JULY 2020 VOL 4 NO 1

A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

Reprints in Dermatology

Common and important skin rashes in primary care

Overview of cutaneous fungal infections

Hidradenitis suppurativa: what's new in pathogenesis and management

Biologics: new therapy for atopic dermatitis

A child with severe wrinkling of the skin of the palms

Rapid onset of erythroderma in a 65-year-old man

Recurrent, painful nodules on a girl's legs

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Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

FOREWORD FROM THE EDITOR-IN-CHIEF, DERMATOLOGY COLLECTION

Dermatological presentations represent a large proportion of all general practice consultations in Australia, with the 2015-2016 BEACH General Practice Activity study finding that 17 out of 100 consultations are related to skin problems. In this sixth issue of *Dermatology Collection* you will find more articles that we consider among the most important published in *Medicine Today* in recent years.

Patients can present to primary care with skin problems ranging from autoimmune and inflammatory conditions to dermatological emergencies.

It is important that GPs are aware of how to diagnose and manage these conditions, and know when to refer patients, whether they are common fungal infections such as tinea and candidiasis or a chronic autoinflammatory skin condition with significant comorbidities such as hidradenitis suppurativa.

I hope you will enjoy this informative collection of dermatology articles.

Gayle Fischer OAM, MB BS, MD, FACD
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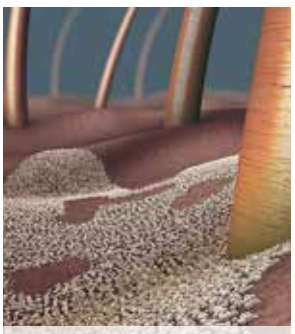
CONTENTS PEER REVIEWED

PAGE 2



PAGE 11

PAGE 25

PAGE 35

Common and important skin rashes in primary care

STEPHANIE BLAKE BMed/MD, MMed
STEPHEN SHUMACK OAM, MB BS(Hons), FACD

Many of the common and serious presentations to primary care that are related to dermatology are listed here. GPs need up-to-date information to help with initial investigation and management strategies, and recommendations for when to refer on.

KEY POINTS

- Patients with skin problems comprise 17% of general practice consultations in Australia.
- Patients can present to primary care with skin problems ranging from autoimmune and inflammatory conditions to dermatological emergencies.
- Autoimmune and inflammatory problems include dermatitis, psoriasis and acne.
- Infectious diseases such as tinea, cellulitis and scabies are also common.
- Occasionally, patients may present with dermatological emergencies such as Stevens-Johnson syndrome and toxic epidermal necrolysis.
- It is important that GPs are aware how to diagnose and manage these conditions, and know when to refer patients.

Dermatological presentations represent a large proportion of all general practice consultations in Australia, with the 2015-2016 BEACH General Practice Activity study finding that 17 out of 100 consultations are related to skin problems.[1] Contact dermatitis, skin neoplasms, skin checks and acne were among the top five reasons for referral to a dermatologist.[1]

Autoimmune and inflammatory skin conditions

Atopic dermatitis

Atopic dermatitis, otherwise known as eczema, is one of the most common dermatological conditions – affecting up to 30% of one-year-olds in Western countries (Figure 1).[2] The incidence declines with age, but this condition still affects about 2 to 5% of adults.[3] Quality of life in patients with atopic dermatitis and their families is significantly affected, particularly their mental health and social functioning.[4,5] The pathogenesis of atopic dermatitis is not yet fully understood, but involves a complex interplay of genetic factors, environmental triggers, skin barrier dysfunction and the skin microbiome.

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Nonpharmacological measures are key in the management of atopic dermatitis and should be initiated in all patients. Patients should use a bland emollient regularly and liberally. Clinicians should also advise patients to use soap-free washes, have shorter, cooler showers and consider bleach baths in patients with recurrent superficial *Staphylococcus aureus* infections.

Topical corticosteroids are the cornerstone of therapy and should be used at appropriate strengths for appropriate sites. Weaker strengths should be used in areas prone to possible adverse reactions (the face, axillae and groin). The most commonly used corticosteroid is hydrocortisone 1% cream or ointment. In other areas of the body, a moderate- to high-potency topical corticosteroid is appropriate – for example, betamethasone dipropionate 0.01% ointment. Corticosteroid phobia is common among patients and their families, and can often result in treatment failure.[6] Ongoing strong reassurance from trusted clinicians can assist in combating this and optimising adherence.

In patients for whom topical corticosteroid therapy and optimisation of their general skin care routine is ineffective, referral to a dermatologist should be considered. Other options that may be prescribed by a dermatologist for patients with moderate to severe eczema include narrow-band ultraviolet (UV) B therapy and oral immunosuppressant therapy with medications such as methotrexate, ciclosporin, mycophenolate mofetil and azathioprine. Initially, all oral immunosuppressant therapies require close monitoring of clinical response and laboratory parameters. However, once a patient is stable on a particular medication, shared care with the GP may be appropriate. Occasionally, courses of oral corticosteroids can be useful in the management of flares. However, prolonged use should be avoided due to their significant side effects and difficulty in stopping the corticosteroids in some patients.

Dupilumab is a potential upcoming biologic therapy for atopic dermatitis, and has been approved by the US Food and Drug Administration and the TGA. It is a monoclonal antibody directed against the IL-4 receptor and, in Phase III trials, about two-thirds of patients demonstrated a 75% reduction in Eczema Area and Severity Index score at one year, with a reduction in flare frequency.[7] It was recently approved by the Pharmaceutical Benefits Advisory Committee for use in severe atopic dermatitis and will be available with PBS-funded prescription later this year or in early 2021. Currently, it is only available through private prescription from dermatologists and immunologists. Dupilumab is associated with an increased risk of infections, particularly upper respiratory tract infections and conjunctivitis. Other promising potential therapeutic options in the future include Janus kinase (JAK) inhibitors and interleukin (IL)-31 and IL-23 antagonists. Oral JAK inhibitors also carry an increased risk for infection, and can cause hyperlipidaemia and lymphopenia.

Psoriasis

Psoriasis is an immune-mediated inflammatory skin condition, in which unknown environmental stimuli cause the release of cytokines, causing the skin cells to rapidly divide (Figure 2). There are a number of subtypes of psoriasis including chronic plaque, guttate, palmoplantar, pustular, flexural, nail, scalp and erythrodermic. The most common of these is chronic plaque psoriasis (CPP), although patients can experience multiple subtypes concurrently.

Patients usually develop CPP in adulthood, before the age of 45 years. Once affected, they rarely experience spontaneous remission, and will usually require lifelong treatment. In Australia, CPP affects about 2 to 6% of the population, and it is estimated that 19,000 Australians are living with a severe form of the disease.[8,9]

Guttate psoriasis is classically associated with a preceding streptococcal infection,

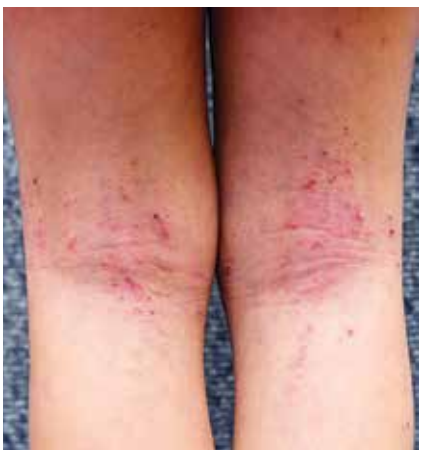

Figure 1. Atopic dermatitis.

Figure 2. Psoriasis.

Figure 3. Alopecia areata..

and typically affects younger patients. It is characterised by smaller, teardrop-shaped plaques, with a generalised distribution, and usually clears spontaneously after a few months. Palmoplantar psoriasis affects the acral surfaces, and the classic plaques of psoriasis are often seen, with patchy or generalised keratoderma.

Scalp psoriasis has the same features as CPP, with erythema, scale and thickened skin across the scalp and hairline. It can be associated with hair loss in severe cases, but does not cause scarring alopecia, and hair usually regrows once the underlying disease is treated. Patients may have nail psoriasis in conjunction with other subtypes, or on its own. Characteristic features include nail plate crumbling, pitting, onycholysis and splinter haemorrhages.

Flexural or inverse psoriasis affects the axillae and groin, and usually does not have the thickening or scale associated with chronic plaque. These patients have erythematous patches in the flexural areas, which can mimic erythrasma or other infectious conditions.

Pustular psoriasis and erythrodermic psoriasis are two severe subtypes that require urgent specialist review and are usually managed in the inpatient setting. Pustular psoriasis presents with small pustules, usually on the hands and feet, but occasionally on the body. These pustules are sterile when swabbed, and can occur in discrete patches or in a generalised distribution. The generalised presentation can progress to erythrodermic psoriasis, which can be life threatening. It is often precipitated by withdrawal of corticosteroids in psoriasis patients, drugs such as lithium and antimalarials, or infection. Due to the disruption of the skin barrier, these patients are prone to dehydration, hypothermia and high-output cardiac failure. It requires aggressive treatment with topical wet wrap therapy, intravenous fluid and electrolyte replacement, and consideration of oral immunosuppressive therapy such as ciclosporin or acitretin, and patients are typically managed in an inpatient setting.

Psoriasis has a significant impact on quality of life and increases patients' risk of inflammatory arthritis, inflammatory bowel disease, cardiovascular disease, metabolic syndrome and lymphoma.[10-12]

Modification of lifestyle factors, such as optimisation of weight and blood sugar, increased exercise and smoking cessation can be useful in reducing disease activity.[13-15] First-line therapy for psoriasis includes topical corticosteroids, which can be combined with vitamin D analogues to better penetrate the thick, scaly plaques. Ready-made preparations include calcipotriol and betamethasone dipropionate as foam, gel or ointment. Patients who have resistant disease can be referred to a dermatologist to trial UV light therapy or oral immunosuppressives such as methotrexate, ciclosporin and acitretin. In severe and resistant disease, biologics such as TNF-α, IL-17 and IL-23 inhibitors can be useful. These agents have an excellent success rate, with 65 to 70% of patients with moderate to severe psoriasis who use IL-23 antagonists achieving almost clear or clean skin.[16] These new biologics are well tolerated, with the most common side effects being increased risk of upper respiratory tract and cutaneous infections.

Alopecia areata

Alopecia areata (AA) is a nonscarring autoimmune form of hair loss and the lifetime prevalence is estimated to be 2% (Figure 3).[17] Disease severity can range from a single episode of self-limiting patchy hair loss to chronic relapsing-remitting disease that may progress to alopecia totalis, a total loss of terminal hair on the scalp, or alopecia universalis, a total loss of hair all over the body. Ophiasis is a rarer subtype, in which patients experience hair loss on their posterior scalp in the occipital region, and is associated with a poorer prognosis. Patients with AA may also have nail changes, most commonly pitting. A classic clinical feature of AA is the presence of exclamation mark hairs, which are very short hairs that are wide at the top of the hair and thinner towards the end. Vellus (fine, nonpigmented) hair may also be present within patches or at the periphery.

Therapy is aimed at arresting disease progression in the acute phase, and may reduce the risk of progression into chronic relapsing AA.[18] Recent consensus guidelines suggest that patients with more than one patch of AA should be considered for active treatment, as more than half of these patients will go on to develop further patches in the subsequent months.[18] Currently, therapies for AA are limited and usually provided in the specialist setting. For those with patchy disease, intralesional steroid injection can be useful; however, this is not feasible for extensive disease. The injections can be very painful and, in younger patients, high-potency topical corticosteroids can be used as an alternative. In patients with resistant disease, topical sensitisers such as diphenylcyclopropenone or irritants such as dithranol can be used to invoke an allergic contact dermatitis and promote hair growth.

Oral corticosteroids or steroid-sparing oral immunosuppressives such as methotrexate can also be used. Oral JAK inhibitors have shown promise in retrospective studies, but are not currently subsidised under the PBS for this condition and, therefore, their cost limits them from being widely used.[19]

Acne

Acne vulgaris is one of the top five reasons for dermatology referral in Australia (Figure 4).[1] It is usually considered a disease

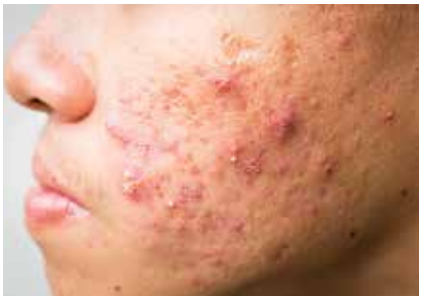

Figure 4. Acne.

of adolescence, triggered by the production of androgens; however, an increasing number of patients, particularly women, experience symptoms into adulthood.[20] Most people will experience some form of acne during their lifetime, and moderate to severe disease affects about 11 to 25% of Australian school children.[21] It is a source of significant stress to patients, with one study reporting that 70% of acne patients feel embarrassed about their disease, and 27% had depression.[22]

Mild to moderate disease can be treated with topical adapalene, a topical retinoid, as monotherapy or in combination with benzoyl peroxide. For patients with resistant disease, oral tetracyclines can be trialled. However, treatment-resistant propionibacteria have been seen even in treatment-naive patients. In females, antiandrogens can be very successful – for example, spironolactone or oral contraceptives containing cyproterone acetate. If, however, the patient is nonresponsive after three to four months of treatment, referral to a dermatologist for isotretinoin should be considered.[23] Patients with significant scarring at presentation, those with severe or resistant disease and those experiencing significant distress as a result of their acne should also be referred early for consideration of isotretinoin therapy.[23] Isotretinoin has high efficacy and a very good safety record. A retrospective review of the adverse events associated with isotretinoin found lower doses were as effective as traditional high-dose therapy, but associated with fewer adverse events.[24] The most common issues seen with isotretinoin are cheilitis (seen in 77 to 97% of patients), eczema (9 to 16%) and fatigue (7 to 20%). Mood changes were noted in up to 4 to 10% of these patients, and were dose dependent.[24]

Allergic and irritant contact dermatitis

Allergic contact dermatitis is the most common skin condition to present in general practice (Figure 5).[1] Common allergens include nickel, fragrance mix (containing the eight most common allergy-causing fragrances used in many products), Balsam of Peru and thimerosal.[25] The disease distribution can assist with the diagnosis – for example, patients with a nickel allergy may present with a rash on their nasal bridge and temples if they wear spectacles with frames containing nickel, a rash on their earlobes and neck if they wear nickel-containing jewellery or a rash on their lower abdomen from their trouser buttons.

Irritant contact dermatitis occurs with an earlier onset, and may present with a papulosquamous eruption or vesicular lesions. It often follows exposure to known allergens such as workplace chemicals or plant-based medicines and frequently affects the hands.

