ISSN 0001-5555

ActaDV

ACTA DERMATO-VENEREOLOGICA

Volume 100 2020 **Theme issue**

Advances in Dermatology and Venereology

A Non-profit International Journal for
Interdisciplinary Skin Research, Clinical and Experimental
Dermatology and Sexually Transmitted Diseases

Frontiers in Dermatology and Venereology

- A series of theme issues in relation to the 100-year anniversary of ActaDV

Official Journal of
- European Society for Dermatology and Psychiatry

Affiliated with
- The International Forum for the Study of Itch

Immediate Open Access

Society for Publication of
Acta Dermato-Venereologica

www.medicaljournals.se/adv

ACTA DERMATO-VENEREOLOGICA

The journal was founded in 1920 by Professor Johan Almkvist. Since 1969 ownership has been vested in the Society for Publication of Acta Dermato-Venereologica, a non-profit organization. Since 2006 the journal is published online, independently without a commercial publisher. (For further information please see the journal's website https://www.medicaljournals.se/acta)

ActaDV is a journal for clinical and experimental research in the field of dermatology and venereology and publishes high-quality papers in English dealing with new observations on basic dermatological and venereological research, as well as clinical investigations. Each volume also features a number of review articles in special areas, as well as Correspondence to the Editor to stimulate debate. New books are also reviewed. The journal has rapid publication times.

All correspondence concerning manuscripts, editorial matters and subscription should be addressed to:

Acta Dermato-Venereologica
S:t Johannesgatan 22, SE-753 12 Uppsala, Sweden

Editorial Manager, Mrs Agneta Andersson
Please send an E-mail

Editorial Assistant: Ms Anna-Maria Andersson
Please send an E-mail

Information to authors: Acta Dermato-Venereologica publishes papers/reports on scientific investigations in the field of dermatology and venereology, as well as reviews. Case reports and good preliminary clinical trials or experimental investigations are usually published as Short Communications. However, if such papers are of great news value they could still be published as full articles. Special contributions such as extensive feature articles and proceedings may be published as supplements to the journal. For detailed instructions to authors see https://www.medicaljournals.se/acta/instructions-to-author.

Publication information: Everything is Open Access and no subscription fee. For publication fees: see https://www.medicaljournals.se/acta/instructions-to-author.

Indexed in: See https://www.medicaljournals.se/acta/about/adv.

Frontiers in Dermatology and Venereology

Centenary theme issues in Volume 100 of *Acta Dermato-Venereologica*
An overview

Current issue

Cutaneous and genital infections
Theme editors: Roderick Hay and Kristian Kofoed

- Skin Infections Caused by *Staphylococcus aureus*, *P. Del Giudice*
- A Hundred Years of Diagnosing Superficial Fungal Infections: Where Do We Come From, Where Are We Now and Where Would We Like To Go? *Y. Gräser, D. M. L. Saunte*
- The Management of Scabies in the 21st Century: Past, Advances and Potentials, *C. Bernigaud, K. Fischer, O. Chosidow*
- Skin Disease in the Tropics and the Lessons that can be Learned from Leprosy and Other Neglected Diseases, *R.J. Hay*
- The Changing Spectrum of Sexually Transmitted Infections in Europe, *A. Stary*

Forthcoming issues

Skin malignancies
Theme editors: Veronique Bataille and Nicole Basset Seguin

- Melanoma Genomics, *J. A. Newton-Bishop, D. T. Bishop, M. Harland*
- Update in the Management of Basal Cell Carcinoma, *N. Basset-Seguin, F. Herms*
- Melanoma Risk and Melanocyte Biology, *J. U. Bertrand, E. Steingrimsson, F. Jouenne, B. Bressac-de Paillerets, L. Larue*
- Melanoma Epidemiology and Sun Exposure, *S. Raimondi, M. Suppa, S. Gandini*
- Biomarkers Predicting for Response and Relapse with Melanoma Systemic Therapy, *S. J. Welsh, P. G. Corrie*
- Cutaneous Melanoma – A Review of Systemic Therapies, *K. A. Lee, P. Nathan*
- It's Not all Sunshine: Non-sun-related Melanoma Risk-factors, *V. Bataille*
- Update of the Management of Cutaneous Squamous-cell Carcinoma, *E. Maubec*

Atopic dermatitis
Theme editors: Magnus Lindberg and Carl-Fredrik Wahlgren
Content details TBA

Previous issues

Itch and pruritic disorders
Theme editors: Elke Weisshaar, Tasuku Akiyama and Jacek Szepietowski

- The Challenge of Basic Itch Research, *E. Carstens, T. Follansbee, M.I. Carstens*
- Mechanisms and Management of Itch in Dry Skin, *C. Sagita Moniaga, M. Tominaga, K. Takamori*
- Non-dermatological Challenges of Chronic Itch, *A.E. Kremer, T. Mettang, E. Weisshaar*
- Itch and Psyche: Bilateral Associations, *R. Reszke, J.C. Szepietowski*
- A New Generation of Treatments for Itch, *E. Fowler, G. Yosipovitch*
- Challenges in Clinical Research and Care in Pruritus, *M.P. Pereira, C. Zeidler, M. Storck, K. Agelopoulos, W.D. Philipp-Dormston, A.G.S. Zink, S. Ständer*

Psoriasis
Theme editors: Lone Skov and Enikö Sonkoly

- Psoriasis and Genetics, *N. Dand, S. Mahil, F. Capon, C.H. Smith, M.A. Simpson and J. Barker*
- The Woronoff Ring in Psoriasis and the Mechanisms of Postinflammatory Hypopigmentation, *J. Prinz*
- Psoriasis and Treatment: Past, Present and Future Aspects, *C. Reid, C.E.M. Griffiths*
- Psoriasis and Co-morbidity, *M. Amin, E.B. Lee, T-F. Tsai, J.J. Wu*
- Pustular Psoriasis: the Dawn of a New Era, *H. Bachelez*

ActaDV
Acta Dermato-Venereologica
ActaDV
Advances in dermatology and venereology

Blistering skin disorders

Theme editor: Kaisa Tasanen

Genodermatoses

Theme editors: Anette Bygum and Matthias Schmuth

ActaDV
Acta Dermato-Venereologica
ActaDV
Advances in dermatology and venereology

CUTANEOUS AND GENITAL INFECTIONS

Theme Editors:

Roderick J. Hay and Kristian Kofoed

TABLE OF CONTENTS

REVIEW ARTICLE

Skin Infections Caused by *Staphylococcus aureus*

Pascal DEL GIUDICE
Infectiology-Dermatology Unit, Hospital of Fréjus-Saint-Raphaël, Fréjus, France

***Staphylococcus aureus* is the most common pathogen involved in skin infections worldwide, regardless of the patient's age, the climate or geographical area. The main skin clinical manifestations can be linked to a few toxins produced by the bacteria, which give rise to a rich and varied clinical spectrum. Panton Valentine leucocidin, exfoliatins, enterotoxins and toxin shock syndrome toxin 1 are the main toxins involved in most dermatological manifestations associated with *S. aureus*. Other less frequent cutaneous manifestations can occur in endocarditis, bacteraemia. Currently, the most important event is worldwide emergence of community-acquired S. aureus resistant to methicillin (CA-MRSA), mainly causing skin infections.**

Key words: skin infections; *staphylococcus aureus*; bacterial skin infections; cellulitis; furuncle; abscess.

Accepted Mar 19, 2020; Epub ahead of print Mar 24, 2020

Acta Derm Venereol 2020; 100: adv00110.

Corr: Pascal del Giudice, Service Infectiologie-Dermatologie- Centre Hospitalier Intercommunal Fréjus-Saint-Raphaël, 240 Avenue de Saint Lambert, FR-83600, Fréjus, France. E-mail: del-giudice-p@chi-fsr.fr

SIGNIFICANCE

This review describes the characteristics of *Staphylococcus aureus* infections of the skin. Most can be linked to a few toxins produced by the bacteria, which give rise to specific clinical manifestations. Panton Valentine leucocidin, exfoliatins, enterotoxins and toxin shock syndrome toxin 1 are the main toxins involved in most dermatological manifestations associated with *Staphylococcus aureus*. Unfortunately, most reports of *Staphylococcus aureus* skin infections do not consider this complexity. This review should help further research into *Staphylococcus aureus* infections of the skin to consider this rich and varied clinical spectrum.

Staphylococcus aureus is the most common pathogen involved in skin infections worldwide, regardless of the patient's age, the climate or geographical area. The main skin clinical manifestations can be linked to a few toxins produced by the bacteria. Panton Valentine leucocidin (PVL), exfoliatins (ETs), enterotoxins and toxin shock syndrome toxin 1 (TSST-1) are the main toxins involved in most dermatological manifestations associated with *S. aureus*. Other less frequent cutaneous manifestations can occur in the context of bacteraemia. The complex role of *S. aureus* in atopic dermatitis is not considered in this review. Currently, the most important event is the worldwide emergence of community-acquired *S. aureus* resistant to methicillin (CA-MRSA), which is mainly responsible for skin infections.

LOCALIZED *S. AUREUS* SKIN INFECTIONS

Localized *S. aureus* skin infections are either primary or secondary. A primary or "spontaneous" cutaneous infection is an infection occurring without preceding clinically evident lesions or secondary to a minimal skin lesion. These infections include impetigo, folliculitis, furuncles, and primary abscesses. Secondary skin infections are those occurring as a consequence of a pre-existing cutaneous lesion (usually incorrectly called "superinfections"). These include impetiginization, secondary abscesses, lymphangitis, cellulitis and secondary wound infection. This distinction between primary and secondary infection is not strict and may appear somewhat theoretical or artificial, but it allows an understanding of the physiopathology of skin infections.

Impetigo

Impetigo is an epidermal infection caused by *S. aureus*, *Streptococcus pyogenes*, or a combination of both. In northern countries *S. aureus* infections are predominant, representing 90% of the bacterial causes, whereas in developing countries *S. pyogenes* is reported to be predominant (1–5). Impetigo mainly affects children and predominates in underprivileged communities (1–5). It is contagious, with the possibility of self-inoculation and the occurrence of small family or community outbreaks.

The diagnosis of impetigo is clinical. For *S. aureus* impetigo, the primary lesion is a fragile bullae. The bullae quickly becomes inflamed and pustular and ruptures to form an oozing erosion or crust (**Fig. 1**). A frequent and typical localization in children is around the mouth, but any area of the skin can be affected. The grouping of multiple lesions can result in polycyclic erosions with circular contours. The general physical state is preserved. There is no fever; sometimes a satellite lymphadenopathy may be present. Several classical variants have been reported, such as giant impetigo, miliary impetigo, pustules, and dry impetigo. Impetigo neonatorum, previously known as pemphigus neonatorum, is generalized impetigo in neonates. Impetiginization characterizes the secondary

doi: 10.2340/00015555-3466
Acta Derm Venereol 2020; 100: adv00110

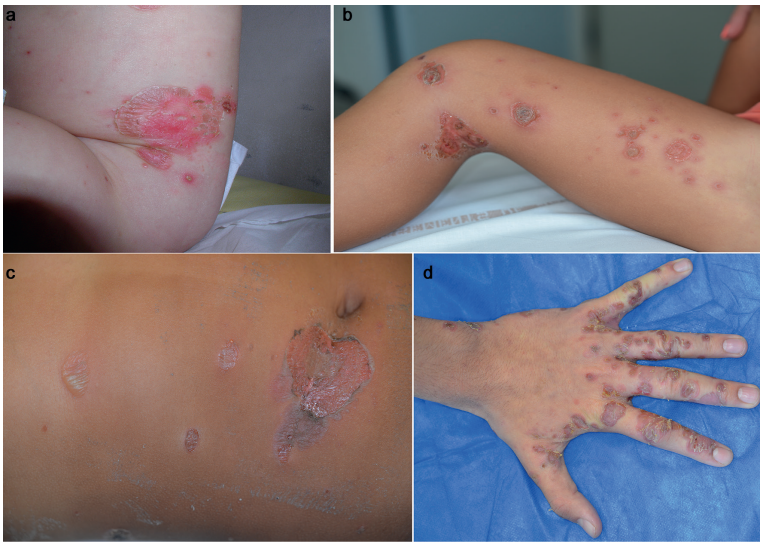

Fig 1. Different clinical presentations of impetigo: a), large dry erosive plaque on adbomen; b) crusted and oozing erosions on the lower limb; c) bullous and oozing erosive lesions on abdomen; d) multiple dry erosions of the hand.

infection by *S. aureus* of a pre-existing dermatosis, usually affecting the epidermis (e.g. eczema, chickenpox, etc.) or secondary to scratching (e.g. pediculosis, scabies, etc.) that results in impetigo or impetigo-like crusted and oozing lesions. A clinical variant of impetigo is ecthyma, in which deep ulceration forms in the dermis (more frequently with *S. pyogenes*). Scabies is a major cause of impetigo in children worldwide and, more specifically, in disadvantaged populations (6–8). Mass or individual treatment of scabies results in a decrease in the prevalence of impetigo in a community (6–8).

The pathophysiology of staphylococcal impetigo is related to the local production of exfoliatin toxins A and B (1, 9–11). The target protein of exfoliatins A and B is desmoglein 1, a desmosomal protein whose role is the cohesion between keratinocytes, and it is mainly located in the most superficial layer of the epidermis (1, 9–11). The main consequence of the action of the toxin on desmoglein 1 is rupture of keratinocyte cohesion and formation of a bullae. Although bullae are not usually reported in impetigo caused by *S. pyogenes*, a similar mechanism could be involved; the streptococcal pyrogenic exotoxin B (SpeB) has been demonstrated to be a proteolytic factor that cleaves the extracellular domains of desmoglein 1 and 3 (12).

According to Koning et al. (13) treatment with topical mupirocin and topical fusidic acid are equally effective to, or more effective than, oral treatment, except in extensive impetigo where research is lacking. Penicillin was not as effective as most other antibiotics (12, 13). Hygiene measures, such as strict attention to handwashing, must be applied to prevent recurrence and cross-transmission.

Regarding the risk of antibiotic resistance in impetigo, rare clones of methicillin-resistant *S. aureus* (MRSA) producing ETA and/or ETB and have been described, mainly from Japan (14–17). In terms of resistance in impetigo, the main concern is with fusidic acid. Resistance to fusidic acid has increased in the early 2000s in some countries of northern Europe, namely Sweden, Norway and the UK. This increase appears to have resulted from the clonal expansion of a strain designated the Epidemic European Fusidic acid resistant Impetigo Clone (EEFIC), which carries the fusidic acid resistance determinant fusB on its chromosome. The high level of use of fusidic acid ointment has been linked to the emergence and spread of fusidic acid resistant *S. aureus* (18–20).

Folliculitis

S. aureus is responsible for the majority of cases of folliculitis (infection of the pilosebaceous follicle).

Superficial folliculitis. In this condition the infection is restricted to the superficial part of the pilosebaceous follicle (follicular ostium). Clinically it manifests as a pustule, centred on a hair associated with a peri-follicular erythema. All parts of the body with high-density hair can be affected: thighs, perineum, arms, back, eyelid (stye). Sycosis barbae (**Fig. 2**), whose spread is favoured by shaving, is a particular clinical form localized on the face, characterized by extensive and chronic lesions. Differential diagnoses include folliculitis caused by other microorganisms, such as dermatophytes in kerions, *Candida albicans* in candida folliculitis, *Malassezia* folliculitis, Gram-negative folliculitis, non-infectious folliculitis (including Behcet's disease) and hidradenitis suppurativa.

Furuncle (boil). Furuncles, or boils, are characterized by a deep and necrotizing form of folliculitis with involvement of the pilosebaceous follicle in its entirety. It presents as a painful inflammatory papule or nodule, centred around a pustule on a hair-bearing area (the hair has usually disappeared due to necrosis) (**Fig. 3**). Within a few days of maturation pus will form, associated with ne-

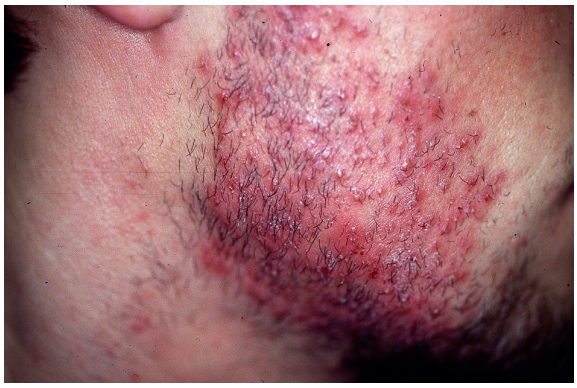

Fig. 2. Sycosis barbae.

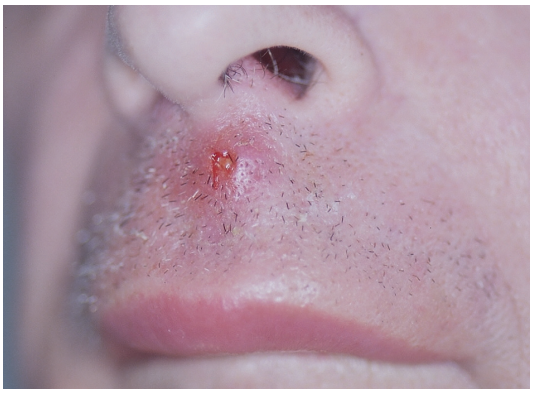

Fig. 3. Furuncle.

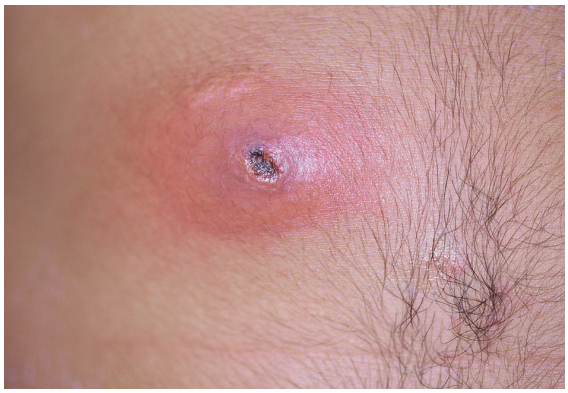

Fig. 4. Primary abscess.

crosis (21). A circular desquamative flange may surround the necrotic centre (22). In recent years it has been found that up to 90% of the *S. aureus*, isolated from furuncles in some areas produce PVL virulence factor (23–26). This leucocidin leads to local destruction of leucocytes with the formation of larger skin lesions, which respond less well to treatment and tend to recur; the organisms can also cause suppurative pneumonia.

The term "furuncle" has sometimes been used in the literature for skin infection caused by other bacteria, such as non-tuberculous mycobacteria (27), but, to avoid confusion, should be reserved for *S. aureus* infection.

A clinical variant of a furuncle is the carbuncle, defined as a cluster of furuncles. Chronic furunculosis is characterized by the repeated formation of furuncles on different parts of the body over several months (21).

Many reports of systemic infection secondary to a furuncle are reported, but this appears to be rare relative to the high frequency of furuncles. Facial malignant staphylococcal infection is a classically described infection, but nowadays it is an exceptionally rare complication of a peri-nasal furuncle leading to a septic facial venous thrombosis that can extend to the cavernous sinus (28).

Abscess

An abscess is a collection of pus. The abscess forms from a tender inflammatory and extremely painful erythematous nodule or plaque. After a few days of evolution, the consistency changes and become soft, indicating the formation of the collection of pus (**Fig. 4**). Abscesses can be primary or secondary. There is no clearly defined size in the literature for an abscess, therefore in primary abscess, the distinction between a large furuncle and a small abscess is difficult or artificial. Fever is rare, cellulitis, lymphangitis, and satellite adenopathies may be associated. The general physical state is preserved. Pus may appear after some days of spontaneous evolution, and if not drained, spontaneous skin necrosis with rupture and drainage of the pus may occur.

S. aureus is by far the main infectious bacteria isolated from abscesses. The majority of primary or spontaneous abscesses are caused by *S. aureus* producing PVL (23, 29–31). Secondary abscesses (accidental direct inoculation, drug addiction, septic injections, etc.) are most often, but not exclusively, due to *S. aureus* (32).

The treatment of suppurative skin infections is based on incision and drainage. The role of antibiotics has been summarized in recent important studies. In the study by Daum et al. (33), 786 participants with a skin abscess 5 cm or less in diameter were treated by incision and drainage and were randomly assigned to receive clindamycin, trimethoprim–sulfamethoxazole (TMP-SMX), or placebo for 10 days; the cure rate among participants in the clindamycin group was similar to that in the TMP-SMX group (221 of 266 participants (83.1%) and 215 of 263 participants (81.7%), respectively; $p=0.73$), and the cure rate in each active treatment group was higher than that in the placebo group (177 of 257 participants (68.9%), $p<0.001$ for both comparisons). Among the participants who were initially cured, new infections at 1-month follow-up were less common in the clindamycin group. Talan et al. (34) compared TMP-SMX with placebo after incision and drainage of abscesses; clinical cure of the abscess occurred in 507 of 630 participants (80.5%) in the TMP-SMX group vs. 454 of 617 participants (73.6%) in the placebo group ($p=0.005$). TMP-SMX was superior to placebo, resulting in lower rates of subsequent surgical drainage procedure, skin infections at new sites, and infections in household members.

Emergence of suppurative skin infection due to community-acquired methicillin-resistant S. aureus. Methicillin has been available since 1961, it was the first semi-synthetic penicillin resistant to penicillinase produced by most of *S. aureus* at that time (35). Its introduction was quickly followed by the appearance of MRSA (35). This resistance is linked to the synthesis of a modified penicillin-binding protein with less affinity to betalactams, PLP2a, leading to resistance to all beta-lactams (except for new cephalosporins ceftaroline and ceftobiprole). The synthesis of this PLP2a is under the control of the *mecA* gene, located on a chromosomal mobile genetic element, called the staphylococcal cassette chromosome mec or SCCmec, bordered at both ends by genes called

chromosome cassette recombinase (ccRA/ccRB or ccRC), which allow horizontal transmission between and within species. Described almost exclusively in hospitals, these hospital-acquired methicillin-resistant (HA-MRSA), clones have spread widely throughout the world. Over time, they have acquired, in addition to the *mecA* gene, other resistance genes against other classes of antibiotics, such as macrolides, fluoroquinolones or aminoglycosides (1). However, these clones are rarely involved in skin infections, except for nosocomial operative site infections.

The epidemiology of MRSA has entered a new era the last 25 years. MRSA with new characteristics have emerged in the community setting, namely outside of healthcare facilities (35–39). First reported in Oceania (Australia and New Zealand), these CA-MRSA are currently present worldwide (35–39). Most strains (80–90%) are isolated from suppurative skin infections (35–39). CA-MRSA infections have specific characteristics that clearly distinguish them from HA-MRSA (35–39); they preferentially affect a young population with no previous medical history (35–39). Unlike HA-MRSA, which are often multi-resistant, CA-MRSA generally remains sensitive to most antibiotics apart from beta-lactams. The genetic origin of CA-MRSA is different, with a few major clonal complexes with relative geographical specificity (35–39), USA 300 being the major clone in the USA. The main SCCmec cassettes for HA-MRSA (SCCmec I, II and III) are significantly longer than those for CA-MRAS (mainly SCCmec IV and V). Almost all of CA-MRSA, including the major clones, produce the PVL toxin, which explains the predominance of suppurative skin infections as clinical presentations of CA-MRSA infections. There are no clinical data to suggest that PVL CA-MRSA skin infections differ from PVL methicillin-sensitive ones (MSSA) and their relative prevalence varies in different countries. As CA-MRSA is isolated mainly from suppurative skin infections, the best way to study its epidemiology is to study those infections. Indeed, some countries, such as the USA, have a high rate of CA-MRSA, at approximately 50% of strains isolated (most USA 300) (40–42) and others have a low rate, at less than 10% (43–45). Outbreaks of CA-MRSA are regularly described mainly in different community settings (military personnel, sports teams, drug users, homosexuals, isolated communities, families, etc.) (46–50).

Acute suppurative paronychia

Acute suppurative paronychia is an acute infection of the eponychial nail folds of the hand or foot. Several bacteria may be implicated, but *S. aureus* is the most common one. The treatment is based on surgical excision; antibiotic treatment plays a minimal role (51).

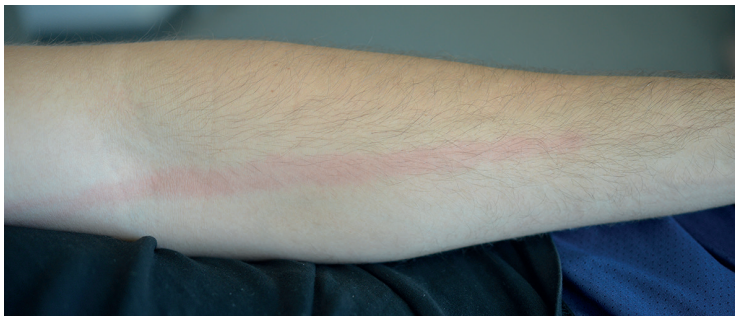

Fig. 5. Lymphangitis.

Lymphangitis

Lymphangitis is caused mainly by *S. aureus* or *S. pyogenes*. It is clinically characterized by an erythematous inflammatory linear band, which usually starts from the origin of the infection towards the draining regional lymph node, namely a local adenopathy (**Fig. 5**). Lymphangitis is sometimes accompanied by fever. Otherwise, general health state is preserved. Treatment is based on systemic antibiotic therapy.

Superficial septic thrombophlebitis

An important feature in the pathophysiology of *S. aureus* infections is its thrombotic capacity. The constitution of a vascular thrombosis allows the infection to develop and cause septic emboli and secondary locations. Staphylococcal skin infection can cause septic thrombophlebitis of the superficial venous network, which can spread to the deep veins. In hospitals, this is most often a complication related to the infection of intravenous catheters. Septic thrombophlebitis is characterized by an inflammatory indurated cord, which begins at the infected site (**Fig. 6**). Treatment is based on antibiotic therapy and treatment of the portal of entry. A particular form of such thrombophlebitis is facial malignant staphylococcal infection (see above).

Cellulitis

Cellulitis may occur associated with an abscess or a thrombophlebitis or complicate an acute or chronic wound as a result of secondary infection. It is more

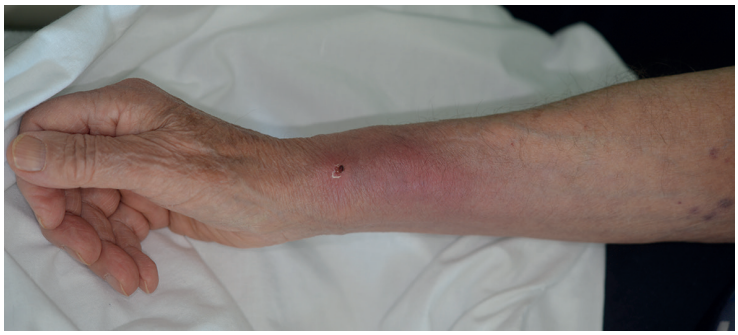

Fig. 6. Thrombophlebitis from catheter site.

common with *S. pyogenes*. The treatment is based on systemic antibiotic therapy.

Necrotizing fasciitis

A few reports of necrotizing fasciitis (NF) associated with *S. aureus* have been published. Miller et al. (52) reported 14 cases in 2005 caused by CA-MRSA. A few other isolated cases have been published since. Given the scarcity of the reports, NF caused by *S. aureus* seems exceptional.

Contiguous infections

These are related to a suppurative focus located near the skin (53). They manifest as an inflammatory mass that simulates an abscess, particularly in the vicinity of septic arthritis, osteomyelitis, bursitis, tenosynovitis or infected false aneurysms or myositis. Sometimes cutaneous fistulization occurs.

Secondary infections of acute or chronic wounds

They are a common situation in practice. Clinically, secondary infections show local inflammatory signs (pain, erythema) or cellulitis, and the possible presence of pus (54). The isolation of *S. aureus* in a wound is not synonymous with local infection, but must be interpreted according to the clinical presentation and, especially, the presence of inflammatory signs. The distinction between secondary infection and colonization may be difficult.

Botryomycosis

S. aureus can cause botryomycosis, a rare, chronic and granulomatous infection characterized by painless slow-growing papulonodules, abscesses and ulcers and, histopathologically, the presence of granules composed of bacterial cocci (55).

