis (VL), also called "kala-azar", which, after treatment, is often followed by a dermal manifestation known as "post-kala-azar" dermal leishmaniasis (PKDL).

Parasite species determine the localization and some of the clinical features of the disease as they have developed successful strategies for surviving the antimicrobial activities of their host cell and may prevent the host from mounting an effective immune response.

Host immune factors determine disease patterns and severity, in a way similar to the concept of shifting immune profiles in leprosy [8, 9]. For instance, a patient with LCL is able to develop cell-mediated immunity (CMI) against the

parasite's antigenic determinants with local and peripheral production of chemo- and cytokines mostly belonging to the Th1 phenotype leading to macrophage activation allowing control of the disease. LCL patients can limit the disease and the number of parasites in their lesions. Exacerbated immune responses are associated with severe local inflammation and tissue damage. Th17+ cells or regulatory T cells (T regs) seem to play a crucial role in this balance [10–12]. In MCL the production of the chemo- and cytokines is not appropriately downregulated and induces more and more severe tissue damage. In DCL the patient may be completely anergic showing a complete lack of CMI against *Leishmania* antigens correlating with a heavy parasite load. HIV and leishmaniasis coinfection is a threat; in VL-endemic areas, HIV infection raises the risk of contracting VL at least 100-fold. And VL accelerates HIV replication and progression to AIDS.

11.4 Clinical Features of Cutaneous Leishmaniasis

Classically, weeks to months or even years (especially in "New World" CL), after the bite, a papule or nodule develops at the site of the bite, which is usually located on the exposed skin of the face, the arms or the legs. In most patients this grows slowly and becomes ulcerated in the course of weeks to months (Fig. 11.3). The ulcer may be covered by a crust, which usually drops off to reveal, typically, a relatively painless ulcer. Secondary bacterial infection should be suspected if the lesion is painful and/or shows purulent discharge, or a differential diagnosis must be considered. The ulcer may be dry or exudative. It usually heals spontaneously over months to years leaving an atrophic scar. Lesions may be single or multiple, and satellite lesions may occur as well as lymphatic "sporotrichoid" spread (nodular lymphangitis).

In "Old World" CL, mucosal lesions are rare but may in fact be caused by any species, especially in the immunosuppressed. HIV and leishmania coinfection causes atypical, extensive and treatment-resistant leishmaniasis. In Southern Europe HIV coinfection represents 70 % of visceral leishmaniasis cases caused by *L. infantum* [13]. In anergic diffuse cutaneous leishmaniasis (ADCL), disseminated macules, papules, plaques, nodules or diffuse skin infiltration are seen. ADCL occurs in *L. aethiopica* and is seen in other species in congenital, HIV- and transplant-related immunosuppression.

In the "New World" form, single or multiple primary lesions may heal spontaneously in 4–6 months, or secondary mucosal leishmaniasis may develop, especially in *L. braziliensis* and also in *L. panamensis* and *L. guyanensis* infection. True mucocutaneous leishmaniasis (MCL) occurs only in *L. braziliensis en L. panamensis* infection. It is caused by metastasis to the oral and upper respiratory tract mucosa by lymphatic (as in *L. aethiopica*) (Fig. 11.4) or haematogenic spread. Clinical signs appear months to over 10 years after skin infection and consist of nodules and infiltration leading to complete destruction of the nose. The pharynx, larynx and trachea may be involved as well. The differential diagnosis is extensive.

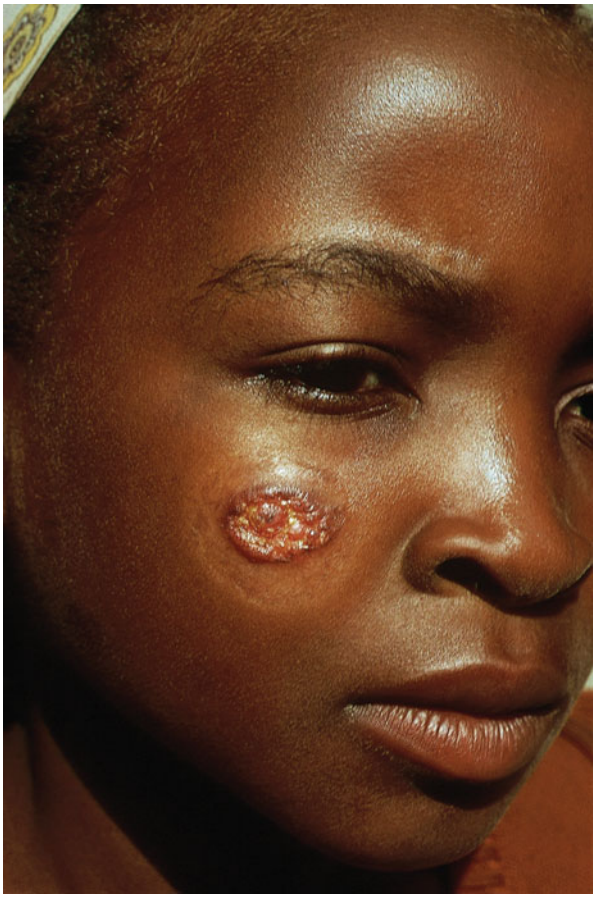

Fig. 11.3 Typical CL ulceration (Courtesy Dr. DL Leiker)

Male-to-female ratios of visceral leishmaniasis have been reported to be around 2:1. Males have higher rates of infection because of an increased environmental exposure to the habitat of the sandfly through occupation and leisure activity. In a few patients, a hypersensitivity reaction, lupoid leishmaniasis or *Leishmania recidivans* (relapsing leishmaniasis) is seen [14] (Fig. 11.5).

Identification of post-kala-azar dermal leishmaniasis (PKDL) is important because it demands long and toxic treatment and because PKDL patients may serve as a reservoir for visceral leishmaniasis (VL).

PKDL may appear after an episode of VL, independent of whether this is treated, partially treated or not treated [15]. Hypopigmented macules, papules, nodules, or facial erythema develop, usually starting around the mouth from where it spreads to other parts of the body depending on severity. It is mainly seen in Sudan and India where it follows treated VL in 50 % and 5–10 % of cases, respectively [16] (Fig. 11.6a, b). Though any organism causing kala-azar can lead to PKDL, it is most

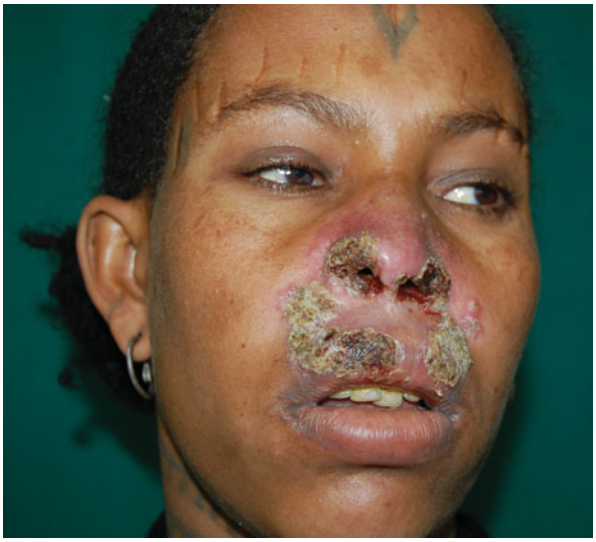

Fig. 11.4 Differential diagnosis in this patient was TB or leishmaniasis. Fine-needle aspiration was negative for leishmaniasis. She was treated for TB without success. Treatment for leishmaniasis was successful. Retreatment was required after relapse (Courtesy Dr. Dassoni Ayder Hospital, Mekelle, Ethiopia)

often associated with *L. donovani* which gives different disease patterns in India and Sudan. PKDL usually follows VL after 0–6 months in Sudan and after 2–3 years in India, though it may develop more than 10 years after VL. In the Indian variant, nodules enlarge with time and form plaques which rarely ulcerate. Nodules in the African variety often ulcerate as they progress. Nerve involvement without functional impairment [17] is common in the African variety but rare on the Indian subcontinent [18]. African PKDL may heal spontaneously; the Indian variety always needs treatment.

11.4.1 CL in Travellers

CL is seen in the local population in endemic regions and also in Western/Northern Europe, the USA and other areas of the world in immigrants, travellers and the military. Examples of the latter are epidemics of *L. major* and *L. tropica* in Dutch military personnel returning from Afghanistan in 2005 and *L. braziliensis* and *L. mexicana* in Dutch military personnel returning from jungle training in Belize [19, 20]. Among travellers, the adventurous traveller, ecotourist and the returning immigrant are most commonly affected, the latter often after visiting relatives in their country of origin.

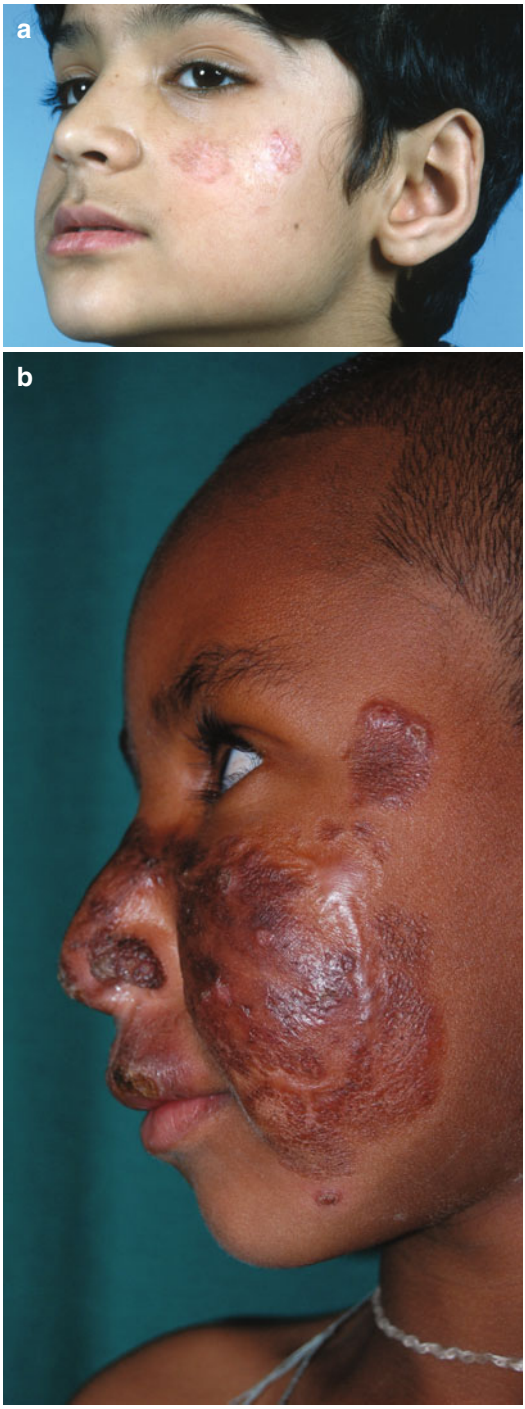

Fig. 11.5 (**a**) *Leishmania recidivans*, patient from Iraq (*L. tropica*). (**b**) *Leishmania recidivans* by *L. aethiopica* (Courtesy Dr. Dassoni Ayder Hospital, Mekelle, Ethiopia)

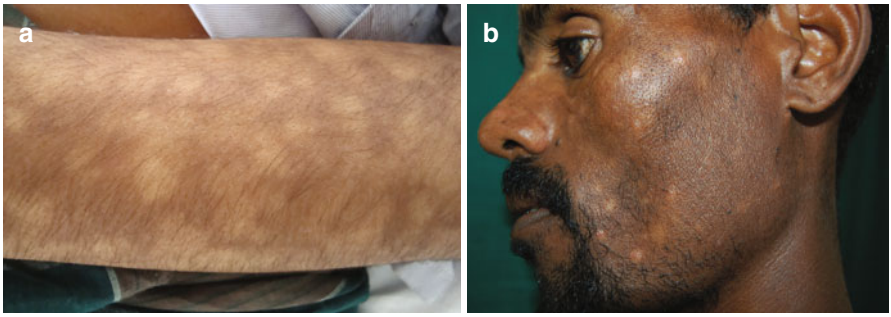

Fig. 11.6 (**a**, **b**) PKDL, hypopigmented macules (Courtesy Dr. Workalemahu Ayder Hospital, Mekelle, Ethiopia)

11.4.2 Old World Leishmaniasis [21]

11.4.2.1 *L. major*

L. major infections tend to be self-healing in the course of weeks up to 6 months, except in case of new foci [22], where a prolonged course is seen. Though they are usually painless, they often show inflammation and ulceration with exudate leading to scarring (Fig. 11.7). They cause CL in North Morocco, Algeria, Tunesia, Lybia, the Middle East, Pakistan, North India, Central Asia and Sub-Sharan Africa.

