Imported Skin Diseases
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CHAPTER 1
Introduction

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International tourism is one of the largest and fastest growing economic sectors in the world with continuous expansion and diversification, and many new destinations, often to less privileged areas.

International tourist visits in 2010 were estimated to be 940 million, and are expected to increase by 4–5% in 2011. In 2020, 1.6 billion international visits are expected. Expenditure on international tourism had reached $919bn (€693bn) in 2010. International tourism is the fourth global export category and accounts for 30% of world exports of commercial services. It is estimated to contribute 5% to the worldwide gross domestic product [1].

As the world develops into a global village, people travel daily from continent to continent and infectious diseases may travel with them. On the one hand, someone with an infection acquired under “tropical” conditions abroad may visit the health services in Europe or North America within 24 hours of his or her departure from the country visited. On the other hand, in some diseases, clinical signs and symptoms may develop weeks to months after return, so the relationship with the past travel is not obvious.

There are three main reasons why patients with “tropical or exotic skin diseases” have been seen more frequently in recent years.

First, leisure time in affluent societies is increasing, and more and more people, including those in the older age groups, take holidays in far-off places. More and more adventure holidays are being taken to places where the risk of acquiring a disease is much greater than in a more protected environment.

Second, there are large immigrant groups in most Western countries, originating from other continents. They may present with skin diseases months or years after settling into their new home country. Also, these
people may regularly visit their family in their country of origin and acquire a skin disease.

Third, there is a group of professional travelers visiting, regularly or for a long period, countries in other continents; this includes members of the military going for training or peace-keeping missions.

Skin diseases are found in a considerable number of travelers. It was reported that among 2004 patients attending an Institute for Tropical Medicine in Berlin, Germany, 14% of the consultations were for skin diseases [2]. From the United States of America, a 2-year survey of 784 travelers to developing countries reported skin problems during travel in 8% of the travelers. In 3% of them these problems continued or had an onset within 14 days after return [3]. Of 12,437 travelers to Nepal, 12.44% were found to have skin diseases in which bacterial skin diseases, fungal skin diseases, scabies, and “skin allergy” were the most prevalent [4]. More recently, in a study from 30 GeoSentinel sites, which are specialized travel or tropical medicine clinics, of travelers returning from six developing regions of the world, it was found that dermatological disorders ranked third in frequency [5].

French researchers reported in a prospective study of French travelers to tropical countries, of whom 38% had visited sub-Saharan Africa, that the most common diagnoses in 269 patients were cutaneous larva migrans (25%) and pyoderma (18%), followed by insect bites, myiasis, tungiasis, urticaria, fever and rash, and cutaneous leishmaniasis in 10% or less. In 39% of the patients the skin lesions developed after the return to France. The median onset after departure from the tropics was 7 days (range 0–52 days) [6]. The most common skin-related diagnoses in 4595 patients seen in GeoSentinel clinics were cutaneous larva migrans (9.8%), insect bites (8.2%), skin abscess (7.7%), and superinfected insect bites (6.8%) [7].

This book has been written and illustrated for the health professionals living in western Europe and North America in order to help in the diagnosis and management of patients with diseases acquired in another, often tropical, environment. In this respect, the book deals with skin diseases that are not common in the Western world.

A wide spectrum of imported skin diseases, the majority infectious in origin, is covered. Sexually transmitted infections as well as dermatological diseases are also discussed.

Skin signs may provide a clue to the diagnosis of sometimes life-threatening systemic infections, and should therefore be recognized as soon as possible by the attending physician. As travel these days is often not only terrestrial but also involves water exposure in the ocean or rivers, a chapter on aquatic skin disorders is included.

The book also deals with emerging diseases such as cutaneous leishmaniasis, which is being diagnosed with increasing frequency in
travelers and also in the military sector, and Buruli ulcer, which is still rare in travelers.

The influence of environmental factors, the characteristics of pigmented skin, which influence the clinical expression of diseases in the colored skin, and disorders of the pigmentary system itself are also addressed. Tables and flow charts of important clinical conditions and the relationship of those skin diseases to the different geographical areas will be helpful in the diagnosis and management of patients with imported skin diseases.

The contributions of the authors, all experts in their respective fields, are greatly appreciated.

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CHAPTER 2

Precautions and Protection

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Key points
- A journey to a tropical country must be adequately planned in advance
- Certain groups of travelers are more at risk
- Measures should be taken to diminish the influence of sun exposure
- Measures should be taken to prevent insect bites

Introduction

When planning a journey to a tropical destination, the visitor should contact, depending on the local circumstances, an institution such as the public health service, a travel clinic, or tropical disease departments at (university) hospitals in order to get proper advice on required vaccinations and prophylaxis such as malaria prophylaxis. This consultation should take place more than 8 weeks before departure and this is especially advisable for people with preexisting diseases and those on complex or immunosuppressive treatments such as biologicals. The advice given in the following text is specifically related to the skin and travelers should remember that taking malarial prophylaxis and due care in drinking water and eating locally are all key to preventing illness while abroad.

A medical kit is advisable for destinations with significant health risks, and could contain the following items for the treatment of skin problems [1]:
- Antiseptic wound cleanser or alkaline soap
- Bandages
- Insect repellent

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Precautions and Protection

Strong steroid cream (to use once or twice on sunburn and insect bites)
Antihistamine tablets
Sterile dressing
Sunscreen
Tweezers
Adhesive strips to close small wounds

And according to destination and circumstances of travel:
Antibiotics targeting the most frequent infections in traveler’s antibacterial ointment
Antifungal powder
Mosquito net and insecticide to treat fabrics (clothes, nets, curtains)

One should also be acquainted with climatic conditions during travel. In general, under conditions of high humidity such as in tropical rain forest areas and during monsoon seasons, fungal and bacterial skin infections are prevalent. Whereas in semiarid and arid areas, sun-exposure-related problems are more common.

Sun exposure

UVB (wavelength 280–315 nm) and UVA (wavelength 315–400 nm) can both have adverse effects on the skin. UVB can induce a skin burn depending on the exposure and skin type. Polymorphous light eruption, solar urticaria, and phototoxic and photoallergic reactions may also occur. Phototoxic reactions are mediated by UVB and commonly result from interaction with drugs such as certain tetracyclines, thiazines, quinolones, and NSAIDs; also, phototoxic reactions through local contact with furcoumarins in plants and perfumes may occur. Photoallergic reactions are generally mediated by UVA, and caused by photoallergens in cosmetics, antiseptics, sunscreens, and certain drugs.

Precautions and protective measures to be taken are as follows [2]:
- Avoid exposure to the sun in the middle of the day, when the UV intensity is greatest.
- Do not overexert yourself on the first few days after arrival in a very hot climate. Heat exhaustion and prickly heat (miliaria) are common.
- Wear clothing that covers arms and legs (covering the skin with clothing is more effective against UV than applying a sunscreen).
- Wear UV-protective sunglasses of wraparound design plus a wide-brimmed sun hat.
- Apply a broad-spectrum sunscreen of sun protection factor (SPF) 15+ liberally on areas of the body not protected by clothing and reapply frequently.
Imported Skin Diseases

- Take particular care to ensure that children are well protected—babies should be protected from the sun but also be dressed in light loose clothing.
- Avoid exposure to the sun during pregnancy.
- Take precautions against excessive exposure while on or in water or on snow.
- Check that medication being taken will not lead to sensitivity to UV radiation.
- If adverse skin reactions have occurred previously, avoid any exposure to the sun and avoid any products that have previously caused the adverse reactions.
- Do physical exercises during air travel, and when older wear elastic stockings, to prevent deep venous thrombosis. Elastic stockings may also prevent the mild or subclinical lower leg edema common to travel in tropical climate, which may predispose to infected minor trauma or insect bites.

Insects

The bite or sting of an insect, and also nearly all arthropods, can not only lead to persistent insect bite reactions, but can also be the source for transmission of infectious diseases like (cutaneous) leishmaniasis, chikungunya and other viral diseases, rickettssioses, and Lyme disease.

Precautions and protective measures to be taken are as follows [2]:

- Protective clothing
- Insect repellents of which N,N-diethyl-3-methylbenzamide (DEET) is most widely used but other agents are also available [3]
- Mosquito nets
- Mosquito coils
- Aerosol sprays

Certain groups of travelers are more at risk of acquiring travel-related diseases such as the following [4]:

- Visitors to friends and relatives. Immigrants in Western countries increasingly travel to their country of origin to visit friends and relatives. It appears, that as a consequence of the places they visit and the way they participate in the local life style, they are at an increased risk of exposure. They also are less likely to take protective measures.
- Travelers with HIV/AIDS may have increased susceptibility to tropical diseases. They have reduced immune response to some vaccines, and are at risk of severe reactions to live vaccines. Access to medical service during travel may be substandard.
Patients on treatment with biologicals and/or on immunosuppressive drugs. An increasing number of immunocompromised persons travel to (sub)tropical regions, also because new therapeutic modalities enable such undertaking. Immune-mediated inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis, share common genetic problems characterized by cytokine dysregulation. Immunosuppressive or immunomodulatory agents are used to treat their disorders. Both, disease and treatment, have implications for vaccination, a well-established strategy to prevent certain important infectious diseases in travelers to the tropics. Live attenuated vaccines, such as for yellow fever, are contraindicated in these patients, whereas inactivated vaccines are safe but might require assessment of the immune response. These travelers, and also those with other underlying conditions such as HIV disease or splenic dysfunction, should seek expert pretravel advice as far in advance as possible [5, 6].

References

CHAPTER 3

Pigmentary Disorders in Black Skin

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Key points
- Dark-skinned people more often seek medical attention for pigment problems than Caucasians do.
- Dark skin often shows uneven pigmentation patterns like Voight's demarcation lines.
- Dark skin readily reacts to even minor trauma and inflammation with pigmentation shifts, most often hyperpigmentation.
- Some pigmentary disorders like Ota-, Ito- and Hori nevus and dermatosis papulosa nigra are seen more often in darker skin types.
- Diagnostic pitfalls are Hori nevus versus melasma and progressive macular hypomelanosis versus pityriasis versicolor.
- Ubiquitous pigment disorders like vitiligo are more conspicuous in black skin and pose bigger problems regarding quality of life.
- Melanoma in black-skinned people mostly presents in an acral lentiginous growth pattern at an advanced stage because of diagnostic delay.

Introduction

Western societies are becoming increasingly multiracial and so is the patient population in medical practice, especially in large metropolitan areas.

Pigment problems can be very disturbing for patients with dark skin, especially when huge contrasts with the constitutional skin color emerge, such as can be seen in blacks with vitiligo. However, pigment problems that might not appear significant at first sight can have important culturally determined psychosocial connotations in dark-skinned patients and should, therefore, always be taken seriously by their doctors.

In this chapter, normal pigmentary variations and a number of common pigment disorders in dark skin have been described.
Normal variations in ethnic skin

Voigt’s or Futcher’s lines
A total of five lines of demarcation between darker and lighter skin areas, the so-called Voigt’s or Futcher’s lines, have been described. These lines can be found on the upper arm anteromedially, the posterior portion of the lower limb, the presternal area, the posteromedial area of the spine, and the bilateral aspect of the chest. About 75% of the African American population has at least one pigmentary demarcation line [1].

Hyperpigmentation at the extensor side of the joints (Figure 3.1)
Stretching of the skin at the joints can possibly be a mechanical trigger for the melanocytes. Arthritis may also cause this hyperpigmentation.

Nail pigmentation
Nail pigmentation manifests as longitudinal linear dark bands in the nail plate, which occurs especially on the thumbs and index fingers [2]. The pigmentation is usually absent at birth and increases with age. Nail pigmentation is mostly seen in blacks with a very dark complexion. It is important to differentiate these lesions from malignant melanoma, nevus and pigmentation secondary to drugs, chemicals and postirradiation changes.

Familial periorbital hyperpigmentation (Figure 3.2)
Periorbital hyperpigmentation is a common finding in otherwise healthy people and has been described as an autosomal dominant hereditary disorder [3]. The hyperpigmentation usually starts during childhood in the
lower eyelids and progresses with age to involve the entire periorbital area. Periorbital hyperpigmentation can also be found in every skin type as an atopic stigma.

**Oral pigmentation**

Oral pigmentation is usually seen on the gingivae. The hard palate, buccal mucosa, and tongue are less frequently involved. These lesions should be distinguished from conditions like secondary syphilis, malignant melanoma, and drug eruptions. Unlike nail pigmentation, the skin color cannot predict the likelihood of oral pigmentation [1].

**Palmar and plantar hyperpigmentation**

Macular hyperpigmentation is commonly seen on palms and soles of black patients. They vary in shape and are mottled in appearance. Clinically, these must be differentiated from palmar/plantar lesions of syphilis, ephelides, nevi, and melanoma.

Where in patients with fair skin pigmented lines in the palms can be a clinical feature of Addison’s disease, this is a normal variation in people with dark skin.

**Mongolian spot** (Figure 3.3)

This is the most common congenital hyperpigmentation, occurring in approximately 80–100% of the Asian and black newborns. It is a form of dermal melanocytosis in which melanocytes have been arrested in their fetal migration from the neural crest to the epidermis. The gray-blue macular lesions vary in size but usually occupy less than 5% of the body surface. The most common locations are the sacrum, buttocks, and back.
Figure 3.3  Mongolian spot

The majority of Mongolian spots intensify in color during the first year of life followed by gradual disappearance. By the age of 10, virtually all Mongolian spots disappear [4].

Abnormal hyper- and hypopigmentations

Nevus of Ota, nevus of Ito, and Hori nevus (Figure 3.4)
These nevi are seen in all races, but affect mostly Asian people. Nevus of Ota or nevus fuscocoeruleus ophthalmmomaxillaris is a dermal melanocytic hamartoma that presents as a bluish hyperpigmentation within the distribution of the first and second branch of the trigeminal nerve [5]. Very often the sclerae are also involved. Histologically and clinically the lesions
resemble Mongolian spots but are, unlike the latter condition, not self-limiting.

The pigmented spots usually appear in childhood and increase in number and extent to become confluent in some areas. The distribution is usually, but not always, unilateral. Malignant transformation has been reported in very rare instances. The nevus of Ito involves the acromio-clavicular region and the upper chest and is similar to the nevus of Ota in its histology.

Acquired bilateral nevus of Ota-like macules (ABNOM) has first been described by Hori et al. in 1984 and is also known as Hori nevus [6]. The condition is characterized by the appearance of small, but later also conflating grayish brown macules in the face, mostly bilateral in the malar regions. Like in nevus of Ota, the histology is characterized by dermal melanocytosis. It is most seen in eastern Asia in women in their 30s and later. ABNOM should be differentiated from melasma. Wood’s lamp assisted inspection of the lesions often provides the clue [7].

All these lesions can be treated fairly successful with Q-switched pigment lasers [8], though postinflammatory hyper- and hypopigmentation occur easily in darker skin warranting precautionary like pre- and post-treatment bleaching regimens [7] and laser therapy [9].

**Transient neonatal pustular melanosis**

Transient neonatal pustular melanosis (TNPM) can be seen in 2–5% of black newborns [10].

The characteristic lesions consist of very superficial vesicopustules without any sign of erythema and ruptured pustules, resulting in hyperpigmented papules with a surrounding collarette of scale in the first phase. Though always present at birth, the lesions can be easily overlooked and noticed for the first time several days after birth.

The lesions usually are 2–3 mm in diameter and can appear everywhere on the body, grouped or solitary. The head, neck, back, fingers, and toes are predilection sites.

In the pustules neutrophils but no bacteria can be demonstrated.

The differential diagnosis of TNPM includes diseases like erythema toxicum and staphylococcal impetigo, which can be differentiated by the typical clinical appearance and the history. The active vesiculopustules disappear in days, but the hyperpigmented macules slowly disappear in weeks to several months.

**Ashy dermatosis**

Ashy dermatosis is seen worldwide but is most common in Latin America and Asia. It is seen somewhat more frequently in women than in men and has no age preference. Clinical manifestations include
asymptomatic, slate-gray or violaceous hyperpigmented macules distributed most commonly over the trunk and proximal extremities and less frequent over the face and neck. The macules vary in size and shape and occasionally demonstrate an erythematous raised border in its early stages. In those cases, the term erythema dyschromicum perstans has been coined [11]. The differential diagnosis should include lichen planus pigmentosus, macular amyloidosis, leprosy, and fixed drug eruption.

The etiology of ashy dermatosis remains unknown. At this time, no evidence-based treatment is available.

**Dermatosis papulosa nigra** (Figure 3.5)

These small, darkly pigmented papules are regarded as a variant of seborrheic keratoses. They were originally described in African Americans but are seen in darker skinned people of many races. The incidence of this hereditary condition in black people rises from about 5% in the first decade to more than 40% by the third decade, and is rather higher in females than in males.

The papules are often numerous in the malar regions and on the forehead and may occur on the neck and trunk. The lesions can be treated with curettage, electro desiccation or laser, all with excellent outcomes [12].

Care has to be taken not to affect the normal surrounding skin in order to prevent the predictable induction of postinflammatory hyperpigmentation (PIH).

*Figure 3.5* Dermatosis papulosa nigra
Pityriasis versicolor
Tinea versicolor or pityriasis versicolor is one of the most common pigmentary disorders worldwide. It appears to be more prevalent in the black population [13], and in tropical regions, it occurs with a prevalence as high as 40%. It is caused by overgrowth of commensal *Malassezia* yeasts and affects most commonly the trunk. Patients have many slightly scaling macules and patches, which can have, as implied by the name versicolor, many different colors such as yellowish-brown, pale yellow, or dark-brown, occasionally reddish or pinkish appearing hypopigmented or hyperpigmented [14]. There is no correlation between pigmentary variation and skin color.

Antifungal therapies usually cure the disease, but the pigment changes will disappear only slowly and recurrences can occur.

Melasma
Melasma is characterized by irregular, usually symmetrical brown patches on sun-exposed skin. The malar prominences, the forehead, the upper lip, the nose, and the chin are the most common sites of involvement, but other areas like the neck and forearms can also be affected. Melasma is not exclusively a disorder of the darker skin types, but it appears to be far more common in Hispanics, Asians, and blacks. Etiologic factors include genetic and hormonal influences (pregnancy, birth control pills), exposure to UV-radiation, cosmetics, phototoxic drugs, and antiseizure medication. Current treatment options include the use of sun blocks, hypopigmenting agents, and chemical peels [15].

Postinflammatory hyperpigmentation
PIH is one of the most common pigmentary disorders in dark skin. Inflammatory skin conditions like infections, bullous and pustular disorders, phototoxic eruptions, papulosquamous disorders, and medical interventions (laser therapy, chemical peels, and dermabrasion) can all cause the increased pigmentation seen in postinflammatory hyperpigmentation. The two processes involved are epidermal hyperpigmentation and/or dermal hyperpigmentation (incontinentia pigmenti). The hyperpigmented areas correspond with the distribution of the original dermatosis. Blacks seem to have more follicular skin problems, and post-acne hyperpigmentations in the face are very common. In epidermal PIH, the lesions are lighter brown and well circumscribed, as compared with the darker gray, poorly circumscribed lesions in predominantly dermal lesions. Dermal PIH can take years to fade away to normal, whereas epidermal PIH usually disappears in 6–12 months [16]. Sun exposure, chemicals, and certain drugs can aggravate PIH. The primary goal of therapy is treatment of the underlying
inflammatory disease. Furthermore, treatment of PIH should always include the daily use of sunscreen. In addition, resurfacing modalities and many topical agents have been used including keratolytics, retinoids, corticosteroids, and depigmenting agents. However, caution is necessary as many of these agents can induce irritation making the problem worse [17, 18].

**Postinflammatory hypopigmentation**

Postinflammatory hypopigmentation is caused by various cutaneous inflammatory diseases. The long use of potent corticosteroids, chemical peelings, and medical interventions (laser, peels) can also play a role [19]. As in PIH, the configuration and distribution reflects the original dermatosis. In postinflammatory hypopigmentation, the melanocytes react with decreased melanin production after an inflammation or trauma. Sunlight exposure or photo (chemo) therapy may lead to repigmentation within months. Prevention of the trigger causing the hypopigmentation is important.

**Pityriasis alba**

Pityriasis alba is an eczematous disorder often occurring in children with an atopic background and dry skin. The lesions are typically hypopigmented, scaly, and asymptomatic, and commonly affect the face but can also be seen on neck, arms, and trunk. Most of the patients are children between 6 and 16 years of age. In many cases, it is hardly noticeable on white skin; the disorder can be very conspicuous in black-skinned children. Sun exposure in conjunction with topical steroids or calcineurin inhibitors and correction of the xerosis cutis is usually effective [20]. Recurrences can occur though.

**Idiopathic guttate hypomelanosis**

One of the most common types of hypomelanosis in elderly people is idiopathic guttate hypomelanosis (IGH). An incidence of more than 60% has been reported. IGH appears as numerous hypopigmented small macules (1–10 mm) on sun-exposed areas, such as the back of the hands, forearms, legs, and occasionally on the face, abdomen, and trunk. This dermatosis affects all races, is more frequent in women, and tends to increase in incidence with age. The etiology and pathogenesis are not well understood, but since the lesions appear mainly on sun exposed areas, actinic damage may be a causal factor [21]. Another factor might be repetitive microtrauma (“Body scrubbing”) [22]. For widespread lesions, no effective treatments are available. In some cases though, autologous punch-grafting can be quite effective (personal experience LN-K).
**Vitiligo**

Vitiligo is characterized by the destruction of skin melanocytes leading to the development of well-defined depigmented chalk white macules, which can be present on any site of the body, but are usually seen on sites of stretch and pressure, in body folds and around body orifices (e.g., mouth). The disease is seen all over the world and in all skin types, affecting approximately 0.5–1% of the population.

In many patients with active vitiligo, the Koebner phenomenon can be observed; new lesions appear on injured or irritated skin.

It is important to differentiate between generalized vitiligo, the most common form with lesions distributed in a more or less symmetrical way and segmental vitiligo, more seen in children, where lesions develop in a unilateral and usually limited way [23].

Generalized vitiligo is considered to be an autoimmune disease and is associated with other autoimmune diseases like thyroid disease, type-1 diabetes, and so on. In many patients, it runs a chronic course with stable periods sometimes with partly repigmentation interchanged by relapses leading to more and larger lesions.

Segmental vitiligo shows a rapid course that stops in a couple of years, leading to stable spots refractory to the usual medical therapies like phototherapy, topical steroids, and calcineurin inhibitors. On the other hand, grafting techniques that replenish the reservoir of melanocytes by grafts from another body region are very successful in these patients, leading to a lasting recovery in most of them.

Understandingly, vitiligo in dark-skinned patients is much more disfiguring than in whites, leading to a more quality-of-life issues [24]. Because of the resemblance to leprosy, vitiligo patients in areas with endemic lepra often suffer from social exclusion.

**Melanoma**

Dark skin is better protected from sunlight, making sun-induced cancers less prevalent. Blacks have an incidence of malignant melanoma 5–18 times less than whites. However, at this moment there is a trend toward increased skin cancer rates in most ethnic groups [25,26]. The prognosis of melanoma is related to the stage of the disease at the time of presentation. African Americans diagnosed with melanoma have a worse prognosis than whites because they are initially seen with a more advanced disease [27] and the same is found in other black-skinned populations [28].

Another significant difference is the primary tumor location. The most common type of melanoma found in African Americans type is the acral lentiginous growth pattern, whereas in whites, the trunk is the most common site [29,27].
Progressive macular hypomelanosis
Progressive macular hypomelanosis is characterized by nonscaly, nonitchy, ill-defined hypopigmented macules on the skin. The macules occur on the front and the back of the trunk (less frequent on the face, the neck and the upper extremities) and are confluent in and around the midline. It occurs in young adults of both sexes but more often in women and can be found all over the world, especially in black populations. Probably, it is caused by a variant of *Propionibacterium acnes* and can be effectively treated by topical therapy including 5% benzoyl peroxide gel and clindamycin lotion [30].

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**References**


CHAPTER 4

Difference Between Pigmented and Nonpigmented Skin

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Key points
The major differences between colored skin and white skin are in the following.
- The clinical expression of erythema, a near absence of it in dark skin
- The de-, hypo-, and hyperpigmentation of darker skins instead
- The larger cohesion between the keratinocytes in the colored skin
- A greater tendency of the colored skin to lichenification
- A greater tendency to keloid formation in the nonwhite skin
- A greater risk of epidermal skin cancers in the white skin
- Vitamin D production, hindered by melanin in colored skin

Introduction

While in other medical specialties the clinical presentation of diseases hardly differs between the different races, in dermatology the aspect of a skin condition is decidedly different in colored skin than it is in light Caucasian skin. Skin diseases are expressed differently in different skins [1]. For instance erythema, redness as a sign of inflammation—the hallmark of European-American dermatology—is difficult to appreciate in a pigmented skin. Pigment changes dominate the picture [1].

Races are different due to genetic differences that manifest themselves in body build, form of head and face, and length and shape of muscles and bones, but even more in the color of the skin, and the color and form of the hair (Figure 4.1). Until recently most publications on ethnic differences in dermatology were not well researched and did not make allowances for different climatic or socioeconomic circumstances [2]. But more and more

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Figure 4.1 Worldwide distribution of indigenous skin colors according to the Von Luschan's Chromatic scale (courtesy University of Amsterdam)
it has become clear that some of the differences are important because they influence the clinical presentation of skin diseases [1, 3–6].

**Erythema**

Due to the overlying pigmentation, erythema, a sign of inflammation, is not easily visible in a black skin (Figure 4.2). Therefore, palpation is even more important in the examination of pigmented skin than it is in white skin. During palpation the other signs of inflammation, calor (heat, warmth), tumor (swelling), and dolor (pain, tenderness) can be appreciated. Sometimes erythema may manifest as a dark violet hue. The condition erythroderma is not clearly visible as such in the black skin and can only be appreciated as exfoliative dermatitis.

**Pigment changes**

Pigment changes (de-, hypo-, and hyperpigmentation) dominate the clinical picture in the dermatology of the pigmented skin.

**Depigmentation** can be seen during the extreme desquamation that may occur when psoriasis is treated aggressively, or when there is a total disruption in the transfer of melanosomes [7], as happens in some forms of cutaneous lupus erythematosus (Figure 4.3). The melanocyte itself can disappear due to cytotoxicity in autoimmune diseases such as vitiligo [8] or as a result of toxic substances as seen in some leucodermas (cheap rubber).

**Hypopigmentation** can be due to an increased desquamation of the skin. The turnover of keratinocytes is increased, whereas the pigment synthesis is not, so that each keratinocyte contains less pigment. In an epidermis of the same thickness this results in hypopigmentation. This can be seen in pityriasis alba, which is probably a mild form of atopic dermatitis,
Imported Skin Diseases

Figure 4.3 (a, b) Discoid lupus erythematosus: in one patient depigmentation, in the other hyperpigmentation

and in postinflammatory hypopigmentation. Another phenomenon that may occur is that the transfer of melanosomes from the melanocyte to the keratinocytes is hindered by edema and inflammatory cells [7], as may occur in eczema (spongiotic dermatitis), or by down regulation of PAR-2, a protease-activated receptor (PAR) involved in melanosome uptake, phagocytosis, from the melanocyte into the keratinocyte [7, 9]. A third possibility is that the pigment synthesis itself is suppressed. This seems the case in the hypopigmented variant of pityriasis versicolor where the yeast Malassezia suppresses melanin synthesis [10], and in tuberculoïd leprosy where the synthesis may be inhibited by autoimmunity [8]. Also, toxic substances like hydroquinone and phenolic detergents may diminish pigmentation [11].

Topical steroids cause hypopigmentation by two mechanisms: (1) the steroid suppresses pigment formation and (2) the epidermis becomes thinner.

**Hyperpigmentation** can be seen when the epidermis is thickened as in lichenification or in untreated psoriasis, which presents with a thicker layer of keratinocytes, each keratinocyte with its share of pigment. However, sometimes keratinocytes contain more pigment, and upregulation of PAR-2 by inflammation may be the reason [7, 9]. Sometimes infectious agents cause hyperpigmentation; in the dark variant of pityriasis versicolor, large melanosomes can be seen, and it has also been shown that Malassezia furfur can produce pigment by itself [12]. Pigment incontinence is a third important cause. In many of the inflammatory conditions, the basement membrane loses its integrity and pigment leaks into the dermis where it is phagocytized by phagocytes, for example, melanophages. Such pigment appears to be blue-black (a pigmented particle always seems blue
Difference Between Pigmented and Nonpigmented Skin

Figure 4.4 (a, b) Subacute lupus erythematosus: distribution, localization, and configuration are the same

when it is located deep in the dermis) and disappears only very slowly, for example, postinflammatory hyperpigmentation.

One should be aware that the same dermatosis might lead to hyperpigmentation in one patient, while in another it may cause hypo- or even depigmentation (Figure 4.3). Even in a single person the same disease may lead to difference in pigmentation.

Although dermatoses appear different in different races, their distribution, localization, and configuration are the same, which may be helpful in establishing the clinical diagnosis (Figure 4.4).

Cohesion

The cohesion between keratinocytes in pigmented skin is stronger than in white skin [13]. Therefore, while scratching a Caucasian skin leads to excoriation and exudative skin lesions, in the pigmented, skin lichenification often occurs, especially in the mongoloid skin where it may show as a gray hue. In the black skin where lichenification is also common, there is often a tendency to develop follicular lesions. This follicular lichenification is often misdiagnosed as lichen nitidus even by an experienced dermatologist.

In comparison with white skin, the stratum corneum in black skin is equal in thickness but more compact; about 16 layers are seen in white versus 20 layers in black skin, probably due to the greater cohesion
between the keratinocytes [13]. Therefore while in white skin, vesicles break easily, in black skin they remain intact (Figure 4.5). As a result, herpes and varicella lesions remain for a long time in dark skin; and “eczematous dermatitis” in this pigmented skin is not wet and polymorphic, but papular and lichenified. These papules in fact are vesicles; a vesicle in black skin is frequently not appreciated as a vesicle, but due to the overlying pigment may be considered to be a papule. Papular eczema is typical for the colored, especially the black skin, and is often not recognized as such. One should realize that, though the macroscopic aspects differ, histopathologically the diseases are the same—spongiotic dermatitis.

Blisters especially in intraepidermal bullous diseases (e.g., pemphigus) in dark skin are larger than the blisters in the white Caucasian skin, again due to the larger cohesion between the keratinocytes in the colored skin, especially in the stratum corneum. Nikolsky’s sign, which is related to a near absent cohesion within the epidermis, however remains a useful test in black skin as well.

**Keloid formation**

Colored skin tends to keloid formation. Even minimal stimuli may induce this (Figure 4.6). It especially happens in the neck, on the earlobes, on
the shoulders, back, and presternal area, the area’s normally covered by a stola. But it may occur anywhere.

A good explanation for keloid formation is not yet available. However, because keloids are more prevalent in certain families and populations, genetic factors most likely have an impact on keloid formation. Recently, DeltaNp63 overexpression and p53 underexpression have been identified in fibroblasts from keloids. DeltaNp63 may be oncogenic since it is able to block p53 expression, a tumor-suppressing protein [14].

**Pigmentation and skin cancer**

Since the number of melanocytes are equal in all skin types, it is the nature, quantity, and distribution of the melanosomes, the organelles that contain the melanin, in the epidermis that plays a crucial role in the determination of skin color and the skin’s sensitivity to UV radiation. In Caucasian skin the melanosomes are small and oval and aggregated in groups of three or more within a membrane situated like an umbrella above the nucleus of the keratinocyte. When keratinocytes move up towards the stratum corneum the melanosomes are broken up. In Black skin they are larger and more rounded and are lying dispersed within keratinocytes and stay intact up to the stratum corneum. They contain two types of melanin: (1) black and brown eumelanin and (2) reddish-brown
pheomelanin. Eumelanin gives a much better protection against UV-light than pheomelanin. This could be the explanation of the differences in prevalence of skin cancer between white and colored skins. But there are other explanations.

Pigmentation protects against skin cancers that result from UV damage to the DNA. It has been shown in vitro that the in presence of L-tyrosine increased melanin production, leads in light skinned individuals to a more elliptical shape of the melanosomes. X-ray microanalyses of these melanosomes showed that in melanocyte cultures of light-skinned individuals there was a larger increase in sulfur content of the melanosomes than in that of the dark skinned. HPLC analysis showed that the ratio between pheomelanin and eumelanin was found to increase more markedly in light-skin-derived melanocytes than in those from the dark skin. Pheomelanin production is a thiol-consuming process and may lead to an increased risk of oxidative stress in these cells and hence an increased cancer risk [15]. This observation together with the limited ability of pheomelanin to absorb UV radiation may also contribute to the higher skin cancer risk in the light-skinned individuals especially among the Celtic phenotype, which has a predominance of pheomelanin.

**Pigmentation and immunity**

It has been suggested that the reduced pigmentation of light-skinned individuals results in higher vitamin D levels and that, because melanin acts like a sun-blocker, dark-skinned individuals, in particular, may require extra vitamin D to avoid deficiency at higher latitudes [16]. The natural selection hypothesis suggests that lighter skin color evolved to optimize vitamin D production in extreme northern and southern latitudes. For example, in 44% of asymptomatic East African children living in Melbourne, a vitamin D level of below 10 ng/ml (25 nmol/L) has been reported [17].

The low level of vitamin D in dark-skinned individuals in northern countries may be contributed to socioeconomic factors but the skin color might be an important reason [18]. Rickets and osteoporosis are less common in blacks, due to a different hormonal status. But there are some indications that when dark-colored individuals are living in temperate climates they develop more infections, autoimmune diseases, diabetes, prostate cancer, breast cancer, and colon cancer [19–22] and get more aggressive forms of those cancers than the lighter skinned, provided those expose themselves to the sun. Vitamin D seems to have a physiological role beyond its well-known role in skeletal homeostasis. Vitamin D3, hydroxy calciferol, is an immunomodulator, targeting various immune cells,
including monocytes, macrophages, dendritic cells, as well as T-lymphocytes and B-lymphocytes, hence modulating both innate and adaptive immune responses [23, 24]. Besides being targets, immune cells express vitamin D-activating enzymes, allowing local conversion of inactive vitamin D into the active 1,25(OH)(2)D(3) within the immune system. Taken together, these data indicate that 1,25(OH)(2)D(3) plays a role in maintenance of immune homeostasis [21, 22].

Other differences

Most physical properties are not well researched. There are studies that suggest that the transepidermal water loss (TEWL) is greater in Black than in Caucasian skin and there is an observation that desquamation of Black skin is greater than that of Caucasian and Mongoloid skin. This may account for the xerosis so often encountered in Black skin. However, most studies do not support these findings [25, 26]. Xerosis can then be explained by cultural factors like frequent washing and use of aggressive soaps.

It is observed that dark-colored skin is more resistant to irritants. This probably can be explained by the fact that the stratum corneum of black individuals is more compact and consists, though of same thickness, of more layers [13].

Microscopic evaluation reveals that Black skin contains larger mast cell granules than Caucasian skin. It is tempting to speculate that this accounts for the observation that black patients report pruritus more frequently than other ethnic groups [6]. Though xerosis by itself may also be an important cause.

A pure physical property of the color of the black skin is that, especially in radiated heat (the sun), it absorbs more heat than a lighter colored or white skin, resulting in more sweating in the dark-colored individual. Contrary to what is often said, the density of eccrine sweat glands of black and white is the same. There may be some differences in the apocrine glands between the different ethnic groups: less dense in East Asians and more in Africans. In the cold, black skin radiates more heat, hence the tendency of black people to dress in warm clothes and to cover themselves at night. In particular, they cover their head, where the close-cropped hair allows the warmth to escape easily.

Hair

Hair differs in distribution, color and form among different ethnic groups [27–29]. Caucasians of Mediterranean origin or Turkish or
Iranian extraction may be extensively hairy, in contrast to Nordic Caucasians, Indians, and Mongoloids. The hair color of Blacks, Mongoloids, and Australoids is almost always black, while the color of Caucasian hair varies from deep black to blonde or reddish. The hair of Mongoloids and Blacks is thick, that of Caucasians usually thin. The hair of Blacks is stiff and curly, that of Mongoloids is straight, while that of Caucasians is straight or wavy. Black hair is oval, while that of the other races are more rounded. The hairs leave the skin at an angle of 90 degrees in white individuals, but with a sharp corner in black individuals.

Curly stiff hairs may cause problems, especially after shaving when the hairs curl inside the skin and cause inflammation, as is seen in pseudofolliculitis barbae and acne cheloidalis nuchae.

The distribution of Black and Mongoloid hair often is less dense than that in Caucasians. There is some indication that the anchoring of Black hair is less strong, which may explain in part traction alopecia that is so often encountered in black patients. Also, their hair seems to be more brittle. But these observations must be weighed against the cosmetic manipulations where curly hair in black people is often subjected to, for example, straightening, weaving, and knotting (Figure 4.7).

References

Difference Between Pigmented and Nonpigmented Skin


CHAPTER 5

Influence of the New Environment on the Skin

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Key points
Skin diseases can be induced by the following “environmental” factors:
- Physical
- Chemical
- Biological
- Social and cultural

Common skin disorders in immigrants from (sub)tropical regions to the temperate climate zone are as follows:
- Dry skin or xerosis is one of the most common skin disorders in people from a warm humid tropical climate coming to a temperate climate.
- Immigrants from (sub)tropical countries, not using gloves and wearing inadequate footwear in the cold season are prone to perniosis.
- Lack of exposure to sunlight can induce or provoke skin diseases, such as psoriasis, that would not have appeared if they had remained in their sunny location.
- Chickenpox—due to lack of immunity—is common in certain immigrant groups coming from (sub)tropical countries to Europe or the United States.
- Use of skin bleaching products—due to “psychosocial pressure”—can lead to various adverse reactions, such as skin atrophy caused by corticosteroids and exogenous ochronosis caused by hydroquinone.

Common skin disorders in tourists from the temperate climate zone to a tropical country, due to the humid, hot, and sunny environment are as follows:
- Miliaria
- Sunburn
- Bacterial infections (pyoderma)
- Fungal and yeast infections
Introduction

In immigrants from (sub)tropical countries moving to the temperate climatic zone as well as in tourists returning home to the temperate climatic zone after a holiday in a (sub)tropical country, a myriad of infectious as well as noninfectious skin disorders can be encountered. Many of these conditions can be linked to the racial or ethnical background of the individual, which is in part genetically related.

Skin disorders peculiar to certain ethnic groups are nowadays designated as ethnic skin disorders. Ethnicity is a concept different from race. It is used for several reasons, including the fact that some groups of people do not fit easily into a race. It is actually an imprecise concept, which implies shared origins, including cultural traditions that are maintained between generations, leading to a sense of identity in a group [1]. Many ethnic skin disorders are diseases of pigmentation and discussed in Chapter 3. Nonpigmentary ethnic skin disorders are numerous, examples of which are lichen amyloidosis, common in Chinese people and keloid, seen especially in people from African descent. Most ethnic skin disorders are common in the countries of origin, so they are not specifically related to migration.

This chapter is about skin disorders that are induced by the change in environment. Both, skin diseases in immigrants from (sub)tropical countries to the temperate climatic zone as well as in tourists returning home from the (sub)tropics to the temperate climatic zone are discussed. We have focused on disorders that are probably related to the new environment or to be more precise: to a lack of adaptation to the new environment. This is in fact a broad subject, with unfortunately a relative paucity of medical publications. In this chapter we have confined ourselves to a discussion of only a few disorders as an example of this topic.

Environment, adaptation, and skin disorders

Skin disorders can be induced by environmental factors, which can be subdivided as follows:

1. Physical factors, for example, sunlight (including UV radiation), ambient temperature (heat, cold), and degree of humidity (moistness, dryness).
2. Biological factors, for example, microorganisms, animals, and plants.
3. Chemical agents and other factors produced by the industrialized societies, which are absent or uncommon in a nonindustrialized environment.
Other nonenvironmental factors determining the development of skin diseases are structure and function of the skin, immunological factors, and finally psychological factors, including behavior.

Structure and function of the skin in people originating from tropical countries, are in some respects different from those of people from a temperate, less sunny climate [2]. Molecular analysis has identified genetic differences between races and ethnic groups, probably related to differences in their environment. Most anthropologists believe that racial variation developed through natural selection processes: different biologic traits in the races developed because these traits facilitated adaptation to a particular environment. For instance, it is believed that darkly pigmented skin evolved to protect people living close to the equator from ultraviolet (UV) light. People living north of the equator on the other hand, probably have paler skin to ensure adequate absorption of UV rays to promote vitamin D formation in the basal layer of the epidermis. Besides the difference in skin color, there are other anatomical differences in the skin between people from diverse regions of the earth. For example, dark-skinned people probably have larger apocrine sweat glands and in greater numbers than white subjects. The stratum corneum of black people is more compact than that of white people, reflecting a stronger intercellular cohesion, and this could be responsible for the fact that continuous scratching in black people often leads to lichenification. However, racial differences have been minimally investigated by objective methods and the data are often contradictory [3].

The immune system, including the so-called skin immune system, plays a major role in defending the body against microbial intruders [4]. In a new environment with microorganisms in the ecosystem that are immunologically unknown to the traveler or immigrant, infectious diseases including skin infections can develop, which would not appear in the old environment. According to the so-called hygiene theory, epidemiological and laboratory studies have implied that the environment during early childhood is important for the risk of developing atopic disorders. The prevalence of asthma, hay fever, and eczema among 1901 internationally adopted boys in Sweden was analyzed in relation to indicators of their early childhood environment. The adopted males who came to Sweden before 2 years of age suffered from asthma, hay fever, and eczema significantly more often than those who came to Sweden between 2 and 6 years of age. This study demonstrates that environment during the first years of life has a profound influence on the risk of suffering from atopic disorders as young adults [5].

Different social and cultural factors, both in immigrants moving from (sub)tropical to Western countries as well as in tourists traveling from Western countries to (sub)tropical regions can induce or contribute to various (skin) diseases. Veiled women wearing covering clothes, often suffer from vitamin D deficiency in Western countries. On the other hand, sun
bathing of tourists in (sub)tropical climates, could lead to massive sunburn and subsequent complications.

In conclusion, from the aforementioned examples it should be clear that the interaction between factors present in a certain climatic zone on the one hand and biological traits and behavior of the individual on the other hand can induce “new” skin disorders in individuals coming from another climatic zone.

### Skin disorders in immigrants

In this section we have described some examples of skin disorders in immigrants from (sub)tropical countries to the temperate climatic zone, due to the change of environment.

We have discussed a few examples of skin disorders in immigrants due to physical environmental factors, such as dry skin and eczema, pernio-sis, and psoriasis; chemical leukoderma as an example of a skin disorder caused by chemical agents in the industrialized society; the occurrence of chickenpox in immigrants, a skin disease related to immunological and changed biological environmental factors; and finally we report on adverse reactions to skin bleaching, which is considered to be related to social and cultural factors.

### Skin diseases due to physical environmental factors

#### Dry skin and dry eczema

Dry skin or xerosis is one of the most common skin disorders in people from a warm humid tropical climate coming to a temperate climate. It is one of the skin disorders related to the humidity level in the new environment (Table 5.1). Dry skin and subsequently dry eczema can develop very soon after arrival, especially during wintertime. Especially in people with a Black ancestry, xerosis cutis is frequently seen. As mentioned in

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<td><strong>Dry environment</strong></td>
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<tr>
<td>Itch</td>
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<td>Dry skin</td>
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<tr>
<td>Ichthyosiform skin</td>
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<tr>
<td>Cracquelé type eczema</td>
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<tr>
<td><strong>Humid (and hot) environment</strong></td>
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<tr>
<td>Miliaria</td>
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<tr>
<td>Bacterial infections (pyoderma)</td>
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<td>Fungal and yeast infections</td>
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</table>
Chapter 4, this is probably due to the higher amount of transepidermal water loss (TEWL) and a higher level of desquamation in Black skin, compared to Caucasian and Mongoloid skin. Furthermore, dry skin and dry eczema are more common in people taking frequent hot and long showers and using soap excessively.

The natural “oily coating” on top of and within the horny layer of the epidermis, called “natural skin emulsion” is composed of an oily component and a watery component, produced by the skin itself. If this coating disappears, the skin loses water and may develop signs of the dry skin syndrome. These range from mild to severe, and are successively: a dry scaly skin, an ichthyosiform skin, and cracquelé eczema, characterized by nummular patches of slight erythema, a mild infiltration, cracks, and scaling (Figure 5.1). If the skin is dark, the erythema cannot be identified. The accompanying symptoms are a “dry feeling,” itching (sometimes severe, even disturbing sleep), and sometimes pain. The disorder can be localized anywhere on the body, but most common are legs and arms, but also the face, especially the lips can be affected.

The diagnosis is easy to make on clinical grounds. It must however be differentiated from other types of eczema, for example, contact dermatitis and atopic dermatitis. Signs and symptoms of other skin conditions can be worsened by dry skin. Complications of eczema can be infection and lichenification.
The disorder can be treated with a class 1 or 2 corticosteroid containing fatty ointment, to be used for a short time, only if eczema is present. An emollient or a urea-containing cream or ointment can be used as maintenance therapy. Finally, it is important to give the patient bathing and general advices: decrease the frequency and duration of showering; use warm, not hot water; do not use soap; dry the skin gently with a towel, patting is better than rubbing; use a hydrating ointment after drying the skin.

**Perniosis (chilblains)**

This is typically a disorder of wintertime, caused by an abnormal vascular reaction to cold in probably genetically predisposed persons. It is a common disorder. Other examples of cold-induced skin disorders are listed in Table 5.2.

Immigrants from (sub)tropical countries, not using gloves and wearing inadequate footwear in the cold season are prone to perniosis. The clinical signs are redness, swelling, or purple patches on the feet and/or hands (Figure 5.2). Sometimes blisters and necrosis can occur. The symptoms are pain and itch. It must be differentiated from other diseases with similar symptoms, like chilblain lupus erythematosus, a variant of systemic lupus erythematosus, and lupus pernio, a variant of sarcoidosis. The treatment is
Influence of the New Environment on the Skin

difficult. One should advice adequate gloves, footwear, and ambient temperature. Vasodilating drugs might be of some use [6].

Psoriasis

Lack of exposure to sunlight (visible and/or ultraviolet) in immigrants in Europe (or other temperate climate regions), coming from sunny (sub)tropical countries can induce or provoke diseases that would not have appeared if they had remained in their former sunny location. Examples (based on epidemiological studies and case reports) are seasonal mental depression [7], osteomalacia, and rickets [8]. Based on experience in the Netherlands, we have the impression that psoriasis might be another example.

Psoriasis is a common genetically determined chronic relapsing skin disorder, clinically characterized (in the white skin) by the presence of sharply delineated patches with erythema, thickening, and scaling. Its worldwide prevalence is approximately 1–3%, although it appears to be uncommon in certain populations, for example, South American Indians. It is suggested that it is less common in people from African descent than in Europeans.

In people with ethnic skin, the disease has the same clinical characteristics as in whites, although the erythema is obscured by pigmentation (Figure 5.3).

After healing, a typical hypopigmented spot can remain, which slowly repigments. The typical localizations of lesions are the extensor sides of knees and elbows, the sacral region, and the scalp, but lesions can appear on virtually any part of the body. The lesions are not or slightly itchy. The clinical characteristics are usually sufficient to enable the diagnosis
to be made. Lesions in dark-skinned people can sometimes cause difficulties in making the right diagnosis. Eczema, especially nummular eczema, can resemble psoriasis; the same is true for neurodermatitis circumscripita (lichen simplex), lichen planus, and parapsoriasis. A skin biopsy for histological investigation can sometimes be helpful in making the right diagnosis. People coming from (sub)tropical countries can have their first episode of psoriasis after coming to Europe. One can speculate that the lack of UV light (which normally suppresses the disease) in the new environment, might be responsible. Psychological stress related with the life in the new environment is another hypothetical explanation.

The treatment for psoriasis is diverse and we refer to textbooks of dermatology.

**Skin diseases related to biological and immunological factors**

**Chickenpox (varicella)**

Chickenpox or varicella is a very contagious disease, caused by the varicella zoster virus. Chickenpox is common in certain immigrant groups coming from (sub)tropical countries to Europe or the United states. In a group of Tamil refugees to Denmark, 38% of the adults and 68% of the children developed chickenpox in the first few months after arrival, due to lack of immunity [9]. Struewing et al. [10] suggest that members of a high-risk immigrant group could benefit from varicella vaccination.

The disease is spread by droplet-airborne transmission. The incubation time is between 10 and 21 days. After a prodromal phase of 2 or 3 days with fever, malaise, and flu-like symptoms, the skin eruption appears (Figure 5.4). Lesions often begin on the face/head region and then spread. Lesions in the mouth and vagina are common. The initial lesion on a white skin is an erythematous macule, followed by a small vesicle, which later transforms in a pustule, subsequently an erosion, and finally a scab. The lesions appear in crops, with new crops appearing for an average of 3–4 days. Total healing takes 2–3 weeks. The eruption can be extremely itchy. On a dark skin, the initial erythematous macules are obscure and after healing “polka dot” hyperpigmented scars can be present for many months and sometimes even years.

The disease is usually mild, but serious complications can occur. These include secondary bacterial infection of the skin, otitis media, pneumonitis, and encephalitis. The differential diagnosis with insect bites can cause problems. Typical prodromal symptoms and lesions on mucosal membranes can be helpful in making the right diagnosis. A definite diagnosis can be made by identifying the virus (or viral antigen) from a lesion or by antibody assessment.
Antiviral drugs like acyclovir and valaciclovir are effective and should be considered for adults, immunodeficient patients, newborns, and individuals with eczema.

**Skin diseases related to chemical agents**

Several disorders can occur after industrial or nonindustrial exposure of the skin to chemical substances, for instance, contact dermatitis (allergic and nonallergic), halogen acne, chemical depigmentation, connective tissue disease, and skin cancer [11]. As an example, we have discussed chemical depigmentation.

**Chemical leukoderma**

Certain chemicals, particularly substituted phenols like p-tert-Butylphenol, are destructive to melanocytes and can so cause white patches in certain, possibly genetically predisposed persons [12]. These depigmentations cannot be easily distinguished from idiopathic vitiligo. The diagnosis of industrial (chemical-induced) leukoderma should be suspected if a worker who potentially has been exposed to depigmenting chemicals develops white patches on the sites of exposure. It should be differentiated from other disorders with depigmentation, like idiopathic vitiligo and disorders with hypopigmentation, like postinflammatory hypopigmentation. Anamnesis, including family history, inspection of the
whole body, and histology of a skin biopsy can be helpful in making the
definite diagnosis. There is no specific treatment, but if there is a wish to
treat, one can try treatment regimes that are advised for vitiligo.

**Skin disorders related to social and cultural factors**

**Adverse reactions to skin bleaching**

Skin bleaching is a globally common but not very well-studied phe-

nomenon among nonwhite persons, in particular women. They use

various chemical skin-bleaching products to hopefully acquire a light skin.

Clinical epidemiological reports show that skin bleaching is an “imported

phenomenon” in European countries. There are indications that due to

“psychosocial pressure” the bleaching practice is intensified in the new

environment by some individuals in certain groups of immigrants: side

effects of skin bleaching occur in immigrants in the Netherlands coming

from Suriname, while it is unknown in this group in their country of

origin [13].