For localised lesions, moderate or high-potency topical corticosteroids (e.g. betamethasone dipropionate 0.05% ointment) are appropriate first-line therapy. The exception to this is lesions in areas that are more prone to possible corticosteroid side effects, such as in flexural areas or on the face, and weak topical steroids (hydocortisone 1%) or topical calcineurin inhibitors can be used in these cases. Patients with extensive disease (greater than 20%) can trial short courses of oral corticosteroids. Identification of the causative agent is pivotal to effective management, and referral to a dermatologist for patch testing to identify topically encountered allergens should be considered in patients whose allergic trigger is not clear.

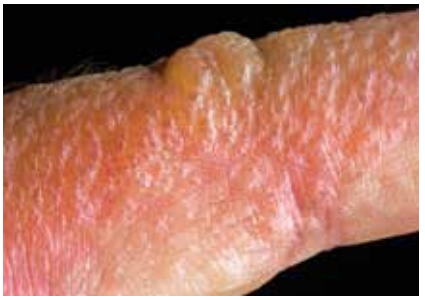

Figure 5. Contact dermatitis.

Infectious skin conditions

Tinea infections

Patients can present with tinea in many different locations. The most common is on the feet, known as tinea pedis. This infection can extend to the nails and cause localised dystrophy. Infection on the body is known as tinea corporis and classically presents with annular, scaly plaques. In children, tinea can affect the scalp, resulting in hair loss. Scalp involvement is not typically seen in adults; however, the beard and eyebrows can be affected.

Tinea pedis and tinea corporis can be managed effectively with topical therapy, such as topical terbinafine applied twice daily for four weeks.[26,27] Before starting oral antifungal therapy, microscopy and culture is highly recommended. Oral antifungals such as terbinafine, fluconazole and itraconazole can be used in patients with resistant disease and those with hair loss. However, monitoring of liver function should be considered when using terbinafine.[28]

Cellulitis

Cellulitis is a skin infection which affects the lower dermis and subcutaneous tissue, and erysipelas is a closely related condition that affects the upper dermis (Figure 6). Patients presenting with either of these conditions usually have a well-demarcated area of erythema, local oedema and pain, often but not invariably with malaise and fever. It is frequently seen in patients with diabetes, venous stasis dermatitis, chronic kidney disease and tinea pedis. Classically, cellulitis is caused by *Streptococcus pyogenes*; however, other organisms such as *Staphylococcus*

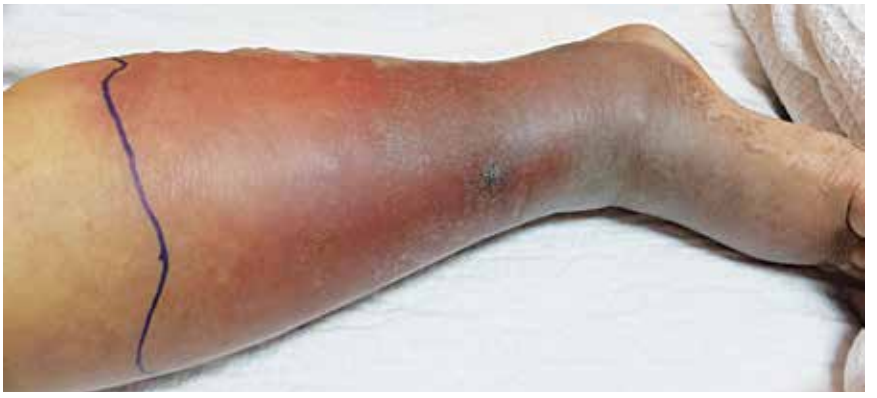

Figure 6. Cellulitis.

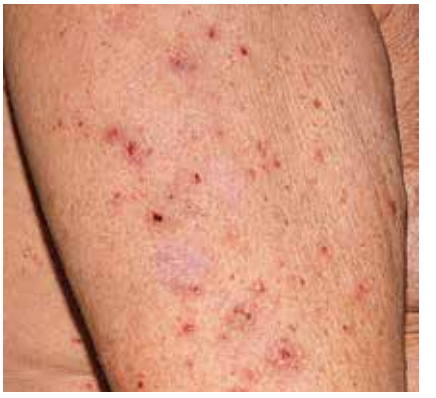

Figure 7. Scabies.

aureus and other rarer organisms may be implicated in erysipelas and atypical cellulitis presentations.

Depending on the patient, stage of infection and comorbidities, classic cellulitis should be treated empirically with phenoxymethylpenicillin or cefalexin or with targeted antibiotics guided by the sensitivities.[29]

Clinicians should remember that there is a wide differential for cellulitis. The most common alternative diagnosis is venous stasis dermatitis, particularly when the rash is bilateral. Patients with severe venous insufficiency often have bilateral leg erythema with swelling, and careful clinical history regarding duration and concurrent infective symptoms should be taken to differentiate between this condition and cellulitis. In venous stasis dermatitis there are often other features of venous insufficiency such as haemosiderin staining, varicosities, lipodermatosclerosis or atrophie blanche. Other commonly seen differential diagnoses include tinea corporis or drug eruptions. In patients who do not respond to initial therapy, further investigation to exclude these conditions or referral to specialty care should be considered. Prolonged courses of empirical antibiotics without identification of a causative organism should be avoided.

Scabies

Scabies is a skin infestation with the *Sarcoptes scabiei* mite, transmitted by direct contact with affected people (Figure 7). In Australia, outbreaks are more common in tropical areas and central Australia as well as nursing homes.

Diagnosing scabies can be difficult due to its varied presentation. Infestation should be considered in high-risk groups who have unexplained itch, persistent lesions resembling insect bite reactions, recurrent impetigo with itch and in older patients with new-onset dermatitis. Nursing home patients often have an atypical distribution, with the torso being the most commonly affected area.

The most commonly seen clinical features in nursing home patients are papules, followed by burrows and hyperkeratosis.[30] Of note, 50% of patients in a prospective cohort study of nursing home patients with dementia did not report any symptoms of their scabies infestation.[30] Clinicians should have a high index of suspicion and low threshold for treating scabies empirically in these high-risk groups.

Dermatological emergencies

Stevens-Johnson syndrome/ toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are dermatological emergencies, with a mortality rate of up to 50% in TEN.[31] Both are characterised by desquamation and mucosal involvement, with less than 10% of body surface area affected in SJS, 10 to 30% in SJS/TEN overlap and 30% or more in TEN. SJS and TEN are rare, with incidence estimated at one to two cases per million per year.[32] SJS tends to be less severe than TEN, and is more commonly caused by infections, such as mycoplasma and herpes simplex virus. These patients typically do not have significant systemic symptoms. In comparison, TEN usually has a drug precipitant, and carries a mortality risk. In SJS/TEN overlap, it can be difficult to differentiate between the two and these cases are typically either drug induced or idiopathic.

The cutaneous findings are usually preceded by a flu-like prodrome and fever, and patients may experience dysphagia, conjunctivitis or photophobia as early features of the mucous membrane involvement. The classic feature of both is a positive Nikolsky sign, where a clinician can induce skin sloughing by applying gentle lateral pressure. The rash and mucositis usually progress rapidly from erythematous macules or targetoid lesions into bullous lesions and desquamation.

Common precipitants include allopurinol, antiepileptics, sulfonamide antibiotics, aspirin and other NSAIDs.[33] A number of human leukocyte antigen (HLA) gene subtypes have been linked to an increased risk of SJS and TEN under certain conditions, such as with allopurinol use in patients with the *HLA-B**58:01 allele and carbamazepine use in patients with the *HLA-B**15:02 and *HLA-A**31:01 alleles.[33-36] Consensus is lacking regarding potentially screening high-risk patients for HLA subtypes

Figure 8. Erythroderma.

before starting certain medications.

Patients with SJS or TEN require urgent referral for inpatient management, as the extensive skin loss can cause hypovolaemic shock, electrolyte imbalance, bacteraemia, acute renal failure and other organ dysfunction. After recovering from the acute stage of the illness, patients may have chronic eye disease, gingival inflammation and oral discomfort, vaginal dryness and dyspareunia, and bronchiectasis or chronic bronchitis, and will require ongoing outpatient monitoring.

Erythroderma

Erythroderma is a generalised, erythematous eruption that can be caused by multiple triggers (Figure 8). Drugs, infections, pityriasis rubra pilaris (PRP), lymphoma and widespread atopic dermatitis or psoriasis can all be associated with erythroderma.[37] Patients present with diffuse erythema, which progresses to extensive exfoliation. Patients with PRP may also present with palmoplantarkeratoderma and islands of sparing (white areas of normal skin within the erythroderma).

As the skin plays a major role in patients' ability to control temperature and hydration, patients with erythroderma can have fever and other constitutional symptoms, hypotension due to dehydration, or high-output cardiac failure. These patients are usually managed aggressively as inpatients, with intravenous fluid replacement, electrolyte monitoring and topical corticosteroid therapy. Targeted therapy depending on the cause of erythroderma should also be started – for example, methotrexate for erythrodermic psoriasis.

Other drug hypersensitivity reactions

Drug hypersensitivity reaction is a frequent and varied presentation in general practice, and can present diagnostic dilemmas (Figure 9). Time from ingestion of the drug can vary from hours to weeks and symptoms may persist even after the causative agent is ceased.

Identifying the causative agent is pivotal in managing these conditions, and creating a drug chart timeline can assist clinicians in isolating potential drug triggers. Patients with a classic maculopapular drug eruption typically develop symptoms four to 14 days after initial exposure, but conditions such as DRESS (drug reaction with eosinophilia and systemic symptoms) usually take two to eight weeks to develop.[38]

Withdrawal of the trigger is the most important step; however, the rash should be treated with topical corticosteroid and emollient therapy. In severe cases, oral corticosteroids may be required.

Conclusion

Patients with skin problems comprise 17% of general practice consultations in Australia. These can vary from autoimmune and inflammatory skin conditions such as dermatitis, psoriasis and acne to infectious diseases such as tinea, cellulitis and scabies to dermatological emergencies such as SJS and TEN. Therefore, it is important that GPs are aware of how to diagnose and manage these conditions, and know when to refer patients to a dermatologist or for inpatient management. MT

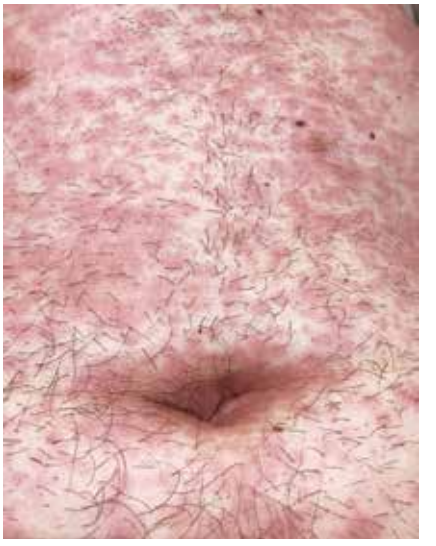

Figure 9. Drug hypersensitivity.

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Overview of cutaneous fungal infections

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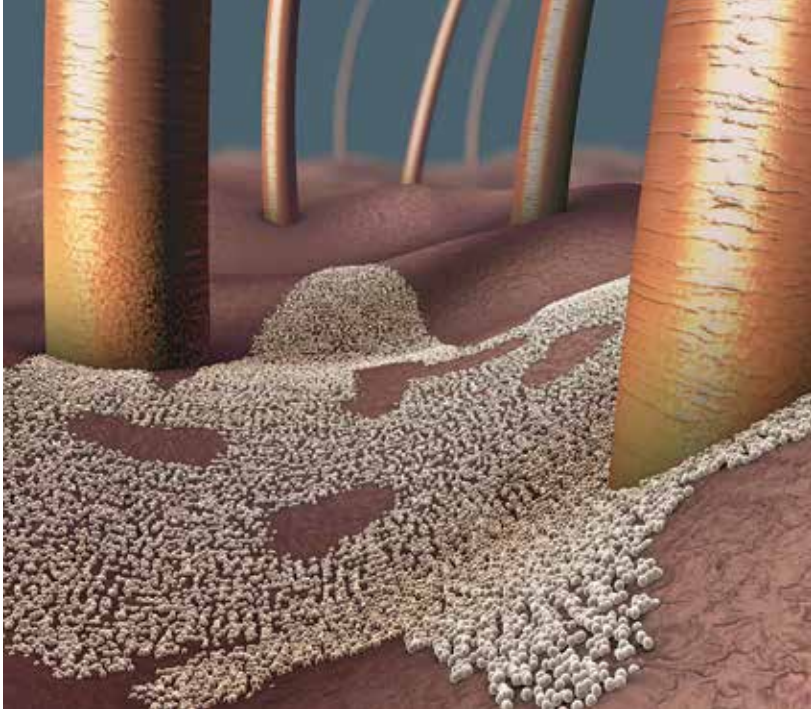
Establishing a diagnosis before starting treatment is essential in the management of fungal skin infections. This can be achieved by having a high index of suspicion regarding the many clinical appearances of fungal infections and by using simple diagnostic tests. The three most common fungal conditions include tinea, pityriasis versicolor and candidiasis; however, this article will mention some rarer conditions including tinea nigra and piedra.

KEY POINTS

- Cutaneous fungal infections present in a large variety of ways, many of which mimic noninfectious conditions. Establishing a diagnosis is essential before starting treatment, especially if oral antifungal therapy is considered.
- If the diagnosis is uncertain, avoid using corticosteroid treatment, which can obscure the fungal infection resulting in tinea incognito.
- Topical antifungal treatment is adequate in most fungal infections; however, for infections of the palms, soles, nails, hairy body areas, tinea incognito, granulomatous lesions and in widespread infection, oral treatment is usually required.
- Referral to a dermatologist is recommended in cases of treatment resistance.
- Investigate for underlying immune deficiency if the infection is widespread or recurrent.



Cutaneous fungal infections are common and are frequently managed by GPs. Fungal infections occur in children and adults of all ages and manifest in a large variety of ways. Nevertheless, the management principles for most superficial mycoses are similar. It is essential to establish the diagnosis microbiologically before starting therapy to avoid masking the underlying true condition with incorrect treatments such as topical corticosteroids.

Most cutaneous fungal infections are caused by either dermatophytes or yeasts. Dermatophytes are organisms that require keratin as a substrate and therefore have no potential to become systemic. They infect hair, nail and skin. There are three genera: *Trichophyton, Microsporum* and *Epidermophyton*. Within the genera, there are many species and these tend to vary depending on geographic location. They are classified as zoophilic when the natural host is a nonhuman animal; geophilic when found in the soil; and anthropophilic when the natural host is human. The last type are adapted to humans and therefore tend to cause low-grade but chronic disease. Other dermatophytes can cause highly inflammatory disease.