SYSTEMIC CUTANEOUS MANIFESTATIONS DUE TO TOXIN-PRODUCING *S. AUREUS*

Toxic shock syndrome

The toxic shock syndrome (TSS) was first described by Todd (1978) in 7 children who had a generalized erythema, fever, hypotension, diarrhoea and multi-organ failure (56). In 1980 many cases were reported in young women who used certain types of tampon (57, 58). The incidence of menstrual TSS in the US peaked in 1980 and has decreased significantly since the removal of these tampons from the market (59).

TSS is due to the production of a toxin by *S. aureus*, mainly TSST-1 and staphylococcal enterotoxins, particularly enterotoxin B and, less commonly, other enterotoxins (56). The 1997 CDC definition (60) includes the following clinical criteria: fever (≥38.9°C) a diffuse macular erythroderma, desquamation (1–2 weeks after onset of illness, particularly on the palms and soles), hypotension, multisystem organ involvement (57). In a study of 130 TSS, Reingold et al. (57) found a skin infection in 30% of cases, a genital focus in 27% (after delivery or abortion), 18% post-surgery focus, and in 13% the source was not identified. The pathogenesis of TSS is linked to the properties of superantigens in *S. aureus* toxins, namely activation of greater numbers of T lymphocytes resulting in the production of high levels of cytokines (33). Skin manifestations of TSS include a generalized erythema (with palm and sole involvement) (**Fig. 7**). Palmar, sole and finger desquamation may occur after recovery (**Fig. 8**). Transient alopecia, nail shedding and increased sweating on the hands and feet have been described (61). Treatment is based on the treatment of the multi-organ failure and the *S. aureus* focus of infection. Some antibiotics acting as protein-synthesis inhibitors with anti-toxaemic properties could provide additional therapeutic benefits (62).

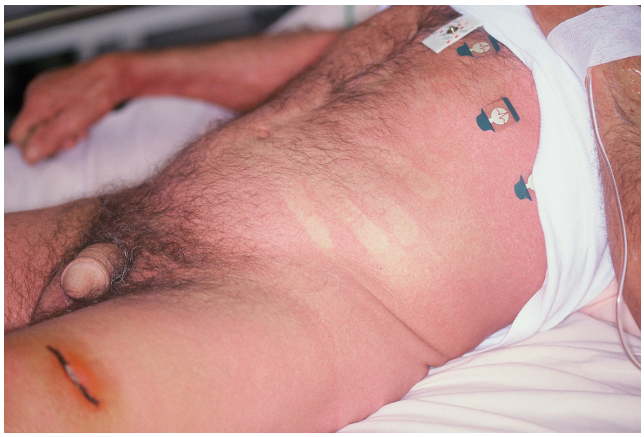

Fig. 7. Erythema of toxic shock syndrome.

In Japan, Takahashi et al. (63) have reported neonates who developed generalized erythema and thrombocytopaenia in the first week of life associated with MRSA-producing TSST-1. They propose neonatal toxic-shock-syndrome-like exanthematous disease (NTED) as the name for this disease. Similar cases have been reported in Europe (64).

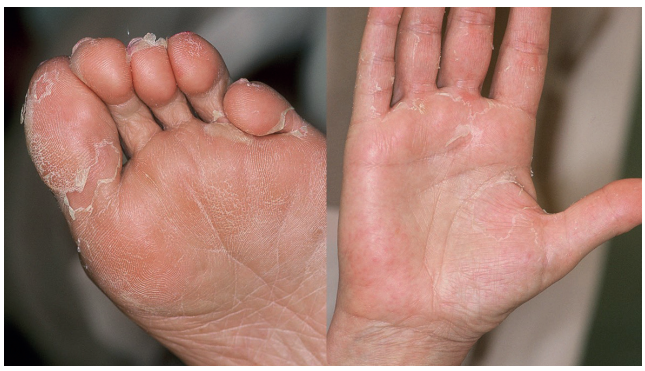

Fig. 8. Distal desquamation after toxic shock syndrome.

"Staphylococcal scarlet fever"

Staphylococcal scarlet fever, also called scarlatiniform erythroderma/rash, was first described in the 1920s. Lina et al. (65) found that 16 out of 17 strains of *S. aureus* isolated from patients with staphylococcal scarlet fever produced TSST-1, enterotoxins, or both. Enterotoxin B was the predominant toxin involved in a study in Taiwan (66). It is possible that most cases of staphylococcal scarlet fever are, in fact, a mild or attenuated clinical manifestation of TSS.

Staphylococcal scalded skin syndrome

When the ETs spread systemically, they can cause SSSS (9–11, 67). It is a generalized blistering disease affecting mainly neonates and young children and, exceptionally, adults with underlying diseases. The disease begins abruptly with fever and generalized erythema, followed by large fragile blisters involving the entire skin surface within the next few hours to days, which rupture rapidly (with a positive Nikolsky sign) (67). Widespread involvement of the entire skin surface can occur, but the mucous membranes are usually spared. Mild forms of SSSS have been described where the SSSS is limited to the body folds associated with a fine generalized desquamation (68). The disease follows localized *S. aureus* infection. Poor renal clearance of the toxins by neonates and by adults with impaired renal function is a major risk factor for developing SSSS. The prognosis of SSSS in children, who are appropriately treated, is good, with a mortality of less than 5%, but it may be fatal in up to 60% of affected adults, usually due to underlying diseases (67). The diagnosis of SSSS is clinically based. Exfoliatins are produced by *S. aureus* at a distant site; the blister fluid in generalized SSSS is usually sterile. The treatment is based on dressings, where there are large blisters, and the eradication of the source of *S. aureus* infection focus.

SKIN MANIFESTATIONS OF *S. AUREUS* BACTERAEMIA

Skin manifestations of S. aureus *endocarditis*

Endocarditis caused by *S. aureus* is classified as acute endocarditis. The description of endocarditis-related skin manifestations is confusing; Janeway lesions and Osler's nodes were described at the beginning of the 20th century (1). Classically reported Janeway lesions are macular, purpuric lesions that occur on hands and feet (**Fig. 9**). Histologically, they show neutrophilic microabscesses in the dermis and vessel thrombosis (69). These lesions are thought to be caused by septic microemboli; results of culture of skin specimens are frequently positive (70–73). Osler's nodes are described as small, painful, nodular lesions on the fingers or toes. Only a few biopsied Osler's nodes gave positive results on culture, and

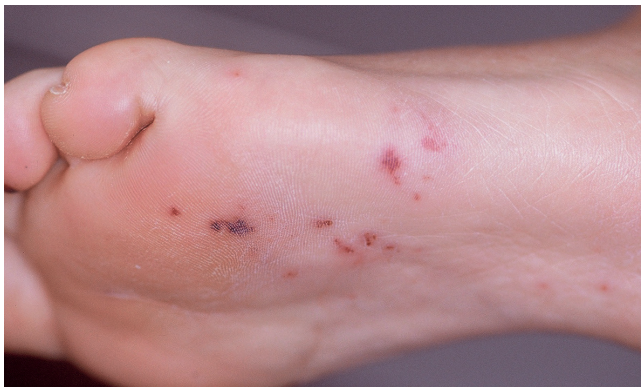

Fig. 9. Purpura during endocarditis.

histological examination showed diverse findings (73). The description of Janeway lesions corresponds better with the skin manifestations of *S. aureus* endocarditis.

Skin manifestations of S. aureus *bacteraemia (without endocarditis)*

Such manifestations related to the frequency of *S. aureus* bacteraemia are extremely rare. Purpuric disseminated eruptions and abscesses are the main clinical manifestations that have been described as a secondary focus of *S. aureus* bacteraemia. Exceptionally, purpura fulminans has also been reported (74).

IMMUNOLOGICAL SKIN MANIFESTATIONS OF *S. AUREUS* INFECTION

Immunological manifestations associated with acute or chronic *S. aureus* infections are rare. A few cases of vasculitis or Henoch-Schönlein purpura have been reported, mainly in the course of *S. aureus* bacteraemia (75–77). Some of these associations may be coincidental.

CONCLUSION

Staphylococcal skin infections are part of a complex group of diseases. Unfortunately, most reports in the literature classify skin infections and *S. aureus* skin infections under the heading "skin and skin structures infections (SSTI)", giving the illusion that all skin manifestations are within the same clinical spectrum. This review shows, on the contrary, how the clinical spectrum of skin manifestations due to *S. aureus* is diverse and related to different physiopathologies. Further reports and studies on skin *S. aureus* infections should take into consideration this rich and varied clinical spectrum of disease.

This review has focused on the clinical and therapeutic aspects of *S. aureus* skin infections, and many other questions are not mentioned, such as the interactions of *S. aureus* with the skin microbiome, the reservoirs of *S. aureus*, the relationships between reservoirs and skin infections, and the decolonization of the reservoirs.

All of these complex topics are currently the subject of intense research.

REFERENCES

1. Stanley JR, Amagai M. Pemphigus, bullous impetigo and staphylococcal scald skin syndrome. N Engl J Med 2006; 355: 1800–1810.
2. Salah LA, Faergemann J. A retrospective analysis of skin bacterial colonisation, susceptibility and resistance in atopic dermatitis and impetigo patients. Acta Derm Venereol 2015; 95: 532–535.
3. Rosen T, Albareda N, Rosenberg N, Alonso FG, Roth S, Zsolt I, et al. Efficacy and safety of ozenoxacin cream for treatment of adult and pediatric patients with impetigo: a randomized clinical trial. JAMA Dermatol 2018; 154: 806–813.
4. Bowen AC, Mahé A, Hay RJ, Andrews RM, Steer AC, Tong SY, et al. The global epidemiology of impetigo: a systematic review of the population prevalence of impetigo and pyoderma. PLoS One 2015; 10: e0136789.
5. Bowen AC, Tong SY, Chatfield MD, Carapetis JR. The microbiology of impetigo in indigenous children: associations between Streptococcus pyogenes, Staphylococcus aureus, scabies, and nasal carriage. BMC Infect Dis 2014; 14: 727.
6. Engelman D, Cantey PT, Marks M, Solomon AW, Chang AY, Chosidow O, et al. The public health control of scabies: priorities for research and action. Lancet 2019; 394: 81–92.
7. Korte LM, Bowen AC, Draper ADK, Davis K, Steel A, Teodora I, et al. Scabies and impetigo in Timor-Leste: a school screening study in two districts. PLoS Negl Trop Dis 2018; 12: e0006400.
8. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, et al. Mass drug administration for scabies – 2 years of follow-up. N Engl J Med 2019; 381: 186–187.
9. Hanakawa Y. Schechter NM, Lin C, Garza L, Li H, Yamaguchi T, Fudaba Y, et al. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. J Clin Invest 2002; 110: 53–60.
10. Amagai M, Matsuyoshi N, Wang ZH, Andl C, Stanley JR. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. Nat Med 2000; 6: 1275–1277.
11. Amagai M, Yamagushi T, Hanakawa Y, Nishifuji K, Sugai M, Stanley JR. Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1. J Invest Dermatol 2002; 118: 845–850.
12. Sumitomo T, Mori Y, Nakamura Y, Honda-Ogawa M, Nakagawa S, Yamaguchi M, et al. Streptococcal cysteine protease-mediated cleavage of desmogleins is involved in the pathogenesis of cutaneous infection. Front Cell Infect Microbiol 2018; 8: 10.
13. Koning S, Van Der Sande R, Verhagen AP, Van Suijlekom-Smit LW, Morris AD, Butler CC, et al. Interventions for impetigo. Cochrane Database Syst Rev 2012; 1: CD003261.
14. Yamaguchi T, Yokota Y, Terajima J, Hayashi T, Aepfelbacher M, Ohara M, et al. Clonal association of Staphylococcus aureus causing bullous impetigo and the emergence of new methicillin-resistant clonal groups in Kansai district in Japan. J Infect Dis 2002; 185: 1511–1516.
15. Liassine N, Auckenthaler R, Descombes MC, Bes M, Vandenesch F, Etienne J. Community-acquired methicillin-resistant Staphylococcus aureus isolated in Switzerland contains the Panton-Valentine leukocidin or exfoliative toxin genes. J Clin Microbiol 2004; 42: 825–828.
16. Shi D, Higuchi W, Takano T, Saito K, Ozaki K, Takano M, et al. Bullous impetigo in children infected with methicillin-resistant Staphylococcus aureus alone or in combination with methicillin-susceptible S. aureus: analysis of genetic characteristics, including assessment of exfoliative toxin gene carriage. J Clin Microbiol 2011; 185: 1511–1516.
17. Hisata K, Ito T, Matsunaga N, Komatsu M, Jin J, Li S, et al. Dissemination of multiple MRSA clones among community-associated methicillin-resistant Staphylococcus aureus infections from Japanese children with impetigo. J Infect Chemother 2011; 17: 609–621.
18. O'Neill AJ, Larsen AR, Skov R, Henriksen AS, Chopra I. Characterization of the epidemic European fusidic acid-resistant impetigo clone of Staphylococcus aureus. J Clin Microbiol 2007; 45: 1505–1510.
19. O'Neill AJ, Larsen AR, Henriksen AS, Chopra I. A fusidic acid-resistant epidemic strain of Staphylococcus aureus carries the fusB determinant, whereas fusA mutations are prevalent in other resistant isolates. Antimicrob Agents Chemother 2004; 48: 3594–3597.
20. Williamson DA, Monecke S, Heffernan H, Ritchie SR, Roberts SA, Upton A, et al. High usage of topical fusidic acid and rapid clonal expansion of fusidic acid-resistant Staphylococcus aureus: a cautionary tale. Clin Infect Dis 2014; 59: 1451–1454.
21. Demos M, McLeod MP, Nouri K. Recurrent furunculosis: a review of the literature. Br J Dermatol 2012; 167: 725–732.
22. Levy AL, Simpson G, Skinner RB Jr. Medical pearl: circle of desquamation – a clue to the diagnosis of folliculitis and furunculosis caused by Staphylococcus aureus. J Am Acad Dermatol 2006; 55: 1079–1080.
23. Couppie P, Cribier B, Prevost G. Leukocidin from Staphylococcus aureus and cutaneous infections: an epidemiologic study. Arch Dermatol 1994; 130: 1208–1209.
24. Del Giudice P, Bes M, Hubiche T, Blanc V, Roudière L, Lina G, et al. Panton-Valentine leukocidin-positive Staphylococcus aureus strains are associated with follicular skin infections. Dermatology 2011; 222: 167–170.
25. Baba-Moussa L, Sina H, Scheftel JM, Moreau B, Sainte-Marie D, Kotchoni SO, et al. Staphylococcal Panton-Valentine leucocidin as a major virulence factor associated to furuncles. Plos One 2011; 6: e25716.
26. Yamasaki O, Kaneko J, Morizane S, Akiyama H, Arata J, Narita S, et al. The Association between Staphylococcus aureus strains carrying Panton-Valentine leukocidin genes and the development of deep-seated follicular infection. Clin Infect Dis 2005; 40: 381–385.
27. Winthrop KL, Abrams M, Yakrus M, Schwartz I, Ely J, Gillies D, et al. An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. N Engl J Med 2002; 34: 1366–1371.
28. Kramkimel N, Sbidian E, Duong TA, Lesprit P, Roujeau JC, Bagot M. Septic facial vein thrombosis due to Panton-Valentine leukocidin-positive Staphylococcus aureus. Arch Dermatol 2009; 145: 1460–1461.
29. Del Giudice P, Blanc V, De Rougemont A, Hubiche T, Roudière L, Bes M, et al. J. Panton-Valentine leukocidin positive Staphylococcus aureus strains cause primary skin abscesses. Dermatology 2009; 219: 299–302.
30. Lina G, Piemont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V et. Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia. Clin Infect Dis 1999; 29: 1128–1132.
31. Issartel B, Tristan A, Lechevallier S, Bruyère F, Lina G, Garin B, et al. Frequent carriage of Panton-Valentine leucocidin genes by Staphylococcus aureus isolates from surgically drained abscesses. J Clin Microbiol 2005; 43: 3203–3207.
32. Miller LG, Daum RS, Creech CB, Young D, Downing MD, Eells SJ, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med 2015; 372: 1093–1103.
33. Daum RS, Miller LG, Immergluck L, Fritz S, Creech CB, Young D, et al. A placebo-controlled trial of antibiotics for smaller skin abscesses. N Engl J Med 2017; 376: 2545–2555.
34. Talan DA, Mower WR, Krishnadasan A, Abrahamian FM, Lovecchio F, Karras DJ, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. N Engl J Med 20; 374: 823–832.
35. Lowy FD. Antimicrobial resistance: the example of Staphylococcus aureus. J Clin Invest 2003; 111: 1265–1273.
36. Deleo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant Staphylococcus aureus. Lancet 2010; 375: 1557–1568.
37. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community and health care-associated methicillin-resistant Staphylococcus aureus infection. JAMA 2003; 290: 2976–2984.
38. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant Staphylococcus aureus carrying Panton-Valentine leukocidin genes:

worldwide emergence. Emerg Infect Dis 2003; 9: 978–984.
39. Tristan A, Bes M, Meugnier H, Lina G, Bozdogan B, Courvalin P, et al. Global distribution of Panton-Valentine leukocidin – positive methicillin-resistant Staphylococcus aureus, 2006. Emerg Infect Dis 2007; 13: 594–600.
40. King MD, King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med 2006; 144: 309–317.
41. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, et al. Methicillin-resistant Staphylococcus aureus infections among patients in the emergency department. N Engl J Med 2006; 355: 666–674.
42. Talan DA, Krishnadasan A, Gorwitz RJ, Fosheim GE, Limbago B, Albrecht V, Moran GJ; EMERGEncy ID Net Study Group. Comparison of Staphylococcus aureus from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. Clin Infect Dis 2011; 53: 144–149.
43. Del Giudice P, Blanc V, Durupt F, Bes M, Martinez JP, Counillon E, et al. Emergence of two populations of methicillin-resistant Staphylococcus aureus with distinct epidemiological, clinical and biological features, isolated from patients with community-acquired skin infections. Br J Dermatol 2006; 154: 118–124.
44. Jappe U, Heuck D, Strommenger B, Wendt C, Werner G, Altmann D, Witte W. Staphylococcus aureus in dermatology outpatients with special emphasis on community-associated methicillin-resistant strains. J Invest Dermatol 2008; 128: 2655–2664.
45. Deplano A, Dodémont M, Denis O, Westh H, Gumpert H, Larsen AR, et al. F. European external quality assessments for identification, molecular typing and characterization of Staphylococcus aureus. J Antimicrob Chemother 2018; 73: 2662–2666.
46. Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, et al. Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med 2005; 352: 1436–1444.
47. Young DM, Harris HW, Charlebois ED, Chambers H, Campbell A, Perdreau-Remington F, et al. An epidemic of methicillin-resistant Staphylococcus aureus soft tissue infections among medically underserved patients. Arch Surg 2004; 139: 947–951; discussion 951–953.
48. Huijsdens XW, van Santen-Verheuvel MG, Spalburg E, Heck ME, Pluister GN, Eijkelkamp BA, et al. Multiple cases of familial transmission of community-acquired methicillin-resistant Staphylococcus aureus. J Clin Microbiol 2006; 44: 2994–2996.
49. Lee NE, Taylor MM, Bancroft E, Ruane PJ, Morgan M, McCoy L, et al. Risk factors for community-associated methicillin-resistant Staphylococcus aureus skin infections among HIV-positive men who have sex with men. Clin Infect Dis 2005; 40: 1529–1534.
50. Diep BA, Chambers HF, Graber CJ, Szumowski JD, Miller LG, Han LL, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant Staphylococcus aureus clone USA300 in men who have sex with men. Ann Intern Med 2008; 148: 249–257.
51. Pierrart J, Delgrande D, Mamane W, Tordjman D, Masmejean EH. Acute felon and paronychia: Antibiotics not necessary after surgical treatment. Prospective study of 46 patients. Hand Surg Rehabil 2016; 35: 40–43.
52. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, Tang AW, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med 2005; 352: 1445–1453.
53. Del Giudice P. Contiguous cutaneous inflammation: different scenarios, unclear outlines. Ann Dermatol Venereol 2018; 145: 561–562.
54. Reddy M, Gill SS, Wu W, Kalkar SR, Rochon PA. Does this patient have an infection of a chronic wound? JAMA 2012; 307: 605–611.
55. Ingen-Housz-Oro S, Leprince P, Ortonne N, Cluzel P, Gautier MS, Wolkenstein P et al Nodules on a sternotomy scar. Lancet Infect Dis 2015; 15: 986.
56. Todd J. Toxic shock syndrome. Clin Microbiol Rev 1988; 1: 432–446.
57. Reingold AL, Hargrett NT, Dan BB, Shands KN, Strickland BY, Broome CV. Non menstrual toxic shock syndrome: a review of 130 cases. Ann Intern Med 1982; 96: 871–874.
58. Broome CV, Hayes PS, Ajello GW, Feeley JC, Gibson RJ, Graves LM, et al. In-vitro studies of interactions between tampons and Staphylococcus aureus. Ann Intern Med 1982; 96: 959–962.
59. Hajjeh RA, Reingold A, Weil A, Shutt K, Schuchat A, Perkins BA. Toxic shock syndrome in the United States: surveillance update, 1979 1996. Emerg Infect dis 1999; 5: 807–810.
60. Toxic shock syndrome. Available from: https://www.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/.
61. Crowther MA, Ralph ED. Menstrual toxic shock syndrome complicated by persistent bacteremia: case report and review. Clin Infect Dis 1993; 1: 288–289.
62. Stevens DL, Ma Y, Salmi DB, McIndoo E, Wallace RJ, Bryant AE. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant Staphylococcus aureus. J Infect Dis 2007; 195: 202–211.
63. Takahashi N, Nishida H, Kato H, Imanishi K, Sakata Y, Uchiyama T. Exanthematous disease induced by toxic shock syndrome toxin 1 in the early neonatal period. Lancet 1998; 351: 1614–1619.
64. Van Der Mee-Marquet N, Lina G, Quentin R, Yaouanc-Lapalle H, Fievre C, Takahashi N, et al. Staphylococcal exanthematous disease in a newborn due to a virulent methicillin-resistant Staphylococcus aureus strain containing the TSST-1 gene in Europe: an alert for neonatologists. J Clin Microbiol 2003; 41: 4883–4884.
65. Lina, G, Gillet Y, Vandenesch F, Jones ME, Floret D, Etienne J. Toxin involvement in staphylococcal scalded skin syndrome. Clin Infect Dis 1997; 25: 1369–1373.
66. Wang CC, Lo WT, Hsu CF, Chu ML. Enterotoxin B is the predominant toxin involved in staphylococcal scarlet fever in Taiwan. Clin Infect Dis 2004; 38: 1498–1502.
67. Ladhani S, Joannou CL, Lochrie DP, Evans RW, Poston SM. Clinical, microbial, and biochemical aspects of the exfoliative toxins causing staphylococcal scalded-skin syndrome. Clin Microbiol Rev 1999; 12: 224–242.
68. Hubiche T, Bes M, Roudiere L, Langlaude F, Etienne J, Del Giudice P. Mild staphylococcal scalded skin syndrome: an underdiagnosed clinical disorder. Br J Dermatol 2012; 166: 213–215.
69. Parikh SK, Lieberman A, Colbert DA, Slivers DN, Grossman ME. The identification of methicillin-resistant Staphylococcus aureus in Osler's nodes and Janeway lesions of acute bacterial endocarditis. J Am Acad Dermatol 1996; 35: 767–768.
70. Maestre A, Mora A, Gutiérrez F, Hidalgo AM, Monmeneu JV, Mirete C, López F. Diagnosis: a Janeway lesion and an Osler's node. Clin Infect Dis 2001; 32; 63: 149.
71. Gil MP, Velasco M, Botella JE, Ballester JE, Pedro F, Aliaga A. Janeway lesions: differential diagnosis with Osler's nodes. Int J Dermatol 1993; 32: 673.
72. Cardullo AC, Silvers D, Grossman ME. Janeway lesions and Osler's nodes: a review of histopathologic findings. J Am Acad Dermatol 1990; 22: 1088–1090.
73. Vinson RP, Chung A, Elston DM, Keller RA. Septic microemboli in a Janeway lesion of bacterial endocarditis. J Am Acad Dermatol 1996; 35: 984–985.
74. Kravitz GR, Dries DJ, Peterson ML, Schlievert PM. Purpura fulminans due to Staphylococcus aureus. Clin Infect Dis 2005; 40: 941–947.
75. Maliske SM, Edwards D, Suneja M. Methicillin-resistant Staphylococcus aureus-related Henoch-Schönlein purpura treated without systemic immunosuppressants. Am J Med Sci 2015; 350: 514–516.
76. Yamaguchi Y, Fujita Y, Ikeda T, Mai Y, Miyazawa H, Matsumura W, et al. Severe septic vasculitis preceding thoracic empyema: staphylococcus aureus enterotoxin deposition in vessel walls as a possible pathomechanism. Acta Derm Venereol 2019; 99: 464–465.
77. Mosher CA, Owen JL, Barker BR. Staphylococcus aureus bacteremia masquerading as leukocytoclastic vasculitis. Am J Med 2016; 129: e5–7.

REVIEW ARTICLE

A Hundred Years of Diagnosing Superficial Fungal Infections: Where Do We Come From, Where Are We Now and Where Would We Like To Go?

Yvonne GRÄSER[1] and Ditte Marie Lindhardt SAUNTE[2–5]

[1]Institute of Microbiology and Infectious Immunology, Charité – University Medicine Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Nationale Reference Laboratory of Dermatophytes, Berlin, Germany, [2]Department of Dermatology, Zealand University Hospital, Roskilde, [3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, [4]Unit of Mycology, Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen, Denmark, and [5]European Academy of Dermatology and Venerology Task Force for Mycology Co-chair

Superficial fungal infections have been known for hundreds of years. During the 20th century new diagnostic methods were developed and the taxonomy changed several times, which, unfortunately, resulted in many fungi having several names (synonyms). The taxonomy is important, as species-specific identification guides clinicians when choosing the most appropriate antifungal agent, and provides an indication of the source of infection (anthropophilic, zoophilic or geophilic). Traditional diagnostic tests (direct microscopy, culture and histopathology) are still widely used, but molecular-based methods, such as PCR, have many advantages, and increasingly supplement or replace conventional methods. Molecular-based methods provide detection of different genus/species spectra. This paper describes recent changes in dermatophyte taxonomy, and reviews the currently available diagnostics tools, focusing mainly on commercially available PCR test systems.

Key words: diagnostic; microscopy; PCR; dermatophytes; dermatomycoses.

Accepted Mar 19, 2020; Epub ahead of print Mar 24, 2020

Acta Derm Venereol 2020; 100: adv00111.

Corr: Ditte Marie L. Saunte, Department of Dermatology, Zealand University Hospital, Roskilde, Health Sciences Faculty, University of Copenhagen, Sygehusvej 5, DK-4000 Roskilde, Denmark. E-mail: disa@regionsjaelland.dk

SIGNIFICANCE

Superficial fungal infections (e.g. ringworm, thrush and fungal nail infections) have been known for hundreds of years. It is crucial to diagnose the fungus correctly, in order to choose the correct anti-fungal medication, and to provide information about the source of infection. Traditionally, diagnosis is based on microscopy, culture and histopathology of the specimen (hair, skin, nails). More recent molecular-based methods have been developed, but there is no standardization as to which fungi they detect. This paper presents an update on fungal taxonomy and describes the diagnostic tools available.

Superficial fungal infections have been known since the 5th century BC, when Hippocrates wrote about thrush in children. It took hundreds of years before the first scientific proof of infection was made by Agostino Bassi in 1835, who showed that the muscardine disease of the silkworm was caused by a fungus (1). In the following years Audouin from France suggested that some human diseases were caused by the same types of plant parasites (fungi). By the end of the 19th century important microbiological methods, such as obtaining pure cultures of the dermatophytes *Trichophyton* and *Achorion schoenleinii*, were introduced. A morphological classification was not established until 1910, when the famous mycologist R. Sabouraud published "*Les teignes*", a monograph based on the standardization of test media and studies on clinical features of skin and hair infections and morphology in cultures (1). At the beginning of the 20th century different nomenclatural systems were suggested, based on clinical presentation and culture characteristics.