Use of skin bleaching products can lead to various adverse reactions,
such as skin atrophy caused by corticosteroids and exogenous ochronosis
caused by hydroquinone, the most widely used bleaching agent. Exoge-

nous ochronosis is clinically characterized by darkening of the skin (Figure

5.5). It is a reticulated and ripple-like sooty pigmentation that must be

differentiated from other types of hyperpigmentation like postinflamma-
tory hyperpigmentation and melasma. The histological picture is pathog-
nomonic, with a dermal infiltrate and yellow-brown banana shaped
deposits in the H&E (hematoxylin and eosin) staining. Unfortunately,
there is no effective treatment known for this disease.

![Figure 5.5 Exogenous ochronosis](image)
Skin disorders in tourists

Tourists from a country in the temperate climate can develop several skin disorders in the tropical “paradise” they visit for leisure. Due to the hot and humid environment they can easily develop bacterial and fungal skin infections. These are discussed in Chapter 6. In this section we have confined ourselves to discussion of miliaria and sunburn as common skin disorders in tourists after a holiday in the (sub)tropics, due to physical environmental influences.

Miliaria

Miliaria or prickly heat is a disorder, commonly believed to be caused by blocking of the ducts of the eccrine sweat glands, probably by common skin bacteria like *Staphylococcus epidermidis* [14]. However, according to Shuster, duct disruption, and not blockage is the immediate cause of the miliaria [15].

Three types of miliaria are recognized, related to the level of the assumed obstruction:

- **Miliaria crystallina**: In this case the obstruction is in the stratum corneum, causing tiny superficial blisters with clear fluid that easily rupture. The disorder is asymptomatic.
- **Miliaria rubra**: This is the most common type; here the blocking is in the epidermis, causing itchy or stinging erythematous or skin-colored nonfollicular papules and papulovesicles (Figure 5.6).
- **Miliaria profunda**: The blocking is at the level of the dermoepidermal junction causing itchy, skin-colored nonfollicular papules.

Figure 5.6  Miliaria rubra
Miliaria is a common disorder in tourists visiting a hot humid climate. It can develop within a few days after arrival. The lesions are localized especially on the trunk, but can also be found on the head and neck region and the extremities. Complications are secondary bacterial infection, causing miliaria pustulosa or other types of pyoderma and disturbed heat regulation. Sweating is the most important means of heat regulation in a hot environment and blockage of sweating can cause body temperature to rise, causing a heat stroke with thirst, dizziness, weakness, and high body temperature.

Miliaria is generally easily diagnosed. It must be differentiated from folliculitis, which is characterized by follicular localized papules and pustules.

No compelling reason to treat miliaria crystallina exists because this condition is asymptomatic and self-limited. Miliaria rubra and miliaria profunda, however, can cause great discomfort. The prevention and treatment of miliaria primarily consists of controlling heat and humidity so that sweating is not stimulated. Measures such as a cool bath or a cool (air-conditioned) environment are generally adequate. Miliaria rubra and miliaria profunda can be treated topically with antipruritic agents. These disorders normally disappear within a few days after arrival in a cooler climate.

**Sunburn (dermatitis solaris)**

Sunburn is an acute inflammatory reaction of the skin, caused by the direct effect of light, which can start as soon as 30 minutes after sun exposure, characterized by erythema, swelling (edema), vesicles, bullae, and erosions of the sun-exposed region (Figure 5.7). The symptoms are a burning
feeling, tenderness, and pain that can be extreme. If a large area of the body is involved, it can be accompanied by systemic symptoms like fever, malaise, nausea and vomiting, dizziness, lowering of blood pressure, and shock. It can be complicated by secondary bacterial infection.

Moreover, next to the acute symptoms of sunburn, it is associated with the development of melanoma, the most hazardous type of skin cancer [16].

Sunburn is caused by ultraviolet radiation, especially UVB (290–320 nm). It is more common close to the equator and at high altitudes. Lighter skinned individuals (skin phototype I–III) are more frequently and severely affected than darker skinned types.

Diagnosis is easy on clinical grounds. The treatment consists of cool compresses, and anti-inflammatory medication like topical or systemic corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

Sunburn can be prevented by avoiding sun exposure, wearing of protective clothing, and the regular use of sunscreens with an adequate SPF (30 or higher).

Sunburn is by far the most common light-induced disorder occurring during a holiday in the (sub)tropics, but a number of other photodermatoses may develop (Table 5.3).

Finally, some preexisting skin disorders can exacerbate or aggravate during sun exposure, for example, herpes simplex and lupus erythematosus.

**Table 5.3** Skin diseases caused by sunlight

<table>
<thead>
<tr>
<th>Disease Type</th>
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<tbody>
<tr>
<td>Sunburn (dermatitis solaris)</td>
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<tr>
<td>Polymorphic light eruption</td>
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<tr>
<td>Solar urticaria</td>
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<tr>
<td>Actinic prurigo</td>
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<tr>
<td>Phototoxic reactions</td>
</tr>
<tr>
<td>Photoallergic reactions</td>
</tr>
</tbody>
</table>

References

CHAPTER 6

Fungal Infections

Roderick J. Hay

Kings College London, London, UK

Key points

Superficial mycoses

- Common
- Tinea capitis in children, tinea pedis and corporis in adults
- Where laboratory diagnosis is not available it is still useful to know which fungi cause dermatophyte infections in the patient’s country of origin.
- Scytalidium infections can mimic dermatophytosis of the foot or nails

Sporotrichosis

- Infection leads to a single granuloma or a chain of inflammatory nodules along a lymphatic duct
- Trauma after contact with plant materials, such as straw; cats may also be a source of infection
- Histology may not show the organisms as there are very few in lesions
- Main differential diagnoses—Mycobacterium marinum infection or leishmaniasis

Mycetoma (Maduromycosis, madura foot)

- Caused by actinomycetes (actinomycetomas) treatable with antibiotics; or fungi (eumycetomas) that respond poorly to chemotherapy
- Usually painless, discharging sinuses are diagnostic
- Key to diagnosis is the demonstration of small particles or grains in the sinus discharge

Chromoblastomycosis (Chromomycosis)

- Seen in tropical areas with high annual rainfall
- Present with large wart-like lesions; risk of squamous cell carcinoma in long-standing lesions
- Respond to itraconazole or terbinafine

Histoplasmosis

- Infection caused by Histoplasma capsulatum (histoplasmosis) or Histoplasma duboisii (African histoplasmosis)
Introduction

Fungal infections or mycoses that affect the skin include some of the commonest human diseases ranging from tinea pedis or athlete’s foot to cutaneous manifestations of deep infections, sometimes rare and, occasionally, life threatening [1]. The latter include diseases such as cryptococcosis that occur in HIV-positive patients during which bloodstream dissemination to the skin may occur. Imported infections may be seen as manifestations of all of these categories, although clinical presentation may occur years after the individual has left the country where they were infected. In considering if a disease has been acquired in a different environment it is important to recognize that there are patients who present after a short visit to a tropical environment because an existing condition has been exacerbated by the different climatic conditions; equally there are those who acquire a new infection as a result of their residence overseas.

There are three main groups of fungal infection: (1) the superficial, (2) the subcutaneous, and (3) the systemic infections (Table 6.1). The superficial infections are worldwide in distribution, although there are regional variations, and they include dermatophyte or ringworm infections, superficial candidosis or thrush, and *Malassezia* infections of which the common skin disease, pityriasis versicolor, is an example. The subcutaneous mycoses, with some exceptions, are largely confined to the tropics and subtropics; here the infection is usually introduced by implantation of the organisms from the external environment. These infections are largely confined to the subcutaneous tissue and dermis but may extend to the epidermis as well as bone. They may present with skin manifestations. The systemic infections involve deep structures. Some are primarily respiratory, and infection follows inhalation. The skin is affected if there is blood stream spread or, more rarely, if the infection is directly introduced into the skin. In the opportunistic systemic fungal infections the organisms gain entry via different routes, for example, gastrointestinal tract and intravenous catheters, but blood stream spread to the skin is possible. In many of these systemic mycoses the frequency of involvement of the skin is variable and unpredictable. However, some infections affecting patients with AIDS are highly likely
**Table 6.1** Classification of mycoses and the main imported infections

<table>
<thead>
<tr>
<th>Superficial mycoses</th>
<th>Tinea capitis. Rare: tinea imbricata</th>
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<tbody>
<tr>
<td>Dermatophytosis</td>
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<tr>
<td>Superficial candidosis</td>
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<tr>
<td>Disease due to Malassezia</td>
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<tr>
<td>Others, for example, Scopulariopsis infections</td>
<td>Infection due to Scytalidium</td>
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</tbody>
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<tr>
<th>Subcutaneous mycoses</th>
<th>All are uncommon imported diseases—in Europe mycetoma and phaeohyphomycosis are probably the two most frequently encountered of the subcutaneous mycoses.</th>
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<tr>
<td>Mycetoma</td>
<td>All are uncommon imported diseases—in Europe mycetoma and phaeohyphomycosis are probably the two most frequently encountered of the subcutaneous mycoses.</td>
</tr>
<tr>
<td>Chromoblastomycosis</td>
<td>All are uncommon imported diseases—in Europe mycetoma and phaeohyphomycosis are probably the two most frequently encountered of the subcutaneous mycoses.</td>
</tr>
<tr>
<td>Phaeohyphomycosis</td>
<td>All are uncommon imported diseases—in Europe mycetoma and phaeohyphomycosis are probably the two most frequently encountered of the subcutaneous mycoses.</td>
</tr>
<tr>
<td>Others, for example, infection due to Conidiobolus or Basidiobolus</td>
<td>All are uncommon imported diseases—in Europe mycetoma and phaeohyphomycosis are probably the two most frequently encountered of the subcutaneous mycoses.</td>
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<tr>
<th>Systemic mycoses</th>
<th>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</th>
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<tr>
<td>Endemic mycoses</td>
<td>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</td>
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<tr>
<td>Histoplasmosis</td>
<td>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</td>
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<tr>
<td>Coccidioidomycosis</td>
<td>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</td>
</tr>
<tr>
<td>Paracoccidioidomycosis</td>
<td>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</td>
</tr>
<tr>
<td>Infection due to Penicillium marneffei</td>
<td>All endemic systemic mycoses can be seen as imported diseases. In Europe the most frequent is histoplasmosis</td>
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<tr>
<th>Opportunistic mycoses</th>
<th>These can occur in any environment</th>
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<tr>
<td>Systemic candidosis</td>
<td>These can occur in any environment</td>
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<tr>
<td>Aspergillosis</td>
<td>These can occur in any environment</td>
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<tr>
<td>Zygomycosis</td>
<td>These can occur in any environment</td>
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<tr>
<td>Cryptococcosis</td>
<td>These can occur in any environment</td>
</tr>
<tr>
<td>Others, for example, Fusarium, Trichosporon</td>
<td>These can occur in any environment</td>
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The pathogenic fungi usually exist as chains of cells, hyphae, or single cells that reproduce by budding, or yeasts, in human tissue. Fungi are said to be dimorphic if they exist in different morphological phases, for example, yeast or mould, at different stages of their life cycle. Some of the systemic mycoses are dimorphic infections.

**Superficial mycoses**

The superficial infections are common in all environments. Most are unlikely to be imported, although traveling conditions in hot and humid climates may lead to the development of tinea or dermatophytosis or Malassezia infections. Both are most likely to have originated from organisms already carried by the traveler but may still present clinically during or after exposure to hot climatic conditions. Tinea cruris (dermatophytosis
of the groin) presenting in someone returning from the tropics would be an example. Likewise tinea pedis can be exacerbated by moist and humid conditions on the foot and can become secondarily infected with Gram-negative bacteria as well. There are however a few less common mycoses that can only be acquired in tropical areas.

Tinea imbricata is a form of tinea corporis that occurs in the West Pacific, Indonesia, and some remote areas of Brazil and Central America. It is caused by *Trichophyton concentricum* and is occasionally acquired by individuals working in an endemic area. It is seldom seen in short-term visitors. It is clinically characteristic, presenting with concentric and often extensive concentric rings of scales on the trunk or limbs. The diagnosis is confirmed by cultural identification of the organism.

Tinea capitis, due to organisms that are nonendemic in Europe, can be imported into a city with visiting children or with immigrants. These are usually due to anthropophilic organisms transmitted from child to child and they present with scaling and hair loss [2]. The organisms range from *Trichophyton violaceum* (East Africa and Indian subcontinent) to *Microsporum audouinii* (West Africa). *Trichophyton tonsurans* has become established in some European cities. Although it is also seen as an endemic infection in Europe, it is likely that the recent surge in infection rates has followed an earlier increased prevalence of infections due to this organism in the United States. It is predominantly, but by no means exclusively, seen in children of African Caribbean origin. It remains important to identify the causes of cases of tinea capitis by microscopy and culture.

Tinea nigra caused by *Phaeoanellomyces werneckii* is also occasionally seen as an imported infection. It presents as a black or brown macule, usually on the palms. There is scaling but generally this is not easy to define. It may be mistaken for an acral lentigo but skin scraping with demonstration of the presence of pigmented hyphae in direct microscopy is the best way of establishing the diagnosis. Often however, these are diagnosed after a biopsy to exclude an early acral melanoma.

*Scytalidium* infections due to *Scytalidium hyalinum* and *Scytalidium dimidiatum* (formerly *Hendersonula toruloidea*) that normally present as scaly dermatosis affecting the palms, soles, and toe webs, or onychomycosis are mainly seen in immigrants from the tropics [3]. There is no good evidence though that community transmission can occur in Europe in the same way as tinea pedis is spread, for example, in changing rooms, swimming baths. They mimic dry type infections caused by *Trichophyton rubrum*. However, occasionally they develop as nail infections in tourists who have spent weeks or months in a tropical environment. They do not respond to the antifungals that are currently available, although some improvements may be seen with terbinafine or itraconazole with topical amorolfine.
Tourists frequently present with pityriasis versicolor on returning from overseas travel. This is not strictly speaking an imported infection but has been acquired under the conditions prevailing in a hot sunny environment against a background of the carriage of *Malassezia globosa*, the usual cause, on perifollicular skin [4]. In a similar way, *Malassezia* folliculitis is also seen in patients recently returned from an overseas holiday when it presents with itchy follicular papules and pustules on the upper trunk or chest. The lack of comedones and the itching helps to distinguish the rash from acne.

**Subcutaneous mycoses**

The subcutaneous mycoses, or mycoses of implantation, are infections caused by fungi that have been introduced directly into the dermis or subcutaneous tissue through a penetrating injury, such as a thorn prick. Although many are tropical infections, some, such as sporotrichosis, are also seen in temperate climates; any of these infections may present as an imported disease in a patient who has originated from an endemic area, sometimes many years after leaving the endemic area. The main subcutaneous mycoses are sporotrichosis, mycetoma, and chromoblastomycosis. Rarer infections include lobomycosis and subcutaneous zygomycosis.

**Sporotrichosis**

Sporotrichosis is a subcutaneous or systemic fungal infection caused by the dimorphic fungus, *Sporothrix schenckii* that grows on decaying vegetable matter such as plant debris, leaves, and wood [5]. The main endemic areas are North, South, and Central America [6], including the southern United States and Mexico, as well as in Africa, Egypt, Japan, and Australia (Figure 6.1). Autochthonous infections are now rare in much of Europe. The most frequent site of this infection is the dermis or subcutis. The organism is introduced into the skin through a local injury. However, there is a rare systemic form of sporotrichosis whose clinical features range from pulmonary infection to arthritis or meningitis.

Subcutaneous sporotrichosis includes two main forms: (1) lymphangitic and (2) fixed infections. The lymphangitic form usually develops on exposed skin sites such as hands or feet (Figure 6.2). The first sign of infection is the appearance of a dermal nodule that breaks down into a small ulcer. Draining lymphatics become inflamed and swollen, and a chain of secondary nodules develops along the course of the lymphatic; these may also break down and ulcerate. In the fixed variety, which accounts for about 15% of cases, the infection remains localized to a single site, such as the face, and an inflamed granulomatus lesion develops that may subsequently ulcerate.
Figure 6.1  Distribution of sporotrichosis

Figure 6.2  Sporotrichosis—lymphangitic type
Fixed lesions have a granulomatous appearance and can closely mimic cutaneous leishmaniasis, whereas the lymphangitic lesions can be caused by other organisms such as *M. marinum*, *Nocardia*, as well as some *Leishmania* spp. Sporotrichosis can occur in individuals coming to a temperate area from overseas—it is rarely seen in tourists but may occur in people undertaking voluntary work such as construction projects.

The best sources of diagnostic material are smears, exudates, and biopsies. The yeasts of *S. schenckii* are scarcely distributed in lesions and very rarely seen in direct microscopic examination or histology. Culture is the best method of diagnosis and the organism can be readily isolated on Sabouraud’s agar. In biopsy material yeasts may be surrounded by an eosinophilic halo or asteroid body.

The traditional treatment is a saturated solution of potassium iodide, which is given in a dose of 1 ml three times daily (TDS) and the doses increased each day very gradually until a daily dose of 4–6 ml TDS is achieved [7]. Potassium iodide is unpleasant to taste and can also induce salivary gland enlargement as well as nausea and vomiting. Alternative treatments include itraconazole, 200 mg daily, or terbinafine, 250 mg daily, which are better tolerated, and intravenous amphotericin B for deep infection. In all cases treatment is continued for at least 2 weeks after clinical resolution.

**Mycetoma (Maduromycosis, madura foot)**

Mycetoma is a chronic localized infection caused by different species of fungi (eumycetomas) or actinomycetes (actinomycetomas) [8]. The infection is characterized by the formation of visible aggregates of the causative organisms, grains, which are surrounded by abscesses. These may drain through sinus tracts onto the skin surface or invade adjacent bone. The disease progresses by direct spread. The organisms are implanted subcutaneously, usually after a penetrating injury, for example, from an implanted thorn. Infections develop very slowly and may present years after an initial, and, often unnoticed, injury. The causative organisms can be found in soil or on plants. Mycetomas are mainly, but not exclusively, found in the dry tropics where there is low annual rainfall (Figure 6.3). They are sporadic infections that are seldom common, even in endemic areas. They are seen regularly as uncommon imported conditions in those originating from the tropics and they may present many years after the individual has left an endemic area.

Actinomycetomas due to *Nocardia* species are most common in Central America and Mexico. In other parts of the world the commonest organism is a fungus, *Madurella mycetomatis*. The actinomycete, *Streptomyces somaliensis*, is most often isolated from patients originating from Sudan and the Middle East.
The clinical features of both eu- and actinomycetomas are very similar. They are most common on the foot, lower leg, or hand, although head or back involvement may also occur. Infection of the chest wall can occur with *Nocardia* infections. The earliest stage of infection is a painless nodule that gradually enlarges with the development of draining sinus tracts over the surface (Figures 6.4 and 6.5). Local tissue swelling, chronic sinus formation, and later bone invasion may result in deformity. Lesions are only occasionally painful particularly when new sinus tracts are about to penetrate to the skin surface.
The appearance of a hard subcutaneous swelling with overlying draining sinuses, and often localized overlying increased sweating, is typical although the earliest lesions without sinuses are difficult to diagnose without a biopsy. The increase in sweating may however occur in such lesions.

Actinomycosis is an endogenous infection originating in the mouth, uterus, or chest and lesions with discharging sinuses, similar to the appearances of a mycetoma, are seen at such sites. Strictly speaking, though, it is not a mycetoma.

X-ray changes include periosteal thickening and proliferation as well as the development of lytic lesions in the bone. Magnetic resonance imaging is very useful in identifying the extent of bone and soft tissue lesions at an earlier stage.

Mycetoma grains may be obtained by opening a pustule or sinus tract with a sterile needle and gently squeezing the edges. Grains are 250–1000-μm white, black, or red particles that can be seen with the naked eye. Direct microscopic examination of grains show whether the grain is composed of the small actinomycete or broader fungal filaments as well as color. In general, it is not possible to distinguish the fine actinomycete filaments in potassium hydroxide (KOH) mounts or, in the case of histopathological sections, in hematoxylin/eosin-stained material. Grains (50–250 μm) are found within neutrophil abscesses and there are also scattered giant cells and fibrosis. The size and shape of grains visualized
in histopathology may help in their identification, although with non-pigmented fungal causes of mycetoma this is seldom sufficient. Culture is also useful although increasingly molecular tests including sequencing have played a role in identification.

Actinomycetomas generally respond to antibiotics such as a combination of sulphamethoxazole-trimethoprim plus rifampin or dapsone and streptomycin [9]. Amikacin may also be used in recalcitrant *Nocardia* infections. The response in all but a few cases is good.

A trial of therapy with itraconazole, terbinafine, or griseofulvin is worth attempting in fungal mycetomas although responses are unpredictable; some cases of *M. mycetomatis* infection respond to ketoconazole. Radical surgery, usually amputation, is the definitive procedure and may have to be used in advanced cases.

**Chromoblastomycosis (chromomycosis)**

Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissues caused by pigmented or dematiaceous fungi that are implanted into the dermis from the environment [10]. The infection can be caused by a number of different pigmented fungi, the commonest being *Phialophora verrucosa, Fonsecaea pedrosoi, Fonsecaea compactum, Wangiella dermatitidis,* and *Cladophialophora carrionii.*

The vast majority of infections are caused by *F. pedrosoi* and *C. carrionii,* which can be isolated from plant debris [11]. As with other subcutaneous mycoses, infection follows implantation through a tissue injury often in agricultural workers. The infection is a sporadic condition in Central and South America, the Caribbean region, Africa, the Far East, and Australia (Figure 6.6). It may occur as an imported infection outside the usual endemic areas but this is a rare occurrence.

The initial site of the infection is usually the feet, legs, or arms. These early lesions are small nodules that slowly expand over months or years. Established lesions are large wart-like nodules or flat atrophic plaques (Figure 6.7). Individual lesions may be thick and often develop secondary bacterial infection. Spread is by direct extension over the skin. Complications of chromoblastomycosis include local lymphedema leading to elephantiasis and squamous carcinomas in some chronic lesions. The early lesions can only be diagnosed by biopsy although once the warty changes have developed other conditions such as verrucous tuberculosis have to be excluded. More extensive lesions have to be distinguished from mossy foot secondary to chronic lymphedema caused by lymphatic filariosis or podoconiosis.

The typical brown sclerotic or muriform fungal cells can be seen in skin scrapings using KOH mounts taken from the skin surface of lesions, particularly those areas where there is a small dark spot on the affected skin
surface. It is always worth scraping the surface of suspected lesions as it provides a rapid diagnosis. Histology of biopsied material is also useful as the pathological changes and presence of muriform cells are both typical. The histology shows a mixed neutrophil and granulomatous response, with small neutrophil abscesses and pseudoepitheliomatous hyperplasia.
The organisms, which are often intracellular and clumped, have a single or double septum and thick pigmented cell wall.

The main treatments for chromoblastomycosis are itraconazole, 200 mg daily, or terbinafine, 250 mg daily [11]; in extensive cases, intravenous amphotericin B (up to 1 mg/kg daily) or one of the aforementioned drugs together with flucytosine may be used. The local application of heat has been described in some instances as helpful in shrinking lesions. The responses of these fungi to different antifungals does not appear to differ significantly, although there is some evidence that \textit{C. carrionii} responds more rapidly to both itraconazole or terbinafine. Treatment is continued until there is clinical resolution of lesions, usually after several months of therapy.

**Phaeohyphomycosis (Phaeomycotic cyst, cystic chromomycosis)**

Phaeohyphomycosis is a rare infection characterized by the formation of subcutaneous inflammatory cysts. It is caused by dematiaceous fungi, the most common of which are \textit{Exophiala jeanselmei} and \textit{W. dermatitidis}, but over 100 other species have been described as causative agents [12]. Although these organisms are pigmented, they form short irregular pigmented hyphae in tissue. The infection may occur in any climatic area, although it is commoner in the tropics. It occurs not infrequently as an imported infection, although it is rarely recognized prior to histology of an excised lesion. It may also appear in immunosuppressed patients. The lesions present as large cysts that may be surgically removed; the diagnosis becoming apparent after excision, for example, around the knee. They may mimic other conditions such as Baker’s cysts. Histologically, the cyst wall consists of macrophages and other inflammatory cells surrounded by a fibrous capsule, and the short fungal hyphae lie within the macrophage zone. Although the fungi in tissue lesions are usually pigmented, this is not always the case. The treatment is surgical excision without chemotherapy, although relapse can occur, particularly in immunocompromized patients.

**Other subcutaneous infections**

Subcutaneous zygomycosis occasionally presents as an imported condition. There are two forms caused respectively by \textit{Basidiobolus ranarum} (\textit{Basidiobolus haptosporus}), and \textit{Conidiobolus coronatus}. They present as localized hard swellings around the limb girdles in the case of the former and the central facial tissues with the latter. The organisms can be seen on biopsy and lesions usually respond to oral treatment with potassium iodide, given in similar doses to those used in sporotrichosis. Ketoconazole or itraconazole have also been used.
Systemic mycoses

The systemic mycoses generally invade deep structures such as the lungs, liver, and spleen as well as skin and mucosal surfaces. They may spread via the bloodstream to produce generalized or localized disseminated infections affecting the skin. There are two main varieties—(1) the opportunistic and (2) the endemic respiratory mycoses. Only the endemic mycoses are occasionally responsible for causing imported infections.

The endemic respiratory mycoses are histoplasmosis (classic and African types), blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and infections due to *P. marneffei*. The clinical manifestations of these infections depend on the underlying state of the patient, and follow broadly similar clinical patterns in all infections. These infections may also affect otherwise healthy individuals. They have well-defined endemic areas determined by environmental conditions. The usual route of entry in these infections is via the lung. They may be seen outside their endemic area as imported infections, although skin lesions are uncommon.

Histoplasmosis

In humans there are two main diseases caused, respectively, by two variants of *Histoplasma capsulatum*—(1) *H. capsulatum* var. *capsulatum* and (2) *H. capsulatum* var. *duboisii*. They can be distinguished because in tissue they produce yeasts of different sizes, the *capsulatum* variety producing cells from 2 to 5 μm in diameter, *duboisii* are cells of 10–15 μm in diameter. The other important difference is their epidemiology [13]. The two types of human infections are histoplasmosis and African histoplasmosis.

The pattern of disease is illustrated best with histoplasmosis. Histoplasmosis results from infection with the dimorphic fungus *H. capsulatum* var. *capsulatum*. The infection starts as a pulmonary infection that, in most individuals, is asymptomatic and heals spontaneously, the only evidence of exposure being the development of a positive intradermal skin test reaction to histoplasmin. However, in addition, there are symptomatic infections such as acute or chronic pulmonary histoplasmosis as well as a disseminated infection that may spread to affect the skin and mucous membranes as well as other sites such as the adrenal. Histoplasmosis occurs in many countries from the Americas to Africa, India, and the Far East (Figure 6.8). In the United States, it is endemic in the central states and around the Mississippi and Ohio River valleys, where often more than 90% of the population may have acquired the infection asymptotically. *H. capsulatum* is an environmental saprophyte that can be isolated from soil, particularly when it is contaminated with bird or bat excreta. The disease is acquired by inhalation of spores, and epidemics of
respiratory infection may occur in persons exposed to a spore-laden environment when exploring caves or cleaning sites heavily contaminated with bird droppings, such as bird roosts or barns. Amongst travelers, therefore, cave explorers are often affected by acute infections. Many patients, though, have no obvious history of exposure. It also causes a rapidly progressive disseminated infection in patients with disease affecting cellular immune capacity, such as AIDS [14].

The spectrum of histoplasmosis includes asymptomatic as well as benign symptomatic infections and a progressive disseminated variety with bloodstream spread to multiple organs. Skin lesions occur but are not common except in HIV/AIDS.

There are a number of different clinical syndromes due to *H. capsulatum*. These are described below:

**Acute Pulmonary Histoplasmosis**: In this form, patients are thought to have been exposed to large quantities of spores such as may be encountered in a cave. It is seen in cavers exploring in a tropical environment. The main symptoms are cough, chest pain, and fever, often with accompanying joint pains and rash—toxic erythema, erythema multiforme, or erythema nodosum. These skin rashes are not common, occurring
in fewer than 15% of patients, but they have been reported to be precipitated by antifungal treatment of the acute infection. The diagnosis is often made on the history of exposure in a suitable environment. The chest X-ray shows diffuse mottling. Serology may not become positive in the early stages of this disease.

**Chronic Pulmonary Histoplasmosis:** This usually occurs in adults and presents with pulmonary consolidation and cavitation, closely resembling tuberculosis. Skin involvement is not seen.

**Disseminated Histoplasmosis:** In acute forms of the disease there is dissemination to other organs such as the liver and spleen, lymphoreticular system, and bone marrow. Patients present with progressive weight loss and fever. This form is the type that is most likely to occur in untreated AIDS patients, who often develop skin lesions as a manifestation of disseminated infection [15]. These are papules, small nodules, or molluscum contagiosum-like lesions that may subsequently develop into shallow ulcers. Diffuse micronodular pulmonary infiltrates may also develop. Patients have progressive and severe weight loss, fever, anemia, and hepatosplenomegaly.

There are also more slowly evolving disseminated forms of histoplasmosis that may present with oral ulcers. Patients may have left an endemic area many years before they present with an isolated lesion such as a chronic oral or laryngeal ulcer or adrenal insufficiency.

The diagnosis of histoplasmosis is established by identifying the small intracellular yeast-like cells of Histoplasma in sputum, peripheral blood, bone marrow, or in biopsy specimens. The identity of the organism should be confirmed by culture; it grows as a mould at room temperature. Serology is often useful in diagnosis. A rising complement-fixation titer indicates dissemination. Precipitins detected by immunodiffusion are also valuable since the presence of antibodies to specific antigens, H and M antigens, correlates well with active or recent infection. The availability of serological tests for the detection of circulating Histoplasma antigens, has been particularly helpful in AIDS patients. In histopathological material, *H. capsulatum* is intracellular and is often seen in macrophages. The cells are small oval cells (2–4 μm in diameter) with small buds.

The choice of therapy for histoplasmosis depends on the severity of the illness. For patients with some disseminated or localized forms of the disease, oral itraconazole (200–400 mg daily) is highly effective. It has also been used for long-term suppressive treatment of the disease in AIDS patients after primary therapy either with itraconazole or amphotericin B. Intravenous amphotericin B (up to 1 mg/kg daily) is given to patients with widespread and severe infections.

Table 6.2 summarizes the clinical skin lesions that may occur with the other systemic mycoses presenting as an imported infection [16–21].
Table 6.2  Skin manifestations and imported systemic mycoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endemic area</th>
<th>Presenting skin features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Blastomycosis  
*Blastomyces dermatitidis* | North America, Central Africa     | Rare as an imported infection                                                            | Culture and histology—large yeasts that produce daughters cells on a broad base | Itraconazole               |
| Coccidioidomycosis  
*Coccidioides immitis* | Dry west coast United States, Mexico, Colombia, Venezuela, Argentina | Occasional erythema nodosum in primary infection  
Ulcers, abscesses, and granulomas rare  
Tourists can acquire acute infections while passing through an endemic region including some common US tourist destinations | Culture, serology, histopathology—large endospore (50–100 μm) containing spherules seen in various stages of development | Itraconazole, amphotericin B |
| Paracoccidiodomycosis  
*Paracoccidioides brasiliensis* | Mexico, Central, and South America | Ulcers and granulomas around orifices, for example, mouth, anus  
Rare if ever seen in tourists. May be present | Culture, serology, histopathology—characteristic multiple budding yeasts in tissue | Itraconazole               |
| Infection due to  
*Penicillium marneffei* | Southeast Asia, Thailand, Southern China, Hong Kong | Multiple papules, often with central umbilication, ulcers  
Risk in HIV-positive travelers to endemic areas | Culture, smears (bone marrow), histopathology—small yeasts with dividing septa | Itraconazole               |
However, the main diseases that can occur are coccidioidomycosis, which may present in travelers with erythema nodosum [18] or erythema multiforme or with disseminated ulcers of skin granulomas. It is more common for coccidioidomycosis to present with internal lesions such as lung granulomas. Paracoccidioidomycosis is also seen rarely as an imported infection with disseminated skin lesions often around the mucocutaneous junctions, for example, mouth (Figure 6.9 or conjunctivae [19]).
P. marneffei infection is also regularly seen in travelers who are HIV positive visiting endemic parts of Asia [20, 21] (Figure 6.10). It often presents with disseminated umbilicated skin papules on the face and trunk. The extent of these lesions is remarkable. Skin biopsy and histology plus culture are usually sufficient. It is a fallacy that these infections are difficult to diagnose although from time to time even an experienced laboratory misses the organisms.

Imported mycoses are seldom common but they are seen regularly and it is important to consider the diagnosis where possible in individuals who have visited remote areas. As always with imported infection it is always important to take an accurate travel history so that the movements of the individual can be correlated with the potential for exposure.

References

CHAPTER 7
Mycobacterial Infections

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Key points

- Think of (atypical) mycobacterial infection in patients with chronic infiltrative lesions and nonhealing ulcers.
- *Mycobacterium marinum* infection (swimming pool granuloma) can be acquired in tropical as well as non-tropical (in particular tropical aquaria) conditions.
- Mycobacterial infections tend to be more extensive in patients with immune suppression and in patients with genetic defects in the immune response.
- Proper management of mycobacterial infections requires expertise in diagnostic procedures and therapeutic regimens.

Introduction

Mycobacterial infections comprise infections that are caused by the different species of the genus *Mycobacterium*. They are thin, slightly curved to straight nonmotile bacilli, which can be visualized only by special staining techniques.

On the basis of clinical criteria they can be divided into the following three groups [1, 2]:

1. Strict pathogens for humans and animals.
2. Potentially pathogenic mycobacteria.
3. Normally saprophytic species that are nonpathogenic or only exceptionally pathogenic. This last group is often referred to as nontuberculous mycobacteria (NTM), mycobacteria other than tuberculosis (MOTT), or “atypical” mycobacteria.

Most mycobacteria give rise to localized and often harmless infections of the skin. In immunocompetent patients the disease is in general localized, although lymphatic spread, so-called nodular lymphangitis, is well known in, for instance, *Mycobacterium marinum* infections.
As mycobacteria are intracellular microorganisms the immunological response of the host is an immune reaction resulting in a granulomatous tissue reaction. In immunocompromised patients, infections with NTM may lead to extensive disease. Recently it was found that patients with genetic deficiencies in cytokine type I receptors suffer from, sometimes fatal, infections by weakly pathogenic mycobacteria.

Mycobacteria responsible for most cutaneous disease are *M. marinum*, *Mycobacterium ulcerans*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium avium-intracellulare*, and *Mycobacterium leprae*. Cutaneous disease may be due to inoculation, by trauma or iatrogenic; may be contiguous with underlying osteomyelitis or lymphadenitis, or may be part of disseminated disease. More rarely, infections are caused by *Mycobacterium szulgai*, *Mycobacterium kansasii*, *Mycobacterium haemophilum* [1–4].

Leprosy, which is supposed to have originated in East Africa or the Near East in the distant past, has still about 250,000 new cases detected yearly. Leprosy with its sometimes devastating consequences is addressed in Chapter 8. Buruli ulcer, named after the area in Uganda where prevalence was high, has spread to new areas, especially in Africa, and is addressed in Chapter 9.

### Tuberculosis

#### Introduction

The range of clinical manifestations of cutaneous tuberculosis provides a classical example of the varying immune response of the host towards an infection with mycobacteria, which also depends on previous exposure to other mycobacteria and the route of infection [5, 6].

Cutaneous tuberculosis has nowadays become a rare disease in inhabitants of the Western world. Therefore, the majority of cutaneous tuberculosis cases will be diagnosed in immigrants.

#### Epidemiology

Cutaneous tuberculosis was diagnosed in 2–4% of outpatients in dermatological clinics in Great Britain at the beginning of the twentieth century. The same figures have been reported in studies from Asia in the middle of the last century and appear to be decreasing.

In the majority the initial (primary) infection is due to inhalation of infected droplets from patients with active pulmonary disease. In circumstances where *Mycobacterium tuberculosis* is common as in Third World countries as well as in some medical settings in the Western world infection by inoculation of the skin can occur.
Clinical picture
Cutaneous tuberculosis can be classified according to the host cell-mediated immune response leading to multibacillary respectively paucibacillary forms (see Table 7.1).

Primary infection (tuberculous chancre)
It occurs due to exogenous inoculation of *M. tuberculosis* in the skin of a nonsensitized person. It is supposed to be an uncommon form of cutaneous tuberculosis. 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 that ulcerates. The ulcer has undermined edges, and is painless. After 3–8 weeks, nontender regional lymphadenopathy develops, which may suppurate to form a “cold” abscess, which then may spontaneously drain with sinus tract formation. This process in general heals spontaneously with atrophic scarring in 3–12 months. Primary lesions are mainly localized on the face and extremities of children, but inoculation by instrumentation, such as injections and surgical procedures, is possible. It may evolve in some cases into scrofuloderma, lupus vulgaris, or verrucous lesions.

*Differential diagnosis:* Other causes of ulceration, and chronic infections such as subcutaneous mycoses, cutaneous leishmaniasis, and malignant tumors.

Scrofuloderma (Tuberculosis Cutis Colliquativa)
It occurs due to contiguous spread from a deeper localized infection such as lymph node or in some cases bone. Initially there is an indurated inflammatory area overlying the deeper infection. Due to suppuration fluctuating nodules develop, which ulcerate with the formation of sinus tracts. In the

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**Table 7.1 Classification of cutaneous tuberculosis**

<table>
<thead>
<tr>
<th>Primary infection</th>
<th>Direct inoculation</th>
<th>Tuberculous chancre</th>
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<tbody>
<tr>
<td><strong>Secondary infection</strong></td>
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<tr>
<td>Multibacillary</td>
<td>Contiguous spread</td>
<td>Scrofuloderma</td>
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<tr>
<td></td>
<td>Autoinoculation</td>
<td>Oralificial tuberculosis</td>
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<td></td>
<td>Hematogenous</td>
<td>Tuberculous gumma</td>
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<tr>
<td></td>
<td></td>
<td>Acute miliary tuberculosis</td>
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<tr>
<td>Paucibacillary</td>
<td>Direct inoculation</td>
<td>Warty tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Hematogenous</td>
<td>Lupus vulgaris</td>
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<tr>
<td>Tuberculids</td>
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<td>Papulonecrotic tuberculid</td>
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<td></td>
<td></td>
<td>Lichen scrofulosorum</td>
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<tr>
<td></td>
<td></td>
<td>Erythema induratamo</td>
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<tr>
<td></td>
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<td>Erythema nodosum</td>
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</table>
course of time cord-like scars or keloids develop. The lesions heal in the course of years with characteristic pattern of fibrosis and scarring. Recurrence of drainage is common. The lesions are mostly localized over the lymph glands in the neck.

_Differential diagnosis:_ Deep mycoses as sporotrichosis and coccidioidomycosis, actinomycosis, hidradenitis suppurativa in axillary lesions, lymphogranuloma venerum in inguinal lesions, and chronic bacterial osteomyelitis when localized over bone.

**Orifical Tuberculosis (Tuberculosis Ulcerosa Cutis et Mucosae)**

It occurs due to autoinoculation of organisms from an active infection at a deeper site. It occurs in patients with extensive disease in whom the immune reaction is suppressed, and therefore bears a poor diagnosis. It is reported to be quite rare. Lesions start with single or multiple nodules, which become fluctuant and ulcerate with the formation of draining sinuses. The lesions are painful. Localizations are, as the name implies, characteristically around the anus, mouth, nose, and genitalia, in patients with advanced disease.

_Differential diagnosis:_ Other diseases with ulcerations as aphtous ulcers, herpes simplex lesions, and ulcerations of venereal diseases.

**Tuberculous Gumma (Metastatic Tuberculous Ulcer)**

It occurs due to hematogenous dissemination from a primary focus, during periods of lowered resistance with bacillemia.

The lesion starts with a subcutaneous nodule or a fluctuant swelling. The overlying skin breaks down, resulting in an undermined ulcer with sinus formation. It then resembles scrofuloderma.

_Differential diagnosis:_ Tertiary syphilitic gumma, subcutaneous mycoses, and cutaneous leishmaniasis.

**Acute Military Tuberculosis (Tuberculosis Cutis Miliaris Disseminata)**

Due to extensive dissemination of _M. tuberculosis_ to skin and other organs in case of complete failure of cell-mediated immune reactivity. It is usually in the form of a generalized eruption of purplish papules, with vesicles on top, which may break resulting in crust formation, and nodules with necrosis and ulceration. The lesions are disseminated over the whole skin with a predilection for the trunk. Due to the absence of cell-mediated immune reactivity, the histopathological picture is a nonspecific inflammation with numerous acid fast bacilli.

_Differential diagnosis:_ The rash is not specific and should be differentiated from other maculopapular and acneiform eruptions. The patient, however, is systemically ill, and this should be an additional clue.
Warty Tuberculosis (Tuberculosis Verrucosa Cutis)

It occurs due to exogenous inoculation of *M. tuberculosis* in the skin of a person with an acquired immune response towards *M. tuberculosis*. Therefore, due to the rapid cell-mediated response the infection stays localized, and regional lymphadenopathy is not prominent. It is reported to be the most common form of cutaneous tuberculosis in Asia.

The lesion develops from an asymptomatic reddish-brown papule into a verrucous plaque of varying shape and size. The surfaces are hyperkeratotic and rough to verrucous (wart-like) with deep fissures. The lesion can be moist from serous exudates to purulent due to secondary bacterial infection. The plaque may heal spontaneously in the course of months to years, with atrophic scarring in one place and extension in the other. Lesions are mostly localized on the limbs and buttocks of children in endemic areas. It was an occupational risk for workers in several professions such as pathologists (so-called prosector’s wart), butchers, and abattoir workers. In these cases disease is mostly localized on the fingers or dorsum of the hands.

*Differential diagnosis: Common wart in the initial stage. Verrucous lesion caused by atypical mycobacteria, some forms of deep mycoses like blastomycosis and chromomycosis, some forms of South American leishmaniasis, verrucous tertiary syphilis, and skin cancer.*

Lupus Vulgaris

It occurs due to reactivation in patients with a high degree of immunity after earlier hematogenous dissemination. However, lupus vulgaris lesions have also been described in warty tuberculosis, scrofuloderma, and after Bacille Calmette-Guérin (BCG) inoculation. It was the most common manifestation of cutaneous tuberculosis in Europe. But the incidence has dropped sharply after World War II. It is common in some developing countries.

The lesions start with brown-red papules, which in the classical form extend to plaques with peripheral activity with an irregular border and central healing with atrophic scar formation with depigmentation (Figure 7.1). The clinical picture can be very variable; besides the plaque form there is a hypertrophic form with nodules, which may form a hyperkeratotic mass. The most destructive type is the ulcerative form, which may erode cartilage and bone, and results in extensive scarring and even deformities. It follows a chronic course, and lesions may persist for decades, with gradual extension and progressive scarring, deformity, and loss of function. The most common localization is the face, with the nose, cheeks, mouth, and earlobes as preferential sites. In Asia and Africa, lesions on legs and buttocks are common. Spinocellular carcinoma may develop in chronic lupus vulgaris lesions.
**Differential diagnosis:** Lupoid variant of cutaneous leishmaniasis, subcutaneous mycoses, sarcoidosis, chronic discoid lupus erythematosus, and basal cell carcinoma.

**BCG infections**
BCG vaccination, with an attenuated strain of *Mycobacterium bovis*, is practised in many areas of the world. The vaccination provokes an immune reaction, which is clinically seen as an infiltrative papule that develops in 10–14 days at the inoculation site. It enlarges into an ulcerative lesion of approximately 1 cm at 10–12 weeks. It heals with scarring. After approximately 3 months the tuberculin skin test reverses from negative to positive. Complications, although infrequently, may occur in the form of progressive ulcerative infection, abscess formation, regional lymphadenitis (sometimes with scrofuloderma), lupus vulgaris, and tuberculids.

**Differential diagnosis:** Depends on the clinical picture of the complication.

**Immunological reactions to tuberculosis elsewhere (tuberculids)**
Tuberculids are a number of dermatological manifestations, especially associated with infection with *M. tuberculosis*. They are supposed to be due to the dissemination of *M. tuberculosis* or antigenic particles to the skin in persons with a well-established immune response. The lesions are usually widespread and symmetrical.
Agreement about the range of tuberculids was hampered by the fact that in general *M. tuberculosis* cannot be demonstrated by special stains in a biopsy nor can it be cultured from a biopsy, and that evidence for active infection elsewhere in the body is lacking. The following are nowadays accepted to be true tuberculids.

**Papulonecrotic Tuberculid**
It is the most common tuberculid nowadays. The clinical picture is that of scattered symmetric, red papules or papulopustules that become reactive with a black scab. They may heal with antituberculous treatment, but may also resolve spontaneously as a depressed scar with a hyperpigmented border.

The presence of *M. tuberculosis* DNA by means of PCR in lesions of papulonecrotic tuberculid supports the tuberculous origin.

*Differential diagnosis*: Prurigo papules, folliculitis, papular lesions of syphilis. Necrotic lesions should be differentiated from pityriasis lichenoides acuta, lymphomatoid papulosis, necrotizing vasculitis, and necrotic insect bite reactions.

**Lichen Scrofulosorum**
Is nowadays a rare manifestation of the tuberculids. Clinically, it is an eruption of small lichenoid papules with a rough surface, often localized perifollicularly and grouped in nummular lichenoid plaques. PCR has also demonstrated the presence of *M. tuberculosis* DNA in lesions of lichen scrofulosorum.

*Differential diagnosis*: Lichenoid eruptions as lichen planus, secondary syphilis, pityriasis lichenoides chronica, lichenoid drug eruptions. Due to the perifollicular distribution it has to be differentiated form keratosis follicularis, lichen nitidus, and pityriasis.

Differentiation from the micronodular form of sarcoidosis may be difficult.

**Erythema Induratum of Bazin (Nodular Vasculitis)**
Erythema induratum, described by Bazin in 1855, has been considered to be associated with tuberculosis. Nowadays it is accepted that it can be induced by numerous triggers including tuberculosis [7]. The clinical picture is that of firm, deep, violaceous nodules and plaques on the back of the lower legs especially in middle-aged women. The histopathological picture is a nodular vasculitis. *M. tuberculosis* DNA has been demonstrated in biopsies from nodular vasculitis [8].

*Differential diagnosis*: Erythema nodosum, panniculitis, polyarteritis nodosa.
Erythema Nodosum
It was, in the past, frequently associated with tuberculosis, but nowadays in the Western world, it is most frequently caused by streptococcal disease, sarcoidosis, drug reactions, and inflammatory bowel disease, but tuberculosis still should be considered in developing countries.

Clinically, it manifests itself as painful erythematous nodules on the lower legs, especially the extensor aspect. The histopathological picture is a panniculitis with vessel involvement, and gives no information on the cause.

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

Treatment
Treatment of cutaneous tuberculosis is commonly done with a multiple drug regimen consisting of isoniazid, ethambutol, pyrazinamide, and rifampicin.

M. marinum infection (swimming pool granuloma) [2, 3, 9–11]

Introduction
Swimming pool granuloma is caused M. marinum, a mycobacterium belonging to the atypical mycobacteria, which causes disease in fresh- and saltwater fish, and occasionally in humans.

Epidemiology
As initial reports of cutaneous disease by M. marinum were associated with swimming pools, it was called swimming pool granuloma. Infection in swimming pools nowadays is rare due to proper chlorination. The distribution is worldwide, occurring in fresh-brackish as well as salt water, and is prevalent in heated water (for instance, in tropical aquaria) in temperate climates, and in pools and the sea in more tropical climates. In principle, any water-related activity carries a potential risk for infection. Infection takes place through, in general superficially, traumatized skin.

Clinical picture
After a relatively long incubation period of 2–6 weeks, the initial lesions start as inflammatory papules. As infection is preceded by trauma, lesions are usually localized on the back of fingers (Figure 7.2) or hand, or around the knee. The papule then gradually enlarges in violaceous nodules or plaques, which may ulcerate or develop a warty surface. As these lesions are painless and enlarge slowly there is generally a delay of months or even
years before a doctor’s opinion is sought. These lesions may heal spontaneously; however, this may take months to years. Deep infections such as tenosynovitis, osteomyelitis, arthritis, and bursitis occur infrequently. *M. marinum* infections are one of the causes of nodular lymphangitis (also called sporotrichoid spread after the lymphatic spread of sporotrichosis). Clinically, it shows nodules and/or ulcerating lesions resulting from spread along the lymphatic vessels. Deep infections and nodular lymphangitis do not heal spontaneously.

**Diagnosis**
The clinical picture, the preferential localization in combination with a history of aquatic activity with skin trauma, should lead to a high index of suspicion. The clinical diagnosis should be confirmed by diagnostic tests. Histopathological examination of a skin biopsy can be nonspecific in the early stage of the disease. After 6 months a granulomatous reaction develops. The presence of acid-fast bacilli by special staining techniques is reported in varying percentage of cases; absence does not rule out *M. marinum* infection. Cultures can be performed from aspirates or biopsies. The optimal growth is at 30–32°C, and cultures should be maintained for 6 weeks. Nowadays, PCR techniques from biopsy material provide the possibility of a diagnosis within days.

**Treatment**
Several treatment options exist. Treatment regimens consist of combinations containing clarithromycin, doxycycline, rifampicin, or ethambutol. More recently the new macrolides such as clarithromycin or doxycycline
may be used as single drug therapy in limited disease. However, no randomized studies have been performed. Response to treatment is slow, and therapy is continued till after clinical cure.

*M. fortuitum infections [2, 3, 12]*

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

**Clinical picture**
The clinical manifestations are localized cases of cellulitis, frequently with draining abscesses or nodules. A history of a penetrating injury with possible soil or water contamination is often reported. Postoperative infections, in general, develop 3 weeks to 3 months after surgery. *M. fortuitum* infections can be treated by monotherapy or combination therapy with, for instance, ciprofloxacin, ofloxacin, amikacin, and clarithromycin.

*M. chelonae infections [2–4, 12]*

**Epidemiology**
*M. chelonae* is described to be more common in Europe. Skin, bone, and soft tissue disease are the most important clinical manifestations.

**Clinical picture**
The clinical manifestations are similar as those due to *M. fortuitum*: localized cellulitis, and draining abscesses or nodules. It may occur at all ages, typically after trauma or a surgical incision.

**Treatment**
Treatment of localized disease is by clarithromycin.

*M. abscessus infections [2, 3, 12–14]*

**Epidemiology**
*M. abscessus* is an environmental ubiquitous present organism. It predominated in skin and soft tissue infections in the recent increase of NTM infections in Taiwan.
**Clinical picture**
The clinical manifestations are similar as those due to *M. fortuitum*: localized cellulitis, and draining abscesses or nodules. It may occur at all ages, typically after trauma or a surgical procedure.

**Treatment**
*M. abscessus* is more resistant to chemotherapeutic agents than the related species *M. chelonae*. For serious infections, a combination of oral macrolides, clarithromycin, and azithromycin, in combination with parenteral medication is advocated.