Another phenomenon found with acute inflammatory fungal infections is the 'id reaction', an immunological response to the fungus causing an eruption of sterile vesicles distant to the infection site. This is most commonly observed on the palms and fingers (Figure 1a).

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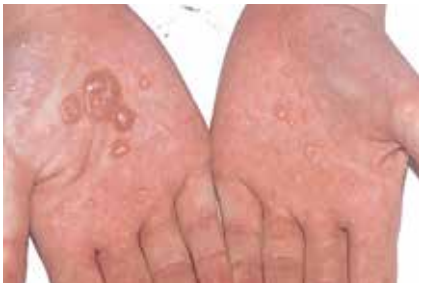
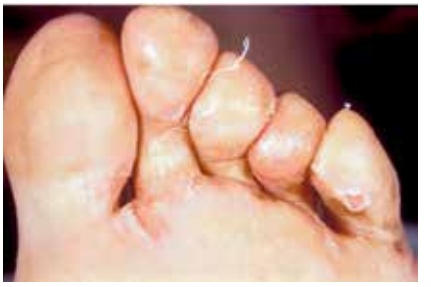




Figures 1a and b. Tinea pedis. a (left). An 'id' reaction in a patient with acute tinea pedis. b (right). Chronic tinea pedis, or athlete's foot, caused by *Trichophyton*.

Candida, a yeast, is a human commensal that can become an opportunistic pathogen. This tends to occur in immunosuppression, diabetes and moist environments, particularly in obese patients and when antibiotic therapy has altered the microbiome. *Candida* species are considerably more limited than the dermatophytes and, when immunosuppression exists, may cause systemic disease. *Candida albicans* is by far the commonest species; however, about 5% of infections are associated with atypical species such as *Candida glabrata*. Vulvovaginal candidiasis is, however, commonly seen in otherwise healthy women.

This article will summarise common cutaneous fungal infections; risk factors for fungal infections; complications of fungal infections; investigations required to diagnose fungal infections; and management of fungal infections.

Types of cutaneous fungal infection

Cutaneous fungal infections are classified into three main groups:

- dermatophytosis – tinea
- yeast infections – candidiasis and pityriasis versicolor
- other fungal infections with minimal inflammatory response – tinea nigra and piedra. This group is a rare relative to dermatophytes and yeasts.

Dermatophytosis – tinea

In most cases, tinea refers to a cutaneous infection caused by a dermatophyte, also known by the lay term ringworm. At other times, the term tinea is used to describe yeast infections such as tinea (or pityriasis) versicolor and mould infections such as tinea nigra.

Dermatophytosis can occur on any skin surface of the body. In a patient with tinea it is important to carefully examine other areas of the skin including the nails, as having any form of tinea predisposes the patient to infection elsewhere.

Specific nomenclature of tinea caused by dermatophyte infection is based on anatomical involvement. For each of these anatomical sites, specific dermatophyte species are present with some variance depending on geographic location.

Tinea pedis

Tinea pedis, also known as athlete's foot, refers to a dermatophyte infection of the foot (Figure 1b) and is commonly caused by *Trichophyton rubrum*, *Trichophyton interdigitale* and *Epidermophyton floccosum*. Of dermatophyte infections, tinea pedis is the most common and is often associated with tinea manuum (hand), tinea cruris (groin) and tinea unguium (nail), with the last acting as a reservoir for recurrent tinea pedis. Tinea pedis is highly contagious with transmission of infection occurring through direct contact with spores shed by infected people. Most often, the infection is acquired by walking barefoot in shared facilities such as swimming pools or locker rooms. Other risk factors predisposing patients to tinea pedis include excessive sweating of the foot and prolonged use of occlusive footwear.

Based on the clinical presentation, tinea can be broadly classified as either acute or chronic.

Acute tinea pedis. Acute tinea pedis, also known as vesiculobullous (inflammatory) tinea pedis, is most commonly associated with *T. interdigitale*. Infections are often recurrent, self-limiting and typically precipitated by activities that cause the feet to sweat. Less frequently, acute ulcerative tinea pedis, characterised by ulcerations and erosions, can also occur and is often associated with secondary bacterial infections.

Patients with acute tinea pedis usually present with unilateral or bilateral blistering and/or scaling of the skin, particularly on the soles, which can be intensely itchy and sometimes painful with a burning sensation.

Chronic tinea pedis. Chronic tinea pedis is predominantly caused by *T. rubrum*, an anthropophilic dermatophyte that can be very chronic and recurrent. This condition is characterised by slow, progressive formation of itchy, red erosions and scales in the lateral toe webbing (interdigital tinea pedis). The skin becomes increasingly macerated as the infection develops and interdigital fissures may form. If left untreated, chronic tinea pedis can extend to the sole, heel and lateral sides of the foot (moccasin tinea pedis), appearing as diffuse white scaly plaques. At this stage, nail involvement occurs frequently.

Differential diagnoses for tinea pedis include:

- psoriasis – often salmon-red in colour, well-demarcated, with heavy silvery scale
- candidiasis – often in moist toe webs with satellite pustules
- bacterial infections – often in moist toe webs
- irritant contact dermatitis – associated with excessive sweating
- contact allergic dermatitis – may have contact history to footwear

Figure 2. Tinea unguium, also known as onychomycosis.

material such as rubber or dyes
- scabies – often involves other areas of the body and finger webs.

Cellulitis secondary to tinea pedis. Tinea pedis is a common cause of lower limb cellulitis and its presence should be examined for in all cases of cellulitis, particularly in recurrent cases. If tinea is found in a patient with cellulitis, aggressive treatment of the fungal infection is mandatory to prevent recurrences of the bacterial infection.

Tinea manuum

Tinea manuum refers to dermatophyte infection of the hand and is often caused by the same dermatophytes as tinea pedis. Direct contact with infected animals or soil can also predispose to tinea of the hand. The distribution is classically of the palms but there is often asymmetry and the existence of a defined edge to the eruption. Tinea manuum is characterised by fine granular scale in the creases with erythema, and may be associated with itch or burning.

Tinea infections commonly present as 'two feet, one hand syndrome' and it is therefore important to examine the feet as well as the hands. The dermatophyte species involved are similar to those that cause tinea pedis.

Differential diagnoses for tinea manuum include:
- psoriasis – often salmon-red in colour, well-demarcated, with heavy silvery scale
- candidiasis – found most often between the fingers with satellite pustules or causing paronychia
- irritant contact dermatitis – scaly red, ill-defined rash involving the dorsum of the hands as well as the palms, with patients often atopic and having a strong occupational element with exposure to moist conditions
- allergic contact dermatitis – usually acute, inflammatory and vesicular involving the dorsum of the hands as well as the palms.

Tinea unguium

Tinea unguium, also known as onychomycosis, refers to a fungal infection of the fingernail or toenail and is most commonly caused by *T. rubrum* and *T. interdigitale*. Toenails are much more likely to be infected compared with fingernails. Multiple nails are usually infected, although involvement of all nails is uncommon (Figure 2). Tinea unguium initially presents as white, yellow, green and/or black discolouration of the nail, with the distal nail most likely to be infected first. If left untreated or in severe cases, the infected nail can be become gradually thickened and disfigured.

Onychomycosis may involve the whole thickness of the nail plate or may be superficial, in which case it presents as thin white plaques on the nail surface. The latter presentation can be caused by dermatophyes but other fungi such as the moulds, for example *Fusarium* and *Aspergillis*, can be found.

Tinea unguium can be difficult to distinguish from noninfective nail dystrophies such as psoriasis. However, it rarely involves every nail as opposed to endogenous diseases. To support the diagnosis, careful examination of the nail itself and other cutaneous signs elsewhere is essential. The diagnosis usually remains unclear and nail clippings should always be sent for culture.

Differential diagnoses for tinea unguium include:
- psoriasis – usually there is other evidence of psoriasis
- traumatic onycholysis
- onychogryphosis – age-related changes often associated with poor peripheral circulation
- lichen planus
- changes secondary to paronychia which usually involve the edge of the nail.

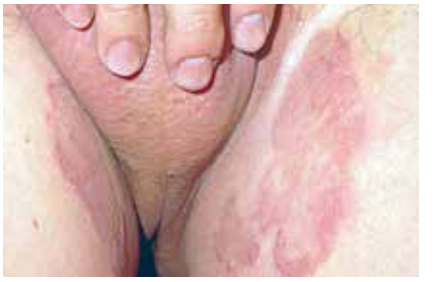


Figure 3. Tinea cruris.

Tinea cruris

Tinea cruris, also known as jock itch, refers to a dermatophyte infection of the groin (Figure 3) and is often caused by the same dermatophytes as tinea pedis. This condition occurs far more frequently in men than in women and is associated with sweating.

Patients with tinea cruris present with a red patch high in the inner aspect of the thighs, typically sparing the scrotum. The infection has a well-demarcated border with or without central clearing. Severe cases may involve the perineum, perianal, gluteal cleft and buttock areas.

Differential diagnoses for tinea cruris include:
- candidiasis – usually satellite pustules are seen
- psoriasis – usually no central clearing and deep mahogany in colour but less scale than in psoriasis elsewhere on the body
- seborrhoeic dermatitis – usually no central clearing
- erythrasma – a bacterial infection that fluoresces coral pink under Wood's light
- contact dermatitis
- intertrigo, particularly in obese patients.

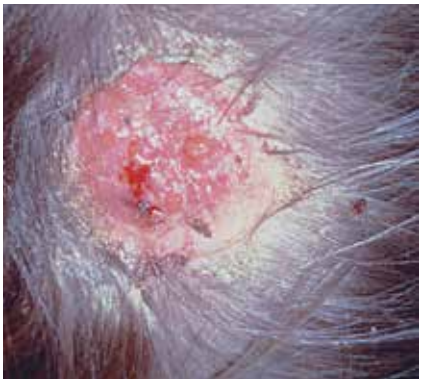


Figure 4. Kerion (inflammatory tinea capitis).

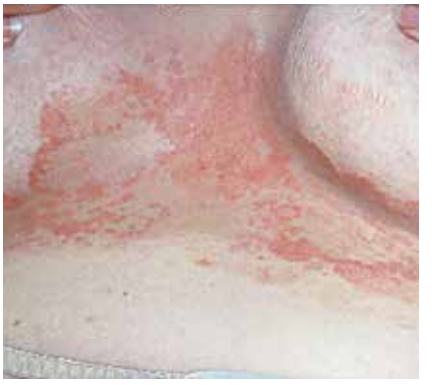


Figure 5. Submammary tinea corporis.

Tinea capitis

Tinea capitis refers to a dermatophyte infection of the scalp and is caused by *Trichophyton* and *Microsporum* genera. Infection can be contracted from infected individuals and animals. Tinea capitis is almost exclusively seen in children. The commonest appearance is of single or multiple areas of patchy alopecia with scale and broken-off hairs. Inflammation is variable but usually not severe. In Australia, *Trichophyton mentagrophytes* is the commonest organism isolated.

Endothrix infection. In endothrix infection, fungal hyphae and spores infect the inner part of the hair shaft. It is caused by the *Trichophyton tonsurans, Trichophyton violaceum* and *Trichophyton soudanense. T. tonsurans* is the commonest in Australia and is more prevalent in overcrowded housing and more common in Aboriginal and Torres Strait Islander populations. Infected patients often present with scaly, noninflamed patches that may be associated with a round area of hair loss. Because of the destruction of the hair shaft, breakage occurs at the level of the scalp causing 'black dot tinea'. There may also be diffuse alopecia. There is no fluorescence on Wood's lamp examination.

Ectothrix infection. In ectothrix infection, fungal hyphae and spores infect the external hair shaft. Some dermatophytes associated with this type of infection include *Trichophyton verrucosum, Microsporum canis* and *Microsporum audouinii*. Patchy hair loss is typical. Wood's lamp examination shows green-yellow fluorescence of the infected hair shaft. These fungi are uncommon in Australia.

Favus. Favus is an uncommon, severe form of tinea capitis caused by *Trichophyton schoenleinii*, which spreads along the entire hair shift. Eventually, this leads to the destruction of the hair shaft leaving behind a yellow cup-shaped crust (scutula) and matted hair.

Kerion. A kerion is a dramatic, inflammatory mass usually occurring in hair-bearing skin. Although the patient is well and afebrile, the appearance can be alarming, with tender pustules and boggy swelling. There is rapid, dramatic hair loss (Figure 4), posterior cervical or auricular lymphadenopathy and, rarely, in severe cases, permanent scarring alopecia. In some carrier states, patients may be asymptomatic with only mild scaling to the scalp. In Australia, the zoophilic *T. mentagrophytes* is the commonest cause but recently there has been an increasing prevalence of African species of dermatophytes such as *M. audouinii, T. violaceum* and *T. soudanense*. These dermatophytes can cause endothrix or ectothrix infections. As tinea capitis is endemic in Africa, asymptomatic carriers may be seen more frequently and therefore extending treatment to family members is required to prevent a reservoir of infection.

Differential diagnoses for tinea capitis include:

- alopecia areata – hair loss areas are usually smooth
- trichotillomania – there is no inflammation and hair is broken off
- scarring alopecias such as lichen planus or lupus erythematosus
- trauma, particularly from hair-styling techniques where hair is pulled into a tight ponytail.

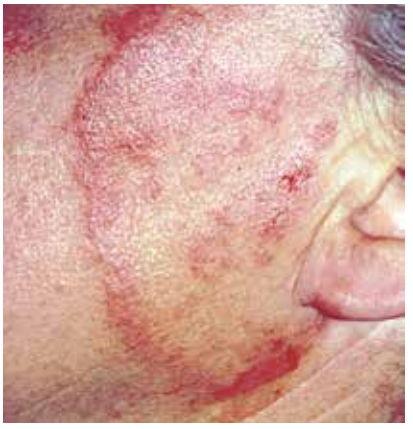
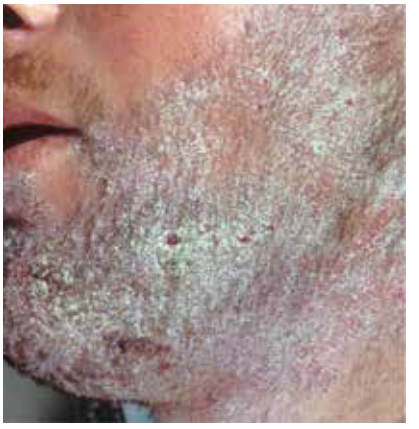
Tinea corporis

Tinea corporis refers to dermatophyte infection of the trunk or limbs and is most commonly caused by the anthropophilic *T. rubrum*. Infection contracted from cats or dogs is often due to *M. canis*. However, in Australia, *T. mentagrophytes* infection is more commonly contracted from guinea pigs and pet mice. It can present independently or with other forms of fungal infection such as tinea pedis and tinea unguium (Figure 5).