11.4.2.2 *L. tropica*

L. tropica is commonly transmitted through anthroponotic cycles in urban West Asian communities (Kabul, Peshawar); different strains induce different clinical spectra of leishmaniasis: cutaneous, mucosal, visceral and viscerotropic (meaning that no hepatosplenomegaly, pancytopenia, hypergammaglobulinemia and cachexia are seen). *L. tropica* CL patients present with often multiple painless dry ulcers which if untreated heal slowly with disfiguring scarring in a year to several years. In some patients a hypersensitivity reaction called lupoid leishmaniasis or leishmania recidivans (relapsing leishmaniasis) occurs. Here, chronic reactivation of lesions occurs at the edges of scars, lasting for many years [14] (Fig. 11.8). *L. tropica* is found in Eastern and sub-Mediterranean regions, particularly Northern Morocco, the Middle East, Saudi Arabia, Iraq and Central Asia, Afghanistan, Pakistan and Kashmir.

11.4.2.3 *L. aethiopica*

There are different clinical manifestations of infection ranging from self-healing ulcers, mucosal and mucocutaneous leishmaniasis and disseminated and anergic diffuse cutaneous leishmaniasis (ADCL). Lesions are usually nodular; they ulcerate

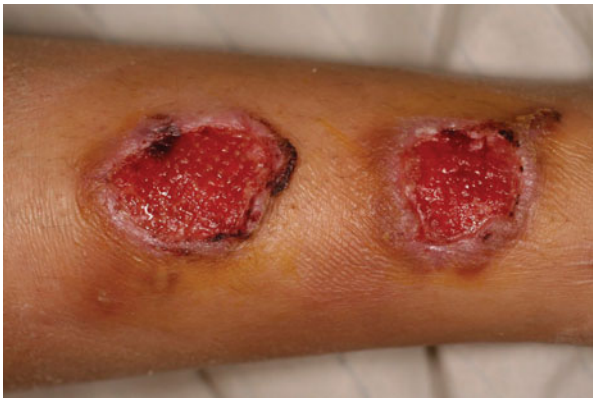

Fig. 11.7 CL by *L. major* in a patient from Pakistan (Courtesy Dr. Rosemarie Moser, Austria)

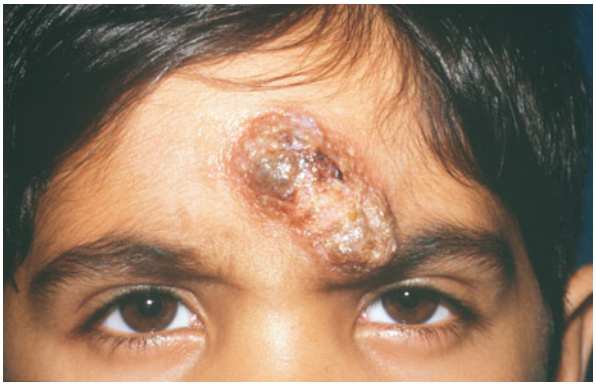

Fig. 11.8 CL by *L. tropica*. Young boy from Iraq

late if at all and take several years to heal. In ADCL multiple papules, nodules or plaques or diffuse infiltration of the skin occurs. ADCL is chronic and recurs after treatment. This may be associated with HIV infection (Fig. 11.9).

L. aethiopica can be found in Ethiopia, Kenya and Eastern Sudan and some claim in South West Africa and in some game reserves in Saudi Arabia too.

11.4.2.4 *L. donovani*

This species causes visceral leishmaniasis and consequently PKDL in India, Bangladesh and Nepal and in Sudan and Kenya. PKDL may occur in an anthroponotic cycle. For PKDL an African type and Indian type are described (Fig. 11.6). The Indian type is described in India, Bangladesh and Nepal and is highly prevalent in VL hyperendemic areas such as Bihar (90 % of the Indian patients) [21].

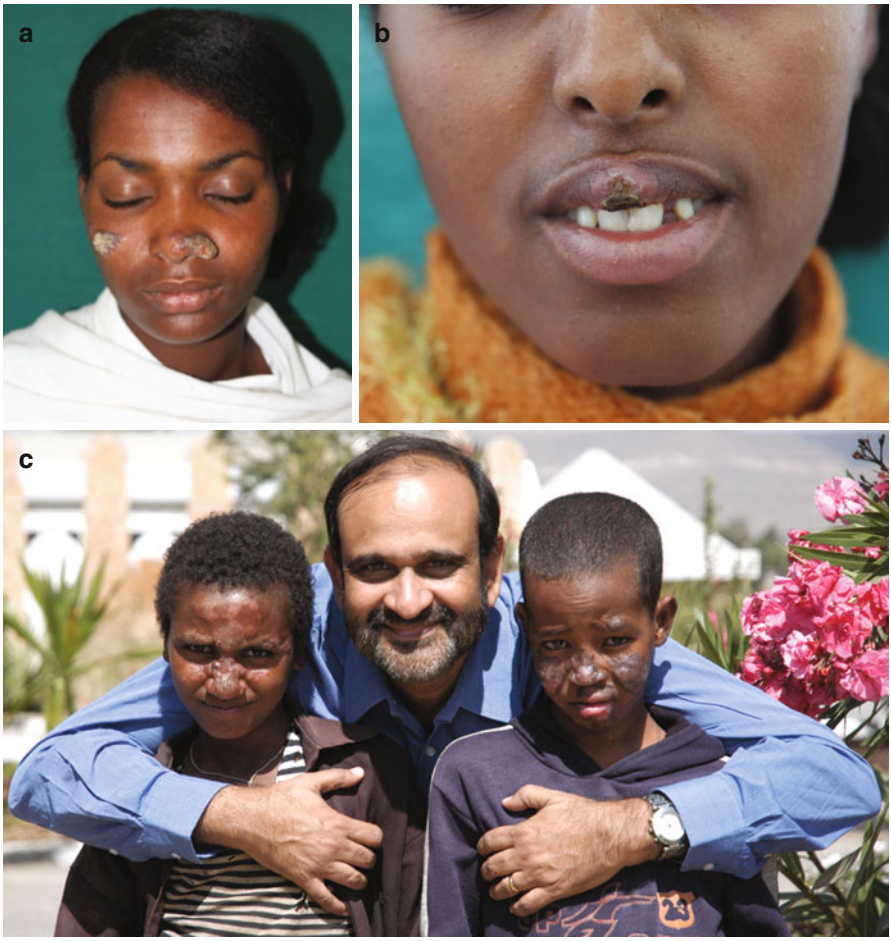

Fig. 11.9 (**a**) Cutaneous and mucosal leishmaniasis by *L. aethiopica* (Courtesy Ayder Hospital, Mekelle, Ethiopia). (**b**) Mucosal leishmaniasis by *L. aethiopica* (Courtesy Ayder Hospital, Mekelle, Ethiopia). (**c**) CL by *L. aethiopica* in two young boys. The boy to the *left* of Dr. S. Verma was in the past diagnosed and treated as leprosy. His lesions have become hyperpigmented because of the clofazimine treatment he received for leprosy

11.4.2.5 *L. infantum*

L. infantum is a common cause of CL in the Mediterranean basin and Southern European countries. Indigenous CL has been reported from the south of France and up to the border with Hungary. Vectors are encountered up to Paris and in the Rhine valley in Germany. If global warming continues, it is only a matter of time that the parasite too moves up further North in Europe. The hosts are mostly domestic dogs. Diverse clinical presentations of CL are seen, ranging from small papules to nodules and ulcers with (Fig. 11.16) or without inflammation (Fig. 11.10). Incubation time and persistence vary considerably. VL may be seen in HIV-infected patients and drug users where transmission may be anthroponotic through shared needles.

11.4.3 New World Species [23, 24]

11.4.3.1 *L.* (*V.*) *braziliensis*

Infection with *L. V. braziliensis* may lead to mucosal involvement in up to 10 % of the infections depending on the region in which it was acquired. Initial infection is characterised by a persistent cutaneous lesion that eventually heals, although as many as 30 % of patients report no prior evidence of skin involvement. Several years later, oral and respiratory mucosal involvement occurs, causing inflammation and mutilation of the nose, mouth, oropharynx and trachea. Small, ground-loving mammals, such as rodents, are the primary reservoirs of *L.* (*V.*) *braziliensis* and the vector transmits the parasite [25]. *L. (V.) braziliensis* is endemic in Central and South America; Belize, Guatemala, Honduras, Nicaragua, Costa Rica, Brazil, Colombia, parts of Peru, Ecuador, Bolivia, Argentina and Paraguay (Figs. 11.11 and 11.14). Sporadic cases have been reported in Surinam.

11.4.3.2 *L.* (*V*). *guyanensis*

This species occurs in Guyana, Surinam and the northern Amazon basin and causes pian bois (forest yaws). It is sometimes called bird-watcher ulcer, as it may be acquired by people who are present at dawn or sunset at the rim of the forest (Fig. 11.15).

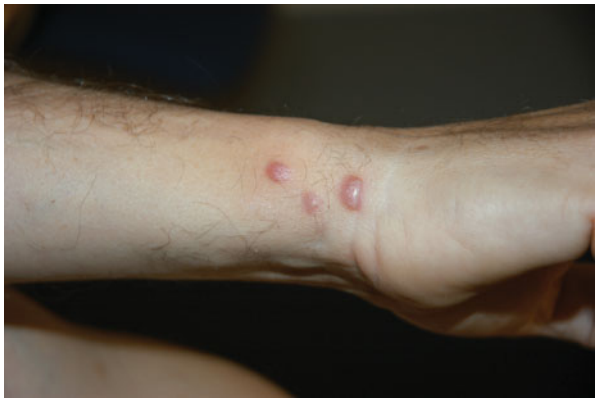

Fig. 11.10 CL caused by *L. infantum* from Portugal. Treatment with cryotherapy was curative; there has been no recurrence for 5 years

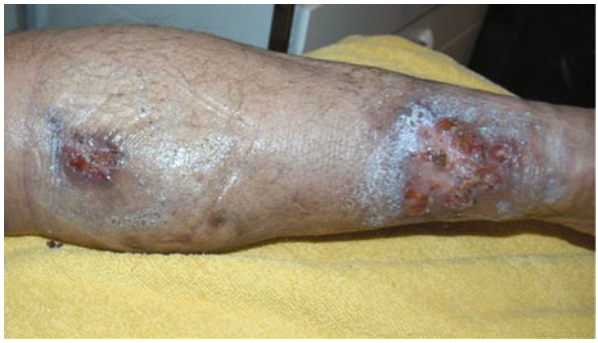

Fig. 11.11 CL by *L.* (*V.*) *braziliensis* (Courtesy Dr. Leo Visser LUMC, Leiden, the Netherlands)

L. V. guyanensis is sometimes described as complex, in which case it includes *L. V. panamensis*. The most common features are 1–6 ulcers usually located above the waist and minor lymphatic involvement; a few MCL patients have been seen.