**M. avium-intracellulare infections [2, 6]**

**Epidemiology**
This mycobacterial species, with over 20 subtypes, occurs worldwide in nature. And it may be isolated in more than 30% of fecal samples of humans.

**Clinical picture**
Pulmonary infection is the most common clinical manifestation. Skin involvement occurs by direct inoculation and in the course of dissemination from primary visceral lesions in immunocompromised hosts as papules, nodules, plaques, and ulcers.

**M. szulgai infections [2]**

**Epidemiology**
The natural habitat of *M. szulgai* is not known. It has, however, been isolated from snails and tropical fish.

**Clinical picture**
The predominant localization of infections is pulmonary. Cases of skin infection have been reported.

**M. kansasii infections [2, 3]**

**Epidemiology**
*M. kansasii* causes diseases in humans throughout the world. It has been isolated from cattle and swine. However, water is most likely its true natural habitat. It can affect 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 are diverse: resembling pyogenic abscess, cellulitis, or sporotrichosis. Cervical lymphadenitis was reported predominantly in children.

*Mycobacterium hemophilum* infections [2]

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

Clinical picture
It appears that pre- or early adolescents of both sexes are more susceptible to a mild and limited form of skin infection. It also causes cases of submandibular lymphadenitis in children.

Treatment
Treatment of cutaneous infections by atypical mycobacteria is preferably done by selecting the drugs based on the antimicrobial susceptibility profile. Empiric therapy should be started until the results of susceptibility testing are available. Empiric therapy is also necessary in cases of negative culture but identification by means of PCR technique. It may also be required when there are negative diagnostic tests with a clinical suspicion of mycobacterial disease; the response to treatment is then a confirmation of the clinical diagnosis (Figure 7.3). Duration of treatment is not fixed.
and is based on clinical judgment. It will require, in general, 2–6 months [2–4, 6, 12].

**General comments**

Although the classification of cutaneous tuberculosis has been applied to infection with *M. tuberculosis* one has to realize that in studies on cutaneous tuberculosis, diagnosis is often made on clinical and/or histopathological grounds, in part supplemented with cultures.

However, recently, clinical manifestations, as described for cutaneous tuberculosis have been reported for NTM such as lichen scrofulosorum by *M. avium*, lupus vulgaris by *M. avium* and *Mycobacterium xenopi*, papulonecrotic tuberculid reaction by *M. kansasii*, and scrofuloderma by *M. hemophilum*. In these more recent cases the infectious organism was identified by culture or PCR [15]. It is, therefore, conceivable that, by application of modern molecular biological techniques on biopsies and cultures, clinical pathology, which formerly would be classified as being caused by *M. tuberculosis*, in fact may be caused by other (nontuberculous) mycobacteria.

As the clinical picture of mycobacterial infection of the skin can be non-specific, a high index of suspicion is warranted. In cases of persistent infiltrative lesions or a nonhealing ulcer investigation for mycobacteria is indicated. As is illustrated by a nonhealing ulcer in a patient, which developed during a travel in Middle America and in which *M. immunogenen* was cultured [16].

**Cutaneous mycobacterial infections and immune suppression**

Coincident with the HIV epidemic the number of infections of the skin with mycobacteria, in particular *Mycobacterium avium* complex, has increased. In patients with HIV and other forms of immune suppression lesions can present as nonhealing nodules, plaques, or ulceration. Depending on the degree of immune suppression widespread skin involvement may occur, presenting as papules, nodules, plaques, with possible abscess formation, and ulcers. Lymph node infection can occur.

Moreover, it has been found that patients with interferon-γ and interleukin (IL)-12 receptor deficiencies are prone to infection with normally nonpathogenic mycobacteria. As the interferon-γ and IL-12 pathways are crucial in the development of immune response to intracellular microorganisms, widespread cutaneous involvement can be found (Figure 7.4) [17].
Nowadays, also in patients on biologic therapies, especially the tumor necrosis factor (TNF-α)-inhibitors, skin infections with NTM have been described [18].

References

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CHAPTER 8

Leprosy

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Key points

In anyone who is born or has lived in a leprosy endemic area, leprosy must be suspected:

- when a hypopigmented or skin-colored macule is seen with loss of sensation to touch, pain, temperature, or with loss of sweating;
- when slightly erythematous, skin-colored or livid papules and nodules are seen; or
- when a patient presents with unexplained sensory loss or muscle weakness.

Leprosy is diagnosed when two out of three cardinal signs are positive:

1. Loss of sensation in a skin lesion
2. Enlarged peripheral nerves
3. A positive skin smear

When only one of the signs is present further investigations are warranted: biopsy, immunological, or electrophysiological studies.

Leprosy is only occasionally encountered in a traveler.

Introduction

The slogan “elimination of leprosy by the year 2000,” later extended to the year 2005, has induced the general belief that leprosy is eradicated. Nothing is less true [1]. During the years 1998–2001 more leprosy patients were diagnosed (700–800,000 per year) than ever documented in the past. However, after 2003 there was a drop in the number of newly registered patients and this number continues to decline [2]. Over 2010 only 228,474 new cases were reported [3]. Figure 8.1 shows the reported prevalence in January 2011.

In 2006 the World Health Organization declared that leprosy had been “eliminated” as a “public health problem.” This would have been a huge achievement if it was true. However, it is shown that changing

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operational and administrative targets played a decisive role in achieving
the elimination targets. Definitions have been changed and treatment
periods shortened. Leprosy services have been dismantled and integrated
into the general health services without proper training and follow-up
[1, 4]. To date the true prevalence of the disease is in some areas more
than twice the registered [5]. With the increase in and the extent of
mobile populations in the world it is a disease to reckon with, a disease
that may lead to severe disabilities when not diagnosed in time and not
treated properly. Doctors’ delay is a big problem in Europe and the United
States [6, 7]. Moreover, it is so in many of the leprosy endemic countries
too, where leprosy is often hardly taught at Medical Schools [8].

Increasingly, leprosy shows as an immune reconstitution inflamma-
tory syndrome (IRIS): seropositive HIV patients infected with *M. leprae*,
when treated with ARVs, recover their cell-mediated immunity and then
develop clinical leprosy, indicating that there may be a pool of *M. leprae* of
unknown size [9].

Until 2005, leprosy was the disease to be eliminated; now it is counted
among the neglected diseases.

**Epidemiology**

Leprosy is still endemic in Middle and South America, in Africa south of
the Sahara, and in Asia from Iran to Indonesia, on some islands in the
Pacific, and in the northern territory of Australia. (Figure 8.1) More than
85% of the leprosy patients live in the following countries: India, Brazil,
Indonesia, Nepal, Mozambique, Madagascar, United Republic of Tanzania,
Democratic Republic of the Congo, and Central Africa.

Leprosy is an infectious disease caused by an intracellular acid-fast bac-
terium: *M. leprae*. In 1873, Armauer Hansen was the first to describe the
bacterium as the cause of leprosy, instigated by the work of Drognat
Landré, a Dutch physician working in Suriname, who from his observa-
tions concluded that leprosy must be a contagious disease [10]. However
the postulates of Koch have still not been fulfilled. It has not yet been pos-
sible to infect someone willfully with *M. leprae*, although anecdotal reports
show infection after tattooing and following the skinning and cleaning of
infected armadillos for the cooking pot [11].

It is generally considered to be an airborne infection, direct from the oro-
nasal-pharyngeal mucosa to oro-nasal-pharyngeal mucosa, but there are
indications that the indirect way of infection through the soil and inocula-
tion into the skin should not be discarded. Even direct skin-to-skin contact
and sexual intercourse may be the cause of infection [11].
Figure 8.1 Leprosy prevalence rates, data reported in January 2011 (reproduced from Leprosy prevalence rates, data reported to WHO as of beginning January 2011, with permission WHO)
It may be theorized that differences between the immune responses elicited by different routes of infection, skin versus nasal mucosa, is responsible for the outcome of the infection. Entrance through the skin may lead to a delayed type of hypersensitivity reaction or resistance, while through the mucous membranes it may lead to tolerance. Balance between those two routes of infection may at least in partum determine the spectrum [11].

However data to date suggest that the response is also modulated by genetic factors, among which are HLA-DR, NRAMP1, and small genetic differences, polymorphisms, in other membrane receptors like IL-2, INF-gamma, Toll-like receptor, and small polymorphisms in the molecular structure of cyto- and chemokines [11, 12]. But the immune system has many ways to compensate for such differences.

Most likely, previous encounters with other microorganisms and autoantigens with antigenic determinants similar to those of \textit{M. leprae} are more important. If genetics have a major impact, it could be that genes of the host, needed by the bacillus to survive in the host cell, are the determining factor. \textit{M. leprae} has a very small genome and needs the metabolism of a host cell to survive.

The final result: resistance, delayed type of hypersensitivity, tolerance, disease or no disease, tuberculoid, borderline or lepromatous leprosy, with or without reactions, is most likely mediated by the orchestration of the cyto- and chemokines induced in harmony with the cellular response [11, 13].

**Clinical spectrum**

The clinical manifestations of leprosy are various, but it has been possible to classify the patients along a clinical spectrum. This was most neatly done coincidentally, but independently by Ridley and Jopling in the United Kingdom and by Leiker in the Netherlands in 1966 [14, 15]. The classification is based on the Cell-Mediated Immune response (CMI) of the patients against \textit{M. leprae}, leading to a clinical spectrum (Figure 8.2). On one side of the spectrum, with a relatively high CMI towards antigenic determinants of \textit{M. leprae}, the tuberculoid (TT) patients are classified. They manifest clinically with one or a few well-defined hypopigmented or erythematous patches, usually with central healing and marked loss of sensation in the patch, sometimes with an enlarged peripheral nerve (Figure 8.3). \textit{M. leprae} is not detectable. On the other side of the spectrum are the lepromatous patients with an absent CMI against the organism. These patients are actually teeming with bacteria; they present the perfect culture medium. The bacteria may be present anywhere in the body with the central
nervous system (CNS) as a possible exception. The patients may show minimal hypopigmented or erythematous patches, ill defined, and usually with the sensation still present. However, they may show glove and stocking anesthesia with symmetrically enlarged peripheral nerves. They also may show papules, nodules, and plaques, which are skin colored, erythematous, hyperpigmented or livid, or show only a diffuse infiltration (skin lines and creases are disappearing): “Lepra bonita” (Figure 8.4). There may be loss of eyebrows (madurosis) and a more or less generalized diminished sweating. Between these two poles of the spectrum, the borderline leprosy group is found, encompassing most of the patients. The clinical range is from borderline tuberculoid (BT) leprosy with a few asymmetrical distributed well-defined tuberculoid patches and a few enlarged nerves, to borderline lepromatous (BL) leprosy with more symmetrically

![Figure 8.2 The leprosy spectrum (courtesy Dr. D.L. Leiker)](image)

Figure 8.2 The leprosy spectrum (courtesy Dr. D.L. Leiker)

![Figure 8.3 (a) TT leprosy: a single well-defined patch. (b) TT leprosy: pure neural with a single enlarged branch of the sural nerve](image)

Figure 8.3 (a) TT leprosy: a single well-defined patch. (b) TT leprosy: pure neural with a single enlarged branch of the sural nerve
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Figure 8.4 LL leprosy: diffuse infiltration; also called “lepra bonita”

distributed hypopigmented or erythematous macules and/or papules and nodules. The latter are mainly located on the colder parts of the body. In the middle of the spectrum is a very unstable group, midborderline (BB) leprosy having lesions with an immune area (the center of the lesion is not involved) and with typical dome-shaped elevated small plaques.

In the borderline range, patients may up- or downgrade (e.g., change their classification within the spectrum). Upgrading indicates that the patient develops more tuberculoid features, downgrading more lepromatous. In upgrading leprosy the bacterial load diminishes and in downgrading the bacteria multiplies. In a downgraded patient, a few patches may show loss of sensation whereas the other newer lesions do not or less. In an upgrading patient new tuberculoid lesions, with loss of sensation may appear or lesions may become atrophic (heal).

Up- and downgrading occurs either unnoticed or is accompanied by a reactional phenomenon called Type-1 leprosy reaction (T1R) or reversal reaction (RR), in which an enhanced CMI toward *M. leprae* antigenic determinants may cause irreversible nerve damage.

Indeterminate leprosy comprises a special group of leprosy patients having one or two slightly hypopigmented or erythematous macules with or without detectable loss of sensation or loss of sweating. The biopsy may show a single bacterium or a minimal lymphocytic infiltration in a dermal nerve. The diagnosis is difficult to establish and some leprologists consider it to be an early, transient form of either multibacillary (MB) or
paucibacillary (PB) leprosy, which either may heal (over 80%) or become frank MB or PB leprosy.

For operational purposes, the leprosy spectrum is simplified to PB and MB leprosy. PB leprosy patients are indeterminate, TT and BT leprosy without *M. leprae* in skin smear or biopsy. MB patients are BT, BB, BL, and LL patients with *M. leprae* in smear or biopsy. However, in many control programs, the smear services are unreliable, therefore these programs have to resort to very simple clinical criteria [16]. The World Health Organization classifies all patients with five or less lesions as PB. The remaining patients are then classified MB.

Leprosy in children may be present as early as 3 months after birth. Usually, depending on the endemicity of leprosy and socioeconomic circumstances, leprosy manifests itself after the age of 6 years. An important reason for this is that the incubation time appears to be between 2 and 5 years. Most children, when diagnosed early, show indeterminate leprosy or leprosy with borderline features, mostly tuberculoid. Since PB leprosy needs only a few bacteria to show clinical symptoms, the clinical manifestations of tuberculoid leprosy develop earlier in life than those of lepromatous leprosy. Lepromatous leprosy, when it develops in children, seems especially confined to the head and the extremities, that is, the colder parts of the body.

**Diagnosis and classification**

Awareness is the most important factor for the diagnosis of leprosy. When a patient lives or has lived in a leprosy endemic country, leprosy must always be considered in the differential diagnosis of a hypopigmented or erythematous patch or a papular or nodular eruption. The same certainly applies for each condition accompanied by peripheral nerve function impairment. Hypopigmented or erythematous patches are frequently seen. An important feature of a leprosy lesion is that it does not itch but shows loss of sensation to fine touch. This can be tested by means of a piece of cotton wool made to a fine thread (Figure 8.5). The skin should not be stroked but touched with the cotton wisp. The sensation in the patch is then compared with the sensation of the surrounding normal skin, by asking the patient to point where the skin was touched. It is remarkable how sensitive this investigation is. Established loss of sensation makes the diagnosis “leprosy” very likely; when an enlarged nerve can be palpated the diagnosis can be considered definite. It may not be possible to test the sensation in very young children. The absence of sweat in a skin lesion after “running,” sun bathing, or exposure to heat may then be a helpful diagnostic tool.
One should be aware that in the face, where hypopigmentation frequently occurs especially in children, loss of sensation occurs late, if it is ever detectable, with the crude tests used. Patches of pityriasis alba are often present in the face. These can be differentiated from leprosy by carefully describing the size and place of each lesion, and requesting that the child be brought back in 3 months. By then, a pityriasis alba spot has most likely disappeared or changed place. A leprosy patch will remain in exactly the same spot and may have enlarged. The evolution of leprosy at this stage is usually slow and it is not dangerous to wait. Be alert for a hypopigmented patch, which suddenly becomes inflamed. This is a sign of danger: a reaction may be imminent! A T1R in the face often leads to facial palsy with lagophthalmus and loss of corneal sensation. This may result in blindness.

Nerves that can be inspected and palpated are the cutaneous nerves in the immediate vicinity of a patch, further, among others, the frontal nerve, on the forehead above the eye, the great auricular lateral in the neck, the ulnar, the median and the radiocutaneous on the lower arm, and the lateral popliteal and the tibial posterior nerves on the lower extremities. Enlarged nerves herald leprosy. Tender nerves may be a sign of reaction and warrant immediate action. Inexperienced examiners should learn to palpate at least the ulnar, the radial, the lateral popliteal, and the great auricular nerves.
When someone has nodules or papules, which are skin colored and firm on palpation, leprosy should be suspected, especially when these are symmetrically distributed on the colder parts of the body, such as ears, nose, cheeks, elbows, buttocks, and knees. A skin smear or biopsy should be positive for *M. leprae*. The presence of enlarged nerves may be helpful. Improper closure of an eyelid and dry spots on the skin of palms or soles may also indicate leprosy and warrant further investigation. The same—of course—applies in the case of lagophthalmus, claw hands, drop feet, painless blisters, and ulcers, but by then severe damage has already occurred.

Classification may be difficult. In short:

PB features are loss of sensation in a well-defined patch with central healing. The patches are few (less than five) and asymmetrically distributed. Only one, maximum two nerves may be enlarged or show signs of neuropathy.

MB features are papules and nodules and/or ill-defined patches with a symmetrical distribution. In particular, small papules may be present along the ears; the earlobes may be swollen and sometimes a lateral madurosis (loss of eyebrows) is present; skin smears are positive. Nerves are symmetrically involved and enlarged.

**Laboratory tests**

There are no laboratory tests available to replace a good clinician. Serology, especially against phenolic glycolipid I (PGL-1), can only be used for the follow-up of an individual MB patient during treatment, in the same way as the bacillary index (BI; logarithmic representation of the count of acid-fast bacteria (AFB) in a AFB-stained skin smear) is used. Serology may be positive in contacts and negative in PB patients [17]. PCR may detect *M. leprae* DNA and Nucleic acid sequence based amplification (NASBA) RNA in nearly all untreated MB patients and often in PB patients too, but certainly not always [18]. Serology and possibly NASBA can be used to detect relapse in MB patients [17–19].

Skin tests, in particular the, often considered obsolete, lepromin test, may be of assistance in the classification, being positive in tuberculoid and negative in lepromatous patients. However, it can be positive in leprosy contacts and even in leprosy noncontacts. The same applies for laboratory tests such as the Lymphocyte Transformation Test. Lepromin is obtained from biological material like human and armadillo and therefore difficult to make. Its use is debated, since it may be contaminated with human or armadillo proteins.

Histopathology is an important and sensitive diagnostic tool, but still the experienced physician remains the “golden standard.” Especially because
a biopsy is from one area and leprosy may manifest differently in different lesions.

**Diagnosis of reactions**

The recognition of reactions is of utmost importance since the reactions may lead to permanent nerve damage and functional impairment [20]. Two nerve-damaging reactions may occur:

- The T1R also called RR, a typical delayed-type hypersensitivity reaction, and
- The Type-II leprosy reaction (T2R) also called erythema nodosum lepromatous (ENL), which seemed to be caused by the formation of immune complexes within the tissues.

A T1R can be suspected when a lesion becomes more inflamed, red, and swollen, and enlarges (Figure 8.6). New patches may appear, especially in MB leprosy. In these patients acro-edema may also occur. Nerve lesions may manifest themselves with increasing loss of sensation and strength. Patients may complain of neuropathic pains. Nerves may enlarge, becoming palpable and tender [20].

ENL, T2R, is a reaction that mainly occurs in MB patients with an established leprosy infection of longer duration. It may be a generalized reaction accompanied by fever and discomfort. The patient is usually ill and shows painful erythematous or skin-colored papules and nodules, which are tender on palpation (Figure 8.7). The lesions often are more easily palpated than seen. The lesions are most commonly situated on the extremities and in the face. T2R, being a generalized disease, may also show neuritis, lymphadenitis, arthritis, orchitis, keratitis, iridocyclitis (cave

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**Figure 8.6** Type-I leprosy reaction; swollen erythematous enlarged lesions
glaucoma), glomerulonephritis, and hepatitis. Even peritonitis has been observed. Each of these symptoms may occur separately or in any combination. T2R is an episodic phenomenon. It occurs and abates apparently spontaneously. More than 90% lasts less than 1 month. When it becomes chronic, an intercurrent condition like anemia, intestinal parasites, or a chronic ulcer may be present. The possibility of a simultaneously occurring tuberculosis infection should also be considered [20].

Both reactions may occur before antimycobacterial treatment is instigated, during treatment and even after treatment, when a patient is bacteriological cured but is still immunological active. Leprosy is foremost an immunological disease. Reactions belong to the natural course of a leprosy infection. Antimycobacterial treatment may either precipitate a reaction or prevent it, but it is certainly not the cause.

**Antimycobacterial treatment**

Two types of treatment regimens are given; one to PB patients and the other to MB patients [21, 22]. The results of these regimes are excellent; hardly any relapses occur.

PB leprosy patients receive six monthly dosages within 9 months, for an adult 600 mg rifampicin once monthly supervised and 100 mg dapsone daily unsupervised. Children receive according to weight. For a white adult Caucasian a maximum dose of 50 mg dapsone may be considered since hemolysis among this group occurs regularly and is mostly not only related to G6PD deficiency.

MB leprosy patients received in addition once monthly 300 mg clofazimine (Lamprene®) under supervision and daily 50 mg clofazimine unsupervised. (When 50 mg clofazimine is not available, 100 mg alternate days may be given). Within 36 months, 24 dosages should be given.

In 1998, the World Health Organization gave new directions. It recommended for Single Lesion Leprosy a single dose treatment consisting of
rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg (ROM-treatment). For children this should be adjusted to age and weight [23].

Single Lesion Leprosy is often seen in children. It heals in over 80% by itself. It is frequently indeterminate leprosy which, when it does not heal and is left untreated, may go into frank tuberculoid or lepromatous leprosy. Whether this single dose treatment will be effective for the non-self-healing Single Lesion Leprosy has not yet been properly established, and may be doubted.

For MB patients the World Health Organization recommended to shorten the treatment period to only 12 monthly dosages, within 18 months. Strong opposition of the leprologists met this recommendation. They feared relapses, especially in patients with a high number of bacteria, and more severe reactions after the discontinuation of treatment. They advised to treat only MB patients with only a few bacteria (low BI) with this shortened course of treatment and none of the others. The shortening was implemented nevertheless and has indeed led to some increase in relapses among the highly bacillary MB patients and moreover to a substantial increase in reactions, both T1R and T2R.

**Treatment of reactions [20, 24, 25]**

When a T1R, RR occurs, prednisolone has to be added to the antimycobacterial treatment, to start with 0.5–1 mg/kg bodyweight in a single morning dose daily. Some may argue that steroids are a dangerous treatment, but they should realize that if left untreated a T1R may lead to lifelong disability, which does not occur when properly treated. When the reaction settles the prednisolone treatment can be slowly tapered off but should, for at least 3–6 months, remain above 0.25 mg/kg. Thereafter it can be tapered off further under careful observation of the nerve function. Voluntary muscle testing (VMT) and graded sensory testing (GST) are extremely useful instruments for this. In patients with a contraindication for the use of steroids ciclosporin may be considered [26].

It must be noted that a T1R regularly occurs after the discontinuation of the antimycobacterial treatment, probably due to the discontinuation of dapsone, which has immunomodulating properties. A reaction occurring after treatment should also be treated with steroids. It is either an autoimmune reaction against antigenic determinants on the patients’ own tissue, which are identical to those of M. leprae, or a reaction against remaining M. leprae antigens.

It is advisable to check on intestinal parasite infections before the steroid treatment is started. However, this should not delay the treatment.

A T2R is an episodic phenomenon and should be treated when it occurs. De Souza Arauyo in 1929 has noted the natural duration of the reaction;
most reactions last only 2 weeks, and nearly all end before a month has passed.

A mild reaction, with some discomfort and a few ENL nodules, responds to mild anti-inflammatories and analgesics. It usually will abate on its own. However, when it is more severe or involves eyes or nerves, steroids are indicated, since damage may occur that might be irreversible. Mostly a dosage of 1 mg/kg suffices. It can be tapered off in 2–4 weeks’ time, the natural course of the reaction. In more severe reactions especially in patients with chronic and recurrent reactions the treatment should be started with 2 mg/kg and tapered down quickly in 3–4 weeks. In case the reaction reoccurs, treatment should be restarted at full dose. When it occurs during tapering off, one may consider doubling the dose and again taper off. A long and continuous maintenance dose of steroids should be prevented. Steroid dependence is at present one of the largest problems in the treatment of chronic T2R. It is possible that the prednisolone 3-month-blister packs, which are easily available from the World Health Organization, is a main culprit. The doses are at the start too low to counteract an immune-complex driven disease and too long for a disease that lasts in the majority of the attacks less than 1 month. The doses in the pack given after a month are too low to prevent a reaction.

When a reaction becomes chronic a careful search for a possible underlying illness should be done. When a cause cannot be found, a long-term course of thalidomide has to be instigated and it is advisable to use clofazimine as well, starting with 300 mg daily which can be tapered off over a period of 3–6 months to 100 mg [27]. Thalidomide may also be used in the treatment of acute T2R reactions. (Starting doses 100–300 mg) [20]. But since this, due to its history, is not easily available it should be reserved for the chronic recurrent cases. It is more helpful than steroids to prevent a recurrence. Combination of low dose steroids and low dose thalidomide seems to be counterproductive. They have a negative interaction.

It has been suggested that TNF-α was the crucial molecule in the pathogenesis of T2R. For that reason, for a period pentoxiphylline was advised as treatment but it showed not to be very active. A biological TNF-α inhibitor may sometimes be of some benefit in a patient with chronic T2R [28]. But recurrences may happen after discontinuation.

If during a T1R or T2R a nerve continues to deteriorate despite adequate treatment where other nerves recover, a nerve release operation should be considered. This should be done under steroid coverage.

**Rehabilitation**

After nerve damage has occurred and has become irreversible, proper care should be taken. This includes health education and physiotherapy...
to keep the hands mobile, the eye protected, and the foot covered with suitable footwear. Neuropathic feet, a not uncommon condition, due often in Western societies to delay in diagnosis, should preferably be treated in a multidisciplinary setting [29]. Dropfoot surgery, eye and hand surgery can be considered. This is often successful in children and young adults when done by experienced surgeons alongside experienced physiotherapists and health educators. Dermatologists are often not familiar with the terminology used by the physiatrists and physiotherapist they refer their patients to.

Impairments are changes in anatomy, physiology, or mental function. Activity limitations are difficulties in functioning at the personal level (activities of daily living) and restrictions in participation are problems at the societal, socioeconomic level, including attitudes. In persons affected by leprosy, even in affluent societies, these are all present.

With the increase in interest in pain it is noticed that a number of “cured” leprosy patients continue to have neuropathic pain, not due to a reaction or any other activity of their leprosy [30]. These neuropathic pains are difficult to handle but a multidisciplinary approach can be contemplated including nerve release surgery.

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Key points

- Buruli ulcer (BU), caused by the environmental organism *Mycobacterium ulcerans*, is the third most common human mycobacterial infection. Incidence is highest in West Africa.
- *M. ulcerans* contains a virulence plasmid coding for “mycolactone,” a necrotizing, immunosuppressive toxin mediating pathogenesis, to include necrotizing skin and bone lesions. Residual scarring is an important public health issue.
- Transmission is unclear. One likely mode is minor skin trauma permitting inoculation of *M. ulcerans*; others are under investigation.
- Geographically, there are multiple strains of *M. ulcerans*, with variable pathogenicity.
- First line therapy for BU is daily rifampicin (oral) + streptomycin (intramuscular) for ≥8 weeks, sometimes with surgery for severe disease. All-oral treatment is being studied.
- Multidisciplinary investigation is providing insight into *M. ulcerans* evolution, genotypic variants, and pathogenesis, improving control and treatment strategies.

Introduction

Buruli ulcer (BU), caused by environmental *Mycobacterium ulcerans*, is an indolent necrotizing disease of the skin, subcutaneous tissue, and bone [1]. BU, listed among World Health Organization’s neglected tropical diseases, is the third most common mycobacterial disease of humans, after tuberculosis and leprosy [2]. The disease was named after the geographic area of the first large epidemic investigated in Uganda (1961), in a county named “Buruli,” now called “Kasongola,” near Lake Kyoga [3]. *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, apoptosis, and immuno-suppression [4, 5].

BU is a growing public health problem, primarily because of its frequent disabling and stigmatizing complications. Since 1998, World Health Organization, working closely with endemic countries, nongovernmental organizations, and universities, has highlighted the growing problem of BU, and developed improved treatment and control programs [6]. However, many questions remain unanswered.

Epidemiology

BU afflicts all age groups but most cases occur in children younger than 15 years old. There are no gender preferences [7]. Most lesions are on the lower extremities, a relatively cooler site.

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 [8]. New BU foci in Africa are being discovered [9]. The disease has been reported, but not necessarily laboratory confirmed, in >30 countries (Figure 9.1). A few cases have been reported in nontropical areas of Australia, Japan, and China. Imported BU is occasionally reported in industrialized countries where BU is not endemic, with approximately 20 cases described.

Focal epidemiology of BU is complex. Incidence rates vary greatly by continent, country, and within areas of a country. As such, case detection rates reported at the national or district levels do not indicate wide variations that often exist at the village level within a given district. In some African countries, over many decades, only a few cases of BU have been reported. In the Americas, BU seems most common in French Guiana, with about 200 cases since 1970. Incidence of BU is low in Asia and Oceania. Since 1971, about 400 cases have been reported in Papua New Guinea. In Australia, the main focus is North Queensland, with 92 cases reported over the past 44 years [10].

BU is directly related to environmental factors and thus considered non-contagious [1, 11]. The epidemiology of BU is strongly associated with wetlands, especially with slow-flowing or stagnant water bodies. The exact mode(s) of transmission from the environment and the ultimate natural source(s) of infection remain obscure. One plausible mode of transmission is local, minor, often unnoticed skin trauma that permits inoculation of M. ulcerans. The route of transmission may be related to geographic region [12].
Figure 9.1 Buruli ulcer distribution by country, as of 2010. Relative endemicity is denoted as high (red), moderate (yellow), and low (green); (*) denotes countries with suspected cases. Imported Buruli ulcer is occasionally diagnosed in industrialized countries (redrawn by Ms. Siripan Phatisawad) (reproduced from Walsh et al. [6])
**M. ulcerans** DNA is detectable in some aquatic insects, prompting investigation into biting insects as vectors infecting humans [13]. Portaels et al. reported the first direct isolation of *M. ulcerans* from nature in 2008 from a water strider, an aquatic insect that does not bite humans [11]. In Australia, BU may be a zoonosis transmitted by mosquitoes, from indigenous marsupials to humans [14]. In Africa, terrestrial mammals are being investigated as reservoirs of *M. ulcerans* [15].

Risk factors for BU, within endemic areas, include failure to wear protective clothing, exposure to unprotected natural water sources, and inadequate care of minor skin wounds [16]. HIV seropositivity may increase risk for BU, and be associated with aggressive BU [17].

**Clinical picture**

**Infection versus disease**

Somewhat similar to tuberculosis, exposure of cutaneous tissues to *M. ulcerans* may lead to one of three outcomes: (1) clearance of the infection, (2) clinical disease soon after infection (primary BU), or (3) subclinical or asymptomatic infection (latent BU) that may subsequently reactivate and produce disease. It is likely that most individuals exposed to *M. ulcerans* clear the infection and never develop the disease. The natural history of BU is presented elsewhere [1].

The incubation period of primary BU is estimated to be 2–3 months. Delayed onset of disease, that is, ≥3 months after leaving an endemic area, may represent activation of latent infection. For example, some individuals who originally resided in a BU endemic area months to years earlier may develop BU at a body site where trauma occurs [1]. In contrast, the incubation period may occasionally be short (≤15 days), with lesions developing in proximity to a bruise or sprain, without clinically detectable damage to the skin. This also suggests activation of latent *M. ulcerans* infection caused by local trauma.

**The disease**

*M. ulcerans* disease presents in a spectrum of lesion morphologies, which may in part depend on time to seek medical care, host immune status, inoculum size, inoculation depth, geographic area, and *M. ulcerans* strain virulence. Delayed care results in an increased frequency of ulcerative forms.

Nonulcerative forms often occur in early stages, sometimes ignored by patients, and occasionally heal spontaneously. Nonulcerative lesions may progress to ulcers, typically after a few weeks to months, causing medical
Imported Skin Diseases

Complicated disease categories include *mixed*, in which different morphologies appear in the same patient at the same or different sites, such as scarring lesion (inactive) adjacent to an ulcerative lesion (active) at the same site (Figure 9.3). *Disseminated* disease involves lesions present at different sites, sometimes in different morphologies. Spreading of the disease may occur by contiguous or lymphohematogenous modes. 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 (Figure 9.4).
Table 9.1 Buruli ulcer (*Mycobacteria ulcerans* infection) spectrum of cutaneous lesions

<table>
<thead>
<tr>
<th>Lesion morphology</th>
<th>Major characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonulcerative</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Papule            | • Initial lesion, most common in Australia  
|                   | • Up to 1 cm, elevated, ulcerates early  
|                   | • Painless |
| Nodule            | • Initial lesion, common in most Africa  
|                   | • 1–3 cm, subcutaneous, firm, overlying skin may be discolored  
|                   | • Painless, often pruritic |
| Plaque            | • ≥2 cm, firm, elevated, well-defined, irregular borders, overlying skin discolored (Figure 9.4)  
|                   | • May or may not arise from a nodule  
|                   | • May ulcerate late, sometimes “stellate” pattern  
|                   | • Painless |
| Edema             | • Often no nodule, spread directly from initial nidus of infection  
|                   | • Rapid spread, may cover entire limb or large portion of face or trunk  
|                   | • Diffuse, nonpitting, vague margins, firm, color changes, scaling  
|                   | • Painless, sometimes fever |
| **Ulcerative**    |                       |
| Ulcerative Minor  | • ≤2 cm, often sharply delineated  
|                   | • May self-heal early |
| Ulcerative Major  | • >2 cm  
|                   | • Chronic; if self-healing, late |

Bone involvement is a serious development. In Africa, osteomyelitis, either contiguous or metastatic, is observed in approximately 10% of patients. *Contiguous* osteomyelitis involves reactive osteitis beneath destroyed overlying skin and soft tissue. Bone becomes devitalized and necrotic. *Metastatic* osteomyelitis likely results from lymphohematogenous spread of *M. ulcerans* from a cutaneous lesion, which may have already become a scar (Figure 9.5). Diagnosis of bone infection is made by radiological examination. Bone disease should be referred for specialty care to reduce the risk of serious consequences, such as limb amputation.
The disease may also be classified in three categories, according to lesion size, which may be helpful for choosing a treatment regimen (see Section “Treatment”):

*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.
Scarring
Poorly managed BU patients often present with atrophic scars. When these occur over a joint, there may be severe disabling sequelae. Adhesion and contracture of periarticular scars reduce joint range of motion, which may then ankylose and become largely immobile. Hypertrophic scars or keloids may also develop, usually on the limbs. Squamous cell carcinoma (Marjolin’s ulcer) may develop in unhealed lesions or scars, the latter especially in hypopigmented areas.

Diagnosis
Many conditions resemble BU, underscoring the importance of a differential diagnosis if BU is suspected. Lesion sampling and laboratory procedures for suspected BU are described in the following text, and in more detail elsewhere [18].

Clinical differential and diagnosis
Differential diagnoses include bacterial, deep fungal and parasitic infections, inflammatory lesions, and tumors. For ulcerative and edematous BU, entities in the differential diagnosis include tropical phagedenic ulcer (TPU) and necrotizing fasciitis, respectively [19]. Both conditions, unlike BU, are painful, and TPU emits an unpleasant odor.

Clinical criteria supporting the diagnosis of BU include:

- ⩾1 painless ulcers lasting at least several weeks, undermined edges;
- nodule, plaque, or edematous lesion, or depressed scar;
- swelling over a painful joint, suggesting bone involvement;
- no fever or regional lymphadenopathy (assumes no bacterial superinfection);
- patient <15 years of age; or
- patient lives in, or has traveled to, a BU endemic region, especially West Africa.

Collection of clinical specimens for laboratory testing
For routine assessment of suspected BU, ulcers should be swabbed at undermined surfaces and, for most other lesion types, fine needle aspiration (FNA) can be used [20]. Lesion biopsies, punch or excisional, not commonly conducted in the field for lack of sterility, 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 osteomyelitis. Sampling at least two sites of each lesion is suggested, which may increase sensitivity over a single sample
by up to 25%. Further guidance for sampling is available elsewhere [21,22].

**Laboratory confirmation**

Laboratory confirmation of BU is important because treatment potentially involves a moderately toxic antibiotic (streptomycin) and sometimes surgery.

Four laboratory tests are available to confirm the diagnosis of BU. Lesion swab material may be used for: (1) direct smear examination for acid-fast bacilli (AFB), that is, Ziehl-Neelsen or auramine stain; (2) *in vitro* culture on mycobacteriological media, at 30–32°C; and (3) PCR amplification of insertion sequence (IS) 2404, considered virtually specific for *M. ulcerans*. The fourth technique, punch biopsy, allows for histopathologic examination. World Health Organization recommends that ≥2 different laboratory tests should be positive to confirm BU.

Laboratory tests differ in sensitivity [23]. 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.

Histopathology may confirm BU or generate a differential diagnosis when otherwise unconfirmed. Culture is often useful for tracking treatment response [23]. At the community level, direct smears are useful, but rapid diagnostic tests are needed. Detection of mycolactone or *M. ulcerans*-specific proteins in lesions or other fluids are in early development [24].

**Treatment**

Historically, the mainstay of BU treatment has been wide excisional surgery. Antibiotics were generally considered ineffective, even though by the 1970s encouraging reports of rifampicin (R) antibiotic therapy for early lesions appeared [25].

In 2004, with supportive experimental and preliminary clinical data [26], World Health Organization advocated a *provisional* antibiotic regimen for BU composed of oral R (10 mg/kg) + intramuscular (IM) streptomycin (S) (15 mg/kg), both given daily for 8 weeks under supervision, with surgery as needed [27].

In 2010, Nienhuis *et al.* reported the first randomized trial of R + S for “early, limited” BU, defined as lesions of <6 months duration composed of nodules or ulcers <10 cm in diameter [28]. R + S, given daily for 8 weeks, or R + S daily for 4 weeks, followed by all-oral R + clarithromycin (CLR)
daily for 4 weeks, all without surgery, healed BU in >90% of patients in 1 year.

Currently, World Health Organization recommends R + S for 8 weeks as first line therapy for all categories (I, II, III). An alternate regimen is R + S for 4 weeks, followed by all-oral R + CLR for 4 weeks. In general, recurrence rates in Category I and II disease after completing an R + S-based regimen appear low (1–2%).

Despite the success of antibiotics for BU, extensive disease often requires surgery. However, the timing of surgery in relation to antibiotic administration is unclear. In Benin, 12 weeks of R + S for BU osteomyelitis did not prevent dissemination to other bones during treatment, despite one or more surgical procedures [29, 30]. Clearly, optimal management of severe BU, such as length of antibiotic treatment and when to perform surgery, needs further investigation [31]. Physiotherapy, especially for Category III disease, should also be considered to prevent contracture deformities [32].

Small case series studies describing 4–8 weeks of all-oral regimens for BU, including R + CLR in Benin and R + moxifloxacin in Australia, are encouraging [33, 34]. All-oral regimens are less toxic, convenient alternatives to R + S that may improve compliance, and are especially relevant in pregnancy, in which streptomycin is contraindicated [35].

BU that develops inflammation or a worsening appearance during antibiotic treatment may be a paradoxical sign of success, possibly associated with a cell-mediated immune response [36]. Lesions developing after treatment completion may represent anamnestic-like immune responses to clear subclinical foci of M. ulcerans bacteria, treatment failures, or reinfections [37]. It is important to distinguish paradoxical reactions from M. ulcerans infection, optimally by laboratory assessment.

**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 [38].

Bacille Calmette-Guérin (BCG) vaccination may protect against BU, estimated for 6–12 months after vaccination, and neonatal BCG vaccination may reduce the risk of BU osteomyelitis [1].

*M. ulcerans*, with hallmarks of an intracellular organism, triggers Th1 cell-mediated immunity (CMI) [39, 40]. This is relevant for developing prophylactic or therapeutic vaccine candidates that boost CMI against *M. ulcerans*. BURULIVAC, a collaborative project funded by the European
Union under the 7th Framework Programme, supports efforts to identify vaccine candidates based on DNA engineering and virulence factors, including mycolactone [41].

**Conclusion**

Many important aspects of BU remain unresolved, such as reservoirs, modes of transmission, risk factors, development of point-of-care tests, optimal management, and prevention. BU remains inadequately recognized by some health professionals, even within endemic countries. A multidisciplinary approach remains indispensable for improved control of BU worldwide.

**Disclaimer:** The views expressed here are those of the author (DSW) and do not reflect the official policy of US Department of the Army, US Department of Defense, or the US Government.

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CHAPTER 10
Ulcerating Pyodermas

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Key points

Pyoderma
- Most common cause of skin ulcers in travelers from the tropics
- Generally because of Staphylococcus aureus or group A β-hemolytic streptococcus
- Cutaneous diphtheria is often overlooked
- Antibiotic-resistant strains are a growing problem

Introduction

Serious (ulcerating) pyodermas, especially in the lower legs of travelers are regularly encountered at the departments for tropical skin diseases in the Western world. The term pyoderma covers several clinically distinct skin lesions that are mainly caused by Staphylococcus aureus or group A β-hemolytic streptococcus. It is a common cause of (purulent) ulcerative skin lesions in developing tropical countries where predisposing factors appear to be hot climate, humidity, poor hygiene, reduced access to water, and overcrowding [1, 2]. Generally, there seems to be no difference in the colonization of chronic wounds in the tropics as compared with those in the temperate developed regions of the world. However, the prevalence of antimicrobial resistance, which is high in some locations in the tropics, may complicate treatment. Microcirculatory disturbances leading to subclinical edema, especially in the lower legs, have been noted in travelers. This edema may delay wound healing in travelers [3].

The most common infectious causes of ulcerations are shown in the flowchart (Figure 10.1). Leishmaniasis should always be considered in returning travelers, but diphtheria is probably often overlooked [4, 5]. Pyoderma and cutaneous diphtheria are discussed in this chapter.
Although ulcerating pyoderma is encountered all over the world, it seems to be more prevalent in the tropics. Environmental factors such as temperature and humidity may also contribute. However, there are only few published studies available on the prevalence or the incidence of pyoderma under tropical conditions [6]. A study performed in Blantyre, Malawi did not show a high incidence of ulcerating pyoderma at the in- and the outpatient population at a hospital [7]. However, ulcerating pyoderma was the most common cause of such ulcers.

β-hemolytic streptococci are present in the throat of about 10% of the normal population. β-hemolytic streptococci group A are transmitted mainly by air in droplets when there is close contact between individuals. Skin lesions and the upper respiratory tract are the primary focal sites of infection. A normal undamaged skin does not provide a favorable environment. It seems that at least a minor trauma is necessary for the development of streptococcal pyoderma. Since protecting clothing is used less under tropical conditions, minor trauma of the skin is more likely to occur providing a port of entry for an infection.

Colonization of the human skin by *S. aureus* is encountered in 30–50% of healthy adults of whom 10–20% are persistently colonized. Carrier sites are the anterior nares, the perineum, the axillae, and the toe webs. Infection may be initiated after colonization of skin lesions, especially moist
lesions. Whether an infection is contained or spreads depends on several complex factors such as the host defense mechanisms and the virulence of the \textit{S. aureus}. Several toxins and enzymes such as protease, lipase, and hyaluronidase contribute in the invasion and the destruction of tissues. It remains unknown whether colonization of the skin is higher in the tropics. There has been a worldwide increase in staphylococcal infections. However, systematic surveillance data on the prevalence from tropical countries are limited. Some data are available on antimicrobial resistance, which shows methicillin-resistant strains as an increasing problem. Special attention must be paid to the community-acquired methicillin-resistant \textit{S. aureus} (CA-MRSA) as an emerging cause of severe skin and soft tissue infections, even in previously healthy individuals. Many CA-MRSA strains produce the toxin Panton-Valentine leucocidin, which is associated with a tendency to produce abscesses, invasiveness, and has a high fatality rate [8]. It has recently been reported as a cause of complicated soft tissue infections in travelers returning from nontemperate climates [9].

Cutaneous diphtheria is still endemic in tropical countries, whereas it is generally travel-related and currently rare in the developed world because of the policy of routine active immunization. Recent large epidemics in eastern Europe have again drawn attention to this disease. Cutaneous diphtheria may be encountered more often in the near future because of the increased travel to and from the endemic countries.

**Clinical aspect**

\textit{S. aureus} and group A \(\beta\)-hemolytic streptococcus remain the two major microorganisms that are responsible for most of the ulcerating skin infections. Infection of the skin with \textit{S. aureus} or group A \(\beta\)-hemolytic streptococcus may have different clinical pictures from folliculitis to true skin ulcers (Figures 10.2 and 10.3). Ecthyma is known as a clinical entity and is characterized by a deep pyogenic ulcerating infection. It usually starts as a vesicle or vesiculopustule on an erythematous base, which subsequently ulcerates. The ulcer is covered with a dark-brown, bloody crust. A tender punched-out ulcer remains after the crust is removed. It is usually found on the dorsal feet, the shins, the thighs, but is less often encountered on the upper part of the body (Figure 10.4). There are usually few lesions, but new lesions may develop without adequate treatment. Both \(\beta\)-hemolytic streptococci and \textit{S. aureus} are present in many ulcers. However, \(\beta\)-hemolytic streptococci are thought to be the primary pathogen.

Pyoderma in travelers is generally encountered as a secondary infection in the skin lesions caused by environmental insults such as insect bites, abrasions, scabies, and atopic dermatitis to the skin.
Corynebacterium diphtheriae is secondarily encountered in a preexisting ulcer such as echtyma or as a superinfection in eczema (Figure 10.5). Systemic toxic complications such as myocarditis and neuritis are rare in immunized individuals. The diagnosis of cutaneous diphtheria is often missed or established at a late stage because it is uncommon in
nonendemic countries and is not clinically very specific. The most typical manifestation is characterized by a chronic, nonhealing ulcer(s) with a punched-out appearance, slightly undermined and covered with a gray adherent membrane. It is painful in the first 2 weeks, becoming painless later, and the hemorrhagic base appears after the (spontaneous) removal of the adhering crust.

Figure 10.4 Multiple punched out lesions on the dorsal foot in a traveler

Figure 10.5 Punched-out ulcer. Culture revealed β-hemolytic streptocci and C. diphtheriae
Diagnosis

The diagnosis of pyoderma is often made on the basis of the clinical picture of persistent painful ulceration especially on the lower legs. One should perform a bacterial culture if facilities are available. Ideally, tissue obtained by biopsy or needle aspiration should be cultured. This is often not routinely performed in daily practice because it is more time-consuming and inconvenient for the patient. However, adequate culture results have been obtained using swabs. The ulcerated lesion should be thoroughly cleansed with saline solution after which specimens from the wound surface and if possible, from under the margins of the wounds should be collected. Susceptibility tests in vitro are also preferable. Methicillin-resistant *S. aureus* and tetracycline-resistant streptococci and staphylococci are frequently encountered in many tropical areas of the world.

Ulceration caused by *C. diphtheriae* should be highly suspected because is clinically not specific. The definite diagnosis is established after isolating and identifying the organism from the ulcer and demonstrating its toxigenicity. The physician must warn the laboratory of the suspicion in advance because *C. diphtheriae* cannot be isolated by routine culture procedures [10].

Treatment

Treatment of ulcerative pyoderma is initially based on the clinical assessment. Gram-stained smears of exudate may be helpful in starting empirical antimicrobial treatment. However, antibiotic treatment should be preferably based on culture results. When culture results are not available, but the clinical condition demands antibiotic treatment, one may start with flucloxacillin orally for at least 10 days as drug of first choice in cases of community-acquired ulcerative pyoderma. Flucloxacillin is a semisynthetic penicillin. It has a low acute and chronic toxicity and a high enteric absorption. The antibacterial activity of flucloxacillin is evident on Gram-positive bacteria and above all in penicillinase-producing staphylococci. Macrolide antibiotics should be prescribed with caution considering the global spread of macrolide-resistant *S. aureus* and β-hemolytic streptococci. Clindamycin is recommended in penicillin-allergic patients. As an alternative, vancomycin may be used. However the first vancomycin-resistant *S. aureus* (VRSA) have been reported. Although there is evidence that topical antibiotic treatment is effective, in extensive pyoderma topical antibiotic treatment is not recommended.

It is generally accepted that ulcers heal more rapidly under occlusive (moist) dressings. There are no documented studies in which the effect
of these occlusive dressing on healing of ulcerative pyoderma was shown. However, occlusive dressings were shown to be safe in chronic ulcers with an even lower infection rate in occluded wounds compared with ulcers treated with conventional dressings.

Special attention should be paid to ulceration in the lower legs in which (sub)clinical edema is often present. This edema may delay or even complicate healing. Edema may be eliminated by adequate compression therapy with elastic or nonelastic bandages or stockings.

Treatment should be started as soon as possible when cutaneous diphtheria is suspected. Neutralizing antitoxin is probably not effective in cutaneous disease. Penicillin and erythromycin are considered drugs of first choice for eradicating *C. diphtheriae*.

**References**

CHAPTER 11
Rickettsioses

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Key points
- Regularly occur in travelers
- Should be considered in travelers with fever of unknown origin
- “Characteristic findings” (headache, malaise, fever, rash) may be absent
- Diagnosis is by serological tests on samples taken 2–3 weeks apart
- Doxycycline is the treatment of choice
- As definite diagnosis is delayed, doxycycline should be started on suspicion

Introduction

Rickettsioses are zoonotic diseases caused by rickettsiae that are transmitted to man by various arthropods, ticks, lice, fleas, and mites. The family Rickettsiaceae consists of two genera, the genus Rickettsia and the genus Orientia. The genus Rickettsia is divided into two groups based on differences in lipopolysaccharides, outer membrane protein A, and evolutionary genetic relationships: the typhus group and the spotted fever group [1–3].

Rickettsioses occur all over the globe and are increasingly recognized in travel medicine [1, 4–6]. This increase is due to better awareness, wider availability of diagnostic methods, and newer diagnostics of PCR and culturing that recently have given new information on the existence and spread of a variety of new (sub)species of rickettsiae [2]. Increased exposure in endemic areas due to adventure (eco)tourism [4] and military operations [7] also plays a role in the reported increase of cases. Various mammals play a role as reservoir but ticks, vector for many Rickettsia species, are also important as reservoir because of transovarial transmission. Transovarial transmission is less important in fleas and mites and does not occur in lice.
The organism

Rickettsiae are obligate intracellular, gram-negative bacteria, microscopically indistinguishable from each other. They invade endothelial cells causing (peri)vasculitis. They can be cultured in eggs and in chick embryo cells and various mammalian and arthropod cell lines [8]. Culturing is only performed in specialized laboratories under strict safety conditions.

Clinical manifestations

After an incubation time of 1–16 days, disease starts abruptly with fever, headache, malaise, arthralgia, and myalgia. A rash appears about 3–5 days after onset, often first macular evolving to maculopapular. The rash is most prominent on the trunk and limbs, usually involves palms and soles (not in epidemic and endemic typhus, see Section “Typhus group”) and spares the face. Without treatment the disease may run for 12–20 days. At the site of the bite of a tick or mite a so-called eschar or tache noire may be present, often already at the onset of fever. It is a small ulcer about 2–5 mm with a black center and a red area around it. An eschar is frequently seen among patients with Mediterranean spotted fever (fièvre boutonneuse) (MSF) (see Section “Mediterranean spotted fever”) and with scrub typhus, rarely among patients with Rocky Mountain spotted fever (RMSF) (see Section “Rocky Mountain spotted fever”).