Patients with tinea corporis present with a scaly, itchy annular (ring-shaped) or arcuate (bowed or curved) rash with clearly defined raised edges and central clearing as the lesion resolves. Pustules may occur in some cases. Infection from animal transmission is much more acute and inflammatory in nature.

Differential diagnoses for tinea corporis are wide and include many rashes that are annular:

- erythema annulare centrifugum – usually with trailing peripheral scale
- nummular/discoid eczema – usually with double-edged peripheral scale
- granuloma annulare – nonscaly annular lesions
- psoriasis – no central clearing, silvery scale and may have other clinical symptoms
- seborrhoeic dermatitis – ill-defined edges
- lichen simplex – history of chronic scratching or rubbing although skin scraping may be required to rule out tinea infection.

Figures 6a and b. Tinea faciei and tinea barbae. a (left). Tinea faciei affects the glabrous skin and is more common in children and women than in men. b (right). Tinea barbae is a more severe infection than tinea faciei and affects the beards of men.

Tinea faciei and tinea barbae

Tinea faciei refers to a dermatophyte infection of the face and is most often seen in children and women. It is caused by a variety of dermatophytes and infection is acquired from tinea infection elsewhere on the body or from direct contact with infected individuals or animals. It presents as red scaly round lesions that often affect glabrous skin such as the chin and upper lip (Figure 6a).

Tinea barbae refers to a dermatophyte infection of the beard and is often a more severe form of infection compared with tinea faciei resulting in kerion or abscess formation (Figure 6b). It generally affects men, especially farmers as the causative dermatophyte is often from infected animals including cattle (*T. verrucosum*) and horses (*Trichophyton mentagrophytes var equinum*).

Differential diagnoses for tinea faciei and tinea barbae include:

- discoid lupus erythematosus, which can look very similar
- bacterial, viral or candidal folliculitis – skin scraping, or swab may be required to differentiate
- contact dermatitis – contact history
- rosacea – no scales, pustules on an erythematous background
- psoriasis – silvery scale and may have other clinical symptoms
- seborrhoeic dermatitis – ill-defined edges.

Majocchi's granuloma

Dermatophyte infections are usually limited to the epidermis. Majocchi's granuloma refers to extension of dermatophyte infections into deeper dermis and subcutaneous tissue. The most common causative dermatophyte for this form of infection is *T. rubrum*. The condition is typically characterised by nodules or abscess formation. Invasion of the dermatophyte into the dermis is thought to be secondary to trauma to the skin or hair follicles, which can occur during shaving. In some cases, in particular immunocompromised patients, inappropriate use of topical corticosteroids to treat dermatophyte infections can also promote the development of Majocchi's granuloma.

Tinea incognita (tinea incognito)

Tinea incognita describes the clinical appearance of tinea infection that has been altered by inappropriate use of immunosuppressant medications such as topical or systemic corticosteroids, or calcineurin inhibitors. Due to the reduced inflammation of the tinea infection, typical clinical features of the infection may not be present. For example, tinea incognito lesions are generally less erythematous and may lack a scaly border. Additionally, the lesions can be more pustular and larger than typical tinea infections. With ongoing use of topical corticosteroid, they may become quite extensive with nodules.

Yeast infections – pityriasis versicolor and candidiasis

Pityriasis versicolor

Pityriasis versicolor, also known as tinea versicolor, is a yeast infection from the genus *Malassezia* (Figures 7a to c). It can occur at any age but usually affects adolescents and young adults. The most commonly involved areas include the upper chest and upper back, then the face, scalp and groin, and less frequently the antecubital fossae (Figure 7a). In prepubertal children it usually involves the forehead where it is easily confused with pityriasis alba. Pityriasis versicolor is characterised by well-demarcated hyper- or hypopigmented lesions, often coalescing and covered with fine, branny scale. The morphology is of multiple coalescing macules with a characteristic appearance. Hypopigmentation occurs due to damage to melanocytes from azelaic acid compounds in the yeast (Figure 7b). Colouration of pityriasis versicolor varies and depends on a combination of factors including natural skin pigmentation, exposure of the area to sunlight and the severity of the disease.

Although pityriasis versicolor is usually asymptomatic or only associated with mild itch, the appearance often motivates treatment for many individuals. The lesions fluoresce a pale greenish colour under Wood's light.

A less common clinical presentation of *Malassezia* infection is folliculitis. The folliculitis occurs predominantly on the trunk and, in children, on the forehead, with follicular papules and pustules.

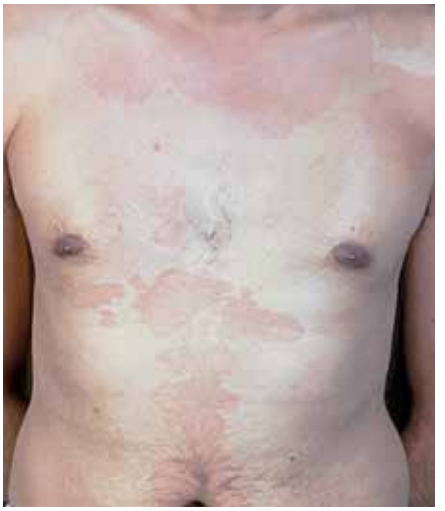
Differential diagnoses for pityriasis versicolor include:

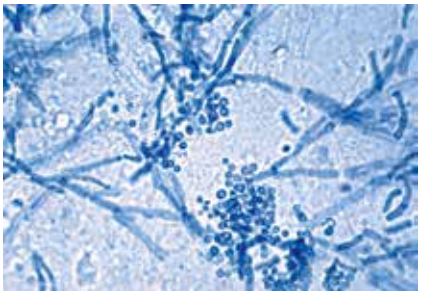
- pityriasis alba – white scaly areas seen on face of children with atopic eczema

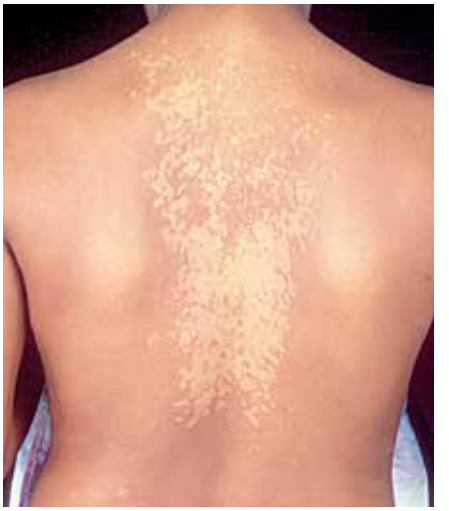
- pityriasis rosea – usually red lesions in a fir tree pattern with trailing inward facing scale
- seborrhoeic dermatitis – on face, mid-chest and mid-back
- dermatophyte infection – lesions often have peripheral scale with central clearing
- vitiligo – complete depigmented macules and patches without scale.

Candidiasis

Candidiasis is an infection caused by the yeast *Candida* with the most common causative organism being *Candida albicans*. Patients who are immunosuppressed, have diabetes or are using corticosteroids and long-term antibiotics are at higher risk of developing candidiasis. The use of antibiotics can destroy the natural bacterial flora on the skin surface, which can then result in the overgrowth of *Candida* as an opportunistic infection. *Candida* can affect many sites on the body (Figures 8a to e).







Figures 7a to c. Pityriasis versicolor. a (above left). Pityriasis versicolor most commonly affects the upper trunk and shoulders. b (above). Depigmented lesions in a patient with pityriasis versicolor. c (left). *Malassezia* as viewed microscopically in 10% KOH, showing the 'spaghetti and meatballs' appearance of the hyphae and spores.

Oral candidiasis. Oral candidiasis, also known as oral thrush, is common and affects the mouth (Figure 8a). In addition to patients who are immunosuppressed, those using inhaled corticosteroids without properly rinsing their mouths afterwards have increased risk of developing oral candidiasis. The infection presents as discrete white patches on the inner surface of the mouth. Over time, these patches can become confluent forming a pseudomembrane, which can be scraped off leaving an underlying erythematous and sometimes ulcerated area. Although most patients are asymptomatic, oral candidiasis may be associated with a cottony sensation, loss of taste and difficulty eating or swallowing secondary to pain.

Differential diagnoses for oral candidiasis include:

- lichen planus – fine white reticulate scale on mucosa (Wickham's striae)
- herpetic infection – painful mucosal ulcers
- erythema multiforme – mucosal ulcers with ocular ulcers and acral target lesions
- pernicious anaemia – raw ulceration, particularly on the tongue.

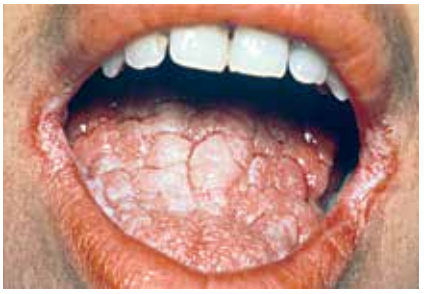
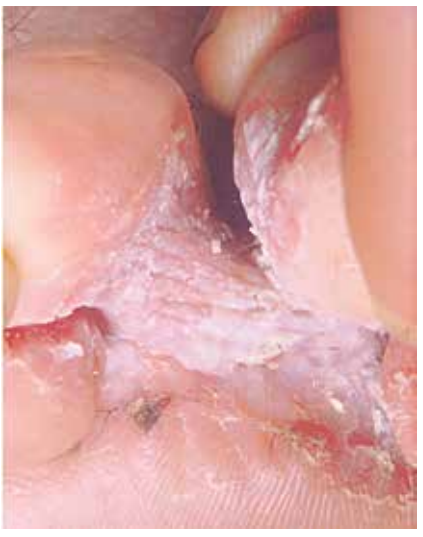
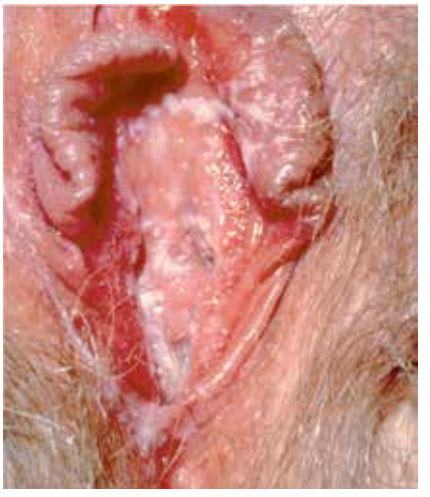
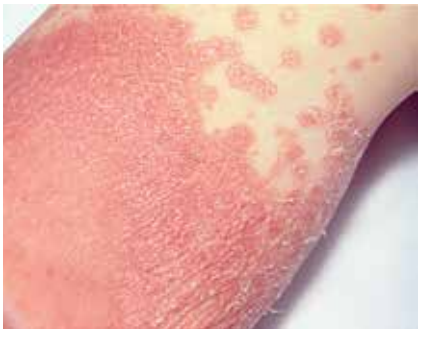
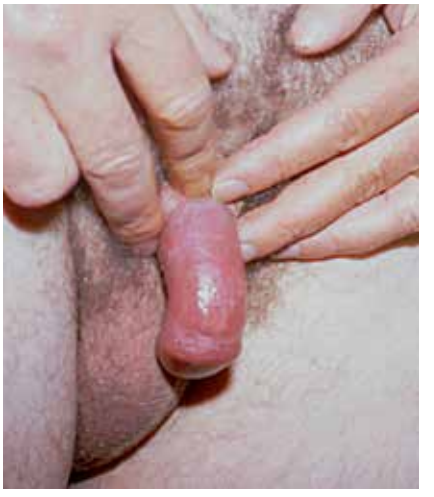
Vulvovaginal candidiasis. Vulvovaginal candidiasis, also known as vaginal thrush, is a common candidal infection of the vulva or vagina. Acute infection causes a thick white vaginal discharge with associated itch, burning and an occasional sensation of dysuria. The vaginal wall is often erythematous and oedematous with white plaques adhering to the wall (Figure 8b). A red scaly rash with satellite pustules can sometimes be seen on the groin and thigh, suggesting spread of the infection. Chronic infection is more subtle with nonspecific redness, pain and itch. Vulvovaginal candidiasis is most symptomatic with an elevated oestrogen state that occurs in premenstruation and pregnancy or with use of exogenous oestrogen.

Differential diagnoses for vulvovaginal candidiasis include:

- bacterial vaginosis
- skin conditions such as contact dermatitis, psoriasis, lichen planus, lichen sclerosus or atopic eczema.

Male genital candidiasis. Male genital candidiasis affects the glans of the penis. It is usually transmitted from an affected sexual partner and is more prevalent in uncircumcised males. Initially, small papules and/or pustules appear on the glans, which may later degrade and discharge leaving behind erythematous erosions with surrounding white scale (Figure 8c). Associated swelling and tenderness can also occur and, in severe cases, inflammation of the urethra or phimosis can result.

Differential diagnoses for candidal balanitis include:

Figures 8a to e. Candidiasis infection. a (above far left). Oral candidiasis, also known as thrush. b (above left). Vulvovaginal candidiasis, also referred to as thrush. c (above right). Balanitis caused by candidiasis. d (far left). Candidiasis between the toes, the cause of about 1% of all cases of athletes foot. e (left). Cutaneous candidiasis, seen in intertriginous zones, characterised by satellite lesions.

- bacterial balanitis
- contact allergic dermatitis
- flexural psoriasis
- Reiter's syndrome
- lichen sclerosus
- lichen planus
- plasma cell balanitis
- fixed drug eruption
- penile intraepidermal neoplasia
- scabies.

Other fungal infections with minimum inflammatory response

Piedra

Piedra is a fungal infection that affects hair follicles and can occur at any age. Piedra is classified into two clinical subtypes based on the clinical appearance and causative organism. Both subtypes are usually asymptomatic.

White piedra is caused by *Trichosporon beigelii* and is prevalent in countries with temperate and semitropical climates. It can affect any hair-bearing areas and presents with multiple lightly pigmented soft nodules on the hair follicles and shafts.

Over time, these nodules eventually cause the hair to break. Topical treatment is often adequate for white piedra.

Black piedra is caused by *Piedraia hortae* and is more common in tropical climates. It predominantly affects the scalp although it can affect other hair-bearing areas. Nodules formed are firmer, darker and more adherent to the hair follicle/shaft compared with white piedra.