11.4.3.3 *L.* (*V*). *panamensis*

This is a species, of the subgenus Viannia, which causes New World CL in Panama and adjacent areas of Central America and Colombia. It is considered to be part of the *L. V. guyanensis* complex. Like *L. V. braziliensis*, it may invade the naso-oropharyngeal mucosa after spreading from the skin lesion via the lymph and blood, causing lesions in the nasal septum, soft palate, uvula, tonsillar pillars, larynx, pharynx, nasal dorsum, lips and cheeks. The mucosal membrane most frequently affected is the nasal septum, mainly in the anterior region. Mucosal invasion may occur simultaneously with active skin lesions, but most often appear 1 or 2 years after the skin lesion.

11.4.3.4 *L. mexicana*

L. mexicana causes CL which manifests as an ulcer at the bite site; here the amastigotes do not spread and the ulcers become visible either a few days or several months after the initial bite. These ulcers heal spontaneously.

11.4.3.5 *L. amazonensis*

L. amazonensis is known to be associated with CL, ADCL and rarely VL in South and Central America. The pathological mechanisms responsible for the variable outcomes of infection in humans are not fully understood; however, it is generally agreed that long-lasting immunity against reinfection can be developed in these cutaneous leishmaniasis patients. ADCL manifests itself when the amastigote spreads cutaneously in those with defective T cell immunity. This type of infection responds very poorly to drug treatment and therefore may cause sores all over the host's body.

11.4.3.6 *L. venezuelensis*

L. venezuelensis is a rare cause of CL.

11.4.3.7 *L. chagasi*/*L. infantum*

Up to recent years, *L. chagasi* was thought to be a separate species. We now know that *L. infantum* migrated from Mediterranean countries to Latin America after the European colonisation of the New World where the parasites were picked up by

their current vectors in their respective ecologies and developed small phenotypic and genotypic differences [26, 27]. The infection may cause VL and CL and occurs mostly in children (VL under 5 years, CL older children).

The main relevant *Leishmania* species, sandfly species, global distribution, clinical manifestations, transmission route and mammalian host are summarised in Table 11.2.

11.5 Diagnosis

Diagnosis is based on the presence of parasites or their DNA in the tissues. The simplest sampling method is to take a (bloodless) smear from the edge (the bottom is often negative) of the lesion or after local anaesthesia making a small cut at the edge and scraping the cut rim. Alternatively a minimal amount of physiological salt is injected and aspirated again under some force. The material obtained is stained with Wright, Giemsa, Haemacolor or Leishman stains. On light microscopy, the amastigotes are seen as pale-blue oval bodies with a dark-blue nucleus and a small point-shaped kinetoplast within the cytoplasm of the tissue macrophages (Fig. 11.12).

Alternatively, the parasite can be cultured in a biphasic medium such as Novy-MacNeal-Nicolle (NNN). This is too time-consuming for routine analysis, but has been a reference technique for analysis of isoenzymes by electrophoresis since the early 1990s. Cultured strains can be compared with reference strains which have been collected over the years. The material obtained can also be inoculated into susceptible animals, such as guinea pigs. However it may take as long as 7–8 months before results are available. This method therefore is not practical.

Molecular identification has the advantage of species identification without the need to culture and is now common practice where these laboratory facilities are available. PCR techniques show high sensitivity when applied to skin biopsy or smear samples and therefore lead to fast diagnosis. They are now commonly used in

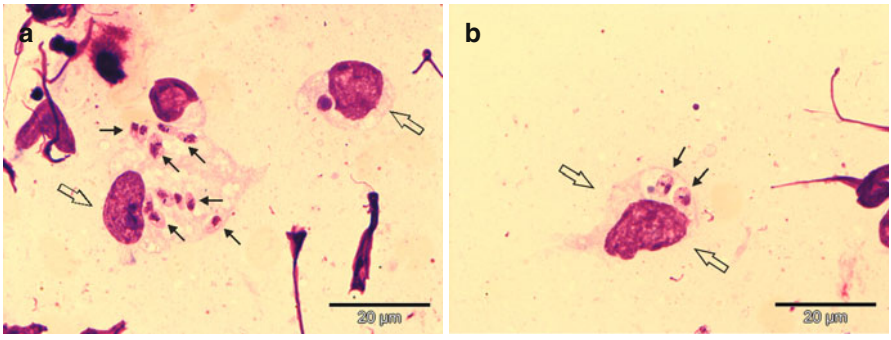

Fig. 11.12 (**a**, **b**) Giemsa-stained skin smear from the patient in Fig. 11.16. *Open arrows* indicate the phagocyte and the small filled arrows indicate two *Leishmania amastigotes*, in which not only a large nucleus is visible but also the characteristic kinetoplast (Courtesy J.J. van Hellemond and R. Koelewijn, Dept. Med. Microbiol. and Infect. Dis., Erasmus Univ. Medical Centre and Rotterdam Harbor Hospital, the Netherlands)

travellers in cases where species identification is needed to guide treatment. Leishmania DNA can be found in successfully treated cases up to years after treatment. In complex relapsing cases therefore culture and smear remain the preferred diagnostic methods because these methods detect viable parasites.

Histopathology is an important tool in CL despite the fact that histology may not show the parasites. Generally the microscopy shows a diffuse dermal infiltrate of histiocytes, lymphocytes, plasma cells and neutrophils with a hyperplastic epidermis. The parasites however are pathognomic (Fig. 11.13). LCL may have an infiltrate with characteristics of an epithelioid cell granuloma and few parasites, correlating with well-developed CMI. More generalised leishmaniasis may reveal a dermal infiltrate of vacuolated macrophages full of amastigotes, with the appearance of a macrophage granuloma.

PKDL demonstrates a mixture of chronic inflammatory cells; these can be arranged as a macrophage or epithelioid cell granuloma. In some cases neuritis is found affecting only lesional cutaneous nerves which show lymphohistiocytic

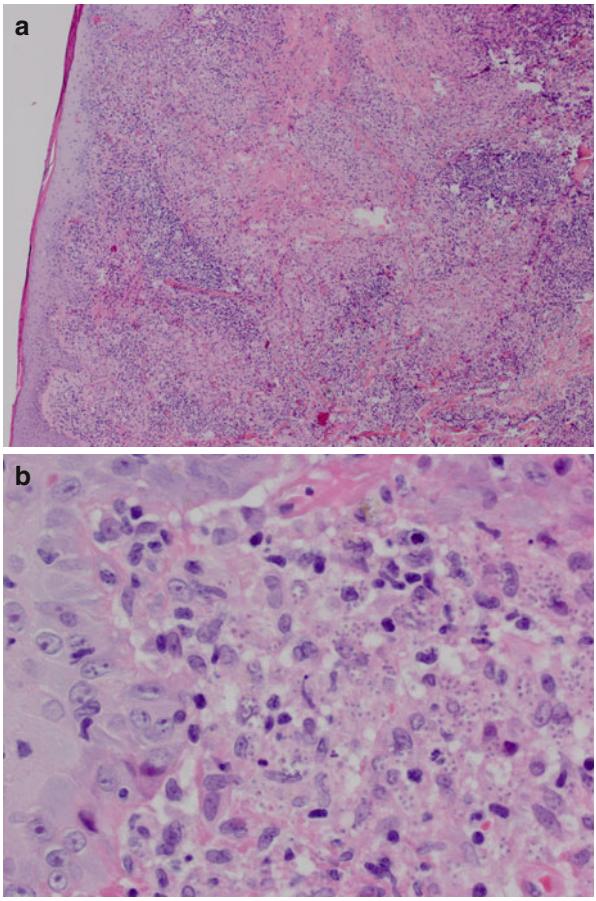

Fig. 11.13 (**a**, **b**) Skin biopsy of CL with a granulomatous inflammation showing many amastigotes in dermal histiocytes. (**a**) HE × 40. (**b**) HE × 400. (Courtesy of Dr S. Koljenovic and Dr V. Noordhoek Hegt, Department of Pathology, Erasmus Medical Centre, Rotterdam, the Netherlands)

infiltration and occasionally parasites (there is no impairment of sensation) [17]. There is no standard diagnostic test for PKDL; however histopathology, PCR, the leishmanin test and even serology may together with clinical suspicion and occurrence in an endemic area lead to the diagnosis [28]. The leishmanin skin test or Montenegro test is an intradermal skin test like the Mantoux test. It is usually produced from locally available leishmania promastigotes. It assesses the CMI against leishmania antigens and is positive in patients with CL and MCL and in patients who have had leishmaniasis. The sensitivity in patients with ulcers is over 90 %. In acute VL it may be negative.

Mucocutaneous lesions may also present with granulomatous changes, but here parasites may be difficult to detect.

Serology is not very useful in CL because of low sensitivity and variable specificity. When considering MCL however serology can be helpful, especially since few parasites will be found on direct examination or culture and rising antibody titres may herald relapse. PCR has been found to be the most sensitive diagnostic technique in MCL.

11.6 Prevention

To date no leishmania vaccine has been successfully produced. Systemic drugs used for treatment are too hazardous to use as prophylaxis. At present the only practical way to protect oneself against leishmaniasis is to use protective clothing, impregnated bednets and insect repellents (Box 11.2). Residual spraying of houses with long-lasting insecticides, e.g. pyrethroids, can reduce transmission. In some areas the intermediate host has to be eliminated [21, 24].

Box 11.2: Protection Against Sandfly Bites
Sandflies are most active from twilight till dawn but they may bite during the day if they are disturbed:

1. Wear protective clothing – long sleeves and trousers.
2. Use insect repellents containing N,N-diethyl-3-methylbenzamide (DEET) or picaridin.
3. Use permethrin- or deltamethrin-impregnated bednets.

11.7 Vaccination

There is some evidence that vaccination in the Middle East had already been used before the Middle Ages. Smears were taken from an infected lesion and inoculated on the buttocks of, in particular, girls, to prevent unsightly scars in the face.

The modern history of a leishmaniasis vaccine dates back to the 1940s with the same "leishmanization". The deliberate inoculation of infective and virulent *Leishmania* from the "exudate" of a lesion on the skin as in the past was used again. Crude, often not reproducible and unsafe, the method of leishmanization gave way to first-generation "modern" vaccines, consisting of killed or live-attenuated parasites with or without adjuvants.

The combination of autoclaved *L. major* promastigotes with BCG as adjuvant was tested in Iran against CL [29] and in Sudan against VL [30]. A limited efficacy was noted in conversion rates to positive skin reaction to leishmania antigen (leishmanin) and unexpectedly in boys (there may be a booster effect because boys are more exposed) [29]. Similar observations had been made earlier in Brazil using killed promastigotes without BCG [31].

The second-generation vaccines were produced much later in the 1990s, when researchers were able to genetically modify the leishmania species or use bacteria or viruses carrying the genes of leishmania species [32].