The taxonomy of superficial fungal infections has changed several times since then, due to the development of new diagnostic methods. Unfortunately, this has resulted in many fungi having several names (synonyms). An attempt to simplify this, by giving "one fungus one name" has been initiated, and the development of molecular diagnostic methods has contributed to this process. This paper describes the latest changes in dermatophyte taxonomy and reviews currently available diagnostic tools.

TAXONOMY

The taxonomy of dermatophytes changed most recently at the beginning of 2017 (2). The phylogenetic tree in **Fig. 1**, based on molecular data, shows the current valid nomenclature of the family *Arthrodermataceae*. *C. serratus* and *G. ceretanicus* were used as outgroups. Before that, the family of *Arthrodermataceae*, encompassing the dermatophyte fungi, included 3 anamorphic (fungi that have no sexual phase in their life cycle, also called imperfect fungi), *Trichophyton*, *Microsporum*, *Epider-*

doi: 10.2340/00015555-3467
Acta Derm Venereol 2020; 100: adv00111

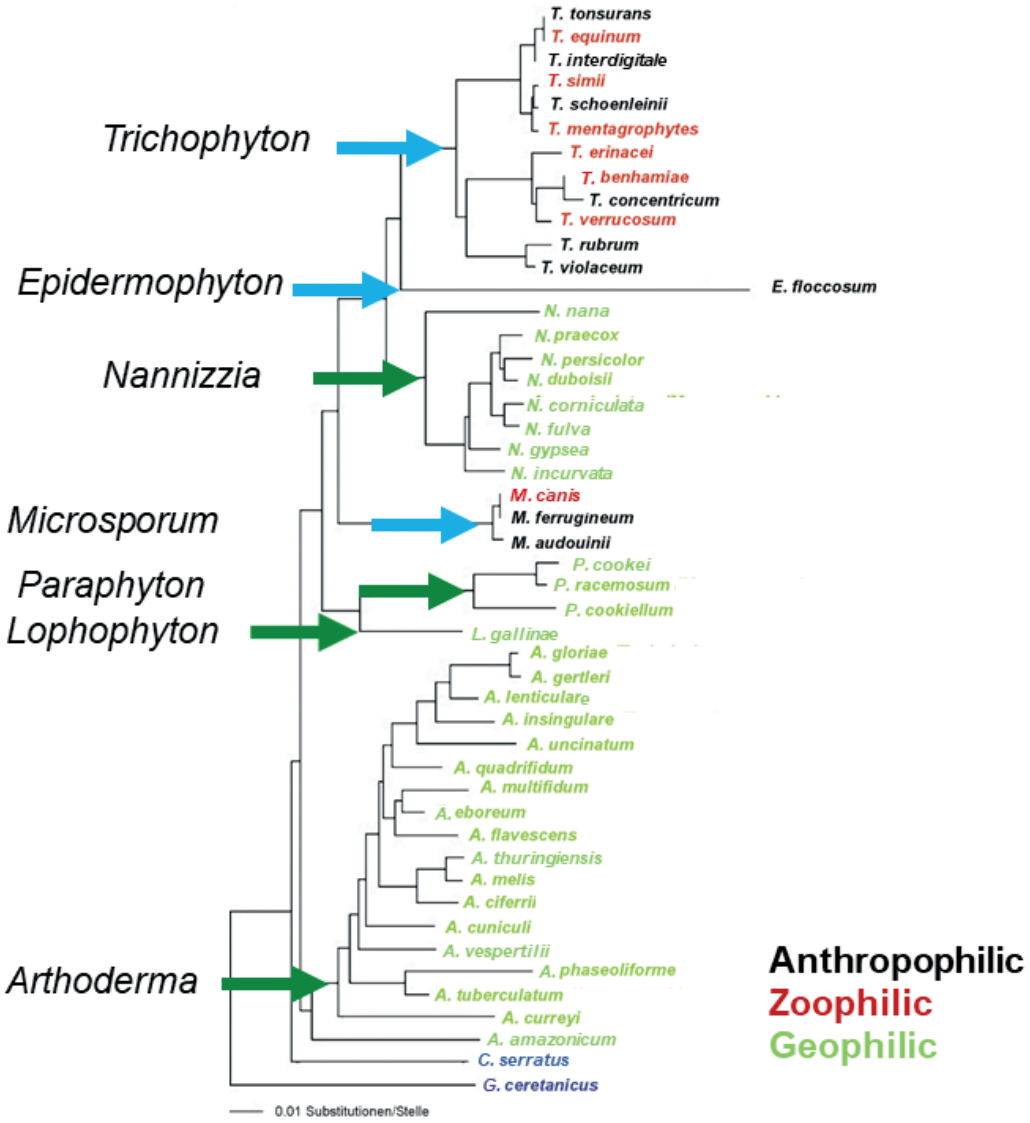

Fig. 1. Phylogenetic tree of the majority of species of the family *Arthrodermataceae*, based on the internal transcribed spacer region of the ribosomal DNA.

mophyton, and one teleomorphic (fungi that have a sexual phase in their life cycle) genus (*Arthroderma*). As early as 2011, this dual nomenclature of fungi was abolished (3), mainly because the basis of taxonomy moved away from using morphological features towards molecular and phylogenetic data. On this basis, the teleomorphic genus in dermatophytes was abolished and 4 additional genera (*Nannizzia*, *Lophophyton*, *Paraphyton* and *Arthroderma*) were introduced to account for the former geophilic *Microsporum* and *Trichophyton* spp. according to the rules of the botanical code. In principle, a separate genus was established at all main clusters (tips of the arrows in Fig. 1) of the phylogenetic multilocus tree. Medical concerns were also addressed, i.e. the anthropophilic and zoophilic species names were retained in the well-known genera *Microsporum*, *Trichophyton* and *Epidermophyton* (2).

At the species level, the nomenclatural changes that affected the medically relevant dermatophytes of the aforementioned genera were minor at this time. Most of these taxonomic changes were proposed at the beginning of the 21st century. For example, the previous 50 anthropophilic and zoophilic *Trichophyton* species were reduced to 19 (4), and in 2017 they were reduced by a further 3 due to the disappearance of the teleomorphic genus. Here, corrections were carried out that mainly affected the classification of the dermatophytes into groups that encompassed their natural sources (anthropophilic, zoophilic, geophilic). For example, the anthropophilic and zoophilic strains of *T. interdigitale*, were separated once again, i.e. the zoophilic strains again received their own species name, *T. mentagrophytes*, whereas the anthropophilic strains were called *T. interdigitale*. Due to this name change, the previous species *T. mentagrophytes*, which was phylogenetically closely related to *T. schoenleinii*, had to be renamed. The name *T. quinckeanum* was used, because the originally described strains of *T.*

mentagrophytes var. quinckeanum clustered here (Fig. 1). The skin fungus, *Trichophyton* sp. of *Arthroderma benhamiae*, which was isolated mainly from guinea pigs, was reduced to *T. benhamiae*. *T. soudanense* was removed from the *T. rubrum* complex and is now again listed as a separate species. New name combinations were also added, which were mostly geophilic species, due to the introduction of new genus names, e.g. *Microsporum gypseum* was renamed *Nannizzia gypsea*. The overall purpose of these changes was to base the new system on genetically robust determinants and to retain well-known dermatophyte names familiar to clinicians (2).

CLINICAL SIGNIFICANCE OF FUNGAL DIAGNOSTICS

Taxonomy may seem remote from everyday clinical practice, but it is important in many ways: first, an accurate diagnosis is important for choosing the correct antifungal treatment (5, 6). Species-specific diagnosis is sometimes also necessary, as different species may have diffierent antifungal susceptibility patterns (7). Secondly, the species name also informs clinicians about the source of the infection. By knowing the source of infection, it is possible to treat the index patient or animal in order to reduce the risk of further spread of disease. Thirdly, sub-species identification (strain typing) is useful in outbreaks as, for example, in India, where a specific *T. mentagrophytes* genotype VIII has been uniformly isolated as a causative agent of a countrywide spread of a chronic, relapsing dermatophyte epidemic (8). By thoroughly studying this sub-species new knowledge about virulence and resistance may become available. Finally, a negative fungal laboratory test is also important as a diagnosis of exclusion, when other dermatological diagnoses have also suspected. Even though identification to genus or species level is important it is not always performed in the clinical setting (9–11). Oral antifungal therapy should not be administered without a confirmed laboratory diagnosis, because up to 40% of the suspected diagnoses are wrong (9), and due to the possible side-effects and drug interaction, particularly in older patients who often have other underlying diseases and take additional medications. A third point is the potentially negative impact that unnecessary treatment may have on the human microbiome, and the increasing threat of drug resistance, which is well recognized with antibacterials, but can be equally applicable to antimycotics.

TRADITIONAL DIAGNOSTICS: DIRECT MICROSCOPY, HISTOLOGY AND CULTURE

Direct microscopy and culture have been used for the purpose of fungal identification over the last 100 years and are still used worldwide. The methods will be described in the following section.

Direct "non-specific" detection of fungal elements in clinical specimens

Direct microscopy is used for the primary identification of fungal elements in specimens after treating with sodium hydroxide or potassium hydroxide (KOH). Conventional light microscopy, without the benefit of any contrast with the background, is difficult to interpret, and stains, such as lactophenol cotton blue, Parker ink, chlorazol black E or Congo red, are therefore often added. Fluorescence microscopy after treatment of the specimen with optical brighteners, such as blankophor or calcoflour, can enhance the detection rate after microscopy (12, 13). *Malassezia* species show characteristic unipolar budding blastoconidia, but with the exception of this genus it is important to note that direct microscopic findings are neither genus- nor species-specific, even though it is possible to distinguish yeasts from hyphae and to detect pigmented fungal cells. Some very experienced technicians may be able to suggest a differentiation between other specific yeasts, dermatophytes and non-dermatophyte moulds, but without absolute certainty (14).

Direct microscopy of hair is important, as the growth pattern of the dermatophyte classifies it as either favus, endothrix (arthroconidia are present within the hair shaft) or ectothrix (where the fungus invades the hair shaft at mid-follicle and the arthrospores then grow out of the hair follicle and surround the surface of the hair shaft). The growth pattern, combined with the conidial size, can be used as a preliminary indication of the genus of the infecting dermatophyte (15–17). Histology is not used routinely in skin and hair infections, but is useful when *Malassezia* folliculitis is suspected, in order to rule out other causes of folliculitis. Some dermatologists use histology routinely for fungal identification in nails, as it may rule out contamination and is able to confirm the growth of the fungus directly in the specimen (11, 18–20). However, the prerequisite for this is an invasive biopsy.

Genus- and species-specific identification

Culture is highly dependent on growth media, e.g. some media are more dermatophyte-specific, while others are better for yeasts and non-dermatophyte moulds. *Malassezia* is lipid-dependent and, as a consequence, is often difficult to culture on normal laboratory media. Culture of nail material is challenging, as up to 30% of microscopy-positive nail specimens are culture-negative (21, 22). This may be due to the presence of non-viable material, either because of insufficient material from the proximal area of infection, or due to previous antifungal treatment.

Combination of the different techniques is usually practiced, as it enhances the chances of fungal detection and provides more clinically useful information. All traditional diagnostic methods are dependent on the skills of the laboratory technicians, whereas molecular

diagnosis does not depend on the acquired skill sets of the laboratory staff, but may have other limitations, as described below.

MOLECULAR-BASED DETECTION OF SUPERFICIAL FUNGAL INFECTIONS

Development of molecular-based methods for detection of dermatomycosis

With the introduction of molecular tools into the taxonomy of dermatophytes approximately 30 years ago, species-specific markers, such as the internal transcribed spacer (ITS) region of ribosomal DNA, were subsequently used for the diagnosis of this fungal group. In the mid-1990s, PCR methods were initially applied to cultured skin material. This included methods such as restriction fragment length polymorphism (RFLP) and random amplification of polymorphic DNA (RAPD) analyses, but also PCR fingerprinting (23–25). Later, so-called in-house PCR methods were developed, which were also able to identify the fungus directly in clinical specimens. These methods are generally based on amplification with a broad range and/or specific primers and, in a second stage, use hybridization with species-specific probes with or without a combination of high-resolution melting curve analysis. A distinction can be made between conventional and real-time PCR techniques. The former are more personnel-intensive because the hybridization step is performed separately and requires additional washing steps (enzyme-linked immunoassay (ELISA), blot or microarray technique) and are more susceptible to contamination because the amplified DNA is further processed manually. On the other hand, the thermal cyclers required are less expensive than real-time devices. However, the advantages of real-time PCR are that both the amplification and hybridization steps are performed in the same closed reaction tube without the risk of contamination. This also eliminates additional bench handling. However, it must be kept in mind that the number of probe hybridizations in conventional techniques is larger (e.g. 78 in the microarray format) than the number of colour labels (4–6), which are used to label different probes in real-time PCR technology. Thus, melting curve analysis is used to extend the spectrum of species to be detected. Nevertheless, these methods are not yet able to differentiate, at the same time, more than 20 clinically relevant dermatophyte species, including the few non-dermatophytes that can play a role in onychomycosis as infectious agents. Such an all-in-one detection test would replace protracted phenotypic diagnostics based on culture, which ultimately requires expert knowledge because morphological features in this fungal group are both polymorphic and partially overlap.

Commercial kits for direct detection of fungal infections on skin, hair and nail samples

Since 2008, commercial systems, that use the above-mentioned detection methods and cover different species spectra, have been available. The Dermatophyte PCR Kit was developed by the Statens Serum Institute (SSI), in Copenhagen Denmark in 2 versions; firstly, as a conventional PCR, and later as a real-time PCR that solely detects *T. rubrum* at species level, as it is the most common pathogen in onychomycosis and tinea pedis

Table I. Species spectra detected by the commercially available test systems

Species/KIT	DPK	FTD	MMD	MMD LF	DG 1.0	DG 2.0	DD	EADM
T. tonsurans	X							V
T. equinum	X							V
T. interdigitale	X							V
T. mentagrophytes	X							V
T. schoenleinii	X						X	V
T. quinckeanum	X						X	V
T. simii	X	nd	nd	nd			nd	V
T. erinacei	X	X	X		X		X	V
T. benhamiae	X	X	X		X		X	V
T. verrucosum	X	X	X		X	V	X	V
T. bullosum	X	nd	nd	nd	X	X	nd	V
T. rubrum	V	V		V	V	V	V	V
T. violaceum	X	V		V	V	V	V	V
E. floccosum	X	V	V	V	V	V	V	V
M. audouinii	X			V	V	V		V
M. ferrugineum	X							V
M. canis	X							V
N. gypsea	X	X	V	V	X	X	V	V
N. fulva	X	X	X	X	X	X	X	V
N. incurvata	X	X	X	X	X	X	X	V
N. persicolor	X	X	X	X	X	X	X	V
pan Dermatophyte	V	X	X	V	X	X	X	V
non Dermatophyte	X	X	V	V	V	V	X	V

Same coloured boxes refer to the detection of species complexes, but not individual species. V: detects, X: do not detect. The identically coloured boxes mark the species in the respective kit, which are detected together (as a complex), i.e. not separated from each other.
Nd: no data; DPK: Dermatophyte PCR Kit; FTD: Fast Track Dermatophytes; MMD: Mentype Mycoderm; MMD LF: Mentype <mycoderm Lateral Flow; DG 1.0: DermaGenius Version 1.0; DG 2.0: DermaGenius Version 2.0; DD: DermaDYN; EADM: Euroarray Dermatomycosis.

(**Table I**). Otherwise, the kit offers the possibility of detecting dermatophytes as a group (pan-dermatophyte), but this will include any non-pathogenic geophilic genera present. The conventional test system is based on a PCR with subsequent size analysis of the amplified DNA fragments in an agarose gel, whereas real-time PCR uses hybridization probes instead. Both test systems can be used for screening for dermatophytes, and this may be followed by subsequent species identification of non-rubrum species via culture or other molecular techniques, such as sequencing (26). In 2011, the FTD Dermatophyte test from Fast Track Diagnostics, was made available in Sliema, Malta. This test system, a 2-tube real-time PCR with probe hybridization, but without melting curve analysis, is able to detect 3 species (*T. rubrum*, *T. violaceum*, *E. floccosum*). The remaining detections are performed at species complex level, i.e. more than 1 species is detected here, but not differentiated from each other. This includes mainly dermatophytes species with different ecological niches: the *T. tonsurans* complex (no differentiation between *T. equinum*, zoophilic and *T. tonsurans*, anthropophilic), the *T. interdigitale* complex (*T. interdigitale*, *T. schoenleinii* antropophilic; *T. mentagrophytes*, *T. quinckeanum* zoophilic) and the *M. canis* complex (*M. canis* zoophilic, *M. audouinii*, *M. ferrugineum* anthropophilic). The kit does not have a detection option for the dermatophytes as a group. Biotype in Dresden, Germany launched the first version of the Mentype MycoDerm kit in 2013. These utilize 2 conventional PCR reactions, which can differentiate 2 species (*E. floccosum* and *N. gypsea*) on the basis of fragment size analyses. There is no differentiation between the *T. tonsurans* and the *T. interdigitale* complexes. *T. rubrum* is identified in a complex together with *T. violaceum*, as is *M. canis* complex. The second version of the test system (Mentype MycoDerm Lateral Flow) was available 2 years later with 3 PCR reactions. Further developments affect, on the one hand, the procedure, because fragment analysis was replaced by probe hybridization on a blot strip. On the other hand, the species spectrum to be detected has been enlarged. Now it is possible to detect *T. rubrum*, *T. violaceum*, *M. audouinii* at species level and *M. canis* in combination with *M. ferrugineum*. The *T. tonsurans* was separated from the *T. interdigitale* complexes. This was also the first kit that could detect *T. benhamiae* in a complex together with *T. erinacei* and *T. verrucosum*. Another concurrent test system, DermaGenius 1.0, from PathoNostics, produced in Maastrict, the Netherlands, based on a single multiplex real-time PCR with melting curve analysis, had the same identification gaps and a similar species spectrum as the FTD Kit. Neither kit included pan-dermatophyte detection. This changed with the 2nd version of the kit (DermaGenius 2.0), which became available in 2018. The species detection is the same as for Mentype MycoDerm Kit Lateral Flow, with 2 exceptions. *N. gypsea* is not included, but *T. verrucosum* is. *T. benhamiae* is clustered together with *T. equinum* (27). At the same time, the DERMADYN kit developed by DYN Diagnostics Ltd in Ha'eshel St., Israel became available. This test system is also based on a 2-tube multiplex PCR with a melting curve analysis and detects a similar spectrum to FTD dermatophytes (Table I). In addition *N. gypsea* is detected, but the *T. simii* complex is not included (28). In 2018, the last of the kits discussed here, Euroarray Dermatomycosis from Euroimmun, was launched in Lübeck, Germany. This is a multiplex PCR reaction with subsequent probe hybridization in the form of a "microarray". This format enables the detection of all relevant (approximately 20) dermatophytes at the species level, including a pan-dermatophyte probe and 6 non-dermatophytes at the species level (*Scopulariopsis brevicaulis*, *Fusarium* and *Candida* spp.). Furthermore, there is species detection for rare pathogens, such as *T. eriothrephon* and *T. bullosum*. Only *T. concentricum*, a pathogen endemic to the Pacific Islands, is not separated from *T. benhamiae*, and *T. soudanense* is not differentiated from *T. rubrum* because the taxonomic change that separated them came after the development of the kit.

Overall, the clinician should be aware that there is a difference between what the commercial tests are able to detect (Table I). Most importantly, the majority of tests do not discriminate between zoophilic and anthropophilic species, which is a necessary step in order to find (and treat) the sources of infection. Another challenge is that many of the non-dermatophytes involved in the pathogenesis of onychomycosis are not detected in many of the kits. The broadest species-specific spectrum is offered by the Euroarray. The other test systems do not detect non-dermatophytes (SSI, FTD), apart from *C. albicans* (DermaGenius), or they provide detection of *Scopulariopsis* and *Candida* to genus level only (Mentype) (Table I).

Non-commercial molecular-based tests

A considerable number of in-house PCR techniques have been developed for the diagnosis of dermatophytes and other skin pathogenic fungi. We do not describe these developments in detail here, because they are not standardized, and in the vast majority of cases are used only by individual, or a few, laboratories involved in routine diagnostics. Of particular interest are the methods based on real-time PCR. Many of these approaches are able to identify up to 6 taxa and dermatophytes in general (29, 30). Ohst and colleagues (31) were able to detect 9 dermatophyte taxa by combining up to 10 PCRs in a sequential algorithm, and Bergmans and colleagues (32) could differentiate 11 species in a single-tube assay with probes and melting-curve analysis. Walser & Bosshard (33) report that using sloppy molecular beacons with species-specific melting temperature signatures allows the identification of 19 dermatophyte species. Until now it has been possible to detect a similar number of

species only by applying post-PCR techniques, such as an oligonucleotide array (34). This may be a promising approach for a commercial test system, if it is possible to increase the sensitivity of the 2nd species-differentiating PCR reaction, which was negative in 76% of cases where PCR1 (pan dermatophytes) was positive.

Another molecular-based method, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), is used to identify micro-organisms based on the characteristic protein spectrum of each species matched with a database. It has been applied to the identification of superficial fungal infection directly on culture material, both yeast, dermatophytes and moulds (35). This technique is fast and reproducible, but until now not applicable directly to clinical hair, skin or nail specimens (36–40). Protein spectra of 7 and 10 dermatophytes species (*T. tonsurans*, *T. rubrum*, *T. interdigitale*, *T. mentagrophytes*, *T. verrucosum*, *T. violaceum*, *M. canis*, *M. audouinii*, *E. floccosum*, *N. gypsea*) are included in the widely used Bruker and Biomerieux reference spectrum databases (41). So far, this method is not able to differentiate the phylogenetically closely related species, e.g. *T. rubrum/soudanense*, *T. interdigitale/mentagrophytes*, *T. tonsurans/equinum* or *T. benhamiae/concentricum* complex (42, 43). Identification can be improved by establishing an in-house database (44). It has also been used to detect antifungal resistance (45).

OTHER DIAGNOSTIC TOOLS

Wood's light, filtered ultraviolet light, is often used as a bedside tool for differentiate tinea capitis caused by a *Microsporum* species (*canis*, *audouinii* and *ferrugineum*) from other dermatophyte infections, as it fluoresces greenish under Wood's light, and endothrix infections are non-fluorescent (17).

Dermoscopy, reflectance confocal microscopy, optical coherence tomography and confocal laser scanning microscopy, all of which are non-invasive methods, can be used as add-on tools to differentiate tinea capitis and/or onychomycosis from other dermatological conditions (17, 20, 46–48).

Dermatophyte screening test media, an agar medium containing a dermatophyte colour indicator can be used for dermatophyte screening. The anti-dermatophyte monoclonal antibody test, an immunochromatographic detection test, is able to confirm a dermatophyte infection, detectable at genus level. Some are known to give a false-positive reaction when non-dermatophytes are grown (22, 49–51).

CURRENT ROUTINE DIAGNOSTIC AND THEIR CHALLENGES

The use of phenotypic methods (microscopy and culture) for the detection of pathogens in tinea is still widespread. They are dependent on the skills of the laboratory technicians and culture is time-consuming. The culture method is still the only diagnostic method that is able to confirm the viability of the fungus, which is important for treatment assessment (11). Microbiological laboratories appreciate the automation possibilities in molecular diagnostics and often have already established similar methods and devices that can also be used for dermatophyte identification. Decisive factors in determining whether to set up a molecular mycology service are the number of samples, the availability of trained personnel for direct microscopy, culturing and cost-effectiveness, which depends strongly on whether and how molecular dermatophyte diagnostics are remunerated. Whether conventional diagnostics will still be used after the wider introduction of the molecular identification method depends primarily on the differentiated pathogen spectrum of the test system used. If not all relevant pathogens are covered, a pan-dermatophyte detection should be used in order not to miss a possible pathogen. However, even then, the detection of potential non-dermatophytes must be considered and, if not included, covered by diagnostics based on culture. It is, therefore, important to be aware of what fungi any locally available molecular test can or cannot detect.

Although molecular diagnostics are up to 30% more sensitive than culture diagnostics, the detection limit is more than one fungal cell (31). Therefore, the clinical specimens must be taken from the correct location and in sufficient quantity. In this respect, there is no difference from culture diagnostics. The detection of pathogenic dermatophytes, whether in culture or PCR, always requires antifungal therapy, because asymptomatic carriers also spread the fungi and can become symptomatic. Disadvantages of the available molecular tests, in general, are that the evolution of fungi can lead to (point) mutations, especially in species-specific sequences used in the primers and probe, so that they can no longer bind, and false-negative results may be generated.

This can be remedied by sequencing with broad-range or only dermatophyte-specific primers, which are more conserved and therefore less susceptible to mutations. Sequencing can then provide accurate species identification. Some laboratories already routinely use these methods for fungal diagnostics. However, the purchase of a sequencing device is expensive and, like an in-house PCR, the method has to be validated. Furthermore, there must be appropriately validated databases to enable correct identification.

CLINICAL AND LABORATORY INTERACTION CAN IMPROVE THE DIAGNOSTIC OUTCOME

It seems logical that there should be coherence between what the clinician suspects and what the mycology laboratory is able to detect. Nevertheless, in our experience

this it often not the case. As described, different fungi have different needs for substrates in order to grow, and some molecular-based tests do not detect all relevant fungi. It is therefore important to inform the mycology laboratory, as a minimum, from which anatomical region (hair, skin or nail) the specimen is obtained, which dermatological disease, and fungal (dermatophyte, *Candida*, *Malassezia* or non-dermatophyte mould) genera is suspected (**Table II**). Furthermore, the attending physician should note on the referral form whether an animal contact is probable and whether, for example, a mycosis with a non-dermatophyte is considered in onychomycosis. The microbiologist needs this information in order to interpret the results of the molecular tests correctly, but also to decide whether a culture should be created in parallel if the kit has gaps in its repertoire.

FUTURE PERSPECTIVES

The advantages of molecular diagnostics for the initial diagnosis of dermatophytosis are beyond question. A few studies have, so far, shown that the method can also be used for therapy monitoring (52, 53). Iwanaga et al., in particular, have demonstrated that the fungal load after 16 weeks of terbinafine therapy is significantly reduced (from 100% to 36%) (53). The patients' culture were already negative at this time, but, microscopically, fungal elements could still be detected in the KOH preparation. The most plausible explanation for this is that resting fungal cells (e.g. in the form of arthroconidia) are still present and may potentially germinate again after discontinuation of therapy. The survival of dormant fungal cells inside the nail is supported by follow-up studies, which after 18 months show a complete cure in only 76% of elderly patients receiving 3-month terbinafine therapy (54). Dormant cells are missed in the culture. Therefore, therapy control with PCR procedures may be suitable in the future, not to mention the short time-span in which such a finding is available, in order to decide whether to continue the therapy. Only very special PCR procedures are able to discriminate between live and dead cells; however, it is not known how long dormant fungal cells survive in the nail, hair or skin of the human body (55).