Infrequently, patients present with hair loss only. Oral antifungal therapy is often indicated for black piedra, with shaving of the hair being the optimal treatment.

Differential diagnoses for piedra include:

- pediculosis (lice infestation)– eggs are pale in colour and do not cover the hair follicles/shaft.

Tinea nigra

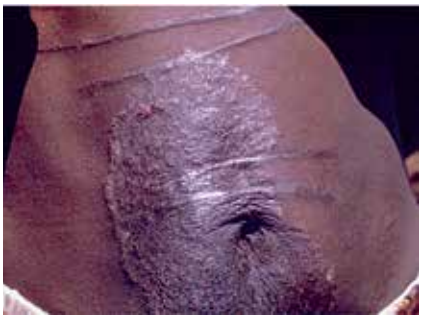
Tinea nigra is caused by a brown mould called *Hortaea werneckii*, which is often found in soil. It is more prevalent in humid climates and associated with hyperhidrosis. It affects the palms and soles and presents as a solitary hyperpigmented macule or patch that progressively grows over time. The infection is very responsive to treatment with clearance of lesions within two to four weeks of topical antifungal therapy.

Differential diagnoses for tinea nigra include:

- benign naevi – pigment network under dermoscopy examination
- extraneous pigment – history of previous skin inflammatory lesion which resolved
- malignant melanoma.

Risk factors

Fungal skin infections can affect anyone, with most infections occurring in



Figures 9a and b. a (left). Skin infection caused by the granular strain of *Trichophyton rubrum* in an Aboriginal woman. b (right). Tinea unguium in an Aboriginal patient.

otherwise healthy individuals. Immunosuppressed populations, including the elderly, people with diabetes, those with HIV/AIDS and those using immunosuppressants, are at higher risk of developing persistent fungal infections. However, healthy persons with the anthropophilic *T. rubrum* may have very persistent infection. These populations are also more likely to develop treatment-resistant or systemic fungal infections. Aboriginal and Torres Strait Islander populations are also at higher risk of certain dermatophyte strains, particularly *T. tonsurans*. However, *T. rubrum* (tinea corporis and tinea unguium) and *T. violaceum* (tinea capitis) are found to be more common in these populations (Figures 9a and b). When examining nonspecific skin lesions in at-risk populations, a greater suspicion for cutaneous fungal infection should be maintained. Additionally, there should be a low threshold to investigate for any associated comorbidities such as diabetes or other immunocompromised states when fungal infections are unresponsive to standard therapy.

TABLE 1. TOPICAL ANTIFUNGAL THERAPY OPTIONS FOR DERMATOPHYTOSIS AND CANDIDIASIS

Treatment	Dosage	Duration
Terbinafine (dermatophytes only)	1% cream or gel, once or twice daily	1 to 2 weeks
Bifonazole	1% cream, once daily	2 weeks
Clotrimazole	1% cream, twice daily	2 weeks
Econazole	1% cream, twice daily	2 weeks
Miconazole	2% cream, twice daily	2 weeks
Ketoconazole	2% cream, once daily	Continue for several days after symptoms resolve
Nystatin	100,000 units/g cream, twice daily	2 weeks
Aluminium acetate wet dressings (chronic tinea pedis)	–	20 minutes, two to three times per day
Tea tree oil-soaked cotton wool (chronic tinea pedis)	–	Overnight

Environmental factors also play an important role in the proliferation of fungal infections. In general, fungal infections thrive in warm and moist environments. Areas of the body that are warmer naturally and more prone to sweat include intertriginous zones such as between the toes, groin and under the breasts. When combined with external factors such as warm climates, exercise, poor hygiene, close living quarters with other infected individuals and/or other risk factors as described above, fungal infections tend to proliferate freely.

Complications

In general, the most significant complication of fungal skin infections is the potential progression towards a secondary bacterial infection. Bacterial infections occur as fungal infection inherently disrupts normal skin integrity. Development of increased erythema extending beyond the site of the fungal infection with associated fever should promptly raise suspicion for cellulitis especially in at-risk populations. Treatment with antibiotics should be commenced in any case involving secondary bacterial infection.

Investigations

Establishing the correct diagnosis of fungal infection is imperative. This is because incorrect diagnosis often leads to incorrect management, frequently with topical corticosteroids. Because topical corticosteroids can mask and worsen any underlying fungal infection, always obtain a skin specimen sample to confirm the diagnosis before using them if there is any doubt.

Specimen collection

Skin, nail and hair from infected sites can be collected to confirm the presence of fungal infection:

- skin specimen – cleanse the skin with alcohol and allow to dry. Using the edge of a blade, gently scrape the scale from an advancing border onto a glass slide or specimen pot

TABLE 2. ORAL ANTIFUNGAL THERAPIES FOR DERMATOPHYTOSIS AND PITYRIASIS VERSICOLOR

Treatment	Dosage – Adult	Dosage – Paediatric	Duration*	Other notes
Terbinafine†	250 mg, once daily If CrCl less than 50 mL/min use 125 mg, once daily	**Use in 1- to 18-year-olds:** **10 to 20 kg:** 62.5 mg, once daily **20 to 40 kg:** 125 mg, once daily **Above 40 kg:** 250 mg, once daily **For tinea capitis, higher dosage can be used:** **10 to 25 kg:** 125 mg, once daily **25 to 35 kg:** 187.5 mg, once daily **Above 35 kg:** 250 mg, once daily	**Skin:** 2 to 4 weeks **Scalp:** 4 to 6 weeks **Fingernails:** up to 6 weeks **Toenails:** up to 12 weeks	• Obtain baseline FBE/UEC/LFTs and monitor if treating for more than 6 weeks • Gastrointestinal side effects are common • Metallic taste in mouth, rarely
Fluconazole	**Skin (tinea):** 150 mg, once weekly or 50 mg, once daily **Nail (tinea):** 150 to 300 mg, once weekly **Pityriasis versicolor:** 400 mg orally as single dose	**Use in 1 month- to 18-year-olds:** 6 to 12 mg/kg, once daily	**Skin:** up to 6 weeks **Nail:** 3 to 12 months	• Obtain baseline FBE/UEC/LFTs and monitor monthly • Gastrointestinal side effects are common
Itraconazole‡	200 mg, once or twice daily	**Use in 1 month- to 12-year-olds:** 5 to 7.5 mg/kg, daily in 1 or 2 doses **Use in 12- to 18-year-olds:** 100 to 400 mg, once daily	**Skin:** daily for 1 to 2 weeks **Fingernails:** twice daily for one week per month and repeat treatment up to 2 months **Toenails:** twice daily for one week per month and repeat treatment up to 3 to 4 months **Pityriasis versicolor:** once daily for 1 to 2 weeks **Pityriasis versicolor prophylaxis:** 1 day per month for 6 months	• Obtain baseline LFTs and serum potassium and monitor further if treating for more than 1 month • Gastrointestinal side effects are common
Griseofulvin†	**Skin and scalp tinea:** 500 mg, once daily **Nails (tinea):** 1 g, once daily (note newer drugs work better than griseofulvin in the nails)	**Use in 1 month- to 12-year-olds:** 10 to 20 mg/kg (maximum 1 g), once daily **Use in 12- to 18-year-olds:** 500 mg to 1 g, once daily	**Skin:** up to 12 weeks **Scalp:** up to 8 weeks **Nails:** up to 12 months	• Monitor complete blood count during prolonged treatment

Abbreviations: CrCl = creatinine clearance rate; FBE = full blood examination; LFTs = liver function tests; UEC = urea, electrolytes and creatinine.

* Paediatric duration may differ. Continue until clinical resolution, cultures should be repeated 3 to 4 weeks after cessation of treatment and consider a repeat course if the result is positive.

† Terbinafine and griseofulvin are not effective for *Malassezia* yeast.

‡ Dosages for itraconazole are based on Sporanox capsules. Sporanox and Lozanoc capsules and oral liquid formulas are not bioequivalent.

- nail specimen – cleanse the nail with alcohol and allow to dry. Clip the nail as short as possible and, using the edge of a blade, scrape the subungual tissue into a specimen pot
- hair specimen – pluck the affected hair with tweezers and collect the proximal portion involving the bulb.

Using a blade, scrape the skin of the affected scalp onto a glass slide or specimen pot.

Potassium hydroxide (KOH) test

The KOH test is a relatively quick and inexpensive test that uses microscopy to confirm the presence of dermatophyte or yeast such as *Candida* and *Malassezia*. Collected specimens are placed on a glass slide and KOH is added, which dissolves the epidermal keratinocytes, leaving behind the fungal elements. Microscopy is then used to view branch-like structures (septate hyphae) in dermatophytes, 'spaghetti and meatballs' appearance

TABLE 3. TOPICAL THERAPY OPTIONS FOR PITYRIASIS VERSICOLOR

Treatment	Dosage	Duration
Econazole	1% solution topically to wet skin, left overnight	3 nights
Selenium sulfide	2.5% shampoo topically to wet skin left for at least 10 minutes or diluted 1:4, left overnight	3 times a week for 3 months
Ketoconazole	2% shampoo topically to wet skin left for at least 5 minutes and wash off	5 days
Miconazole	2% shampoo topically, once daily for 10 minutes and wash off	10 days

(hyphae and spores, Figure 7c) in *Malassezia* yeast and pseudohyphae in *Candida*. The test is very high in specificity but low in sensitivity as the results are highly dependent on the quality of the specimen and the operator's skill.

In deeper infections involving the dermis or subcutaneous tissue such as Majocchi's granuloma, the KOH test will be negative as it can only demonstrate fungus in the stratum corneum. In this case, a skin biopsy should be performed.

TABLE 4. ORAL ANTIFUNGAL THERAPY OPTIONS FOR ORAL AND MUCOSAL CANDIDIASIS

Treatment	Dosage	Duration
Miconazole gel	**Use in adults and children over 2 years of age:** 2% gel, 2.5 mL topically then swallowed, four times daily after meals **Use in children under 2 years of age:** 1.25 mL topically then swallowed, four times daily after meals	1 to 2 weeks, continue for at least 7 days after symptoms resolve
Amphotericin B lozenges	**Use in adults and children over 2 years of age:** 1 lozenge (10 mg) sucked then swallowed, four times daily after meals	1 to 2 weeks, continue for 2 to 3 days after symptoms resolve
Nystatin drops	**Use in adults and children:** 100,000 units/mL, 1 mL topically then swallowed, four times daily after meals	1 to 2 weeks, continue for 2 to 3 days after symptoms resolve
Fluconazole	**Use in adults:** 150 mg, for cutaneous and vulvovaginal candidiasis 50 to 200 mg, daily for oropharyngeal candidiasis **Use in children:** 3 to 12 mg/kg, once daily	Single oral dose 1 to 2 weeks
Itraconazole*	**Use in adults:** 100 to 200 mg, once daily **Use in children:** 5 to 75 mg/kg, once daily in 1 to 2 doses)	2 weeks
Voriconazole	**Use in adults and children over 12 years:** Above 50 kg, 6 mg/kg, intravenously, every 12 hours for the first 24 hours followed by 4 mg/kg, intravenously, every 12 hours ***Or*** Above 40 kg, 400 mg, orally every 12 hours for 2 doses, followed by 200 to 300 mg orally twice daily Under 40 kg, 200 mg, orally every 12 hours for 2 doses, followed by 100 to 150 mg, orally twice daily **Use in children 12 to 15 years and less than 50 kg and children 2 to 12 years:** 9 mg/kg, intravenously every 12 hours for 2 doses followed by 8 mg/kg, intravenously twice daily or 9 mg/kg, orally twice daily.	2 to 4 weeks
Posaconazole (reserved for serious refractory fungal infections)	**Use in adults and children over 13 years:** 200 mg, once daily for 1 day then 100 mg, once daily **Use in serious refractory fungal infection for adults:** 300 mg, intravenously twice daily for 1 day then 300 mg, intravenously, once daily	–

*Dosages for itraconazole are based on Sporanox capsules. Sporanox and Lozanoc capsules and oral liquid formulas are not bioequivalent.

Microscopy and culture

Skin, nail and hair specimens can be sent for microscopy, to provide immediate confirmation, and culture in a specimen pot with results returned within three to six weeks. It is important to interpret microscopy results alongside clinical findings because of the high false-negative rates, particularly in nail clippings. With cultures, false-negative results can occur due to insufficient sample, previous treatment with antifungal therapy or non-specific species. When fungal infection is suspected, consider retesting or a trial of therapy to see if there is a clinical response.

Wood's light

Wood's light is rarely helpful for diagnosing tinea as most species responsible for infections do not fluoresce. It does confirm the differential diagnosis of erythrasma, however, and in pityriasis versicolor, affected areas may fluoresce a pale green colour under Wood's light. It is also useful in some cases of tinea capitis.

Skin biopsy

Consider a skin biopsy if the above methods are inconclusive. A punch biopsy under local anaesthetic can be performed. The specimen is placed in a formalin-containing pot and is reviewed by a histopathologist, with or without the addition of periodic acid-Schiff (PAS) stain. This is a very reliable test.

Management options

As a general principle, it is important to advise patients about nonpharmacological measures to reduce the risk of infection including drying the skin after a shower, using drying powder on intertriginous zones and wearing nonocclusive clothing, underwear and footwear.

Dermatophyte infection

Treatment of dermatophytosis with either topical or oral antifungal agents is dependent on the location and severity of the infection. Topical therapies including terbinafine, bifonazole, clotrimazole, econazole and miconazole are used to treat local infection of the trunk, limb, face or interdigital areas (Table 1). For localised chronic tinea pedis with maceration, aluminium acetate wet dressings (Burow's solution diluted 1:20 with water) can be applied for 20 minutes, two to three times per day, or tea tree oil-soaked cotton wool can be applied overnight between the affected toes.

Oral therapies including terbinafine, itraconazole, fluconazole and griseofulvin are used for hair-bearing areas, palms, soles and nails (Table 2). Generally, a higher dosage is recommended for treatment of tinea capitis. Oral therapy should also be considered in infections that have failed topical therapy, recurrent or widespread infection, tinea incognita and deep infections, as topical agents are not able to penetrate deeper layers of the skin.

Pityriasis versicolor

Both topical and oral treatments are appropriate for pityriasis veriscolor. Topical options such as econazole, selenium sulfide and ketoconazole are available for treatment of pityriasis versicolor (Table 3). Oral therapy (fluconazole, itraconazole) is indicated when the infection fails to respond to topical treatment and often for folliculitis (Table 2). Repeated topical or oral therapy and even prophylactic treatment with oral itraconazole can be considered in recurrent pityriasis versicolor.

