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A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

Reprints in Dermatology

Rosacea: what triggers it and how to control it

Allergy testing in paediatric atopic dermatitis

Treatment of actinic keratoses – be sure first

The importance of recognising postadolescent acne in women

Treatment options for cutaneous warts

Biologics and psoriasis today

COLLECTION
REPRINTS IN DERMATOLOGY
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A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

FOREWORD FROM THE EDITOR OF REPRINTS IN DERMATOLOGY

Dermatology continues to receive little attention in the crowded undergraduate program at most medical schools. This is a problem in general practice as dermatological conditions constitute about 10 to 15% of presentations, sometimes more. At the postgraduate level, GPs receive further education on dermatology but less than half of it comes from dermatologists with hands-on experience and knowledge of the latest advances.

This collection of dermatology articles from *Medicine Today* contains updates on a number of common and important conditions that are seen often in general practice, including rosacea, psoriasis, acne in women, cutaneous warts and the Australian epidemic, skin sun damage. The controversial topic of allergy testing in eczema is also explored. The update on the latest biologic agents for psoriasis, which affects at least 2% of the population, outlines the new options available for patients whose disease is at the severe end of the scale.

This collection provides an overview of these diverse topics, with practical information on diagnosis and management.

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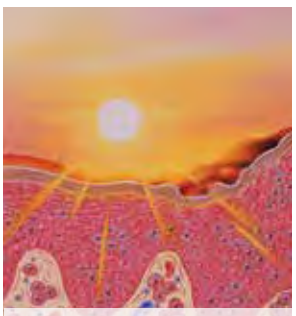

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Triggers and treatment of rosacea

SHIEN-NING CHEE MB BS, MMed
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KEY POINTS

- Rosacea is a common condition characterised by flushing, erythema, inflammatory lesions and telangiectasia.
- The cause is multifactorial and not completely understood: genetics, neurovascular dysregulation and infections may be involved.
- Diagnosis of rosacea is based on clinical findings, although investigations may be required to exclude differential diagnoses.
- Treatment is tailored to the individual and aims to control symptoms and signs, but not cure the disease.
- Referral of the patient to a general dermatologist is recommended when rosacea does not respond to conventional therapy.
- Referral of the patient to an ophthalmologist is recommended if eye involvement is suspected.

Rosacea is a common chronic inflammatory skin condition that can lead to significant facial changes, ocular involvement and decreased quality of life. Its cause is multifactorial and not completely understood. Treatment aims to control, but not cure, the disease.

Rosacea is a common chronic inflammatory skin disease primarily affecting the facial convexities. It is characterised by vascular lability, leading to flushing, telangiectasia and fixed erythema, and cutaneous inflammation, manifesting as papules, pustules and lymphoedema. Although not life-threatening, rosacea may have a significant impact on a patient's self-esteem and quality of life. Early diagnosis and treatment will reduce morbidity.

Epidemiology

Estimated prevalence rates of rosacea range from 0.9 to 22%. The largest studies estimate prevalence at 2 to 3% of the general population.[1]

Rosacea tends to occur in adults over the age of 30 years. In groups aged younger than 35 years or older than 50 years, men and women are affected equally; however, there is a predominance in women in the 36- to 50-year age group.[1] Incidence is highest in people with skin types I and II, although it does also occur in people with Asian and pigmented skin types.[2]

Pathophysiology

The pathophysiology of rosacea is multifactorial and not completely understood. At present, rosacea is thought of as a complex inflammatory disorder arising in genetically predisposed individuals.

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Genetics

Rosacea often affects multiple family members. Recent analyses have found distinct genetic profiles for each rosacea subtype, with expression of more than 500 different genes compared with healthy skin.[3] The skin of patients with rosacea has been found to be dry and acidic, with altered sebum fatty acid composition.[4]

Neurovascular dysregulation and augmented immune detection and response

Precipitating and exacerbating factors associated with rosacea include alcohol intake, heat, cold, exercise, smoking, eating spicy food, drinking hot beverages and stress. Patients with rosacea have a greater immunological response to these triggers, resulting in cellular infiltration, increased vasculature and an influx of proteolytic enzymes into the stratum corneum.