To date, there has been no significant development of resistance in dermatophytes to the use of antimycotics. This has suddenly changed with the Indian epidemic, which has lasted for approximately 6 years, and goes hand in hand with the use of over-the-counter ointments containing antimycotics (e.g. terbinafine), antibiotics and steroids (e.g. clobetasol). Terbinafine resistance or partial resistance in *T. mentagrophytes* strains with genotype VIII and *T. rubrum* reach rates of more than 65% and

Table II. Helpful information for the clinician to differentiate between suspected fungal pathogens, which is needed for the laboratory for choosing the most appropriate diagnostic methods

Anatomical region	Help for the clinician to differentiate between suspected fungal pathogens			Essential information for the microbiologist	Information helpful for the microbiologist
	Disease	Most common clinical signs	Age	Suspected pathogen	Exposure
Scalp (hair region)	Tinea capitis	Broken hairs Kerion Favus Alopecia Scaling	Children	Dermatophyte	Animal exposure Endemic contacts Woods light results Earlier treatment
	Seborrhoeic dermatitis/ Dandruff	Greasy skin scales on erythematous skin	Newborn Adults	*Malassezia*	
Face	Tinea faciei	Area with raised erythematous border or red patch	All ages, but mostly children	Dermatophytes	Animal exposure Signs of tinea capitis
	Seborrhoeic dermatitis	Greasy skin scales on erythematous skin primary centro-facial and eyebrows	Adults	*Malassezia*	
Upper body	Pityriasis versicolor	Hypo- or hyperpigmented maculae	Young and adults	*Malassezia*	Immunosuppression
	Malassezia folliculitis	Monomorphic pustules mainly located at seborrhoeic areas. No comedones	Young and adults	*Malassezia*	Immunosuppression
	Tinea corporis	Area with raised erythematous border or red patch. Skin scales	All ages	*Dermatophyte*	Animal exposure Other signs of tinea
Hands	Tinea manuum	Area with raised erythematous border or red patches. Skin scales. Hyperkeratosis.	All ages		Other signs of tinea e.g. tinea pedis
Groin & pubic area	Cutaneous candidiasis	Erythematous skin folds with satellite pustules (and skin scales)	All ages	*Candida*	Immunosuppression
	Tinea cruris	Area with raised erythematous border or red patch. Skin scales	Adults	*Dermatophytes*	
	Seborrhoeic dermatitis	Greasy skin scales on erythematous skin	Adults	*Malassezia*	
Feet	Cutaneous candidiasis	Interdigital maceration	All ages	*Candida*	Immunosuppression
	Tinea pedis	Interdigital maceration, skin scales, raised erythematous boarder, 'Moccasin foot', thickening of the soles	All ages	*Dermatophytes*	
	Cutaneous non-D mould infection	Interdigital maceration	Mostly adults	Non-D moulds	Immunosuppression
Nails	*Candida* onychomycosis	Paronychia Nail dystrophy	All ages	*Candida*	Immunosuppression Moist exposure
	Tinea unguium	Hyperkeratosis, superficial white discoloration, yellow streaks.	All ages, but prevalence increases with age	*Dermatophytes*	Concomitant tinea pedis?
	Non-D onychomycosis	Hyperkeratosis, discoloration, paronychia/ inflammation, nail dystrophy	All ages, but prevalence increases with age	Non-D moulds	

Non-D: non-dermatophyte.

17%, respectively, in India and are spread globally (56). This means that *T. mentagrophytes* strains will have to be fine-typed by molecular genetics in order to determine the exact identity, or a susceptibility test has to be performed. The advantage of the latter is that breakpoints can be defined; the disadvantage is that the inoculum, due to the filamentous growth and the often poor conidia formation of the fungi, is challenging and therefore not done routinely. Molecular methods, in particular sequencing with detection of specific genetic mutations leading to antifungal resistance (e.g. squalene epoxidase gene mutation leading to terbinafine resistance), which are independent of the fungal growth could overcome this problem (8, 56–59).

CONCLUSION

The diagnosis of superficial fungal infections has evolved from the first microscopic description more than 100 years ago to current techniques that are able to detect a wide range of clinically relevant fungi using molecular-based techniques. Worldwide traditional diagnostic methods, such as direct microscopy and culture, are still used, as they are cheap and the equipment is already available. The development of molecular-based methods has already improved a lot during the last years, from only being able to detect fungi in cultures to now being able to detect fungi directly in clinical samples. The molecular species-specific fungal detection of clinically relevant fungi is possible, as well as detection of specific mutations causing antifungal resistance. If it were possible to combine all these tests, it would enable the clinician to obtain the correct species identification, the possible source of infection and the susceptibility pattern of the involved pathogen by sending a single sample. The evolution of the diagnosis of superficial fungal infections is not far from this goal.

ACKNOWLEDGEMENT

Professor Roderick Hay is acknowledged for his constructive comments and for reviewing the text.

Conflicts of interest: DMLS was paid as a consultant for advisory board meeting by AbbVie, Janssen, Sanofi and received speaker's honoraria and/or received grants from the following companies: Abbvie, Galderma, Astellas, Novartis and Leo Pharma during the last 3 years. YG received speaker's honoraria and grants from Euroimmun.

REFERENCES

1. Kane J, Summerbell R, Sigler L, Krajden S, Land G. Laboratory handbook of dermatophytes: a clinical guide and laboratory manual of dermatophytes and other filamentous fungi from skin, hair and nails. In: Kane J, editor. Belmont: Star Publishing Co.; 1997.
2. de Hoog GS, Dukik K, Monod M, Packeu A, Stubbe D, Hendrickx M, et al. Toward a novel multilocus phylogenetic taxonomy for the dermatophytes. Mycopathologia 2017; 182: 5–31.
3. Hawksworth DL, Crous PW, Redhead SA, Reynolds DR, Samson RA, Seifert KA, et al. The amsterdam declaration on fungal nomenclature. IMA Fungus 2011; 2: 105–112.
4. Gräser Y, Scott J, Summerbell R. The new species concept in dermatophytes-a polyphasic approach. Mycopathologia 2008; 166: 239–256.
5. Chen X, Jiang X, Yang M, González U, Lin X, Hua X, et al. Systemic antifungal therapy for tinea capitis in children. Cochrane Database Syst Rev 2016; 5: CD004685.
6. Fuller LC, Barton RC, Mohd Mustapa MF, Proudfoot LE, Punjabi SP, Higgins EM. British Association of Dermatologists' guidelines for the management of tinea capitis 2014. Br J Dermatol 2014; 171: 454–463.
7. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol 2017; 177: 47–62.
8. Nenoff P, Verma SB, Vasani R, Burmester A, Hipler U, Wittig F, et al. The current Indian epidemic of superficial dermatophytosis due to Trichophyton mentagrophytes —a molecular study. Mycoses 2019; 62: 336–356.
9. Effendy I, Lecha M, Feuilhade de CM, Di CN, Baran R. Epidemiology and clinical classification of onychomycosis. J Eur Acad Dermatol Venereol 2005; 19: 8–12.
10. Narang T, Bishnoi A, Dogra S, Singh TD, Mahajan R, Kavita K. Disease burden and prescription patterns treating dermatophytosis in North India: salient findings from an online survey of 1041 dermatologists. J Eur Acad Dermatology Venereol 2019; 33: e391–e393.
11. Saunte DML, Piraccini BM, Sergeev AY, Prohić A, Sigurgeirsson B, Rodríguez-Cerdeira C, et al. A survey among dermatologists: diagnostics of superficial fungal infections – what is used and what is needed to initiate therapy and assess efficacy? J Eur Acad Dermatol Venereol 2018; 33: 421–427; jdv.15361.
12. Monod M, Jaccoud S, Stirnimann R, Anex R, Villa F, Balmer S, et al. Economical microscope configuration for direct mycological examination with fluorescence in dermatology. Dermatology 2000; 201: 246–248.
13. Ovrén E, Berglund L, Nordlind K, Rollman O. Dermatophytosis: fluorostaining enhances speed and sensitivity in direct microscopy of skin, nail and hair specimens from dermatology outpatients. Mycoses 2016; 59: 436–441.
14. Pihet M, Le Govic Y. Reappraisal of conventional diagnosis for dermatophytes. Mycopathologia 2017; 182: 169–180.
15. Gupta AK, Hofstader SL, Adam P, Summerbell RC. Tinea capitis: an overview with emphasis on management. Pediatr Dermatol 1999; 16: 171–189.
16. Morar N, Dlova NC, Gupta AK, Aboobaker J. Tinea capitis in Kwa-Zulu Natal, South Africa. Pediatr Dermatol 2004; 21: 444–447.
17. Hay RJ. Tinea Capitis: current status. Mycopathologia 2017; 182: 87–93.
18. Karaman BF, Açıkalın A, Ünal İ, Aksungur VL. Diagnostic values of KOH examination, histological examination, and culture for onychomycosis: a latent class analysis. Int J Dermatol 2019; 58: 319–324.
19. Velasquez-Agudelo V, Cardona-Arias JA. Meta-analysis of the utility of culture, biopsy, and direct KOH examination for the diagnosis of onychomycosis. BMC Infect Dis 2017; 17: 166.
20. Lipner SR, Scher RK. Onychomycosis. J Am Acad Dermatol 2019; 80: 835–851.
21. Monod M, Bontems O, Zaugg C, Lechenne B, Fratti M, Panizzon R. Fast and reliable PCR/sequencing/RFLP assay for identification of fungi in onychomycoses. J Med Microbiol 2006; 55: 1211–1216.
22. Monod M, Méhul B. Recent findings in onychomycosis and their application for appropriate treatment. J Fungi 2019; 5: 20.
23. Kawasaki M, Aoki M, Ishizaki H, Nishimura K, Miyaji M. Phylogeny of Epidermophyton floccosum and other dermatophytes. Mycopathologia 1996; 134: 121–128.

24. Mochizuki T, Sugie N, Uehara M. Random amplification of polymorphic DNA is useful for the differentiation of several anthropophilic dermatophytes. Mycoses 1997; 40: 405–409.
25. Graser Y, El Fari M, Presber W, Sterry W, Tietz HJ. Identification of common dermatophytes (trichophyton, microsporum, epidermophyton) using polymerase chain reactions. Br J Dermatol 1998; 138: 576–582.
26. Gräser Y, Czaika V, Ohst T. Diagnostic PCR of dermatophytes – an overview. JDDG J der Dtsch Dermatologischen Gesellschaft 2012; 10: 721–725.
27. Uhrlaß S, Wittig F, Koch D, Krüger C, Harder M, Gaajetaan G, et al. Halten die neuen molekularen Teste – Microarray und Realtime-Polymerasekettenreaktion – zum Dermatophytennachweis das, was sie versprechen? Hautarzt 2019; 70: 618–626.
28. Sherman S, Goshen M, Treigerman O, Ben-Zion K, Carp M-J, Maisler N, et al. Evaluation of multiplex real-time PCR for identifying dermatophytes in clinical samples – a multicentre study. Mycoses 2018; 61: 119–126.
29. Wisselink GJ, van Zanten E, Kooistra-Smid AMD. Trapped in keratin; a comparison of dermatophyte detection in nail, skin and hair samples directly from clinical samples using culture and real-time PCR. J Microbiol Methods 2011; 85: 62–66.
30. Alexander CL, Shankland GS, Carman W, Williams C. Introduction of a dermatophyte polymerase chain reaction assay to the diagnostic mycology service in Scotland. Br J Dermatol 2011; 164: 966–972.
31. Ohst T, Kupsch C, Gräser Y. Detection of common dermatophytes in clinical specimens using a simple quantitative real-time TaqMan polymerase chain reaction assay. Br J Dermatol 2016; 174: 602–609.
32. Bergmans AMC, van der Ent M, Klaassen A, Böhm N, Andriesse GI, Wintermans RGF. Evaluation of a single-tube real-time PCR for detection and identification of 11 dermatophyte species in clinical material. Clin Microbiol Infect 2010; 16: 704–710.
33. Walser M, Bosshard PP. Development and evaluation of a pan-dermatophyte polymerase chain reaction with species-level identification using sloppy molecular beacon probes. Br J Dermatol 2019; 180: 1489–1497.
34. Li HC, Bouchara J-P, Hsu MM-L, Barton R, Chang TC. Identification of dermatophytes by an oligonucleotide array. J Clin Microbiol 2007; 45: 3160–3166.
35. Patel R. A Moldy Application of MALDI: MALDI-ToF mass spectrometry for fungal identification. J Fungi 2019; 5: 4.
36. Denis J, Machouart M, Morio F, Sabou M, Kauffmann-LaCroix C, Contet-Audonneau N, et al. Performance of matrix-assisted laser desorption ionization–time of flight mass spectrometry for identifying clinical Malassezia isolates. J Clin Microbiol 2017; 55: 90–96.
37. Cassagne C, Normand A-C, L'Ollivier C, Ranque S, Piarroux R. Performance of MALDI-TOF MS platforms for fungal identification. Mycoses 2016; 59: 678–690.
38. Karabıçak N, Karatuna O, İlkit M, Akyar I. Evaluation of the Bruker matrix-assisted laser desorption–ionization time-of-flight mass spectrometry (MALDI-TOF MS) system for the identification of clinically important dermatophyte species. Mycopathologia 2015;180: 165–171.
39. Hedayati MT, Ansari S, Ahmadi B, Taghizadeh Armaki M, Shokohi T, Abastabar M, et al. Identification of clinical dermatophyte isolates obtained from Iran by matrix-assisted laser desorption/ionization time-offlight mass spectrometry. Curr Med Mycol 2019; 5: 22–25.
40. Intra J, Sarto C, Tiberti N, Besana S, Savarino C, Brambilla P. Genus-level identification of dermatophytes by MALDI-TOF MS after 2 days of colony growth. Lett Appl Microbiol 2018; 67: 136–143.
41. Normand A-C, Cassagne C, Gautier M, Becker P, Ranque S, Hendrickx M, et al. Decision criteria for MALDI-TOF MS-based identification of filamentous fungi using commercial and in-house reference databases. BMC Microbiol 2017; 17: 25.
42. Su H, Packeu A, Ahmed SA, Al-Hatmi AMS, Blechert O, İlkit M, et al. Species distinction in the Trichophyton rubrum complex. J Clin Microbiol 2019; 57. pii: e00352-19.
43. Suh S-O, Grosso KM, Carrion ME. Multilocus phylogeny of the Trichophyton mentagrophytes species complex and the application of matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry for the rapid identification of dermatophytes. Mycologia 2019; 110: 118–130.
44. da Cunha KC, Riat A, Normand A-C, Bosshard PP, de Almeida MTG, Piarroux R, et al. Fast identification of dermatophytes by MALDI-TOF/MS using direct transfer of fungal cells on ground steel target plates. Mycoses 2018; 61: 691–697.
45. Delavy M, Dos Santos AR, Heiman CM, Coste AT. Investigating antifungal susceptibility in Candida species with MALDI-TOF MS-based assays. Front Cell Infect Microbiol 2019; 9: 19.
46. Veasey J V., Meneses OMS, da Silva FO. Reflectance confocal microscopy of tinea capitis: comparing images with results of dermoscopy and mycological exams. Int J Dermatol 2019; 58: 849–851.
47. Pharaon M, Gari-Toussaint M, Khemis A, Zorzi K, Petit L, Martel P, et al. Diagnosis and treatment monitoring of toenail onychomycosis by reflectance confocal microscopy: Prospective cohort study in 58 patients. J Am Acad Dermatol 2014; 71: 56–61.
48. Rothmund G, Sattler EC, Kaestle R, Fischer C, Haas CJ, Starz H, et al. Confocal laser scanning microscopy as a new valuable tool in the diagnosis of onychomycosis – comparison of six diagnostic methods. Mycoses 2013; 56: 47–55.
49. Li X-F, Shen Y-N, Chen W, Chen H, LV G-X, Liu W-D. A new medium for diagnosis of dermatophyte infection. Eur J Dermatology 2009; 19: 34–37.
50. Rahman MA, Chowdhury OA, Debnath MR, Ahmed SM, Das S, Choudhury R, et al. Comparison among different culture media for the detection of dermatophytes. Mymensingh Med J 2018; 27: 626–630.
51. Tsunemi Y, Hiruma M. Clinical study of Dermatophyte Test Strip, an immunochromatographic method, to detect tinea unguium dermatophytes. J Dermatol 2016; 43: 1417–1423.
52. Kupsch C, Czaika V-A, Deutsch C, Gräser Y. Trichophyton mentagrophytes – a new genotype of zoophilic dermatophyte causes sexually transmitted infections. J Dtsch Dermatol Ges 2019; 17: 493–501.
53. Iwanaga T, Ushigami T, Anzawa K, Mochizuki T. Pathogenic dermatophytes survive in nail lesions during oral terbinafine treatment for tinea unguium. Mycopathologia 2017; 182: 673–679.
54. Loo DS. Onychomycosis in the elderly: drug treatment options. Drugs Aging 2007; 24: 293–302.
55. Soejima T, Minami J-I, Xiao J-Z, Abe F. Innovative use of platinum compounds to selectively detect live microorganisms by polymerase chain reaction. Biotechnol Bioeng 2016; 113: 301–310.
56. Süß A, Uhrlaß S, Ludes A, Verma SB, Monod M, Krüger C, et al. Ausgeprägte Tinea corporis durch ein Terbinafin-resistentes Trichophyton-mentagrophytes-Isolat vom indischen Genotyp bei einem Säugling aus Bahrain in Deutschland. Hautarzt 2019; 70: 888–896.
57. Singh A, Masih A, Khurana A, Singh PK, Gupta M, Hagen F, et al. High terbinafine resistance in Trichophyton interdigitale isolates in Delhi, India harbouring mutations in the squalene epoxidase gene. Mycoses 2018;61: 477–484.
58. Khurana A, Masih A, Chowdhary A, Sardana K, Borker S, Gupta A, et al. Correlation of in vitro susceptibility based on MICs and squalene epoxidase mutations with clinical response to terbinafine in patients with tinea corporis/cruris. Antimicrob Agents Chemother 2018; 62: e01038-18.
59. Saunte DML, Hare RK, Jørgensen KM, Jørgensen R, Deleuran M, Zachariae CO, et al. Emerging terbinafine resistance in trichophyton: clinical characteristics, squalene epoxidase gene mutations and a reliable EUCAST method for detection. Antimicrob Agents Chemother 2019; 63. pii: e01126-19.

Centenary theme section: CUTANEOUS AND GENITAL INFECTIONS

REVIEW ARTICLE

The Management of Scabies in the 21st Century: Past, Advances and Potentials

Charlotte BERNIGAUD[1–5], Katja FISCHER[2,4] and Olivier CHOSIDOW[1,4,5]

[1]Dermatology Department, AP-HP, Henri Mondor hospital, Paris-Est University, Créteil, France, [2]QIMR Berghofer Medical Research Institute, Infectious Diseases Program, Herston, Brisbane, Australia, [3]3Research group Dynamyc, EA7380, Faculté de Santé, EnvA, USC ANSES, Paris-Est University, Créteil, France, [4]IACS (International Alliance for the Control of Scabies, and [5]GrIDIST, Groupe Infectiologie Dermatologique – Infections Sexuellement Transmissibles, French Society of Dermatology

Scabies is one of the most common skin diseases worldwide, affecting 150–200 million people yearly. Scabies affects young children in particular, and has the greatest impact in poor overcrowded living conditions. The burden of the disease is now well characterized, including group A *Streptococcus* and *Staphylococcus aureus* bacterial superinfections, with reports of nephritis, acute rheumatic fever, or fatal invasive sepsis secondary to scabies. Management of scabies remains largely suboptimal from diagnosis to treatment, and progress in the development of new therapeutic measures leading to cure is urgently needed. This review gives an overview of the current limitations in the management of scabies, an update on recent advances, and outlines prospects for potential improvements.

Key words: scabies; Sarcoptes scabiei; neglected tropical disease; ivermectin; permethrin; moxidectin; acaricide discovery and development; ovicidal.

Accepted Mar 19, 2020; Epub ahead of print Mar 24, 2020

Acta Derm Venereol 2020; 100: adv00112

Corr: Charlotte Bernigaud, Department of Dermatology, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, FR-94010 Créteil, France. E-mail: charlotte.bernigaud@aphp.fr

SIGNIFICANCE

Scabies is more than just a disease that provokes a horrendous itch. For more than a century, researchers, clinicians and public health physicians, together with policymakers, have worked to improve the management of scabies. Finally, in 2017, scabies was added to the WHO list of neglected tropical diseases after a long and still ongoing process of documenting the morbidities and burden caused by the disease. This additional and increased research activity, resulting in high-impact publications, has increased our knowledge of the biology, pathology and management of scabies, and has opened doors to new strategies.

Scabies (Latin *scabere* " to scratch") is a common parasitic disease caused by the microscopic mite *Sarcoptes scabiei* var. *hominis* (1). The burrowing mite causes intense itching, associated with typical skin lesions. The disease has been known for over 2,500 years; the Greeks and Romans were the first to write about its contagious nature. The mite was first identified and illustrated in the 17th century (2). Despite marked advances in parasitology in the 19th and 20th centuries, research into scabies has been hampered largely by limited access to the parasite and by low interest in an ectoparasite that mainly affects the poor. The earliest understanding of the mite biology and transmission was provided by Kenneth Mellanby, a British entomologist, in the 1940s during World War II (3, 4). Further advances in the physiopathology and host-parasite interactions have been made in the last 30 years (5, 6), mainly through the development of experimental animal models (7, 8). The therapeutic options for the management of scabies increased considerably in the 1970–80s with the discovery of ivermectin, one of the most important drugs currently used to treat scabies; the researchers were recently awarded, 35 years after its discovery, the 2015 Nobel Prize for Physiology and Medicine (9).

Currently, the recent expansion of multi-omics techniques will enable scientists to design large-scale mite and host molecular and biochemical analyses to develop new diagnostic tools or treatments in the near future (10–13). Scabies was, for a long time, not appropriately considered to be a true health target. In the past 10 years, stupendous efforts, made by a group of experts brought together in the International Alliance for the Control of Scabies (IACS), have given scabies the recognition it deserves (14). Thus, in 2017, the WHO decided to add scabies to the list of neglected tropical diseases and has called for large-scale action to achieve control and eradication (15).

WHY DO WE NEED TO IMPROVE SCABIES TREATMENT?

Scabies is a prevalent disease, which is present in all parts of the world, with greatest prominence in disadvantaged populations living in tropical and subtropical regions, and has a documented significant burden. The latest estimates suggest that 150–200 million people have scabies in the world every year, and that the scabies burden is particularly high in Asia, Oceania, and Latin America (16). Young children in underprivileged populations

living in crowded conditions are more often at risk (17). Transmission of scabies occurs mainly via skin-to-skin contact and, less frequently, via fomites within a patient mite-contaminated environment (generally in the context of severe forms of scabies; see below). As scabies is contagious, persons sharing the same household with patients may frequently be affected. This is especially the case in severe scabies, i.e. profuse or crusted scabies, in which the mite burden per person is dramatically increased, small epidemics around a single case can easily develop, and are fuelled by overcrowded households and transient lifestyles. The risk of transmission is known to depend on the patient's mite load, household size and population concentration, and how individuals interact with each other. Indeed, people living in clustered communities or in crowded housing conditions are at higher risk of scabies and outbreaks. In high-income nations, high endemicity of scabies is often reported in closed communities and institutional settings, such as hospitals, child-care and elderly-care residential facilities (18, 19), prisons, schools, homeless populations, and refugee camps (20–22).

For a long time, the scabies mite has been erroneously perceived as an ectoparasite that just causes itching. However, recent epidemiological studies indicate increasingly substantial morbidity, and even mortality (23), due to scabies infection, mostly caused by bacterial infections appearing with the parasitic infestation (14, 24). It has been hypothesized that scratching of lesions in response to the immense itch is present more often in scabies than in any other pruritic skin affections (25). The discomfort caused by the intense itch can have direct consequences, i.e. depriving patients of sleep (26), interfering with concentration at work or school, leading to a negative impact on attendance, performance (27) and quality of life (28). Scratching scabies lesions themselves leads to breaches in skin barrier that creates an entry point for opportunistic commensal or pathogenic bacteria that can become invasive, such as group A *Streptococcus* (GAS) and *S. aureus* (29). These bacteria lead to secondary infection of the epidermis, also known as pyoderma or impetigo, which can become more severe and cause skin and soft-tissue infections (including necrotizing fasciitis), septicaemia, or more invasive bacterial infections (24). In some cases, immune-mediated diseases can occur following infection, such as glomerulonephritis (30) or acute rheumatic fever (31), both of which can become chronic. This association between scabies parasites and bacterial pathogens is observed mainly in tropical or subtropical areas of the globe and in remote locations (17); with some data suggesting that up to 40% of impetigo lesions can be linked with scabies, especially among young children (32, 33). This particular link was established early in the 1970s, with epidemiological studies showing epidemics of acute glomerulonephritis in Trinidad (34) or Southern Africa (35) contemporaneously with scabies outbreaks, or in interventional studies in the field showing reduction in childhood haematuria following scabies treatment (30), or reduction in impetigo or skin sores prevalence paralleling a reduction in scabies numbers during mass drug administration (MDA) campaigns (36–38). More recent fundamental experimental work has supported and, in part, explained these observations with evidence of direct effects of mite gut proteins (serpins and serine proteases) in downregulating the innate host immunity including complement defence and neutrophil function, thereby modulating the microenvironment around the mite, allowing associated bacteria to flourish (39–43). Beyond the itch, scabies still causes a significant social impact, affecting quality of life and school or job absenteeism amongst infested patients. Its marked social, economic and psychological ramifications are underscored, but are sufficient to justify global improvement in its management.

WHO DO WE NEED TO TREAT?

Typically, the first symptoms of scabies are severe itch that worsens at night (44) and typical skin lesions caused by the penetration and progress of the mite through the epidermis. Most scabies lesions are found in classical sites, such as finger webs, hands, wrists, periumbilical skin, buttocks, genitals, periareolar region in females, or feet (1). In adult patients, the head is usually not affected, although it may be involved in infants, and babies (45). Burrows, vesicles, pustules, nodules, or excoriated pruritic papules are the most common lesions observed, all of which indicate the presence of a mite within the epidermis (**Fig. 1**A). The severe forms of scabies include profuse and crusted scabies. Both presentations are characterized by a very high parasite burden, with hundreds, thousands or even millions of mites per patient, and the development of extensive lesions. In such forms of scabies, hyperkeratotic skin (rather than real crusts) may be restricted to a finger, toe, or the scalp, for example, or diffusely affect multiple skin sites, including the face and palms and soles (1). This condition is seen in the elderly or in patients with underlying immunodeficiency from any cause (transplant recipients, corticosteroid use including topically-applied medication, HIV-, or HTLV-1-infested patients) (46–48).

The diagnosis of scabies is easy if a burrow, the specific lesion of scabies, is observed at a typical site of predilection. However, burrows may not be visible and diagnosis of scabies can be challenging, leading to misdiagnosis and mismanagement. Clinical diagnostic algorithms have been created to assist health-workers in recognizing scabies using a combination of parameters of patient history and clinical arguments, such as, for example, a history of diffuse itch, presence of lesions in typical skin areas, and itching in household members (49, 50). These diagnostic aids, which have proved reliable in endemic regions,

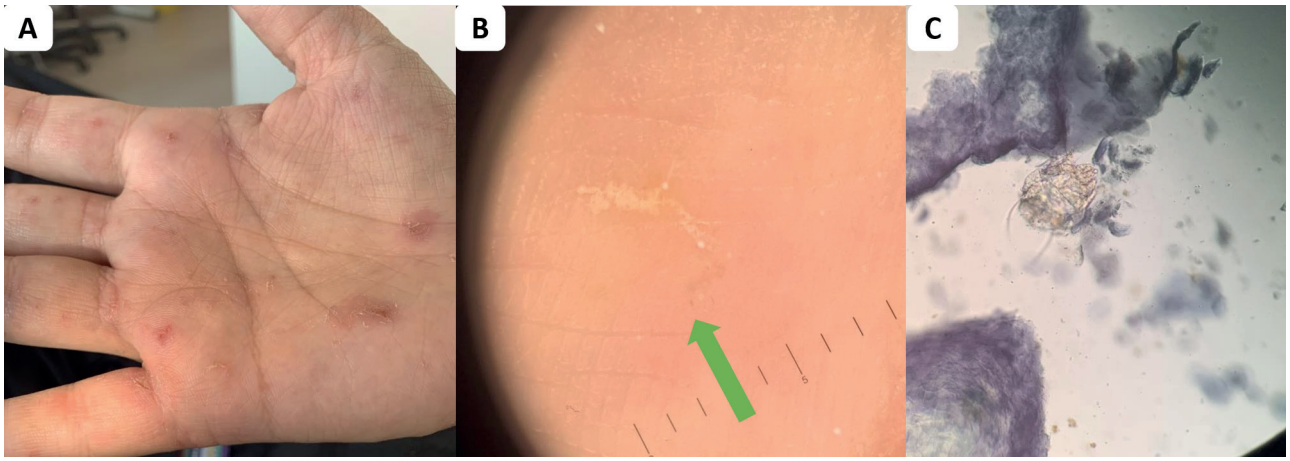

Fig. 1. Typical lesions of ordinary scabies. (A) Scabies lesions on the palm of the right hand with linear burrows, tiny vesicles and papular scabies lesions. (B) A burrow lesion from patient in (A) using dermoscopy showing the "jet-with-contrail" and an image of a brown triangle at the end, the "deltawing jet" (10-fold magnification). (C) Direct examination of skin scraping from patient in (A), showing an adult scabies mite (x10, lactophenol cotton blue staining).

have to be extrapolated and optimized across a larger range of settings, from the dermatologist's daily practice offices to resource-poor field settings, regardless of local prevalence. With this in mind, consensus criteria for the diagnosis of scabies were developed recently using a 4-round Delphi process including 34 international experts under the aegis of IACS (51). The IACS 2019 Criteria includes 3 levels of definition (confirmed scabies, clinical scabies, and suspected scabies case) and 8 subcategories. The accuracy and reproducibility of scabies diagnosis using these criteria have yet to be validated, as well as the ease of using it for GPs, experts in dermatology and other specialties, and non-expert health-workers (52).