Thanks to genome sequencing, some methods use antigenic determinants from the parasite's surface to elicit an immunological response [33, 34]. Particular proteins that are expressed during more than one life cycle of the parasite are used. More recently, the ability to manipulate the Leishmania genome itself to create genetically modified parasites has been used, by introducing or eliminating genes.

The prospect of DNA vaccines emerged when it was discovered that directly injecting relatively small circles of DNA that encode for not yet known proteins could lead to a specific immune response, avoiding use of the parasite itself. Tested formulations of cationic solid lipid nanoparticles loaded by cysteine proteinase (CP) genes as a novel anti-leishmaniasis DNA vaccine delivery system are able to deliver immunogenic CP genes efficiently. This data proves the potential of this system as a promising DNA vaccine carrier for leishmaniasis to cover the main drawback of naked pDNA delivery which is rapidly eliminated from the circulation [35].

Eliciting an immune response to *Leishmania* is easier said than done. Many early vaccines that showed promise lacked the ability to elicit an effective protective immune response. This is complicated by the fact that *Leishmania* as a parasite lives within immune system cells (dendritic cells, macrophages). *Leishmani*a parasites survive within host cells, hiding and inhibiting the cell's own interior defence systems.

IDRI's (Infectious Disease Research Institute) VL vaccine candidate, LEISH-F3+GLA-SE, is a promising vaccine. This defined, purified, recombinant vaccine is comprised of two fused *Leishmania* parasite proteins and an adjuvant to stimulate a protective immune response against the parasite. After completion of a phase 1 clinical trial of 36 US adult volunteers to test safety and immunogenicity, the vaccine was shown to be safe and to induce potent immune responses in healthy volunteers. The IDRI vaccine is a highly purified, recombinant vaccine [36].

It has been suggested that CD8 T cells should be targeted for the development of a vaccine against infection caused by *Leishmania* (*Viannia*) parasites. TLR1/TLR2 modulation may be useful in vaccines where CD8 T cell responses are critical. CD8 T cells may have an essential role in mediating host defence, as CD8 depletion reversed protection in vaccinated mice; vaccinated mice depleted of CD4 T cells remained protected. Hence, vaccine-induced protection is dependent upon TLR1/

TLR2 activation resulting in the generation of antigen-specific CD8 cells and restricting IL-13 and IL-10 responses [37].

Spurred by global warming, mass migration and rapid urbanisation, cases are being reported in previously unaffected areas. Treatment is often toxic and ineffective, drug resistance is a threat and supplies may be limited. As discussed previously experimental vaccines show promise, and so commercial vaccines would provide a solution [36]. Yet for all we know about the way our own immune system works, there is still much to be learned before effective immunisation for leishmaniasis becomes a reality.

11.8 Treatment

Treatment options for CL are well described [38], but their reported efficacy is extremely variable and their evidence base is weak. Studies providing evidence are few in number and they are hampered by the great diversity in clinical features, natural course and treatment responses recorded. This in turn results from the parasites intrinsic and the patient's genetic variability [22]. Local or personal experience and availability of various drugs usually guide treatment choice. Apart from the WHO guideline [38], local guidelines are being developed in a number of countries [39–42] as there is no international consensus. Species-directed guidelines specifically directed towards travellers are being produced in several countries and international groups such as the European LeishMan consortium [43, 44, 207, 209, 210].

The choice of treatment for CL depends on a number of factors: the species of the parasite; the size, number and localization of the lesions; lymphatic spread or dissemination; the immune status of the host; cost and availability of the treatment; risk-benefit ratio; and patient preferences.

Treatment can be local (topical or intralesional), oral or parenteral. Sometimes a "wait-and-see" approach with just local wound care is justified. Local treatment is usually the first choice in Old World leishmaniasis, with the exception of CL caused by *L. aethiopica*, because of the risk of developing mucosal lesions and ADCL. New World CL is usually treated systemically because of the theoretical future risk of developing MCL. Here *L. mexicana* is the exception, as it may be treated locally.

Widely accepted treatment options are:

Local

- Cryotherapy
- Topical paromomycin sulphate
- Intralesional pentavalent antimony (with or without cryotherapy)
- Thermotherapy

Systemic

- Pentavalent antimonials (IV, IM)
- Pentamidine (IV, IM)
- Amphotericin B and liposomal amphotericin B (IV)
- Miltefosine (oral)
- Antifungal azoles (oral)

Other options have been advocated in small uncontrolled series and case reports but lack evidence. Examples are electrosurgery, curettage, excision, CO2 laser treatment, photodynamic therapy, imiquimod cream, allopurinol, dapsone, pentoxifylline and several plant-derived products. A summary of treatment options and recommendations is given in Table 11.3.

11.8.1 Cryotherapy

Cryotherapy kills the parasite and the infected cells and can be used on small, uncomplicated Old World lesions. A 10- to 30-s freeze-thaw-refreeze cycle repeated every 1–4 weeks is repeated up to the time of healing (up to four sessions usually suffice). This is effective in the majority of uncomplicated *L. tropica* and *L. major* infections. Cure rates in different studies varied from 60 % to 100 % [46–56]. Cosmetic results may be disappointing or reasonable. Cryotherapy may result in temporary or permanent depigmentation. There may be (usually temporary) sensory loss [57]. Combination treatment of cryotherapy with intralesional antimonials is more effective than either treatment alone [58, 59].

11.8.2 Topical Paromomycin (Sulphate)

Paromomycin (aminosidine) is a broad-spectrum aminoglycoside antibiotic which inhibits bacterial protein biosynthesis by binding to 16S ribosomal RNA. It also inhibits protein synthesis in *Leishmania* and may have other effects as well [60]. Its main side effect is irritation. Several studies in the past have shown some effect of paromomycin ointment as monotherapy in different bases and different treatment schedules [61–67]. Paromomycin with gentamycin was more effective than paromomycin alone against American species such as *L. panamensis* [68]. Paromomycin was effective in a 15 % preparation with or without gentamicin in Tunisia for 79–83 % of the patients as monotherapy for ulcerative *L. major* disease, placebo-treated patients healed in 58–59 % of cases [69]. Patients applied the ointment once daily for 20 days. Systemic exposure to paromomycin was less 10 % of that after IM administration, and local irritation was the only noted side effect. An inflammatory vesicular response is seen often and is considered helpful for resolution. Together with miltefosine there is potentiation of each other's activity [70].

11.8.3 Intralesional Pentavalent Antimony

Local infiltration with pentavalent antimony produces a maximum concentration in the lesions and has few systemic side effects, but does not reach metastatic infections. The basic aim is to fill the infected part of the dermis with sodium stibogluconate

Table 11.3 Treatment options for cutaneous leishmaniasis (CL) [20, 42, 43, 89]

The choice of treatment for CL depends on:			
1. The species of the parasite (expected spontaneous healing, risk of future DCL, ADCL, ML, MCL or VL)			
2. The size of the lesion (<= or > than 4 cm)			
3. Number of lesions (< or = > than 5)			
4. Localisation of the lesions (local/intralesional treatment near the eye, on the nose or ear and over joints may be too painful, difficult to perform or show side effects. Cosmetically or functionally relevant areas warrant treatment)			
5. Age of the patient (intralesional treatment is difficult in very young children)			
6. Lymphatic/sporotrichoid spread or dissemination			
7. The immune status of the host (HIV coinfection, use of immunosuppressive drugs)			
8. Cost and availability of the treatment			
9. Risk-benefit ratio			
10. Patient preferences			
Systemic treatment is generally indicated in mucosal lesions, lymphatic spread or dissemination and immunosuppression			
Old World	Clinical manifestations	Considerations	Treatment recommendations
L. major	CL, often spontaneous healing with residual scarring in 3–6 months, 10–20 % prolonged healing	1. In case of: Spontaneous improvement Small (≤ 4 cm) In cosmetically and functionally acceptable area Number of lesions <5 No immunosuppression Patient preference Follow-up possible 2. Alternative to 1 In children > age 5 and adults In areas not too painful (ear, nose, over joints) 3 and 4. Alternative to 1 and 2 5. All other cases and alternative in case of local treatment failure	1. Local wound care 2. Intralesional pentavalent antimony +/− superficial cryotherapy 3. Paromomycin ointment 4. Fluconazole 200 mg/day × 6 weeks 5. Oral miltefosine 2.5 mg/kg/day × 20 days OR parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks OR parenteral liposomal amphotericin B 5 doses of 3–4 mg/kg per dose over 10 days
New World			
L. tropica	CL, often spontaneous healing in a year or longer	1. In case of: Spontaneous improvement Small (<= 4 cm) In cosmetically and functionally acceptable area No immunosuppression In children > age 5 and adults In areas not too painful (ear, nose, over joints) 2. Alternative to 1 3. All other cases and alternative in case of local treatment failure	1. Intralesional pentavalent antimony +/− superficial cryotherapy 2. Thermotherapy (photodynamic therapy?) OR fluconazole 200 mg/day × 6 weeks 3. Oral miltefosine 2.5 mg/kg/day × 20 days OR parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks

(continued)

Table 11.3 (continued)

New World	Clinical manifestations	Considerations	Treatment recommendations
L. aethiopica	CL, ADCL, MCL	1. Systemic treatment usually required because of risk of mucosal spread and ADCL 2. May be an option in single localised CL (41)	1. Pentamidine 4 mg/kg/day 1–3 × per week for 4–8 weeks OR oral miltefosine 2.5 mg/kg/day × 20 days OR parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks Repeat course for ADCL when needed 2. Cryotherapy
L. infantum	CL, variable clinical presentations and duration, VL	1. and 2. In case of: Spontaneous improvement Small (<4 cm) In cosmetically and functionally acceptable area Number of lesions <5 No immunosuppression Absent lymphadenopathy Patient preferences 1. In children > age 5 and adults In areas not too painful (ear, nose, over joints) 3. Alternative in other cases or treatment failure Cave risk of VL especially in the immunocompromised	1. Intralesional pentavalent antimony +/− cryotherapy OR 2. Local wound care 3. Parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks OR parenteral liposomal amphotericin B 5 doses of 3–4 mg/kg per dose over 10 days OR oral miltefosine 2.5 mg/kg/day × 20 days
L. donovani	VL, PKDL	1. African type PKDL 2. Alternative in prolonged cases of African type PKDL First choice in Indian type PKDL	1. Local wound care 2. Liposomal amphotericin B 5 mg/kg total dose, given as single infusion or as 5-day course OR oral miltefosine 2.5 mg/kg/day × 20 days OR parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks
New World			
L. mexicana	CL spontaneous healing in 5–8 months	1. Spontaneous improvement Small (< 4 cm) In cosmetically and functionally acceptable area Number of lesions <5 No immunosuppression Patient preferences 2. Alternative to 1 In children > age 5 and adults In areas not too painful (ear, nose, over joints) 3. Alternative to 1 and 2	1. Local wound care 2. Thermotherapy (photodynamic therapy?) 3. Paromomycin ointment OR fluconazole 200 mg/day × 6 weeks

Table 11.3 (continued)