In many patients the disease is mild with nonspecific manifestations of fever and flu-like symptoms, the rash may be absent or hardly noticeable (like frequently in murine typhus, see Section “Murine, endemic typhus”) making that many cases remain undiagnosed or get a label of “fever of unknown origin.” Historically, epidemic typhus (see Section “Epidemic, louse-borne typhus”) was known to be a severe disease with a high case fatality rate. Severe complications of meningoencephalitis, renal, cardiac and respiratory failure, and extensive vasculitis are well known to occur in patients with RMSF and scrub typhus but have more recently also been described in patients with MSF [2, 3, 9].

Diagnosis

Isolation of the organism (definite diagnosis) is performed in specialized laboratories only. The recently developed PCR on eschar biopsies and blood is not widely available. Diagnosis relies on serology, in practice the Immune Fluorescence Antibody test (IFA) on serum samples taken 2–3 weeks apart. Antibodies appear late in the disease course, about 7–10 days
after the start of fever. A diagnosis of rickettsiosis has to be suspected on clinical and epidemiological grounds and presumptive treatment with doxycycline has to be started [2, 4].

**Treatment**

Doxycycline is the treatment of choice for all rickettsioses, definitely so for severe, life threatening disease, even in pregnancy and elderly patients [8]. Advaices on regimes vary slightly; 100 mg twice per day for 5 days, and for 7–10 days in more severe disease is often advised. Alternatively, duration of treatment up to 2–3 days after fever resolution is advised. MSF may even be treated for 1 day only. Alternatives, all with less clinical experience, are the newer macrolides-like azithromycin (once daily for 3 days) and clarithromycin (7 days) but not erythromycin. The macrolide, josamycin, has been used successfully in pregnant women. Fluoroquinolones and rifampin are effective, but β-lactam antibiotics, aminoglycosides, and cotrimoxazole are not [2, 4].

**Prevention**

Protection against tick bites by wearing long trousers and long-sleeved clothes, preferably sprayed or impregnated with insecticide (permethrin), and use of insect repellent with \( \text{N,N-diethyl-m-toluamide (DEET)} \) is recommended. Inspection for and removal of ticks is important; transmission is related to the duration of attachment of ticks and occurs only after several hours of attachment. Thus, careful inspection and removal even hours after possible exposure is important. Weekly doxycycline proved effective chemoprophylaxis for scrub typhus [10]. Malaria chemoprophylaxis with daily doxycycline is likely to be protective against rickettsiosis but this has not been studied and not been proved. There is no effective vaccine.

**Rickettsioses in travelers**

In travelers, African tick bite fever is the most commonly reported rickettsiosis, followed by murine typhus, MSF, and scrub typhus. RMSF is endemic in large parts of the United States and in foci of Central and South America, but has only rarely been reported in travelers who were camping or hiking in endemic areas. Epidemic typhus is extremely rare in travel medicine [see 4, 11] as are other rickettsioses, like North Asian and Queensland tick typhus [5].
Table 11.1  Classification into biogroups and diseases of most frequently observed rickettsioses in travelers

<table>
<thead>
<tr>
<th>Genus, biogroup, disease</th>
<th>Species</th>
<th>Vector</th>
<th>Geography</th>
<th>Occurrence in travelers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rickettsia Typhus group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemic typhus</td>
<td><em>Rickettsia prowazekii</em></td>
<td>Body lice</td>
<td>Worldwide; presently highlands Africa (East, Central, South), Himalaya, Central and South America</td>
<td>Very rare</td>
</tr>
<tr>
<td>Murine typhus</td>
<td><em>Rickettsia typhi</em></td>
<td>Rat fleas</td>
<td>Worldwide; Southern United States, Central and South America</td>
<td>Regularly (Underdiagnosed)</td>
</tr>
<tr>
<td>Spotted fever group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td>Dermacentor and Amblyomma ticks</td>
<td>North, Central, and South America</td>
<td>Very rare</td>
</tr>
<tr>
<td>Mediterranean spotted fever</td>
<td><em>Rickettsia conorii</em></td>
<td>Rhipicephalus and Haemaphysalis ticks</td>
<td>Mediterranean and Caspian littorals, Middle East, Indian subcontinent, Africa</td>
<td>Occasional</td>
</tr>
<tr>
<td>Astrakhan, Israeli, India tick typhus</td>
<td><em>R. conorii caspia</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>R. conorii israelensis</em></td>
<td><em>R. conorii indica</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African tick bite fever</td>
<td><em>Rickettsia africai</em></td>
<td>Amblyomma ticks</td>
<td>Rural sub-Saharan Africa, West Indies</td>
<td>Common</td>
</tr>
<tr>
<td>Orientia Scrub typhus</td>
<td><em>Orientia tsutsugamushi</em></td>
<td>(Larval) mites, chiggers</td>
<td>Southeast Asia, Western Oceania</td>
<td>Occasional</td>
</tr>
</tbody>
</table>

Specific diseases

As mentioned, two groups are distinguished: the typhus group and the spotted fever group. Table 11.1 gives information on biogroups, diseases, causative organisms, vector, areas of occurrence, and occurrence in travelers.
Typhus group

Epidemic, louse-borne typhus
Epidemic, louse-borne typhus, caused by *Rickettsia prowazekii*, transmitted among humans by body lice, is a disease of war, concentration and refugee camps, and prisons. It is one of the most devastating diseases in human history with large outbreaks during wars, for example, the American War of Independence, Napoleon’s attack on Russia, the First and Second World War, and more recently, the wars in Central Africa, with epidemics in Rwanda and Burundi. It is presently found in the cooler highlands of East and South Africa (Ethiopia, Rwanda, Burundi, Lesotho, and others), in South America, in the Andes, and in Asia in Himalaya, but foci exist in Central America, Algeria, and the Balkan. It is an acute disease with fever, commonly with neurological signs, a rash in up to 80%, and a fatality rate between 20% and 40%.

After recovery, patients may harbor the bacteria without clinical manifestations for many years to become clinically manifest with a mild disease under not well-defined conditions of less resistance (Brill-Zinsser disease). Flying squirrels in the east of the United States may be infected with a less virulent strain of *R. prowazekii*. Occasionally humans become infected and experience a mild disease [12].

Murine, endemic typhus
Murine, endemic typhus is caused by *Rickettsia typhi* (*Rickettsia mooseri*) that is transmitted to man by fleas from a reservoir in rats. Murine typhus, also called shop typhus, is found worldwide where many rats are found, in shops, harbors, port cities, beach resorts, and areas with lots of garbage. Studies in infected volunteers showed that the incubation period was 8–16 days. A rash appears in about 40% of patients around 6 days after onset. The macular, later maculopapular rash is often discrete and may become purpuric in severe cases. Severe disease may occur with respiratory failure and neurologic complications of confusion, coma, and seizures, but generally it is a mild disease that probably often does not get diagnosed. The case-fatality rate may be 1% [4, 12].

Spotted fever group

African tick bite fever
African tick bite fever is caused by *Rickettsia africae* and transmitted to man by aggressive cattle ticks, *Amblyomma* spp., that are found in large parts of rural sub-Saharan Africa and in the West Indies where *R. africae* infection is also diagnosed [4]. Cross country walking, hunting, safari,
ecotourism, tracking, adventure racing, and military expeditions are risk activities [1, 5]. Clinical presentation includes fever (not always present), constitutional symptoms, one or several inoculation eschars with regional lymphadenitis, and a rash that may be maculopapular but often is vesicular (Figures 11.1a and 11.1b) and that may be accompanied by mouth blisters. Travelers may consult the family doctor with several vesicular lesions that may be diagnosed as bacterial, notably staphylococcal, infection for which flucloxacillin is prescribed. As this does not help, the traveler may consult a specialist in travel medicine. African tick bite fever is usually a self-limited, mild disease [1, 4, 5].

Mediterranean spotted fever

MSF is caused by *Rickettsia conorii* and transmitted to man by dog ticks, *Rhipicephalus* spp., mainly *Rhipicephalus sanguineus*, and *Haemophysalis leachi*. Four subspecies of *R. conorii* have been proposed: (1) *R. conorii conorii*, (2) *R. conorii israelensis*, (3) *R. conorii caspia*, and (4) *R. conorii indica* [2]. Typical risk behavior is contact with dogs that are important transport hosts, bringing infected ticks to man. Dogs are only transient reservoirs, other reservoirs probably being wild rabbits and hares, possibly also hedgehogs and other small rodents [2]. MSF is endemic to the Mediterranean region including the Balkan, around the Black Sea, and in East and South Africa. *R. conorii conorii* comprises several different isolates: Malish, Moroccan, and Kenyan. The diagnosis MSF is now reserved for infections by *R. conorii conorii*; infections by *R. conorii israelensis*, *R. conorii caspia*, and *R. conorii indica* are called Israeli tick typhus, Astrakan (Caspian) spotted fever, and Indian tick typhus, respectively [2, 3]. These diseases are characterized by fever, a maculopapular rash appearing within 2–3 days after
onset, and an inoculation eschar at the site of the tick bite. In published series of cases the eschar is not found in 14–40% [2] but careful examination is necessary as they may be localized on scrotum, between buttocks, in axillae, at the scalp. Multiple eschars do occur but are rare; multiple eschars should raise the suspicion of infection by *Rickettsia aeschlimanii* that is transmitted by *Hyalomma* spp., ticks that in contrast to *Rhipicephalus* readily bite humans [2]. The incubation period is generally 6 (1–16) days. In severe diseases central nervous system (CNS) involvement and multiple organ failure may occur. The fatality rate in complicated cases may go up to 20%. Guillain-Barré polyneuropathy has been described [13]. Risk factors for severe disease are older age, immunosuppression, diabetes, cardiac and respiratory insufficiency, chronic alcoholism, and glucose-6-phosphate-dehydrogenase (G6PD) deficiency [2].

Delayed and inappropriate treatment also play a role [2, 3]. Comparable diseases are Siberian, or North Asian and Queensland tick typhus, Japanese spotted fever among others. In general, these are mild diseases [4].

**Rocky Mountain spotted fever**

RMSF caused by *Rickettsia rickettsii*, is very rarely diagnosed in travelers [4, 5]. Inhabitants of the East, Southeast, and Midwest United States and of parts of South America who frequent tick-invested habitats, such as wooded and grassy areas, are at risk for this potentially severe disease. Man is infected by dog tick bites, *Dermacentor* and *Amblyomma* ticks. Characteristic clinical symptoms are fever, headache, and myalgia. An inoculation eschar is usually absent. An erythematous rash usually starts on ankles and wrists, spreads all over the body and may become hemorrhagic in severe cases (Figure 11.2). CNS involvement may occur and multiple organ failure resulting in the death of the patient. With prompt recognition and treatment, death should be uncommon, yet 3–5% of cases reported in the United States in recent years have been fatal [14]. Risk factors for severe disease and death include delayed diagnosis and treatment and age above 40. In recent years infections by *Rickettsia parkeri*, transmitted by *Amblyomma* ticks were described from the United States and South American countries. The clinical picture resembles that of RMSF but it is less severe, no fatalities have been reported yet. More than 90% of patients had an eschar [15].

**Scrub typhus**

Scrub typhus is endemic in rural South and Southeastern Asia and the Western Pacific. People engaged in logging, working in rice fields, and
military personnel (World War II; Vietnam War) are at risk. The disease is caused by *Orientia tsutsugamushi*. Man is infected by the bite of larval trombicolid mites (chiggers) that typically bite humans on the lower extremities or in the genital region. Most patients present with fever and generalized lymphadenitis. About half of them have an inoculation eschar. The clinical course is usually mild, but severe complications may occur such as meningoencephalitis, pneumonitis, renal failure, and disseminated intravascular coagulation. Fatality rates range between 1% and 35%. Travelers have been infected in Thailand, less frequently in India, Vietnam, Malaysia, and the Philippines [4].

**References**

CHAPTER 12

Viral Diseases

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Key points

- Viral skin diseases encompass a wide variety of illnesses ranging from mild exanthems to life threatening diseases
- Viral diseases such as condyloma, verruca vulgaris, genital and/or orolabial herpes, and molluscum compromise a large proportion of a dermatologist’s daily practice
- With the increase in travel and humanitarian medicine, there is a rise in imported viral skin diseases
- Dermatologic findings can often be one of the first or major manifestations of a viral infection, allowing the dermatologist to play a crucial role
- Early diagnosis and prompt treatment alters prognosis significantly in life threatening acute viral illnesses
- Most recommended method of diagnosis is clinical with confirmation with biopsy and/or culture if needed

Introduction

Viral infections contribute to a vast number of imported skin diseases from nations worldwide. Imported conditions such as hepatitis, human T-cell lymphotrophic virus (HTCLV), and human immunodeficiency virus (HIV) are currently on the rise. Other more exotic diseases such as dengue, yellowfever, monkeypox, Lassa fever, and measles have had very recent outbreaks. With continued global warming, the fungus Geomyces destructans has decimated fruit bat populations worldwide; as a result more mosquitoes and mosquito-borne viral illnesses can be expected to surface. Viral skin diseases vary in their clinical manifestation, geographic
distribution, and severity. Here we have reviewed the most prominent viral infections with specific attention to their accompanying cutaneous manifestations, diagnosis, and treatment.

**Chikungunya virus**

**Epidemiology**
In 2005 and 2006 there were two major outbreaks of the chikungunya virus in India and Reunion (an island in the Indian Ocean). Subsequently the transmission of the disease has occurred in separate waves to virtually all continents, including North America (United States) and Europe (France and Italy). In 2007, chikungunya fever was transmitted to Italy for the first time, presumably from an Indian man visiting relatives. Since then, 205 cases have been identified in Italy [1].

**Clinical features**
Chikungunya is an *Alphavirus* transmitted by *Aedes* mosquitoes. This arthropod-borne virus often presents with the triad of fever, arthralgia, and rash. The eruption is macular or maculopapular in nature and commonly occurs on the trunk and extremities (Figure 12.1). In most cases, resolution of symptoms occurs 10–13 days after initial exposure; however, myalgia and arthralgia can persist for up to 1 year [2].

**Diagnosis**
Diagnosis is based on viral isolation during the first 2–4 days of illness using PCR or serological markers, with an acute IgM or a fourfold IgG rise.

![Chikungunya rash](image)

*Figure 12.1* Chikungunya rash (courtesy Anke Heitkamp MD)
**Treatment**
Treatment of chikungunya infection is supportive. Elimination of breeding sites via insecticides and use of mosquito nets are effective prevention modalities. No vaccine is currently available.

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**Dengue fever**

**Epidemiology**
Dengue is an RNA virus of the family *Flaviviridae* transmitted by the *Aedes aegypti* mosquito vector. Approximately 100–200 suspected cases of dengue are introduced into the United States by travelers annually [2] (Figure 12.2). In 2009, the first case in 75 years was reported in Florida with a subsequent 65 cases confirmed in 2010. Historic numbers of dengue outbreaks were reported in 2010 in southern Florida and associated US territories (Puerto Rico and US Virgin Islands). Over 21,000 cases have been reported in Puerto Rico, making it the largest outbreak in history [3].

**Clinical features**
Dengue virus is classified into four different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), each of which has 60–80% homology with the other. Infection with one strain can only produce lifelong immunity to that particular strain. In fact, severe complications have occurred in individuals previously exposed to DENV-1 who contract DENV-2 or DENV-3, or those previously exposed to DENV-3 who acquire DENV-2 [2].

Dengue fever clinically presents with an abrupt onset of high fever followed by headache, myalgia, retro-orbital pain, nausea, vomiting, arthralgia, and fatigue. Three to four days following onset of symptoms, a centrifugal rash (morbilliform or a scarlatiniform eruption) occurs (Figure 12.3). The lesions tend to spare the palmoplantar regions and can be pruritic. Dengue is commonly called “break-bone” fever because of the associated debilitating joint and muscle pain.

**Diagnosis**
Diagnosis is based on serologic testing using ELISA with IgM-capture or a fourfold rise in IgG titers.

**Treatment**
Treatment is supportive and nonspecific. Currently, there is no vaccine available but progress on a tetravalent vaccine, which will include four different strains of the virus, is being made [2]. The use of insecticides and adequate solid waste disposal are effective means of prevention.
Yellow fever

Epidemiology
Yellow fever was the first recognized flavivirus. The virus most likely originated in Africa and has had repeated outbreaks in the Americas until the twentieth century. Today, the virus is still endemic in sub-Saharan Africa and South America [1, 2]. Despite introduction of the vaccine in the twentieth century, the disease was imported by a Belgian traveler returning from Gambia in 2001, and from Suriname to the Netherlands in 2000 [1].

Clinical features
The disease initially manifests as a nonspecific febrile illness that usually remits a week after exposure. In severe cases, disease progression occurs with extensive hepatitis, jaundice (for which the disease was named), and bleeding diathesis, which can lead to “vomito negro/black vomit.” Cutaneous findings can include petechiae and/or ecchymoses, which occur due to the associated coagulopathy [2].

Diagnosis
In early disease, viral culture is the preferred method of diagnosis, but serology (IgM or fourfold rise in IgG) can also be used [2].

Treatment
Treatment is supportive; mortality can reach 20–50%. Focus is on prevention, especially for imported disease. Immunization with the live attenuated vaccine is recommended 7–10 days before travel to endemic regions; boosters are required every 10 years [2].
**West Nile virus**

**Epidemiology**
West Nile virus is another mosquito-transmitted flavivirus, which can cause fatal neurologic disease in severe cases. The virus was first isolated in the West Nile district of Uganda, and is prevalent in Africa, southern Europe, the Middle East, Western Asia, and Australia. In 1999, a strain of West Nile virus prevalent in Israel was imported into New York City, and since then the virus has spread across the United States becoming endemic [1]. It is now the most common cause of epidemic meningoencephalitis in North America [1].

**Clinical features**
Approximately 80% of patients infected with West Nile virus are asymptomatic [2]. Of the remainder, most develop West Nile fever, a nonspecific febrile syndrome, which can include a macular rash on the trunk that may desquamate. One in every 150 patients will have disease progression to the central nervous system (CNS), producing meningoencephalitis or poliomyelitis-like paralysis. Neurologic involvement is more common in the elderly and the immunosuppressed [2].

**Diagnosis**
Diagnosis is via serology (IgM or rising IgG) or detection of viral RNA [2].

**Treatment**
The disease is self-limited and treatment of neurologic disease is supportive. Without a current vaccine, prevention is key, directed at avoiding mosquitoes [2].

**Hemorrhagic fevers**

**Ebola and Marburg**

**Epidemiology**
Ebola and Marburg viruses comprise the Filoviridae family and cause deadly and virtually identical hemorrhagic disease. Person-to-person transmission is by direct contact with bodily fluids. Outbreaks are typically limited to sub-Saharan Africa. An isolated case of Ebola occurred via an accidental needlestick in 1976 in a United Kingdom laboratory processing material from patients in Africa. Since then, only evidence of the Ebola-Reston strain, which has never caused disease in humans, has appeared in countries outside of Africa. Marburg was first identified in 1967 in Marburg, Germany, where a small outbreak occurred in laboratory staff
handling African monkeys. In 2008, imported Marburg occurred in an American and a Dutch patient, both of whom had recently traveled to Uganda [1].

**Clinical features**

After a week-long incubation, generalized symptoms of fever, headache, diarrhea, sore throat, and cough occur. Cutaneous manifestations, which appear in over half of the patients, include a nonpruritic morbilliform eruption with fine scaling, which is followed by a dark, diffuse erythema of the entire body [2]. Bleeding is frequent, characterized by generalized petechiae on the trunk and extremities.

**Diagnosis**

Definitive diagnosis is by detection of viral antigen or RNA via PCR. Disease should be suspected in individuals who recently traveled to Africa or work with primates that may be infected.

**Treatment**

Treatment is supportive; mortality may reach 90% [2]. Infection control and quarantine are critical.

**Lassa fever and the South American hemorrhagic fevers**

**Epidemiology**

The family *Arenaviridae* contains Lassa virus and the closely related South American hemorrhagic fevers, including Junin virus (Argentine hemorrhagic fever), Machupo virus (Bolivian hemorrhagic fever), Sabia virus (Brazilian hemorrhagic fever), and Guanarito virus (Venezuelan hemorrhagic fever). They are all zoonotic pathogens transmitted through rodents. Lassa virus is endemic to Africa; however, since 1969 there have been close to 30 imported cases, in the United States (5 cases), the United Kingdom (12 cases), Germany (3 cases), the Netherlands (2 cases), Israel, Japan, and Canada (1 case each) [5]. The South American hemorrhagic fevers have remained limited to their respective countries in South America.

**Clinical features**

Incubation period is approximately 1–3 weeks. Unlike other hemorrhagic fevers, onset is insidious; initial symptoms include fever and pharyngitis. Subcutaneous hemorrhage can cause petechiae. Capillary leak syndrome is the hallmark of disease, causing facial but not peripheral edema, as well as pleural and pericardial effusions [2]. Imported cases occur in travelers to endemic countries in West Africa, including Nigeria, Sierra Leone, and Burkina Faso.
Diagnosis
Diagnosis is usually by ELISA of Lassa antigen or IgM/IgG antibodies.

Treatment
Treatment is mainly supportive; however ribavirin has been shown to reduce mortality in Lassa fever [2].

Crimean-Congo hemorrhagic fever
Epidemiology
Crimean-Congo hemorrhagic fever is caused by a Nairovirus, in the Bunyaviridae family. It is a tick-borne disease found in Africa, the Middle East, central and eastern Europe, and Asia. In Europe, the virus has been endemic to Bulgaria since the 1950s, but outbreaks have occurred in Albania, Kosovo, Turkey, Ukraine, and Russia, and recently in Greece [6]. In 2004, a French woman working in Senegal imported the disease into France [7].

Clinical features
Patients present with a sudden onset of fever, myalgia, and evidence of inflammatory hepatitis [2]. Hemorrhage usually occurs in many organs, and skin involvement, although nonspecific, can manifest as a diffuse, fine petechial eruption extending over the entire body surface.

Diagnosis
Diagnosis is by isolation of the virus via cell culture or IgM/IgG serology. Suspicion should be high for individuals working in livestock or agriculture, as well as health care workers in endemic areas.

Treatment
There is no definitive treatment. Ribavirin has been used but efficacy is variable [2].

Rift valley fever (RVF)
Epidemiology
RVF belongs to the family Bunyaviridae and causes epizootic disease (primarily affects livestock but can be passed to humans). It is transmitted via various mosquito vectors. Close contact with infected animals increases the risk for human transmission. Imported cases of the disease have been reported from regions of Africa, Saudi Arabia, and Yemen where sacrificial slaughtering of animals occur during religious festivals [1].
Clinical features
Patient presentation can vary from asymptomatic to symptoms of mild fever, headache, and arthralgia, which can further progress into transaminitis or hemorrhagic fever.

Diagnosis
Diagnosis is based on viral isolation, serology (IgM or increase in IgG), or detection of viral RNA in tissue or serum [2].

Treatment
Treatment centers on supportive and symptomatic care. Animal immunization is available with live-attenuated and killed virus vaccines. A formalin-inactivated vaccine for humans is available for high-risk individuals but has not yet been licensed [2].

Hepatitis

Epidemiology
The hepatitis family is comprised of hepatitis A (picornaviridae), hepatitis B (hepadnaviridae; HBV), hepatitis C (flaviviridae; HCV), hepatitis D (deltaviridae), hepatitis E (caliciviridae), and the more recently discovered hepatitis G (flaviviridae). Viral hepatitis is prevalent worldwide (Figures 12.4 and 12.5). Cutaneous manifestations occur with HBV and HCV infections, with HCV being responsible for most. Imported cases of HBV have been reported from sexual contact with immigrants of endemic nations such as China, India, Africa, and the Middle East [1]. In United States, Japan, and Egypt, HCV is the most common cause of chronic liver disease; imported cases from these regions into Europe are reportedly on the rise [1, 8].

Hepatitis B (HBV)
Clinical Features
The majority of cutaneous findings due to acute HBV infection result from immune complexes involving HBsAg. Approximately 20–30% of patients can have a serum sickness-like illness with urticaria (most common), angioedema, hematuria, and/or proteinemia [2]. In Europe and Japan, there is a high incidence of papular acrodermatitis of childhood (Gianotti-Crosti Syndrome) after acute HBV infection [4]. The skin manifestations are characterized by 5-mm papules that first appear on the buttock and thighs, extending to the extremities and face, with relative sparing of the trunk.

In chronic HBV carriers, cutaneous findings are mostly nonspecific and related to cirrhosis, including jaundice, spider nevi, and palmar erythema.
Figure 12.4 Prevalence of Hepatitis B [4]
Figure 12.5 Prevalence of Hepatitis C [4]
Two common skin lesions related to chronic HBV are mixed cryoglobulinemia (MC) and polyarteritis nodosa (PAN). However, MC is more commonly associated with HCV infection (70% versus 5%) [4]. Cutaneous findings of MC include palpable purpura, petechia, urticaria, and ulcerative lesions. PAN is also an immune complex disease affecting medium and small arteries in the kidney, CNS, and skin. Approximately 7% of PAN cases are associated with HBV infection. Patients present with tender subcutaneous nodules on the lower extremities that can further progress to painful ulcerations.

**Diagnosis**

Diagnosis of HBV-associated skin diseases can be made with clinical findings in addition to serology and/or histopathology. On histology, both MC and PAN show a neutrophilic vasculitic pattern. HBsAg IgM and complement can be detected in endothelial membranes with immunofluorescence [2]. Serologic studies are consistent with acute or chronic hepatitis infection and liver enzymes are often elevated.

**Treatment**

Treatment of HBV-related skin disease is usually supportive. Antihistamines are recommended for urticaria, angioedema, or pruritus associated with serum-sickness-like syndrome. For MC related to HBV, treatment of the virus with entecavir and peginterferon is recommended, in addition to systemic steroids or cyclophosphamide for severe, and dapsone or colchicine for milder cases [8]. In PAN, plasma exchange has been used in severe disease. The HBV vaccine was introduced in 1986 and is currently the effective mode of prevention.

**Hepatitis C (HCV)**

**Clinical Features**

In addition to the nonspecific cutaneous findings associated with chronic liver disease, urticaria, erythema multiforme-like reactions, erythema nodosum, prurigo, livedo reticularis, and Henoch Schonlein purpura have been associated with the virus [8]. About 80% of diagnosed MC is secondary to HCV infection. Porphyria cutanea tarda is a disease induced by HCV in predisposed individuals [2, 9]. Porphyria cutanea tarda (PCT) usually manifests as subepidermal bullae, hypertrichosis, hyperpigmentation, and superficial erosions in sun exposed areas of the skin. Photosensitization of the excess porphyrins is deemed to be the mechanism of development of the skin lesions [10].

The condition of lichen planus has also been associated with HCV, mainly in areas with the greatest risk of exposure to the virus such as Japan [10]. Skin findings usually consist of flat-topped violaceous papules
on the dorsum of the hands and wrists. Erosive types of chronic lichen planus (LP) have also been strongly associated with HCV [2].

**Diagnosis**

HCV infection is usually diagnosed by serology and HCV RNA load. Detection of HCV RNA indicates current infection. For patients with PCT, iron studies should also be performed in order to rule out hemochromatosis.

**Treatment**

Treatment of the cutaneous illnesses associated with HCV infection involves treatment of the viral infection itself. Current standard of care is peginterferon and oral ribavirin. In 2011, the FDA approved the new antivirals telaprevir and boceprevir for patients with chronic HCV who have failed standard treatment [11, 12].

The presence of MC is an indication for antiviral therapy, regardless of the stage of liver disease [13]. In cases of MC unresponsive to antiviral therapy, rituximab and plasmapheresis have been used [8, 9]. In patients with concomitant PCT and hemochromatosis, phlebotomy is indicated. HCV-associated LP is most commonly treated with topical steroids and/or calcineurin inhibitors [10].

**Herpes virus**

Herpes viruses are comprised of six main genera: (1) *Simplexvirus* (HSV 1 and 2), (2) *Varicellovirus* (HHV 3 or VZV), (3) *Lymphocryptovirus* (HHV 4 or EBV), (4) *Cytomegalovirus* (HHV 5 or CMV), (5) *Roseolovirus* (HHV 6 and 7), and (6) *Rhadinovirus* (HHV 8).

**Herpes simplex virus 1 and 2**

Transmission of herpes simplex virus (HSV 1 and 2) occurs via direct oral or genital mucus membrane contact.

**Clinical features**

The oral mucosa is the most common site for HSV 1 infection, while HSV 2 usually affects the genital areas. Both oropharyngeal (cold sores) and genital herpes are characterized by painful crops of vesicles followed by ulceration and crusting.

**Diagnosis**

The diagnosis is made with PCR, serology, viral culture, or direct fluorescent antibodies to the virus.
Treatment
Acyclovir is recommended for treatment of HSV infections. More recently, valacyclovir (prodrug of acyclovir) and famciclovir (prodrug of penciclovir) have proven to be more efficacious than acyclovir [2].

Varicella zoster virus (VZV)
Epidemiology
VZV has two clinical manifestations; the primary infection is chickenpox (varicella), while the reactivation of latent virus is shingles (herpes zoster). VZV infection is common worldwide, although the virus may be more transmissible in tropical climates [2].

Clinical features
Primary varicella infection presents with fever and a rash starting on the head and spreading to the trunk and extremities. The eruption evolves from maculopapular to vesicular, then pustular, and finally scabs over. Most common complication of primary varicella is bacterial superinfection, usually by Staphylococcus or Streptococcus. Superinfection may present as cellulitis, impetigo, furuncles, or bullous lesions [2, 14].

Herpes zoster (shingles) is usually localized to a single unilateral dermatome, but bilateral zoster has been reported [2]. Early lesions are papules on an erythematous base progressing to vesicles and pustules that crust over. Complications include postherpetic neuralgia (PHN), hypopigmentation, and hyperpigmentation [2, 15].

Diagnosis
Diagnosis of varicella and herpes zoster is generally made with clinical history and exam.

The most preferred confirmatory test is PCR and/or direct immunofluorescence. PCR can be used to detect virus in skin cells, saliva, blood, vesicular fluid, or respiratory secretions.

Treatment
Treatment of primary varicella infection is usually symptomatic, but acyclovir has been approved for decreasing the duration and severity of varicella if used within 24–72 hours of the onset of symptoms [15]. In herpes zoster, early treatment has been shown to reduce development of PHN. Currently valacyclovir or famciclovir are the treatments of choice for zoster. Gabapentin in addition to valacyclovir has been shown to further reduce PHN [16].
**Epstein Barr virus (EBV)**

**Epidemiology**
The most common clinical manifestation of EBV is infectious mononucleosis [2].

EBV is transmitted through intimate contact with asymptomatic shedders. The virus infects human B-cells and transforms them into atypical lymphocytes. EBV is also associated with Hodgkin’s and Burkitt’s lymphoma. Burkitt’s lymphoma is predominantly found in equatorial Africa.

**Clinical features**
The viral prodrome is characterized by malaise, headache, and fatigue followed by fever, sore throat, and cervical adenopathy. Small petechiae on the hard and soft palates are visible in a third of the patients. Macules, papules, vesicles, and petechiae or purpura occur in 3–16% of patients [2].

**Diagnosis**
Elevated heterophil antibodies or peripheral smear showing atypical lymphocytes are used for diagnosis.

**Treatment**
EBV infection is usually a self-limited disease and the majority of patients need only supportive care. Treatment of Burkitt’s lymphoma includes concomitant chemotherapy and rituximab.

**Cytomegalovirus (CMV)**

**Epidemiology**
CMV (HHV 5) is a ubiquitous pathogen transmitted via direct contact with oral mucosa [17]. Seropositivity ranges from 50% to 90% in adults; CMV is the most common congenital infection worldwide [2, 17].

**Clinical features**
Immunocompetent patients rarely show cutaneous signs of CMV infection [17]. In immunocompromised individuals, mucocutaneous ulcers are the most common manifestation, but many other lesions have been described, including crusted papules, nodules, morbilliform eruptions, urticaria, and vesiculobullous eruptions [17]. In cases of congenital infection, the “blueberry muffin rash” petechial rash is characteristic.

**Diagnosis**
The diagnosis of CMV infection usually begins with viral serology, but this is neither sensitive nor specific. Light microscopy can reveal characteristic
CMV inclusion disease. Viral culture, DNA in situ hybridization, and PCR are also useful [18].

**Treatment**
Symptomatic CMV infection is managed with ganciclovir or valganciclovir, with foscarnet and cidofovir for resistant cases [18].

**Human herpesvirus 6 (HHV-6)**

**Clinical features**
HHV-6 is the etiological agent of exanthema subitum, or roseola infantum (“Roseola”). Exanthema subitum most commonly occurs in children and is characterized by the abrupt onset of high fever followed by the “rose red” maculopapular exanthem with a white halo [19]. The eruption is generally nonpruritic and does not desquamate.

**Diagnosis/treatment**
HHV-6 is usually benign and self-limiting, with the majority of cases diagnosed with clinical findings alone. Serological assays for HHV-6 antibody are available and useful in nonclassical presentations. Treatment is supportive.

**Human herpesvirus 7 (HHV-7)**

HHV-7 is a lymphotropic herpesvirus closely related to HHV-6 with similar epidemiology; however, it has yet to be definitively linked to a single clinical disease. Transmission is likely through salivary secretions [2].

**Clinical features**
Studies have shown HHV-7 involvement in exanthema subitum and there is suspicion it may be involved in pityriasis rosea (PR).

**Diagnosis/treatment**
HHV-7 diagnosis is made with serological testing or detection of HHV-7 DNA with PCR. No treatment is currently available or recommended.

**Human herpesvirus 8 (HHV-8)**

HHV-8, or Kaposi’s sarcoma-associated herpes virus (KSHV) is the causative agent of Kaposi’s sarcoma (KS). Classic KS has a high incidence in Italy, Greece, Turkey, and Israel [20]. AIDS-associated KS is predominant in HIV+ homosexual men worldwide [20].

**Clinical features**
KS presents as small violaceous macules, patches, or plaques in the oral mucosa, genital mucosa, or gastrointestinal tract [2].
**Diagnosis/treatment**

The diagnosis of KS is made by skin biopsy. Treatment consists of highly active antiretroviral therapy (HAART) for AIDS-associated cases, radiotherapy to lesions, or intralesional interferon-alpha or tumor necrosis factor-alpha. Classic and endemic KS have been successfully treated with systemic chemotherapeutic agents [20].

**Human immunodeficiency virus (HIV)**

**Epidemiology**

HIV is perhaps the most devastating virus in today’s world. It is a zoonotic retrovirus whose transmission requires contact with blood or bodily fluid. Since AIDS was first described in 1981, HIV has become a worldwide pandemic disproportionally affecting certain areas [21, 22]. Today, the prevalence of HIV is highest in sub-Saharan Africa and the Caribbean and currently rising in eastern Europe, China, and India. The CDC has reported HIV importation from these various nations into the United States and United Kingdom via new immigrants [4, 9]. HIV-positive travelers and immigrants are also at higher risk of acquiring and importing other diseases.

**Clinical features**

Skin disorders are pervasive in HIV patients; up to 92% develop cutaneous manifestations of some kind [21]. The first possible cutaneous sign of HIV infection is during the acute retroviral syndrome, a collection of transient symptoms affecting 40–90% of newly infected patients [23]. A morbilliform eruption is present in 40–80% of patients; mucocutaneous oral or genital ulcers are also common [23].

Several primary dermatologic disorders affect HIV-infected patients much more commonly than the general population including seborrheic dermatitis, atopic dermatitis, psoriasis, and xerosis [21]. Many cutaneous infections and neoplasms occur frequently in HIV patients and can help classify them into clinical categories of disease severity. Bacillary angiomatosis, persistent or resistant candidiasis, oral hairy leukoplakia, and recurrent or multidermatomal zoster are conditions that indicate moderate disease progression, while coccidioidomycosis, cryptococcosis, HSV, histoplasmosis, KS, and mycobacterial infections are considered AIDS-defining illnesses [2, 21, 23].

**Diagnosis**

Detection of anti-HIV antibody via ELISA with confirmatory western blot is the gold standard for HIV diagnosis, unless infection is early, during which plasma HIV RNA is required [21].
Treatment
HAART is the mainstay of therapy. Treatment of cutaneous disease does not differ greatly from treatment in the normal population; skin disease is often resistant, but may improve with CD4 count elevation [2, 24].

Human T-cell lymphotrophic virus

Epidemiology
Human T-cell lymphotrophic virus type I is a human retrovirus discovered in 1980; transmission can be vertical, sexual, or blood borne [25]. About 20 million people worldwide are infected with HTLV-1. Japan, Africa, the Caribbean, and Central and South America are areas with the highest prevalence of infection [25].

Clinical features
Adult T-cell leukemia/lymphoma (ATLL), an aggressive malignancy of mature T-cells, was the first disease etiologically linked with HTLV-1 [25]. It occurs in less than 5% of those infected with HTLV-1. Skin involvement is common in ATLL; clinical findings include macules, patches, papules, plaques, nodules, tumors, or erythroderma [2, 25]. Infective dermatitis is a pediatric manifestation of HTLV-1 infection [26, 27]. Patients have extensive eczematous dermatitis and recurrent infections with Staphylococcus aureus or β-hemolytic Streptococcus [26]. Infective dermatitis is associated with later development of ATLL and HAM/TSP (HTLV-1-associated myelopathy/tropical spastic paraparesis) [26]. It should be suspected for very severe, resistant eczematous disease in children native to HTLV-1 endemic areas.

Diagnosis/treatment
The diagnosis of infective dermatitis in an HTLV-1 positive patient is clinical. It is treated with long-term systemic antibiotics, although the disease is often recalcitrant [26, 27]. Diagnosis of ATLL requires HTLV-1 seropositivity along with cytologic and histopathological evidence of disease. It is resistant to most chemotherapy, and prognosis remains poor [26].

Human papilloma virus (HPV)

Epidemiology
The HPV is an oncogenic DNA-virus with a worldwide distribution. There are a variety of HPV subtypes that have been associated with cancers, making HPV the most common cause of cancer deaths in developing
countries [28]. Transmission is through contact with skin or genitalia of infected individuals. The highest rates of genital HPV are in patient ages 18–28 years.

**Clinical features**

*Verruca vulgaris* (common warts) appear as hyperkeratotic papules, sometimes with verrucous features on virtually any cutaneous surface of the body. *Condyloma acuminatum/verruca acuminata* (genital warts) can also be accompanied by symptoms of burning, itching, bleeding, or pain [2, 28]. If untreated and nonresolving, genital warts can go on to develop into precancerous lesions and eventually neoplasia [2]. HPV strains 16, 18 are responsible for 80–90% of cervical cancers [2, 28].

**Diagnosis**

Diagnosis is generally based on clinical appearance, but can be aided by histological examination via a biopsy. Electron microscopy or PCR confirm the presence of HPV [2].

**Treatment**

Therapy includes topical acidic preparations such as trichloroacetic acid, and destructive procedures such as cryotherapy and electrodessication. The HPV vaccines have been FDA approved for use against select HPV subtypes known to contribute to malignancy (subtypes 16 and 18). The quadrivalent vaccine also protects against HPV subtypes 6 and 11. The vaccines are recommended in males and females ages 9–26 for the prevention of genital warts, and cervical and/or vaginal cancer.

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**Measles**

**Epidemiology**

Measles, caused by *Morbillivirus*, is the most notorious member of the *Paramyxoviridae* family; it is highly contagious, and transmitted by respiratory droplet contact [2, 30]. Endemic disease was eradicated from the United States in 2000, and Europe’s current goal is 2015 [30]. Even in countries that have interrupted endemic transmission, imported cases of measles are a continuing source of infection (Figure 12.6). In the United States from 2001 to 2008, 88% of the 557 reported cases were either directly imported or related to imported cases; the remaining 12% were from unknown sources [31]. Furthermore, there have been more reported cases per year in 2009–2010 than combined from 2001 to 2008.
Figure 12.6 Incidence of measles worldwide [29]

Map of priority countries (47)

Source WHO/VB database, 2006

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2006. All rights reserved.
Clinical features
A 2–4 day prodrome of fever, malaise, coryza, and cough begins after 10–12 days of incubation [31]. The pathognomonic koplik spots can be seen soon afterward, appearing as bluish-white spots on an erythematous base on the buccal mucosa opposite premolar teeth. 1–2 days later, the classic morbilliform exanthematous eruption begins at the hairline, spreading inferiorly and centrifugally. The rash may involve the palms and soles and may desquamate; it typically resolves in 4–6 days [2, 31, 32].

Diagnosis/treatment
The diagnosis of measles is clinical. Koplik spots, when seen, are pathognomonic. However, since measles is now rare in the Western world, confirmation with detection of IgM antibody is recommended [31]. Treatment is supportive.

Parvovirus B19
Parvovirus B19 is the only member of the family Paroviridae known to infect humans. Transmission is normally via aerosolized respiratory droplets and rarely via blood transfusion [33]. It has a worldwide distribution and an increasing prevalence with age [2, 33].

Clinical features
The most characteristic cutaneous manifestation is in erythema infectiosum (fifth disease), which presents as a “slapped cheek” appearance of the face, and a pink lacy eruption comprised of reticulated macules and papules on the trunk and extremities [2, 33].

Diagnosis
The diagnosis is usually clinical but may be confirmed with serology. IgM antibody detection is used for confirmation of acute disease, while IgG indicates past infection [2].

Treatment
Treatment for erythema infectiosum is usually supportive. Currently no vaccine is available for parvovirus B19. PPGSS usually has spontaneous resolution with no known sequelae.

Pox virus
Multiple genera of Poxviridae can infect humans including Orthopoxivirus (vaccinia, cowpox, variola, and monkeypox viruses), Parapoxivirus (Orf,
Imported Skin Diseases

bovine papular, pseudocowpox viruses), and Molluscipoxvirus (Molluscum contagiosum virus). Monkeypox is the main imported disease.

**Smallpox**

**Epidemiology**
Smallpox is caused by the variola virus and is highly contagious and deadly. The most recent outbreak in the United States occurred in Texas in 1949 and the last endemic case of smallpox was reported in Somalia in 1977 [34]. Smallpox is transmitted through inhalation of aerosolized virus particles or contact with bodily fluid or fomites.

**Clinical features**
Smallpox presents with a febrile prodrome prior to rash onset. The eruption is initially maculopapular turning into well-circumscribed vesicles, and then pustules in a centrifugal distribution. The pustules dry, scab over, and then fall off leaving a pitted scar.

**Diagnosis**
Diagnosis is confirmed via a rise in antibody titer (equal to or more than fourfold) or fluorescent antibody staining of smears taken from lesions [2, 35]. Patients must be quarantined and health officials contacted for proper infection control.

**Treatment**
There is currently no known treatment for smallpox. The smallpox vaccine used for disease prophylaxis. Vaccination up to 3 days after exposure can prevent disease.

**Vaccinia/cowpox/monkeypox**

**Clinical features**
Vaccinia virus is a constituent of the smallpox vaccine. Papules can appear a few days after vaccination followed by erythematous pustules. Cowpox infects cows, rodents, and humans who come into contact with the infected animals. Infected individuals develop papules at the inoculation site followed by vesicles. Monkeypox can be transmitted via handling or consuming the meat of wild monkeys or via close contact with infected humans. Symptoms are similar to smallpox except for more pronounced cervical and/or inguinal lymphadenopathy. In 2003, the CDC banned the importation of rodents from Africa to the United States due to an outbreak of monkeypox in Wisconsin [1].

**Diagnosis**
Diagnosis is based on virus isolation by PCR or serology by hemagglutination.
Treatment
No specific treatment exists for vaccinia or cowpox; however, cidofovir is used in severe cases of monkeypox. A vaccine exists that can be used as prophylaxis or within 4 days of exposure to monkeypox.

**Orf Disease**
This *Parapoxvirus* infects sheep, goats, and humans. Transmission to humans occurs by contact with infected animals or fomites [36].

**Clinical features**
The skin lesion initially appears as a purulent papule on a raised erythematous base followed by an inflamed weeping nodule, early crusting, late crusting, and regression.

**Diagnosis**
Diagnosis is based on the history and physical exam and confirmed by cell culture or direct fluorescent antibody testing [2, 36].

**Treatment**
Orf disease is usually a self-limiting illness and lesions spontaneously regress within 6 weeks [36].

**Rubella**

**Epidemiology**
The rubella virus is a *Togavirus* transmitted from person to person via inhalation of infected droplets from respiratory secretions or contact with fomites. Today, most cases of rubella infection are imported from other countries. Recently the CDC issued a warning regarding rising numbers of imported rubella from Germany, Vietnam, China, Cambodia, Malaysia, and Thailand [1]. Health officials have subsequently advised spouses of immigrants from these countries to get vaccinated in order to prevent contraction of disease during pregnancy.

**Clinical features**
Rubella, also known as German measles or 3-day measles, presents with headache, conjunctivitis, sore throat, rhinitis, malaise, cough, and lymphadenopathy. Exanthematous pink erythematous macules and papules usually appear on the forehead and spread centrifugally. The disease itself is self-limited, but in nonimmunized pregnant women it can cause severe congenital birth defects.
**Diagnosis**

Diagnosis is based on viral isolation during the first 2–4 days of illness using PCR or serological tests demonstrating an acute rise in IgM or fourfold rise in IgG [2].

**Treatment**

Treatment is mainly symptomatic. Several line-attenuated rubella vaccines are in use for prophylaxis. Vaccination is contraindicated in pregnancy or in patients who are immunosuppressed [2].

**References**


Sexually Transmitted Infections

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Key points

- Sexually transmitted infections (STIs) are common in people who have more than one sexual partner. They are common in those who for any reason travel and have had sex with new partners when traveling.
- Thus, they may infect people who are faithful but who have a partner who has become infected.
- They are no respecter of any person or position in society.
- Although there may be genital/anal symptoms, in women and men who have sex with men (MSM), STIs may be asymptomatic.
- Diagnostic and treatment recommendations for STI are updated continuously. Up to date instructions are available via websites of appropriate institutions.
- Education to prevent STIs must be available to all who intend to travel.
- Facilities for free and confidential treatment must be available in all major centers of population.
- Never forget syphilis. Never forget human immunodeficiency virus (HIV).
- Remember Chlamydia genital infection is the most frequent microbial STI in heterosexuals in industrialized countries.
- Antimicrobial resistance in Neisseria gonorrhoeae is ongoing. Ceftriaxone is the recommended treatment although in 2011 treatment failure has been reported. Strategies will need to be devised to monitor and contain this problem.
- Since 2003, lymphogranuloma venereum has been endemic among MSM in industrialized countries.
- World Health Organization STI diagnostic Initiative (SDI) is a priority program designated to develop affordable and reliable point of care (POC) tests for STIs that are predominant in low resource countries.
Introduction

Historical allusions
There is nothing new in knowledge that travel for whatever reason increases the risk of sexually transmitted infections (STI). The rapid introduction of what is now considered to be early infectious syphilis throughout Europe in the late fifteenth and early sixteenth centuries with the disbandment of soldiers after the invasion of Italy by Charles VIII in 1494 is part of the history of medicine in Europe [1]. Other examples date from the colonial period. There are well-documented records from British and Dutch colonial authorities of STI rates in India and the Netherlands East Indies, now Indonesia. More than half the British army stationed in India by 1895 was hospitalized for venereal disease (VD) with a loss of more than a million military man-days [2]. Similarly in the Dutch East Indies, in the military, the incidence of STIs (including syphilis) reached 52% for Europeans in 1881 and 26.3% for Indonesians in 1882 [3].

Human immunodeficiency virus (HIV) epidemic

Recently in the early years of HIV epidemic in China to 1995, those areas in Yunnan in the southwest were the first to notice the rise of HIV through sexual transmission from young women returning from Thailand [4].

Somehow, travelers do not seem to think they are personally at risk of acquiring HIV although they may be aware that HIV is an STI [5]. An analysis of 757 patients in London showed 18.6% had new sex partners in their last trip abroad, but only one-third used condoms all the time. 5.7% had contracted their STI from their last trip abroad [6].

If that is the case from an industrialized country, the risks are under recognized from developing countries. Incidence of HIV seropositivity in female sex workers varies from small incidences in single figures in Europe to over three quarters in some sub-Saharan African countries [7]. The prevalence of coexistent gonorrhea has varied between 20% and 63% depending on the type of commercial sex worker (CSW) used. In many countries, CSWs are found in over half, to have two or more STIs [8].

Men who have sex with men (MSM)

While the risk of travel and STIs in MSM (i.e., homo- and bisexual men) especially with HIV infection and syphilis have been recognized in liberal countries in western Europe throughout the HIV epidemic [9], it has been less well-realized in transitional, post-Communist societies in eastern Europe because of discrimination. Yet it has been noted since the 1980s [10] in Germany that MSM from eastern Europe are at risk to HIV and
other STIs and only recently has this been recognized in epidemiological trends [11].

This chapter includes a key section on how and when to screen for STIs based on adaptation of syndromic management.

**The importance of STIs in visitors**

The main aim is to raise awareness for the clinician that the individual with a STI may or may not be aware that they are infected as there may be no or few signs or symptoms initially. Travel history should always be considered. Sexual encounters while away from home are risky. Even when a sexual encounter has occurred locally there may be a risk that any STI resulting has been initially been imported into the locale. Thus, not only international travel helps spread STIs but resistant strains of already frequent STIs, foremost gonorrhea [12], may be brought into any community. Their spread needs expert monitoring.

**Publicity**

- Prospective travelers which include holiday makers and tourists should be made aware of risks of STIs from not only their personal physicians but through educational publicity in the media. Not only should correct use of the condom for penetrative sex be encouraged, but the dangers of alcohol, street drugs, and hard drugs need to be explained as well.

**Prophylaxis**

- Where possible vaccines should be provided well in advance for STIs. At present, the feasible ones are hepatitis A and B
- It is not good practice to allow self-medication with antibiotics as pre- or postprophylaxis; although in many countries “over the counter” availability of antibiotics is poorly regulated. This practice allows for build up of antibiotic resistance and allows for suboptimal and false hope treatment.

**Risky groups**

- Some groups of travelers have been well-recognized to be most at risk; MSM, truckers, seamen, long haul airline personnel, sex tourists, young travelers, military personnel, and sex workers. Some travelers may not realize how vulnerable they are, for example, older tourists, businessmen away from home, conference attendees, and short-stay tourists.
- There are also tourists with sex as the main purpose to go on holiday. Destinations such as Thailand and Gambia are popular. In the novel “Platform” the French writer Michel Houellebecq has written with vigor on the interaction between sex tourism and mass tourism. After returning home an “exotic” STI may manifest itself in holiday travelers.
**Practicalities of managing STIs as imported skin disease**

**Reasons**

- However much the patient may entreat the doctor to give him or her quick and seemingly easy treatment without proper history or investigation, it is not appropriate for the patient to receive this suboptimal treatment. Instead, if STI is suspected, appropriate national and/or international specialist guidelines for STI management should be followed [13]. Since diagnostic and treatment recommendations are updated continuously, one should rely only on the latest guideline version, which can be obtained via websites of appropriate institutions (e.g., who.int, cdc.gov, bashh.org, soa.nl) [14]. There can be no excuse nowadays not to follow them.