As yet, a simple test for scabies based on molecular markers is still not available. Non-invasive methods have been developed for directly identifying the mite in diagnostic scrapings (53). The gold standard remains the visualization of the parasite (adults or immature forms), eggs, eggshell fragments or mite faecal pellets by light microscopic examination of a skin scraping. New technologies have been customized. Their sensitivity and specificity are summarized in **Table I**. Light microscopy examination has an excellent specificity (Fig. 1B), but is highly operator-dependent and is time-consuming, as repeated scrapings may be necessary. Dermoscopy or epiluminescence microscopy are tools used in daily clinical practice by dermatologists for a variety of cutaneous disorders, including parasitic infestations (54). The diagnosis of scabies using dermoscopy is confirmed by the observation of the "jet-with-contrail" pattern in the skin, representing a mite and its burrow, or an image of a black or brown triangle, the "delta-wing jet" sign representing the head of the mite (Fig. 1C) (55). Videodermatoscopy utilizes a dermoscope with a video camera connected to a computer that allows very high magnification and can be used to assess the viability of living mites. These are expensive techniques and therefore some authors have adapted low-cost equipment, used in botanical or entomology investigation, for use in the medical assessment of scabies (56). Reflectance confocal microscopy has been developed more recently for pigmented skin lesions, to differentiate malignant melanoma from benign naevi. The system uses an 830-nm wavelength diode laser and provides high optical resolution to penetrate to a depth of 200–300 µm into the skin. Imaging of the scabies mites and eggs using this device has been described (57). Some authors have tried to develop diagnostic techniques using molecular tools, such as matrix-assisted laser desorption ionization – time of flight (MALDI-TOF), antigen detection system or PCR specifically targeting scabies DNA. With PCR, while most studies have found a very high specificity,

Table I. Comparison of the specificity and sensitivity of the different currently available diagnostic non-invasive methods for scabies. Adapted from Chosidow & Sbidian (62) and Micali et al. (53)

	Clinical diagnosis algorithm	Skin scraping and light microscopy	Burrow ink test	Adhesive tape test	Epiluminescence microscopy (dermoscopy)	Videodermatoscope	Reflectance confocal microscopy	PCR-based method
References	(49)	(55)/(63)	(64)	(63)	(55)/(63)	(65)	(65)	(59)/(66)
Sensitivity, %	96.2	90/46	36.6	68	91/83	95	92	75.7/37.9
Specificity, %	98	100/100	100	100	86/46	97	100	100/100
Positive predictive value, %	87.7	100/100	–	100	88/47	97	100	–/100
Negative predictive value, %	99.4	90/77	–	85	90/85	95	92	–/61.7
Duration of the procedure	15 min for the entire body	30 min	5 min	10 min	5–10 min for the entire body	5–10 min for the entire body	60 s to 10 min for each lesion	Half a day
Prices, USD	–	US$ 500	–	US$ 10	US$ 500–700	US$ 25,000	US$ 150,000	US$ 200

often close to 100%, sensitivity was continually low, ranging from 30% to 60% (58–60), poorer compared with parasite observation either by microscopic or dermoscopic examination (61). No biomarker-based diagnostic kits have been developed for use as a simple and rapid method to identify mite infection without dermatological skills.

Improvement in scabies management is essential and will come from better identification of which patients need to be treated. Thus, the accurate and definitive diagnosis of scabies is crucial. Non-invasive diagnostic tools have been developed, but will have to be improved further.

HOW CAN WE TREAT SCABIES?

Treatment of small clusters (individual and family level)

Treatment must be prescribed for all confirmed cases of scabies, and should be given to all household and family contacts. The options available for treatment of scabies are summarized in **Table II**. Topical medicines were considered first-line treatment until the arrival of oral ivermectin in 1981, which was, at first, reserved for recurrent, difficult-to-treat cases, those with superinfected or eczematous skin, or for patients with crusted scabies (67). Topical agents should be applied to the entire skin surface, from "head-to-toe", avoiding the eyes, nose, and mouth. The application period depends on the specific instructions from the manufacturer. Adverse events are reported with all topical medicines for scabies, but they appear to be limited. Oral ivermectin is given at a standard dose of 0.2 mg/kg and may be associated with lower rates of complete cure if given only once (68–70). This could be explained by the limited ovicidal activity of the drug (71) and the short half-life of ivermectin in the skin, which was shown in 2 experimental trials in a porcine scabies model (72, 73). Giving the drug with a high-fat content meal has been proposed in order to increase its absorption and, accordingly, this might increase its efficacy (74, 75). Most scabicides act by affecting the nerve and muscle function of the parasite, and they are active only against mobile stages (larva, nymph and adults) and not eggs (13). The optimal interval between dosing in the 2-dose regimen still needs to be optimized and should be a short window between larval hatching (occurring at day 2–4 of the mite life-cycle) and the development of the adult stage that can be fertilized (at day 5–8, maximum day 15). Two recent Cochrane systematic reviews of data from respectively 22 (76) and 15 (77) randomized controlled trials (RCTs) placed topical 5% permethrin and ivermectin at the same level of efficacy and safety, and are consequently considered as the reference treatments. Between these 2 systematic reviews, performed in 2010 and 2017, no newer trials were included in the evaluation, but the conclusions were different based on

Table II. Comparison of treatments in use to treat scabies in humans

Drugs	Formulations	Recommended treatments	Cost (Euros)	Efficacies (%)*	Main adverse reactions	Use in children	Use during pregnancy	Use in breastfeeding women
Ivermectin	200 µg/kg Pills	Repeat after 7 days	€19 for 4 tablets at 3 mg=€38 for a complete treatment (weight 70 kg)	70–100	Nausea, rash, dizziness, itching, eosinophilia, abdominal pain, fever, tachycardia	Not approved in children <15 kg or 5 years of age	Only recommended in France	Only recommended in France
	1% Cream/lotion	Overnight (8–12 h) – from head-to-toe – repeat once after 7–14 days	€20 for 15 g cream=€80 for a complete treatment	69–85	Pruritus, burning, stinging, eczema	Not approved in children	Not recommended	Not recommended
Permethrin	5% Cream	Overnight – from head-to-toe – repeat once after 7–14 days	€19 for 30g cream=€38 for a complete treatment	86–100	Pruritus, burning, stinging, eczema	Safe in children ≥2 months of age	Approved	Not recommended
Benzyl benzoate	10–25% Lotion or emulsion	Apply from head-to-toe for 24 h On days 1, 2 and repeat after 7 days	€15 for 125 mL emulsion=€30 for a complete treatment	48–92	Pruritus, burning, stinging, pustules, skin irritation, eczema	Safe in children ≥ 1 month of age	Authorized if necessary	Not recommended
Crotamiton	10% Cream	Overnight on days 1 and 2	€7 for 40g cream	63–88	Pruritus, skin irritation, eczema, erythema, anaphylactic reaction	Safe in children	Not recommended	Not recommended
Precipitated sulphur	6–33% Cream or lotion	Apply from head-to-toe for 3 consecutive nights	–	39–100	Messy application, malodour	Safe in children	Authorized	–
Malathion	0.5% Aqueous lotion	Repeat after 7 days	€12 for 100 ml=€24 for a complete treatment	47–72	Pruritus, burning, stinging, skin irritation, CNS toxicity, dizziness, seizure	Not approved in children <2 years of age	Withdrawn from the European market	Withdrawn from the European market
Lindane	1% Lotion or cream	Overnight Repeat after 7 days	–	64–96	CNS toxicity, dizziness, seizures, renal and hepatic toxicity reported with overdosage	Withdrawn from the European market	Withdrawn from the European market	Withdrawn from the European market

*Efficacies according to Strong & Johnstone (76). Updated from Bernigaud C. et al. (13).
CNS: central nervous system.

the regimen of the drugs used. Strong & Johnstone (76) concluded, in 2010, that topical permethrin 5% was the most efficacious agent for the treatment of scabies. Rosumeck et al. in 2017 (77), reviewing the same trials as in 2010, concluded that topical permethrin was equal to ivermectin when 2 doses were given. Overall, among all the therapeutic trials analysed, a significant heterogeneity in the methods and outcome measurements was found, making the conclusions difficult to evaluate. A French randomized clinical trial, cluster-designed with a robust protocol, is currently recruiting patients with common scabies to establish finally which treatment, 5% topical permethrin or 0.2 mg/kg oral ivermectin, both given twice at 10 days' interval is the most efficacious (SCRATCH, NCT02407782) (78). Treatment also depends on the availability of the drug in the different countries. For example, since it was first approved in France for the treatment of scabies in 2001, oral ivermectin has been licensed only for this indication in 10 nations as first-line treatment, and is mostly used off-label and may not even be accessible in other countries. In those countries, available and cheaper medications are preferred, such as sulphur preparations and benzyl benzoate. To widen access to this key effective medication, in June 2019 the WHO added ivermectin to the 21st WHO Essential Medicines List (79).

Follow-up is necessary after treatment, to evaluate the cure of the patient and to prevent re-infestation. Treatment success should be expected in approximately two weeks. Itching can persist for up to one month after successful treatment. Causes of apparent treatment failure with an effective treatment include incorrect diagnosis, dermatitis secondary to the mite or topical agent, incorrect application of the topical agent, poor penetration of the agent into hyperkeratotic skin or nails, and re-infestation from scabies-infested close contacts (80). Parasite resistance has been reported for both permethrin (81, 82) and ivermectin (83, 84), but its clinical importance remains a matter of debate. Studies are lacking and surveillance for better documentation is warranted. Treatment failure has been observed, mainly because drugs are not 100% effective (74– 93% clearance is observed with permethrin and 68–86% with ivermectin (77)). Some authors recently tried to determine which factors were associated with treatment failure (85, 86). These 2 studies found that incorrect decontamination of furniture or fomites was a key factor in treatment failure. While living mites can be found in samples of environmental dust from floors and furniture of patients with scabies (87), the indirect transmission of mites by fomites is thought to be rare (3), at least in common scabies. Studies are needed to evaluate the impact of environment-decontamination procedures on the success of the treatment (88) in non-profuse cases of scabies and in cases of severe scabies with high mite-load, in order to optimize cure rates. Simplified and generalized algorithms, based on high-throughput experimental data that can be used in a large range of settings, including resource-poor population, were suggested recently (89).

Appropriate treatment should also be given for severe secondary bacterial infection. Topical antibiotic creams (e.g. mupirocin or fusidic acid) are not recommended in cases with profuse lesions. Systemic antibiotics have to target GAS and *S. aureus* (including MRSA in specific areas). Oral trimethoprim-sulphamethoxazole (cotrimoxazole) or intramuscular benzathine penicillin G are used in tropical endemic regions (90), whereas pristinamycin, amoxicillin/clavulanic acid or cephalexin may be used in non-tropical regions. For the itch, there is no specific treatment. Antihistamines can assist, but it is their sedative properties that are effective, rather than an anti-pruritic mechanism (91).

For the treatment of crusted scabies, there is no consensus as, to date, no randomized controlled trials have been performed. Most records come from small studies, and experience in northern Australia, where highly infested patients are seen (47). They suggest a regimen of multiple doses of oral ivermectin with repeated topical permethrin and keratolytic therapy.

For the treatment of children, only topical treatments have been approved. The application time in children can differ from that in adults. Oral ivermectin cannot be used if the patient's body weight is less than 15 kg. Recent reports using ivermectin off-label in infants and young children (aged 1–64 months, body weight 4–14.5 kg) are highly reassuring on the safety and efficacy of this treatment in this age group (92). Recommendations for use of ivermectin in infants may change in the near future. For the treatment of pregnant women, only one country allows the use of ivermectin, as a second-line treatment after 5% topical permethrin, at any trimester of the pregnancy supported by an expert recommendation (93). Most exclusions of women from ivermectin treatment are for basic precaution rather than any anticipated foetal toxicity. In practice, thousands of women have been treated inadvertently before their pregnancy becomes known in onchocerciasis eradication programmes in Africa. Occurrence of miscarriage, stillbirth, or birth defects in the reference population did not differ significantly (94, 95). Continued surveillance is necessary, as well as more fundamental work to enable this target population to be treated adequately.

Treatment of large clusters (collectivity level)

As scabies is a contagious disease spread by skin-to-skin contact, people living in crowded communities are at greater risk. In these collectivity settings, because patients and their close contacts have to be treated all at the same time and because prevalence can be very high in some communities, the opportunity of MDA has emerged to control scabies in endemic spaces (96). The first MDA was performed in a scabies-endemic

region of Panama in the 1970s by Taplin et al. (97). Successively, multiple programmes have evolved in all parts of the world to control scabies by MDA, firstly with lindane, topical permethrin, followed by the use of oral ivermectin (summarized in Table SI[1]). Only one trial, the Skin Health Intervention Fiji Trial (SHIFT) has randomized 3 islands in Fiji to 1 of 2 intervention strategies, i.e. oral ivermectin and topical permethrin, compared with standard care as control (36). At 12 months, mass treatment with ivermectin was found to be the most effective, with a relative reduction of 94% from baseline in the prevalence of scabies and 67% in impetigo. During all these years, many MDA programmes have resulted in successful and significant reduction in the prevalence of scabies in highly endemic or endemic settings. Controversial results have been reported only from Australia (see Table SI[1]), presumably because the adherence of the target population with the treatment regimen was poor. Fewer data exist on the sustainability of success of MDA in the longer term, but this approach seems to be efficient (98, 99), especially in communities with a scabies prevalence higher than 5% (100). Interestingly, the treatment of scabies alone also seems to result in a significant reduction in GAS impetigo (36) and kidney complications, signified by the reduction in haematuria (30). A recent study has indicated that it is not necessary to add antibiotics during MDA for scabies to reduce the prevalence of impetigo (37). Although, as most MDAs target only one disease, some programmes have looked at the potential to integrate scabies MDA in other schemes for neglected tropical diseases eradication programmes (101), such as onchocerciasis, lymphatic filariasis, trachoma, schistosomiasis, yaws, or infection with soil-transmitted helminths. On a smaller scale, combining ivermectin and albendazole administration to treat both lymphatic filariasis and onchocerciasis, or scabies and lymphatic filariasis (102), or scabies and strongyloidiasis (103) were found to be effective and safe. On a larger scale, the co-administration of azithromycin and ivermectin for targeting trachoma and scabies in the Choiseul Province, Solomon Islands, was also found to be effective, feasible and secure in 26,188 enrolled participants (104). Remarkably, MDAs for scabies control have had additional unintended downstream effects, as they have been found to be efficient in controlling head lice (105) and Anopheles farauti, the vector of malaria in the Solomon Islands (106). All these interesting programmes provide positive results and robust evidence to encourage MDA with ivermectin to control scabies in highly endemic populations on a larger scale. Optimization of these programmes will be required in order to understand factors associated with success, defining the appropriate regimen to use, and determining the numbers of rounds of MDA (24).

Similarly, controlling scabies at a larger scale by MDAs has been extrapolated for smaller outbreaks in closed institutions, such as schools (107), prisons (108), age-care facilities (18), and, more recently, in asylum seekers (109).

HOW WILL WE TREAT SCABIES IN THE NEAR FUTURE?

As mentioned above, treatment either with a topical acaricide or oral treatment with ivermectin are the current standards of care for common scabies. Most patients with scabies infection will recover with a suitable medical intervention, but patients often require multiple treatments and/or a combination of topical and systemic drugs. The major limitations of current therapies are poor compliance with repeated treatments, limited activity against eggs, and half-lives too short to cover the whole 14-day life cycle of the mite (13). The recent development of an experimental porcine scabies model provides real potential to conduct translational preclinical and pharmacokinetic studies with new drug candidates.

In order to optimize and improve the therapeutic options for scabies treatment, the concept of translating existing drugs used in the veterinary clinic to humans was investigated (72, 73). Moxidectin is a molecule compound suitable for oral administration. It is a member of the same family as ivermectin, and was recently developed and approved by the US Food and Drug Administration (FDA) for treatment of onchocerciasis. Moxidectin has a very interesting pharmacological profile: rapid absorption, large distribution, and a much longer half-life in plasma and, importantly, in the skin than ivermectin (72), potentially covering the entire life-cycle of the scabies mite. In a pilot trial in the experimental pig model for scabies performed in France, moxidectin used orally, at a single dose of 0.3 mg/kg, was found to be more effective than the conventional 2 doses of ivermectin at 1-week interval (0.2 mg/kg) (72). A multicentre clinical phase II trial in humans is in progress in Australia and France, with the aim of developing moxidectin as a new single-dose treatment for scabies (NCT03905265) (117).

The use of higher doses of ivermectin for treatment of scabies is also an interesting option and currently under investigation (118). The clinical development of ivermectin for scabies and other parasites might have been rushed, and the dose of 0.2 mg/kg was not derived after high-level dose-ranging studies; it was based on a reasoned, but arbitrary, decision. An emerging hypothesis is that the parasite infection may need a higher dose of ivermectin to achieve a cure. This concept was first raised for head lice infestation, as the standard dose of oral ivermectin (0.2 mg per kg body weight) was found to be poorly effective. Further studies found that

[1]https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3468

treatment with 0.4 mg/kg ivermectin (a double dose) was approximately 95–100% effective (119). Similar results were reported for other parasitic infections (118). Dose-ranging experimental studies in the pig model are ongoing to determine whether higher doses of ivermectin are more effective at controlling scabies infestation. In France, a French Ministry of Health-approved randomized controlled clinical trial is in process, comparing the efficacy of ivermectin given orally as the higher double dose of 0.4 mg/kg with the conventional treatment dose of 0.2 mg/kg, given 3 times 7 days apart (on D0, D7 and D14), supplemented in both arms with daily application of emollient therapy and topical 5% permethrin on D0 and D7 (GALECRUSTED, NCT02841215) (120).

Other novel treatments are also in development, using herbal compounds (121, 122) and even entomopathogenic fungus (123). The use of advanced molecular and biochemical technologies will help to design new therapeutic tools. These next-generation drugs are needed immediately and should be tailored to scabies mites.

CONCLUSION

The worldwide prevalence of scabies remains high, and currently available treatments may not be sufficiently effective to control the disease. During the past 20 years, at the beginning of the 21st century, a lot of important work has been completed concerning the management of scabies, mainly driven by IACS, a global advocacy body formed in 2012. We hope that the next 10 years will provide a significant improvement for patients infested with scabies, and that new drugs and diagnostics will enhance the therapeutic options for the benefit of patients and their families.

ACKNOWLEDGEMENTS

Conflicts of interest: CB received research support from Bioderma Laboratoire Dermatologique and Codexial Dermatologie. OC received drugs, donated free of charge, for research from Codexial Dermatologie and lecture fees from Zambon Laboratoire, Codexial Dermatologie and MSD France. CB and OC act as unpaid scientific advisors for Medicines Development for Global Health. The authors have no other potential conflicts of interest to declare.

REFERENCES

1. Chosidow O. Clinical practices. Scabies. N Engl J Med 2006; 354: 1718–1727.
2. Currier RW, Walton SF, Currie BJ. Scabies in animals and humans: history, evolutionary perspectives, and modern clinical management. Ann N Y Acad Sci 2011; 1230: E50–60.
3. Mellanby K. Transmission of scabies. Br Med J 1941; 2: 405–406.
4. Mellanby K, Johnson CG, Bartley WC, Brown P. Experiments on the survival and behavior of the itch mite, Sarcoptes scabiel DeG. var hominis. Bull Entomol Res 1942; 33: 267–271.
5. Arlian LG, Morgan MS. A review of Sarcoptes scabiei: past, present and future. Parasit Vectors 2017; 10: 297.
6. Holt DC, Fischer K. Novel insights into an old disease: recent developments in scabies mite biology. Curr Opin Infect Dis 2013; 26: 110–115.
7. Mounsey K, Ho M-F, Kelly A, Willis C, Pasay C, Kemp DJ, et al. A tractable experimental model for study of human and animal scabies. PLoS Negl Trop Dis 2010 Jul 20; 4: e756.
8. Arlian LG, Runyan RA, Achar S, Estes SA. Survival and infectivity of Sarcoptes scabiei var. canis and var. hominis. J Am Acad Dermatol 1984; 11: 210–215.
9. Laing R, Gillan V, Devaney E. Ivermectin – old drug, new tricks? Trends Parasitol 2017; 33: 463–472.
10. Fernando DD, Marr EJ, Zakrzewski M, Reynolds SL, Burgess STG, Fischer K. Gene silencing by RNA interference in Sarcoptes scabiei: a molecular tool to identify novel therapeutic targets. Parasit Vectors 2017; 10: 289.
11. Mofiz E, Holt DC, Seemann T, Currie BJ, Fischer K, Papenfuss AT. Genomic resources and draft assemblies of the human and porcine varieties of scabies mites, Sarcoptes scabiei var. hominis and var. suis. GigaScience 2016; 5: 23.
12. Swe PM, Zakrzewski M, Waddell R, Sriprakash KS, Fischer K. High-throughput metagenome analysis of the Sarcoptes scabiei internal microbiota and in-situ identification of intestinal Streptomyces sp. Sci Rep 2019; 9: 11744.
13. Bernigaud C, Samarawickrama GR, Jones MK, Gasser RB, Fischer K. The challenge of developing a single-dose treatment for scabies. Trends Parasitol 2019; 35: 931–943.
14. Engelman D, Kiang K, Chosidow O, McCarthy J, Fuller C, Lammie P, et al. Toward the global control of human scabies: introducing the International Alliance for the Control of Scabies. PLoS Negl Trop Dis 2013; 7: e2167.
15. NTD_STAG_report_2017.pdf. [cited 2019 Sep 4]. Available from: https://www.who.int/neglected_diseases/NTD_STAG_report_2017.pdf?ua=1.
16. Karimkhani C, Colombara DV, Drucker AM, Norton SA, Hay R, Engelman D, et al. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. Lancet Infect Dis 2017; 17: 1247–1254.
17. Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. Lancet Infect Dis 2015; 15: 960–967.
18. Cassell JA, Middleton J, Nalabanda A, Lanza S, Head MG, Bostock J, et al. Scabies outbreaks in ten care homes for elderly people: a prospective study of clinical features, epidemiology, and treatment outcomes. Lancet Infect Dis 2018; 18: 894–902.
19. Bouvresse S, Chosidow O. Scabies in healthcare settings. Curr Opin Infect Dis 2010; 23: 111–118.
20. Di Meco E, Di Napoli A, Amato LM, Fortino A, Costanzo G, Rossi A, et al. Infectious and dermatological diseases among arriving migrants on the Italian coasts. Eur J Public Health 2018; 28: 910–916.
21. Lugović-Mihić L. The increase in Croatia's scabies incidence: how did refugees and traveling contribute? Travel Med Infect Dis 2019; 29: 74.
22. Arnaud A, Chosidow O, Détrez M-A, Bitar D, Huber F, Foulet F, et al. Prevalences of scabies and pediculosis corporis among homeless people in the Paris region: results from two randomized cross-sectional surveys (HYTPEAC study). Br J Dermatol 2016; 174: 104–112.
23. Lynar S, Currie BJ, Baird R. Scabies and mortality. Lancet Infect Dis 2017; 17: 1234.
24. Engelman D, Cantey PT, Marks M, Solomon AW, Chang AY, Chosidow O, et al. The public health control of scabies: priorities for research and action. Lancet Lond Engl 2019; 394: 81–92.
25. Brenaut E, Garlantezec R, Talour K, Misery L. Itch characteristics in five dermatoses: non-atopic eczema, atopic dermatitis, urticaria, psoriasis and scabies. Acta Derm Venereol 2013; 93: 573–574.
26. Worth C, Heukelbach J, Fengler G, Walter B, Liesenfeld O, Feldmeier H. Impaired quality of life in adults and children with scabies from an impoverished community in Brazil. Int J Dermatol 2012; 51: 275–282.
27. Worth C, Heukelbach J, Fengler G, Walter B, Liesenfeld O,