New World	Clinical manifestations	Considerations	Treatment recommendations
L(V) brazilienzis	CL, MCL	1. CL, MCL 2. Alternative for CL if Small (< 4 cm) In cosmetically and functionally acceptable area Number of lesions <5 No immunosuppression Patient preferences	1. Parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks OR parenteral liposomal amphotericin B OR oral miltefosine 2.5 mg/kg/day × 20 days 2. Thermotherapy OR paromomycin ointment
L. guyanensis	CL, spontaneous healing in 6–8 months	2. In case of treatment failure	1. Pentamidine 4 mg/kg/day × 3–4 days on alternate days OR oral miltefosine 2.5 mg/kg/day × 20 days 2. Parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks OR paromomycin/gentamycin ointment
L. panamensis	CL	2. In case of treatment failure	1. Pentamidine 4 mg/kg/day × 3–4 days OR oral miltefosine 2.5 mg/kg/day × 20 days 2. Parenteral pentavalent antimony 20 mg SbV/kg/day × 2–3 weeks OR paromomycin/gentamycin ointment
L. infantum/chagasi	Like *L. infantum* in the Old World	Like *L. infantum* in the Old World	Like *L. infantum* in the Old World
L. peruviana	CL, MCL,	Like *L.* (*V.*) *braziliensis*	Like *L.* (*V.*) *braziliensis*

There are very little consistent data on *L. peruviana*, *L. amazonensis and L. venezuelensis*

Sb(V). This means carefully infiltrating the area around the lesion, including the base of the lesion. A fine-gauge (25G) needle is used to inject the drug under pressure while the needle advances. Injection into the dermis is difficult, as the tissue space is small. The drug must not be injected into the subcutaneous tissue, where it is rapidly absorbed and does not reach the site of infection. The infiltration is performed in a V-shaped pattern, advancing the needle into the base of the lesion. The solution is injected under the edges of the lesion and the entire lesion until the surface has blanched. Treatment can be given every 2–7 days; generally a total of two to eight times is enough. Nonresponding lesions should be reviewed in 1 month, when a decision to switch treatment can be made. Intralesional infiltration is painful and requires some experience to perform [71]. Intralesional injections of 0.5–2.0 mL of 100 mg/ml Sb(V) have been shown to be effective when injected. When ten such injections were given to patients in Egypt, 85 % were cured within 3 months [72]. In India,

once-weekly injections of Sb(V) (5–7 weeks) were compared with a twice-weekly schedule (3–4 weeks), resulting in faster cure rates in the twice-weekly group, but similar, high, cure rates after 20 weeks (92 resp 96 %) [73]. The combination of cryotherapy and intralesional meglumine antimoniate produced better cure rates (89–91 %) than either cryotherapy (57–68 %) or intralesional meglumine antimoniate alone (44–75 %) in 634 patients infected with *L. major* or *L. tropica* [58, 59].

11.8.4 Heat Therapy

Because *Leishmania* species are temperature sensitive, local treatment with heat or cold provides an alternative to pharmaceutical therapy in suitable cases. In 2003, the FDA approved the ThermoMed device (ThermoSurgery Technologies, Inc) for the treatment of cutaneous leishmaniasis. This device heats the skin through radiofrequency waves directed to a specified area and depth, applying one or two cycles of heat (50 °C) for 30 s. This treatment requires local anaesthesia because it is painful and causes a second-degree burn which may easily become superinfected. A major advantage is that it is usually a single treatment. In a recent study conducted in Afghanistan involving CL caused by *L. tropica*, a single thermotherapy treatment showed similar healing rates and was as well tolerated as a 10-day infusion of SSG for *L. major* infection [74]. Although the lesions treated in this study were small, the initial results look promising. Further studies may demonstrate this to be a useful therapy for mild disease.

11.8.5 Other Local Treatments [75]

Application of imiquimod has, in some cases, led to a higher cure rate by boosting innate immunity. Imiquimod stimulates the production of nitric oxide by macrophages, which decreases the number of parasites in vitro [76]. Topical imiquimod has been used in combination with pentavalent antimonials for treatment of cutaneous leishmaniasis [76, 77]. CO2 laser has been described as well as excision, curettage, photodynamic therapy and electrocoagulation with or without other treatments but lack evidence. A topical formulation of miltefosine (Miltex) has been approved for use in the treatment of cutaneous malignancies. It contains 6 % miltefosine in a vehicle. There have been two clinical trials with Miltex for CL, one in Syria involving 16 patients with nodular CL (applied twice daily) and a second trial in Colombia involving 19 patients (applied once daily for 4 weeks). Neither trial demonstrated efficacy against CL [78].

Local treatment might be considered as a treatment option for travellers suffering from New World CL, provided that there are no risk factors for developing MCL such as multiple lesions, big lesions (>4 cm), localisation of the lesion on the head or neck and immunosuppression or acquisition of infection in the high Andean countries, notably Bolivia [75].

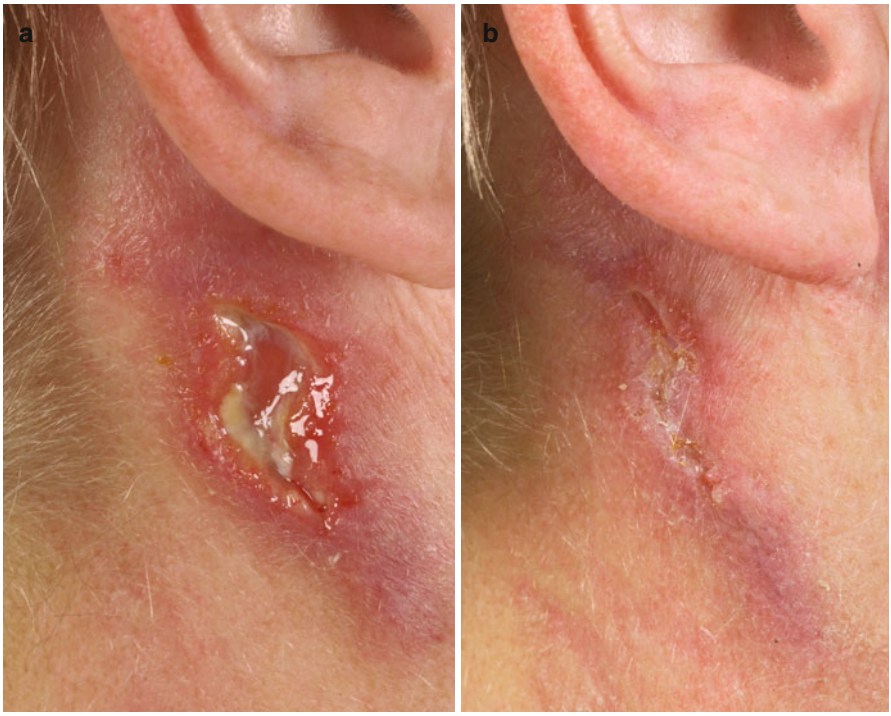

Fig. 11.14 (**a**, **b**) CL by *L. (V.) braziliensis* in a traveller from Ecuador. (**a**) Before treatment. (**b**) After 14 intravenous injections of SSb

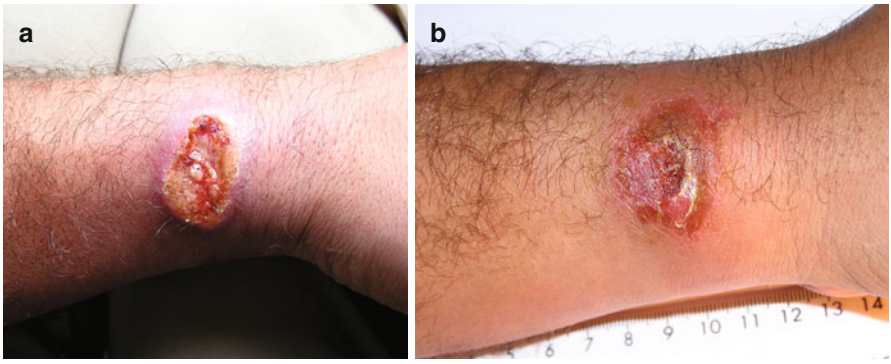

Fig. 11.15 (**a**, **b**) CL caused by *L. V. braziliensis complex* (most likely *L. V. guyanensis*) in a traveller from Surinam. The lesions typically follow skin lines. (**a**) Before treatment, (**b**) after four intravenous injections of pentamidine 4 mg/kg given every other day. Total clearance followed 3 weeks later

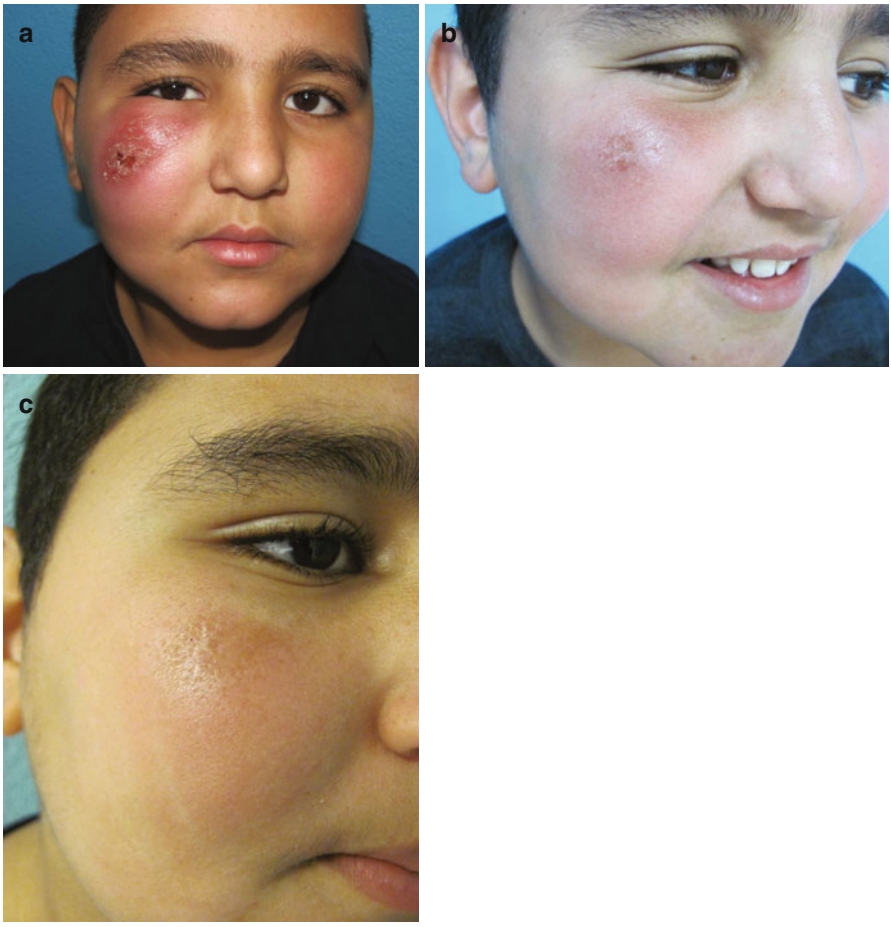

Fig. 11.16 (**a**–**c**) CL by *L. infantum*. This 12-year-old boy travelled to an area in North Morocco where *L. major* is endemic. PCR showed *L. infantum*, which was probably acquired when passing through Spain and Gibraltar. His skin lesion was teeming with parasites and showed a lot of inflammation, a year after he was infected. Due to the size of the lesion, he was treated systemically with miltefosine, 2.5 mg/kg/day × 20 days with very good response. (**b**) 6 months after treatment. (**c**) 1 year after treatment [212]

11.8.6 Systemic Treatments

Most of the knowledge on drug use in CL is acquired from treating VL.

The pentavalent antimonial compounds sodium stibogluconate (*Pentostam*) and *meglumine antimoniate* (*Glucantime*) are the first-line drugs used in the treatment of leishmaniasis. They are by most experts considered interchangeable, the result being that in some countries the one, in others the other drug is or is not available.