- Why? In no other form of dermatological practice would it be acceptable to receive out-of-date investigation, treatment, and follow up.

- Poor practice means that crucial screening for asymptomatic coexistent STIs is not done.

- Antibiotic resistance especially in gonorrhea is not monitored. Despite changing diagnostic molecular biologic technologies (MBT) involving nucleic acid amplification techniques, the rise of quinolone and cephalosporin resistance in *N. gonorrhoea* [15] needs to be monitored with appropriate monitoring using methods based on culture initially.

- *Chlamydia trachomatis* diagnosis by MBT is considered gold standard. It must not be missed.

- HIV diagnosis is missed with appalling long-term consequences for the individual.

- Syphilis is no longer a disease just occurring in MSM, previously considered a marginalized discriminated section of society, but has been increasingly been recognized as occurring in heterosexual networks [16].

- Only by good holistic care of STIs can the patient be educated and helped to understand how to help himself or herself prevent STIs in the future.

- Contact tracing/partner notification where possible must be considered. It is not ethical for the clinician treating that patient to let others who may have contracted a STI be left with potentially unheeded STIs.

As this chapter is for clinicians to use on a practical basis, it is not intended to be a primary text on STIs, but assumes that the user will already have that knowledge. The authors considered that a syndromic approach for advice to clinicians for screening STIs whether they have been imported or not would be best applied for this.
**Key section advice for clinicians**

STI SCREENING GUIDELINES of Washington State Clinical Laboratory Advisory Council. Reviewed/Revised up to May 2008 [17, 18] are easy to find on the web, comprehensive, and easy to follow but may also be adapted for local conditions such as Lymphogranuloma venereum (LGV) infection in MSM [19] in Europe or monitoring by culture of resistance patterns in gonorrhea. Thus, for this chapter they are slightly adapted.

**Who should be screened?**

**Asymptomatic screening**

**Women**
- *C. trachomatis*—nucleic acid amplification test (NAAT).
- *N. gonorrhoeae*—under age 25 or multiple sex partners.
- Cervical cancer (pap smear or HPV test) in women after the age of 30 years.

Pregnant women—see Box 13.1.

**MSM**
- Syphilis (*Treponema pallidum*)—serologic screening test with either a treponemal antibody test (e.g., treponema pallidum particle agglutination assay (TPPA), enzyme immune assay (EIA)) or a nontreponemal cardiolipin test (e.g., Venereal Disease Research Laboratory (VDRL) or rapid plasma regain (RPR)). In case the screening test is positive, a confirmatory test, a nontreponemal antibody test (e.g., VDRL or RPR) or a nontreponemal cardiolipin test (e.g., TPPA, EIA), is performed. In case of a genital ulcer, darkfield microscopy of ulcer exudate and/or MBT on *T. pallidum* is performed [20].
- HIV—HIV antibody screening test with confirmatory test (but in many centers p24 antigen for use in initial window stage is now feasible).
- *C. trachomatis*—urethral/rectal infection. In case rectal Chlamydia is diagnosed, additional serovar determination to exclude LGV is indicated [19].
- *N. gonorrhoeae*—urethral, rectal, and/or pharyngeal infection.
- Hepatitis A and B if immune status is unknown.
- Hepatitis C in HIV coinfected MSM.

**Symptomatic testing (listed by symptom and organisms/syndrome to consider testing for)**
- Urethritis/cervicitis
  - *C. trachomatis*, *N. gonorrhoeae*
  - Less frequent causes of urethritis: *Trichomonas vaginalis* (wet mount, DNA hybridization assay, rapid antigen detection test), Herpes simplex
virus (HSV) (nonrapid antigen detection test, culture (not everywhere now)), *Mycoplasma genitalium*

- Genital ulcers/inguinal lymphadenopathy
  - Syphilis
  - HSV (Figure 13.1)
  - Chancroid

**Box 13.1 Pregnant women (adapted from “Washington Guidelines”)**

Imported STIs in pregnant women are important as worldwide enforced and economic migration is occurring at the present time [21]. There is an ethical duty on the clinician to make sure that mother and the unborn child are free from STIs (Figure 13.2).

- **HIV Testing**: Though in some countries this is voluntary, it would seem more reasonable from a public health point of view for this to be comprehensive. Testing should be done on the first visit and if the woman is at high risk (whatever factors in that locale) she should be retested before 36 weeks gestation.
- **Serology for Syphilis**: At first examination and if at high risk, at 36 weeks (see above)
- **Serology for Hepatitis B Surface Antigen (HBsAg)**: Performed on all women at the first prenatal visit and repeated late in pregnancy for women at high risk of hepatitis B infection.
- **C. trachomatis**: Repeat during the third trimester for women aged <25 years and women with a new, or more than one sexual partner.
- **N. gonorrhoeae for Women at Risk**: Repeat during third trimester if risk continues.
- **Test for Hepatitis C Antibodies (anti-HCV)**: For women with a history of injection drug use, repeated exposure to blood products, prior blood transfusion or organ transplants.
- In USA, pap smear—although in other countries this might not be routine.
- Evaluation for BV might be conducted at the first prenatal visit for asymptomatic women at high risk for preterm labor.

*Figure 13.1* Recurrent genital herpes
- LGV serovars L1, L2, L3 (Europe MSM often with HIV apart from tropical sources.)
- Granuloma inguinale
- Vaginal infection
  - *T. vaginalis*
  - *Candida albicans*
- Bacterial vaginosis (BV) (three of four criteria—homogenous discharge, pH > 4.5, positive amine odor test, clue cells on microscopy)
- Genital warts-human papillomavirus (HPV)—clinical diagnosis, pap smear, HPV screen, biopsy
- Pelvic inflammatory disease
  - *N. gonorrhoeae*
  - *C. trachomatis*
- Epididymitis—*N. gonorrhoeae, C. trachomatis*, enteric bacteria (urine culture)
- Proctitis/proctocolitis/enteritis—*N. gonorrhoeae, C. trachomatis* (think of lymphogranuloma in MSM), HSV, syphilis. Enteric pathogens—patients with HIV may require additional tests
- Liver disease—follow locally approved hepatitis and testing guidelines
- Ectoparasites—*Pediculus pubis, Sarcoptes scabiei*
  But it remains that the individual clinician is in the best position to determine which tests are most appropriate according to the symptomatology of a particular patient.
Clinical Considerations: All patients at risk for STI should undergo a standardized examination that includes:

1. specific, relevant history (sexual risk behavior, previous STI, sexual orientation, travel history);
2. physical examination; and
3. laboratory tests.

The examination should be followed with a written clinical assessment based on (1) the history, (2) physical examination with a discussion of any abnormalities, and (3) a management plan that includes all laboratory tests requested and therapies initiated for if the patient should return for follow up or subsequent communication by text, telephone, e-mail, or other electronic means.

Recent trends

This section gives some examples of studies on STIs where human migration in one form or another has been of importance.

Africa

• There is no doubt that sub-Saharan Africa has been the part of the world most affected by HIV/AIDS. Migration especially by men for many reasons has played a large role in both the epidemiology of HIV as well as other STIs. But research of STIs during the last 30 years in Africa has generated a substantial body of new knowledge [22].

• Syndromic Management [23]: Most of the studies have originated and evolved through international cooperation. It is important to treat patients presumptively at their first visit while awaiting results from the laboratory.

• Chancroid [24]: An outbreak in Manitoba, Canada in the early 1980s led to a center for research in this being set up in Nairobi, Kenya where it was more frequent. From there epidemiology, optimal culture media for isolation of Haemophilus ducreyi and treatment regimens were defined (Figure 13.3).

• STI Control in Populations at High Risk of STI: Initial effective services for the treatment and prevention of STI among sex workers and their clients in Nairobi were used as a model for similar services in Kinshasa and Abidjan with subsequent reduction in both HIV and other STIs [22]. The Mwanza [25] community randomized intervention trial is vitally important in that it showed that with improved management of curable STIs the incidence of HIV could be significantly reduced. However, a trial of periodic mass treatment for STI in Rakai [26] district in Uganda showed no impact on HIV incidence. It has been thought that it might be that...
in Rakai the HIV epidemic was more mature and that the main cause of genital ulceration was HSV.

**Antimicrobial resistance in *N. gonorrhoeae* [27]**

Ongoing cooperative studies throughout Europe have shown that rates of resistance to ciprofloxacin the previously recommended treatment were high across Europe (42–52%) indicating its usage is not appropriate. High-level resistance to tetracycline and penicillin remained relatively constant at 16% and 12%, respectively.

Ceftriaxone is the latest evidence-based option available to treat gonorrhea. In 2011, treatment failure to ceftriaxone was reported in Japan [28]. Disturbingly these ceftriaxone-resistant strains are also resistant to many antibiotics such as penicillin, sulfonamides, tetracyclines, quinolones, and macrolides [29, 30]. Therefore, the existence of multiresistant gonorrhea is a fact and there is a serious risk that in the coming years the treatment of gonorrhea will become more problematic than the past 70 years. It is necessary to formulate measures to prevent the spread of multiresistant gonorrhea by international cooperative monitoring so that timely changes in the patient management can be considered (Figure 13.4).

**LGV and MSM [31, 32]**

Since 2003, LGV is endemic among MSM (a well-traveled discrete group) with high-risk sexual behavior, especially in Europe but it is also found in North America and Oceania. Recently several endemically transmitted heterosexual cases of LGV have been reported from Spain and Portugal. LGV among MSM is a cause of proctitis and occasional genital ulcer-adenopathy disease. It seems to be separate from heterosexual LGV in Europe occasionally imported from endemic countries. Its importance is in the necessity of
imported skin diseases

Figure 13.4 Gonorrhea with right epididymo-orchitis

Excellence of diagnosis requiring molecular diagnostic test facilities and its concomitancy with HIV, syphilis, and hepatitis C infections.

Chlamydia among backpackers

- *C. trachomatis* is the most common bacterial STI in many developed nations. Australia is a popular destination for young backpackers. However, a study from Sydney showed prevalence of Chlamydia was 3.5% in this group not higher than in most general populations [33].

World Health Organization STI Diagnostic Initiative (SDI)

The World Health Organization has launched a priority program that is designated to develop affordable and reliable point-of-care (POC) tests for STIs that are predominant in low resource countries (http://www.who.int/std_diagnostics). In this program, World Health Organization has formulated the ASSURED criteria that POC tests have to meet: Affordable, Sensitive, Specific, User-friendly, Robust and rapid, Equipment-free, Deliverable to those who need them [34]. The POC test result should be readily available, while the patient waits, to ensure
prompt treatment. This is especially important where patient return for treatment is low.

**Take-home message**

Education about sexual risks and promotion of condom use before travel and knowledge of access to public sexual health services needs to be always freely available.

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CHAPTER 14
Endemic Treponematoses

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Key points
- Treponemal diseases still are widespread in many regions of the world.
- Treponematoses occurring in humans comprise the endemic nonvenereal treponematoses (yaws, pinta, and endemic syphilis), and venereal syphilis.
- Children are at the highest risk to acquire the endemic treponematoses.
- Lack of public health surveillance and prophylactic control measures have resulted in disease resurgence of especially yaws in several tropical regions of the world, among people living in unhygienic circumstances in remote, often inaccessible regions.
- Latent cases are still highly prevalent and millions of people continue to be at risk of acquiring the endemic treponematoses.

Introduction
Treponemal diseases still are widespread in many regions of the world. Treponematoses occurring in humans comprise the endemic nonvenereal treponematoses (yaws, pinta, and endemic syphilis), and venereal syphilis. These diseases share prominent cutaneous manifestations and a chronic relapsing course. At present the causative agents of the different treponematoses cannot be distinguished from each other serologically or by other means. Venereal syphilis, caused by Treponema pallidum ssp. pallidum has a completely different mode of transmission, epidemiology, and clinical presentation (see Chapter 13). Children are at the highest risk to acquire the endemic treponematoses (see Table 14.1), where sexual transmission does not play a pathogenetic role. Transmission occurs by skin and mucous membrane contact from person to person. In yaws, breaks in the skin provide an entry for the treponemes. Endemic syphilis is most probably transmitted directly or indirectly by skin-to-skin or mouth-to-mouth contacts with infectious lesions, and by contaminated
Table 14.1 Nonvenereal endemic treponematoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Synonyms</th>
<th>Treponema Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaws</td>
<td>frambesia tropica, frambesia, pian, bouba, parangi, paru</td>
<td>Treponema pallidum ssp. pertenue (T. pertenue)</td>
</tr>
<tr>
<td>Endemic syphilis</td>
<td>bejel, frangi, njovera, loath, firjal, dichuchwa, bishel</td>
<td>Treponema pallidum ssp. endemicum (T. endemicum)</td>
</tr>
<tr>
<td>Pinta</td>
<td>carate, mal del pinto, azul, cute, cativa</td>
<td>Treponema carateum (T. carateum)</td>
</tr>
</tbody>
</table>

fingers. The mode of transmission of pinta is not entirely clear; it occurs probably by direct skin or mucous membrane contact [1–5].

Mass treatment campaigns against the endemic treponematoses, were very successful in the 1950s and 1960s, with support by the World Health Organization and the United Nations Children’s Fund (UNICEF). The incidence of the endemic treponematoses has been greatly reduced. Unfortunately, eradication was not accomplished. Lack of public health surveillance and prophylactic control measures have resulted in disease resurgence of especially yaws in several tropical regions of the world, among people living in unhygienic circumstances in remote, often inaccessible regions. Latent cases are still highly prevalent and millions of people continue to be at risk of acquiring the endemic treponematoses [5–8].

Yaws nowadays is prevalent in Africa and Southeast Asia in rural warm tropical regions with high humidity. Endemic syphilis still exists among isolated closed communities under unhygienic, primitive conditions, under dry, arid circumstances in the eastern hemisphere, among nomads and seminomads in Saudi Arabia and in Sahel countries in Africa. Pinta is still prevalent in tropical Central and South America in remote rural regions [7, 9, 10].

Clinical picture

In endemic treponematoses, an early (infectious) and a late (noninfectious) stage are discerned. Most often four stages have been discerned (a primary, secondary, tertiary, and latent stage), like in venereal syphilis. Different stages may show overlapping [1–5].

In contrast to venereal syphilis, in yaws, pinta, and endemic syphilis, congenital infection and neurologic and cardiovascular involvement are assumed to be absent or extremely rare.

Yaws and endemic syphilis may nowadays present an atypical form or a milder, “attenuated” form in some regions, with less florid skin lesions,
especially in areas with a low prevalence, possibly by the widespread use of antibiotics, by improvement of social conditions, by a mutation or an adaptation of the causative organism, or by altered immune responses of the host. In HIV-infected patients, new problems with the diagnosis and treatment of sexually transmitted syphilis are described. Thus far, these problems have not yet been reported in endemic treponematosis; endemic treponematoses occur “where the highways end,” in regions where HIV infection has not yet been introduced [8].

**Yaws**

The first (early stage) lesion, “mother yaw” (Figure 14.1), appears after an incubation period of 9–90 days. Legs, feet, and buttocks are most often affected. Sometimes, instead of a solitary primary lesion, multiple primary lesions occur. Early stage lesions can develop into ulcerated papillomatous lesions, which are highly infectious. After or during spontaneous disappearance of initial lesions relapses of more disseminated lesions can occur, which may be preceded or accompanied by fever, malaise, headache, and generalized lymphadenopathy. These early (secondary) stage skin lesions (Figure 14.2) often resemble the “mother yaw.” Macules, papules, and nodules can also be seen. Handpalms and footsoles may show hyperkeratosis (crab yaws). Hyperkeratotic lesions can occur in both early and late yaws. In the early stage bone and joint manifestations can already occur. Most important are osteitis and periostitis. After the early skin manifestations have subsided, a latent period of variable duration follows. This period can be interrupted by one or more relapses of skin lesions. In the majority of patients latency lasts lifelong.
The destructive late stage develops in approximately 10% of patients. Irreversible lesions of skin, bone, and joints are notorious (gangosa, saber tibia (Figure 14.3), gondou) [1–4].

**Endemic syphilis**

The primary lesion frequently remains unobserved in endemic syphilis, since the oropharyngeal mucosa is often involved in the primary phase. The first presentation of the disease frequently is a small ulcer or papule on the mucous membranes, nonitchy skin eruptions, and generalized lymphadenopathy, resembling yaws or sexually transmitted syphilis. Anogenital or axillary (Figure 14.4) condylomata lata, comparable to those in yaws and sexually transmitted syphilis, occur.

In the late stage, affection of skin, bones, joints, and nasopharynx may lead to severe destruction [1–5].

**Pinta**

In the early stage of pinta, a papule or an erythematous squamous plaque (Figure 14.5) occurs usually on the legs, feet, or hands. The initial lesions may become pigmented, hyperkeratotic, and scaly, accompanied by local lymphadenopathy. After several months or even years, more extensive skin lesions may appear. Changes in skin pigmentation can be the result of these skin lesions.
Imported Skin Diseases

Figure 14.3  Sabre tibia. This irreversible condition is caused by chronic, untreated osteoperiostitis (reproduced from Perine et al. [1], used with permission of the World Health Organization)

In late (tertiary) pinta disfiguring pigmentary changes, achromia, skin atrophy, and hyperkeratoses are the main features (Figure 14.6). Pinta is considered the most benign of the endemic treponematoses: no mutilations occur. It is assumed that only the skin is affected in this chronic disease [1–4].

Figure 14.4  Axillary condylomata of early endemic syphilis. Identical lesions are common in yaws (reproduced from Perine et al. [1], used with permission of the World Health Organization)
Laboratory tests

A diagnosis of endemic treponematoses is based on clinical, geographic, epidemiologic, and laboratory findings. No serologic test can differentiate any of the treponemes. Serologic tests for endemic treponematoses are identical to those of venereal syphilis.
In use are treponemal tests such as the *Treponema pallidum* hemagglutination assay (TPHA), the fluorescent treponemal antibody-absorbed test (FTA-abs), enzyme immunoassay (EIA) tests, and nontreponemal tests such as the Venereal Disease Research Laboratory (VDRL) test and rapid plasma reagin (RPR) test. The pattern of reactivity after infection and the persistence of positive serological test results after treatment are similar in nonvenereal and venereal treponematoses. Positive serological test results (in all stages except the very early stage), the presence of treponemes in dark-field examination of exudates of cutaneous lesions, and examination of skin biopsies (see Figure 14.7) confirm the diagnosis.

**Treatment**

The current recommended treatment is: a single intramuscular injection of benzathine penicillin 1.2 million units (0.6 million units for children younger than 10 years old) for all patients and contacts. Family members, contacts of patients, and patients with latent infection should receive the same doses as those suffering from active disease. No resistance to penicillin has as yet been reported. For penicillin-allergic persons, tetracyclines and erythromycin are alternatives.

**Conclusion**

It is highly unlikely that the different treponematoses will be eradicated. During relapsing infectious periods, persons with latent infection will periodically present with infectious lesions. All contacts exposed are at risk.
of contracting the disease [1]. After the mass treatment campaigns of the past, the clinical picture of yaws and endemic syphilis has changed in some regions, with milder attenuated atypical disease, making a proper diagnosis more difficult. Patients do not develop lifelong immunity. Therefore, early detection and treatment campaigns remain crucial. Continuing surveillance by seroepidemiological evaluation remains urgently needed. As is known from the past, treatment campaigns, continuing health education, and improvement of social and medical conditions are of utmost importance [1, 7, 9, 10]. Eradication programs should be integrated into other existing health programs, for instance, vaccination programs, mother and child health clinics, and tuberculosis and leprosy programs. Together with existing primary health care services these measures will certainly offer new possibilities to interfere with the spread of the treponematoses.

Due to the increasing frequency of worldwide travel and trends in migration, yaws, endemic syphilis, or pinta can turn up anywhere in the world and confront the medical profession with a diagnostic dilemma, especially in latent stage or late stage disease. In a patient originating from an endemic region a positive treponemal serology must arouse suspicion of a nonsexually transmitted treponematosis. Shared antigens give rise to cross-reactive antibodies common to all treponemal diseases, thus so far precluding a differential diagnosis on the basis of serologic tests. A careful history and evaluation in patients from endemic regions is still of utmost importance.

After proper treatment, early infectious lesions of yaws and endemic syphilis heal within 2 weeks. Healing of the cutaneous lesions of early pinta takes more time. Recognition and treatment of patients suffering from endemic treponematoses in an early stage can prevent later-stage sequels. Without institution of therapy, late stage manifestations can lead to severe handicaps [1–5, 10].

References


CHAPTER 15

American Tegumentary Leishmaniasis

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Key points

- Leishmaniasis is among the most neglected of the tropical diseases. Ninety percent of all cases of tegumentary forms of these disorders concentrate in five countries, including Brazil.
- American tegumentary leishmaniasis (ATL) is caused by the neotropical Leishmania species classified in the subgenera Viannia and Leishmania.
- The vectors of leishmaniasis are phlebotomines belonging to the genus Lutzomya and Psychodopygus.
- ATL presents multiple clinical, immunological, and pathological aspects comprising a spectral manifestation.
- The ATL spectrum includes subclinic or asymptomatic infection, self-healing skin lesions, localized cutaneous leishmaniasis (LCL), mucosal leishmaniasis (ML), disseminated leishmaniasis (DL), and diffuse cutaneous leishmaniasis (DCL).
- Susceptibility and progression of the disease are associated with CD4+ T-helper 2 (Th2) response, which induces the production of interleukin (IL)-4, IL-5, IL-10, and transforming growth factor, whereas the control and resolution of the infection is related to Th1 response.
- It has been suggested that even in moderately immunosuppressed HIV-infected individuals, cutaneous leishmaniasis (CL) is characterized by a higher rate of recurrence or reinfection and is more difficult to treat.

Introduction

American cutaneous leishmaniasis (ACL), American tegumentary leishmaniasis (ATL) also known as espundia, pian bois, bush yaws, uta,
chiclero’s ulcer, and other local names, is an infectious disease caused by different protozoan parasites belonging to the genus *Leishmania*. The disease is endemic in many countries of Central and South America, presenting a variable clinical spectrum. Leishmaniasis represents an increasing health problem in the world mainly because of new settlements in endemic areas, the opening of new roads in forest zones, tourism, and the movement of new immigrants into endemic areas.

**Epidemiology**

- Leishmaniasis is among the most neglected of the tropical diseases. The worldwide prevalence of leishmaniasis including the visceral form of the disease is about 12 million. According to the World Health Organization, there are 2 million new cases every year (a number that is growing), and 350 million people are considered to be at risk.
- Ninety percent of all cases of tegumentary forms of these disorders concentrate in five countries, including Brazil (Figure 15.1). Brazil is one of the most endemic countries in the Americas. According to the Brazilian Ministry of Health a total of 22,818 cases were diagnosed in 2010. In the Brazilian Amazon basin, an increasing number of patients has been observed. The Amazon region responds for approximately 40% of the cutaneous leishmaniasis (CL) cases in Brazil. Just in the federal state of Amazonas a total number of 1248 cases was reported in 2010.

Leishmaniasis was regarded mainly as an occupational disease, affecting people working in tropical forested areas where they are exposed to the natural transmission cycle of the disease. However, changes in these environments have led to the proliferation of various species of the vector, their associated parasites, and reservoirs around rural settlements. Furthermore, there is an increasing number of reports concerning the presence of vectors and infection in peri-urban zones, which were not previously endemic areas.

**Etiology and pathogenesis**

ACL is caused by the neotropical *Leishmania* species classified in the subgenera *Viannia* and *Leishmania* (Table 15.1).

The vectors of leishmaniasis are phlebotomines belonging to the genus *Lutzomya* and *Psychodopygus*. Phlebotomines are small mosquito-like insects that inoculate the parasite into the skin while taking a blood meal and are widely disseminated throughout the tropical and subtropical regions. Only the females are hematophagous. Generally, the infection is zoonotic. One species of *Leishmania* may be associated with one, or many domestic
Figure 15.1 Geographic distribution of American tegumentary leishmaniasis
Table 15.1 Classification of New World \textit{Leishmania}

<table>
<thead>
<tr>
<th>Subgenus Viannia</th>
<th>Subgenus Leishmania</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Leishmania} (V.) braziliensis</td>
<td>\textit{Leishmania} (L.) mexicana</td>
</tr>
<tr>
<td>\textit{Leishmania} (V.) peruviana</td>
<td>\textit{Leishmania} (L.) pifanoi</td>
</tr>
<tr>
<td>\textit{Leishmania} (V.) guyanensis</td>
<td>\textit{Leishmania} (L.) amazonensis</td>
</tr>
<tr>
<td>\textit{Leishmania} (V.) panamensis</td>
<td>\textit{Leishmania} (L.) garnhami</td>
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<tr>
<td>\textit{Leishmania} (V.) lainsoni</td>
<td>\textit{Leishmania} (L.) vezuelensis</td>
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<td>\textit{Leishmania} (V.) naiffi</td>
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<tr>
<td>\textit{Leishmania} (V.) colombiensis</td>
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<tr>
<td>\textit{Leishmania} (V.) shawi</td>
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<tr>
<td>\textit{Leishmania} (V.) lindenbergi</td>
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</tbody>
</table>

and wild vertebrate reservoirs. Humans are commonly accidental hosts, although there are situations in which they may be the reservoir in an anthroponotic cycle.

During their life cycle, \textit{Leishmania} species are found in two morphological forms—amastigotes and promastigotes. In humans and other mammalian hosts, they exist within macrophages as round to oval non-flagellated amastigotes, 2–3 μm in diameter. In the arthropod vectors, the parasites exist as elongated flagellated promastigotes, 10–15 μm in length and 2–3 μm in width. \textit{Leishmania} are intracellular organisms that primarily infect the macrophages and dendritic cells (DC). After deposition of the promastigotes by the female sandfly vector in the mammalian host, these flagellated forms are taken up by the macrophages and DCs, where they change to and replicate as amastigotes. After several asexual divisions, the amastigotes rupture the cell and are released. They are then rapidly taken up by other macrophages. Some parasites may remain in the skin causing cutaneous lesions, while others can spread from the skin via lymphatics and blood stream within some weeks after the infection. Parasites may then localize in the nasal, buccal, and pharyngeal mucous membranes leading to mucocutaneous ulcerative lesions in predisposed hosts. The life cycle is completed when the vector ingests the amastigotes from the reservoirs (humans are rare), which then undergo a transformation back to the promastigote form and multiply. Once the promastigotes are fully developed, they migrate from the vector’s midgut to the pharynx and proboscis, where they remain until they are inoculated into a new mammalian host.

\textbf{Immunological response}

After human infection with \textit{Leishmania} parasites, the individuals will develop different degrees of susceptibility to infection, with a wide spectrum of clinical manifestations, or no disease.
ATL presents multiple clinical, immunological, and pathological aspects comprising a spectral manifestation. The host immune response, as well as parasite biological behavior that may increase or attenuate its pathogenic role, host coinfections, and environmental factors are associated to the wide range of clinical manifestations and therapeutic outcome. The ATL spectrum includes subclinic or asymptomatic infection, self-healing skin lesions, localized cutaneous leishmaniasis (LCL), mucosal leishmaniasis (ML), disseminated leishmaniasis (DL) and diffuse cutaneous leishmaniasis (DCL).

The best-known experimental model of leishmaniasis is the infection with *Leishmania major*, one of the etiologic species of the Old World leishmaniasis. In this murine model, while susceptibility and progression of the disease are associated with CD4+ T-helper 2 (Th2) response, which induces the production of interleukin (IL)-4, IL-5, IL-10, and transforming growth factor \( \beta \), the control and resolution of the infection is related to T-helper 1 (Th1) response. The secretion of interferon-\( \gamma \) (IFN) and IL-2 by Th1 cells also plays an important role in determining resistance to leishmanial infection. Although the elimination of the parasites occurs through an effector mechanism involving an IFN-\( \gamma \)-mediated activation of infected macrophages in the murine model of the disease, the operative mechanism in humans is still not clear.

In the human disease, there is a close relationship between the host immune response and clinical outcome. For instance, patients with CL are able to develop a cellular immune response against *Leishmania*, with local and peripheral production of Th1 cytokines leading to macrophage activation against the parasite, allowing a partial control of the disease. CL patients can limit the disease and the number of parasites in their lesions, but there are several evidences that an exacerbated immune response is associated with intense local inflammation and tissue damage. Accordingly, in ML patients, the increased production of tumor necrosis factor (TNF)-\( \alpha \) and IFN-\( \gamma \) by CD4+ cells along with the decreased IL-10 function suggests that the disease results because inflammatory cytokines are not appropriately downmodulated and induce tissue damage. It is interesting to notice that patients with anergic diffuse cutaneous leishmaniasis (ADCL) show a complete absence of the cellular immunity against *Leishmania* correlating with a heavy parasite amount in tissue.

In comparison to cell-mediated response, humoral immunity is not correlated with resolution of the disease. Most patients do not develop protective lifelong-immunity after infection. Although different types of vaccines are being investigated, such as killed or attenuated whole parasites, synthetic or recombinant peptides, or recombinant live vaccine-vectors, an effective vaccine for the prevention of leishmaniasis is still not available.
Clinical features

According to patient’s cell-mediated immune response and the species of the infecting *Leishmania*, a spectrum of clinical forms of the disease can develop, including LCL, mucocutaneous leishmaniasis (MCL), DL and ADCL.

Localized cutaneous leishmaniasis

LCL is the most frequent form of the disease. It becomes clinically apparent after a variable incubation period. Clinically, LCL may present as a single (Figure 15.2) or multiple deep ulcerated skin lesions with raised, indurated edges and a sloughy base affecting any exposed parts of the body (Figure 15.3). In Mexico and Central America, the lesions localized on the pinna of the ears are called chiclero’s ulcer. The lesions may present as papules, nodules, and can also have infiltrative, verrucous, and vegetative appearance (Figure 15.4). There may be satellite lesions, an invasion of proximal lymphatic vessels, which sometimes give a sporotrichoid aspect, and local lymphadenopathy. Therefore, leishmanial parasites can invade the mucous membranes of the mouth, nose, pharynx, and larynx, giving rise to the mucocutaneous forms of the disease. In some patients, the lesions may evolve to spontaneous self-healing over months to years,
Figure 15.3  Localized cutaneous leishmaniasis—infiltrated lesion with central ulceration

Figure 15.4  Multiple cutaneous lesions
leaving atrophic scars. Nevertheless, most of the cases require systemic treatment to end the disease and prevent subsequent mucocutaneous involvement.

The causative agent of LCL can be any member of the neotropical subgenera *Viannia* and *Leishmania*. The most important parasite associated with this form of disease is *Leishmania (Viannia) braziliensis*. *Leishmania (Viannia) guyanensis* is the second most prevalent *Leishmania* species in Brazil and probably the main species causing LCL in the Brazilian Amazon above the north edge of the Amazon river.

**Mucocutaneous leishmaniasis**

A small number of patients may simultaneously present skin and metastatic mucosal involvement (Figure 15.5). However, the majority of patients show MCL as a result of an old, prolonged, untreated, or mistreated, and usually self-healing ulcerated skin lesion.

The time between the disappearance of the skin lesion and development of the mucosal involvement is variable, ranging from 2 to 35 years (average of 10 years). Clinically, the lesions are characterized by the involvement of the nasal mucosa in almost all cases, and in one-third of the patients a second site is affected, usually the pharynx, palate, larynx, or upper lip. The patients generally complain of permanent nasal stuffiness and obstruction, usually showing on physical examination an ulcerated cartilaginous

**Figure 15.5** Mucocutaneous leishmaniasis—cutaneous lesions and involvement of the lip and nose
mucosa or a nodule on the inferior turbinate or septum. Granulomas may also be posteriorly located requiring nasendoscopy to be seen. The main pathological feature is necrosis of the nasopharyngeal mucous tissues, which can lead to perforation of the septum and later complete destruction of the nose (Figure 15.6), palate, and lips, causing palatal dysfunction, dysphagia, dysphonia, aspiration, and severe disfigurement. The latter clinical feature is known as *espundia* in South America. Ultimately, death can occur due to secondary infection and/or laryngeal obstruction leading to acute respiratory failure or starvation. Spontaneous healing of MCL is unknown.

The most frequent etiologic agent of this clinical form of leishmaniasis is *L. (V.) braziliensis*. A smaller proportion of MCL cases is caused by *Leishmania (Viannia) panamensis* and *L. (V.) guyanensis*.

**Anergic diffuse cutaneous leishmaniasis**

In 1946, this rare form of leishmaniasis was described in Venezuela by Convit and Lapenta. Similar cases from other South American countries and also Central and North Americas were subsequently reported. According to the first description, ADCL is characterized by the presence of nodular skin lesions, plaque, ulcerations in areas submitted to trauma, and infiltrative disseminated cutaneous lesions distributed over the whole body. The disease also presents a negative Montenegro cutaneous test and failure
to respond to antimonials and other specific therapies. The disease shows a close clinical resemblance to lepromatous leprosy. Although ADCL usually presents a protracted course, there is no tendency to visceralization. The Montenegro skin test and lymphocyte proliferation assay are negative, which demonstrate the deficient cell-mediated immune response characteristic of this form of leishmaniasis. The causative agents of ADCL are *Leishmania (Leishmania) pifanoi*, *Leishmania (Leishmania) mexicana* and *Leishmania (Leishmania) amazonensis*.

ADCL in Brazil is predominantly caused by *L. (L.) amazonensis*. The involvement of nasopharyngeal mucous membrane is rare.

**Disseminated cutaneous leishmaniasis**

DL is an emergent form of ATL, initially described in Bahia, Brazil by Torres in 1920. The immunopathogenesis of DL is poorly understood. A complex network involving host, parasite, and the environment is implicated in the development of the disease. For instance, *L. braziliensis* antigens derived from DL cases differ from *L. braziliensis* antigens from CL cases in the stimulation of cytokine production. Evaluation of the peripheral cytokine production in DL cases shows lower IFN-γ and TNF-α production when compared with CL, suggesting that a peripheral decrease in the type 1 immune response allows parasite dissemination. However the in situ product of Th1 cytokines is preserved, while the production of chemokines that attract activated T cells to the multiple cutaneous lesions favor inflammation and tissue damage.

DL is characterized by the appearance of an ulcer usually in extremities, followed by multiple mixed lesions (acneiform, papular, and ulcerated lesions), distributed in at least two noncontiguous parts of the body (Figure 15.7). Many cases presents a dissemination phase, where the patient typically reports the finding of a single initial lesion usually in one extremity followed, after a period of few days, by disseminated lesions that may involve the entire body. The rapid spread of the lesions and occurrence of systemic symptoms (fever, chills, malaise) suggest direct hematogenic dissemination. A high frequency of nasal mucosal involvement is observed in as many as 38% of the disseminated cases. Histopathology shows a mononuclear infiltrate with lymphocytes and macrophages and very few parasites. The Montenegro skin test can be positive or negative. DL differ from DCL caused by *L. amazonensis*, which is characterized by the presence of multiple nonulcerative nodular lesions, a negative Montenegro skin test, and a high number of leishmania within macrophages. DL is a hard to cure disease; the treatment is done with Sbv 20 mg/kg/day, during 30 days, but more than 60% of cases will require more than one course of Sbv to cure.
American tegumentary leishmaniasis and HIV coinfection

Over the past two decades, leishmaniasis, in particular visceral leishmaniasis (VL), has been recognized as an opportunistic disease in HIV-infected patients. The distribution of both infectious agents overlaps in numerous parts of the world (e.g., Mediterranean basin, South America, India, and many African countries). In contrast to the literature on VL, only scarce data are available on CL caused by dermatropic species in HIV-infected patients. However, a study from French Guiana suggests that even in moderately immunosuppressed HIV-infected individuals, ACL is characterized by a higher rate of recurrence or reinfection and is more difficult to treat than it is in HIV-negative individuals.

The presence of *Leishmania* and HIV concomitantly in the same host cell (the macrophage) has enhanced reciprocal effects that influence the expression and multiplication of either one or both pathogens. A vicious circle is established whereby the protozoan parasite *Leishmania* induces a more robust HIV-1 production and the virus mediates a greater parasitic replication. Thus, both pathogens exert a synergistic detrimental effect on the cellular immune response because they can establish infection in similar host immune cells.

In coinfected patients, the clinical picture ranges from a few spontaneously healing lesions to diffuse external or internal disease, which may be accompanied by severe mucous membrane involvement. Solitary or
multiple nodules, papule, verrucous, eczematoid, plaque, hyperkeratotic, warty, zosteriform, erysipeloid, and sporotrichoid lesions have been described (Figure 15.8). The cutaneous lesions may occur before, after, or at the same time as visceral lesions. However, exclusive cutaneous involvement does occur, although such presentation is rare.

Clinical deterioration is frequently reported in approximately 10–25% of AIDS patients with advanced, symptomatic disease and low CD4+ cell counts, who had started HAART, regardless of an immunologic improvement and a reduction in plasma HIV loads. This phenomenon has been called immune reconstitution inflammatory syndrome (IRIS) and is believed to be a result of an inflammatory response to hidden or preexisting but partially treated opportunistic infections. The spectrum of pathogens associated with IRIS continues to increase, with a predominance of infections with mycobacteria, however, atypical cases of ACL due to *L. (V.) braziliensis* and *L. (V.) guyanensis* in association with IRIS have been reported.

**Differential diagnosis**

Skin lesions that can mimic LCL include traumatic ulcerative lesions, superinfected insect bites, myiasis, fungal and mycobacterial infections, sarcoidosis, neoplasms, and many other skin diseases.

The following diseases should be considered in the differential diagnosis of MCL: leprosy, lethal midline granuloma, venereal syphilis, yaws, rhinoscleroma, and blastomycosis.

ADCL should be differentiated from lepromatous leprosy.
Diagnosis

The diagnosis of ACL is based on the presence of the parasites in tissues. The most effective method is a skin smear from the lesion. The smear is obtained by scraping the edge of the ulcer with a blade or making a shallow slit in the lesion and scraping the cut edge. The contents are then stained with Wright’s, Giemsa, or Leishman. On light microscopy, the amastigotes are seen as pale-blue oval bodies presenting a dark-blue nucleus and a small point-shaped kinetoplast within the cytoplasm of tissue macrophages (Figure 15.9).

Alternatively, the parasites can be cultured in a biphasic medium, such as Novy-MacNeal-Nicole (NNN), or a similar medium. Although cultures should not be discarded as negative before 4 weeks, some strains will not grow in culture. In such cases, the material can be inoculated into susceptible animals, such as hamsters. However, it may take 7–9 months to give a result, being therefore not very practical for use in routine.

Although the histopathology of the cutaneous lesions is highly variable, ranging from ulceration to hyperplasia, the histopathological examination is still an important diagnostic tool. Generally, light microscopy shows diffuse dermal infiltrate containing histiocytes, lymphocytes, plasma cells, and neutrophils. The number of parasites is usually inversely proportional to the duration of the lesion.

LCL lesions due to Viannia species demonstrate scarce parasites and usually, a mild infiltrate consisting of few macrophages and frequent lymphocytes and plasma cells, which gives the infiltrate characteristics of an epitheliod granuloma. On another hand, localized lesions due to L. (L.)
*amazonensis* reveal a heavy dermal infiltrate of vacuolated macrophages full of amastigotes, which gives the infiltrate a macrophagic granuloma appearance.

Mucocutaneous lesions may also present granulomatous changes, *Leishmania* parasites are difficult to detect. ADCL lesions are characterized by a dense infiltrate of plasma cells, giving the infiltrate an aspect of a macrophagic granuloma. In cases of DL, the histopathological examination reveals an infiltrate of lymphocytes and plasma cells in the dermis with rare macrophages and parasites.

Compared to the aforementioned diagnostic methods, the polymerase chain reaction (PCR) is the best approach to diagnose ACL. Aside from being highly sensitive and specific, it is also more rapid than the other methods currently available. There are primers to identify different parasite species. As the characterization of parasites may influence the treatment, PCR should be used as a routine examination, especially where CL is endemic and caused by different parasites. Unfortunately, this very sensitive method is still expensive and not available in most of the endemic areas.

Tests of immune function are available, but are more valuable for following the course of the disease than diagnosing it. They include enzyme-linked immunosorbent assays (ELISA), the Montenegro test, and in vitro lymphocyte proliferation assay for cell-mediated immunity. The ELISA test uses purified leishmanial antigens, showing elevated antibody levels usually in the early stages of the disease. The Montenegro skin test, also known as leishmanin test, is used to measure the cell-mediated immune response by injecting 0.1 ml of a phenol-killed preparation of promastigotes in the anterior aspect of the forearm. After 48–72 hours, the reaction is measured and an induration of 5 mm or more is considered positive. The lymphocyte proliferation assay also evaluates the cell-mediated immune by measuring the proliferation of peripheral blood lymphocytes in response to a crude extract of promastigotes after a 6-day period of incubation. The Montenegro skin test and lymphocyte proliferation assay indicate both present and past infection.

**Prophylaxis**

To date, no vaccine exists for visceral or any other form of leishmaniasis. Therefore, measures to combat the vectors should be employed. The increasing incidence and domesticity of ACL reservoirs and vectors also increase the feasibility of interventions to interrupt transmission around houses. Residual spraying of houses can reduce the transmission through the interruption of *Leishmania* life cycle.
**Treatment**

The drugs of choice for the treatment of ACL are the meglumine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®), both pentavalent antimony derivatives. Amphotericin B and pentamidine are the second-line treatment.

According to the Brazilian Ministry of Health, the recommended dose for LCL and DL is 10–20 mg/kg/day of intravenous or intramuscular Glucantime for a period of 20 days. If there is no complete healing of the lesions 3 months after the end of the treatment, a second or third course can be administered after the initial treatment. Reported side effects include arthralgia, myalgia, loss of appetite, nausea, vomiting, abdominal pain, pruritus, fever, weakness, headache, dizziness, insomnia, edema, hepatitis with increased transaminases and alkaline phosphatase, acute renal failure, pancreatitis, and electrocardiographic dose-dependent changes, such as change in ventricular repolarization with inversion of the ST-segment, increased QT interval, ischemic changes, and bigeminal, polymorphous and polyfocal extrasystoles.

MCL shows a highly variable response to antimonials, and for some authors, there is no cure with this drug. Amphotericin B or pentamidine are better alternatives.

The use of pentavalent antimony associated with pentoxifylline, which downregulates TNF-α production, cured MCL refractory cases and also accelerated healing time and avoided further antimony courses in MCL.

The recommended treatment with Pentamidine is three doses of 4 mg/kg (maximum daily dose of 300 mg) intramuscularly every 48 hours. For the treatment of MCL, 10 doses of pentamidine should be administered. Once the therapy is completed, the patient is followed with ELISA titles every 6 months. In our experience, pentamidine is the first-line therapy for both LCL and MCL in the Brazilian Amazon when miltefosine is not available.

Amphotericin B is the second or third therapeutic option for LCL. It is a very important drug for difficult to treat cases of MCL. The dose is 1.0 mg/kg intravenously every other day, in a total of 2–3 g. The patient needs to be hospitalized for the treatment with this drug.

Miltefosine is a phospholipid drug originally developed as an anti-neoplastic agent. It is the first clinically active oral antileishmanial drug commercially available for the treatment of both VL and CL. The drug was recently (2005–2006) registered for treatment of leishmaniasis in Colombia, Guatemala, Honduras, and Ecuador. In one study conducted in the Brazilian Amazon, miltefosine was more effective than antimonials in the treatment of CL caused by *L. (V.) guyanensis*. For CL acquired in Brazil, physicians should be aware that *Leishmania* speciation may be necessary to better treat patients or tourists living in or traveling to the
Brazilian Amazon. The CL caused by *L. (V.) guyanensis* has a low cure rate with antimonial, and miltefosine should be considered as a treatment option. Miltefosine is administered orally at the total target daily dosage of 2.5 mg/kg of body weight (maximum daily dose of 150 mg) for 28 consecutive days. Miltefosine was also used to treat CL caused by *L. braziliensis* in Brazil, with higher cure rates than pentavalent antimony.

Other described systemic treatments are prolonged high-dose of oral ketoconazole, fluconazole, and rifampicin.

Several local therapeutic approaches have been reported. The topical application of paromomycin sulfate, an aminoglycoside antibiotic that proved to be effective against leishmanial parasites in vitro, remains controversial. Intralesional application of pentavalent antimony compounds, including sodium stibogluconate and meglumine antimoiate have shown response rates between 72% and 100%.

The efficacy of 5% topical imiquimod in combination with pentavalent antimonial was shown to lead to a higher rate of clinical cure of CL when compared to the use of antimonial alone. Therapy with rhGM-CSF, a glycoprotein that induces the growth of granulocyte and/or macrophage colonies, by topical application and intralesional injection led the lesions to heal faster than therapy with antimonial alone.

CO₂ laser was also described for the treatment of CL. In a trial with 132 patients, this therapeutic approach was statistically more effective than treatment with antimonial. Other surgical approaches include cryotherapy excision, curettage, and eletrodissecation. Experimental approaches such as photodynamic therapy are also reported; however, further studies are required to prove the efficacy of this method.

In HIV-*Leishmania* coinfection patients presenting cutaneous lesions, the therapeutical options are mainly pentavalent antimony and amphotericin B in same the dose used for immunocompetent patients. Pentamidine is not indicated because it may cause sterile abscess. Coinfected patients require close monitoring of CD4 cell count, and secondary prophylaxis with pentavalent antimony should be considered. There have been obvious favorable results of miltefosine treatment for both CL and VL.

### Further reading


CHAPTER 16
Leishmaniasis: Old World

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Key points
- Old World cutaneous leishmaniasis (OWCL) is mainly a zoonosis.
- The species of *Leishmania* spp. involved in human disease include *Leishmania tropica*, *Leishmania major*, *Leishmania aethiopica*, and *Leishmania donovani* complex.
- OWCL manifest in different clinical forms including: localized simple, disseminated, complex, lymphangitic, lupoid or *recidivans*, diffuse anergic, and post-kala azar dermal leishmaniasis (PKDL).
- Particular species of *Leishmania* spp. are responsible for specific clinical presentation.
- Systemic or intralesional pentavalent antimonials remain the treatment of choice for most cutaneous infections by Old World leishmanial parasites. Definite randomized control trials are not available and current attempts to generate therapeutic guidelines rest on experience, published case series, and anecdotal reports.
- The introduction of miltefosine is a new approach for the treatment of cutaneous leishmaniasis.

Introduction

The term Old World cutaneous leishmaniases (OWCL) is given to a group of parasitic diseases caused by protozoan flagellate organisms of the genus *Leishmania* order Kinetoplastida, family Trypanosomatidae. Cutaneous leishmaniasis affects humans as well as a variety of wild and domestic animals that function as a reservoir in the transmission cycle as this is commonly a zoonosis. However, in some instances the affected human can be the source of infection in an anthroponotic cycle, such as observed in Afghanistan and Sudan in cases of localized simple cutaneous infection by *Leishmania tropica* or else cases of post-kala-azar dermal leishmaniasis (PKDL) caused by *Leishmania donovani* in India and Sudan. The parasites are transmitted to humans by the infective bite of the phlebotomine sandfly and particular species of vectors are adapted to transmit particular
species of the parasite that subsequently determines the type of clinical disease. The main species of leishmanial parasites causing disease in the Old World are: *Leishmania major*, *L. tropica*, *Leishmania aethiopica*, *L. donovani donovani* and *Leishmania donovani infantum*.

Each form of clinical leishmaniasis manifests distinct features that make them individually different from the other types within the spectrum. They are unique in etiology, transmission vector, reservoirs, epidemiology, and geographical distribution. These individual features are also relevant to design an effective therapeutic intervention and to establish the expected prognosis. This chapter presents a brief summary of the most important individual features from recently described research on particular *Leishmania* species and this is followed by a practical general discussion on epidemiology, clinical/laboratory diagnosis, treatment, and control.

**L. major**

This is the main cause of localized simple cutaneous leishmaniasis in an endemic pattern as found in Iran, North Morocco, Algeria, Middle East, North India, Pakistan, Central Asia, and sub-Saharan Africa. This species is also responsible for outbreaks of cutaneous simple leishmaniasis in Sabzevar County, Iran, where surveys in children have found a prevalence of 9% for scars and 6% for active ulcers. This is a zoonotic infection and *Rhombomys opimus* has been found to be the main reservoir host and *Phlebotomus papatasi* the main vector [1].

With regard to virulence factors, it has been described that *L. major* protein disulfide isomerase is particularly expressed in virulent strains and enzymatic inhibitors have resulted in lower virulence and decreased parasitic growth [2]. Phosphoglycans also play a role in the persistence of parasites for a long time and are involved in disease expression. In view that *L. major* infections tend to be universally self-healing it has been postulated and found that the infection induces a CD4+ Th1 helper immune response, which initially controls and limits infection and subsequently confers permanent immunity to reinfection by the same species.

Professional antigen presenting cells in the host are a main feature of the Th1 protective immune response in leishmaniasis and this role has been demonstrated in experimental systems. Dendritic cells are important to transport leishmania parasites and signals of the infection from the skin to local lymph nodes in mice models and this role has been confirmed in both Langerhans and plasmacytoid cells. The acute inflammatory cellular infiltrate also plays a significant role as infected neutrophils secrete chemokines to attract macrophages that ultimately become the host cell for leishmania parasites [3].
**L. tropica**

*L. tropica* causes localized or disseminated simple cutaneous leishmaniasis in eastern Mediterranean and sub-Mediterranean regions. This species is widely found in cases from northern Morocco, Central Asia, Afghanistan, Pakistan, Iraq, Kashmir, and Saudi Arabia. The infection is commonly transmitted through an anthroponotic cycle in urban Asian communities (Kabul, Peshawar). For many years now, it has been recognized that different strains of *L. tropica* have the ability to induce a variable spectrum of clinical disease, that is, cutaneous, mucosal, visceral, or viscerotropic clinical pictures. Most commonly, skin lesions are nonulcerative and nonprogressive, however, cases have been reported with an exceptionally virulent and chronic clinical course. There seems to be a specific enzymatic compound that determines the variable spectrum of disease [4]. Cysteine proteases from *L. tropica* are virulence factors that are essential for growth and pathogenicity of amastigotes in the mammalian host. Different authors have found mucosal leishmaniasis in children in Saudi Arabia caused by *L. tropica*, and in certain regions of the Middle East such as Jordan, particular zymodemes have been described as a cause of simple cutaneous infection. Finally, there is a well-recognized clinical picture that seems to result from hypersensitivity to leishmanial antigens and particularly seen in 0.5–4% of children with cured localized infection. This small proportion of children and adults with healed *L. tropica* infections develop leishmaniasis recidivans also called lupoid leishmaniasis particularly on the face, several years after cure [5].