Hengge U, et al. Acute morbidity associated with scabies and other ectoparasitoses rapidly improves after treatment with ivermectin. Pediatr Dermatol 2012; 29: 430–436.
28. Jin-Gang A, Sheng-Xiang X, Sheng-Bin X, Jun-Min W, Song-Mei G, Ying-Ying D, et al. Quality of life of patients with scabies. J Eur Acad Dermatol Venereol 2010; 24: 1187–1191.
29. Chosidow O, Fuller LC. Scratching the itch: is scabies a truly neglected disease? Lancet Infect Dis 2017; 17: 1220–1221.
30. Lawrence G, Leafasia J, Sheridan J, Hills S, Wate J, Wate C, et al. Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. Bull World Health Organ 2005; 83: 34–42.
31. Thornley S, Marshall R, Jarrett P, Sundborn G, Reynolds E, Schofield G. Scabies is strongly associated with acute rheumatic fever in a cohort study of Auckland children. J Paediatr Child Health 2018; 54: 625–632.
32. Mason DS, Marks M, Sokana O, Solomon AW, Mabey DC, Romani L, et al. The prevalence of scabies and impetigo in the Solomon Islands: a population-based survey. PLoS Negl Trop Dis 2016; 10: e0004803.
33. Romani L, Koroivueta J, Steer AC, Kama M, Kaldor JM, Wand H, et al. Scabies and impetigo prevalence and risk factors in Fiji: a national survey. PLoS Negl Trop Dis 2015; 9: e0003452.
34. Svartman M, Finklea JF, Earle DP, Potter EV, Poon-King T. Epidemic scabies and acute glomerulonephritis in Trinidad. Lancet Lond Engl 1972; 1: 249–251.
35. Turnbull PR. Aetiology of acute glomerulonephritis. Br Med J 1973; 2: 666.
36. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, et al. Mass drug administration for scabies control in a population with endemic disease. N Engl J Med 2015; 373: 2305–2313.
37. Marks M, Toloka H, Baker C, Kositz C, Asugeni J, Puiahi E, et al. Randomized trial of community treatment with azithromycin and ivermectin mass drug administration for control of scabies and impetigo. Clin Infect Dis 2019; 68: 927–933.
38. Romani L, Marks M, Sokana O, Nasi T, Kamoriki B, Cordell B, et al. Efficacy of mass drug administration with ivermectin for control of scabies and impetigo, with coadministration of azithromycin: a single-arm community intervention trial. Lancet Infect Dis 2019; 19: 510–518.
39. Mika A, Reynolds SL, Mohlin FC, Willis C, Swe PM, Pickering DA, et al. Novel scabies mite serpins inhibit the three pathways of the human complement system. PloS One 2012; 7: e40489.
40. Reynolds SL, Pike RN, Mika A, Blom AM, Hofmann A, Wijeyewickrema LC, et al. Scabies mite inactive serine proteases are potent inhibitors of the human complement lectin pathway. PLoS Negl Trop Dis 2014; 8: e2872.
41. Swe PM, Fischer K. A scabies mite serpin interferes with complement-mediated neutrophil functions and promotes staphylococcal growth. PLoS Negl Trop Dis 2014; 8: e2928.
42. Swe PM, Reynolds SL, Fischer K. Parasitic scabies mites and associated bacteria joining forces against host complement defence. Parasite Immunol 2014; 36: 585–593.
43. Swe PM, Christian LD, Lu HC, Sriprakash KS, Fischer K. Complement inhibition by Sarcoptes scabiei protects Streptococcus pyogenes – an in vitro study to unravel the molecular mechanisms behind the poorly understood predilection of S. pyogenes to infect mite-induced skin lesions. PLoS Negl Trop Dis 2017; 11: e0005437.
44. Jannic A, Bernigaud C, Brenaut E, Chosidow O. Scabies itch. Dermatol Clin 2018; 36: 301–308.
45. Boralevi F, Diallo A, Miquel J, Guerin-Moreau M, Bessis D, Chiavérini C, et al. Clinical phenotype of scabies by age. Pediatrics 2014; 133: e910–916.
46. Elosua-González M, García-Zamora E. Crusted Scabies. N Engl J Med 2017; 377: 476.
47. Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. J Infect 2005; 50: 375–381.
48. del Giudice P, Sainte Marie D, Gérard Y, Couppié P, Pradinaud R. Is crusted (Norwegian) scabies a marker of adult T cell leukemia/lymphoma in human T lymphotropic virus type I-seropositive patients? J Infect Dis 1997; 176: 1090–1092.
49. Mahé A, Faye O, N'Diaye HT, Ly F, Konaré H, Kéita S, et al. Definition of an algorithm for the management of common skin diseases at primary health care level in sub-Saharan Africa. Trans R Soc Trop Med Hyg 2005; 99: 39–47.
50. Steer AC, Tikoduadua LV, Manalac EM, Colquhoun S, Carapetis JR, Maclennan C. Validation of an integrated management of childhood illness algorithm for managing common skin conditions in Fiji. Bull World Health Organ 2009; 87: 173–179.
51. Engelman D, Fuller LC, Steer AC, International Alliance for the Control of Scabies Delphi panel. Consensus criteria for the diagnosis of scabies: a Delphi study of international experts. PLoS Negl Trop Dis 2018; 12: e0006549.
52. Osti MH, Sokana O, Gorae C, Whitfeld MJ, Steer AC, Engelman D. The diagnosis of scabies by non-expert examiners: a study of diagnostic accuracy. PLoS Negl Trop Dis 2019; 13: e0007635.
53. Micali G, Lacarrubba F, Verzì AE, Chosidow O, Schwartz RA. Scabies: advances in noninvasive diagnosis. PLoS Negl Trop Dis 2016; 10: e0004691.
54. Micali G, Lacarrubba F, Massimino D, Schwartz RA. Dermatoscopy: alternative uses in daily clinical practice. J Am Acad Dermatol 2011; 64: 1135–1146.
55. Dupuy A, Dehen L, Bourrat E, Lacroix C, Benderdouche M, Dubertret L, et al. Accuracy of standard dermoscopy for diagnosing scabies. J Am Acad Dermatol 2007; 56: 53–62.
56. Micali G, Lacarrubba F, Verzì AE, Nasca MR. Low-cost equipment for diagnosis and management of endemic scabies outbreaks in underserved populations. Clin Infect Dis 2015; 60: 327–329.
57. Lacarrubba F, Verzì AE, Micali G. Detailed analysis of in vivo reflectance confocal microscopy for Sarcoptes scabiei hominis. Am J Med Sci 2015; 350: 414.
58. Wong SSY, Poon RWS, Chau S, Wong SCY, To KKW, Cheng VCC, et al. Development of conventional and real-time quantitative PCR assays for diagnosis and monitoring of scabies. J Clin Microbiol 2015; 53: 2095–2102.
59. Hahm JE, Kim CW, Kim SS. The efficacy of a nested polymerase chain reaction in detecting the cytochrome c oxidase subunit 1 gene of Sarcoptes scabiei var. hominis for diagnosing scabies. Br J Dermatol 2018; 179: 889–895.
60. Angelone-Alasaad S, Molinar Min A, Pasquetti M, Alagaili AN, D'Amelio S, Berrilli F, et al. Universal conventional and real-time PCR diagnosis tools for Sarcoptes scabiei. Parasit Vectors 2015; 8: 587.
61. Fukuyama S, Nishimura T, Yotsumoto H, Gushi A, Tsuji M, Kanekura T, et al. Diagnostic usefulness of a nested polymerase chain reaction assay for detecting Sarcoptes scabiei DNA in skin scrapings from clinically suspected scabies. Br J Dermatol 2010; 163: 892–894.
62. Chosidow O, Sbidian E. La gale: une reconnaissance méritée! Ann Dermatol Venereol 2012; 139: 425–427.
63. Walter B, Heukelbach J, Fengler G, Worth C, Hengge U, Feldmeier H. Comparison of dermoscopy, skin scraping, and the adhesive tape test for the diagnosis of scabies in a resource-poor setting. Arch Dermatol 2011; 147: 468–473.
64. Woodley D, Saurat JH. The Burrow Ink Test and the scabies mite. J Am Acad Dermatol 1981; 4: 715–722.
65. Cinotti E, Labeille B, Cambazard F, Biron AC, Chol C, Leclerq A, et al. Videodermoscopy compared to reflectance confocal microscopy for the diagnosis of scabies. J Eur Acad Dermatol Venereol 2016; 30: 1573–1577.
66. Delaunay P, Hérissé AL, Hasseine L, Chiaverini C, Tran A, Mary C, et al. Scabies polymerase chain reaction with standardized dry swab sampling: an easy tool for cluster diagnosis of human scabies. Br J Dermatol 2020; 182: 197–201.
67. Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. N Engl J Med 2010; 362: 717–725.
68. Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. J Am Acad Dermatol 2000; 42: 236–240.

69. Bachewar NP, Thawani VR, Mali SN, Gharpure KJ, Shingade VP, Dakhale GN. Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and ivermectin in patients of scabies. Indian J Pharmacol 2009; 41: 9–14.
70. Sharma R, Singal A. Topical permethrin and oral ivermectin in the management of scabies: a prospective, randomized, double blind, controlled study. Indian J Dermatol Venereol Leprol 2011; 77: 581–586.
71. Bernigaud C, Fernando DD, Lu H, Taylor S, Hartel G, Guillot J, et al. In vitro ovicidal activity of current and underdevelopment scabicides – which treatments kill scabies eggs? Br J Dermatol 2020; 182: 511–513.
72. Bernigaud C, Fang F, Fischer K, Lespine A, Aho LS, Dreau D, et al. Preclinical study of single-dose moxidectin, a new oral treatment for scabies: efficacy, safety, and pharmacokinetics compared to two-dose ivermectin in a porcine model. PLoS Negl Trop Dis 2016; 10: e0005030.
73. Bernigaud C, Fang F, Fischer K, Lespine A, Aho LS, Mullins AJ, et al. Efficacy and pharmacokinetics evaluation of a single oral dose of afoxolaner against Sarcoptes scabiei in the porcine scabies model for human infestation. Antimicrob Agents Chemother 2018; 62. pii: e02334.
74. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol 2002; 42: 1122–1133.
75. Miyajima A, Hirota T, Sugioka A, Fukuzawa M, Sekine M, Yamamoto Y, et al. Effect of high-fat meal intake on the pharmacokinetic profile of ivermectin in Japanese patients with scabies. J Dermatol 2016; 43: 1030–1036.
76. Strong M, Johnstone P. Interventions for treating scabies. Cochrane Database Syst Rev 2007; 3: CD000320.
77. Rosumeck S, Nast A, Dressler C. Ivermectin and permethrin for treating scabies. Cochrane Database Syst Rev 2018; 4: CD012994.
78. F. Boralevi, University Hospital, Bordeaux. Oral ivermectin versus topical permethrin to treat scabies in children – ClinicalTrials.gov. [cited 2019 Sep 01]. Available from: https://clinicaltrials.gov/ct2/show/NCT02407782.
79. WHO-MVP-EMP-IAU-2019.06-eng.pdf. [cited 2019 Sep 01]. Available from: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1.
80. Chosidow O. Scabies and pediculosis. Lancet Lond Engl 2000; 355: 819–826.
81. Pasay C, Walton S, Fischer K, Holt D, McCarthy J. PCR-based assay to survey for knockdown resistance to pyrethroid acaricides in human scabies mites (Sarcoptes scabiei var hominis). Am J Trop Med Hyg 2006; 74: 649–657.
82. Andriantsoanirina V, Izri A, Botterel F, Foulet F, Chosidow O, Durand R. Molecular survey of knockdown resistance to pyrethroids in human scabies mites. Clin Microbiol Infect 2014; 20: O139–141.
83. Currie BJ, Harumal P, McKinnon M, Walton SF. First documentation of in vivo and in vitro ivermectin resistance in Sarcoptes scabiei. Clin Infect Dis Off Publ Infect Dis Soc Am 2004; 39: e8–12.
84. Mounsey KE, Holt DC, McCarthy JS, Currie BJ, Walton SF. Longitudinal evidence of increasing in vitro tolerance of scabies mites to ivermectin in scabies-endemic communities. Arch Dermatol 2009; 145: 840–841.
85. De Sainte Marie B, Mallet S, Gaudy-Marqueste C, Baumstarck K, Bentaleb N, Loundou A, et al. Gales en échec de traitement: étude observationnelle. Ann Dermatol Venereol 2016; 143: 9–15.
86. Aussy A, Houivet E, Hébert V, Colas-Cailleux H, Laaengh N, Richard C, et al. Risk factors for treatment failure in scabies: a cohort study. Br J Dermatol 2019; 180: 888–893.
87. Arlian LG, Estes SA, Vyszenski-Moher DL. Prevalence of Sarcoptes scabiei in the homes and nursing homes of scabietic patients. J Am Acad Dermatol 1988; 19: 806–811.
88. Williams C, Fuller LC. Why does scabies treatment fail? Br J Dermatol 2019; 180: 710–711.
89. Bernigaud C, Fernando DD, Lu HC, Chosidow O, Fischer K. Revisiting guidelines for the environmental control of scabies 2018 ASP Annual Conference of the Australian Society of Parasitology. St Kilda, Melbourne, Australia; September 2018.
90. Bowen AC, Tong SYC, Andrews RM, O'Meara IM, McDonald MI, Chatfield MD, et al. Short-course oral co-trimoxazole versus intramuscular benzathine benzylpenicillin for impetigo in a highly endemic region: an open-label, randomised, controlled, non-inferiority trial. Lancet Lond Engl 2014; 384: 2132–2140.
91. Sanders KM, Nattkemper LA, Rosen JD, Andersen HH, Hsiang J, Romanelli P, et al. Non-histaminergic itch mediators elevated in the skin of a porcine model of scabies and of human scabies patients. J Invest Dermatol 2019; 139: 971–973.
92. Levy M, Martin L, Bursztejn A-C, Chiaverini C, Miquel J, Mahé E, et al. Ivermectin safety in infants and children under 15 kg treated for scabies: a multicentric observational study. Br J Dermatol 2019 Jul 25. [Epub ahead of print].
93. Scabicides et grossesse [cited 2019 Sep 01]. Available from: https://lecrat.fr/spip.php?page=article&id_article=585.
94. Pacqué M, Muñoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. Lancet Lond Engl 1990; 336: 1486–1489.
95. Kamgno J, Pion SD, Chesnais CB, Bakalar MH, D'Ambrosio MV, Mackenzie CD, et al. A test-and-not-treat strategy for onchocerciasis in Loa loa-endemic areas. N Engl J Med 2017; 377: 2044–2052.
96. Engelman D, Steer AC. Control strategies for scabies. Trop Med Infect Dis 2018; 3. pii: E98.
97. Taplin D, Arrue C, Walker JG, Roth WI, Rivera A. Eradication of scabies with a single treatment schedule. J Am Acad Dermatol 1983; 9: 546–550.
98. Marks M, Romani L, Sokana O, Neko L, Harrington R, Nasi T, et al. Prevalence of scabies and impetigo three years after mass drug administration with ivermectin and azithromycin. Clin Infect Dis Off Publ Infect Dis Soc Am 2019 May 25. pii: ciz444.
99. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, et al. Mass drug administration for scabies – 2 years of follow-up. N Engl J Med 2019; 381: 186–187.
100. Martin D, Wiegand R, Goodhew B, Lammie P, Mkocha H, Kasubi M. Impact of ivermectin mass drug administration for lymphatic filariasis on scabies in eight villages in Kongwa District, Tanzania. Am J Trop Med Hyg 2018; 99: 937–939.
101. Engelman D, Fuller LC, Solomon AW, McCarthy JS, Hay RJ, Lammie PJ, et al. Opportunities for integrated control of neglected tropical diseases that affect the skin. Trends Parasitol 2016; 32: 843–854.
102. Mohammed KA, Deb RM, Stanton MC, Molyneux DH. Soil transmitted helminths and scabies in Zanzibar, Tanzania following mass drug administration for lymphatic filariasis – a rapid assessment methodology to assess impact. Parasit Vectors 2012; 5: 299.
103. Kearns TM, Speare R, Cheng AC, McCarthy J, Carapetis JR, Holt DC, et al. Impact of an ivermectin mass drug administration on scabies prevalence in a remote Australian Aboriginal community. PLoS Negl Trop Dis 2015; 9: e0004151.
104. Romani L, Marks M, Sokana O, Nasi T, Kamoriki B, Wand H, et al. Feasibility and safety of mass drug coadministration with azithromycin and ivermectin for the control of neglected tropical diseases: a single-arm intervention trial. Lancet Glob Health 2018; 6: e1132–1138.
105. Coscione S, Esau T, Kekeubata E, Diau J, Asugeni R, MacLaren D, et al. Impact of ivermectin administered for scabies treatment on the prevalence of head lice in Atoifi, Solomon Islands. PLoS Negl Trop Dis 2018; 12: e0006825.
106. Kositz C, Talina J, Diau J, Asugeni R, Whitehorn C, Mabey D, et al. Incidental mosquitocidal effect of an ivermectin mass drug administration on Anopheles farauti conducted for scabies control in the Solomon Islands. Trans R Soc Trop Med Hyg 2017; 111: 97–101.
107. Kaburi BB, Ameme DK, Adu-Asumah G, Dadzie D, Tender EK, Addeh SV, et al. Outbreak of scabies among preschool

children, Accra, Ghana, 2017. BMC Public Health 2019; 19: 746.
108. Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. Br J Dermatol 2000; 143: 520–523.
109. Beeres DT, Ravensbergen SJ, Heidema A, Cornish D, Vonk M, Wijnholds LD, et al. Efficacy of ivermectin mass-drug administration to control scabies in asylum seekers in the Netherlands: a retrospective cohort study between January 2014 – March 2016. PLoS Negl Trop Dis 2018; 12: e0006401.
110. Taplin D, Porcelain SL, Meinking TL, Athey RL, Chen JA, Castillero PM, et al. Community control of scabies: a model based on use of permethrin cream. Lancet Lond Engl 1991; 337: 1016–1018.
111. Carapetis JR, Connors C, Yarmirr D, Krause V, Currie BJ. Success of a scabies control program in an Australian aboriginal community. Pediatr Infect Dis J 1997; 16: 494–499.
112. Wong LC, Amega B, Connors C, Barker R, Dulla ME, Ninnal A, et al. Outcome of an interventional program for scabies in an Indigenous community. Med J Aust 2001; 175: 367–370.
113. Wong L-C, Amega B, Barker R, Connors C, Dulla ME, Ninnal A, et al. Factors supporting sustainability of a community-based scabies control program. Australas J Dermatol 2002; 43: 274–277.
114. Marks M, Taotao-Wini B, Satorara L, Engelman D, Nasi T, Mabey DC, et al. Long term control of scabies fifteen years after an intensive treatment programme. PLoS Negl Trop Dis 2015; 9: e0004246.
115. Andrews RM, Kearns T, Connors C, Parker C, Carville K, Currie BJ, et al. A regional initiative to reduce skin infections amongst aboriginal children living in remote communities of the Northern Territory, Australia. PLoS Negl Trop Dis 2009; 3: e554.
116. La Vincente S, Kearns T, Connors C, Cameron S, Carapetis J, Andrews R. Community management of endemic scabies in remote aboriginal communities of northern Australia: low treatment uptake and high ongoing acquisition. PLoS Negl Trop Dis 2009; 3: e444.
117. Dose-finding study of moxidectin for treatment of scabies – ClinicalTrials.gov. [cited 2019 Sep 01]. Available from: https://clinicaltrials.gov/ct2/show/NCT03905265.
118. Chosidow O, Bernigaud C, Do-Pham G. High-dose ivermectin in malaria and other parasitic diseases: a new step in the development of a neglected drug. Parasite Paris Fr 2018; 25: 33.
119. Chosidow O, Giraudeau B, Cottrell J, Izri A, Hofmann R, Mann SG, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. N Engl J Med 2010; 362: 896–905.
120. Efficacy study between two different dosages of an antiparasitic in patients with crusted scabies – ClinicalTrials.gov. [cited 2019 Sep 01]. Available from: https://clinicaltrials.gov/ct2/show/NCT02841215.
121. Fang F, Candy K, Melloul E, Bernigaud C, Chai L, Darmon C, et al. In vitro activity of ten essential oils against Sarcoptes scabiei. Parasit Vectors 2016; 9: 594.
122. Thomas J, Carson CF, Peterson GM, Walton SF, Hammer KA, Naunton M, et al. Therapeutic potential of tea tree oil for scabies. Am J Trop Med Hyg 2016; 94: 258–266.
123. Al Khoury C, Guillot J, Nemer N. Lethal activity of beauvericin, a Beauveria bassiana mycotoxin, against the two-spotted spider mites, Tetranychus urticae Koch. J Appl Entomol 2019; 143: 974–983.

Centenary theme section: CUTANEOUS AND GENITAL INFECTIONS

REVIEW ARTICLE

Skin Disease in the Tropics and the Lessons that can be Learned from Leprosy and Other Neglected Diseases

Roderick J. HAY
Kings College London and the International Foundation for Dermatology, London UK

Skin disease is a common illness in most tropical regions where the pattern of clinical, presentations is dominated by infections. Along with common diseases such as pyodermas and fungal infections, a group of conditions known collectively as the neglected tropical diseases of the skin or Skin NTDs, which are the targets for worldwide control or elimination are also seen in health care facilities. These diseases range from the common, such a scabies, to those that are less frequent including leprosy and mycetoma. The initiative to use skin presentations of tropical diseases as a route to diagnosis by front line health workers is both logical and welcome. However, this requires training and monitoring and as the work gets under way, it is critically important that time invested in this programme is backed by firm and lasting commitment at regional and national levels.

Key words: skin disease; tropics; NTDs; scabies; tinea; mycetoma; leprosy.

Accepted Mar 19, 2020; Epub ahead of print Mar 24, 2020

Acta Derm Venereol 2020; 100: adv00113.

Corr: Roderick Hay, The International Foundation for Dermatology, Willan House, 4 Fitzroy sqaure, London W1T 5HQ, UK. E-mail: roderick.hay@ifd.org

SIGNIFICANCE

Skin diseases are very common in the tropics. They include illnesses like ringworm, impetigo and scabies. A recent WHO programme has been to take advantage of the fact that many of the serious diseases seen in the tropics, such as leprosy and river blindness, first appear in the skin and that by detecting them, because of their appearances in the skin, their treatment and control becomes much more feasible.

Skin disease is estimated to affect more than 900,000,000 persons globally each year. It is therefore unsurprising that it is one of the common disorders seen at front line health care level in all regions (1). In most countries with a tropical climate between 20–40% of new consultations at primary care level are motivated by skin problems, although this varies, depending on the underlying prevalence of skin disease and the existence of local variations in the normal pattern and distribution of skin disease (1). Generally, in hot climates, this picture is dominated by infections, including bacterial skin infections such as pyodermas and cellulitis, mycoses including dermatophytosis as well as Candida and Malassezia infections. Viral skin infection is generally less common although warts and herpes simplex are seen regularly and the presence of an underlying high level of HIV in the community can be associated with local spikes in the prevalence of molluscum contagiosum and extensive plane warts resembling epidermodysplasia verruciformis (2). Likewise, the prevalence of scabies is variable and changes over time and, while often it affects more than 5% of the population in the tropics, it can reach even higher levels of more than 10%; these prevalence rates have been reported from Ethiopia and the West Pacific and have driven major public health initiatives designed to control the infection (3).

There is less data on the social and economic costs of these infections in poor communities, although they may have a significant impact on overstretched resources. One study in Mexico estimated that, over a 3-month period, households in rural areas were using over 24$ per household to treat scabies – and generally the treatment given was ineffective (4). This used up all cash reserves destined for other needs such as additional food. In Papua New Guinea managing tropical ulcer, or just one skin disease, accounted for more than 30% of the health budget of individual aid posts (primary health centres) in one region (5). Skin infections in the tropics are also associated with significant levels of disability and morbidly which can vary both with region and individual circumstances. For instance, the presence of tinea pedis in patients with lymphoedema, living in areas endemic for lymphatic filariasis, is a major risk factor for the development of recurrent episodes of cellulitis which lead to pain and debility, as well as loss of work (6). Alleviating disability and preventing further damage in patients with tropical ulcerated conditions such as the neuropathic ulcers in leprosy or the massive limb and scrotal swelling in lymphatic filariasis are major challenges to local resources (7). Yet linking their management to that of patients with other conditions with similar needs, such as diabetic foot or podoconiosis, is increasingly used as an effective form of integrated care package, even in remote rural areas (8, 9). Beyond physical incapacity skin disease may also be associated with severe mental

illness particularly depression and in addition it affects household and societal relationships through discrimination and stigma (10). In some countries there has been both community discrimination as well as discriminatory legislation against patients with some skin diseases, including leprosy. This is now changing. In most areas such legislation, which was often introduced many years ago, has been repealed thereby allowing patients to participate in various activities that had previously been prohibited and even simple but important interventions such as ceasing to use the word "leper" or listing leprosy as grounds for divorce are making a difference (11).

While the pattern of skin disease is dominated by infection in tropical countries, it is important to recognise that other skin diseases may have an important impact on health. Although previously sparsely distributed in hot climates eczema, particularly atopic eczema, is now seen more frequently in clinical services and there is evidence that the prevalence of atopic eczema is increasing in some tropical areas (12). There are also specific problems encountered in particular population groups. Oculocutaneous albinism, with its attendant risk of early non-melanoma skin cancer, is more common in tropical regions than the colder north, affecting those living in countries from Central America, to Sub-Saharan Africa and the Pacific Region (13, 14). This poses a strain on resource-limited health systems as, if it is ignored and patients left without sun-protection advice as well as treatment, there is a high risk of fatal squamous cell carcinoma. Certain populations are also susceptible to other specific skin conditions. For instance, some native American groups are genetically predisposed to actinic prurigo which may cause severe itching and persistent debilitating light sensitive dermatoses (15). This is difficult to manage in rural populations whose main occupation is agriculture.

NEGLECTED TROPICAL DISEASES OF THE SKIN

Skin disease or diseases that present in the skin are also important in a different context. Many of the important disabling infections that dominate health care in the tropics, such as onchocerciasis and leishmaniasis, are known collectively as Neglected Tropical Diseases or NTDs. Recently the World Health Organisation, supported by other agencies and scientific journals, has focused on a strategy of integrating preventative, curative and supportive care, as well as research, for NTDs, whose elimination or control forms a core part of global health strategy. A key element of this initiative has been to group these neglected diseases into clusters; in one such cluster diseases such leprosy, lymphatic filariasis, yaws and scabies constitute a group of disorders known as Skin NTDs (16) (see **Table I** for the full list). In order to focus on implementing their control and addressing health inequalities, it has been important to recognise and include the common readily treatable skin conditions, such as impetigo and fungal infections, together with the more serious neglected diseases such as leprosy, as part of an overall skin-centred strategy. By developing integrated schemes for case detection, management and mapping, it will be possible to maximise the advantages of an economy of scale and to rationalise the use of scarce resources (17–19). There is also a further practical benefit to be derived from combining the management of disability caused by these problems, in combatting discrimination and stigma and in sensitising communities and providing health education.

Table I. The neglected tropical diseases of the skin (skin NTDs)

- Buruli ulcer
- Cutaneous leishmaniasis
- Post-kala-azar dermal leishmaniasis
- Leprosy
- Lymphatic filariasis (LF) (lymphoedema and hydrocoele)*
- Mycetoma, chromoblastomycosis and other deep fungal infections
- Onchocerciasis
- Scabies
- Yaws

*Integrated strategy for morbidity management of two tropical endemic diseases with these complications - LF and Podoconiosis.

In furtherance of this initiative a new handbook on the recognition of skin diseases and Skin NTDs has been produced by the WHO and is available in 5 different languages (20). Other strategies to address Skin NTDs such as improving access to training programmes, developing common management pathways and co-distribution of drugs used for mass administration are in development. There have been a number of new initiatives arising from this work and designed to improve case detection, as well as to provide specialist support, that range from the development of diagnostic apps (21) usable in the field on handheld devices, to the provision of diagnostic algorithms and the use of long range expert support through electronic messaging and communication e.g. Telederm and Whats-App technologies (22, 23).

SPECIFIC AND COMMON TROPICAL SKIN INFECTIONS

Fungal disease

The reason for the dominance of skin infections in tropical countries is thought to reflect the prevalence of factors that favour spread and pathogenesis, such as climate and overcrowding, particularly household overcrowding. But there are other changes encountered that are different from those encountered in temperate climates, including the clinical patterns of infection. For instance, with dermatophyte infections, onychomycosis and tinea pedis are frequent presentations in colder climates whereas, in the tropics, tinea capitis and tinea corporis are much commoner. This is also subject to variation in different areas. In sub-Saharan Africa, for instance, tinea capitis is endemic in school children and prevalence rates in schools can

exceed 20% (24–26). Furthermore several studies in recent years have emphasised a changing pattern of infection with *Trichophyton tonsurans* beginning to become more prevalent in both West and East Africa, whereas, previously, *T. violaceum* and *Microsporum audouinii*, although still common, dominated the pattern of disease (24–26). There is little to no surveillance for scalp infection in these countries and effective treatment through oral antifungal therapy is costly and inaccessible to most. Although local communities recognise that, normally, tinea capitis does not persist into teenage years the more inflammatory symptomatic forms of scalp ringworm, including kerion, pose a dilemma as effective management requires control of tinea capitis within the community, a strategy which is currently not achievable. There are other distinctive features of superficial fungal infection in the tropics. In India, for instance, there is a widespread epidemic of recalcitrant dermatophyte infection caused by *Trichophyton rubrum* and increasingly a strain of *T. mentagrophytes* (27, 28). This results in extensive tinea corporis and some strains of *T. mentagrophytes* appears to have mutations in the squalene epoxidase gene, meaning that terbinafine, which targets this enzyme, is less effective. Other factors which may have affected spread of this infection include the ready availability and use of topical potent corticosteroid combinations and low-quality generic antifungals. Over the past few years similar cases have been seen in Europe. The main differences seen in this new epidemic, which is affecting India and some adjacent countries and migrant populations in the Middle East and Europe, are the widespread nature of the infection and its persistence despite adequate treatment or an initial response followed by early relapse. In other tropical countries, particularly in isolated communities, there is persistence of endemic tinea imbricata caused by *T. concentricum* which can result in chronic and very widespread scaling and itching. New endemic areas for tinea imbricata continue to be reported (29) – the latest being in the Solomon Islands and amongst the Batek people of Malaysia (30).

Bacterial infections

Amongst the bacterial infections, there are also differences in the pattern of skin infection seen in the tropics. In colder environments *Staphylococcus aureus* is the main cause of skin infections. But Group A streptococcal infections are commoner in the tropics than in northern climates and the complications of nephritis (31) and rheumatic fever (32) are a potential public health problem in these regions. Streptococcal skin infection is particularly seen in association with scabies (31, 32). The relationship between streptococci and scabies mites is a complex one, as the mites produce different substances, such as Scabies Mite Inactivated Protease Paralogues or SMIPPs (33) which may interfere with complement activation and phagocytosis. As a result, scabies infestation has a direct impact on the development of streptococcal infection. As a result although traditional dermatological teaching often emphasized the need to treat secondary bacterial infection first and then the scabies infestation, current work with the oral drug ivermectin used as mass drug treatment of scabies has shown that this will not only combat the scabies mites, but also bacterial infection declines as well which supports a direct role for scabies mites in predisposing to bacterial infection (34).