Candida

Candidiasis can be treated both topically and orally. Topical therapy such as imidazole cream or nystatin is usually commenced initially (Table 1). Low-potency corticosteroids such as 1% hydrocortisone cream can be added to the treatment regimen if there is concurrent inflammation. Oral agents such as fluconazole and itraconazole are indicated if topical agents are contraindicated or if the infection is severe (Table 4).

When is referral required?

Referral to a dermatologist should be considered in patients with cutaneous fungal infections if:

- the condition is not responsive to treatment despite three to four weeks of therapy
- the infection is worsening and spreading
- there are complications in the treatment.

Conclusion

Cutaneous fungal infections can affect many areas of the body and present in a variety of ways. Recognition of common clinical patterns and use of simple diagnostic tests can aid in diagnosis and allow for optimal management. Always interpret investigation results with clinical examination. A negative test with a strong clinical suspicion warrants retesting or a trial of antifungal therapy. Consider investigating for underlying comorbidities in unusual, recurrent or severe cases. If there are complications in treatment or non-response, referral to a dermatologist is indicated. MT

Further reading

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Hidradenitis suppurativa

What's new in pathogenesis and management

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Hidradenitis suppurativa is a chronic autoinflammatory skin condition with significant comorbidities. Advances in our understanding of its pathogenesis are leading to new potential treatments.

Hidradenitis suppurativa (HS) is a chronic, autoinflammatory skin condition characterised by the development of inflammatory nodules and abscesses in intertriginous, hair-bearing areas.[1] It is associated with several comorbidities, including metabolic syndrome, polycystic ovary syndrome, inflammatory bowel disease (IBD) and depression.[2-6] The prevalence of HS is 1 to 4%, and it affects three times as many women as men.[1] HS is associated with a reduced quality of life, psychosocial impact and physical pain.[7] There is often a significant delay between disease onset and diagnosis, and this may be due to lack of recognition of the disease in its early stages in addition to poor awareness of HS among medical practitioners and the general public.

Over the past few years, our understanding of the pathogenesis of HS has evolved. This review focuses on evolving and emerging concepts of HS pathogenesis and its implications for management with biologic treatments. Diagnosis and first-line management of HS are summarised in the Box.

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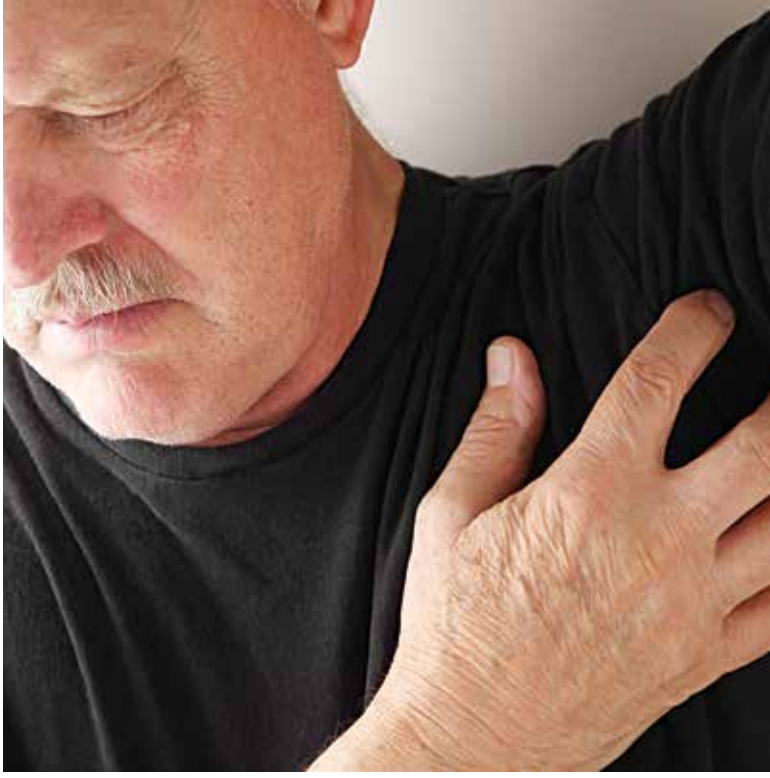

KEY POINTS

- Hidradenitis suppurativa (HS) is an autoinflammatory skin condition involving the innate immune system.
- The pathogenesis of HS is not fully understood; inflammation has been regarded as secondary to follicular occlusion but is now considered the likely initial event.
- Genetics, the skin and gut microbiome and biofilms are also likely to play significant roles in HS pathogenesis.
- HS is part of the follicular occlusion tetrad, and evidence is emerging that the other members (acne conglobata, dissecting cellulitis of the scalp and pilonidal sinus) are anatomical variants of HS.
- Biologics such as interleukin-23 and interleukin-1 are emerging off-label treatments for patients with HS, although large-scale randomised clinical trials are lacking.

Evolving models of pathogenesis of HS

The pathogenesis of HS is not fully understood. Classically, it has been considered an inflammatory skin disease triggered by occlusion of hair follicles, with secondary inflammation. New evidence suggest that HS should be considered a disease with multifactorial causes including genetic factors, the skin and gut microbiome, skin biofilms and dysregulation of the innate immune system.

Genetic factors

About one-third of patients with HS have a family history of the disease.[8] Several genetic variants have been identified in the genes encoding the gamma-secretase enzyme complex, which regulates the function of the Notch cell membrane protein. Notch is responsible for normal skin function in humans and animals, and disruption of gamma-secretase function in mice has been shown to result in the formation of epidermal cysts and epidermal hyperplasia reminiscent of HS in humans.[9] However, most patients with

DIAGNOSIS AND FIRST-LINE MANAGEMENT OF HIDRADENITIS SUPPURATIVA

Diagnosis of hidradenitis suppurativa

Hidradenitis suppurativa (HS) is diagnosed based on history and clinical findings. There is no diagnostic test available.

Most commonly, patients report a history of recurrent painful 'boils' or abscesses in their axilla, groin, inframammary or abdominal fold areas. These lesions may have a malodorous exudate. Less commonly, patients with more extensive disease develop lesions in other areas, such as posterior ears, neck, limbs and trunk.

On examination, nodules and abscesses are usually present, with sinuses and hypertrophic scarring in more severe cases (Figure 1). Double-headed comedones are highly suggestive of HS, and their presence in the absence of inflammatory lesions suggests early or quiescent disease.

Common differential diagnoses for HS include acne, folliculitis and *Staphylococcus aureus* skin infections.

Figure 1. Axilla in a patient with hidradenitis suppurativa, showing abscesses (green arrows), a draining sinus (yellow arrow) and early hypertrophic scarring (blue arrow).

First-line management

- Antimicrobial chlorhexidine or triclosan-based body washes and gels, which are available over the counter, can be used daily.
- Topical clindamycin gel is appropriate to use in affected areas in patients with active inflammation, such as during flares.
- Oral doxycycline 100 mg daily or minocycline 50 mg twice daily should be used for three to four months to assess for response. If the patient's condition does not improve on treatment with one antibiotic, the other should be tried.
- Patients with HS should be assessed for comorbidities such as metabolic syndrome, polycystic ovary syndrome, depression and anxiety.
- Patients who smoke should receive smoking cessation counselling.
- Patients with a body mass index in the overweight or obese range should be encouraged to lose weight and referred where appropriate to a dietitian, physiotherapist or exercise physiologist to facilitate this. Low-friction exercise (such as swimming and aquarobics) is better tolerated by those with painful lesions and reduces the risk of worsening skin lesions.
- Most patients with HS should be referred to a dermatologist to confirm the diagnosis and facilitate access to biologic treatment for those with moderate-to-severe disease resistant to antibiotic therapy.
- As well as antibiotics, antimicrobials and biologic therapies, other treatments for HS include:
  - antiandrogens in women
  - laser therapies
  - intralesional corticosteroid injections
  - short-term oral corticosteroids
  - surgical treatments, including incision and drainage, local excision and wide excision with skin grafting and deroofing.

  Most of these treatments should be guided by a dermatologist.
- Several hospitals across Australia run specialist HS clinics; contact your local hospital dermatology department for further information.

HS do not have mutations in the gamma-secretase complex genes, suggesting that pathogenesis is multifactorial.[10] Additionally, Notch disruption in mice via knockout is associated with disrupted barrier function, epidermal differentiation and alopecia, which are not seen in humans with HS.[11] Caution is needed in interpreting results from animal models of HS.

The skin microbiome and biofilms

HS has previously been viewed as an infective disease. However, it is now recognised as an autoinflammatory condition with a significant burden of comorbidities associated with systemic inflammation. Although the role of bacteria in disease pathogenesis requires further elucidation, the inflammatory process is thought to be driven by cutaneous microbiome dysbiosis.[12] A study showed that perilesional skin in affected individuals has greater microbial diversity than lesional skin.[13] The axillary microbiome has also been shown to be altered, with reduced diversity, in perilesional skin in affected individuals versus healthy controls.[14]

Biofilms, composed of bacteria and the extracellular matrix that they produce, have been identified in both chronic HS lesions and perilesional skin and are often associated with treatment resistance.[15] The development of a biofilm may partly explain the chronicity and treatment resistance of lesions, as well as disease recurrence after surgical excision. Additionally, biofilms may be implicated in disease progression over time. It is known from chronic wound studies that biofilms cause host immune alterations and induce the release of proinflammatory cytokines.[15]

The cutaneous microbiome is a growing area of scientific interest in a number of skin diseases, and establishing what constitutes the 'normal' microbiota is a crucial next step. Similarly, ongoing research is needed to identify the role of biofilms in HS pathogenesis, progression and treatment resistance.

TABLE. PHENOTYPES OF HIDRADENITIS SUPPURATIVA*[25]

	Paediatric group	Female group	Male group	Genetic group
Clinical presentation	• Early onset • Axillary, groin and gluteal areas most often affected	• Predominantly axillary and inframammary involvement (Figure 2)	• Predominantly gluteal involvement	• Extensive, variable and severe cutaneous involvement • May involve typical areas (axillary, inguinal and gluteal) and atypical areas (posterior ears, neck and limbs, Figure 3)
Disease associations	• Often associated with latent metabolic conditions such as insulin resistance and PCOS • Patients usually overweight rather than obese	• Usually overweight or obese • Metabolic syndrome and PCOS • Often the highest burden of comorbidities and psychological distress	• Usually current smoker • Visceral rather than central adiposity • Associated with hyperlipidaemia	• Usually strong family history • Some cases may be a recognised syndromic variant, but not all fit these categories
Management implications	• Likely to progress in severity without aggressive management • Weight loss beneficial in halting progression to type 2 diabetes and normalising hormones • Laser hair removal may be of benefit in long term	• The most difficult phenotype to treat • Indication for early rather than late surgery to control disease	• Some individuals experience disease 'burn out'	• Evidence supports management with anti-IL-1-beta therapies • Should be referred for genetic counselling

Abbreviations: IL-1-beta = interleukin 1-beta; PCOS = polycystic ovary syndrome.
* Adapted from Vekic et al (2018).[25]

Inflammatory pathways

Classically, HS has been considered a cutaneous disease characterised by follicular occlusion with a secondary inflammatory response. However, some evidence suggests that follicular occlusion is secondary to the underlying inflammatory process, thought to be driven by interleukin (IL)-1.[12] Additionally, the interleukins IL-12, IL-17 and IL-23 and tumour necrosis factor-alfa (TNF-alfa) have all been identified in active HS lesions.[16] Phase 3 studies are now underway to assess the efficacy and safety of anti-IL-17 and anti-IL-23 treatments in patients with HS.

The skin-gut-brain axis

The evolving skin-gut-brain axis model of skin disease may be applicable to HS. Neural and systemic inflammation secondary to gut dysbiosis may contribute to the association between HS and depression and anxiety via bidirectional signalling, rather than the link being exclusively a result of the experience of the physical symptoms and associated emotional impact of HS. Research in germ-free mice models has shown depressive-like behaviours after transplantation of faecal microbiota from patients with major depressive disorder versus microbiota from healthy controls.[17]

Alterations in the gut microbiome can increase gut permeability, resulting in local and systemic inflammation through bacterial translocation, as seen in patients with non-alcoholic fatty liver disease.[18] Gastrointestinal microflora can also be associated with skin disease, as seen in the association between rosacea and *Helicobacter pylori*.[19]

The skin-gut axis may also explain the association between IBD and HS through alterations to gut microflora. IBD is associated with gut dysbiosis and impaired gut epithelial function.[20] Further research is required to establish this relationship.

Emerging concepts in HS

Follicular occlusion tetrad

HS belongs to the follicular occlusion tetrad, which also includes acne conglobata, dissecting cellulitis of the scalp and pilonidal sinus. All four diseases in this tetrad share common histological and cytochemical findings, indicating that they are likely to represent anatomical variants of a single disease process.[21,22] Further studies comparing histological, inflammatory mediator and clinical outcomes in these diseases are necessary to elucidate the true relationship.[23] It is likely that the local skin microbiome is involved.

HS phenotypes

HS is not a homogeneous disease.[10] There is preliminary work on differentiating HS phenotypes.[24] A recent simple classification system into paediatric, female, male and genetic forms is based on age of onset, body site involvement and associated comorbidities (Table, Figure 2 and Figure 3).[25] It is hoped that an improved definition of phenotypes will allow more targeted therapies and better understanding of prognosis.

Precise correlation between HS phenotype and genotype is not currently possible. This probably reflects the multiple factors involved in HS pathogenesis.

Emerging treatments

Current systemic treatments for patients with HS include oral antibiotics and the

Figure 2. Inframammary lesions in a 38-year-old woman with hidradenitis suppurativa.

TNF-alfa blocker adalimumab. Patients whose condition fails to respond adequately to these treatments currently have no alternative biologic treatment options available through the PBS in Australia. Recognition of the role of interleukins in HS has led to trials of interleukin inhibitors in the treatment of patients with HS. Some of these are available off-label and on compassionate grounds for patients with HS.

Ustekinumab, an IL-12 and IL-23 inhibitor, was shown in a small open-label study to be effective in treating patients with HS. In this study, 47% of patients achieved a 50% or greater reduction in inflammatory lesion count.[26] Ustekinumab is not PBS listed for HS and is used off-label in Australia for these patients. Other IL-23 inhibitors such as tildrakizumab are used in Australia off-label via compassionate access. At present, several phase II trials of IL-23 inhibitors are underway.

Anakinra, an antagonist of IL-1 (a central proinflammatory cytokine), was shown in a small randomised controlled trial to be effective in patients with moderate to severe HS; 78% of participants achieved a 50% or greater reduction in inflammatory lesion count.[27] Anakinra may be available via compassionate access for patients with treatment-resistant HS through dermatologists. It is not PBS listed for HS. Administration requires a daily injection, which some patients find painful.