**L. aethiopica**

*L. aethiopica* infection manifests in two different clinical forms, self-healing localized cutaneous leishmaniasis and anergic diffuse cutaneous leishmaniasis. Cutaneous leishmaniasis is endemic in Ethiopia, Kenya, eastern Sudan, and Southwest Africa; however, this species has also been identified in wild reservoirs in Saudi Arabia [6]. The overall prevalence of localized cutaneous infections on the western side of Ethiopian Rift Valley has been identified in 4% of general population and 8.5% in the age group 0–10 years. Approximately 50% of clinical cases suffer active disease for 9 months and 10% for over 3 years and scars are present in up to 35% of residents. A positive leishmanin skin test has been found in 55% of children without signs of disease and *Phlebotomus pedifer* has been identified as the only vector for *L. aethiopica* [7].

In view that this particular species causes localized or diffuse anergic forms of clinical disease, efforts have been directed at the identification of
virulence factors or genetic variability within the species. DNA PCR fingerprinting techniques have disclosed ample genetic heterogeneity that correlates with the geographical distribution; however, the polymorphism does not seem to be responsible for the different clinical pictures observed in different hosts and a total of 10 different strains have been described to date.

In vitro evidence shows that promastigotes from patients with localized disease induce Th1 cytokines, whereas those from anergic cases, where antigen specific nonresponsiveness is found, the cytokine pattern reveals a Th0 or Th2 type of response. Ultrastructural studies have revealed that both parasites and host’s cells differ widely depending on whether they are from localized or diffuse cutaneous leishmaniasis cases. Cases with diffuse anergic illness are characterized by macrophages with larger parasitophorous vacuoles, higher number of amastigotes per vacuole, larger promastigotes, and larger amastigotes. It has been demonstrated that in nonhuman primate experimental systems the active lesions and subsequent healing of localized infections, are followed by an effective delayed-type hypersensitivity (DTH) reaction and permanent immunity to challenge by parasites from localized or diffuse cases. Murine models have confirmed that the control of infection involves a successful DTH reaction in both skin and lymphatic tissues.

Finally, research has shown that the IgG antibody response from patients with diffuse cutaneous leishmaniasis recognizes antigens of higher molecular mass (∼90 kDa) than those recognized by cases with localized infections (∼<25 kDa). Healed localized cutaneous leishmaniasis by *L. aethiopica* may relapse many years after cure following infection by HIV.

**L. d. donovani and L. d. infantum**

The first of these species is responsible for visceral leishmaniasis (VL) and relevant to dermatologists in that it causes PKDL in India, Bangladesh, Nepal, and in Africa, particularly Sudan. *L. d. infantum* can also cause VL, however, it commonly determines localized or disseminated cutaneous leishmaniasis in the Western Mediterranean basin including all southern European countries. *L. d. infantum* has been reported to cause pure lymphadenitis without any skin involvement. A high number of asymptomatic individuals in the general population have been infected as determined by positive leishmanin skin test in Tunisia (45–80% of subjects) as well as in Spain where random serology in Castilla-Leon revealed a 5% of positive seroprevalence, with even higher values of up to 64% in those with HIV infection [8].

The role of symptomatic or asymptomatic dogs as domestic reservoirs in *L. d. infantum* infection has been well recognized and characterized
in Mediterranean European and African countries. Serological sur-
veys in Algiers have found 37% positive mostly asymptomatic dogs
by immunofluorescent-antibody test (IFAT), and a similar picture was
described in Greece [9]. On the contrary, there is a minimal or absent risk
of infection for northern European dogs taken on holidays to Mediter-
ranean countries.

Most cases of *L. d. infantum* are transmitted by *Phlebotomus perniciosus,*
and *Phlebotomus longicuspis* in this area [10].

Epidemiological and laboratory-based research on the variable clini-
cal expression of *L. d. infantum* infections has described a high number
of strains within this particular species. Over a period of 10 years, for
instance, a total of 20 different strains have been recognized by zymodeme
analysis in Spain [11], and specific investigations in HIV-infected individ-
uals have reported 20 zymodemes in visceral and cutaneous leishmaniasis
by the same parasite in 15 years [12].

The above variability has further biological implications as it has been
observed that parasites causing infection in immunocompromised individ-
uals have different DNA sequences than those isolated from an immuno-
competent host, suggesting that this difference may be responsible for the
increased pathogenicity in the immunocompromised.

**PKDL**

This is a particular type of dermatosis that manifests during or after treat-
ment and commonly following clinical cure of VL. The affected lesional,
but not the healthy-looking skin tissue, contains amastigotes, antigenic
products, or *L. donovani* DNA, which are useful to make a positive diag-
nosis. PKDL is highly relevant in the anthroponotic cycle of VL infection
and is very uncommon in the context of HIV coinfection. In spite of the
fact that the immunology of PKDL is not completely understood, a limited
body of evidence from research suggests that this dermatosis results from
the attack of the immune system to surviving amastigotes in the skin after
treatment. It has been found that following treatment of VL the periph-
ERAL blood mononuclear cells produce IFN-γ and this coincides with the
appearance of PKDL. It has also been reported that high concentrations
of IL-10 during VL infection predicts the development of PKDL, and that
CD4+ T helper lymphocytes are decreased in number when compared
to CD8+ cells in hypopigmented PKDL skin lesions. Finally, cases with
HIV coinfection with VL have been reported to develop PKDL following
immune recovery from HAART.

There are two main types of PKDL with unique features, that is, the
Indian and the African types. The former has been described in India,
Bangladesh, and Nepal and it is prevalent in hyperendemic areas with VL such as Bihar. This type manifests in approximately 5–10% of cases with VL and the clinical picture of PKDL follows the visceral disease in 2 or 3 years, however, cases can manifest after 10 years of the treated episode with VL. Indian PKDL always requires treatment with antimonials for 4 months or more.

The African type of PKDL has been observed in Sudan, Kenya and East Africa and cases can be caused by *L. d. donovani* or *L. d. infantum*. PKDL has been recorded in up to 50% of cases with VL in Sudan where *P. orientalis* is the main vector and the onset of the dermatological manifestations takes place at the time or within 6 months of the visceral episode. PKDL is particularly severe in children and a number of clinical observations have found increased morbidity and mortality in the presence of malnutrition, anemia below 9 g/dl hemoglobin, high levels of CRP, splenomegaly, diarrhea, vomiting, or bleeding. PKDL can heal spontaneously within 1 year and genetic susceptibility to both visceral disease and PKDL has been suspected in Sudan.

**Epidemiology, geographic distribution, etiology, and mode of infection in OWCL**

OWCL are distributed in most of the Mediterranean basin (southern Europe, Asia Minor, northern Africa), the Middle East, Central Asia, parts of India, China, and a few countries in sub-Saharan Africa. The disease has been found in 62 Old World countries and the World Health Organization has estimated that 500,000 new cases of cutaneous leishmaniasis occur worldwide every year.

The *Leishmania* parasite is a dimorphic protozoan that occurs as a flagellated promastigote with an approximate size of $25 \times 3 \mu m$, living within the sandfly’s intestinal tract. The infective form inside the host’s macrophages manifests as a $2–6 \mu m$ in size, oval or round amastigote. The *Leishmania* parasites present in the skin of humans or animal reservoirs as amastigotes are taken up with a blood meal by the female Phlebotomine sandfly (Diptera). At least 40 different species of Phlebotomine sandflies relevant in the transmission of leishmaniasis have been described in the Old World. Following ingestion, the protozoan organisms undergo a process of differentiation in the vector’s rear- or midgut that takes a few days for most species and they finally reach the stage of infective metacyclic promastigote present in the salivary glands of the sandfly. The inoculum with infective promastigotes is transmitted through the bite of female sandflies while taking the next blood meal from the vessels in the superficial dermis of a new host. A variety of factors such as the size of
the inoculum, number of bites, and the host’s genetic, nutritional, and immunological status determine the outcome of overt clinical disease or else elimination of the parasites without any symptomatic manifestation. For those who develop clinical illness within the next few weeks following the infective bite, this may manifest as localized simple cutaneous leishmaniasis, disseminated picture with multiple lesions, anergic forms of diffuse cutaneous leishmaniasis, or else PKDL that starts at the time or months following systemic treatment for VL.

Apart from humans that are relevant as reservoirs in anthroponotic cases of leishmaniasis there is a large number of wild and domestic hosts in the zoonotic transmission of the disease. The most commonly identified hosts include gerbils, hamsters, mice, rats, foxes, dogs, donkeys, and goats. In particular, dogs represent the most important domestic reservoir for infections by *L. donovani* complex in the Mediterranean basin.

The OWCL affect individuals of all age groups and both genders as well as entire populations in hyperendemic regions in rural and urban areas. Clinical cases can present sporadically or else in outbreaks or true epidemics such as reported in Kabul, Afghanistan, and Sudan. Numerous population surveys have found high infection rates between 5% and >80% of the general population in Mediterranean, Asian, and African countries, and several studies have described that children in the Middle East, Central Asia, and Sudan have a higher risk to infection and overt cutaneous disease than the general population.

The most used epidemiological tools for surveys are the presence of scar, active skin infection rates, serology, leishmanin skin test, and more recently, DNA molecular testing in blood specimens. The incidence and prevalence rates of different types of leishmaniases do not remain constant through time as several factors such as temperature, altitude, rain precipitation, season, sandfly activity, reservoirs, and population movements modify the frequency of infection and ultimately of clinical disease. Apart from the millions of indigenous population at risk, particular groups of individuals become exposed to infective bites when traveling to endemic regions. Cutaneous leishmaniases from both the Old and New Worlds have been reported as an emerging infection for travelers, military personnel, missionaries, visitors, and refugees who may develop the condition upon return to nonendemic regions of the world [13]. In the author’s experience at the specialized “Skin Infections and Tropical Dermatology Clinic” (Hospital for Tropical Diseases, London, UK) patients present sporadically and also following mini-outbreaks in dozens of military personnel deployed to endemic regions for *L. tropica* and *L. major*. Risk factors for the traveler include sleeping outdoors, without protective net or insect repellents at the time of sandfly activity.
Localized cutaneous simple leishmaniasis

All of Old World *Leishmania* species can cause this clinical form of disease. On clinical grounds the typical cutaneous elementary lesion in localized leishmaniasis is an ulcer surrounded by an erythematous-violaceous nodular border that fails to heal in weeks or a few months (Figure 16.1). The morphological spectrum however is variable and clinical leishmaniasis may manifest in papular, plaque, nodular, crust, and pure lymphangitic forms among others (Figure 16.2). The clinical symptoms manifest on average between 4 and 12 weeks following the infective sandfly bite and...
different species induce a variable range of pathogenic potential and timing for events of clinical disease. For instance, *L. major* causes a particular type of rural, zoonotic, wet ulcer that heals spontaneously in 6–8 months, whereas lesions caused by *L. tropica* are often described as a dry urban anthroponotic type of disease that can take more than a year to heal and often only after treatment. Nodular, papular, or ulcerated forms caused by *L. aethiopica* can take longer to heal and parasites can be identified in clinical lesions for up to 5 years. The typical sore in simple cutaneous leishmaniasis is circular or oval in shape and measures between 1 and 5 cm in size. Spontaneous healing in simple leishmaniasis results in a flat or atrophic scar with mild erythema that resolves over several months. The healing process may result in milia cyst formation in cases treated by oral purine analogs, intralesional antimonials or in those with spontaneous cure.

The lesions in simple leishmaniasis are predominantly found on exposed regions of skin and on areas with relatively thin skin covering bone prominences such as forehead, mastoidal region, zygoma, chin, wrist, hand dorsum, or malleolar regions. The lesions tend to be asymptomatic, however, pain is common in cases with superimposed bacterial infection, cellulitis, or following recurrent mechanical trauma (Figure 16.3).

**Disseminated and complex cutaneous leishmaniasis**
This type is commonly caused by *L. tropica, L. aethiopica, L. d. infantum*, and less commonly by *L. major* infections. The clinical picture and presentation pattern is similar to the localized forms except that several lesions are found on the particular anatomical region and tend to have a prominent lymphangitic component with local and regional lymph node enlargement. An initial single lesion located on an acral part of a limb may disseminate proximally through lymphatics and the timing for new, more recent

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*Figure 16.3* Disseminated leishmaniasis with cellulitis and lymphangitis
Disseminated leishmaniasis with complex lesions

Ulcers becomes obvious on taking the clinical history. Ulcers, crateriform sores, or other type of skin lesion that manifest in different anatomical regions and at about the same time suggest, on the other hand, multiple infective bites. Disseminated and complex forms tend to manifest with larger lesions, heavier parasitic load, and longer duration than those found in simple localized disease (Figure 16.4). This form of leishmaniasis requires treatment.

**Lupoid or recidivans leishmaniasis**

This is a chronic form of clinical disease where parasite and DNA-based investigations are negative. The condition is seen in healed lesions by *L. tropica* infection and lasts for several years. It seems that a hypersensitivity reaction to leishmanial antigens results in a papular or nodular eruption several months or a few years after the original sore of simple or complex leishmaniasis. The lupoid lesions commonly appear on the periphery of the scar tissue and tend to progress slowly. On empirical grounds, the small papules or nodules can be treated with intralesional antimonials, surgical excision, thermosurgery, and/or oral allopurinol.

**Diffuse cutaneous anergic leishmaniasis**

This type of chronic clinical disease caused by *L. aethiopica* adopts a relapsing pattern following treatment. A single original lesion disseminates locally at first and subsequently to different anatomical sites and typically presents with heavy parasitic load and anergy with a lack of DTH response on leishmanin intradermal test. The *Leishmania* parasites can persist for long periods of time after partial therapeutic response and become responsible for severe disease upon reactivation. This infection requires longer
therapeutic courses with systemic antimonials and a single standard curative regime is not available.

**PKDL**

PKDL disease appears late after clinical cure of VL. The morphological clinical features include hypopigmented patches or plaques, maculopapular rash, erythematous eruptions, nodules, lichenoid eruptions, and verrucous plaques, few or numerous, disseminated, and affecting trunk and limbs. The skin lesions can start around the mouth and then disseminate to the trunk and limbs and on the face; they can also cause ocular involvement with blepharitis, conjunctivitis, and uveitis. Cases have been described with generalized lymphadenopathy and the skin lesions can occur more frequently and be worse in sun-exposed areas, however, involvement of mucosal areas in nasopharynx, oral, genital, anorectal, and laryngeal vocal chords has been described. Most of the patients with the African type heal spontaneously within 1 year, whereas the disease requires treatment in all Indian type cases. In general, the disease is more severe in children. The clinical features and the temporal relationship between the VL and PKDL signs together with the demonstration of parasites in lesional skin are the pillars for a positive diagnosis.

**Differential clinical diagnosis**

Simple and complex leishmaniases may reveal identical or very similar clinical features to a number of other cutaneous infectious and noninfectious disorders. Some of the commonest differentials include *Mycobacterium marinum* and other tuberculous and nontuberculous (NTM) infections, sporotrichosis, leprosy, pyogenic infections, ecthyma, mycetoma, cutaneous diphtheria, anthrax, sarcoma, lymphoma, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma, keratoacanthoma, actinic reticuloid, poikiloderma, and papular eruptions. Lupoid leishmaniasis can be identical to lupus vulgaris or sarcoidosis, and diffuse anergic leishmaniasis to lepromatous leprosy. PKDL has to be differentiated from a large list of skin diseases including leprosy, lymphoma, sarcoma, sarcoidosis, vitiligo, pinta, pellagra, miliaria rubra, syphilis, and onchocerciasis among other conditions.

**Diagnostic procedures**

A positive diagnosis of leishmaniasis on clinical grounds is quite simple in endemic regions of the world where the general population and the
health personnel are familiarized with the clinical course and cutaneous symptoms. The returning traveler to nonendemic regions, however, presents a clinical challenge due to a lack of training and knowledge on this condition in extraleishmanial latitudes. The gold standard for diagnosis is the presence of parasites in lesional skin and there are a number of investigations to demonstrate this, however, the diagnosis can be supported by several or in some cases by one of the criteria listed below [14]. Two of the most important factors for a positive diagnosis are the following: firstly, the correct sampling of lesional skin carried out by an experienced clinician, and secondly, to be aware that a diagnosis of leishmaniasis can be firmly established in spite of negative diagnostic tests for parasites:

- History of exposure in endemic region in previous weeks or months.
- History of sandfly bites in the previous weeks or months.
- History of high-risk activities such as jungle/desert trekking or sleeping outdoors.
- Presence of nonhealing, nodular, violaceous ulcer for 4–6 weeks or much longer.
- Presence of a nonhealing skin lesion and local/regional lymphatic tissue involvement in the context of relevant history of exposure in an endemic area.
- Presence of amastigotes in Giemsa-stained smears from lesional skin.
- Demonstration of intracellular amastigotes in dermis of H&E skin specimens.
- Presence of leishmanial granulomata in the dermis in H&E skin specimens.
- Growth of promastigotes from lesional skin in NNN biphasic culture medium.
- Demonstration of leishmanial DNA by PCR in lesional skin.

In view of the fact that a positive parasitological or molecular diagnosis is not always available or possible, the author has found that a combination of investigations can lead to a definite diagnosis of leishmaniasis. In order to achieve a fast, specific, sensitive, and species-specific diagnosis, all skin specimens from cases with clinical cutaneous leishmaniasis have to be subjected to at least four different laboratory tests:

1. Giemsa-stained slit skin smear, ulcer scrapings, or biopsy imprint smear
2. Parasitological culture in Novy-MacNeal-Nicolle medium
3. Histopathological investigation on H&E slides
4. Molecular diagnosis to identify species-specific DNA by PCR

Additional serological or intradermal leishmanin (Montenegro reaction) testing can be required for patients with PKDL, *L. donovani* infections, the immunocompromized host, and as a tool for seroepidemiological surveys.
In the author’s experience and based on published literature the identification of amastigotes by Giemsa-stained smears has a low sensitivity (50–70%) whereas the presence of granuloma in H&E skin biopsy specimens scores higher at around 70% (without amastigotes) to 100% (presence of amastigotes). The histological investigation has the advantage of offering a specific diagnosis as other granulomatous conditions, infectious and non-infectious, can be readily identified or ruled out. On the other hand, the slit skin smears are easy to use in field conditions where direct microscopy is available for an instant diagnosis. In spite of the fact that both methods are widely available in most endemic regions of the Old World, they are not conclusive with regards the identification of leishmanial species or subspecies. The parasitological culture requires basic laboratory technology and once the promastigotes develop in a few days, it has the advantage to allow for the identification of particular species by PCR-based methods or else by zymodeme analysis in a reference laboratory. The culture of particular Leishmania species can be unsatisfactory and this is due to a variety of reasons including bacterial and fungal contaminants, chronicity of specimen, sampling specimen with a low parasitic burden, all of which may result in a decreased diagnostic sensitivity.

Several PCR methods to identify leishmanial DNA have been available for nearly two decades and they have been adapted for clinical laboratory and field-based diagnosis. Most of the PCR methods have used leishmanial minicircle DNA. Specimens of any kind from lesional skin can be successfully used including frozen or paraffin-embedded skin, cotton swab exudate, fresh or archival Giemsa smears, material from fine needle aspiration, and lesional skin or exudates in lysis buffer or ethanol. Most authors have reported a PCR overall sensitivity between 90% and 100% of cases, with the advantage of the identification of species and subspecies if appropriate primers are available. A few surveys however, have found very low sensitivity in chronic cases. New approaches for PCR (nested, real-time), RFLP analysis, and fingerprinting techniques allow for the sequencing of specific leishmanial DNA at the subspecies level.

Serological tests are mainly used to diagnose VL and have been useful in PKDL. A number of L. d. infantum recombinant antigens have been characterized for diagnosis and a direct agglutination test (DAT) can be useful in the diagnosis of cutaneous leishmaniasis by L. aethiopica with sensitivity of 90% and 92% specificity.

**Treatment**

Overall most cases of simple cutaneous leishmaniasis caused by any of the Old World species, can be cured by 6–10 weekly intralesional injections
of sodium stibogluconate (inject 0.5–2 ml of 100 mg/ml sodium stibogluconate solution, once weekly). In cases where intradermal injections are not feasible or acceptable, a number of orally administered purine analogs (allopurinol 10–20 mg/kg/day for 8–10 weeks) or antifungals can result in clinical cure (itraconazole 100–200 mg/day; terbinafine 250 mg/day; fluconazole 150 mg/day; all for 8–10 weeks or until 2 weeks after clinical cure). A considerable number of cases of simple cutaneous leishmaniasis by *L. major* or *L. tropica* affecting individuals in endemic regions heal spontaneously and are never treated. The burden of poverty, poor education, and the lack of diagnostic or therapeutic facilities determine the above. Other successful therapeutic approaches in simple small lesions include cryotherapy, surgical excision, thermosurgery, photodynamic therapy (PDT) and topical 15% paromomycin in paraffin with aminoglycoside antibiotics or urea.

Infections with complex lesions caused by any of the Old World species require systemic treatment or else a combination of drugs. Intravenous (IV) pentavalent antimonial (pentostam) is the drug of choice and is administered by IV daily infusion at 20 mg/kg for 21–28 days for complex lesions. Cases with African PKDL require 2 months and those of Indian PKDL several months. In cases of diffuse cutaneous leishmaniasis by *L. aethiopica* pentamidine at 4 mg/kg per week for as long as necessary is first therapeutic choice. *L. aethiopica* infections in Kenya have been treated by pentostam at 20 mg/kg twice daily for 30 days with a successful therapeutic outcome and no relapse.

Pentavalent antimonials have a rapid absorption and excretion and disrupt the synthesis of macromolecules in parasite cells. Amastigotes have a greater sensitivity to antimonials than promastigotes and sodium stibogluconate cumulates in the macrophage secondary lysosomes following leishmanial infection. Adverse effects include shivers, skin rash, fever, myalgia, arthralgia, pancreatitis, hepatitis, and cardiotoxicity. Close monitoring, blood investigations, ECG, and experience are essential when administering these compounds.

Allopurinol has an antiprotozoal activity as leishmanial enzymes display high affinity for this compound that inhibits and disrupts the protein synthesis. It has been successfully used in combination with intralesional or IV antimonials to treat both cutaneous leishmaniasis and VL. In the author’s experience, therapeutic failures to IV pentostam (*L. tropica, Leishmania Viannia braziliensis*, and *Leishmania mexicana* complex infections) have responded to a combined regime with intralesional weekly pentostam injections and oral allopurinol for 8–12 weeks. This regime has also been successful to treat cases with chronic lupoid leishmaniasis by *L. tropica*.

Triazole and allylamine antifungals disrupt the ergosterol synthesis and azoles have been found to be active against several species of leishmania
promastigotes and to a lesser extent versus amastigotes. The disruption of the membrane and metabolic function has been observed against *L. donovani, L. brasiliensis,* and *Leishmania amazonensis.* Ketoconazol exhibits good effect against *L. mexicana,* and most azoles are efficacious in *L. major* infections.

Amphotericin B and liposomal amphotericin are effective in VL and PKDL. This is a polyene antibiotic that disrupts the plasma membrane of the parasite cell. It has been used as a second choice in cases resistant to antimonials and particularly for intractable cases of cutaneous and mucocutaneous leishmaniasis or those with HIV coinfection. Amphotericin B is used at a dose of 1 mg/kg body weight/day. On the other hand, the liposomal preparation results in decreased toxicity and higher plasma concentrations, and ambisome at a dose of 2 mg/kg body weight in days 1–4 and day 10 has resulted in 90% cure in cases of VL.

Miltefosine (hexadecylphosphocholine) has recently been introduced for the treatment of OWCL after successful treatment of VL in India [15]. It inhibits phospholipid and sterol biosynthesis and interferes with cell signal-transduction pathways. It was equally effective in *L. major* treatment in Iran [16], and has successfully been used in *L. major* in Afghanistan [17] and *L. donovani/infantum* in Europe [18].

**Prevention**

Prevention and control measures are directed at several levels: host, vectors, reservoirs, and environment. Common initiatives include the use of one or several of the following strategies: protective clothing, insecticide-treated nets, avoidance of bites, protection during sleep, control of rubbish, control reservoirs, early diagnosis, residual spraying of animal shelters and households, and impregnated dog collars. Resistance to DDT insecticide by *P. papatasi* and *Phlebotomus argentipes* has been reported in India. Imidacloprid/permethrin combination of repellent/insecticide for dogs is highly effective.

**References**


CHAPTER 17
Onchocerciasis/Filariasis

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Key points
- Imported filarial infections are rare, but often present with skin manifestations.
- Consider onchocerciasis whenever a traveler or immigrant from an endemic area complains of itching or has an itchy rash. A careful travel history is essential as the latency period may be up to 3 years after leaving an endemic area.
- A combination of doxycycline for 6 weeks plus a single dose of ivermectin is advised for imported cases of onchocerciasis.
- A combination of doxycycline for 4–6 weeks, plus a single dose of ivermectin or albendazole may be used for imported lymphatic filariasis.
- Loiasis should be excluded before using ivermectin.

General

Introduction
Filariae (nematode parasites of the family Filariidae) are responsible for devastating problems in man, including blindness, itchy unsightly rashes, and elephantiasis with over 150 million infected people in tropical and subtropical regions. There are three main diseases: (1) lymphatic filariasis, is usually caused by Wuchereria bancrofti (in certain areas of the world it is caused by Brugia malayi and Brugia timori), (2) onchocerciasis is caused by Onchocerca volvulus, and (3) loiasis is caused by Loa loa. Most recent World Health Organization estimates indicate that there are 120 million infected people with lymphatic filariasis, 37 million with onchocerciasis, and 14.4 million live in areas at high risk for loiasis. The other filarial species than can infect man are Mansonella streptocerca, Mansonella perstans, and Mansonella ozzardi. Skin manifestations are a prominent feature in returned travelers with filarial infection.

**Figure 17.1** Geographical distribution of onchocerciasis. (a) African Programme for Onchocerciasis Control (APOC) and ex-Onchocerciasis Control Programme (OCP) countries (reproduced with permission from World Health Organization [1]). (b) Geographic distribution of onchocerciasis in the Americas (reproduced with permission from World Health Organization [2]).
Epidemiology

Geographical distribution

Lymphatic filariasis occurs in 81 tropical countries in Africa, Asia, the Pacific, and Central and southern America (Haiti, the Dominican Republic, Guyana, and Brazil). *B. malayi* is found in Southeast Asia and the Far East, and *B. timori* is limited to the Timor Island of Indonesia. Onchocerciasis is endemic in 27 countries in sub-Saharan Africa and smaller foci of infection have been found in Yemen and in 13 foci in six countries in central and southern America (Mexico, Guatemala, Ecuador, Colombia, Venezuela, and Brazil). Transmission has now been eliminated or interrupted in ten of the foci in the Americas, is suppressed in one Venezuelan focus, and is on-going in one focus in Venezuela and one in Brazil (Figure 17.1).

Loiasis is limited to Central and West Africa (mostly Cameroon, Democratic Republic of Congo, Angola, Gabon, Central African Republic, Nigeria, Chad, and Sudan). Infection with *M. streptocerca* occurs in West and Central Africa. *M. perstans* is endemic in much of tropical Africa and South America and parts of the Caribbean. *M. ozzardi* infection occurs only in the American continent in the West Indies, Central America, and South America (northern Argentina, Brazil, Colombia, Ecuador, and Peru).

Cases of imported filarial infections are relatively rare. Between 1997 and 2004 filarial infections comprised 0.62% (*n* = 271) of the 43,722 medical conditions reported to the GeoSentinel Surveillance Network (a global network of specialized travel/tropical medicine clinics on six continents) [3]. A retrospective study of 6168 immigrants and travelers diagnosed with one of the 13 core neglected tropical diseases (NTD) at a Tropical Medicine Referral Unit in Spain found that onchocerciasis was the most frequent NTD in immigrants (*n* = 240; 9.1%) and in individuals who traveled to visit friends and relatives (*n* = 14; 5.4%). Onchocerciasis, acquired mainly in sub-Saharan Africa, was also the second most frequent NDT in travelers (*n* = 17; 0.5%). There was only one case each of lymphatic filariasis in immigrants and travelers and no cases in individuals who visited friends and family [4].

Figure 17.2 shows the total number of laboratory reports of filariasis by genus between 1990 and 2009 for England, Wales, and Northern Ireland. In these countries laboratory-confirmed infections are reported via LabBase to the Communicable Disease Surveillance Centre (CDSC), Colindale, London but as this is a voluntary system the reports are likely to be an underestimate. The main organisms responsible for filarial infection in England, Wales, and Northern Ireland are *O. volvulus*, *L. loa*, and *M. perstans*. For those in whom travel data were available, the majority specified recent travel to Africa, especially Cameroon and Nigeria.
Mode of infection

Infected larvae are deposited into the skin by infected arthropod vectors during a blood meal. The larvae then migrate either to the lymphatics (in lymphatic filariasis) or subcutaneous tissues of the human host’s body where they develop into adults that can live for several years. In lymphatic filariasis, the adult worms live in lymphatic vessels and lymph nodes; in onchocerciasis the adults are coiled up within fibrous subcutaneous nodules; in loiasis the adult worms reside in subcutaneous tissue where they migrate actively; adult worms of *M. streptocerca* are found in the dermis and subcutaneous tissue, *M. ozzardi* are thought to be in subcutaneous tissue, and *M. perstans* in body cavities and surrounding tissues. After mating, the adult female worms produce microfilariae that circulate in the blood, except for those of *O. volvulus* and *M. streptocerca*, which concentrate in the skin. The microfilariae of *O. volvulus* also preferentially invade the eye. When the biting insect next collects a blood meal it coincidentally ingests microfilariae, which then undergo further development within the insect into infective larvae. During a subsequent blood meal, the larvae infect the vertebrate host and develop into adults, a slow process, which in the case of *Onchocerca* may take up to 18 months. Adult worms of the agents of lymphatic filariasis live for 5–7 years whereas adults of *O. volvulus* live for 10–14 years. The relevant vectors for lymphatic filariasis are mosquitoes (*Anopheles* in Africa, *Culex quinquefasciatus* in the Americas, and *Aedes* and *Mansonoria* in the Pacific and Asia); *Simulium* blackflies for
O. volvulus; Chrysops tabanid deerflies for L. loa; midges (Culicoides) for M. perstans and M. streptocerca, and both midges and blackflies for M. ozzardi.

**Clinical picture**

**Expatriate syndrome**

It has become increasingly recognized that individuals who have not grown up in endemic areas but visit such regions and acquire a filarial infection may develop prominent symptoms and signs of inflammation rather than the chronic clinical signs typically found in long-term residents. Thus expatriates with lymphatic filariasis develop lymphangitis, lymphadenitis, genital pain (from inflamed lymphatics), urticaria, and peripheral eosinophilia. Individuals with onchocerciasis may present with itchy, slightly urticated papules, and/or edema of the skin. In loiasis, Calabar swellings, urticaria, and occasionally asthma have been documented. The reason for these different clinical manifestations appears to be differing host responses to filarial antigens between those with long-standing (including prenatal) exposure and those who are exposed for the first time in later life. Immigrants to developed countries from endemic areas may present with more typical signs of chronic infection.

**Onchocerciasis**

**Clinical picture**

**Cutaneous signs**

The first indication of infection is usually pruritus. Other early manifestations include a papular rash, transient urticaria, arthralgia, and fever.

A detailed travel history over the previous 1–3 years is essential, as the patient may not have realized the significance of foreign travel that had happened some time before the onset of his symptoms. The prolonged time-interval between a visit to an endemic region and the onset of symptoms is due the time required for infective larvae to develop into adult worms. After mating, the adult female produces microfilariae that gradually accumulate in number before causing symptoms. Latency periods ranging from 3 months to 3 years [6, 7] have been documented. Persons who have not grown up in, but have spent many years in endemic areas may present with symptoms within shorter time spans.

Returned visitors from endemic areas usually present with pruritus and/or an itchy papular rash. The papules are small and often concentrated over one area of the body such as a leg, arm, shoulder, or waist [8]. Often there is accompanying nonpitting lymphatic-type edema of the limb [9, 10] and swelling can also occur independently in the absence of
any rash [11]. Sometimes the signs are rather subtle and small itchy pink, slightly urticated papules may be all there is to see [6] (Figure 17.3).

**Box 17.1 Pointers for diagnosis of onchocerciasis**

A diagnosis of onchocerciasis should be considered whenever a traveler or immigrant from an endemic area complains of itching or has an itchy rash. A careful travel history is essential as symptoms may develop 3 months to 3 years after leaving an endemic area.

Life-long residents in endemic areas may develop a variety of skin lesions, either singly or in combination. If such individuals migrate to a developed country then they may present with more florid clinical signs. The various forms of onchocercal skin disease have been classified into acute papular onchodermatitis (APOD), chronic papular onchodermatitis (CPOD), lichenified onchodermatitis (LOD), atrophy, and depigmentation [12].

**Acute papular onchodermatitis (APOD)**

APOD is common in children and young adults and consists of small itchy monomorphic papules that are usually widely scattered over the upper trunk and arms. In more severe cases small pustules are seen with or without accompanying edema of the skin causing a peau d’orange appearance.

**Chronic papular onchodermatitis (CPOD)**

CPOD occurs in children and adults and comprises itchy papules that are larger than those of APOD and more variable in size. They are distributed over the trunk and limbs and are often concentrated around the pelvic
girdle. Postinflammation hyperpigmentation is often present with excoriation (Figure 17.4).

**Lichenified onchodermatitis (LOD)**
LOD is typically found in adolescent boys and is usually confined to one limb, particularly the leg. Extremely itchy hyperpigmented papules, nodules, and plaques eventually progress into confluent lichenified areas. There is associated swelling of the limb and soft enlargement of the draining lymph nodes.

**Atrophy**
The term onchocercal atrophy is reserved for adults who are less than 50 years old and in whom the skin appears to be prematurely aged. It is not characteristically itchy. Particularly around the pelvic girdle and upper thighs, the skin appears thin and excessively wrinkled due to degenerative inflammatory changes leading to loss of dermal elastic fibres. Hanging groin is the specific finding of loose redundant folds of skin in the groin caused by massive enlargement, followed by subsequent fibrosis, and shrinkage of the inguinal lymph nodes beneath atrophic skin [14].

**Depigmentation**
Patchy depigmentation with “spots” of normally pigmented skin centered around hair follicles typically occurs over both shins and less frequently in the groins and on genital skin. It is common in older residents of endemic areas and is not itchy.

In a multicountry prevalence survey of endemic villages in Africa [15] onchocercal skin disease affected 28% of the population aged 5 years or
above. The commonest type was CPOD (13%), followed by depigmentation (10%), and APOD (7%). A survey of 83 immigrants in Israel from the Kuwara highland of Northwest Ethiopia, which has a high prevalence of onchocerciasis, revealed that the commonest skin finding was CPOD in 46 patients (55%) followed by depigmentation and atrophy (16% and 14%, respectively) [16]. Skin snips were positive in 40 patients (48%).

**Onchocercal nodules (onchocercomata)**
Residents of endemic areas often have essentially asymptomatic smooth firm subcutaneous nodules ranging from pea-size to several centimeters in diameter. In Africa nodules can be readily palpated over bony prominences such as the iliac crest whereas in Central and South America nodules are more common on the scalp. The nodules consist of coiled adult worms surrounded by a fibrous capsule and have been reported in immigrants [17, 18].

**Ocular signs**
Ocular signs are relatively rare in patients with imported onchocerciasis but it is essential to refer the patient for formal ophthalmological assessment. The easiest way to visualize microfilariae is to ask the patient to adopt a head-down position for 2 minutes and then examine them on a slit-lamp. Tiny microfilariae may be seen wriggling in the anterior chamber. Live microfilariae in the cornea are more difficult to see as they are transparent. Dead microfilariae in the cornea, however, may be seen as opaque straightened-out microfilariae surrounded by inflammatory infiltrate. These “fluffy” lesions of punctate keratitis resolve spontaneously. Long-term residents in endemic areas may develop the potentially blinding complications of sclerosing keratitis, iridocyclitis, choroidoretinitis, choroidoretinal atrophy, optic neuritis, and optic atrophy. In the study of Ethiopian immigrants in Israel [16], 65 patients underwent a thorough eye examination, of whom 45 patients (69%) had ocular complaints.

**Systemic symptoms**
Musculoskeletal symptoms such as backache and hip pain have been reported in returned workers [19].

**Burden of disease in endemic countries**
The socioeconomic effects of onchocerciasis are most acute in Africa. The most serious complication is blindness, and onchocerciasis is the second leading infectious cause of blindness worldwide with approximately 500,000 blind. In endemic areas in Africa, 42% of the adult population has been found to complain of pruritus [15]. By extrapolation, an estimated 6 million people in Africa are thought to have troublesome pruritus
secondary to onchocerciasis [20]. The pruritus is severe, causing insomnia and general debilitation. In endemic regions onchocercal skin disease may have detrimental psychosocial effects and can reduce the marriage prospects of adolescent girls.

**HIV coinfection**
A case-control study in an onchocerciasis hyperendemic area of Uganda found no association between onchocercasis and HIV infection [21] and no difference was found in the efficacy of treatment with ivermectin, nor in the occurrence of side effects. HIV-infected onchocerciasis patients have been shown to have (1) reduced antibody responses to *O. volvulus* antigens [22] and (2) impaired cellular immune responses [23]. A study of 72 onchocerciasis patients with onchocercal skin disease (OSD) in western Uganda revealed that a subgroup of six individuals who were coinfected with HIV, had a significantly higher burden of skin disease [24].

**Diagnostic procedures**

**Skin snips**
Skin-snipping is the current standard test but it may be negative in prepatent or light infections in returned travelers. A small bloodless tent of skin is raised with a needle and the apex shaved off with a scapel. A corneoscleral punch may also be used. The skin snip is placed in saline in the well of a microtitre plate and after 30 minutes to 2 hours, with the aid of a dissecting microscope, microfilariae may be seen to have migrated out of the tissue. The result may be expressed as just positive or negative or quantified as the number of microfilariae per mg skin. At least one snip is taken from each iliac crest and the sensitivity is increased by taking additional snips from the scapular region and calf. If a rash is present, a skin snip should be taken from the area with the rash.

**Other parasitological methods of diagnosis**
1 Detection of intraocular microfilariae using a slit-lamp—see Section “Ocular signs.”
2 Demonstration of adult worms by histological examination of excised nodules. This is not a routine procedure.
3 Demonstration of microfilariae by histological examination of skin biopsy. Again this is not a routine diagnostic procedure, but if a skin biopsy has been taken, microfilariae may be seen in the upper dermis on routine H&E staining. *O. volvulus* microfilariae have the following distinguishing features: (1) a cephalic space (7–13 μm) followed by closely approximated anterior nuclei, (2) a caudal space (9–15 μm) preceded by elongated terminal nuclei, and (3) a tail with a finely tapered point.
4 Although not a routine procedure, living adult filariae within onchocercomas can be demonstrated by ultrasonography.
Mazzotti test
If skin snips are negative, but onchocerciasis is still suspected, the next step is to give a single oral dose of 50 μg of diethylcarbamazine (DEC) and observe the patient carefully. Infected persons may develop intense pruritus 20–90 minutes later. An acute papular rash with edema may develop or an existing rash may be exacerbated. Fever, cough, and musculoskeletal symptoms may also occur. Symptoms and signs reach a peak within about 24 hours and gradually subside over the next 48–72 hours. If necessary, antihistamines, aspirin, and other analgesics may be given for symptomatic relief and occasionally steroids are required for severe symptoms. The Mazzotti test is contraindicated in patients who are heavily infected (who will have positive skin snips) as more severe reactions can occur with pulmonary edema and collapse. The Mazzotti test is also contraindicated in patients with optic nerve disease as it may trigger deterioration in vision.

DEC patch test
This “Mazzotti” patch test assesses the local reaction of 10% DEC in NiveaR cream or Nivea milk applied to the skin. It is more sensitive than skin-snipping but its use has not been evaluated in cases of imported onchocerciasis.

Full blood count
A peripheral eosinophilia may be present.

Future diagnostic methods
Serodiagnosis
A specific serological test for onchocerciasis is not available for routine use yet. A filaria ELISA may be performed but it does not differentiate between the various filarial infections and cross-reactivity exists with other helminths. A positive serological test does not distinguish between past and current infection. It is hoped that a specific serological test using a cocktail of recombinant antigens may become available for routine use.

PCR Diagnosis
PCR-based assays are only available as research tools at present. PCR is more sensitive than skin-snipping in lightly infected individuals. PCR-based assays to detect the repetitive DNA sequence known as O-150 (found only in O. volvulus) has 100% species specificity and 100% sensitivity. PCR has also been shown to to detect parasite DNA in skin scrapings.
**Treatment**

**Ivermectin**

Ivermectin is microfilaricidal and has some effect on late stages of embryogenesis but as it does not kill the adult worms (which can live for 10–12 years), levels of microfilariae can reaccumulate over many months and treatment has to be repeated (at frequent doses ivermectin has some limited macrofilaricidal effect). A large double-blinded multicountry trial in endemic regions in Africa has confirmed the efficacy of ivermectin over placebo in improving pruritus and reduction in prevalence of APOD, CPOD, and LOD [25]. Ivermectin in this setting was equally effective whether given at 3-monthly, 6-monthly, or annual intervals.

For treatment of individuals outside of endemic areas, a single dose of ivermectin, 150 $\mu$g/kg, may be given every 3–6 months until asymptomatic. In contrast to mass treatment programs in Africa where reactions are rare, 17/33 (55%) of a series of patients in London had reactions, so it is advisable that the first dose of ivermectin is given in hospital. Treatment should be repeated if there is recurrence of pruritus, rash, or eosinophilia [26, 27].

**Doxycycline**

*Wolbachia* symbiotic endobacteria have been identified as essential for filarial worms’ fertility and these offer new targets for treatment. Additional treatment with doxycycline to sterilize worms enhances ivermectin-induced suppression of microfilaridermia. A combination of doxycycline, 200 mg/day, for 6 weeks plus ivermectin is now advisable for individuals with imported Onchocerciasis [28]. Doxycycline is given prior to ivermectin to deplete *Wolbachia*, thereby reducing inflammatory reactions induced by ivermectin.

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**Box 17.2 Treatment of individuals with imported onchocerciasis**

- **Doxycycline**: 200 mg orally once daily for 6 weeks, PLUS
- **Ivermectin**: 150 $\mu$g/kg orally (single dose), 4–6 months following the end of doxycycline therapy

**NB**: Doxycycline is contraindicated in pregnancy and children. Ivermectin may be effective if given immediately at the end of doxycycline treatment but in the studies to date it was given after 4–6 months.

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**Future treatments**

A macrofilaricide that can kill adult worms is desirable so that a single course of treatment could be potentially curative. Phase 3 trials of moxidectin, a veterinary deworming agent, are underway [29].
Prevention
Prevention of Simulium fly bites
Visitors to endemic areas can limit their exposure to fly bites by keeping away from rivers and banks, which are known breeding sites. Protective clothing such as long-sleeved shirts and long trousers and an insect-repellent are advisable especially in the early morning and late evening, which are peak biting times.

Control programs
The World Health Organization Onchocerciasis Control Programme (OCP) 1974–2002
This major program covered 11 West African countries and successfully interrupted transmission by controlling the blackfly vector by aerial larviciding of rivers. More recently it uses mass distribution of ivermectin to control recrudescences.

The Onchocerciasis Elimination Programme in the Americas (OEPA) 1991–2012
This program utilizes 6-monthly mass ivermectin therapy and aims to eliminate clinical manifestations of onchocerciasis and interrupt transmission.

The African Programme for Onchocerciasis Control (APOC) 1995–2015
This is the largest control program and comprises large-scale annual community-directed treatment with ivermectin (CDTI) in 19 non-OCP countries and 4 ex-OCP countries in Africa. Mectizan® (ivermectin) has been generously donated by Merck and Co., Inc. After 5 or 6 years of CDTI, profound reductions in the odds of pruritis and all forms of OSD were seen [30]. Caution is needed in areas coendemic with loiasis because ivermectin can cause serious encephalopathic adverse effects in patients with high *L. loa* microfilarial loads.

Integrated Control Programs
Integrated control programs for onchocerciasis and lymphatic filariasis employ annual mass treatment with ivermectin and albendazole. GlaxoSmithKline (GSK), formerly SmithKline Beecham, has donated albendazole and Merck and Co., Inc. expanded their ivermectin donation for lymphatic filariasis control in Yemen and African countries where onchocerciasis and lymphatic filariasis are coendemic because of the contraindications of DEC in individuals with onchocerciasis.
Lymphatic filariasis

Introduction
Of the 120 million people infected worldwide, 40 million are seriously incapacitated and disfigured. The prevalence of the disease is increasing as unplanned growth of cities creates numerous breeding sites of the mosquito vector.

Clinical picture
Short-term travelers are at low risk for this infection. Travelers to endemic areas for extended periods of time and extensively exposed to mosquitoes may become infected. Most cases seen in developed countries are in immigrants from endemic countries.

Expatriates who are exposed to infection for the first time (e.g., military personnel sent to endemic areas) develop acute lymphangitis around developing larval and early adult stages, associated with an eosinophilic inflammatory infiltrate. Newcomers to endemic areas develop acute and chronic manifestations of the disease much more rapidly than residents who have been exposed since birth, and lymphedema may develop within 6 months and elephantiasis within 1 year of arrival.

Residents of communities endemic for lymphatic filariasis may have “asymptomatic” infections or develop acute or chronic presentations. Approximately half of all individuals in endemic areas appear clinically normal but have microfilariae circulating in their blood and have covert lymphatic and renal damage (microscopic hematuria and proteinuria). This state of asymptomatic microfilaria is associated with downregulation of the immune system.

Acute manifestations
The most common acute problem is “filarial fevers” affecting the limbs or scrotum, which is caused by bacterial or fungal superinfection of tissues with already-compromised lymphatic function. More recently it has been suggested that a better term would be DLA (dermatolymphangioadenitis) to reflect the fact that these inflammatory episodes start peripherally with features resembling cellulitis.

Less frequently, “filarial fevers” are triggered by an inflammatory response, which starts in the lymph node with “retrograde” extension down the lymphatic tract and an accompanying “cold” edema.

Tropical pulmonary eosinophilia is a rare syndrome, mainly in Asia, characterized by nocturnal cough and wheezing and fever. Patients have an immunologic hyperresponsiveness to filarial antigen with high levels of
peripheral eosinophilia, total serum IgE, and specific IgG and IgE antifilarial antibodies.

**Chronic changes**

The most common chronic manifestation is hydrocele, which increases in prevalence with age. Other chronic manifestations include lymphedema and elephantiasis of the limbs (Figure 17.5) or genitalia and breasts. Such patients are rarely microfilaremic. The folds, crevices, and warty protuberances of an elephantine limb harbor bacteria and fungi that intermittently breach the epidermis and cause local and systemic infection. Chyluria is another chronic presentation.

**Diagnostic procedures**

**Antigen detection**

Circulating filarial antigen (CFA) detection should now be regarded as the gold standard for diagnosing *W. bancrofti* infections. It has excellent specificity and greater sensitivity than previous parasite-detection methods and can be used on finger-prick blood samples collected at any time of the day. All individuals with microfilaremia plus some amicrofilaremic patients with lymphedema or elephantiasis will have detectable CFA. In
addition, some individuals who appear normal also have detectable CFA that disappears after treatment with DEC. Two commercial versions of this assay are available, one based on ELISA technology, which yields a semi-quantitative result, and the other based on a simple card (immunochromatographic) test, which provides a positive/negative result.

Detection of microfilariae by microscopic examination of blood sample
Microfilariae only circulate in the blood at or near the peak biting time of the vector, so it is important to time blood samples with the known periodicity of the microfilariae. The vectors in Africa are all night-biting, so blood samples in these areas have to be taken within a few hours either side of midnight. A thick blood smear should be made and stained with Giemsa or hematoxylin and eosin. Yields may be increased by passing heparinized blood through a Millipore filter, which retains the microfilariae that can then be easily visualized on microscopy. Yields may also be increased by giving 6 mg/kg DEC and repeating the blood film 15 minutes later as DEC releases more microfilariae into the circulation. *W. bancrofti* and *Brugia* species have an acellular sheath that is stained and visible on light microscopy. There are no nuclei in the tail of *W. bancrofti*, whereas *B. malayi* has terminal and subterminal nuclei.

PCR diagnosis
Molecular diagnosis using PCR is available for *W. bancrofti* and *B. malayi*.

Serology
In the expatriate syndrome, preexposure levels of IgG and especially IgG₄ antibodies to filarial antigens will be very low, so elevated levels, together with the clinical picture will be helpful diagnostically, though these tests cannot differentiate between the various types of filarial infection.

Ultrasonography
Adult worms may be can be visualized by ultrasonography.

Treatment
**Doxycycline**
For individual patients living outside a transmission area, treatment regimens including doxycycline 200 mg/day for 4–6 weeks are emerging as the optimal treatment. Doxycycline is usually followed by single dose treatment with ivermectin 150 µg/kg or albendazole 400 mg, 3–4 months after the onset of doxycycline treatment [28]. Doxycycline 200 mg/day for 6 weeks plus a single dose of ivermectin has been shown to render infected Ghanian residents of an endemic area completely amicrofilaremic after 12 months [31]. Loiasis should be excluded before using ivermectin.
**Box 17.3 Treatment of individuals with imported lymphatic filariasis**

Doxycycline 200 mg orally once daily for 4–6 weeks, PLUS
Single dose ivermectin 150 μg/kg or albendazole 400 mg orally 3–4 months after the onset of doxycycline therapy

*NB*: Doxycycline is contraindicated in pregnancy and children.

**DEC**

Traditional treatment for lymphatic filariasis has been DEC, which is microfilaricidal and also effective in killing some, but not all adult worms. For bancroftian filariasis, the recommended regime for individual patients is DEC 6 mg/kg daily in divided doses for 12 days. Treatment is best initiated with smaller doses for 2–3 days and antihistamines or corticosteroids may be required to reduce allergic reactions due to disintegration of microfilariae. A single 6 mg/kg dose has similar efficacy in reducing levels of microfilariae. Combination of treatment with ivermectin is synergistic. Coinfection with onchocerciasis and loiasis should be excluded prior to using DEC.

**Albendazole**

Albendazole can be macrofilaricidal for *W. bancrofti* if given daily for 2–3 weeks. More recently single dose treatment regimes have been found to be very effective. A single dose combination of albendazole 400 mg with either ivermectin or DEC 6 mg/kg can effectively suppress *W. bancrofti* microfilaremia for a year.

Surgical treatment, including nodovenous shunts and excision of redundant tissue can improve elephantiasis.

One of the most significant advances in treatment has been the recognition that much of the progressive pathology is due to bacterial and fungal superinfection of tissues with impaired lymphatic function. Rigorous attention to hygiene of affected limbs and measures to improve lymphatic drainage reduce the frequency of “filarial fevers” and even slowly improve lymphedema and elephantiasis.

**Prevention**

Protection from mosquito bites through use of personal repellents, bednets, or insecticide-impregnated materials is prudent. A prophylactic regime of DEC 6 mg/kg per day × 2 days each month may be effective in preventing infection.
The Global Programme for Elimination of Lymphatic Filariasis (GPELF) 1999–2020

This program aims to eliminate lymphatic filariasis as a public health problem. Fifty-three endemic countries have started mass drug administration to interrupt transmission, representing the largest mass drug administration program ever conceived. DEC is used in combination with albendazole outside Africa and ivermectin plus albendazole is used within Africa, because coendemicity with onchocerciasis prevents use of DEC because of side effects. Single doses of the two drugs are given together at annual intervals and this needs to be repeated for at least 5 years.