NEGLECTED TROPICAL DISEASES

Mycetoma

Mycetoma is a chronic infection, whose first signs are localised swelling and the development of papules and sinus tracts on the skin surface. It is caused either by actinomycetes or filamentous bacteria (actinomycetoma) (**Fig. 1**) or fungi (eumycetoma) in tropical regions from Mexico to Thailand (35). The countries with the highest prevalence are Mexico and Sudan (35). In 2016, mycetoma was formally declared to be a neglected tropical disease by WHO, becoming the first fungal infection to be given this designation. The decision was largely based on the lack of progress in controlling this infection and achieving early diagnosis which reduces the risk of disability caused by the disease that, if unchecked, can proceed to cause severe limb deformities and osteomyelitis (36). There has been a corresponding lack of research on new drug development, new diagnostics and epidemiology. The call for change was taken up in

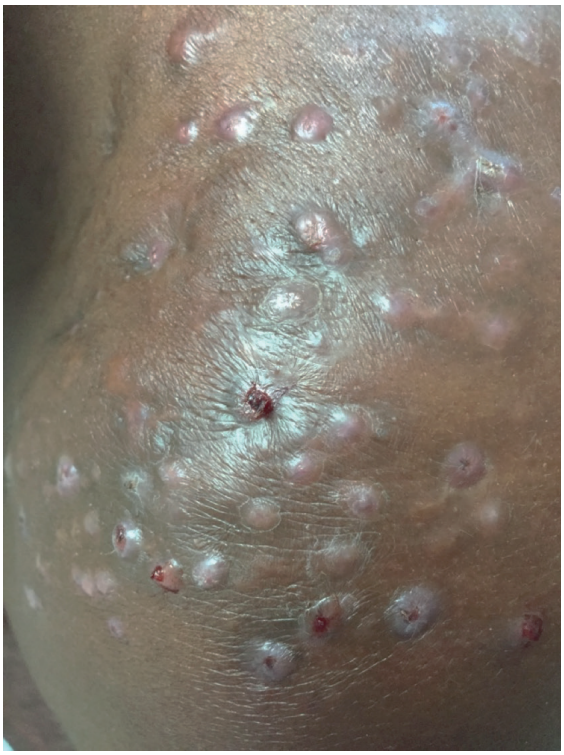

Fig. 1. Actinomycetoma due to *Nocardia brasiliensis*.

February 2019 in a large conference on mycetoma held in Sudan and attended by the Director of the NTD programme for WHO (37).

However, despite slow progress there are several new interesting findings about this infection. In Sudan there is an associated increase of infection in communities where cattle are grazed close to houses and the organism *M. mycetomatis* has been identified close to the thorn hedges around corrals used to pen the livestock (38). The taxonomy of the genera of fungal mycetoma agents has also been changed with several new species identified. For instance, we now recognise *M. mycetomatis*, *M. tropicana*, *M. pseudomycetomatis* and *M. fahalii* (39). This may have implications for accurate laboratory diagnosis and the choice of treatment options. *M. fahalii*, for instance, is not sensitive to itraconazole. There is now a new clinical trial of fosravuconazole for treatment of fungal mycetoma due to *M. mycetomatis*, based on in vitro data supporting the potential effectiveness of this group of antifungals (40). There are also newer approaches to the treatment of actinomycetoma caused by *Nocardia* species which have been found to respond to a wide range of antibiotics including imipenem, moxifloxacin and linezolid, in addition to the more traditional dapsone and cotrimoxazole (41). Yet there remain formidable problems in some of the simplest aspects of disease such as in detection of cases at community level (42) and improving access to laboratory diagnosis, as identification of the causative organisms is a key step in selecting the best treatment for patients (43).

Leprosy

Leprosy has long been a scourge in many tropical countries. While it causes skin lesions, which, if untreated, can be extensive and destructive, nerve damage leads to progressive sensory loss and destructive trophic changes. Changes in immunological responses to the infection, Type 1 and Type 2 leprosy reactions, lead to aggressive local and systemic reactions which are potentially fatal (44). These severe symptomatic reactions are accompanied by tissue swelling, rash, arthritis and eye disease as well as further nerve damage. Most cases of human leprosy are caused by *Mycobacterium leprae*, although a second species, *M. lepromatosis*, is now recognised (45). There is a difference of 9.1% in nucleotides between the two, confirming that they are distinct species rather than clonal variants (46). The latter causes leprosy in certain parts of the world. In Mexico for instance it is probably the commoner of the two as a cause of human disease, and it is responsible for cases of the form of leprosy known as diffuse lepromatous leprosy or Lucio's leprosy where there can be vasculitic ulceration of lesions (46). *M. lepromatosis* has also been detected in Brazil, Myanmar and Singapore (47). In other countries *M. leprae* remains the dominant organism.

Although once endemic in Europe dermatologists in our region now only see imported cases, although it was not so long ago that Gerhard Amauer Hansen carried out his methodically planned studies in Norway, where leprosy was still endemic in the 19th century, to prove the infectious and transmissible nature of the infection. Only one autochthonous case has been reported in Europe, from Italy, in recent years (48). Elsewhere the burden of leprosy in endemic areas has shrunk over the years, although it is still seen in most parts of the tropics. There have been many attempts to identify potential natural sources of *M. leprae* in the environment, yet none of these have yielded results, although two animal species can be infected naturally – the 9-banded armadillo and the red squirrel (49).

A decline in the numbers of cases of leprosy towards the end of the twentieth century followed intensive case detection and the evolution and deployment of a series of drugs with potent antileprosy activity. This also involved the pioneering of suitable effective drug combinations, as well as heightened awareness at national and regional levels (50). A key aspect of leprosy has been the recognition that it presents in a spectrum, with some forms having distinctive changes on the skin and in the nerves accompanied by large numbers of organisms, whereas in others the skin lesions are different and bacteria very sparse or undetectable. These are the multibacillary and paucibacillary forms known as lepromatous and tuberculoid leprosy respectively, although variants intermediate between these two poles of the spectrum such as borderline lepromatous and tuberculoid forms, as well as an indeterminate form, are seen regularly (**Fig. 2**) (51). The other key feature of leprosy is that, as it is not possible to repair the damaged and defunct nerves, once this destructive process has been completed, patients are left with denervated areas resulting in anaesthetic limbs. These are prone to trauma and ulceration as well as trophic change and disfigurement even if the patient is freed from active infection as a result of treatment. Early

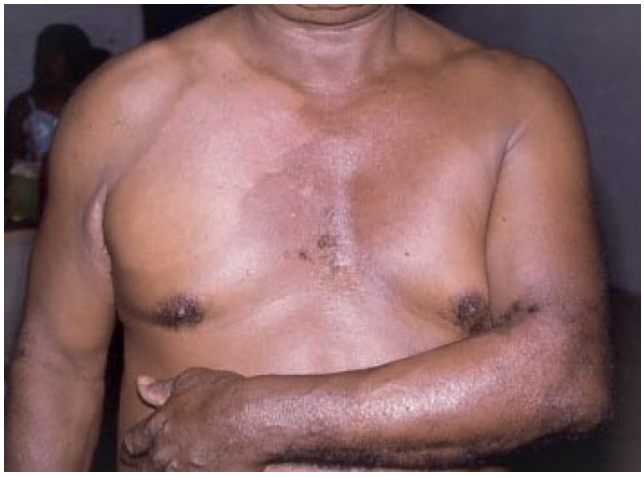

Fig. 2. Leprosy – borderline tuberculoid leprosy on the chest wall.

recognition and treatment of individual cases is the way to prevent this disabling consequence of leprosy. In addition to purely clinical features of the disease, combatting disability and stigma remain other important components of leprosy care, even in the 21st century.

In the course of identifying major health goals to coincide with the millennium, elimination of leprosy was promoted as a suitable target. Ironically, attention was often drawn away from implementation of rigorous programmes for the detection of disease, as case numbers appeared to be on the decline, and, in order to deliver this target, diagnostic criteria were softened. As a result, there was a reduction in planned case detection programmes in some countries, which given the long incubation period of the disease, subsequently allowed the numbers of new cases to stabilise and, in some areas, to increase. Several countries such as India and Brazil are still reporting substantial case numbers and it is likely that the current official figures from other regions are a significant underestimate of the actual picture, as reporting leprosy depends on implementing programmes for the detection of new patients.

The current classification of leprosy used by WHO is based on assessment of the number of skin lesions; patients with less than 5 lesions are classified as paucibacillary (PB) and those with more than 5 as multibacillary (MB) forms of leprosy (52). There are some flaws in this scheme; for instance, acid-fast bacilli (AFB) have been detected in cases classified as PB. Such cases, presumably, provide a risk of onward transmission of the infection. Given the importance of improved case finding there have been a number of different initiatives designed to improve detection rates and simplify the process of making the diagnosis. These include both laboratory-based and clinical actions. The two traditional laboratory-based testing methods the slit skin smear and histopathology of skin biopsies, while useful, have limitations as both are susceptible to variations in observer skills or the availability of staining facilities and depend on an adequately trained work force. So one priority has been to devise a simple laboratory based test deliverable in front line health care environments – a point of care test – using techniques that can be implemented with minimal resource such as a simplified molecular tool or a card antigen detection test (53). Although a great deal of work has been carried out and is still evolving, no single antigen or PCR probe has been identified that will unequivocally identify patients with leprosy of both multibacillary and paucibacillary forms or distinguish between patients and contacts who have no active disease (54). In part this may be due to bacterial load – tuberculoid leprosy, where there is a high level of immunity and very low numbers of organisms, is potentially a difficult target. It is also worth considering the adoption of other options, such as using a combination of different laboratory tests, including some that might be combined with an algorithm based on clinical findings.

The most recent molecular results have focused on *M. leprae*-specific repetitive element RLEP and 16S rRNA which are the most frequent markers used in experimental studies to detect the presence of bacilli with up to 80% sensitivity, although the range of results is wide, starting from as low as 15% (51, 55). Combining molecular methods with a different test system including detection of organisms in smears may be another route for successful diagnosis (56).

Other methods, that have been attempted, have adopted a different strategy, focusing on novel surveillance and training programmes for clinical recognition of leprosy in its many different forms or the identification of the simplest features of the disease that would allow a primary health worker to refer suspected cases to a more expert team – this forms the basic premise of the new WHO training manual (20). Behind most of these programmes lies a realisation that direct clinical observation needs to be supported by at least one or two other signs such as the presence of detectable nerve damage e.g. through loss of sensation or enlargement of peripheral nerves. The detection of both requires training. Attempts to use such approaches in the field as part of broader Skin NTD programmes, aimed at detecting a range of endemic NTDs, are now under way (17, 57).

In order to rationalise the need for extensive programmes for case recognition, a new strategy is being delivered that centres around the treatment of contacts of leprosy patients with single dose rifampicin. It is known as post exposure prophylaxis or PEP (58, 59). While the idea behind this has merits, there are potential problems inherent in the widescale deployment of this strategy, notably that it does not appear to protect contacts of patients with multibacillary leprosy who are the greater sources of spread; also it only protects for up to 2 years post treatment and is only effective in some contacts of leprosy patients (60). There is also a social downside as in drawing attention to the presence of cases of leprosy in small communities, unless there is adequate local patient support, there is a consequent risk of discrimination and social ostracisation. A further practical problem is that it risks diverting attention and resource from the strategy that can deliver control i.e. new case detection, even though this is essential for identifying contacts. Measures are being taken to seek ancillary methods, such as drug combinations or different dosages, to widen the scope and inclusivity of PEP, although this may prove difficult to activate and assess, as the existing PEP scheme has already been adopted as policy in many areas.

Leprosy is a complex disease which has long been feared in many societies and sending mixed messages about elimination has served to confuse as well as divert attention from delivering a potentially achievable goal – a world free of leprosy.

THE WAY FORWARD

The skin remains the key entry point for diagnosis and management of many tropical diseases including NTDs and HIV related skin disease, as well as other common skin diseases such as pyoderma, eczema and fungal infection. Addressing all of these is a difficult task as it means increasing the public profile of skin disease in areas where resources are limited and there is inevitable competition with other calls on financial and clinical support, such as diabetes and cardiovascular disease. But the first step to maximise the potential of using the skin, as the entry point for a radical rethink of health strategies, is to sensitise those responsible for national health care in Ministries of Health and regional health offices about the importance of proper identification and management of diseases that are seen on the skin as a means of health improvement, well beyond the confines of the skin itself. Public support, through advocacy at community level, and through regional or national media services is also key to this mission. But in all this it is important to remember a key message learned from experience with other tropical diseases in the past, that it is important to be unrelenting in reminding and re-reminding all those involved in health care, from Ministry officials to front line workers, not to forget the disease that they aim to control as soon as there appears to be an improvement in its overall burden, whether this is leprosy or scabies. To coin a soccer metaphor, by "taking ones eye off the ball" it is possible to undo years of hard work and surveillance – and for the sake of what?

REFERENCES

1. Hay RJ, Nicols R Williams HE, Bolliger IW, Dellavalle RP, Margolis DJ, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 2014; 134: 1527–1534.
2. Maurer TA Dermatologic manifestations of HIV infection. Top HIV Med 2005; 13: 149–154.
3. Engelman D, Cantey, PT, Marks M, Solomon AW, Chang AY, Chosidow O, et al. The public health control of scabies: priorities for research and action. Lancet 2019; 394: 81–92.
4. Hay RJ, Estrada Castenon R, Alarcon H, Chavez Lopez G, Lopez Fuentes LF, Paredes Solis S, et al. Wastage of family income on skin disease – a study of skin infection in Guerrero, Mexico. Br Med J 1994; 309: 848–849.
5. Morris GE, Hay RJ, Srinavasa A, Bunat A. The diagnosis and management of tropical ulcer in East Sepik Province of Papua New Guinea. J Hyg Trop Med 1989; 92: 215–220.
6. Chandrasena N, Premaratna R, Gunaratna IE, de Silva NR. Morbidity management and disability prevention for lymphatic filariasis in Sri Lanka: Current status and future prospects. PLoS Negl Trop Dis 2018; 12: e0006472.
7. Eneanya OA, Garske T, Donnelly CA. The social, physical and economic impact of lymphedema and hydrocele: a matched cross-sectional study in rural Nigeria. BMC Infect Dis 2019; 19: 332.
8. Chandler DJ, Fuller LC The skin-A common pathway for integrating diagnosis and management of NTDs. Trop Med Infect Dis 2018;3. pii: E101.
9. Tora A, Mengiste A, Davey G, Semrau M. Community involvement in the care of persons affected by podoconiosis-A lesson for other skin NTDs. Trop Med Infect Dis 2018; 3. pii: E87.
10. Bewley A The neglected psychological aspects of skin disease BMJ 2017; 358: 3208.
11. Kurian O. Leprosy and inequalities in India's health care: beyond the persistent rhetoric of 'elimination'. ORF Occasional Paper 2019; 184: 1–24.
12. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. Pediatr Allergy Immunol 2007; 18: 560–565.
13. Hong ES, Zeeb H, Repacholi MH Albinism in Africa as a public health issue. BMC Public Health 2006; 6: 212.
14. Kossintseva,I, Dutz J. The moon children of Kuna Yala: Albinism in San Blas islands of Panama: Review, directions in research and aid. J Am Acad Dermatol 2011; 64: Suppl 1, AB26.
15. Rodríguez-Carreón AA, Rodríguez-Lobato E, Rodríguez-Gutiérrez G, Cuevas-González JC, Mancheno-Valencia A, Solís-Arias MP, et al. Actinic prurigo. Skinmed 2015; 13: 287–295.
16. Hay RJ, Asiedu K. Skin-related neglected tropical diseases (Skin NTDs) – a new challenge. Trop Med Infect Dis 2018; 4. pii: E4.
17. Barogui YT, Diez G, Anagonou E, Johnson RC, Gomido IC, Amoukpo H, et al. Integrated approach in the control and management of skin neglected tropical diseases in Lalo, Benin. PLoS Negl Trop Dis 2018; 12: e0006584.
18. Engelman D, Fuller LC, Solomon AW, McCarthy JS, Hay RJ, Lammie PJ, et al. Opportunities for integrated control of neglected tropical diseases that affect the skin. Trends Parasitol 2016; 32: 843–854.
19. Kebede B, Martindale S, Mengistu B, Kebede B, Mengiste A, H, Kiros F, et al. Integrated morbidity mapping of lymphatic filariasis and podoconiosis cases in 20 co-endemic districts of Ethiopia. PLoS Negl Trop Dis 2018; 12: e0006491.
20. WHO https://apps.who.int/iris/bitstream/handle/10665/272723/ 9789241513531-eng.pdf?ua=1.
21. Mieras LF, Taal AT, Post EB, Ndeve AGZ, van Hees CLM. The development of a mobile application to support peripheral health workers to diagnose and treat people with skin diseases in resource-poor settings. Trop Med Infect Dis 2018; 3: pii. E102.
22. Faye O, Bagayoko CO, Dicko A, Cissé L, Berthé S, Traoré B, F, et al. (Teledermali Team). A teledermatology pilot programme for the management of skin diseases in primary health care centres: experiences from a resource-limited country (Mali, West Africa). Trop Med Infect Dis 2018; 3. pii: E88.
23. Williams V, Kovarik C. Long-range diagnosis of and support for skin conditions in field settings. Trop Med Infect Dis 2018; 3. pii: E84.
24. Coulibaly O, L'Ollivier C, Piarroux R, Ranque S. Epidemiology of human dermatophytoses in Africa. Med Mycol 2018; 56: 145–161.
25. Moto JN, Maingi JM, Nyamache AK. Prevalence of Tinea capitis in school going children from Mathare, informal settlement in Nairobi, Kenya. BMC Res Notes 2015; 8: 274.
26. Hogewoning AA, Adegnika AA, Bouwes Bavinck JN, Yazdanbakhsh M, Kremsner PG, et al. Prevalence and causative fungal species of tinea capitis among schoolchildren in Gabon. Mycoses 2011; 54: e354–359.
27. Pathania S, Rudramurthy SM, Narang T, Saikia UN, Dogra S. A prospective study of the epidemiological and clinical patterns of recurrent dermatophytosis at a tertiary care hospital in India. Indian J Dermatol Venereol Leprol 2018; 84: 678–684.
28. Nenoff P, Verma SB, Vasani R, Burmester A, Hipler UC, Wittig F, et al. The current Indian epidemic of superficial dermatophytosis due to Trichophyton mentagrophytes-A molecular study. Mycoses 2019; 62: 336–356.
29. Leung AKC, Leong KF, Lam JM. Tinea imbricata: an overview. Curr Pediatr 2019; 15: 170–174.
30. Bernama State News http://www.bernama.com/statenews/berita.php?id=1711298.
31. Marks M, Romani L, Sokana O, Neko L, Harrington R, Nasi T, et al. Prevalence of scabies and impetigo three years after mass drug administration with ivermectin and azithromycin. Clin Infect Dis 2019. pii: ciz444. [Epub ahead of print].

32. Thornley S, Marshall R, Jarrett P, Sundborn G, Reynolds E, Schofield G. Scabies is strongly associated with acute rheumatic fever in a cohort study of Auckland children. J Paediatr Child Health 2018; 54: 625–632.
33. Bergström FC, Reynolds S, Johnstone M, Pike RN, Buckle AM, Kemp DJ, et al. Scabies mite inactivated serine protease paralogs inhibit the human complement system. J Immunol 2009; 182: 7809–7817.
34. Romani L, Whitfeld MJ, Koroivueta J, Kama M, Wand H, Tikoduadua L, et al. Mass drug administration for scabies – 2 years of follow-up. N Engl J Med 2019; 381: 186–187.
35. Fahal AH. Mycetoma: a thorn in the flesh. Trans R Soc Trop Med Hyg 2004; 98: 3–11.
36. Abbas M, Scolding PS, Yosif AA, El Rahman RF, El-Amin MO, Elbashir MK, et al. The disabling consequences of mycetoma. PLoS Negl Trop Dis 2018; 12: e0007019.
37. WHO. https://www.who.int/neglected_diseases/news/Mycetoma-Global-conference-calls-for-action/en/.
38. de Hoog GS, Ahmed SA, Najafzadeh MJ, Sutton DA, Keisari MS, Fahal AH, et al. Phylogenetic findings suggest possible new habitat and routes of infection of human eumycetoma. PLoS Negl Trop Dis 2013; 7: e2229.
39. de Hoog GS, van Diepeningen AD, Mahgoub el-S, van de Sande WW. New species of Madurella, causative agents of black-grain mycetoma. J Clin Microbiol 2012; 50: 988–994.
40. Ahmed SA, Kloezen W, Duncanson F, Zijlstra EE, de Hoog GS, Fahal AH, et al. Madurella mycetomatis is highly susceptible to ravuconazole. PLoS Negl Trop Dis 2014; 8: e2942.
41. Welsh O. Response to newer therapeutic modalities for actinomycetoma by Nocardia species. Int J Dermatol 2018; 57: 65–66.
42. Estrada-Castañón R, Estrada-Chávez G, Chávez-López MG. Diagnosis and management of fungal neglected tropical diseases in community settings-mycetoma and sporotrichosis. Trop Med Infect Dis 2019; 4. pii: E81.
43. Ahmed AA, van de Sande W, Fahal AH. Mycetoma laboratory diagnosis: PLoS Negl Trop Dis 2017; 11: e0005638.
44. Polycarpou A, Walker SL, Lockwood DN. A systematic review of immunological studies of erythema nodosum leprosum. Front Immunol 2017; 8: 233.
45. Han XY, Seo Y-H, Sizer KC, Taylor S, May GS, Spencer JS et al. A new mycobacterium species causing diffuse lepromatous leprosy. Am J Clin Pathol 2008; 130: 856–864.
46. Han XY, Sizer KC, Thompson EJ, Kabanja J, Li J, Hu P, et al. Comparative sequence analysis of Mycobacterium leprae and the new leprosy-causing Mycobacterium lepromatosis. J Bacteriol 2009; 191: 6067–6074.
47. Han XY, Sizer KC, Velarde-Félix JS, Frias-Castro LO, Vargas-Ocampo F. The leprosy agents Mycobacterium lepromatosis and Mycobacterium leprae in Mexico. Int J Dermatol 2012; 51: 952–959.
48. Cusini M, Marzano A V , Barabino G, Benardon S. A case of autochthonous leprosy in an elderly Italian patient leaving in Milan province with peculiar clinical presentation. J Am Acad Dermatol 2017; 76. Suppl 1, Page AB3.
49. Schilling AK, Avanzi C, Ulrich RG, Busso P, Pisanu B, Ferrari N et al. British red squirrels remain the only known wild rodent host for leprosy bacilli. Front Vet Sci 2019; 6: 8.
50. van 't Noordende AT, Korfage IJ, Lisam S, Arif MA, Kumar A, van Brakel WH. The role of perceptions and knowledge of leprosy in the elimination of leprosy: A baseline study in Fatehpur district, northern India. PLoS Negl Trop Dis 2019; 13: e0007302.
51. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. Int J Lepr Other Mycobact Dis 1966; 34: 255–273.
52. WHO. https://www.who.int/lep/leprosy/en/.
53. Tatipally S, Srikantam A, Kasetty S. Polymerase chain reaction (PCR) as a potential point of care laboratory test for leprosy diagnosis – a systematic review. Trop Med Infect Dis 2018; 3. pii: E107.
54. Gama RS, Gomides TAR, Gama CFM, Moreira SJM, de Neves Manta FS, de Oliveira LBP, et al. High frequency of M. leprae DNA detection in asymptomatic household contacts. BMC Infect Dis 2018; 18: 153.
55. Chaitanya VS, Cuello L, Das M, Sudharsan A, Ganesan P, Kanmani K, et al . Analysis of a novel multiplex polymerase chain reaction assay as a sensitive tool for the diagnosis of indeterminate and tuberculoid forms of leprosy. Int J Mycobacteriol 2017; 6: 1–8.
56. Reja AH, Biswas N, Biswas S, Dasgupta.S, Chowdhury I, HBanerjee, S, et al. Fite-Faraco staining in combination with multiplex polymerase chain reaction: A new approach to leprosy diagnosis. Indian J Dermatol Venereol Leprol 2013; 79: 693–700.
57. Yotsu RR. Integrated management of skin NTDs-lessons learned from existing practice and field research. Trop Med Infect Dis 2018; 3. pii: E120.
58. Barth-Jaeggi T, Steinmann P, Mieras L, van Brakel W, Richardus JH, Tiwari A, et al (LPEP study group). Leprosy Post-Exposure Prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin. BMJ Open 2016; 6: e013633.
59. Tiwari A, Dandel S, Djupuri R, Mieras L, Richardus JH. Population-wide administration of single dose rifampicin for leprosy prevention in isolated communities: a three year follow-up feasibility study in Indonesia. BMC Infect Dis 2018; 18: 324.
60. Lockwood DNJ, Krishnamurthy P, Kumar B, Penna G. Single-dose rifampicin chemoprophylaxis protects those who need it least and is not a cost-effective intervention. PLoS Negl Trop Dis 2018; 12: e0006403.

REVIEW ARTICLE

The Changing Spectrum of Sexually Transmitted Infections in Europe

Angelika STARY
Outpatients Centre for the Diagnosis of Infectious Venerodermatological Diseases, Vienna, Austria

As long as 400 years ago, syphilitic ulcers and gonococcal discharge were observed in connection with sexual intercourse. War, poverty, and lack of efficient therapeutic options led to a high incidence of venereal diseases, many of which had devastating outcomes. This situation continued until the beginning of the 20th century, when the microbial aetiology of venereal diseases was discovered. The infection rate dropped with the availability of antibiotic therapy after the Second World War. However, since the beginning of the 21st century, a steady increase in sexually transmitted infections (STIs) has been recognized worldwide. The number of reported cases of syphilis is increasing in Europe, especially in men having sex with men (MSM). Antibiotic resistance in several genital pathogens, such as *Neisseria gonorrhoeae* and *Mycoplasma genitalium*, causes therapeutic problems. Viral genital infections have become a therapeutic challenge, especially for prevention of STIs. Due to better knowledge of the long-term consequences of STIs and the connection between genital cancer and papillomavirus infections, sexual health services with screening programmes have been established in many European countries. There is general awareness of the importance of human papilloma virus vaccination programmes for young adolescents as a preventive strategy for genital cancer.

Key words: sexually transmitted infection; venereal disease; syphilis; gonococcal resistance.

Accepted Mar 19, 2020; Epub ahead of print Mar 24, 2020

Acta Derm Venereol 2020; 100: adv00114.

Corr: Angelika Stary, Outpatients Centre for the Diagnosis of Infectious Venerodermatological Diseases, Franz Jonasplatz 8-2-3, AT-1210 Vienna, Austria. E-mail: angelika.stary@meduniwien.ac.at

SIGNIFICANCE

Sexually transmitted infections (STIs) refer to a broad spectrum of bacterial, fungal, viral and protozoal infections that share a common mode of transmission through sexual contact. While syphilis was recognized as long ago as 1496, it took several centuries to detect *Treponema pallidum* as the agent, and to describe *Neisseria gonorrhoeae* as the cause of gonorrhoea. Discovery of penicillin, and molecular biological diagnostic advances, were enormous steps forward in the control of STIs, leading to a decrease in the reported numbers of infections worldwide. However, the development of antibiotic resistance in gonococci, and the emergence of new viral infections, such as genital herpes, human papilloma virus and HIV/AIDs, have changed the pattern of STIs. Despite efforts to prevent, diagnose, and treat STIs, they remain a major problem.

Although STIs are defined by a common mode of transmission, the diseases vary enormously in their aetiology and clinical manifestations. They may be bacterial, viral, protozoal or ectoparasitic in nature. The number of sexually transmitted or transmissible pathogens is permanently increasing and many of them can be divided into subtypes with differing clinical manifestations, e.g. *Chlamydia trachomatis* (**Table I**) (1).

The so-called venereal diseases (VD) include syphilis, gonorrhoea, chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale, and were recognized as exclusively sexually transmitted when the relevant laws and regulations were written in many countries. Evolution from the term VD to the term sexually transmitted diseases (STDs) or STIs reflects the recognition of the increasing number of symptomatic or asymptomatic infections or conditions due to the high number of sexually transmitted pathogens. While some of them are transmitted predominantly, or even exclusively, by sexual intercourse, others may qualify as sexually transmissible (e.g. hepatitis B virus, HIV, yeasts), and non-sexual routes of transmission may even predominate (2).