However, no in vivo studies have compared the efficacy and toxicity of these drugs where host variability has been controlled. Biochemical studies of *Leishmania* have detected differences between the two drugs with regard to DNA topoisomerase I inhibition, a phenomenon that has a possible impact on treatment efficacy. Animals inoculated with a parasite strain and treated with either drug showed a similar rate of lesion reduction, significantly more than untreated controls ($p < 0.01$). Parasite burden was also comparable, and no significant differences were found in the cure rate. The results confirmed clinical observations regarding the similar efficacy of the two drugs, as well as the higher local toxicity of Pentostam [79]. In vitro it is found that Glucantime-resistant *Leishmania* promastigotes are sensitive to Pentostam [80]. A decreased effect of Glucantime was described in Iranian patients when cutaneous leishmaniasis was complicated with a secondary bacterial infection [81].

Sodium stibogluconate (Sb(V)) has an intrinsic antileishmanial activity. Initial studies suggested that Sb(V) inhibits macromolecular biosynthesis in amastigotes [82] possibly via perturbation of energy metabolism due to inhibition of glycolysis and fatty acid beta-oxidation [83]. However, the specific targets in these pathways have not yet been identified. Sb(V), but not Sb(III), specifically inhibits type I DNA topoisomerase (enzyme that regulates the overwinding or underwinding of DNA) by inhibiting unwinding and cleavage. Sb(III)-mediated inhibition seems to be specific for *L. donovani* topoisomerase, since Sb(III) fails to inhibit calf thymus topoisomerase I and *Escherichia coli* DNA gyrase [84, 85]. This mode of action seems probable since in vivo sensitivity and resistance of *Leishmania* towards antimonial drugs have been shown to correlate with the effect of such a complex [86].

For VL Sb(V) resistance has reached such a level that the drug should no longer be used in relevant areas, specifically Bihar (*L. donovani* VL); however elsewhere resistance is also increasing [87]. In patients with HIV coinfection, Sb(V) has been replaced by deoxycholate amphotericin B/liposomal amphotericin B as first-line treatment [88, 89]. In Eastern Sudan the high post-kala-azar dermal leishmaniasis rate and relatively high relapse rate suggest that treatment with Sb(V) should be reconsidered [90, 91].

Trivalent antimony Sb(III), which was first used in 1912 in a case of mucocutaneous leishmaniasis, was replaced by the much less toxic pentavalent compounds Sb(V) in the 1920s [92]. Although Sb(III) is probably responsible for the antileishmanial activity of Sb(V), trivalent compounds seem of historical interest only. The presently available products, sodium stibogluconate (Pentostam®, Glaxo-Wellcome, UK) and meglumine antimoniate (Glucantime®, Specia, France), were developed in the 1940s. Sodium stibogluconate and meglumine antimoniate are complex compounds of pentavalent antimony Sb(V) complexed in carbohydrates [93].

Dose: Originally sodium stibogluconate was advised as an intramuscular injection of 10 mg Sb(V) per kg, once daily for 6–10 days and meglumine antimoniate at 28-mg Sb(V) per kg per day for 12–15 days, to be repeated after 10 days of rest [94]. The clinical impression that meglumine antimoniate was both more effective and more toxic may at least partly be explained by the much higher dose given [93].

Based on randomised comparative studies of patients with visceral leishmaniasis in Kenya [95] and India [96], with cutaneous leishmaniasis in Panama [97] and with mucocutaneous leishmaniasis in Brazil [98], the advised dose of Sb(V) was increased from 10 to 20 mg/kg/day with a maximum of 850 mg per day [99], a maximum later abolished; 20 mg/kg per day became the standard. The advice of Bryceson [100] based on body surface area for efficacy and toxicity is regrettably not followed [93].

Sodium stibogluconate (Pentostam®) comes in vials of 100 ml with 100 mg Sb(V) per ml. Dosing is relatively easy: a person of 55, 60 or 65 kg receives 11, 12 or, respectively, 13 ml. Meglumine antimoniate (Glucantime®) comes in ampoules of 5 ml with 85 mg SbV per ml, 425 mg SbV per ampoule. Dosing is more complicated: at 55 kg one should receive 2.6 ampoules, at 60 kg 2.8 and at 65 kg three ampoules. There might well be a tendency to give full ampoules resulting in either over- or underdosing [93, 101]. Generic Sb(V) is available and applicable [93].

Duration: Based on clinical experience [102, 103] and comparative studies [104], the duration of treatment was increased from the traditional 6–10 days to 30 days in Kenya and 40 days in India [105].

Once-Daily versus Multiple-Daily Administration: Traditionally antimony is administered once per day. Because of the short elimination half-life of about 2 h [106], twice- or thrice-daily administration would seem indicated as described by Bryceson [100]. Small studies on multiple-daily dosing in Kenya showed quicker disappearance of parasites from splenic aspirates and good tolerance [107]. Macrophages accumulate antimony during a 4-h exposure and retained it for at least 3 days, and amastigotes within macrophages have a higher antimony content 6 days after injection than immediately after the injection [108]. Clinically, antimony is effective at once-daily dosing. The duration of exposure is therefore better reflected by the terminal elimination half-life of 76 h than the initial half-life of 2 h as described by Chulay [107]. In more recent reviews [105, 109], multiple dosing per day is not mentioned anymore.

Toxicity: In the treatment of VL, toxicity of Sb(V) does not frequently lead to discontinuation of treatment [93]. Toxicity did not limit treatment in severely debilitated patients in Sudan during the war [110]. In VL, assessment of toxicity is difficult because abnormalities may be due to the disease, its treatment or the interaction between the two [93].

In patients with *Leishmania*/HIV coinfection, a high frequency of serious toxicity due to antimony is reported [88, 89, 111]: acute pancreatitis, acute renal failure and leucopenia. Frequently reported complaints are arthralgia and myalgia, generally in the second and third week of treatment, headache and abdominal pain. Acute pancreatitis has been reported both in immunocompromised and immunocompetent patients [112]. A systematic study of amylase and lipase levels during antimony treatment for leishmaniasis revealed that “chemical pancreatitis” regularly occurred with or without abdominal pain but without hypo- or hyperglycaemia [113]. In patients treated with Sb(V), who experience abdominal pain or nausea and vomit-

ing, amylase levels should be assessed, and if found increased, the treatment should be interrupted. After a few days, it can generally be resumed without further problems [114]. The cardiotoxicity of trivalent antimony is well known [115]. Long-term exposure to Sb(V) with conversion of Sb(V) to Sb(III) may lead to increase in cardiac calcium currents and toxicity [116]. High doses of Sb(V) are toxic: once-daily 30 mg/kg or 3×20 mg/kg per day led to QT prolongation, tachyarrhythmia and even death [117]. A dose of 20 mg/kg/day up to 30 days is considered safe [118], although ECG recording once or twice per week is advisable. A dose of 3×10 mg/kg/day, seemed toxic in India [119], however was well tolerated in Kenya [87], probably a genetic difference. In a series from India, 32 patients (10 %) treated with a standard course of Sb(V) experienced cardiotoxicity; in 20 patients this proved fatal [87]. However the variability in Sb(V) and Sb(III) content of the different products and different lots (generic) makes comparison difficult [93].

Efficacy: General conclusions on efficacy are difficult to draw; the dose and duration have to be adapted to the region, the race and the sensitivity pattern of the local parasite. The dose and duration have increased over time with the increasing problem of "antimony resistance". When given in the proper dose and for durations adequate for the area and the given parasite, antimony should be efficacious, with cure rates above 90 % in areas where secondary resistance is not widespread [93]. Rates of death, of non-response and of relapse should be low.

An overview of treatment results in the Mediterranean region up to 1995 mentions good treatment results with unresponsiveness and relapse in a few cases only [120], but in Italy, since 1995, meglumine antimoniate was gradually replaced by lipid amphotericin B. Since 2001 almost all patients are treated with liposomal amphotericin B. Reasons were toxicity of antimony drugs, increase in failure rates and cost-effectiveness of lipid amphotericin B, mainly because of much shorter hospitalisation [121].

Definite "cure" should probably be defined as clinical, haematological and biochemical response and no relapse at 6 months of follow-up [93]. PKDL complicates the matter. In Sudan, PKDL is seen frequently during or shortly after treatment. It often does not require treatment and generally clears in 6 months [122]. In India, PKDL may occur many years after treatment of VL. It requires treatment, in the past with many courses of Sb(V) but now, with increasing Sb(V) resistance with alternative treatment [123]. In Tunisia a review was done of the antimony treatment of CL. Since the treatment with antimony gave an unacceptable percentage of side effects (25 %) and intolerances (15 %), it was concluded that Sb(V) systemic has no place in the treatment of this basically self-healing disease [124].

Summary: Pentavalent antimony is given as intramuscular or intravenous injection in a dose of 20 mg Sb(V) per kg body weight once daily. The minimal duration should be 20 days in the Mediterranean region; elsewhere longer treatment up to 40 days (India) is advised, without interruption [109, 125]. Weekly assessment of haematological and biochemical parameters (haemoglobin, leukocytes, platelets, transaminases, amylase, lipase, creatinine) and a weekly ECG are recommended.

Pentavalent antimonials should not be used when there is pre-existent cardiac, hepatic or renal pathology or in pregnancy. Treatment may have to be interrupted because of severe thrombocytopenia (very rare), increase of liver enzyme or amylase levels to more than five times the normal values (rare) or QT interval prolongation and dysrhythmias (rare) or severe arthralgia.

11.8.7 Pentamidine

Pentamidine isethionate, a diamidine drug (Pentacarinat®, Aventis, France), damages the kinetoplast DNA mitochondrial complex, blocks RNA and protein synthesis and leads to apoptosis [126]. It is the drug of choice for the treatment of Ethiopian CL [127, 128] and for the treatment of patients with *L.* (*V.*) *guyanensis* and *panamensis* [129]. It is of limited value in the treatment of visceral leishmaniasis when miltefosine (lipid-associated) amphotericin B, antimonials and aminosidine are available. Parenteral pentamidine should be administered via IV infusion over 60–120 min or via deep IM injection. Usually three or four injections of 4 mg/kg separated by an interval of 48 h in otherwise healthy patients with CL are well tolerated. All adverse effects were reversible, and no cases of new diabetes mellitus were found among >2,200 patients observed with a low-dose regimen [45, 129, 130]. However the higher dosages needed for the treatment of mucosal leishmaniasis >2,000 mg may cause diabetes mellitus [131]. This was seen before in the treatment of Ethiopian leishmaniasis, not for pentamidine isethionate but for pentamidine mesylate [132]. Probably this could be explained by the higher-dosage pentamidine in the latter preparation (Kager P. personal communication). For *L. aethiopica* pentamidine isethionate still remains the drug of choice as already recommended by Bryceson, 4 mg salt/kg body weight IM once weekly, despite the small risk of side effects [133–135].

Toxicity: The toxicity of high-dose pentamidine precludes wide application. In up to 50 % of the patients, adverse effects occur. These include hypotension, phlebitis, pain at the injection site, abscess formation, cardiac effects with arrhythmias, ventricular tachycardia, anaemia, leukopenia and thrombocytopenia, increase in liver enzyme activity, nephrotoxic effects, kidney failure, pancreatitis, hypo- and hyperglycaemia, permanent diabetes mellitus and, in an unknown percentage of cases, even coma and death [136]. However, toxicity seems to be dose related [137].

Dose, Duration, and Efficacy: In India, pentamidine has been used to some extent in the treatment of visceral leishmaniasis, and in the early 1980s, cure rates with relatively short courses of 15 injections were 95–100 %. In the late 1980s and early 1990s, pentamidine monotherapy showed a cure rate of 78 % only [138]. Another study on Sb(V)-unresponsive patients showed a cure rate of 77 % after 20 injections [102]. Toxicity with these high-dose courses was considerable. Because of the decreasing effectiveness and the considerable toxicity, pentamidine was considered unsuitable for first-line treatment in India [139].