Loiasis

Clinical picture

Travelers to at-risk areas who stay for long periods of time are more likely to become infected than short-term travelers. Loiasis is often asymptomatic, though nonspecific symptoms of pruritus, pain or swelling of a limb, and urticaria can occur over several months as the fourth-stage larvae develop into adult worms. About a year after infection the characteristic manifestation of loiasis, Calabar swellings develop (Figure 17.6). These are more common in expatriate Europeans and are thought to represent local hypersensitivity reactions to the subcutaneous passage of an adult worm. The swellings, which develop suddenly, are itchy, erythematous, edematous lesions, 2–10 cm in diameter, and sometimes painful. They can occur anywhere on the skin but are more common on the face and hand. The swellings slowly resolve over several hours to a few days but can recur. The adult worm can sometimes be seen temporarily as it passes across the eye underneath the conjunctiva causing irritation and unilateral palpebral edema, but “eye-worm” is more common in residents of endemic areas.

Figure 17.6 Calabar swelling on the cheek due to infection with *Loa loa* (courtesy of Maclean [32])
Other clinical signs include a localized lymphadenopathy, fever, irritability, confusion, epilepsy, orchitis, and hydrocele. Nephropathy, cardiomyopathy, and pulmonary damage are rare. The adult worms can live for up to 17 years.

**Diagnostic procedures**

**Parasitological methods**

Microfilariae may be demonstrated in a Giemsa-stained smear of daytime blood, with the sensitivity increased by passing the blood through a Millipore filter. *L. loa* microfilariae are sheathed and have nuclei reaching the very end of the tail. Quantification of the number of microfilariae per ml helps to direct treatment. Microfilariae are not found in the blood before about 5 months after the onset of Calabar swellings and expatriates often have negative peripheral blood examination. The adult worm may be surgically extracted from the subcutaneous tissue or conjunctiva as a minor procedure.

**Immunological markers**

Infected travelers may have pronounced eosinophilia and high antifilarial antibodies but these are not specific tests. *Loa*-specific serological tests are available as research tools.

**Histology**

A skin biopsy may sometimes reveal microfilariae in dermal blood vessels.

**Molecular diagnosis**

Molecular diagnosis is not routinely available yet but a *L. loa*-specific repetitive DNA sequence is known.

**Treatment**

The current recommended treatment for patients with \(<8000\) mf/ml is DEC, which kills both the microfilariae and the adult worms. A gradual dosing regime may be followed: DEC 1 mg/kg is given as a single dose initially, doubled on 2 successive days, and then adjusted to 2–3 mg/kg three times a day for a further 18 days. Rapid killing of microfilariae in heavy infections can provoke an encephalopathy. Prednisolone 20 mg od for 4 days starting 1 day before DEC may be given if the patient is microfilaremic. Before starting DEC, coinfection with *O. volvulus* should be excluded because of the risk of Mazzotti reactions with DEC. Long-term follow-up is necessary and retreatment should be considered if symptoms recur.

Albendazole 200 mg twice daily for 3 weeks can be used to slowly reduce microfilariae in patients with \(\geq8000\) mf/ml to reduce the level to
<8000 mf/ml prior to treatment with DEC. In extremely severe infections apheresis in specialized centres may be necessary.

Ivermectin (200 μg/kg) is also effective but it is not macrofilaricidal. Its use in immigrants from endemic areas may cause encephalopathy in patients with very high *L. loa* microfilarial loads. *L. loa* do not contain *Wolbachia* so doxycycline is not a treatment option.

**Prevention**
DEC 300 mg weekly may be taken by travelers for as long as exposure continues.

**Mansonelliiasis**

**Clinical picture**
Mansonella infection can be asymptomatic or cause mild symptoms only. *M. streptocerca* can cause pruritus and papular eruptions similar to that seen in onchocerciasis. More widespread lichenification and hypopigmented macules also occur. Infections caused by the two other *Mansonella* species are usually asymptomatic. *M. perstans* infection can also cause angioedema, pruritus, fever, headaches, arthralgias, and neurological problems, and *M. ozzardi* can cause a variety of symptoms including pruritus, arthralgias, headaches, fever, and lymphadenopathy.

**Diagnostic procedures**
Diagnosis is by skin snip. Microfilariae of all species of *Mansonella* are unsheathed. The features that distinguish microfilariae of *M. streptocerca* from *O. volvulus* are the smaller size of their nuclei and the appearance of their anterior and posterior ends. The cephalic space of *M. streptocerca* microfilariae is longer than it is wide and is followed by a line of four staggered but not overlapping elongated nuclei. The tail curves into a characteristic “shepherd’s crook” appearance.

**Treatment**
DEC, which has activity against both adult worms and microfilariae, may be given at 6 mg/kg per day for 14 days. A single dose of ivermectin 150 μg/kg is microfilaricidal.

Doxycycline also targets *Wolbachia* in *M. perstans* [28].

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Key points

- **Skin Manifestations in Schistosomiasis**: Each stage of infection may be accompanied by different skin manifestations:
  1. Cercarial penetration may give rise to cercarial dermatitis. Rare in areas endemic for human schistosomiasis. Common directly after exposure to cercariae of nonhuman schistosomes, in temperate zones.
  2. During the acute phase, 2–10 weeks after infection, generalized urticarial reactivity may be seen.
  3. During patent infection, displaced eggs in the skin may cause prominent, sometimes hyperpigmented, papular lesions. Female genital schistosomiasis (FGS) is common though difficult to diagnose in many *Schistosoma haematobium*-infected areas.
- Diagnosis varies with the stage of infection.
- Praziquantel-based treatment is not indicated in skin manifestations related to the early stages of infection.

Introduction

Schistosomiasis is caused by flukes of the genus *Schistosoma*. The major species involved are *Schistosoma mansoni* and *Schistosoma japonicum*, which inhabit the venules of the portal and mesenteric system, and *Schistosoma haematobium* that is found in the venous plexis of the urinogenital system. The characteristic feature of these helminths is that the adult worms are truly blood parasites but their offspring is excreted with stools or urine of the infected host. Only a part of the eggs produced manages to reach the intestinal lumen or the bladder cavity; many others do not successfully accomplish the migration from veins to intestines and bladder. They die en route and are the cause of subsequent pathology at the predilection sites or elsewhere. The adult worms are of a benign nature and do not normally cause any pathology [1].
Life cycle and epidemiology

The life cycle of the parasite is complex. It involves a definitive and an intermediate host, two free-living stages, responsible for the infection of humans (cercariae) and snails (miracidia), and both a sexual and an asexual multiplication. The population biology is characterized by the facts that the free-living stages are extremely short-lived (less than 48 hours), the egg production is low (no more than approximately 300 eggs per gram feces per day in *S. haematobium* and *S. mansoni*), and the life span is very long. On average, worms are believed to live for 3–5 years but some survive for 30 years or even longer.

There are four different phases of the life cycle, and each causes a characteristic type of pathology and disease:

1. The penetration of cercariae through the intact human skin may result in so-called cercarial-dermatitis or swimmers’ itch. This phase is of short duration.
2. The phase of acute schistosomiasis or Katayama syndrome is characterized by a hypersensitivity-type reaction to the excretion of schistosome metabolites into the host’s circulation. The onset of this phase may be as early as 2 weeks postexposure; it normally subsides by the time egg excretion starts, 7–10 weeks after the infection.
3. The phase of established infection starts with egg production and may last many years. The symptoms and signs of infection during that stage are caused by the immunopathological host reaction to schistosome eggs that get stuck in the tissues. Sometimes eggs get astray and get stuck in unusual sites: ectopic schistosomiasis may be the result.
4. The final stage can be characterized as the phase of complications due to more or less irreversible fibrotic changes in the periportal and urogenital regions.

Transmission of schistosomiasis is restricted to the tropics and even there the distribution is highly focal. It is dependent on ecological conditions favorable or unfavorable for the survival and multiplication of the intermediate host snails. The prevalence of infection is often high, particularly in school age children, and is associated with the intensity of exposure to infested water bodies, that is, with the absence of safe water.

Clinical features

The most prominent clinical features and the cause of significant morbidity of schistosomiasis in endemic areas are the presence of (sometimes bloody) diarrhea, hepatomegaly, and splenomegaly in *S. mansoni* and *S. japonicum* infections. In *S. haematobium*, hematuria and sandy patches in bladder and
genitals are common presentations. Portal hypertension that is caused by intense granulomatous and fibrotic reactions around eggs that were captured in the liver, hepatomegaly, splenomegaly, and esophageal and rectal bleedings, mark the late stage of intestinal and hepatosplenic schistosomiasis, or “Symmers’ fibrosis.” The late consequences of S. haematobium are related to bladder calcifications and hydronephrosis and a variety of lesions in patients with extensive genital localizations. These manifestations are largely associated with the intensity of present or past infection, that is, the worm load.

**Diagnosis**

Diagnosis varies with the stage of infection and is based on a combination of exposure to surface water in an endemic area, clinical data, stool examination for eggs and possibly serology to determine the presence of specific antibodies and PCR to detect genus- or species-specific DNA. First-line laboratory diagnosis is complicated by the fact that eggs are not excreted yet in the first two phases of infection. During the phases of established and late chronic infection egg excretion may be very low and eggs are easily missed. Serology is useful in travelers normally living in nonendemic areas but of little help in endemic regions due to the long persistence of antibodies after clinically successful treatment. PCR procedures are increasingly of importance in situations where eggs are not easily detected because of aberrant localization of worms and eggs. It is, for instance, successfully used in patients with genital lesions [2].

**Skin manifestations**

Skin manifestations are not normally part of the clinical picture in established infections. Yet, they are occasionally seen in infections with each of the three species of human schistosomes. In the early phase of infection they are caused by cercarial penetration of the human skin, or by the allergic reaction as a component of the Katayama syndrome. Later they may be due to eggs in the genital system or to eggs that get astray, in situations referred to as cases of ectopic schistosomiasis.

**Cercarial dermatitis**

The duration of passage through the dermis is normally short. The cercariae lose their tail and the so-called schistosomulae rapidly pass the dermis to be transported to deeper layers. The clinical picture of cercarial dermatitis develops in a matter of minutes, and mostly within 1 hour
after penetration. In less than a day, the schistosomulae pass the skin and reach the lungs; the dermatitis vanishes and symptoms disappear within 2–3 days. Mostly this phase of infection is insignificant or absent. In a highly endemic area in Congo, I used to be told by the local people that in particular sites exposure to the surface water was unhealthy because it caused itching. In those sites snail and cercarial concentrations were shown to be very high (personal observations). Mostly, however, this phase of infection with the human parasite remains unnoticed by the local population. The situation may be different when previously uninfected adults get exposed to (high densities of) cercariae. Intense itching shortly after swimming is commonly described by European or American visitors to endemic countries who are later shown to be infected [3]. A history of cercarial dermatitis is reported in 10–36% of travelers later diagnosed with schistosomiasis [4].

Cercarial dermatitis is much more intense when the cercariae belong to schistosome species unable to successfully develop in humans, such as those of *Ornithobilharzia ocellata* of birds. The schistosomulae of this and related species penetrate the human skin and migrate through the skin but fail to continue further development to adult worms. After some days they die but meanwhile a much more intense picture of cercarial dermatitis may have developed (Figure 18.1).

There is no specific means of diagnosis as antibodies have not been formed yet and eggs can of course not be found either. The diagnosis is clinical only.

![Figure 18.1](https://www.dermatlas.org)

*Figure 18.1* (a and b) A more serious and extensive Swimmers’ itch due to infestation with cercariae of a nonhuman Schistosome species. These brothers, developed an intensely itchy rash immediately after swimming at a beach near Boston. Itching occurred within minutes of leaving the water, blanching papules with central pustules developed several hours later, and small blisters appeared on day 3. Complete resolution occurred in about a week. They were treated with an oral antihistamine and a topical corticosteroid (© Dermatlas; http://www.dermatlas.org)
**Urticarial reactions during the Katayama syndrome**

Urticarial reactivity is generally recognized as a component of the toxemic phase of infection in nonimmune persons referred to as the Katayama syndrome. Urticaria, however, are seen in no more than a minority of the Katayama patients. Prostration, fever, profuse sweating, and eosinophilia are the accompanying signs of acute schistosome infection. Although originally described for patients with heavy *S. japonicum* infection, the Katayama syndrome can be seen in *S. mansoni* and *S. haematobium* patients as well. Symptoms occur in approximately 50% of new infections and are seen 14 days to 3 months after exposure. Most people recover spontaneously after 2–10 weeks [3, 4].

Laboratory diagnosis depends on serology but may fail because seroconversion normally occurs 4–8 weeks after infection. Promising but hitherto inconclusive results are being obtained with PCR [5].

**Ectopic schistosomiasis**

The great majority of migrating schistosomules efficiently reach their predilection sites in the urogenital system for *S. haematobium*, and in the mesenterial and portal system for *S. mansoni* and *S. japonicum*. It is not amazing that occasionally worms get astray during the process of migration to their predilection sites and both adult worms and their eggs get stuck in aberrant sites. Young schistosomes require some time to firmly establish in their predilection site: *S. haematobium* eggs, for instance, are found much more frequently in stool specimens in the early weeks of egg excretion than some months later. In 1905, Symmers described a couple of copulating worms in the lung of an Egyptian person who died from the consequences of urinary schistosomiasis [6]. In an extensive postmortem study in Egypt, schistosomal pulmonary emboli were demonstrated in one-third of all cadavers [7]. Indeed, ectopic lesions are by no means rare! Neuroschistosomiasis may be the result when granulomes develop around eggs in the central nervous system; skin manifestations arise from eggs deposited in the skin [8].

Ectopic cutaneous schistosomiasis, sometimes referred to as “bilharziasis cutanea tarda,” presents as a papular eruption, sometimes as groups of papules or plaques (Figure 18.2). Sometimes they are observed to slowly grow and to form warty or even “cauliflower projections” [9]. Often, but not always, the papules are hyperpigmented. The skin lesions are most frequently found in the perigenital area of female patients. Extragenital skin lesions are seen less frequently. In the cases that have been reported, clusters of granulomatous papules have been found on the skin of the trunk, the back, periumbilical region, and in the neck and clavicular regions. Rarely other sites are involved like breasts or limbs [10].
The localization and presentation of skin lesions are rather variable. The patient’s complaints vary from asymptomatic to painful lesions. A slight pruritus is the most common complaint [10].

Anastomoses between the pelvic venous plexus and the subcutaneous plexus of the genitorectal area explain the relative frequency of skin lesions in that area. Those lesions are most often seen in severe chronic *S. haematobium* infections.

The occurrence of cutaneous lesions cannot be explained in one straightforward way. The generally clustered nature of the papules suggests that adult egg-laying worms have been swept into abnormal foci. It has been stated that ectopic localizations of the lesions are a sign of a “less stable parasite–host relationship.” Further evidence for such unstable host–parasite relationship comes from the observation that many of the extra-genital skin lesions are seen shortly after exposure (<6 months), when the adult worms have hardly settled and started egg production. In a well-studied case of hyperpigmented lichenoid schistosome papules in the neck of a 12-year-old Nigerian boy, hematuria developed 3 weeks after presentation of the skin lesions [11]. By that time many *S. haematobium* eggs were found in the urine sediment.

Diagnostic confirmation of the etiology of the skin lesions is entirely based on the demonstration of schistosome eggs or DNA in biopsy specimens. Often eggs are not, or not yet, found in urine or stool specimens.

**Genital schistosomiasis**

In the context of this book it is relevant to stress that in addition to the well-recognized predilection sites of the intestinal and bladder plexus,
Schistosome infection may give rise to genital schistosomiasis as well. The presence of anastomoses between the plexus venosus uterovaginalis and the plexus venosus vesicalis explain the frequent occurrence of particularly *S. haematobium* worms and eggs in the genital system and most commonly in uterus and cervix.

The most common and pathognomonic lesions in female genital schistosomiasis (FGS) are those of “sandy patches” on the uterine cervix (Figure 18.3) [12]. Two different types of sandy patches are nowadays recognized: “grainy sandy patches,” linked to egg granulomas and “yellow sandy patches,” which may mimic a variety of sexually transmitted diseases. FGS may result in genital itch, abnormal yellowish discharge, dyspareunia, and postcoital bleeding.

Epidemiological studies in sub-Saharan Africa indicate that between 33% and 75% of *S. haematobium*-infected women suffer from FGS of the lower genital tract [13], while no eggs could be found in urine analysis of 30–50% of the FGS-cases. Indeed, the presence or absence of FGS cannot be diagnosed on the basis of standard urine analysis. Diagnosis is based on recognition of the sandy patches in colposcopy, and/or the demonstration of *S. haematobium* eggs in genital tissue.

**Treatment**

Praziquantel is the drug of choice for all forms of schistosomiasis. The cure rate of a standard dose of praziquantel (once 40 mg/kg) depends on the worm load but is definitely less than 100%. A somewhat higher dosage or a second treatment might be indicated. Apart from praziquantel to kill the egg producing adult worms, additional treatment to cope with
abscess-forming inflammation may be needed. In patients with a pronounced swimmers’ itch, an oral antihistamine and topical steroids might be indicated. In patients with Katayama syndrome, treatment is generally postponed until egg production starts, since praziquantel is inefficient in infections with immature stages of the parasite. Recent studies suggest artemether might be effective in very recent infections [14]. In patients with skin or genital lesions caused by schistosome eggs trapped in the tissues, praziquantel is the drug of choice. Lesions, however, do not resolve quickly after successfully removing the adult egg-laying schistosomes.

References

CHAPTER 19

Tungiasis

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Key points

- Tungiasis is a zoonosis occurring in resource-poor communities in South America, the Caribbean, and sub-Saharan Africa.
- The infestation is acquired when skin comes into contact with soil on which adult sand fleas thrive.
- Tungiasis is a dynamic process with lesions altering their morphological aspect continuously.
- The diagnosis is made clinically.
- The surgical extraction of the flea under sterile conditions is the only reliable treatment.

Introduction

Tungiasis is a parasitic skin disease due to the penetration of the female sand flea Tunga penetrans into the epidermis of its host and its subsequent development. Once embedded in the stratum corneum, the flea undergoes a peculiar hypertrophy, during which the abdominal segments enlarge to the size of a pea. Through a tiny opening in the skin hundreds of eggs are expelled for a period of about 3 weeks [1]. After all eggs have been released, the involution of the expanded abdomen begins. Three to four weeks after penetration, the parasite dies in situ and eventually is sloughed from the epidermis by tissue repair mechanisms. Hence, tungiasis is a self-limited condition. However, in individuals, living in an endemic area, reinfection is the rule and sequels are common. Repeated infestation leads to a chronic inflammation of the foot with persistent pain and difficulty of walking [2].

Tungiasis is known since the sixteenth century. The first description of the disease was provided by Hans Staden von Homberg zu Hessen, a
German adventurer who lived several years with the Tupinambá Indians in an area that nowadays is the State of Rio de Janeiro in Brazil [3].

Being comparatively rare in travelers, the ectoparasitosis is frequently misdiagnosed and patients are subjected to inappropriate diagnostic and therapeutic procedures.

**Epidemiology: geographic distribution, mode of infection**

The sand flea *T. penetrans* is one of the few parasites that have spread from the western to the eastern hemisphere. Originally, the ectoparasite occurred only on the American continent. There is anecdotal evidence that the flea was introduced to Angola with ballast sand of a sailing ship that left Brazil in 1872. Within a few decades, *T. penetrans* spread from the coast of Angola along trading routes and with advancing troops. At the end of the nineteenth century the parasite had reached East Africa and Madagascar. Today, tungiasis is found on the American continent from Mexico to northern Argentina, on several Caribbean islands, as well as in almost every country of sub-Saharan Africa [4].

In endemic countries, the distribution of tungiasis is uneven and most cases occur in circumscribed foci. Typically, these are urban squatter settlements, traditional villages along the coast or underdeveloped communities in the rural hinterland, that is, places rarely visited by the mainstream tourist. Tungiasis is considered a neglected disease of marginalized populations.

In resource-poor communities, prevalence may be up to 50% in the general population [5]. Prevalence and parasite burden are related, and in typical foci, individuals may harbor between a few and more than 100 sand fleas [2]. There is a clear seasonality in incidence with only few cases occurring during the rainy season and a high attack rate during the dry season [5].

Tungiasis is a zoonosis affecting a broad range of domestic and sylvatic animals. Depending on the setting, dogs, cats, pigs, and rats are the most important reservoirs [6].

As the designation “sand flea” suggests the ectoparasitosis is thought to be associated with sandy soil. However, sand fleas easily propagate on different types of soil, in banana plantation and in backyards. Even dust-filled crevices in a floor are suitable places for off-host propagation, provided there is some organic material larvae can feed on and the soil temperature is sufficiently high to allow development from the egg to the adult flea [7]. The infestation occurs when walking barefoot over soil or when nude skin comes into contact with soil where adult sand fleas are present. This
Imported Skin Diseases may be at a beach, on unpaved tracks, peridomestic or inside a dwelling, when the house has no solid floor. Typically, tourists become infected at the beach [8]. Infestation may occur at any time of the day. After a sand flea has explored the skin and has identified a suitable site, usually the toes, the sole, the heel, or the lateral rim of the foot, it rapidly penetrates the stratum corneum and is completely burrowed in the epidermis within 30 minutes to several hours [1]. The process of penetration usually is not perceived.

Clinical picture

It is important to understand that tungiasis is a dynamic process with lesions altering their morphological aspect continuously [9]. By consequence, the macroscopic appearance of tungiasis in a returned traveler essentially depends on the stage of development of the embedded flea.

On the basis of clinical and morphological criteria, the natural history of tungiasis can be divided into five stages [1]. In stage I (flea in statu penetrandi, 30 minutes to several hours), a tiny reddish spot of about 1 mm appears with or without an erythematous halo (Figure 19.1). In stage II (beginning hypertrophy, 1–2 days after penetration), the lesion becomes more obvious as a growing whitish or mother-of-pearl papule develops. In the protruding rear cone of the flea, the anal–genital opening appears as a central black dot surrounded by erythema (Figure 19.2). In stage III (maximal hypertrophy, 2 days to 3 weeks after penetration), the hypertrophy becomes macroscopically visible. A round, watch glass-like elevation with well-defined borders and tight consistency appears frequently surrounded

![Figure 19.1](image)Recently penetrated sand flea at the base of a toe. The black dot surrounded by the erythema indicates the abdominal segments of the parasite
Figure 19.2. Lesion in late stage II at the rim of the nail. The circular yellow-whitish area are the enlarged abdomen segments neosome that glimmer through the stratum corneum by local desquamation (Figure 19.3). Emission of eggs and feces is typical in this stage (Figures 19.3 and 19.7). In stage III, the lesion is painful and the patient has the sensation of a foreign body expanding under the skin. In stage IV (3–5 weeks after penetration), a black crust covers an involuted lesion with a dead, decaying parasite (Figure 19.4). At the end of stage IV, the carcass of the ectoparasite is slowed from the epidermis resulting in a circular impression in the skin. The stamp-shaped imprint in the stratum corneum is characteristic of stage V (6 weeks to several months after penetration) (Figure 19.5).

Figure 19.3. Two lesions at the base of a toe in late stage III and one in late stage II. The distal lesion shows a wrinkled appearance, an indication that regression of the lesion has already begun. Next to the stage II lesion, an egg is visible. A fissure has formed below the distal metatarsal joint.
Typically, *T. penetrans* affects the periungual area of the toes. Other predilection sites are the heel, the sole, the interdigital area, and the lateral rim of the foot. However, sand fleas can be found on almost every part of the body, for example, hands, elbows, neck, buttocks, and the genital region [10]. If several lesions occur simultaneously they are usually located in clusters (Figures 19.4 and 19.7). In single cases, lesions may take the aspect of a tumorous growth and in histological sections appear as a pseudoepitheliomatous hyperplasia [11] (Figure 19.6).

The natural history of sand flea disease may be changed by two events: bacterial superinfection and manipulation of the lesion by the patient or
his carer. Bacteria are either passively carried into the epidermis by a penetrating flea or are actively introduced by scratching or manipulating the lesion with a nonsterile instrument.

In the endemic area, bacterial superinfection is present in virtually all cases [12]. In tourists, superinfection is less common. Superinfection first leads to the formation of a microabscess, then to a pustule and eventually to suppuration. *Staphylococcus aureus* and streptococci are the microorganisms most frequently isolated, but other aerobic and anaerobic bacteria (including clostridia) are also found [12]. In nonvaccinated individuals, tungiasis may lead to tetanus. Pathogenic microorganisms may reach the dermis (and eventually enter into the circulation), since the proboscis of the parasite is placed in a capillary of the dermis.

If the flea is completely taken out with a sharp instrument such as a needle, a nail, or a thorn, a sore remains that easily becomes superinfected. If the ectoparasite ruptures during manipulation or the mouth part remains embedded in the dermis, an intense inflammation ensues.

### Diagnosis

The diagnosis is made clinically taking into consideration the dynamic nature of the macroscopic appearance of the lesion together with travel history of the patient. The use of a dermatoscope is helpful. The patient typically complains about local itching, pain, and the sensation of a foreign body. The simultaneous presence of two or more identical lesions at the toes, particularly along the nail rim, is diagnostic. The observation of eggs being expelled or attached to the skin around the lesion and the release of brownish threads of feces are pathognomonic signs (Figures 19.3
Figure 19.7 A cluster of three lesions at the rim of the nail. Two fecal threads are located left to the cluster. One fecal thread is being ejected. Fecal material is spread in dermal papillae and 19.7). Feces threads are of a helical structure and often spread into the dermal papillae. Expulsion of eggs can be provoked by massaging the hypertrophy zone slightly.

The differential diagnosis differs according to the stage. Important differential diagnoses are summarized in Table 19.1.

Table 19.1 Differential diagnosis of tungiasis according to stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Differential diagnosis</th>
<th>Indicators of tungiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Partially penetrated foreign body (e.g., thorn)</td>
<td>Itching, developing erythema, flea disappears completely in the skin with several hours</td>
</tr>
<tr>
<td>II</td>
<td>Foreign body, insect sting, acute paronychia</td>
<td>Itching; circular whitish, mother-of-pearl papule increasing in size with a central black dot; untypical location for insect stings (e.g., nail rim)</td>
</tr>
<tr>
<td>III</td>
<td>Myiasis, dermoid cyst, wart, pustule/abscess of bacterial origin, dracontiasis</td>
<td>Circular watch-glass like elevation with a tight consistency surrounded by desquamation, lesion diameter increases from day to day, expulsion of eggs, expulsion of fecal threads, flea faeces dispersed in dermal papillae, sharp localized pain; dracontiasis usually located on the instep or above the ankles</td>
</tr>
<tr>
<td>IV</td>
<td>Local gangrene, melanoma</td>
<td>Development of black crust within a couple of days, rear cone of flea visible in the center of the black crust, size of lesion gets smaller from day to day</td>
</tr>
</tbody>
</table>
Biopsy of the lesion followed by a histopathological examination is not indicated except in lesions with a pseudoepitheliomatous appearance. Histological sections usually demonstrate the presence of the ectoparasite or of chitinous fragments and a characteristic pattern of inflammation [9].

**Treatment and prevention**

Hitherto, surgical extraction of the flea under sterile conditions is the only reliable treatment. The opening in the epidermis must be widened, for example, with a scalpel, until the neosome is completely liberated. Then the entire flea has to be carefully taken out with tweezers. After the extraction of the parasite, the wound should be treated with a topical antibiotic. The tetanus immune status has to be checked. A randomized controlled trial has shown that oral ivermectin is not effective [13].

Wearing of closed shoes and socks protects to a certain degree. The daily inspection of the feet and immediate extraction of embedded fleas prevents complications. The twice-daily application of Zanzarin®, a repellent based on coconut oil, reduced the infestation rate in an area with an intense transmission by almost 90% [14, 15]. If applied regularly, it protects travelers effectively against invading sand fleas, even if no shoes are worn.

**Key features**

Tungiasis is a zoonosis occurring in resource-poor communities in South America, the Caribbean and sub-Saharan Africa. The infestation is acquired when skin comes into contact with soil on which adult sand fleas thrive. Tungiasis is a dynamic process with lesions altering their morphological aspect continuously. The diagnosis is made clinically. The surgical extraction of the flea under sterile conditions is the only reliable treatment.

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CHAPTER 20

Cutaneous Larva Migrans

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Key points

- Parasitic disease caused by penetration of animal hookworm larvae into epidermis.
- Usually acquired on tropical and subtropical beaches.
- Intense itching and discomfort.
- Serpiginous lesion.
- Treatment with oral albendazole or ivermectin, or topical thiabendazole.

Introduction

Cutaneous larva migrans (ground itch, plumber’s itch, duck hunter’s itch) is a parasitic skin disease caused by the penetration of larvae—most commonly of dog and cat hookworms—into the epidermis [1,2]. In the human host, the larvae cannot complete their life cycle and are unable to develop into adult worms. They continue migrating in the epidermis for a limited period of time after which they die, disintegrate and are resolved by skin repair mechanisms. The characteristic clinical picture is a pruritic serpiginous lesion, also called “creeping eruption.” The lesion visibly moves in the skin from day to day.

Cutaneous larva migrans is the most common dermatological problem in travelers returning from tropical and subtropical areas [3]. The first description of a “creeping eruption” dates back to 1874 [4]. Fifty-five years later, a nematode larva in a skin biopsy was identified, and the dermatosis was attributed to animal hookworms [5, 6].
**Epidemiology: geographic distribution, mode of transmission**

The dog and cat hookworm *Ancylostoma braziliense* is the most common cause, but other species can also cause the infestation, such as *Ancylostoma caninum*, *Gnathostoma spinigerum*, or *Uncinaria stenocephala* [7]. Nematodes of other animals such as sheep, goat, cattle, and sylvatic animals may also cause cutaneous larva migrans. The human nematode *Strongyloides stercoralis* is associated with a similar syndrome known as “larva currens.”

Cutaneous larva migrans is common in tropical and subtropical regions throughout the world. In typical endemic areas in developing countries, a high proportion of dogs and cats are infected with animal hookworms. Animal feces are spread by heavy rains, and eggs are distributed over a large surface. Thus, the risk of exposure increases during the rainy season. First stage larvae hatch from eggs within some days after feces have been deposited. About 7 days later, larvae develop in the soil into the infective third stage and are able to penetrate into the epidermis of its host. In a warm and humid environment, where larvae are protected from direct sunlight and desiccation, they can survive for several months.

As in resource-poor communities of low and middle income countries many people walk barefoot and children crawl or sit on the ground, point prevalence of cutaneous larva migrans may be as high as 3–4% in the general population [8, 9]. Most cases of cutaneous larva migrans seen by physicians in industrialized countries are travelers returning from the tropics and subtropics [10–12]. However, infestation occurs sporadically also in temperate zones, and cases have been described, for example, in Australia, France, the United States, Great Britain, Germany, and New Zealand [13–16].

The infestation of humans with animal hookworms occurs accidentally. Individuals become infested when the skin has been in contact with soil contaminated by animal feces, in which larvae of animal hookworms thrive. In contrast to human hookworms the larvae of animal hookworms cannot penetrate the basal membrane and therefore remain sequestered in the epidermis. As man is a dead end, the disease is self-limiting. In the epidermis, the larvae migrate aimlessly for a period of weeks and in single cases up to several months causing the clinical picture of an intensively itching creeping eruption.

Travelers typically get infested when walking to and at beaches of tropical and subtropical countries that are contaminated with dog and cat feces [17]. An airport-based study on international travelers exiting Brazil showed that all patients who had acquired cutaneous larva migrans during their stay had visited beaches [18]. The infestation can also be acquired at any place where unprotected skin comes into contact with
soil contaminated by animal feces, such as sand boxes, playgrounds, construction sites, and crawl spaces under houses. Rarely, infestation occurs via fomites, such as towels or clothes.

**Clinical picture**

Cutaneous larva migrans begins with a reddish papule at the penetration site a few hours after contact with the infective larva. One to several days after penetration, the characteristic erythematous serpiginous, slightly elevated track appears which with time may reach more than 20 cm (Figures 20.1 and 20.2). The larvae migrate between a few millimeters and several centimeters per day [9].
The infestation is accompanied by intense itching impeding patients from sleeping normally. The pruritus is generally more intense at night, and patients consider the condition as extremely uncomfortable, particularly when several eruptions are present simultaneously [9]. Pain may be present. Secondary infection is common and a result of scratching. Sporadically, larvae may invade the viscera and cause eosinophilic pneumonia (Loeffler’s syndrome) [19]. Vesiculobullous lesions are observed in 9–15% of cases (Figure 20.3) [3,11]. Erythema multiforme is rarely seen as a complication in previously sensitized individuals.

Hookworm folliculitis has been described in travelers returning from tropical countries in single cases [20,21]. The uncommon clinical manifestation is characterized by papulopustular inflammation of follicles (Figure 20.4). This form of cutaneous larva migrans is more resistant against treatment, and repeated doses of oral drugs (ivermectin/albendazole) may
be necessary. Topical tiabendazole is not effective in hookworm folliculitis [22].

In travelers, lesions are usually located on the feet, buttocks, and thighs—areas that come in contact with contaminated sand while walking or sitting on the beach [10–12, 18, 23]. Rarely, lesions are found also on the arms, elbows, legs, knees, and back. In fact, cutaneous larva migrans may occur at any topographical site of the body including the face, the oral cavity, and the genitals (Figures 20.5–20.7). A patient may present multiple tracks affecting different topographical areas [9].
Figure 20.7 Cutaneous larva migrans on the nose of a tourist. Infestation occurred by a contaminated towel that had been fallen on the ground. Other sites infested were the buttocks, the knee, the scrotum, and the arm

Diagnosis

The diagnosis of cutaneous larva migrans is based upon the characteristic clinical picture together with a travel history in which the patient remembers contact with soil. The infestation can be diagnosed by the naked eye. An elevated linear or serpiginous lesion, with or without an erythematous papule (the latter indicating the entry site of the larva) associated with pruritus is pathognomonic. A biopsy is not indicated and—if done—rarely reveals the migrating larva. The anterior end of the track does not necessarily indicate the localization of the larva, as the inflammatory response may be delayed. Laboratory investigations are not helpful. Eosinophilia may or may not be present.

As a differential diagnosis larva currens has to be considered, which is caused by autoinfection with *S. stercoralis*. Larvae of *S. stercoralis* migrate faster than those of animal hookworms (up to several centimeters per hour) and lesions usually start in the perianal area, from where they move towards the abdomen.

Cutaneous gnathostomiasis caused most commonly by the nematode *Gnathostoma spinigerum* is endemic in Southeast Asia, but occurs also in Latin America. It is acquired by eating uncooked fish, frogs, or flesh from other animals containing encysted larvae. The third stage larvae migrate in the skin and subcutaneous tissue, but may also enter the central nervous system and other organs. The disease is characterized by itching migratory subcutaneous swellings and migration of larvae in the skin, causing eruptions. Often, the patients have general symptoms such as headache and fatigue.
Other differential diagnoses include scabies, loiasis, myiasis, cercarial dermatitis (induced by penetrating cercaria of different schistosome species), superficial mycosis (tinea), herpes zoster, and contact dermatitis.

**Treatment and prevention**

The drug of choice is ivermectin. A single dose of oral ivermectin (200 μg/kg) kills the larvae and resolves the symptoms quickly [22]. Treatment failure is rare and usually resolves after a second dose. Ivermectin has been used in millions of individuals in the developing world in onchocerciasis and lymphatic filariasis control operations without any significant

**Figure 20.8** Sign prohibiting the presence of dogs on a beach in Brazil (a) and a playground in Paris (b) as a means of prevention
adverse events. The drug is contraindicated in children <15 kg (or <5 years of age) and pregnant/breastfeeding women. Oral albendazole (400 mg daily for 3 days) shows also excellent efficacy and is a good alternative for ivermectin. Thiabendazole ointment (10–15%) applied to affected areas three times daily for 7 days is as effective as the oral treatment, but requires compliance. It is not effective in hookworm folliculitis. Oral thiabendazole should be avoided, as it is not well tolerated. Freezing the edge of the track with liquid nitrogen or carbon dioxide is obsolete, as it is ineffective, painful and may cause ulcerations. Secondary infections should be treated with a topical antibiotic.

To prevent infestation of tourists, animals should be banned from beaches and playgrounds (Figures 20.8a and 20.8b).

The only means of prevention on individual level is avoiding that unprotected skin comes into contact with possibly contaminated ground. This can be achieved by wearing shoes while walking on beaches in endemic areas and not lying directly on the sand at beaches or greens where dogs or cats have been observed. Lying on towels does not protect sufficiently, and a sun chair or mattress should be used. Areas where the sand is humidified by the tide are safe. Towels and clothes should not touch the ground when hung up for drying. In general, places where dogs and cats stroll around should be avoided.

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Cutaneous Larva Migrans


CHAPTER 21

Myiasis

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Key points

Myiasis refers to human infestation by diptrid fly larvae (maggots):

- Facultative myiasis occurs when larvae enter living tissue from nearby decaying tissue.
- Obligatory myiasis is true parasitism, in which a portion of the larvae’s development must occur in tissue.
- Accidental myiasis refers to larvae found in the intestinal or urinary tracts, usually as a result of ingestion and subsequent migration.

Introduction

Myiasis (derived from the Greek myia = a fly) refers to the invasion of human or animal tissues by the larvae (maggots) of flies (Diptera). A wide variety of body areas can be involved and this results in different clinical classifications including cutaneous, dermal, traumatic, gastric, rectal, and urogenital myiasis. The larvae feed on tissue (living or dead), or in the case of intestinal myiasis, on ingested food. Human myiasis can be facultative, obligate, or accidental. It is more often encountered in the tropics and is uncommon in temperate zones. Facultative myiasis occurs when larvae enter living tissue after residing in nearby, decaying, or vegetable tissue in a wound. Obligatory myiasis refers to true parasitism, in which a portion of the larvae’s developmental stage is spent in living tissue. Most commonly, this occurs in animals such as sheep, cattle, and horses but human tissue invasion by the human botfly of Central and South America is well documented. “Accidental” myiasis (pseduomyiasis) refers to larvae found in the intestinal or urinary tracts. These larvae are typically inadvertently ingested with food, or have wandered into these areas of the body. There is no dipterous obligate intestinal parasite.
of humans. While typically a benign event, stomach pain, nausea, and vomiting can result from accidental myiasis [1].

**Pathogenesis**

Several families of flies that result in myiasis in humans exist and is discussed in the following text.

**Calliphoridae (metallic flies)**

**Genus Cochliomyia**

The New World screwworm *Cochliomyia hominivorax* (previously known as *Cochliomyia americana* and *Callitroga americana*) or “human-eater,” is an obligate parasite of cattle and other livestock. The species name, “human-eater,” refers to the once held thought that it resulted in the deaths of hundreds of prisoners on Devil’s Island [2]. In the United States, Mexico, and areas of South America, the release of many sterilized male flies, and other successful eradication techniques, has led to the eradication of screwworm. Additional campaigns continue in Central America.

Adult flies have three distinct dark longitudinal stripes on the dorsal thorax, are green-blue in color and range in size from 8 to 10 mm. Their dorsal bristles are poorly developed and it has a hairless thoracic squama, a membranous lobe on the posterior border of the wing.

Once an egg hatches, larvae of *C. hominivorax* burrow deeply and feed aggressively on living tissue. Not only can they penetrate unbroken skin but they may also infest wounds, scabs, sores, and even healthy mucous membranes. The larvae have distinct spicules that encircle the anterior margins of all body segments, unlike the housefly maggot.

**Genus Chrysomya**

*Chrysomya bezziana*, the Old World screwworm, is an obligate parasite in living tissues such as wounds. This is in contrast to larvae from other species that develop in carrion and decomposing matter. It occurs throughout much of tropical Africa, India, the Arabian peninsula, Southeast Asia, the Indonesian and Philippine islands to New Guinea and the west coast of the Persian Gulf, including Iraq.

Morphologically, these larvae differ from *C. hominivorax* in that their thoracic squama contain fine hairs on the dorsal surface and they contain four to six projections on the anterior spiracles, not the usual seven to nine found in *C. hominivorax*. However, the life cycle of *C. bezziana* is very similar to *C. hominivorax*, and adults of both types can be found on decaying matter, flowers, and decomposing corpses.
Genus **Cordylobia**

*Cordylobia anthropophaga*, also known as the tumbu or mango fly, is a cause of furuncular and plaque myiasis, characterized by coalescing furuncles. It is found in Africa, from Ethiopia in the north to Natal and the Transvaal in the south. Adults are relatively large, ranging in size from 9 to 12 mm, with a yellow to light brown color and two dark gray, poorly defined dorsal longitudinal thoracic stripes. The abdominal segment has four visible segments, each approximately equal in size. These robust flies have wings that are tinted brown.

*Cordylobia rodhaini* (also known as Lund’s fly), the only other species of *Cordylobia* known to infest humans, has a more limited distribution in tropical Africa, principally the rainforest areas. In most cases, there is more than one lesion, and very extensive furuncular myiasis due to *C. rodhaini*, acquired in Ethiopia, has been reported in an Italian man.

Females may lay up to 100–300 white and banana-shaped eggs on sand or soil in shaded areas, especially if contaminated by urine or feces, and also on laundry hanging out to dry or babies’ diapers. In the wild, rats are the usual host, but around human habitation dogs and humans are common hosts. Once on a human, the larva uses its powerful oral hooks to attach itself to the host and rapidly penetrates the skin, leaving only its posterior spicules at the top of its abdomen in contact with the air. When development is complete (usually in 14–16 days) it leaves the host and falls to the ground, where they bury themselves and pupate.

Other genera

Several larvae may act as secondary invaders of wounds in humans and include members of the genera *Phormia* (black blowflies), *Lucilia* [*Phaenicia*] (greenbottle), and *Calliphora* (bluebottle). A study of wound myiasis in urban and suburban United States demonstrated that the majority of species identified were blowflies, the most common being *Lucilia sericata* [2]. Homelessness, alcoholism, and peripheral vascular disease were frequent cofactors.

There has been a recent resurgence of interest in the use of maggots for wound debridement, and the larvae of *L. sericata* are used for this purpose [3]. When using maggots for debridement, it is obviously important to choose only maggots that remain in necrotic rather than living tissue and to avoid species that invade viable tissue.

**Sarcophagidae (flesh flies)**

Genus **Sarcophaga**

Wound infestation by members of this genus has been reported. The species are large, 10–15 mm in length, gray in color and have overlying
hairs. Their thorax is marked by three prominent black longitudinal dorsal stipes. Occasionally, a chessboard appearance of the abdomen may be seen as dark square patches alternate on a gray background. *Sarcophaga cruentata* (also known as *Sarcophaga haemorrhoidalis*) is the most widely distributed and common species. Most often, these larvae result in accidental intestinal myiasis. Approximately 40–60 larvae will be deposited on decaying food, excreta or carcasses where they serve as primary scavengers. The larvae of *Sarcophagidae* are distinguished from *Calliphoridae* in that they have posterior spiracles situated in a deep pit.

**Genus Wohlfahrtia**
As with *Sarcophaga*, these can cause wound myiasis. Female flies deposit approximately 120–170 larvae, not eggs, in wounds or beside body orifices. *Wohlfahrtia magnifica* is likely the most important species and is an obligate myiasis-producing fly in humans and animals such as camels and sheep. The larvae of *W. magnifica* may be deposited in the ear, eye, and nose, and can cause extensive destruction of healthy tissue resulting in deafness, blindness, and even death. *W. magnifica* occurs throughout the Mediterranean basin, East and Central Europe, and Asia Minor.

*Wohlfahrtia vigil vigil* and *Wohlfahrtia vigil opaca* are North American species whose females deposit larvae on unbroken and soft skin, resulting in furuncular myiasis. Human furuncular myiasis from these species occurs only in infants, as the larvae are unable to penetrate adult skin.

**Oestridae**
The Oestridae contain four subfamilies, three of which are obligate parasites of domestic animals (Oestrinae, Gasterophilinae, and Hypoderminae). The Cuterebra subfamily has several species that can cause myiasis in rodents, monkeys, and livestock. Another member of this subfamily, *Dermatobia hominis*, causes myiasis in people and animals in Central and South America.

**Genus Cuterebra (rodent or rabbit botfly)**
Rabbits and rodents are the natural hosts for the larvae of these flies, which are among the most frequent causes of North American-acquired human furuncular myiasis [4].

**Genus Dermatobia (human botfly)**
*D. hominis* (Figures 21.1 and 21.2) is the only species in this genus. Slightly larger than the bluebottle fly at 12–18 mm, it has vestigial mouthparts, a similar abdomen (dark-blue metallic colored), yellow head and a blue-gray
Dermatobia hominis (human botfly) larva in tissue

Figure 21.1 Dermatobia hominis (human botfly) larva in tissue

It can be found in the neotropical areas of the New World, extending from southern Mexico to northern Argentina. It occurs where temperature and humidity are relatively high, principally in lowland forests, especially in woodland paths at along forest and scrub areas. *D. hominis* causes cutaneous myiasis in a wide range of mammalian hosts, including humans, and is particularly important as a parasite of cattle.

The female fly sticks approximately 6–30 eggs on to the body of other insects such as day-flying mosquitoes, blood-sucking flies and even ticks, which then serve as vectors to carry her eggs to the host (a process known as phoresy). The process is a wonder of nature, as the female fly deftly grabs the insect vector in mid-air and deposits eggs on its abdomen. Embryos begin to develop into first-star larvae but refrain from hatching

Figure 21.2 Dermatobia hominis (human botfly) larva
until the vector lands and feeds on a potential host. The larvae then emerge and within 10 minutes are able to burrow into the subcutaneous tissues. The burrow results in a boil-like lesion with an opening, through which the larvae breathe. Larval development lasts approximately 50–60 days, following which the larva emerges, drops to the ground and pupates. Persistent boil-like lesions in anyone who has returned from an endemic area should always raise suspicions of botfly myiasis (Figure 21.3) [5, 6].

**Genus Gasterophilus (horse botfly)**

A form of migratory cutaneous myiasis known as “creeping eruption” is caused by *Gasterophilus* larvae. These botflies are principally parasites of the alimentary tract of horses, but occasionally larvae of certain species, including *Gasterophilus intestinalis*, *Gasterophilus haemorrhoidalis*, and *Gasterophilus pecorum*, penetrate human skin.

**Genus Oestrus**

*Oestrus ovis* (sheep nostril fly), which develops in the nasopharyngeal passages of sheep and goats, and *Rhinoestrus purpureus* (Russian botfly), which parasitizes horses and donkeys, are occasionally responsible for human myiasis, especially ophthalmomyiasis. The larvae will only be noted in the conjunctival sulcus when the eyelid is everted.

**Genus Hypoderma (warble flies)**

The larvae of *Hypoderma* species are obligate parasites of cattle. Humans are abnormal hosts, and the larvae usually do not mature fully. After penetrating the skin, the larvae produce migratory subcutaneous swellings.
Systemic illness, with myositis, pleurisy and pericarditis, and marked eosinophilia, may accompany infestation.

**Muscidae**

*Fannia canicularis* (lesser housefly) and *Musca domestica* (housefly) may deposit their eggs in wounds and ulcers, giving rise to facultative wound or urogenital myiasis. Urogenital myiasis results when ovipositing flies lay their eggs near genital orifices, resulting in larvae entering the genital canal, causing pain and the even the eventual excretion of larvae within the urine.

**Clinical features**

Flies and their larvae result in different clinical manifestations depending on the setting and the location of the body they affect. Facultative wound myiasis is a complication of war wounds in tropical areas, and can be seen in invalids with poor access to health care. It is an occasional occurrence in most parts of the world, particularly during hot weather when wounds or ulcers are exposed. Wounds with alkaline drainage (pH of 7.1–7.5) are said to optimum for blowflies. The larvae (maggots) can be seen, sometimes in large numbers, in the suppurating tissues, and their removal of necrotic tissue and beneficial effect on granulation has led to their use in maggot debridement therapy. Interestingly, not all cases of facultative myiasis need to occur in a wound, as larvae of *L. sericata* have been reported in healthy tissue of the ear and nose in the United States [7].

Obligatory cutaneous myiasis, which can occur in the setting of mild constitutional symptoms and eosinophilia, occurs in two main clinical forms. Humans are not the intended host and so obligate myiasis is a zoonosis. In humans, obligate myiasis typically results from screwworm flies and the human botfly. The most common clinical form is the furuncular form, in which a boil-like lesion develops gradually over a few days. Each lesion has a central punctum, which discharges serosanguinous fluid. The larvae itself burrow quickly but leave the posterior end, which contains a group of spiracles in direct contact with the air. The movements are usually noticed by the patient, as is associated pain. Lymphangitis and regional lymphadenopathy may result from the accompanying inflammatory reaction. Once the larva has emerged, or has been removed, the lesions rapidly resolve. The flies causing furuncular myiasis in humans are *D. hominis*, *Cuterebra* species, *C. anthropophaga* and *C. rodhaini*, and *W. vigil* and *W. opaca*.

The second principal clinical form is a creeping eruption, in which larvae burrow just beneath the skin in a tortuous, thread-like red line with
a terminal vesicle (*Gasterophilus*), where the larva lies ahead of the vesicle in apparently normal skin, or a series of inflammatory nodular lesions (*Hypoderma*). *Hypoderma* species also produce furuncular lesions.

**Diagnosis**

The diagnosis of furuncular myiasis is typically aided by the history of a visit to an endemic area and the presence of boil-like lesions in which the patient is aware of movement. Ultrasonography can facilitate diagnosis and assist in location of the larvae [8]. The differential diagnosis for a boil-like lesion is broad and may includes staphylococcal infections, cat-scratch, tick-bite granuloma, tungiasis, parasitic worms, to name a few.

It is important to identify any larvae recovered in cases of myiasis as this will enable determination of whether they are facultative or obligatory parasites, and thereby their pathogenic potential. Most laboratories recommend killing any recovered larvae by immersion for 30 seconds in very hot (>80°C), but not boiling water as directly killing the larvae in preservative will change the morphology through contraction [9, 10]. The hot water method prevents decay and best preserves color. Larvae should be preserved in a solution of 70–95% ethanol. A solution of 70% isopropyl alcohol can be used if ethanol is not available. Formalin solution should not be used for preservation as it causes hardening of the larval tissue, adversely affecting processing [11].

**Treatment**

The best treatment of myiasis is prevention through the appropriate use of protective clothing, repellents, and sanitation. Exposed food should be discarded, fruits and vegetables should be washed prior to consumption, wounds should be cleaned and covered, medical equipment should be protected from flies, sleeping outdoors during daytime should be avoided, the use of insect repellents should be encouraged and doors and windows should be equipped with good screens, with cracks and crevices sealed.