In most STIs clinical symptoms first occur at the point of entry of the microorganism and appear as ulcers ("genital ulcer disease" (GUD): syphilis, chancroid, genital herpes), mucosal inflammation or discharge (gonorr-

Table I. Venereal diseases and sexually transmitted infections (STIs)

Venereal diseases	STIs
Syphilis	Chlamydia trachomatis
Gonorrhoea	Mycoplasma genitalium
Chancroid	Mycoplasma hominis
Lymphogranuloma venereum	Ureoplasma urealyticum
Granuloma inguinale	Anaerobic bacteria
	Trichomonas vaginalis (TV)
	Candidiasis
	Pediculosis pubis
	Scabies
	Human immunodeficiency virus (HIV)
	Herpes simplex virus (HSV)
	Human papilloma virus (HPV)
	Hepatitis B virus (HBV)
	Ebola virus
	Zika virus

doi: 10.2340/00015555-3470
Acta Derm Venereol 2020; 100: adv00114

hoea, chlamydial and *Mycoplasma genitalium* infection, trichomoniasis), or even neoplasia. In certain STIs the infection may spread to neighbouring (gonococcal salpingitis/epididymitis) and distant organs (gonococcal septicaemia, secondary syphilis, neurosyphilis). While usually benign (genital warts), human papilloma virus (HPV) infections with high-risk genotypes may occasionally bear the risk of malignancy and possibly result in invasive carcinoma of the vulva, cervix, penis or anal region (3). Hepatitis B (HBV), scabies and HIV-disease, mainly affect extragenital sites.

The major complications of STIs include AIDS, cancer, pelvic inflammatory disease (PID) and related sequelae, neurological symptoms, sexually-acquired reactive arthritis (SARA), complications of pregnancy and the puerperium, congenital, perinatal and postnatal infection of the foetus/infant and a variety of other diseases.

HISTORY OF SEXUALLY TRANSMITTED INFECTIONS IN EUROPE

More than 100 years ago, Europe was the leading region in research on STIs. The vision that diseases in the genital tract might be caused by microorganisms was discussed in Paris in 1836, by Donne, who made some important discoveries about *Trichomonas vaginalis* (former name: Trico-monas vaginale), suggesting that it might not only be a harmless commensal, but a sexually transmissible microorganism causing symptoms (4).

As long ago as the 16th century, syphilis had been recognized as sexually transmitted, and was identified as a "venereal disease", stigmatizing the infected individual. This situation continued for 400 years, until the cause of syphilis had been detected and described in Europe. Fritz Schaudinn and Eric Hoffmann, in 1905, recognized pale rotating spiral organisms when using a Zeiss microscope to examine the secretion of an erosive vulval papule from a woman with secondary syphilis (5). They named the microorganism Spirochaeta pallida and published their discovery in the paper "Preliminary report on the presence of Spirochaetes in syphilitic lesions and in Papillomas". This was the beginning of intensive research into syphilis, a little over 100 years ago.

At that time, opinions on the cause of syphilis were diverse, until Karl Landsteiner was able to validate the presence of the microbe in specimens by dark-field microscopy, and created the new genus classification *Treponema pallidum* (6). This observation was followed by an enormous increase in publications on syphilis. A few years later, the "Wassermann reaction" was developed, and the results were presented at a conference in Vienna in 1908 during a congress for internal medicine. This was the first step to a reliable serological diagnosis of syphilis, which, in modified form, is still the recommended diagnostic procedure. Treatment of syphilis ranged from mercury, organic arsenicals, bismuth, and fever cycles, or even their combination. This was often followed by mild to severe side-effects, including death. In the pre-penicillin era, infections with *Treponema pallidum* were a serious cause of disability or even death, and the 10th leading cause of death in the USA in 1923–25 (7). These tortuous treatments ended with the discovery of penicillin by Alexander Fleming in St Mary's Hospital in London.

For a long time gonorrhoea was overshadowed by the severe syphilitic epidemic that threatened the infected population. The recognition of a different genital pathogen was another important scientific advantage in microbiology. Albert Neisser was the leading person in detecting gonococci in smears from men with urethral discharge (8). However, there were doubts, and the cultivation of the microbes was difficult, and they were indistinguishable from other bacteria. In Prague, Wertheim inoculated the urethra of men with pure cultures of *Neisseria gonorrhoeae* and induced the typical clinical picture of gonorrhoea. He also re-cultivated the bacteria from the symptomatic men, finally silencing doubters (9).

By the beginning of the 20th century the aetiology of syphilis, chancroid and gonorrhoea had been discovered, but the identity of urethral infections now known to be caused by *Chlamydia trachomatis* was still not defined. Halberstaetder & Prowazek described inclusion bodies in scrapings of the infected eyes of orangutans in 1907 (10). Lindner postulated a connection between genital (trachoma) and ocular infections; but it took time to discover the organism by cultivation in embryo egg cells and, furthermore, by modern immunological assays and finally by molecular biology (11).

Penile and anal warts were well known for many years, their clinical designation was changed from konylos to condylomata acuminatum, and these were described by different authors, along with an association with gonorrhoea ("gonorrhoeal warts") (12).The hypothesis that anogenital condylomas were caused by a virus identical to skin warts was finally proven by electron microscopy in the late 1960s. Since papillomaviruses could not be cultured either in cell culture-like viruses, or on agar plates, it needed the ability to prepare cloned viral genomes and compare with virus extracted from different anatomical sites to realise that there were differences between papilloma viruses on the mucous lesions in the genital areas and the skin.

During the First World War there were high numbers of different kinds of genital infections with inadequate facilities for treatment. Venereal ablution rooms and washing units were established for infected individuals, especially those with gonorrhoea and syphilis. VD had become a problem for the soldiers and, in particular, for the US army. The importance of medical examinations and Wassermann tests was recognized. Prostitutes were regulated in several countries, and notification of infected individuals became mandatory. After the First World War the International Union against Venereal Diseases and

Treponematoses (IUVDT) was formed in 1923, with the aim of encouraging member nations to collaborate in the prevention and control of VD. There was agreement on the need for a European network in diagnosis, treatment, and post-treatment surveillance of infected individuals and their contacts. While VD clinics were opened in Europe with improvement in health education and clinical and diagnostic development, the interest in STIs had almost disappeared in the USA. It was Thomas Parran (13) who brought the VD problem to national attention. He established programmes for syphilis control, with compulsory blood tests before marriage and during pregnancy, and established contact tracing (14). Clinical services began to improve and VD reporting also became mandatory in parts of the USA.

The Second World War had an enormous impact on the epidemiological situation of VD. Soldiers were looking for sex, not only in Europe, but also in Africa and in the Far and Middle East of Asia, and war poverty added to a high and uncontrolled incidence of STIs. The development of penicillin and other antibiotics after the Second World War changed the pattern of syphilitic and gonococcal infections, with a dramatic decline in the number of early infections throughout the world. The policy of mass testing for syphilis was established in the USA, and this was followed by mass treatment. In many European countries and in the USA the importance of VD diminished. However, despite the availability of effective treatment and better diagnosis, the symptoms of STIs re-emerged, and many men developed epididymitis, became sterile, or even developed uraemia. The resurgence of VD and STIs was due to population movements, oral contraception, the so-called sexual revolution, and the reduced use of condoms to prevent transmission. In addition, resistant microbes became a problem for gonorrhoea in developing, as well as in developed, countries.

SEXUALLY TRANSMITTED INFECTIONS IN EUROPE IN THE 21ST CENTURY

Worldwide, over 357 million new cases of 1 of the 4 major STIs (chlamydia, gonorrhoea, syphilis and trichomoniasis) occur each year in men and women aged 15–49 years, and, according to data from the World Health Organization (WHO), more than 1 million STIs are acquired every day (15, 16). During the last decade, the numbers of genital infections in European countries were collected by the European Centre for Disease Control (ECDC) through annual data collection and online reporting (TESSy).This offers a better insight into the epidemiological situation and STI surveillance in EU/EEA countries, and includes the European gonococcal antimicrobial surveillance programme (Euro-GASP) (17). Reporting, contact tracing, and treatment of STIs is legally regulated and controlled in most, but not all, European countries, and laws have been changed during the last decade. In most of the countries, gonorrhoea, chancroid, and syphilis are mandatory reportable infections, but the procedure differs regarding what and how much on information should be reported. In many European countries, reporting of *Chlamydia trachomatis* infection is recommended, and, in a few countries, even mandatory.

The organization of medical services for STIs varies across Europe. Dermato-venereology is the recognized specialty in Europe, Asia, and Latin America, but not in the anglophone regions. In 1948, in the UK and in Ireland, municipal authorities established a separate specialty, called "venereal diseases" with clinics and services specifically for the management of venereal diseases. In the 1970s, the name changed to genitourinary medicine (GUM) in order to minimize the stigma associated with the term "venereology" in the general population. In contrast to the European Academy of Dermatology and Venereology (EADV), STIs are not part of remit of Dermatology associations in the USA.

In the past 50 years there has been an extraordinary improvement in the quality of science, diagnostic facilities, and the number of services concerned with STIs and HIV, as well as more options for treatment and prevention. The emergence of HIV has influenced the epidemiology and clinical pattern of STIs. Knowledge of the impact of STIs/HIV on reproductive health has increased the recognition of STIs, with public benefit. In Europe the number of reported STIs decreased with the threat of acquiring HIV, but since the beginning of this century, a steady increase has occurred again, when the status of HIV infection was changed to that of a chronic disease. The number and rates of new diagnoses of STIs have increased in the EU/EEA since the 1990s, predominantly due to transmission between men who have sex with men (MSM), except for chlamydia where the increase has been associated with more sensitive diagnostics. Improved molecular biological methods can detect asymptomatic infections in both, men and women (18, 19). Although the surveillance methods vary across Europe, data suggest that HIV-positive men contribute a significant proportion of cases of syphilis, lymphogranuloma venereum (LGV) and gonorrhoea.

SYPHILIS

Despite simple and sensitive diagnostic tests and treatment effectiveness with a single dose of long-acting penicillin, syphilis remains a global public health problem. Since the beginning of this century the infection is re-emerging and affects two-thirds (66%) of MSM, with a high proportion of HIV-infected individuals. (**Fig. 1**) This was especially recognized after, and in connection with, the availability of efficient antiretroviral treatment and with pre- and post- retroviral prophylaxis (PREP and PEP). In 2016, 28 EU/EEA Member States reported

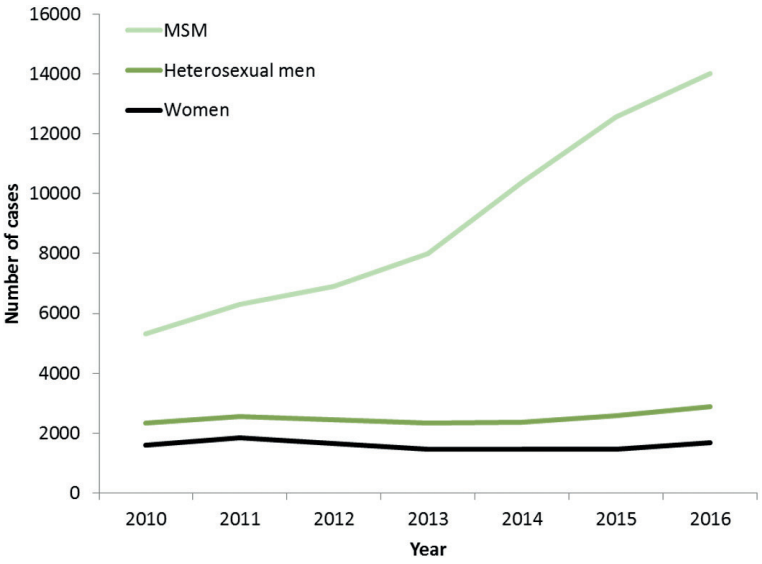

Fig. 1. Number of confirmed syphilis cases by gender, transmission category and year, EU/EEA countries reporting consistently, EU/EEA, 2010–2016. Source: Country reports from the Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Latvia, Lithuania, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom. Permission to publish this figure is given by Gianfranco Spiteri, ECDC. Gianfranco.Spiteri@ecdc.europa.eu.

approximately 30,000 syphilis cases to the ECDC, a rate of 6.1 per 100,000 population, being 8 times higher in men than in women.

The clinical presentation of syphilis has not changed and it can easily be treated, since, so far, no resistance against penicillin has been recognized. However, early forms of neurosyphilis, notably ophthalmic syphilis, often remain under-diagnosed. Syphilis still causes several hundred thousand stillbirths and neonatal deaths every year in developing nations. Therefore, strong advocacy and community involvement are needed to ensure that syphilis is still given a high priority on national health agendas.

NEISSERIA GONORRHOEA

Gonococcal infections are the second most prevalent European and worldwide bacterial STIs. Infection rates vary considerably across Europe, with higher rates reported in northern Europe. In 2016 almost half of the reported cases (46%) were in MSM (ECDC). The number of reported cases increased over the last 15 years in the European region, until 2016, while in the UK the gonococcal cases remained stable in 2015 and 2016 (**Fig. 2**).

In contrast to *Treponema pallidum*, *Neisseria gonorrhoeae* has developed resistance to all antimicrobials previously used as first-line treatments. Most institutions, such as WHO, CDC, ECDC, and IUSTI Europe, currently recommend dual therapy with ceftriaxone (injectable, in variable volumes), together with azithromycin as first-line drugs (20). Alternatively, cefixime (400 mg once orally) has been preferred in many countries, due to its acceptance by patients as an oral single-dose regimen (21). However, the susceptibility to both extended-spectrum cephalosporins (ESCs) is decreasing worldwide (22, 23). The increase in azithromycin MICs or resistant strains, affects the mainstays of dual gonococcal treatment with third-generation cephalosporins and macrolides. The British Association for Sexual Health and HIV (BASHH) has already changed the recommendation from dual therapy to a single-shot therapy with ceftriaxone, at a high dosage of 1 g, influenced by the diagnosis of a gonococcal strain with resistance to both first-line drugs. Progression of resistance of Neisseria gonorrhoea in Europe and a realistic danger of multidrug-resistant gonorrhoea is an ever-present concern (24, 25). In this regard, performance of gonococcal culture is still necessary. In order to obtain better diagnostic information on resistant strains, a real-time PCR-based assay was designed to detect the genomic DNA of strains harbouring mosaic pen A-alleles and to discriminate them from *N. gonorrhoeae* and *Neisseria* spp. strains harbouring other genes (26). A new treatment study with zoliflodacin was performed, with successful results for urogenital and rectal infections, but was less efficacious in the treatment of pharyngeal infections (27).

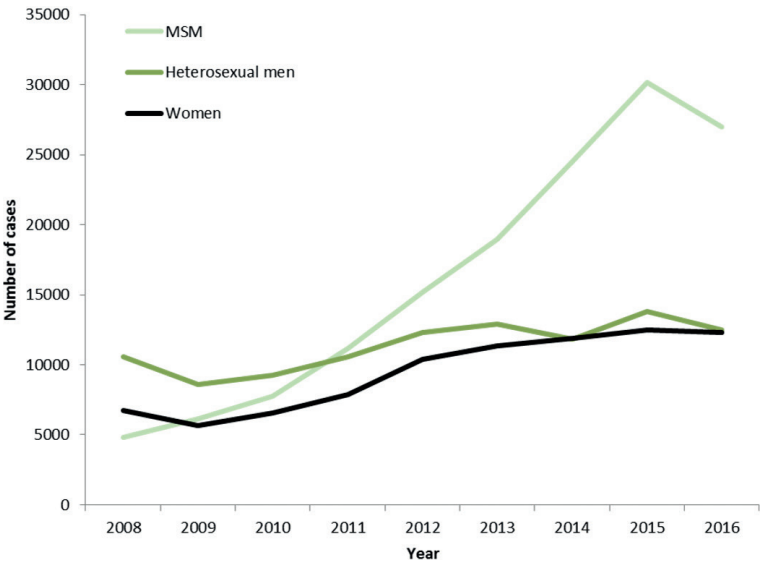

Fig. 2. Number of confirmed gonorrhoea cases by gender, transmission category and year, EU/EEA countries reporting consistently, EU/EEA, 2008–2016. Source: Country reports from the Cyprus, the Czech Republic, Denmark, France, Latvia, Lithuania, Malta, the Netherlands, Norway, Romania, Slovenia, Sweden and the United Kingdom. Permission to publish this figure is given by Gianfranco Spiteri, ECDC. Gianfranco.Spiteri@ecdc.europa.eu.

CHLAMYDIA TRACHOMATIS

Notification rates of chlamydia infections vary considerably across Europe, and continue to be highest among young adult women and heterosexuals. Over recent years, the overall trend appeared stable, both at the European and at the country level, with 150–250 cases per 100,000 population.

A special subgroup of *Chlamydia trachomatis* are the genotypes LGV1-3, causing the Lymphogranuloma venereum (LGV). In 2016, LGV data were reported by 22 European countries, out of which France, the Netherlands, and the UK accounted for 86% of the 2,043 notified cases. Almost all cases were reported among MSM with a 70% HIV-positivity rate (**Fig. 3**) (28). In addition to the classical clinical symptoms, with ulcers and inguinal buboes, rectal ulcerations are caused by these chlamydia strains, especially in infected HIV-positive individuals (29–31). Treatment recommendations are summarized in the guidelines of IUSTI Europe and the EADV (32).

MYCOPLASMA GENITALIUM

M. genitalium has been described recently as an important cause of genital infections in men and women, with a clinical pattern similar to *Chlamydia trachomatis*. It is the aetiological agent in 15–25% of symptomatic men with non-gonococcal urethritis and probably approximately 10% of women having pelvic inflammatory disease (PID) (33). Detection by nucleic acid amplification tests is the only diagnostic method available, and new CE-marked tests are approved for diagnostic use in Europe. Diagnosis and treatment is recommended in symptomatic patients. One of the main concerns is the lack of a universally effective treatment. Doxycycline has a cure rate of only 30%, whereas azithromycin is significantly more effective, with cure rates approaching 90% in macrolide-susceptible infections. However, an increase in macrolide resistance is reported in Europe, and has to be considered in treatment recommendations (34–36).

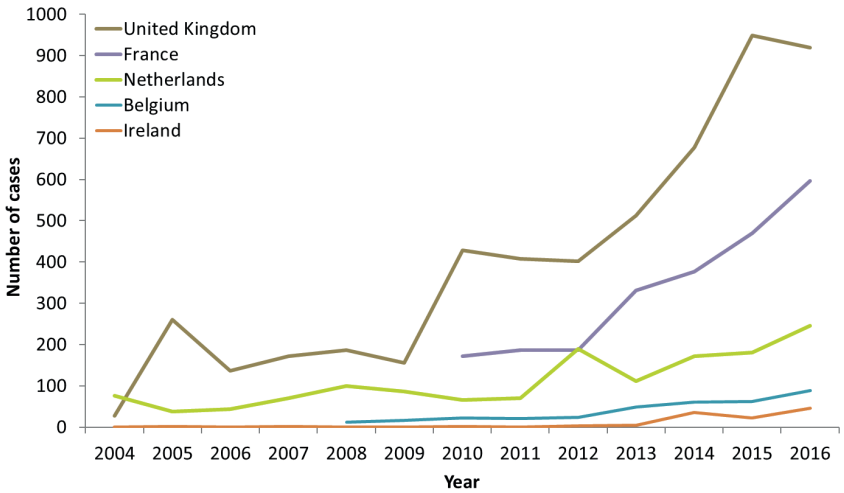

Fig. 3. Confirmed lymphogranuloma venereum cases among the five EU/EEA Member States reporting the largest number of cases in 2016, 2007–2016. Permission to publish this figure is given by Gianfranco Spiteri, ECDC. Gianfranco.Spiteri@ecdc.europa.eu.

VIRAL SEXUALLY TRANSMITTED INFECTIONS

The 21st century, in general, has been characterized by a steep rise in viral STIs, in comparison with bacterial STIs. The major impact of STIs on public health today predominantly derives from viral rather than bacterial infections. This is mainly because the latter are usually amenable to curative treatment, whereas most viral STIs still represent a major therapeutic challenge. Viruses causing STIs belong to various families, such as herpes viruses (e.g. genital herpes), human papilloma viruses (HPV, high- and low-risk groups causing genital warts, intraepithelial neoplasia, genital cancer), hepadnaviruses (hepatitis B), and retroviruses (HIV-disease). Antiviral drugs are effective against HSV infections, and are recommended prophylactically if a high number of genital relapses are observed annually. HSV can cause serious problems, including brain infections, to the newborn at the time of delivery. A close association exists between course and frequency of HIV infection and that of other STIs. Sexually promiscuous patients with GUD and/or gonorrhoea or chlamydial infections are at a particularly high risk of contracting HIV. Once infected, such individuals shed considerably more virus than HIV-infected persons without genital lesions. Conversely, STIs may accelerate the course of HIV-disease; this can be deduced from the observation that different viruses upregulate HIV transcription. These facts imply that the implementation of screening and treatment programmes for STIs will not only reduce the incidence of these infections, but also help to control the spread of HIV infection.

For viral STIs, vaccination against Hepatitis B and HPV has become common, especially in the West and Centre of Europe. The prevalence of high-risk HPV in Europe is 2–16%. Although the majority of acquired genital HPV infections appear to be subclinical or asymptomatic, several high-risk strains of HPV play a central role in the pathogenesis of most squamous cell cancers, and cause the most common cervical carcinoma with potentially life-threatening consequences. High- and low-risk HPV genotypes are also inducing other cancers or genital warts in the genital tract in women and men. Vaccines to protect against high- and low-risk genital HPV infections are available worldwide and modulate the progression of HPV disease (37). Vaccination programmes

are already established in many European countries, and offer pre-adolescent girls and boys HPV prevention free of charge as a public health issue.

In summary, the number and rates of new cases of STIs, such as chlamydia, gonorrhoea and syphilis, have increased in the EU/EEA since the 1990s. STIs are among the most frequently reported infections globally, indicating that national strategies, clinical services, and public health activities are beneficial public health instruments for the prevention and control of STIs and their long-term sequelae.

REFERENCES

1. de Vrieze NH, de Vries HJ. Lymphogranuloma venereum among men who have sex with men. An epidemiological and clinical review. Expert Rev Anti Infect Ther 2014; 12: 697–704.
2. Ganem D, Prince AM. Hepatitis B virus infection – natural history and clinical consequences. N Engl J Med 2004; 350: 1118–1129.
3. Garland SM, Joura EA, Ault KA, Bosch FX, Brown DR, Castellsagué X, et al. Human papillomavirus genotypes from vaginal and vulvar intraepithelial neoplasia in females 15–26 years of age. Obstet Gynecol 2018; 132: 261–270.
4. Donne MA. Animacules observes dans les matieres purulentes et le produit des secrertions des organes genitaux de l'homme et de la femme; extrait dúne lettre de MA Donne. CR Acad Sci Paris 1836; 3: 385–386.
5. Schaudinn F, Hoffmann E. Vorläufiger Bericht über das Vorkommen von Spirochaetenin syphilitischen Krankheitsprodukten und bei Papillomen. Arb K Gesundheitsamt 1907; 22: 527–534.
6. CDC. Leading causes of death, Long-term complications from syphilis occurred in 28% in US Army soldiers in 1914. Available from: https://www.cdc.gov/nchs/data/dvs/lead1900_98.pdf.
7. Moore JE. An evaluation of public-health measures for the control of syphilis. an epidemiological study. Lancet 1951; 1: 699–711.
8. Neisser A. Die Micrococcen der Gonorrhoe. Dtsch Med Wochenschr 1882; 8: 279–282.
9. Wertheim E. Reinzüchtung des Gonococcus Neisser mittels des Plattenvrfahrens. Dtsch Med Wochenschr 1891; 17: 1351–1352.
10. Halberstaetder L, Prowazek S. Über Zelleinschlüsse parasitärer Natur beim Trachom. Arb K Gesundh Amt 1907; 26: 44–47.
11. Lindner K. Zur Ätiologie der gonokokkenfreien Urethritis. Wien Klin Wochenschr 1910; 23: 283–284.
12. Bäfverstedt B. Condylomata acuminata – past and present. Acta Derm Venereol 1967; 47: 376–381.
13. Parran T. Shadow on the Land: Syphilis. New York City, N.Y.: Reynal & Hitchcock. 1937, p. 1–309.
14. Oriel JD. The scars of Venus. A history of venereology. London: Springer Verlag; 1994, p. 1–223.
15. WHO. Available from: https://www.who.int/en/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis).
16. WHO. Available from: http://www.who.int/reproductive-health/publications/rtis/ghss-stis/en/.
17. Euro-GASP external quality asseement scheme for Neisseria gonorrhoeae antimibrobioal suspeptibility testing 2018. Available from: www.ecdc.com.
18. European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 1990–2010. Stockholm: ECDC; 2012.
19. ECDC Technical report: Developing a national strategy for the prevention and control of sexually transmitted infections. Available from: www.ecdc.europa.eu.
20. Kirkcaldy RD, Harvey a, Papp JR, De Rio C, Sorge OO, Holmes KK, et al. Neisseria gonorrhoeae antimocrobial susceptibility surveillance – the gonococcal isolate surveillance project, 27 sites, United States, 2014. Surveillance Summaries 2016: 65: 1–19.
21. Yokoi S, Deguchi T, Ozawa T, Yasuda M, Ito S, Kubota Y, et al. Threat to cefixime treatment of gonorrhea. Emerg Infect Dis 2007; 13: 1275–1277.
22. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug – and extensively drug-resistant Neisseria gonorrhoeae. Expert Rev Anti Infect Ther 2009; 7: 821–834.
23. Lewis DA. The gonococcus fights back: is this time a knock out? Sex Transm Infect 2010; 86: 415–421.
24. Blank S, Daskalakis DC. Neisseria gonorrhoeae – rising infection rates, dwingling treatment options. N Engl J Med 379: 19: 1795–1797.
25. UK case of Neisseria gonorrhoeae with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad. Health Protection Report Advanced Access Report Volume 12:11.19.
26. Shimuta K, Igawa G, Yasuda M, Deguchi T, Nakayama SI, Ohnishi MJ. A real-time PCR assay for detecting a penA mutation associated with ceftriaxone resistance in Neisseria gonorrhoeae. J Glob Antimicrob Resist 2019; 19: 46–49.
27. Taylor SN, Marrazzo J, Batteiger BE, Hook EW, Sena AC, Long J, et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. N Engl J Med 2018; 379: 1835–1845.
28. Saxon C, Hughes G, Ison C. Asymptomatic lymphogranuloma venereum in men who have sex with men, United Kingdom. Emerg Infect Dis 2016; 22: 112–116.
29. Stoner BP, Cohen SE. Lymphogranuloma venereum 2015: clinical presentation, diagnosis, and treatment. Clin Infect Dis 2015; 61 Suppl 8: S865–S873.
30. Ronn M, Hughes G, White P, Simms I, Ison C, Ward H. Characteristics of LGV repeaters: analysis of LGV surveillance data. Sex Transm Infect 2014; 90: 275–278.
31. Seth-Smith HM, Galan JC, Goldenberger D, Lewis DA, Peuchant O, Bebear C, et al. Concern regarding the alleged spread of hypervirulent lymphogranuloma venereum Chlamydia trachomatis strain in Europe. Euro Surveill 2017; 13: 22. pii: 30511.
32. de Vries HJ, Zingoni A, Kreuter A, Moi H, White JA. European guideline on the management of lymphogranuloma venereum. J Eur Acad Dermatol Venereol 2015; 29: 1–6.
33. Ong JE. Aung, Read TRH, Fairley ChK, Garland S., Murray G, et al. Clinical characteristics of anorectal mycoplasma genitalium infection and microbial cure in men who have sex with men. Sex Transm Dis 2018; 45: 522–526.
34. Hokynar K, Hiltunen-Back E, Mannonen L, Puolakkainen M. Prevalence of mycoplasma genitalium and mutations associated with macrolide and fluoroquinolone resistance in Finland. Int J STD AIDS 2018; 29: 904–907.
35. Jensen JS, Bradshaw C. Management of Mycoplasma genitalium infections – can we hit a moving target? BMC Infect Dis 2015; 15: 343.
36. Braam JF, van Dommelen L, Henquet CJM, van de Bovenkamp JHB, Kusters JG. Multidrug-resistant Mycoplasma genitalium infections in Europe. Eur J Clin Microbiol Infect Dis 2017; 36: 1565–1567.
37. Huh WK, Joura EA, Giuliano AR, Iversen OE, de Andrade RP, Ault KA, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. Lancet 2017; 390: 2143–2159.