11.8.8 Amphotericin B and Liposomal Amphotericin B

Amphotericin B deoxycholate is a polyene antibiotic used in systemic fungal infections. It is very active in vitro and in vivo against *Leishmania* parasites. It binds to sterols (primary ergosterol) in the plasma membrane of fungi and *leishmaniae*. Mammalian and leishmanial membranes both contain sterols, a primary membrane target for amphotericin B. Because mammalian and leishmanial membranes are similar in structure and composition, this is a mechanism by which amphotericin B causes toxicity in humans, by binding to the cholesterol [140]. The activity of amphotericin however is higher against ergosterol than against cholesterol. Amphotericin B molecules can form pores in the host membrane as well as the *Leishmania* membrane. This impairment in membrane barrier function can have lethal effects.

It has to be given by intravenous infusion. Administration is often accompanied by adverse effects ranging from fever and chills to severe anaemia, hypokalaemia and renal failure [141, 142]. These can be reduced by adequate hydration and infusion over several, even 24 h [143]. Administration however requires hospitalisation. Until the early 1990s, its use in leishmaniasis was almost exclusively restricted to MCL [141], for which it is an effective treatment [98]. In the early 2000s, amphotericin B became the first-line treatment of VL in Bihar, India, because of antimony resistance, failure and toxicity of pentamidine and non-availability of alternatives [144, 145].

In search of less toxic, possibly more effective formulations, lipid-associated formulations of amphotericin B were developed. Two products, liposomal amphotericin B (Ambisome®, Nextar, San Dimas, California, USA) and amphotericin B lipid complex (formerly ABLC, now Abelcet®, Liposome Company, Princeton, New Jersey, USA), have been studied extensively [93]. Of a third preparation, amphotericin B colloidal (or cholesteryl) dispersion (formerly Amphocil®, now Amphotec® Intermune, Sequus Pharmaceuticals Menlo Park, California, USA), few reports are available [93]. Other preparations include liposomal amphotericin B produced in India and "heated amphotericin B" [93, 145].

Dose, Duration, and Efficacy: Amphotericin B is very effective both in patients not yet treated and in those not cured after treatment with antimony or pentamidine. High cure rates are obtained in India but African and New World strains seem less susceptible [145]. A dose of 1 mg/kg body weight daily, infused in 2 h for 20 days or on alternate days for 30 days, is recommended [145] also for children and pregnant women [146]. Treatment of CL should be decided by the clinical presentation of the lesions, etiological species and its potential to develop into ML [145]. Febrile reactions (80–100 %), loss of appetite (up to 30 %) and thrombophlebitis (up to 18 %) are frequent but severe toxicity, nephrotoxicity, is rare [145]. The incidence of adverse reactions was not dose dependent [146] and not different in a daily or alternate-day schedule [147]. Incremental doses were not necessary [148]. Several patients died of cardiac complications when amphotericin B was given immediately after a course of Sb(V). There were no deaths when an interval of 10 days was allowed for [149].

Dose, Duration, and Efficacy of Lipid-Associated Amphotericin B: Liposomal amphotericin B (Ambisome®) has been shown to be effective and non-toxic in the

treatment of immunocompetent and immunocompromised patients. L-AmB at a total dose of 18–21 mg/kg is the recommended regimen in the Mediterranean region and South America. It is also the treatment of choice for HIV-VL coinfection. Studies in Italy in 88 immunocompetent patients, 56 of these children, led to the recommendation of a total dose of liposomal amphotericin B of >20 mg/kg, given in five doses of 3–4 mg/kg per dose over 10 days. Adverse reactions were not frequent and not serious [150]. In cases of severe and complicated visceral leishmaniasis with cachexia and coexistent other infections, treatment of 14 days at 3–4 mg/kg/day is probably to be advised [151]. WHO-supported trials resulted in the recommendation that for India and Kenya, liposomal amphotericin B should be used at a dose of 2 mg/kg/day on days 1–4, and on day 10, and for Brazil at 2 mg/kg/day on days 1–10 [152]. Liposomal amphotericin B is approved by the FDA for treatment of visceral leishmaniasis. Although various regimens have been suggested in the published literature, the FDA-approved regimen for immunocompetent patients consists of 3 mg/kg daily, by IV infusion, on days 1–5, 14 and 21 (total dose of 21 mg/kg). The FDA-approved regimen for immunosuppressed patients consists of 4 mg/kg daily on days 1–5, 10, 17, 24, 31 and 38 (total dose of 40 mg/kg). Some immunosuppressed patients may need even higher total doses and/or secondary prophylaxis (chronic maintenance therapy), in particular, HIV-coinfected patients with CD4 counts <200 cells/mm^3 [93]. However, standard approaches to antileishmanial treatment have not been established. But 3–4 mg/kg/day on days 1–5 and 10 may suffice for European, African and Brazilian VL, while in India a dose of 2–3 mg/kg/day seems sufficient [88]. So one might well advise on 3 mg/kg/day on days 1–5 and day 10 for all immunocompetent patients with VL [93]. Infusion of liposomal amphotericin B, 10 mg/kg once per day for 2 days, cured 40 of 41 children in Greece [153]. In India an open randomised study comparing a single infusion of 5 mg liposomal amphotericin B ($n=46$) and 1 mg/kg per day for 5 days ($n=45$) showed "cure" at 6 months in, respectively, 42 (91 %) and 42 (93 %) patients [154]. Locally produced liposomal amphotericin B and amphotericin B dissolved in Intralipid® solutions have been used in small numbers of patients [137, 155]. Amphotericin B lipid complex (Abelcet®) at 3 mg/kg/day for 5 days cured all patients in a study in India, but it was economical to treat at 1 mg/kg/day for 5 days and to retreat those who relapsed (3 of 19 in the study) with 2 or 3 mg/kg/day, again for 5 days [93, 141]. Almost all patients treated with amphotericin B lipid complex experience fever and chills during the first infusion. During later infusions reactions were less frequent and less severe [141].

Amphotericin B remained as the single most effective agent [156] until the advent and availability of miltefosine [157]. Comparison of amphotericin B (group 1), liposomal amphotericin B (group 2) and amphotericin B lipid complex (group 3) showed comparable cure rates. There are however some differences in cost [158].

Amphotericin B colloidal dispersion (ABCD, Amphocil®) 2 mg/kg/day for 7 days was used successfully in Brazil in small studies [159]. ABCD at a total dose of 7.5 mg/kg, 10 mg/kg or 15 mg/kg all given over 6 days gave similar cure rates of 97 %, 96 % and 97 %, respectively, in a randomised study of 405 patients in India [160]. In the two high-dose groups, two patients discontinued treatment because of toxicity. Fever and chills occurred in more than half of the patients in all groups.

In a more recent randomised multicentre trial, ABLC 3 mg/kg/day, for 5 and 10 days, and Sb(V) 20 mg/kg/day for 28 days were compared [111]. Cure rates were low and side effects numerous, leading to discontinuation of treatment.

Summary: Amphotericin B and lipid-associated amphotericin B preparations are highly effective in the treatment of VL and some of the New World MCLs, both for newly diagnosed patients and for antimony and pentamidine-resistant cases. For CL it is usually not needed but effective. Cure rates close to 100 % are to be expected [93]. The advised dose of amphotericin B is 1 mg/kg/day, infused over 2 h for 20–30 days on alternate days for 10–15 doses. Short courses of liposomal amphotericin B at a dose of 3–4 mg/kg/day on days 1–5 and day 10 are effective, and in India, short courses of low-dose liposomal amphotericin B at 5 mg/kg total dose, given as single infusion, or as 5-day course cured >91 % of 91 patients [93]. Two infusions of liposomal amphotericin B (10 mg/kg) may be a sufficient treatment for children with Mediterranean VL [153]. Lipid-associated amphotericin B is less toxic than amphotericin B but it is very expensive. It does require shorter hospitalisation which may offset the high costs of the drug in countries where hospitalisation is expensive, i.e. in Europe and the USA [161].

Liposomal amphotericin B is the least toxic and might even be given on an outpatient basis or in a day-care setting. Amphotericin B lipid complex probably requires a short course of 5 days at a low dose of 2 mg/kg/day, but has infusion-related effects and may require hospitalisation. Data on amphotericin colloidal dispersion are relatively limited. The frequent infusion-related adverse events also require hospitalisation [93]. For *Leishmania*/HIV-coinfected patients and immunocompromised patients in general, treatment should be extended to 14 days and longer as needed, and "secondary prophylaxis" with biweekly or monthly doses is required until CD4 counts are 350 per mm3 and higher [93].

11.8.9 Miltefosine

Miltefosine (Impavido®) (Zentaris, Frankfurt am Main, Germany), hexadecylphosphocholine, was developed as an oral antineoplastic agent. It is an alkylphosphocholine drug with demonstrated activity against various parasite species and cancer cells as well as against some pathogenic bacteria and fungi. It is a new drug for visceral and cutaneous leishmaniasis. The cure rate of miltefosine in phase III clinical trials is 95 % [93]; studies in Ethiopia show it is also effective in Africa [162]. In an observational study of 34 Dutch soldiers with *Leishmania* major infection who had failed to respond to intralesional antimony, 30 responded to miltefosine [163]. In HIV and *Leishmania* coinfection, even in resistant cases, two-thirds of the cases have been shown to respond to miltefosine. Clinical trials in Colombia showed a high efficacy for CL [42]. In mucocutaneous cases caused by *L. braziliensis*, it has shown to be more effective than other drugs. For over 10 years, it has been licensed in India for the treatment of VL. It is the first and still the only oral drug that can be used to treat VL and CL.

Its mode of action in leishmaniasis is not yet fully understood; induction of apoptosis of the parasite seems plausible [164]. However, it is not yet established whether miltefosine can bring about apoptosis-induced death in all the forms of the *Leishmania* parasite. *Leishmania* species show different sensitivities to miltefosine. *L. donovani* parasites from Nepalese patients were sensitive, whereas *L. braziliensis* complex parasites from patients in Peru were insensitive with the exception of *L.* (*V.*) *lainsoni* parasites [155]. A study in Iran, comparing miltefosine to IM meglumine antimonite in CL, showed comparable efficacy (81.3 vs. 80.6 %) [165]. Oral miltefosine, 50 mg thrice daily for 60 days or twice daily for 90 days, could be an effective treatment for PKDL [166]. Miltefosine shows better tolerance than parenteral alternatives. Also the expense and inconvenience of hospitalisation are avoided, which makes it an attractive alternative. In October 2006, it received orphan drug status from the US Food and Drug Administration.