Interleukin-17 has been identified in HS lesions, along with IL-1 and TNF-alfa.[28] The efficacy and safety of anti-IL-17 biologic treatments in HS is under investigation, with phase III trials currently or soon to be underway. However, the association of HS with IBD is a concern. IL-17 is gut protective in mice models, with blocking of IL-17 associated with increased gut permeability.[29] As discussed above, increased gut permeability is implicated in bacterial translocation and disease pathogenesis. Exacerbations of IBD have been observed in trials of IL-17 biologics in patients with psoriasis, and their use is therefore avoided in those who have psoriasis and concomitant IBD.[30] Further human studies are required to assess whether IL-17 plays a similar role in gut homeostasis in humans as in mice.

Implications for practice

Patients with HS should be screened extensively for comorbidities, such as metabolic syndrome, depression and hyperandrogenism. Optimising treatment of these comorbidities is important to reduce HS disease severity and decrease systemic inflammation. Smoking cessation and weight loss should be strongly encouraged for the same reason. All patients with HS benefit from low-friction exercise such as swimming, as this improves concurrent metabolic syndrome and facilitates weight loss.

Additionally, patients with common comorbidities such as metabolic syndrome and polycystic ovary syndrome should be screened for HS. This will help identify patients with mild HS, in whom treatments are more efficacious, and aggressive early management is likely to lead to optimal long-term outcomes. Patients with these comorbidities should be asked about blackheads, abscesses, nodules and pustular lesions in their axillary, inguinal and gluteal regions, and should also be examined for the presence of these lesions.

At present, the only biologic treatment for moderate-to-severe HS that is available on the PBS is adalimumab, a TNF-alfa blocker. This is a nonspecific targeted therapy that is used in other inflammatory conditions such as IBD and rheumatoid arthritis.

All patients with known or suspected HS should be referred to a dermatologist for review and specialist management. This will enable patients to access adalimumab, in addition to off-label and clinical trial treatments when clinically indicated.

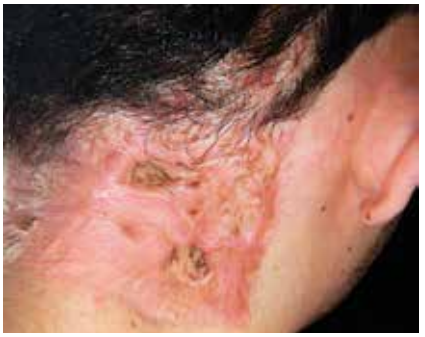

Figure 3. Lesions on the back of the neck, an atypical area, in a 35-year-old man with hidradenitis suppurativa.

Conclusion

HS is a complex autoinflammatory disease associated with debilitating cutaneous manifestations and a high burden of comorbidities. Patients with HS should be extensively screened for associated comorbidities. Likewise, screening for HS should be part of standard care for patients with common comorbidities such as metabolic syndrome, to identify those with latent and early cases of HS.

Ongoing research examining pathways of disease pathogenesis in HS is required, particularly to identify the inciting causes of HS and determine why it progresses in severity. This will enable us to optimise patient outcomes through new treatments, and allow us to identify how best to prevent the disease and disease progression. MT

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Biologics

New therapy for atopic dermatitis

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The recent TGA approval of dupilumab, a biologic therapy aimed at targeting specific immune markers, provides new hope in the treatment of adults with moderate-to-severe atopic dermatitis.

Atopic dermatitis (AD) can be burdensome to the individual and the healthcare system.[1] Although 30% of the population are susceptible to AD, of this cohort less than 1% have severe AD. However, the condition is chronic and relapsing and can be debilitating.[2] In various forms of severity (i.e. mild, moderate or severe), AD can greatly affect daily function and activities, carrying with it the burden of symptoms such as itch and pain (especially if superimposed infection occurs), which subsequently adversely affect quality of life, with negative psychological impact.[3] There is a wide spectrum of clinical presentations and combinations of symptoms in AD. Figures 1 to 3 illustrate severe AD. GPs are often at the forefront of managing AD in the community, with dermatology expertise required for severe and refractory disease.

Pathophysiology

AD is influenced by a complex interplay between immunoglobulin E (IgE) mediated sensitisation, the immune system and environmental factors. Epithelial barrier dysfunction involving filaggrin gene defects could be a consequence of both genetic mutations and local inflammation.[3-6] Four cells play a key role in its physiopathology:

- dendritic cells
- T-helper cells
- activated eosinophils
- keratinocytes.[7]

First, dendritic cells polarise T cells, which results in IgE mediation and non-IgE mediated sensitisation.[8] This then stimulates T-helper 2 (Th2) cells to release pro-inflammatory cytokines interleukin (IL) 4, IL-5 and IL-13. The next category of cells, T-helper cells, consists of T-helper 1 (Th1) and Th2 cells. Th1 cells secrete cytokines in acute, exudative lesions, whereas Th2 cells secrete interferon gamma in chronic lesions.[9] The third group of cells are the activated eosinophils, which play a role in local inflammation. The fourth group are keratinocytes, which express high levels of Th2 polarising cytokine (thymic stromal lymphopoeitin), which amplify or sustain the allergic response.[10-12] A greater understanding of this underlying immune pathway has paved the way for new research into, and treatments for, AD.

Current treatment

Current treatment revolves around topical therapies and, less commonly, systemic therapies. Topical therapies involve emollients, topical corticosteroids of varying potencies and topical calcineurin inhibitors such as pimecrolimus and tacrolimus.[13]

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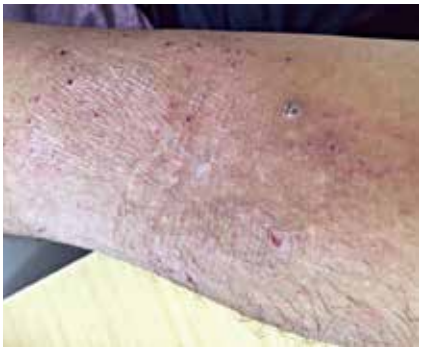

Figure 1. Flexural atopic dermatitis.

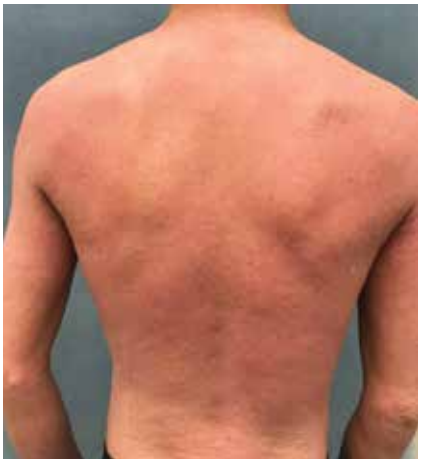

Figure 2. Widespread atopic dermatitis involving on back and arms.

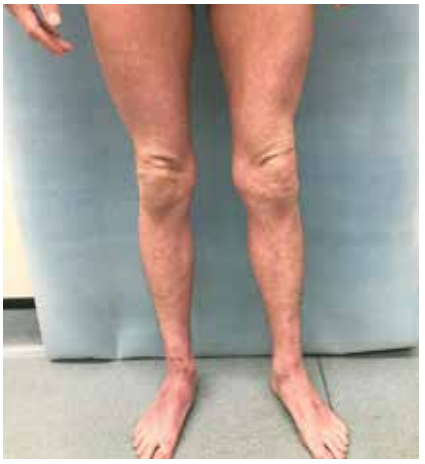

Figure 3. Widespread atopic dermatitis involving lower limbs.

Phototherapy may also be effective in a number of patients, but this requires regular treatment and is therefore time consuming to the patient. Some patients require hospital admissions for wet dressings, and this is a significant burden on both the patient and the healthcare system.

Systemic treatment options include immunosuppressants (cyclosporin has been the mainstay of treatment for many years), along with the off-label use of methotrexate, azathioprine and mycophenolate. Systemic glucocorticoids are occasionally utilised in acute exacerbations but rarely have a place in the long-term management of patients with AD.

For many years the treatments outlined above have remained the only options available for the management of patients with AD. However, the scope of treatment is now expanding with the addition of targeted biologic therapies.

Biologic therapy for atopic dermatitis

In recent times, biologics have been investigated as a potentially safer and more effective alternative to current treatment therapies. This type of therapy is focused on trying to control T-helper response through the blockade of IL-4, IL-13 and IL-31 targets.

What are some of the benefits of biologic therapy? Many patients struggle with the strict regimen required with topical treatments, which necessitates correct technique and frequent application. This can impact patient compliance and have a detrimental effect on quality of life. In addition, some patients are unnecessarily worried about the use of topical corticosteroids – referred to as 'steroid phobia' – and may refuse treatment.[14-16] Biologics may offer a favourable alternative to these arduous and continuing treatments. Their safety and efficacy have been shown in clinical trials, and it is expected they may also offer a favourable cost-benefit ratio given the severity of refractory disease and use of resources, including hospitalisations.[17]

Dupilumab, a fully human anti-interleukin-4 receptor (anti-IL-4) alpha monoclonal antibody that inhibits both IL-4 and IL-13 signalling, has been extensively studied in clinical trials with promising results and is now available through private access in Australia for adults and adolescents aged 12 years and above with moderate-to-severe AD, following TGA approval for use in Australia in 2019.[18] Dupilumab is already approved for use and available in Europe, the United States and Japan.

Dupilumab trials

With the release of dupilumab for the treatment of moderate-to-severe AD in adults and adolescents in 2019, we are anticipating entering an exciting new era in the treatment of AD. Promising trials included three randomised, double-blinded, placebo-controlled phase III trials: SOLO 1 and SOLO 2, followed by LIBERTY AD CHRONOS. The SOLO 1 and SOLO 2 trials were both 16-week monotherapy trials where patients either received dupilumab or placebo weekly, or dupilumab every other week (alternating with placebo). The LIBERTY AD CHRONOS trial was subsequently conducted as a 52-week trial where patients either received dupilumab weekly or every other week, or placebo weekly. The trials involved the use of concomitant topical corticosteroids and regular moisturiser. In all three trials, dupilumab was found to be superior to placebo.[18-20] Furthermore, dupilumab has been shown to improve quality of life in adult patients.[19,21]

Dupilumab therapy and precautions

The recommended dose of dupilumab is 300 mg subcutaneously every fortnight, following an initial dose of 600 mg.[19] It is not designed for episodic use. The following adverse reactions were observed in clinical trials (in order of most frequent): injection site reaction, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritis, other herpes simplex infection

and dry eyes.[19] The safety and efficacy of dupilumab has not been established in asthma, despite trials investigating this, therefore patients with comorbid asthma should not discontinue their regular asthma treatments without consultation. Similarly, patients with parasitic infections were excluded from trials, hence the effect of dupilumab on the immune system is unknown. In terms of drug interactions, live vaccines should be avoided, and interactions with CYP450 substrates must be considered. The use of dupilumab in pregnant and breastfeeding women has not been studied.

Other targeted biologic therapies

In addition to the success of dupilumab trials, targeted biologic therapies aimed at blocking other parts of the immune process in AD are being investigated. These include the anti-IL inhibitors, janus kinase (JAK) enzyme inhibitors and phosphodiesterase (PDE4) inhibitors.

Tralokinumab, an anti-IL-13 antibody, is being investigated in a phase III monotherapy clinical trial in patients with moderate-to-severe AD. Lebrikizumab, an anti-IL-13 antibody, is being investigated in a phase II clinical trial. Nemolizumab, an IL-31 antibody, is being investigated in another phase II clinical trial, which has shown improvement in itch. ABT-494, a JAK enzyme inhibitor, is being studied in a phase IIb clinical trial. The outcomes of other clinical trials have been variable.[20]

Conclusion

Biologics could revolutionise the treatment of moderate-to-severe AD in adults and benefit maintenance therapy regimens, leading to improved quality of life. Results have been promising in previous research and in countries where it is approved and available for use. It is hoped that this trend will continue in Australia now that dupilumab has been granted TGA approval and private access. Its use is aimed to be an adjunct to current standard therapies including emollients and topical corticosteroids, not as a sole replacement. Information dissemination will assist the role of the GP with awareness and an appreciation of dupilumab introduction in a select population of patients. Although the specific PBS criteria are yet to be determined, it will likely require specialist approval for severe AD. It will be important for the wider medical community to be aware of potential associated adverse events. The future may look towards paediatric and further adolescent extension of biologic research and treatment options. MT

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COMPETING INTERESTS: None.

A child with severe wrinkling of the skin of the palms

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Test your diagnostic skills in our regular dermatology quiz. What is the cause of this child's rapid and severe skin wrinkling that affects her palms after exposure to a small amount of water?

Case presentation

A 12-year-old girl presents with a lifelong history of rapid severe wrinkling of the skin of her palms after minimal exposure to water. The episodes are asymptomatic and self-resolve within 40 to 60 minutes after drying. Her soles are not affected.

The girl's medical background is unremarkable. Her parents have accepted the palm skin wrinkling as normal for her, but they are concerned about the appearance and wondering if anything can be done about it.

On examination, before water exposure there are no gross abnormalities of the patient's palms or other skin areas. After simple wetting of her palms in a stream of water from a tap her palms promptly wrinkle, with the formation of oedematous whitish plaques and papules (Figure). She does not complain of discomfort, pruritus or pain. After drying, her palms return to normal.

Figure. The girl's wrinkled palms after exposure to a stream of tap water.

Differential diagnoses

This condition is called aquagenic wrinkling of the palms (AWP). Causes to consider include the following.

- **Normal variant.** Wrinkling after prolonged exposure to water is a normal physiological response driven by the intracellular absorption of water and the activation of the sympathetic nervous system, resulting in vasoconstriction and puckering of the above skin layers, which is observed grossly as wrinkling. Normal aquagenic wrinkling typically occurs after about 11 minutes of immersion.[1] The rapidity of this patient's response to a small amount of water suggests other diagnoses should be considered before settling on normal physiological wrinkling.
- **Hyperhidrosis.** Rapid wrinkling of the hands with a burning sensation has been reported in a patient concomitantly with palmar hyperhidrosis after exposure to water.[2] That patient was administered a topical 15% aluminium chloride hexahydrate solution every other day and was then able to be immersed in water for up to 30 minutes without symptoms. In the case presented above, the patient and her parents did not report any excessive sweating on her palms or other areas of her body.
- **Drug-induced AWP.** Some medications have been reported to induce wrinkling of the palms on exposure to water, especially COX inhibitors, such as aspirin,[3,4] indomethacin[5] and rofecoxib.[6] The effect ceases after discontinuation of the drug. This patient had not been given any medications in the three months before review.
- **AWP secondary to cystic fibrosis (CF) carriage.** This is the correct diagnosis. AWP is characterised by the transient development of oedematous whitish plaques on the palms, namely the 'hand-in-the-bucket' sign, on exposure to water. It was first reported and is still primarily reported in patients with CF and in CF carriers.[7,8] A case-control study showed that the average time to wrinkling was less in CF

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carriers compared with controls, and even less in patients with CF.[1] More recently, it was reported that the specific ΔF508 mutation within the *CFTR* gene predisposes patients to AWP.[9] To help understanding of the genotype-phenotype correlations, a case-control study was performed and showed that patients who were homozygous for the ΔF508 mutation had the highest wrinkling scores compared with CF patients with heterozygous or other mutations.[10] The molecular mechanism by which CF causes AWP is incompletely understood; however, it is thought to be related to the excessive intracellular water absorption and retention that is caused by the malfunctioning chloride channel that the mutated *CFTR* gene encodes. In Australia, one in 25 Caucasian people is a carrier of the CF gene.