The larvae of furuncular myiasis producers can sometimes be expressed by firm pressure around the edges of the lesions, but the punctum may require surgical enlargement. An exception is the larva of *D. hominis*, which has a bulbous anterior end equipped with rows of backward-pointing spines. Traditional methods of treatment include occluding the punctum with pork fat, which blocks the breathing hole of the larva and stimulates premature extrusion [12]. The same principle may be achieved with mineral oil, petrolatum, butter, or a transparent occlusive bandage. Occlusion is less effective in the advanced stages of the infestation. Surgical
Table 21.1 Summary table of myiasis

<table>
<thead>
<tr>
<th>Larvae</th>
<th>Common name</th>
<th>Geographic location</th>
<th>Clinical lesion</th>
<th>Time of year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatobia hominis</td>
<td>Human botfly</td>
<td>Central and South America</td>
<td>Furuncular</td>
<td>Year-round</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Cordylobia anthropohaga</td>
<td>Tumbu fly, mango fly</td>
<td>Tropical Africa</td>
<td>Furuncular</td>
<td>Year-round</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Cordylobia rodhaini</td>
<td>Lund's fly</td>
<td>Tropical Africa, principally in rainforests</td>
<td>Furuncular</td>
<td>Year-round</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Cuterebra genus</td>
<td>Rabbit botfly, rodent botfly</td>
<td>Eastern United States, Ontario, Pacific Northwest</td>
<td>Furuncular</td>
<td>August–October</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Wohlfahr Wohlfahrtia</td>
<td>None None</td>
<td>Eastern and central North America, central and southern Europe, Russia, Pakistan,</td>
<td>Furuncular</td>
<td>June–September</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Wohlfahrtia vigil</td>
<td>Horse botfly</td>
<td>Western and southwestern North America, Worldwide</td>
<td>Furuncular</td>
<td>June–September</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Gasterophilus genus</td>
<td>Warble fly</td>
<td>Northern hemisphere</td>
<td>Migratory</td>
<td>Winter months</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Hypoderma genus</td>
<td>Warble fly</td>
<td>Northern hemisphere</td>
<td>Migratory</td>
<td>Winter months</td>
<td>Occlusion, squeezing out the larva; possible excision</td>
</tr>
<tr>
<td>Oestrus ovis</td>
<td>Sheep nostril fly</td>
<td>Worldwide in areas where sheep are tended</td>
<td>Ophthalmomyiasis</td>
<td>Spring–Fall</td>
<td>Manual removal</td>
</tr>
<tr>
<td>Rhinocelstra purpureus</td>
<td>Russian botfly</td>
<td>Southern Europe, Asia Minor, Africa</td>
<td>Ophthalmomyiasis</td>
<td>Spring–Fall</td>
<td>Manual removal</td>
</tr>
<tr>
<td>Species</td>
<td>Common Name</td>
<td>Geographic Distribution</td>
<td>Phenomena</td>
<td>Seasonal Activity</td>
<td>Control Measures</td>
</tr>
<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td><em>Fannia canicularis</em></td>
<td>Housefly</td>
<td>Worldwide</td>
<td>Wound (rarely urogenital)</td>
<td>Year-round</td>
<td>Manual removal</td>
</tr>
<tr>
<td><em>Musca domestica</em></td>
<td>Lesser housefly</td>
<td>Worldwide</td>
<td>Wound</td>
<td>Year-round</td>
<td>Manual removal</td>
</tr>
<tr>
<td><em>Cochliomyia hominivorax</em></td>
<td>New World screwworm</td>
<td>Central and South America</td>
<td>Wound</td>
<td>Year-round</td>
<td>Tissue irrigation, manual removal; +/- larvicides</td>
</tr>
<tr>
<td><em>Chrysomya bezziana</em></td>
<td>Old World screwworm</td>
<td>Africa, Australia, Asia</td>
<td>Wound</td>
<td>Year-round</td>
<td>Tissue irrigation, manual removal; +/- larvicides</td>
</tr>
<tr>
<td><em>Wohlfahrtia magnifica</em></td>
<td>Wohlfahrt’s wound myiasis fly</td>
<td>Southeastern Europe, southern and Asiatic Russia, North Africa, Middle East</td>
<td>Wound</td>
<td>Year-round</td>
<td>Tissue irrigation, manual removal; +/- larvicides</td>
</tr>
<tr>
<td><em>Sarcophaga cruentata</em></td>
<td>Red-tailed flesh fly</td>
<td>Worldwide</td>
<td>Wound (rarely urogenital)</td>
<td>Year-round</td>
<td>Wound: tissue irrigation, Manual removal; +/- larvicides, Laxatives, oral larvicides</td>
</tr>
<tr>
<td><em>(S. haemorrhoidalis)</em></td>
<td></td>
<td></td>
<td>Intestinal (rare)</td>
<td>Year-round</td>
<td></td>
</tr>
</tbody>
</table>

*Source:* Adapted from Baird et al. [4] and McGraw and Turiansky [18].
management is another option for treatment of furuncular myiasis and involves enlargement of the punctum by cruciate incisions [7]. This allows for removal of an intact larva. The injection of lidocaine beneath the nodule may be sufficient to push the larva out, and injection of lidocaine into the blind end of the cavity is also said to facilitate its nonsurgical removal. Regardless, it is important to remove each maggot carefully and intact to prevent subsequent foreign body reactions. A commercial snake venom extractor has also proved effective in removing a *D. hominis* larva.

Surgical removal has been recommended for extraction of the larvae in migratory myiasis. *Hypoderma* larva can be extracted through a cruciate excision [13]. As the larva of *Gasterophilus* species are superficially located in the skin, they can be extracted by simply making a small incision over the leading edge of the advancing lesion and using the tip of sterile needle to remove the larva [14, 15].

Debridement and irrigation has been advocated for removal of larvae from wound myiasis, along with treatment of secondary infection [16]. In most cases, a first generation cephalosporin would be appropriate, as the most common cause of infection is methicillin-sensitive *Staphylococcus aureus*.

Topical ivermectin has been used to treat wound myiasis caused by *C. hominivorax*, and oral ivermectin has been employed in the management of cavitary myiasis, where manual removal of larvae would be painful and unpleasant, and also in infestation with *Hypoderma* [17].

Table 21.1 provides a summary of the major organisms that result in myiasis. The table includes scientific and common names for the larvae, their typical geographic location, usual clinical presentation, most common time of presentation, and treatment options.

### References


CHAPTER 22

Persistent Insect Bites

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Key points

- Persistent or recurring single or multiple urticarial papules occurring during or after travel are most likely to be persistent insect bites/papular urticaria.
- Persistent insect bites are commonly caused by mosquitoes, fleas, flies, bedbugs, lice, or mites.
- Persistent insect bites occur in formerly naive individuals: infants in endemic areas, or travelers naive to the area.
- The severe itch often leads to scratching and bacterial superinfection.
- Protective clothing, insect repellents containing \( N,N\)-diethyl-3-methylbenzamide (DEET) or picaridin, and permethrin-impregnated bed nets are effective preventive measures.

Introduction

Travelers to tropical or subtropical countries almost inevitably encounter biting and stinging insects. Such an encounter usually leads to an annoying itchy urticarial papule, which disappears in a few hours or days. Persistent insect bites or papular urticaria (PU) do not disappear for weeks to months or come and go for long periods after the original bite or bites. Flare-ups may be precipitated by new bites elsewhere on the skin. A generalized response shows numerous pruritic papules, often occurring in crops, always with excoriations and these are easily secondarily infected. The actual terminology for these conditions remains somewhat unclear although it now appears to be generally accepted that PU are a hypersensitivity response to arthropods. In this chapter, I use the term persistent insect bite for the persisting or recurring lesion at the site of a bite, the term PU for the response consisting of numerous pruritic papules.
Epidemiology

Insects are found all over the world. Insects, which have commonly been implicated in persistent insect bite reactions are mosquitoes and fleas, others are flies, bedbugs, lice, and mites, though virtually any arthropod should be considered to be able to induce persistent reactions or PU [1, 2]. Mosquitoes are significant for their prime role in transmission of numerous diseases such as malaria, filariasis, encephalitis, dengue, and yellow fever. Approximately, 3000 species of mosquito have been described. Mosquitoes have six legs, two wings, two antennae, and a proboscis for sucking blood [3]. Female mosquitoes are the bloodsucking insects; they need blood to be able to produce eggs. Both males and females feed on nectar. Mosquitoes breed in wet swampy areas. Any amount of still water may become a breeding ground for mosquitoes. In rural areas, not only large rice fields but also small ponds or wells may host mosquito eggs. In urban areas, any ditch, pot, or gutter holding water will do. Mosquitoes will bite on exposed skin areas.

Fleas are wingless insects, which feed on birds and mammals. They cannot fly but are fast movers and may jump up from the floor to about knee-high. Therefore, fleabites typically appear around the ankles and lower legs. Pets such as dogs and cats carry fleas into homes worldwide. Human fleas are also widespread, but prevail in areas of poverty.

Bedbugs have become a major challenge over the past decade, as their incidence has increased and their control has been hampered by resistance to commonly used pesticides. They hide in bed headboards, furniture, and mattresses, and behind wallpaper during the day and come out at night to feed on the sleeping victim in the bed. They can travel along with their victims in clothing and other luggage.

Pathogenesis

The exact pathogenesis of persistent insect bite reactions and PU is still unclear. Several immune mechanisms have been implicated. Both immediate and delayed hypersensitivity reactions play a role. Skin tests with deer ked extract in five patients with persistent reactions to deer ked bites showed positive delayed reactions in all patients, and immediate reactions in three patients. All six controls were negative [4]. Penneys [5] studied circulating IgG antibodies to mosquito salivary gland proteins in relation to intensity of exposure to mosquitoes in 13 individuals. In those with a history of little or average exposure, antibody binding was found; in those with extensive exposure, little antibody binding was found. This seems to correlate with the skin reactions where massive exposure to mosquito
bites at an early age leads to tolerance. Cuellar et al. found that children with 2–5 years duration of PU due to fleabites evidenced more IgE bands than those with shorter or longer years duration of symptoms. In sera from healthy children and those with shorter than 2 or longer than 5 years duration of PU IgG1 and IgG3 recognized a greater proportion of proteins from flea abstract [6]. The same group studied the role of dendritic cells (DCs) in 10 patients with PU and found that the involvement of DCs in an immune response produced in PU is mediated through the altered expression of membrane molecules [7]. Heng et al. [8] found immunoglobulin and complement deposits in the skin of three patients with PU, suggesting a role for immune complexes in the pathogenesis with complement activation initiated through the classical pathway. Jordaan and Schneider [9] did not find immunoglobulin or complement deposits in their group of 30 patients.

However, there are distinct stages in mosquito- and fleabite immunity that have been consistently described by several authors [5,10]:

1. A 5–7 day induction phase without symptoms.
2. Initiation of delayed hypersensitivity. After a few weeks pruritic papules or vesicles appear within a day after a fresh bite and may persist for weeks.
3. Immediate hypersensitivity (IgE-mediated) consisting of urticarial wheals within 30 minutes after a bite, followed by a late delayed reaction consisting of pruritic papules that may persist for weeks. The delayed reaction gradually fades leaving:
   - (a) an immediate reaction only; and
   - (b) ultimately a lack of reaction (tolerance).

Children between the ages of 1 month and 7 years worldwide go through these phases as they meet insects, respond to them, and develop tolerance [11, 12]. After developing tolerance, they will respond to repeated bites in the same way as most adults. They only develop a transient wheal but do not develop persistent papules. When persistent insect bites or PU develop in travelers, they have presumably been exposed to insect antigens that were new to them and start their response in stage 1, in contrast to the more commonly occurring immediate response to familiar insects. Unfortunately in travelers it is often impossible to identify the offending insect.

Travelers returning home from a 2- or 3-week holiday will often state that their itchy rash started on the way home or during the last few days of their holiday. This correlates with development stages described earlier. In many of them, the next few weeks are symptomatic and the reaction then fades leaving them free of symptoms presumably because contact with the offending insect has ceased. The reaction may recur upon returning to the same area. In some people, the lesions persist or keep flaring up for months to years after returning home however. Calnan [13] postulates
that this may be due to occult continued exposure, cross-sensitivity to another antigen, or continued presence of the allergen (saliva, broken off mouthpart) in the skin.

**Clinical picture**

The immediate response to an insect bite consists of the classic wheal and flare reaction. A typical persistent insect bite presents as a pruritic urticarial papule located on exposed skin (Figure 22.1).

The papule may be 2–10 mm in diameter. Sometimes, a (micro)vesicle surmounts the papule. Bullous reactions also occur. Larger lesions may appear as plaques. In PU, numerous erythematous urticarial papules are found in clusters or groups, often on exposed skin (Figure 22.2), or in a generalized distribution (Figure 22.3).

Because of severe itchiness, the lesions are often excoriated. In time, the papules become firm and hyperpigmented (Figure 22.4).

Long-standing severely itching persistent insect bites may progress to prurigo nodularis. Scratching in warm and humid climates easily leads to bacterial superinfection with Staphylococcus aureus or Streptococcus pyogenes (Figure 22.5).

When travelers have excoriated insect bites on the lower legs, a long flight home, with resulting edema of the lower legs, may delay healing [14]. Large ulcers may be the result.

*Figure 22.1* Persistent insect bite recurring on the arm of a traveler 2 weeks after returning from Thailand
In immunocompromised patients such as AIDS patients and patients with chronic lymphocytic leukemia, very severe papulovesicular and bullous, delayed and persistent, reactions to insect bites have been seen [15,16].
Figure 22.4 Long-standing persistent insect bites with lichenification and hyperpigmentation

**Histopathology**

Jordaan and Schneider [9] studied the histopathologic features of lesions in 30 children with PU in South Africa. More than 50% of their cases showed mild acanthosis, mild spongiosis, exocytosis of lymphocytes, mild subepidermal edema, extravasation of erythrocytes, a superficial and deep moderately dense mixed inflammatory cell infiltrate and interstitial eosinophils. They stress that the histopathologic features of PU are not specific, and describe four histopathologic variants: lymphocytic, eosinophilic, neutrophilic, and mixed variants. Garcia *et al.* [10] studied the histopathologic features of papules and wheals in 45 Colombian

Figure 22.5 Excoriated insect bites with bacterial superinfection
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patients and found a mainly perivascular and superficial inflammatory infiltrate with mixed population of mononuclear cells and granulocytes, mainly eosinophils. The wheals and papules could not be differentiated histologically. Rantanen [4] studied 11 skin biopsies from 19 patients with persistent pruritic papules from deer ked bites. The lesions were between 1 day and 4½ months old. All showed an insect bite reaction: a marked dermal mononuclear infiltrate with various admixtures of eosinophils, sometimes reaching the subcutis. Plasma cells and macrophages were frequent, especially in old papules. The histological features are consistent with persistent insect bite reaction.

Treatment and prevention

In treatment of persistent insect bites and PU one should aim to:

1. provide symptomatic relief;
2. identify and remove the offending insect; and
3. prevent recurrence.

Treatment can be extremely difficult. Symptomatic relief is gained primarily with topical corticosteroids. Single bites are mostly treated with potent corticosteroids, or milder ones under occlusion. When this is not effective intralesional corticosteroids, excision or cryotherapie may be tried. PU may, to some extent, respond to antihistamines, especially sedative antihistamines. Topically, lotions or gels containing menthol, camphor, and/or pramoxine that may be compounded with topical corticosteroids provide some relief of pruritus, as may doxepin 5% cream. For extensive lesions with severe itch, a short course of systemic corticosteroids is sometimes required. Oral antibiotics are needed in superinfection. Despite these options lesions may persist and cause severe pruritus. Beacham and Kurgansky [17] successfully treated two patients with psoralen plus ultraviolet (PUVA) therapy; Millikan [18] used a modified Goeckerman-type regime. In analogy to treatment options for nodular prurigo, Naafs [19] suggests thalidomide and cyclosporin in severe recalcitrant cases.

Identifying the offending insect in travelers is very difficult. People will usually remember being bitten but often have no idea what actually bit them. The distribution pattern of the lesions on the body may be helpful. Millikan [18] proposed the following diagnostic patterns: bites found on exposed areas may be caused by mosquitoes, flies, gnats, scabies, and other mites; bites on ventral surfaces by mites other than scabies and bugs; and bites around elastic areas of clothing by ticks, bugs, and Lepidoptera (moths). Household pets may carry fleas and should be examined
and treated. Bedding and clothing may harbor bedbugs. These should be sought and exterminated.

Protection from insect bites is best achieved by wearing protective clothing.

Insect repellents containing $N,N$-diethyl-3-methylbenzamide (DEET) have been considered by far the most effective protection against insect bites since the 1950s. It is effective against all insects, for example, mosquitoes, flies, mites and fleas, and many arthropods including ticks, and safe to use. DEET is available in concentrations of 5–95% and its duration of activity is directly related to the concentration used, up to a plateau at 50% concentration. Fradin and Day [20] found that a 6.65% formulation protects for 2 hours, a 23.8% concentration for an average 5 hours. DEET 20–33% with extended duration protects 6–12 hours [21]. Over recent years picaridin (KBR 3023)-based insect repellents have gained popularity. They are available in 7% (3–4 hours protection) and 15% (6–8 hours protection) formulations. Although there are few comparative studies, the effectivity of picaridin against mosquitoes, flies, and ticks appears to be similar to that of DEET. In addition, picaridin has the advantage of being odorless, not greasy, and relatively pleasant to apply. It does not damage plastic the way DEET does and is less irritative to the skin. Oil of lemon eucalyptus (active ingredient: $p$-menthane 3,8-diol (PMD)), a plant-based repellent, provides protection against malaria mosquitoes, with similar effectiveness as low concentration DEET and picaridin formulations. It is not proven to be effective for ticks [21].

When used according to the manufacturers instruction, DEET in its current formulation is considered safe to use, even in children (over the age of 2 months), in doses ranging from 10% to 30% depending on the expected time of exposure. Instructions include once daily application, application to exposed skin only (no occlusion), no direct application to hands and face, and washing the product off when returning indoor. The lowest feasible concentration should be used because of reported serious neurotoxic side effects. Picaridin has low toxicity but is not recommended for use in children under the age of 2 years. Oil of lemon should not be used under the age of 3 years. Permethrin 0.5% has been in use since 1973 as a highly effective repellent and is used to impregnate clothing, shoes, and bed nets. It should not be applied to the skin.

References


CHAPTER 23

Beetle Dermatitis

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Key points

- Beetle dermatitis is a toxic inflammatory skin reaction, commonly blisters (blistering beetle dermatitis, BBD).
- Sometimes resembles contact dermatitis.
- Skin lesions usually develop some hours after contact with beetles.
- Differential diagnosis: herpes virus infections, liquid burns, phototoxic reactions, allergic and irritant contact dermatitis.
- Characteristic clinical features are linear appearance of skin lesions, predilection sites, and the presence of kissing lesions; histopathology can be helpful in unclear cases.
- No specific treatment available. First approach rinsing the skin lesion with water. Topical corticosteroids and systemic antihistamines helpful in case of severe itch.

Introduction

Beetles (Order Coleoptera) comprise 40% of all known insects. Today about 370,000 species of beetles have been identified [1], but only a few of them are relevant in human medicine (Table 23.1). They are found in almost all habitats, are mainly terrestrial, and the majority of them feed on plants or debris, whereas some are predaceous on other insects. The life cycle of beetles involves larval and pupal stages before emergence of the adult. Adult beetles are usually 7–15 mm long and generally characterized by a particularly hard exoskeleton and leathery forewings (elytra) [1–3].

Beetle dermatitis is an inflammatory skin reaction, which is commonly blistering (blistering beetle dermatitis, BBD) and sometimes resembles contact dermatitis. Skin lesions usually develop some hours after contact with beetles and are caused by contact with their toxic body fluids after crushing of the insect on the skin [1–3]. Those toxins are, for example, cantharidin (families Meloidae and Oedemeridae) and pederin (genus Paederus) [1]. Depending on the location of toxin contact, the eyes may be affected with
## Table 23.1 Overview of human pathogenic beetles and their relevance in human medicine

<table>
<thead>
<tr>
<th>Suborder</th>
<th>Polyphaga</th>
<th>Adephaga</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>Coleoptera</td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>Meloidae</td>
<td>Oedemeridae</td>
</tr>
<tr>
<td>Genus (Example)</td>
<td>Lytta vesicatoria (Spanish fly)</td>
<td>Helocis repanda</td>
</tr>
<tr>
<td></td>
<td>Mylabris</td>
<td>Oxycopis thoracica</td>
</tr>
<tr>
<td></td>
<td>Epicauta</td>
<td>Ditylus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paederus fuscipes litoralis</td>
</tr>
<tr>
<td>Features</td>
<td>Adults are rather soft-bodied, long-legged beetles with the head deflexed, fully exposed, and abruptly constricted behind to form an unusually narrow neck, the pronotum much narrower at the anterior end than the posterior and not carinate (keeled) laterally, the forecoxal cavities open behind.</td>
<td>Prothorax is widest in the front half, narrowing towards the elytra. The elytra are parallel sided and often finely ridged. The antennae are threadlike but are slightly saw-toothed in a few species.</td>
</tr>
<tr>
<td>Venom</td>
<td>Cantharidin</td>
<td></td>
</tr>
<tr>
<td>Toxical effect</td>
<td>Cantharidin penetrates the epidermis readily and produces violent superficial irritation, resulting in vesication a few hours later. If sufficient quantities are absorbed topically, renal dysfunction may result (Frazier).</td>
<td>Highly toxic alkaloid, which causes acute dermatitis after 12–36 with burning sensations, erythema and blistering.</td>
</tr>
</tbody>
</table>

Venom Cantharidin Pederin Adephagan are fantastic producers of chemicals in a variety of forms. These chemical characters are, for the most part, clearly understudied in many groups.
conjunctivitis and keratitis [4]. Although not life threatening, beetle dermatitis can cause very annoying, and in some cases, very painful lesions with secondary scarring. It is a quite common problem in many regions of the world, most frequently seen in regions with a warm climate with an increasing incidence due to global warming [5]. Three families of beetles are mainly responsible for beetle dermatitis (Table 23.1) [6]:

1. Meloidae
2. Oedemeridae
3. Staphylinidae

**Epidemiology and geographic distribution of beetles inducing skin reactions**

**Meloidae**

The archetype for BBD is the eruption produced by species of the family Meloidae. More than 200 worldwide distributed meloid species are known to produce BBD [7, 8]. The most notorious of the meloid blister beetles is *Lytta vesicatoria*, the “Spanish fly,” which is found in southern Europe in the summer when BBD occurs.

**Oedemeridae**

The least known family to cause BBD is the Oedemeridae. In contrast to reports of Meloidae, the reports of oedemerid BBD are limited to the Pacific Basin and the Caribbean. Approximately 1500 species of Oedemeridae are found worldwide and are attracted by white light [9].

**Staphylinidae**

Staphylinidae (rove beetle) is the largest of these families, containing at least 26,000 species worldwide. Rove beetles are slender elongated insects ranging from 5 to 10 mm length. Although they have wings and are able to fly, they have a tendency to crawl and run with extreme agility, resulting in a superficial similarity to ants. When disturbed, they commonly arch their abdomen up over their body in a scorpion like posture. Within the family of Staphylinidae, members with vesicating properties are limited to the genus *Paederus*, numbering more than 600 species (Figure 23.1) [2]. *Paederus* species are worldwide distributed and prefer moist habitats. They feed not only on decaying vegetables and animal matter but are also predatory on other small insects. They are nocturnal and attracted by incandescent light, a feature that commonly brings them into contact with humans.

Outbreaks of beetle dermatitis caused by *Paederus* species may affect some hundred individuals and usually occur in crowded or poor accommodation, in a humid and tropical environment, and locations near bright
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Figure 23.1 Beetle of the species *Paederus fuscipes*, one of the most common causes of blistering beetle dermatitis

lights. Recent outbreaks, for example, have been reported from an US military base in Iraq [10], a factory in China [11], a suburban hospital in South India [12], and a primary school in Malaysia [13].

**Adephagan beetles**

The coleopteran suborder Adephaga is divided into two groups on the basis of their habitat, namely, aquatic Hydradephaga and terrestrial Geadephaga. The taxonomy and systematics of the at least 11 adephagan families is not well resolved, yet, and many of the more than 40,000 known species show a specialized, species specific behavior. Most species are predators, but some feed algae or pollen, or live as ectoparasits on other insects. The habitats of terrestrial species range from rain forests to alpine regions. Typically, adephagan species possess paired pygidial glands located posterodorsally in the abdomen. These glands produce and secrete a variety of chemicals for defending purposes, such as aromatic aldehydes or norsesquiterpenes. All Adephaga deliver compounds in one of three ways depending on taxon. These are:

1. **Oozing**
2. **Forceful spraying**
3. **Crepitation**

The glands of some genus (e.g., *Dytiscidae*) are not equipped with muscles for discharging large amounts of substance. Therefore, chemicals ooze out from the glandular openings. This is in part facilitated by turgor pressure and by indirect action of nearby muscles. In contrast, many genus, most notably *Carabidae*, have intrinsic muscles directly associated
with the glands. In this case, secretions can be ejected with varying amounts of force. For example, *Pasimachus subsulcatus* was found to be capable of forcibly discharging a spray of several centimeters [14]. The final and most stunning type of delivery, crepitation, is limited to the brachinine lineage of *Carabidae* and near related lineages. In case of defense, these beetles squirt a hot spray of water and steam at 100°C containing chemical noxes on predators [15]. The accompanying popping sound led them to be called bombardier beetles. Their preferred habitats comprise temperate climate zones.

**Pathomechanisms and clinical appearance of beetle dermatitis**

Beetle dermatitis develops due to skin contact with highly potent irritants contained in the body fluids of beetles. These irritants are released when the insects are brushed, pressed, or crushed against the skin [1]. Usually beetles do not have a bite or sting venomous to humans. The patient may be unaware of contact with the insect because the primary contact with the beetle is painless and rarely recalled. The most common seen clinical feature of beetle dermatitis is a toxic-irritative dermatitis with blistering eruptions. An overview of cutaneous reactions is given in Table 23.2. The

<table>
<thead>
<tr>
<th>Toxic</th>
<th>Toxic by hair of pillars</th>
<th>Allergic</th>
<th>Stings or bites</th>
<th>Transferred disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cantharidin, Pederin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloidae</td>
<td>Oedemeridae</td>
<td>Staphylinidae</td>
<td>Dermestes</td>
<td><em>Zabrotes subfasciatus</em></td>
</tr>
<tr>
<td>Clinic</td>
<td>Blister beetle dermatitis</td>
<td>Histaminliberation on the affected skin area</td>
<td>Allergic rhinitis and conjunctivitis</td>
<td>Injuries caused by bites</td>
</tr>
</tbody>
</table>
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Figure 23.2 Beetle dermatitis induced by Paederus spp. on the forearm

reactions are listed in the various modes of skin contact and pathophysiologic responses. By far the most common manifestation of beetle-induced reactions in human beings is the blister dermatitis, so subsequently we have concentrated on them. The lesions are erythematovesicular to start with, but within a day or two turn necrotic, giving rise to a burnt or charred appearance (Figure 23.2). In this stage, symptoms like burning, itching, and pain are almost always associated. A characteristic feature is the development of kissing lesions, where a blister comes into contact with another area.

**Meloidae, Oedemeridae**

Skin blisters due to Meloidae and Oedemeridae are caused by cantharidin, which is an odorless bicyclic terpene (exo-1,2-cis-dimethyl-3,6-ep-oxyhexahydro-phthalic anhydride) [16]. Cantharidin is stored in the hemolymph, genitalia, and some other compartments of the beetles. It is an inhibitor of the protein phosphatases 1 and 2A and releases or activates neutral serine proteases that act specifically on the dense desmosomal plaque [17]. The progressive disappearance of the dense desmosomal plaque leads to the detachment of tonofilaments from desmosomes with the appearance an intraepidermal blister and of acanthosis [18, 19]. The action of cantharidin after skin contact is usually restricted to the epidermis, therefore lesions heal without scarring.

Clinically, the contact with cantharidin causes no skin reaction or pain initially. Nevertheless, after 2–3 hours the first skin reaction is a localized erythema that develops at the site where the beetle was crushed. After 2–4 days often linear, itchy and increasingly painful blisters on a red rash occur [20]. The lesions of oedemerid BBD appear to be smaller than those
of meloid BBD because most oedermerid species are smaller than meloids. Of note, there is a high interindividual variation in susceptibility to blistering from cantharidin as some subjects never develop blisters despite heavy exposure. Skin lesions usually heal within 1 week but may remain itchy for some time. Postinflammatory hyperpigmentation may persist for months.

Taken into account that up to 6 mg of cantharidin were found in one meloid beetle (normal range 0.2–0.7 mg, females have significant lower concentrations than males), systemic intoxication after ingestion of the agent is a possible scenario, especially in children [16]. Symptoms develop 2–4 hours after ingestion and comprise hematemesis, fever, impaired consciousness, and/or convulsion [21].

**Staphylininae**

*Paederus* (Staphylininae) species produce pederin. It is biochemically different to cantharidin; therefore, pederin BBD clinically differs compared with that caused by Meloidae and Oedemeridae. Pederin is a highly toxic amide with two tetrahydropyran rings. It is only produced by female beetles, and males and larvae store maternally derived pederin in their hemoplymph. The manufacture of pederin is the result of endosymbiosis of *Pseudomonas* species that live within *Paederus* [2,22]. Pederin blocks mitoses, inhibits DNA and protein synthesis, and releases epidermal proteases that lead to blister formation [2].

Patients of all age groups can be affected, depending on the patient’s outdoor activities and the beetle habitat. Several patients recalled walking through a spider web before developing the rash. The crushing of *Paederus* beetles on the skin has no immediate effect, but in clinical experience and observations acute dermatitis appears within 12–36 hours after contact with the irritant. Due to delayed onset of symptoms, contact with the insect is only rarely recalled. Skin lesions correspond in shape and dimension to the area over which the substance was released. Clinically, *Paederus* dermatitis in characterized by sudden onset of stinging and burning sensations with vesicles and pustules on erythematosus skin. Blisters are usually described as being multiple and minute, although many cases with bullae up to 1 cm of diameter are described. Lesions typically appear linear and striking diagnostic clues are kissing ulcers and drip marks. Skin lesions predominantly affect exposed areas, especially the face, neck, shoulders, and forearms. Sporadic lesions are also reported on the chest and abdomen.

Pederin caused skin lesions are usually of a greater severity than those caused by cantharidin. Skin lesions usually heal within 1–2 weeks, but in some cases, lesions persist for a longer time and may remain itchy for
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some time. Complications comprise postinflammatory hyperpigmentation, secondary infections, and extensive exfoliating or ulcering dermatitis [2].

Ocular involvement is a relatively common finding. It is usually caused by transfer of pederin from the skin to the eyes by the finger, although ocular symptoms may be the only manifestation. It usually presents with unilateral periorbital dermatitis, but some patients develop severe periorbital edema or keratoconjunctivitis (“Nairobi eye”) [23]. Systemic involvement due to pederin intoxication is described in only a few anecdotic cases.

Diagnostic procedures

Diagnosis of beetle dermatitis can be easily made in most cases by the clinical history and the typical cutaneous lesions. However, histopathology may provide useful information. Oedemerid and meloid BBD show identical histopathologic features. Early lesions are characterized by a neutrophilic spongiosis with intraepidermal vesiculation. In contrast, late lesions show epidermal necrosis with a surviving layer of suprabasal cells. In some areas even the basal layer may be destroyed and rarely epithelial necrosis extends down to hair follicles to the level of the sebaceous duct. There is also a moderate perivascular and interstitial infiltrate of lymphocytes and histiocytes in the superficial and mid-dermis. Neutrophils are found superficially and associated with papillary edema, whereas eosinophils are rare.

Exposure to pederin causes a wider spectrum of histopathologic changes, ranging from epidermal necrosis and blistering in the acute stages to marked acanthosis with mitotic figures in the late stages. Pederin dermatitis is an entomologic model of irritant contact dermatitis, having histopathologic features of intraepidermal and subepidermal blistering, epidermal necrosis, and acanthosis [23].

Differential diagnosis

Beetle dermatitis may be confused with herpes virus infections, liquid burns, phototoxic reactions, and allergic and irritant contact dermatitis. Characteristic clinical features of BBD such as linear appearance of skin lesions, predilection sites and the presence of kissing lesions in synopsis with histopathology should enable for the right diagnosis.

Prevention and treatment

However, insecticides are an efficient—not always very environment-friendly way—to reduce the number of insects including beetles. In
densely populated buildings such as hospitals, it is sometimes mandatory to treat rooms with insecticides to prevent epidemics of beetle dermatitis [12, 13]. Repellents, which by definition are used to remove arthropods from the host, are effective only at a certain extent to avoid beetle contact. An effective way to prevent beetle contact during the night is the use of mosquito nets treated with insecticides as used very effectively in the prophylaxis of malaria. People living in endemic areas furthermore should learn to recognize beetles in order to avoid crushing them on the skin [23].

There is no specific treatment available due to the toxic nature of the lesions. The first treatment approach especially in fresh lesions should be to rinse the skin lesion with water [2]. Topical corticosteroids and systemic antihistamines may be helpful in case of severe itch; nevertheless both treatments are of limited effect. Antibiotics are valuable to prevent superinfections. In many cases, analgesics are needed due to sometimes very strong pain related to the skin lesions.

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CHAPTER 24

Aquatic Skin Disorders

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Key points

- Aquatic skin disorders are more frequently seen.
- Most encountered are cnidarian envenomations, which:
  - can cause systemic reactions;
  - may be recurrent without new envenomations; and
  - need treatment after contact.
- In fresh and salt water specific bacterial infections are found:
  - Commonly used antibiotics are not useful in most cases.
- Wounds acquired in the aquatic environment may take longer time to heal.

Introduction

More than 70% of our earth is covered with water. For that reason is it not strange that more dermatoses related to the aquatic environment are seen by dermatologists and other doctors? Due to the increase in modern mobility with low fare rates, people tend to travel to more exotic places for leisure aquatic activities or to practice aquatic sports. Also, there is a demographic trend to move to coastal areas. Another fact is that people wear less protection when it comes to bathing suits. Marine creatures have the most potent venom known to humans; some are life threatening. For this reason, it is important to recognize the cutaneous and systemic symptoms in order to make a correct diagnosis and give adequate treatment. Aquatic dermatology is not taught in residency training programs. The first major book was published in 1978 by Fisher: *Atlas of Aquatic Dermatology*. In 1985, Mandojana and Letot published *Dermatologie Aquatique*. In 1987, an issue of *Clinics in Dermatology* was dedicated to aquatic dermatology. The chapters were written by 29 contributors. Williamson published in 1987 *The Marine Stinger Guide*, which gave excellent information about the aquatic creatures in the Australian area. Mandojana was the first to attempt to get
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a systemic approach in the field of aquatic dermatology. They are ordered to the type of mechanism (e.g., sting and bite) involved [1]:

1 Irritation (contact dermatitis):
   (a) Direct chemical (allergic and toxic), jellyfish, chlorinated water, sponges, algae, sea cucumbers, sea moss, fish, and so on.
   (b) *Diving gear*: irritant, allergic, and toxic.

2 Infection:
   (a) *Primary*: cercarial dermatitis or “swimmer’s itch” (*Schistosoma* species).
   (b) *Secondary*: bacteria (*Pseudomonas* species), mycobacterioses (*Mycobacterium marinum*), bacilli (*Erysipelothrix* species), *Vibrio* species, algae (*Prototheca* species) and other miscellaneous infections.

3 Wounds.
   (a) *Active*: stings (hydroids, Portuguese man-of-war, shells (cones), puncture, and suction (cephalopods (Octopi)) wounds (annelids (leeches)), and abrasion (elasmobranches: manta ray skin), and so on.
   (b) *Passive*: abrasions and cuts (corals), punctures (fish spines, spiny creatures (echinoderms)), spiculous creatures (sponges), bristly creatures (worms), and so on.

4 Hypersensitivity reactions: aquagenic urticaria, aquagenic pruritus of the elderly, aquagenic pruritus, and “bath itch” (polycythemia rubra vera).

5 Aquatic sports-related lesions: “swimmer’s ear,” water-ski cord strangulation of extremities, and so on.

6 Dermatitis by ingestion: scrombroid fish (tuna, etc.) and ciguatera (usually by large tropical fishes).

7 Bites:
   (a) *Serious*: destructive (sharks, moray eels, etc.) and venomous (sea snakes, etc.).
   (b) *Other*: fishes, worms, sea lice, and miscellaneous.

8 *Barotrauma*: mask and diving suit squeeze.

9 *Electric shock*: fresh water electric eels, and so on.

In this chapter, the most important and most frequently occurring aquatic dermatoses are discussed.

**Cnidarian envenomations**

The phylum Cnidaria (formerly known as coelenterata) encompasses three major classes:

1 *Scyphozoa* (jellyfish)

2 *Hydrozoa*: (hydroids, “fire-coral,” Portuguese man of war)

3 *Anthozoa*: (sea anemones and hard and soft corals)
Cnidarian stings are the most frequently encountered injuries in the aquatic environment. Thus far 9000 cnidarian species have been identified. All of them share the same envenoming organ. The nematocyst consists of a sack-like structure (cnidoblast) filled with venom and a coiled thread (Figure 24.1).

The nematocyst can be activated by direct pressure or by changes in the direct environment. The thread penetrates the entire epidermis and the venom is directly delivered in the papillary dermis. Because of this the venom is quickly brought into the circulation. Nudibranchs and octopi that eat cnidariae use the intact nematocysts for their own protection and bring them to their skin. Tentacles broken after a storm and that float free can still sting humans. The sea bather’s eruption is caused by these free-floating parts [2]. The venom consists mainly of toxic or antigenic proteins and enzymes (collagenase, proteases, elastases, nucleases, hyaluronidase, and phosphatase). Other are histamine, histamine-releasers, serotonin and kinin-like substances [3, 4]. The most common immediate symptom of a jellyfish sting is an acute local dermatitis: a linear, urticarial erythematous eruption that follows the pattern of the contact of the tentacles. The lesions can be necrotizing or ulcerative. A burning pain or a pruritic sensation can be felt. Depending on the species, the forming of long lasting and scarring skin lesions can occur (Figure 24.2).

Recurrent eruptions from jellyfish stings are frequently reported lasting from several months up to a year. The most venomous jellyfish is the *Chironex fleckeri* (southeast pacific jellyfish). It is found in the northern and western parts of Australia.
Full thickness necrosis can occur in several days after contact. Other systemic reactions can lead to hemolysis, acute renal failure, cardiac and respiratory arrest. Fatalities may occur in 10–20% of the *C. fleckeri* stings. An antivenom is available for *C. fleckeri* envenomations [5]. From a dermatological point, it is important to treat the eruption with potent steroids (sometimes even systemic) to prevent chronic reactions and postinflammatory hypo- or hyperpigmentation with severe scarring or atrophy. Secondary infection by aquatic bacteriae is common.

**Systemic reactions**
Some jellyfish can provoke systemic, toxic reactions. This may include headache, malaise, weakness, diaphoresis, and lacrimation. Less common are ataxia, dizziness, fainting, local cramping, muscle spasms, convulsions, paresthesias, arthralgia, chills, vomiting, diarrhea, blurred vision, throat constriction, respiratory depression, and coma. The best way is to avoid the contact with these organisms. Wearing special protective clothing can make a big difference in the contact [5, 6]. During the Chironex season in Australia, beaches are protected by special nets. The public is well informed when there are sightings (Figure 24.3).

**Treatment**
Avoid further nematocyst discharge and immobilize the extremity. The inactivation of the nematocysts is best done by pouring vinegar (4–6% acetic acid) on the afflicted area for at least 30 seconds. Some authors
promote the use of meat tenderizer although its effectiveness has never been established. Most of the venoms are thermo-labile. For that reason apply local hot water (42–45°C). Remove the tentacles with a raiser or C-card. Check the ABC (airway, breathing, and circulation) and treat the systemic reactions with epinephrine, corticosteroids and antihistamines [2,5,6].

Hydrozoa and Anthozoa can cause a milder stinging sensation with erythematic and swelling. In a later stage, papular urticaria, hemorrhage, morbilliform rash, and vesicular and pustular formation takes place. In the case of “fire coral” (*Millepora* spp.), not only the burning sensation can occur but also cuts from the hard lime carbonate skeleton can cause serious wounds [7, 8].

**Sponge dermatitis**

A variety of species can produce irritation when in contact with the skin. They cause this by their sharp silica spicules or by irritation like "glass
wool.” A number of sponges are toxic. Two syndromes can occur after sponge contact:

1 Pruritic dermatitis (like plant allergic contact dermatitis). The most well-known sponge that causes this is the “fire sponge” (*Tedania ignis*) that is found in the Hawaiian and Caribbean islands. In general within a few hours, the skin becomes pruritic and burns. Afterward it appears mottled and purpuric. Most reactions subside within 3–7 days. Sometimes fever, chills, malaise, dizziness, nausea, and muscle cramps occur.

2 Irritant contact dermatitis from the penetrations of the silica spicules. Severe cases can develop into an exfoliative dermatitis. There is no really effective treatment. Potent steroids provide the most benefit but they have no effect on the initial toxic reaction. Soak the affected area in vinegar (4–6% acetic acid) and use topical disinfectants [8].

**Seaweed dermatitis**

*Lyn*gh*bya majuscula* is a subtropical seaweed well known for its acute toxic reaction. After storms dislodged, fragments of seaweed enter bathing suits. The victim develops a stinging, burning, or pruritic sensation within minutes or hours. In the swimming suit area, escharotic blistering may develop. After washing with water and soap, low-potency steroids are helpful. The eruption usually subsides within a week [6,8].

**Primary infections**

**Cercarial dermatitis ("swimmer’s itch")**

This is a maculopapular cutaneous eruption caused by a *Schistosoma* species, in cercarial form derived from blood flukes that infect animals. Only a short exposure is necessary to penetrate the skin. An intense pruritic papular dermatitis of 7–10 days ensues [1,6,8].

**Sea bather’s eruption**

It has many causative agents. Most are cnidarian nematocysts. It can occur in covered or in exposed skin. After 4–24 hours after exposure, a mild macular dermatitis to a maculopapular or vesicular eruption can form. Sometimes systemic reactions occur that are similar to the ones found after cnidarian contact (Figure 24.4). Delayed reactions are reported. Symptomatic treatment remains the best option for both conditions [1,6,8].
Secondary infections

*Erysipelothrix rhusiopathiae* is a gram positive, facultative aerobic bacillus that can survive for months. The infection it causes is known as “fish handlers disease,” “seal finger,” “speck finger,” or “erysipeloid of Rosenbach.” It is known as an occupational hazard. A mild dermatitis occurs 1–7 days after a wound. There is an edematous halo circumscribed by a centrifugally advancing, raised, well-demarcated, and marginated erythematous ring around the central area. If untreated, the reaction will usually run its course in 1–3 weeks. Sometimes arthritis, septicemia, or endocarditis may occur. Aqueous penicillin G is given IV.

*Vibrio vulnificus* is a particularly virulent marine *Vibrio* (gram negative, free-living bacterium). It is found in water temperatures between 13°C and 20°C. They are natural habitants. The infected area rapidly becomes erythematous, edematous and painful, with fast spread of the cellulitis to the adjacent areas. Hemorrhagic vesicles of bullae develop at the site of primary infection. A period of necrotizing vasculitis follows that turns into necrotic ulcers (Figure 24.5). Other signs include fever-like chills and sepsis. *Vibrio vulnificus* is highly fatal by septic shock. *Vibrio para-haemolyticus* can produce similar life-threatening syndromes with necrotizing myonecrosis. After a rapid diagnosis the initial treatment with the adequate antibiotic is essential. The antibiotics of first choice are trimethoprim/sulfamethoxazole or ciprofloxacin.
Aeromonas hydrophila (gram negative) is found in fresh water. A puncture wound may become cellulitic in 8–24 hours with erythema, edema, and purulent discharge. It may resemble typical streptococcal cellulitis. The same antibiotics can be used as described by the vibrio infections.

Chromobacterium violaceum is a gram negative rod that is found in (sub)tropical fresh water rivers. The skin symptoms are secondary to bacteremia leading to diffuse pustular dermatitis, vesicles, ecchymatic macules, macupapular rash, subcutaneous nodules, ulcers, and cellulitis. It is sensitive to trimethoprim/sulfamethoxazole [1,6,8].

Venomous and nonvenomous fish stings and wounds

**Sting rays**
Wounds are either lacerations or punctures. Pain is immediate. Systemic reactions may occur. Thorough irrigation is useful, but never close the wound by sutures. Antibiotic prophylaxis may be used.

**Barracudas (Sphyraena spp.) and moray eels**
Barracudas (Sphyraena spp.) and moray eels are not aggressive. Both may strike if they are disturbed. They can hold or strike and release. The wounds must be well irrigated with fresh water. Antibiotic prophylaxis can be useful [7].

**Echinoderm (sea urchins, star fish) injuries**
Echinoderms are benthic invertebrates with a radical, symmetric collomate body. There are three classes (Echinoidea, Holothurioidea, Asteroidea).
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Figure 24.6 Sea urchin granulomas

There are hundreds of species of the sea urchin. In some species the spines, which are mostly located on the upper surface, are tipped with poisonous glands. Envenomation can also be caused by the seizing organs (pedicellariae) on the lower surface. People step on sea urchins or brush against them. This causes several puncture wounds which can be extremely painful. The broken spines remain embedded or leave the skin unbroken. A “tattooing” pattern is frequently seen. Most of the fragments are absorbed after a while or eliminated through the epidermis. If the spines enter near a joint, destruction and synovitis can occur. In the skin the development of foreign body granulomas is a regular finding after these injuries [1,6,7] (Figure 24.6).

If there is any doubt as to the diagnosis, an X-ray of the joint is useful. The spines are radio opaque. The therapy is symptomatic. Several therapies are advised by local people but their use has never been proven in studies. The Acanthaster planci (crown of thorns) is the most venomous tropical starfish (Asteroidea). They produce an acute painful puncture wound or a chronic swollen lesion with lymphadenopathy. Their spines are as hard as wood. Frequently, these injuries are complicated by infection. Wounds need to be doused with vinegar or isopropylalcohol and afterward placed in nonscalding hot water (42–45°C) [6, 7].

Bristle worms (Phylum: Annelida; Class: Polychaeta) have rows of thin, chitinous bristles that grow from the lateral parts of their bodies. When a worm is disturbed the bristles become erect. They penetrate the skin like polyester spines. Some of these are venomous. A pruritic, erythematous, papular and edematous eruption can develop with a burning sensation. Necrosis and paresthesias are rare. The wounds are self-limited but secondary infection is not rare. Remove the bigger bristles with a forceps and
the smaller ones with adhesive tape. After this, use vinegar (4–6% acetic acid). For persistent inflammatory reactions topical steroids may be useful [1,7].

As stated in the introduction the field of the aquatic dermatology is a growing one and it is not possible to highlight all the aquatic dermatoses. For that reason a brief overview of the most frequently encountered aquatic dermatoses has been presented.

References


Further reading

CHAPTER 25

Geographic Distribution

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This chapter correlates the geographical distribution with the skin diseases acquired during travel. These tables can be consulted, and can be helpful in establishing a diagnosis (Tables 25.1–25.6).

Table 25.1  Climatic zones with associated skin diseases

<table>
<thead>
<tr>
<th>Rainy Monsoon</th>
<th>Semi</th>
<th>Acid</th>
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<tbody>
<tr>
<td>Bacterial infection</td>
<td>Bacterial infection</td>
<td>Photodermatoses</td>
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<td>Superficial fungal infection</td>
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<td>Photodermatoses</td>
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<tr>
<td>Persistent insect bite</td>
<td>Persistent insect bite</td>
<td>Veld sore</td>
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<tr>
<td>Subcutaneous myiasis</td>
<td>Creeping eruption</td>
<td>Cutaneous diphtheria</td>
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<tr>
<td>Dengue</td>
<td>Dengue</td>
<td>Cutaneous leishmaniasis</td>
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Table 25.2  Common skin diseases from South and Middle America

<table>
<thead>
<tr>
<th>Travelers</th>
<th>Immigrants</th>
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<tbody>
<tr>
<td>Persistent insect bite</td>
<td>Scabies</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>Subcutaneous mycosis</td>
</tr>
<tr>
<td>Cutaneous larva migrans</td>
<td>Mycobacterial skin disease</td>
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<tr>
<td>Tungiasis</td>
<td>Leprosy</td>
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<tr>
<td>Larva currens</td>
<td>HIV-related skin disease</td>
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<tr>
<td>Aquatic dermatoses</td>
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<tr>
<td>Pyoderma</td>
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<td>Dengue</td>
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</table>
## Table 25.3  Common skin diseases from Africa

<table>
<thead>
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<th>Immigrants</th>
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<tbody>
<tr>
<td>Persistent insect bite</td>
<td>Scabies</td>
</tr>
<tr>
<td>Myiasis</td>
<td>Subcutaneous mycoses</td>
</tr>
<tr>
<td>Cutaneous larva migrans</td>
<td>Mycobacterial skin disease</td>
</tr>
<tr>
<td>Tungiasis</td>
<td>Leprosy</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis</td>
<td>Lymphatic filariasis</td>
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<td>Buruli ulcer</td>
<td>Onchocercias</td>
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<tr>
<td>Onchocercias</td>
<td>Trypanosomias</td>
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<tr>
<td>Schistosomias</td>
<td>HIV-related skin diseases</td>
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<tr>
<td>Lymphatic filariasis</td>
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<tr>
<td>Beetle dermatitis</td>
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<tr>
<td>Spider bites</td>
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<td>Pyoderma</td>
<td></td>
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<tr>
<td>Cutaneous diphtheria</td>
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<td>Rickettsial fevers (African Tick Bite Fever)</td>
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## Table 25.4  Common skin diseases from Middle East and India

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<tr>
<td>Cutaneous leishmaniasis</td>
<td>Leprosy</td>
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<tr>
<td>Pyoderma</td>
<td>HIV-related skin diseases</td>
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<tr>
<td>Chikungunya</td>
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<tr>
<td>Rickettsial fever</td>
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<td>Aquatic dermatoses</td>
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## Table 25.5  Common skin diseases from Southeast Asia

<table>
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<tr>
<td>Cutaneous larva migrans</td>
<td>Leprosy</td>
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<tr>
<td>Larva currens</td>
<td>HIV-related skin diseases</td>
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<td>Gnathostomias</td>
<td>Aquatic dermatoses</td>
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<tr>
<td>Schistosomias</td>
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<tr>
<td>Chikungunya</td>
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<td>Dengue</td>
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<tr>
<td>Typhoid</td>
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<tr>
<td>Pyoderma</td>
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Table 25.6 Common skin diseases from Australia and Oceania

<table>
<thead>
<tr>
<th>Travelers</th>
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<tr>
<td>Persistent insect bite</td>
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<td>Aquatic dermatoses</td>
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<tr>
<td>Spider bites</td>
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</table>
When suspecting an imported skin disease, the reader can consult one of the following flow charts. The charts present a symptomatic approach with the following clinical entities (Figures 26.1–26.6):

1. Itch
2. Ulceration
3. Fever and rash
4. Eschar
5. Nodular lymphangitis
6. Diagnosis of leprosy

---

**Figure 26.1** Itch
Figure 26.2 Ulceration

Figure 26.3 Fever and rash

Figure 26.4 Eschar
Figure 26.5 Nodular lymphangitis

Figure 26.6 Diagnosis of leprosy
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