Dose, Duration, and Efficacy: From a pilot and a phase II study, it transpired that miltefosine 100 mg/day for 4 weeks (meaning 2.5 mg/kg/day for a 40-kg patient, the mean weight of an adult patient in India) was efficient and practicable (miltefosine is dispensed as 50-mg capsules) [167]. Main side effects are gastrointestinal disturbance in the first days of treatment, which does not affect the efficacy. Vomiting was common in the miltefosine-treated patients (38 %); diarrhoea was reported in 20 % [168]. In an open-label, randomised phase III trial comparing miltefosine 2.5 mg/kg/day for 28 days (299 patients) to the standard treatment, amphotericin B 1 mg/kg/day on alternate days for 15 injections (99 patients), efficacy of miltefosine at 6 months was 94 % and of amphotericin B 96 % in the intention to treat (ITT) analysis [169]. Reversible ASAT and creatinine increases were seen in, respectively, 17 % and 16 %. Miltefosine is teratogenic. To the partners of the male patients treated with miltefosine, 48 live infants without congenital abnormalities were later born. However, miltefosine appears to be eliminated at a slower rate than was previously thought. It was still detectable in human plasma samples taken 5 months after the end of treatment [170]. The presence of subtherapeutic miltefosine concentrations in the blood beyond 5 months after treatment might contribute to the selection of resistant parasites, and, moreover, the measures for preventing the teratogenic risks of miltefosine must be reconsidered [171]. This may led to some reluctance to take miltefosine. With the potential of development of resistance because of the long half-life of the drug [172], an appeal was made to restrict prescription to a supervised public sector distribution system, free of charge, like for tuberculosis [173].

Thirty-nine *Leishmania*/HIV coinfected patients (38 European, one Indian), who had received various antileishmanial treatments, were treated with miltefosine 100 mg/day for a mean of 55 days. Mean weight was 59 ± 11 kg, range 43–99 kg; thus the dose was relatively low [93]. Thirty-three also received HAART. After the "standard course" of 4 weeks, 16 were "cured" and nine were improved. Most relapsed and needed further treatment. Twenty-two received a second, nine a third and four a fourth course. Some patients had prolonged, uninterrupted treatment up to >2 years [174]. In Ethiopia where the incidence of *Leishmania*/HIV coinfection

is increasing, miltefosine and generic Sb(V) were compared in an open, randomised trial [162]. 580 male patients were enrolled to receive miltefosine 100 mg/kg/day, 28 days (290 patients) or i.m. Sb(V) at 20 mgSb/kg/day, 30 days (290 patients). HIV seroprevalence was 29 % in the 375 patients who consented in testing. The 34 patients who had already been treated with Sb(V) were equally divided to the two treatment groups. There was no difference in initial cure rate (miltefosine 88.3 % and Sb(V) 87.6 %), but the mortality was lower in the miltefosine group (2.1 % than in the Sb(V): 9.7 %). Initial treatment failure (end of treatment) was more frequent in the miltefosine group: 7.9 % versus 0.7 %. There were more initial failures in HIV-infected patients (17.5 % versus 4.6 %), and there was a higher seroprevalence in those who failed than in those who were cured (63.3 % versus 26.0 %). Relapses were more common in the miltefosine group, 10.3 % vs. 2.4 %. Excluding those who were lost to follow-up (per-protocol analysis), cure rates in non-HIV-infected patients were comparable: 93.4 % (miltefosine) and 94.6 % (Sb(V)) [162].

Miltefosine was considered an acceptable alternative to Sb(V) even in this population with many severely ill patients with massive splenomegaly, anaemia, malnutrition, inability to walk unaided and HIV coinfection. The high death rate in this study is likely to be a reflection of the severity of disease in these patients [93]. In the miltefosine studies in India, severely ill patients and HIV-infected patients were excluded, and the death rate was low, <0.2 %.

An open-label, randomised, phase III clinical trial was carried out in the Colombian army. Miltefosine, 50-mg capsule, was taken orally three times per day for 28 days ($N = 145$) or Sb(V), 20 mg/kg body weight per day for 20 days by intramuscular injection ($N = 143$). The efficacy of miltefosine by protocol was 69.8 % (85/122 patients) and 58.6 % (85/145 patients) by ITT. For Sb(V), the efficacy by protocol was 85.1 % (103/121 patients) and 72 % (103/143 patients) by ITT. No association was found between drug efficacy and *L.* (*V.*) *braziliensis* or *L.* (*V.*) *panamensis* species of *Leishmania* responsible for infection [175]. In this study miltefosine was inferior to Sb(V). However side effects of Sb(V) were numerous [93].

Toxicity: Vomiting and diarrhoea are frequent adverse events and are dose related. In dose-finding pilot studies in India [176], a dose of 200 mg/day (about 4 mg/kg/day) appeared to be the maximum tolerable dose; one of five patients treated with 250 mg/day died of nephrotoxicity on day 21. Four patients (one of five receiving 200 mg/day and three of five receiving 250 mg/day) discontinued treatment because of vomiting. In two more patients receiving 200 mg/day, considerable increases in creatinine levels occurred.

Of 45 patients treated with 100-, 150- or 200-mg miltefosine per day, 28 days, 44 were cured (one was lost to follow-up). The patients who discontinued treatment from day 7 to 17 were also cured. Reasons to discontinue were vomiting (2), diarrhoea (2) and hepatotoxicity (1,200 mg) and nephrotoxicity (1,200 mg). Thirty-one had at least one episode of vomiting, mostly in weeks 1 and 2, and 24 experienced diarrhoea also mostly in weeks 1 and 2. There was reversible nephrotoxicity in the

first 3 weeks in 13 and mild rise of ASAT in the first week. There were no indications of ophthalmologic toxicity as seen in animal studies [177]. Animal studies showed embryotoxic, foetotoxic and teratogenic effects and also reproductive toxicity in male rats. Pregnancy is a contraindication, and women of reproductive age should use effective contraception up to 4 months after treatment [178]. Sperm examinations in Colombian patients treated with miltefosine for cutaneous leishmaniasis appeared normal so it was concluded that there was no concern for male reproductive toxicity [179]. Conversely, recently it was shown in a retrospective, observational study that a large proportion of miltefosine-treated males (1.3–2.1 mg/kg/day, 28 days) experienced a substantial treatment-related reversible reduction of ejaculate [163].

Summary: Miltefosine as the first available oral treatment of visceral leishmaniasis is a very promising development. Toxicity (vomiting and diarrhoea) probably limits the dose to a maximum of 200 mg per day. Treatment duration is not well established; several patients who stopped treatment before 28 days because of adverse events were cured without further treatment [93]. Miltefosine is an effective treatment of visceral leishmaniasis in immunocompetent patients in India at a dose of about 2.5 mg/kg/day and duration of treatment of 28 days. Dose and duration for visceral leishmaniasis in other areas and for immunocompromised patients have not yet been established. It is already an accepted first- and second-line option for several types of New World and Old World CL. Toxicity may preclude daily doses higher than 150–200 mg; efficacy of doses <2 mg/kg/day is not assessed. The optimal total dose needed has not been established. Pharmacokinetic and pharmacodynamic studies are warranted [180].

11.8.10 Antifungal Azoles

The antifungal azoles ketoconazole, fluconazole and itraconazole interfere with the parasite cell membrane biosynthesis. They have shown variable results in the treatment of leishmaniasis. Ketoconazole has greater hepatic toxicity than itraconazole and is therefore no longer recommended. Fluconazole (200 mg/day for 6 weeks) is well tolerated and was effective in 79 % (vs 34 % placebo) of patients in a *L. major* endemic region in Saudi Arabia [181]. Itraconazole (100–400 mg/day for 6–8 weeks) showed a cure rate of 60–70 % in *L. tropica* [182] and *L. major* [183]. A Pakistani study compared itraconazole with Sb(V) for CL in 200 patients. The itraconazole group had a cure rate of 75 %, the meglumine antimonite group 65 %. Sb(V) was superior for lupoid type of lesions and for the control of lymphatic spread [184]. Most of these studies showed flaws. A double-blind placebo-controlled Iranian study confirmed earlier Iranian data that found itraconazole to be ineffective against *L. major* [185, 186]. Eleven of 21 Indian patients treated with fluconazole were initially cured but all relapsed within 8 weeks. High-dose (5–8 mg/kg/day) oral fluconazole therapy was effective for CL in Venezuela and deserves further study [187, 188]. Study of a role in the secondary prophylaxis in HIV infection seems warranted.

11.8.11 Other Systemic Treatments

11.8.11.1 Aminosidine (Paromomycin)

Aminosidine is an aminoglycoside antibiotic identical to paromomycin. It is produced by a *Streptomyces* species. Paromomycin is a protein synthesis inhibitor in non-resistant cells by binding to 16S ribosomal RNA. It is active against *Leishmania* in vitro and in animals. Highest activity was against *L. major* and *L. tropica*, while of the New World species, *L. panamensis* was most, and *L. mexicana* was least sensitive. *L. donovani* species showed variable sensitivity, and combination of antimony and paromomycin had an additive effect in vivo in mice infected with Ethiopian *L. donovani* and a variable synergy in vitro against Indian and Ethiopian *L. donovani* [189].

Dose, Duration, Efficacy, and Toxicity: Monotherapy at doses of 16–20 mg/kg/day IM for a duration of 21 days showed an efficacy of 93–97 % [190, 191] combination with antimony was synergistic [192]. A multicentre study from East Africa shows that the dose of 11 mg/kg of paromomycin, successfully used in India, was not sufficient for effective cure in Africa. The dose has been increased to 20 mg/kg [91]. It was not effective in Peruvian MCL [193]. Assessment of toxicity has been limited in these small studies. Aminosidine being an aminoglycoside has the potential of oto- and nephrotoxicity.

Summary: Aminosidine at a dose of 16–20 mg/kg/day for 21 days seems a safe and effective drug for the treatment of VL. It acts synergistically with Sb(V) and may help delaying further development of Sb(V) resistance. It is likely to be a good candidate for combination treatment with miltefosine [70].

11.8.11.2 Allopurinol

Allopurinol, an analogue of hypoxanthine, is metabolised by *Leishmania* spp. and *Trypanosoma cruzi* whereby aberrant nucleotides are formed that, incorporated into the RNA of the protozoa, interfere with normal protein synthesis [194]. Allopurinol showed antileishmanial activity in in vitro cultures and in animal models, but results in vivo have been variable, both in visceral and in cutaneous leishmaniasis. Most reports are about noncontrolled trials, mostly in combination treatments with Sb(V) treatment [195–198] but also with the antifungal azole drugs keto-, flu- and itraconazole, in the treatment of visceral leishmaniasis and as secondary prophylaxis in patients coinfected with *Leishmania*/HIV [199, 200].

Dose and Duration: In the dose used in leishmaniasis, 7 mg/kg × 3 per day for prolonged periods of time, adverse effects are more likely than with the dose used for gout. Adverse effects include rash, itching, fever, eosinophilia, hepatic granulomas, interstitial nephritis and vasculitis, bone marrow depression and exfoliative dermatitis, TEN (toxic epidermal necrolysis). Allopurinol monotherapy in VL is of no use. Its place in combination therapy remains undecided [93]. The derivative

allopurinol ribonucleoside, much more effective in vitro, has been used to limited extent in cutaneous leishmaniasis but is not further developed [201].

11.8.11.3 Dapsone

Dapsone has been used with success in Indian CL [202].

11.8.12 Other new developments

Several plant products are in various stages of research and development: licochalcone A from the Chinese liquorice plant *Glycyrrhiza*, PX-6581 [203] from the Vietnamese plant *Maesa balansae* [204], several quinolines, one from *Galipea longiflora* from Bolivia [203].

Anacardic acids from cashew nuts are in research as a topical treatment for LCL [205].

A promising new development is the use of human antimicrobial peptides (AMPs) which have powerful broad-spectrum antimicrobial activity with distinctive modes of action and are considered as promising therapeutic agents. The defensins, members of the large family of AMPs, are immunomodulatory molecules and important components of the innate immune system. Human neutrophil peptide-1 (HNP-1), which is produced by neutrophils, is one of the most potent defensins. Sara Dabirian et al. described obvious antiparasitic activity of recombinant HNP-1 (rHNP-1) against *Leishmania major* promastigotes and amastigotes [206].

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