Diagnosis and investigations

The diagnosis of AWP is based on a clinical history and physical examination. Genetic testing for CF carriage is recommended for future genetic counselling.

Management

There is currently no targeted therapy for AWP. However, some patients have reported relief with antiperspirants such as daily 20% aluminium chloride hexahydrate, bathing the affected area (typically just the hands) in salt water and supportive therapies such as antihistamines to reduce itch (not a common feature). Botulinum type A toxin injections have been reported to be successful, even in patients without known hyperhidrosis.[11] It is important to be aware of this skin sign because it is a diagnostic clue that a patient may be a CF carrier or have atypical CF, which has important clinical consequences for the patient and their future progeny.[12]

Future progress

With the advent and approval of small molecules such as ivacaftor, lumacaftor and tezacaftor that directly target the malfunctioning chloride channel that the *CFTR* gene encodes, it may be possible that in future topical formulations of these drugs may be applied to patients with AWP. MT

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COMPETING INTERESTS: None.

Rapid onset of erythroderma in a 65-year-old man

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Test your diagnostic skills in our regular dermatology quiz. What is the cause of this mildly pruritic rash?

Case presentation

A 65-year-old man presents with mildly pruritic, erythematous plaques in a generalised distribution (Figure 1). He noticed the eruption on his distal arms, face and trunk three weeks ago, but it has recently started to involve his hands (Figure 2). He does not take any regular medications, and he denies any past history of eczema or psoriasis.

On examination, the patient has erythroderma but no rash on his extensor surfaces or gluteal cleft. There is thickening of the skin of his palms with overlying scale and some orange discolouration.

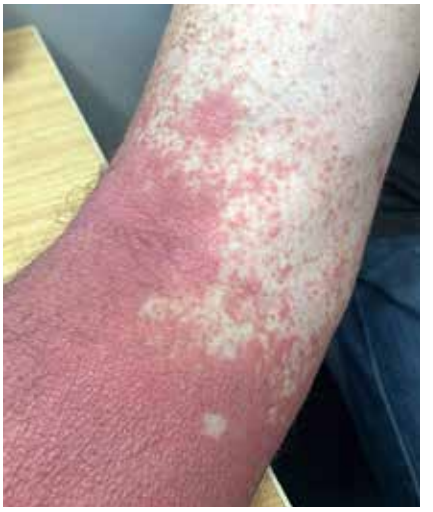

Figure 1. The rash on the patient's arm.

Figure 2. Thickening and orange colouration of the palm.

Differential diagnoses

Conditions to consider among the differential diagnoses include the following.

- **Psoriasis.** This common inflammatory skin condition presents with erythematous plaques overlying the extensor surfaces. Patients typically develop psoriasis before the age of 45 years, which makes it a less likely diagnosis in this case. In addition, the patient's symptoms have progressed more rapidly than would be expected in psoriasis.
- **Cutaneous T cell lymphoma.** Cutaneous T cell lymphoma (CTCL) can present with widespread erythema, such as in Sézary syndrome, or with discrete scaly plaques, as in the plaque stage of mycosis fungoides. The hands are not a classic site for CTCL, making it a less likely diagnosis in this case.
- **Drug hypersensitivity.** Drug eruptions can be polymorphic in presentation, and clinicians should have a high index of suspicion for a drug trigger in patients who present with widespread erythema. Classic drug hypersensitivity reactions tend to present with maculopapular eruptions; the palmar surfaces are not usually affected. It can be difficult to elicit the triggering agent, and all medications started in the past three months (even if now ceased) should be considered. In this case, the palmar keratoderma and lack of any significant drug history made hypersensitivity less likely.
- **Pityriasis rubra pilaris (PRP).** This is the correct diagnosis. This scaly, reddish-orange eruption can be widespread or localised in distribution. The exact cause of

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PRP is unknown, although some cases may be inherited or have a drug precipitant. Patients with psoriasis can present with palmoplantar symptoms, making it difficult to differentiate between psoriasis and PRP. The erythema in PRP tends to have 'islands of sparing' (localised areas of unaffected skin), which can assist in making the diagnosis. Presentations of CTCL can be difficult to differentiate from PRP, and biopsy can be of assistance. Other features that may be present in CTCL include ulceration and poikiloderma, which are not present in PRP.

Investigations and diagnosis

Histology can help to differentiate PRP from its clinical mimics. At least one skin sample should be obtained for haematoxylin and eosin staining; multiple samples can improve diagnostic yield. An alternating orthokeratosis and parakeratosis is usually seen, along with acanthosis and psoriasiform hyperplasia in the epidermis. The neutrophilic infiltrate and spongiform epidermal changes associated with psoriasis are not present; with PRP there is usually a sparse mixed infiltrate. The follicular plugging seen clinically is also observed in the sample, with parakeratosis at the edge of the follicular orifice.

Management

PRP is a rare condition, and there are limited high-quality trials assessing the effectiveness of treatment. Currently recommended therapies for PRP are similar to those used in psoriasis. For patients requiring systemic therapy, oral retinoids (acitretin/isotretinoin) are most effective, although methotrexate (off-label use) and ultraviolet phototherapy can be used in some cases. Topical corticosteroids can be useful as an adjunct therapy or, in patients with limited disease, as monotherapy.

There are case reports describing successful off-label treatment of PRP with biological agents such as infliximab or adalimumab, but these agents are reserved for treatment-resistant disease.[1,2] In patients with HIV-associated PRP, antiretroviral therapy should be started as well as treatment for PRP. Blood tests, including full blood count, liver and renal function tests, and screening for hepatitis B and C, HIV and tuberculosis should be performed in severe cases, before starting immunosuppressive therapy.

Classic adult PRP, as described in this patient, is the most common subtype of PRP (about 55% of cases) and has an excellent prognosis, with up to 80% of patients experiencing spontaneous remission at three years.[3] The prognosis for the classic juvenile subtype is similarly good. Other, less common subtypes of PRP have different prognoses. Atypical adult PRP has a poor prognosis, with less than 20% of patients experiencing remission at three years.[4] HIV-associated PRP is also quite resistant to treatment.

Outcome

The patient was started on oral acitretin 50 mg once daily, which was reduced to 37.5 mg daily for one month. He had an excellent response, with approximately 80% response at two months. MT

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COMPETING INTERESTS: None.

Recurrent, painful nodules on a girl's legs

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Test your diagnostic skills in our regular dermatology quiz. What are these painful lesions and how should this patient be managed?

Case presentation

A 10-year-old girl presents with a 12-week history of recurrent, painful, red nodules on her lower legs (Figures 1a and b). Each lesion lasts three to four weeks, resolving with bruising. She has been previously well, with no significant medical or family history.

Figures 1a and b. Poorly demarcated, erythematous, subcutaneous nodules involving the back (a) and front (b) of the child's lower legs. Note the absence of ulceration or suppuration.

Differential diagnoses

Conditions to consider among the differential diagnoses of painful, erythematous nodules involving the distal lower limbs in children include the following.

- **Cellulitis.** In the immunocompetent paediatric population, cellulitis is most commonly caused by *Streptococcus pyogenes*.[1] In contrast to adults, lower limb cellulitis is uncommon in children and the head and neck area more commonly affected; even in adults, bilateral extremity cellulitis is rare.[1] Cellulitic areas are swollen, warm and painful, with spreading, well-defined, erythematous borders (Figure 2). There is usually accompanying fever, malaise and chills. Bacterial swabs can be of use to isolate the organism; however, skin swabs are often negative unless there is surface exudate. Other causative organisms include *Staphylococcus aureus* (methicillin-sensitive or methicillin-resistant) in immunocompetent hosts and atypical organisms such as *Pseudomonas aeruginosa* in immunocompromised individuals.[1]
- **Insect bite reaction.** Insect bite reactions have a variety of morphological appearances but generally appear on exposed areas acutely as grouped, erythematous urticarial papules with associated excoriation due to intense pruritus induced by release of histamine and other immune mediators at the puncture site (Figure 3). Chronic reactions manifest as wheals, urticarial papules and prurigo nodularis-like lesions that can persist for weeks to months after the initial inciting injury and flare with every new insult.[2] Exaggerated cutaneous reactions to insect bites can appear as bullous or nodular erythematous lesions, and may indicate underlying infection with Epstein-Barr virus or haematological malignancy (e.g. chronic lymphocytic leukaemia).[3]
- **Panniculitis.** The panniculitides represent a diverse group of inflammatory disorders involving the subcutis. All present in a similar way, with painful, poorly demarcated erythematous subcutaneous nodules whose geographic distribution differs with the underlying cause. Classification of the panniculitides is complex, but histologically the conditions are divided on the basis of inflammation (septal, lobular or mixed septal-lobular) and vasculitis (present or absent).[4] Causes of panniculitis are generally quite rare, particularly in children, and include infection (*Streptococcus spp.*, *Mycobacterium tuberculosis*), trauma, cold exposure, alpha-1 antitrypsin deficiency, connective tissue disorders and malignant infiltration of subcutaneous tissue.[4]
- **Bruises.** The limbs, particularly the extensor surface of the knees and elbows, pretibial and 'facial T' areas are common sites for ecchymoses to occur following accidental trauma in a child.[5] However, there are important

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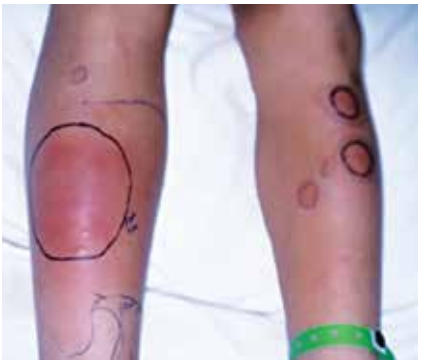

Figure 2. Cellulitis.

conditions to exclude in a child with recurrent ecchymoses or those resulting from minimal trauma, such as underlying thrombocytopenias (e.g. thrombotic thrombocytopenic purpura), coagulopathies (von Willebrand disease, haemophilias), vitamin C deficiency, Ehlers-Danlos syndrome, and Henoch-Schönlein purpura.[5] It is important to be aware of nonaccidental injury in a child with ecchymoses in areas that are not normally prone to unintentional injury (e.g. ears, neck, cheeks, trunk, proximal extremities and genitalia), associated fractures and inconsistent history, or 'falls' in an immobile child.[5]

- **Tuberculid.** The term 'tuberculid' describes a group of exanthems in individuals with demonstrated immunity to *M. tuberculosis* as result of prior infection or sensitisation.[6] This includes a condition known as erythema induratum of Bazin, a delayed-type hypersensitivity reaction to tuberculosis antigens, commonly triggered by low temperatures, that manifests as symmetrical subcutaneous nodules with ulceration and subsequent atrophic, hyperpigmented scars that favour the lower limbs.[6]
- **Erythema nodosum (EN).** This is the correct diagnosis. EN, which is the most common form of panniculitis at any age, is a hypersensitivity reaction that presents with an acute symmetrical eruption of erythematous, tender subcutaneous nodules and plaques that can arise anywhere but commonly involve the pretibial areas.[7] The lesions tend to be poorly defined because they are deep. There may be a history of an upper respiratory tract infection (URTI) or accompanying fever, malaise and arthralgia. In children, a preceding URTI due to *Streptococcus spp.* is the most common cause, with the URTI preceding the EN nodules by one to three weeks.[7] Other causes include infections (e.g. *Yersinia, M. tuberculosis*), drugs (e.g. oral contraceptive pill), inflammatory bowel disease and sarcoidosis (known as Löffler's syndrome).[7] Up to half of cases are idiopathic. The nodules in EN do not ulcerate and last between two and six weeks, showing spontaneous bruise-like regression without scarring or atrophy (known as erythema contusiformis).[7] Chronic EN, which can last for months to years, is characterised by unilateral, migratory nodules that are associated with streptococcal infections and are more common in women.[7] Incisional biopsy to the level above the fascia reveals a predominantly septal panniculitis with associated oedema, pathognomonic Miescher microgranulomas (perineutrophilic collections of macrophages) and without primary vasculitic changes.[7]

Management

The principles of management for EN include symptomatic treatment of the nodules as well as identification of underlying causes, particularly in recurrent or chronic EN lesions lasting longer than six weeks, as seen in this case. Bed rest, leg elevation and analgesia (especially NSAIDs) are first-line symptomatic treatment of EN; however, oral prednisone is effective when there is severe pain and a rapid positive outcome is essential for social reasons. Oral saturated solution of potassium iodide has also been shown to be of some benefit, particularly for chronic EN.[7]

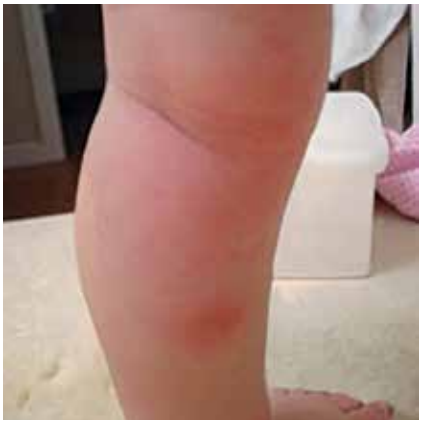

Figure 3. Insect bite reaction.

Outcome

For this child, a biopsy was performed and confirmed the diagnosis of EN. A full blood count and chest x-ray were normal, with only a mild elevation of CRP (9 mg/L). Tests for serum antistreptolysin O titre (ASOT) and angiotensin converting enzyme (ACE) were also negative. As the EN was chronic, the patient was referred for endoscopy and was found to have Crohn's disease. Subsequent treatment with oral prednisone resolved the skin lesions, and she was referred to a gastroenterologist for follow up. MT

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