Some of the factors implicated in causing rosacea include cathelicidin, vascular endothelial growth factor and substance P. The understanding of the innate immune response and host defence peptides, known as antimicrobial peptides (AMPs), is an exciting area of research in general medicine. The concentration of an AMP known as cathelicidin LL-37, is increased in patients with rosacea-prone skin. Such discoveries may have ramifications for future targeted therapies.[3,5,6]

Infection

Certain infections have been implicated as causes of rosacea. The face mite *Demodex folliculorum*, an obligatory parasite of human pilosebaceous follicles, has been identified in elevated numbers in patients with rosacea. It is hypothesised that an immune defect allows the mite to penetrate the dermis and stimulate an exaggerated immune response, giving rise to the papules and pustules of rosacea.[7] In other studies, abundant numbers of the commensal Gram-positive bacterium *Staphylococcus epidermidis* have been detected in patients with pustular rosacea. Significantly, strains were the beta-haemolytic variant, differing from the nonhaemolytic form isolated from normal controls.[8,9] Although *Helicobacter pylori* has also been implicated in the development of rosacea, studies have yielded contradictory results.[10]

Clinical features

The clinical presentation of patients with rosacea is variable. Areas of the body typically affected are the central convex areas of the face (cheeks, nose, chin and forehead). Occasionally the scalp, upper chest, back and even limbs may be involved.[11]

Diagnosis of rosacea is based on the presence of the clinical features listed below.[12]

- Presence of one or more of the following primary features:
  - flushing (transient or reversible erythema): a history of frequent blushing or flushing spontaneously or in response to various stimuli is common
  - erythema (fixed or persistent) of the facial skin: this is common
  - inflammatory lesions: these typically appear as dome-shaped red papules with or without pustules; comedones are absent
  - telangiectasia: these are usually linear, dilated capillaries of varying diameter, fine, medium or coarse.
- Possible presence of one or more of the following secondary features:
  - burning or stinging sensations
  - erythematous plaques
  - rough or scaly central facial skin
  - oedema accompanying or following facial erythema
  - ocular manifestations, including burning sensation, dry gritty eyes, conjunctival hyperaemia
  - involvement of peripheral locations, e.g. limbs
  - phymatous changes due to sebaceous tissue hypertrophy: the most common form, rhinophyma, affects the nasal skin.

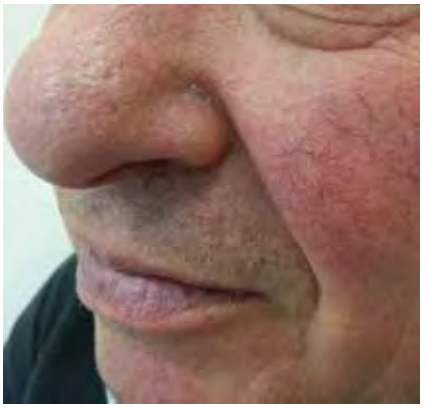


Figure 1. Erythematotelangiectatic rosacea.

Subtypes of rosacea

There are four primary subtypes of rosacea. One subtype may progress to another or they can occur in isolation.

Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea is characterised by flushing and persistent central facial erythema (Figure 1). Telangiectases may be present, and patients may report central facial oedema, stinging, burning, roughness or scaling.[12]

Papulopustular rosacea

Papulopustular rosacea is characterised by persistent central facial erythema with transient papules and/or pustules in the central facial distribution (Figure 2). Comedones are absent, in contrast to acne, and burning and stinging may be present. This subtype of rosacea is often seen in combination with or develops after erythematotelangiectatic rosacea.[12]

Phymatous rosacea

Phymatous rosacea refers to hypertrophy of sebaceous glands and fibrous thickening of the skin due to chronic inflammation (Figure 3). It clinically manifests as tissue enlargement, prominent pores and nodularity of the skin surface.

The most common presentation is rhinophyma, characterised by coarse thick nasal skin particularly involving the nasal tip; it is commonly referred to as 'alcoholic'

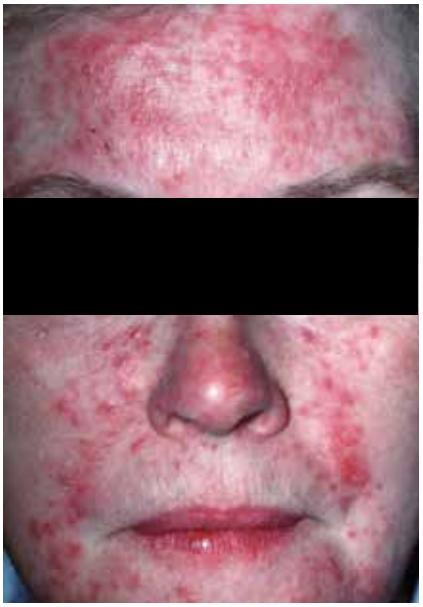


Figure 2. Papulopustular rosacea.

or 'potato' nose. Interestingly, other locations may be involved, including the ears (otophyma), forehead (metophyma), eyelids (blepharophyma) and chin (gnatophyma). This subtype is often seen in combination with, or develops after, erythematotelangiectatic or papulopustular rosacea subtypes.[12]

Ocular rosacea

Ocular rosacea occurs in up to 70% of patients with rosacea. One-third of these patients may develop corneal involvement, which is potentially sight-threatening.[13,14] Further details are given below in the section 'Associations and complications' on page 7.

Differential diagnoses

Seborrhoeic dermatitis

Seborrhoeic dermatitis may coexist with rosacea. It is best differentiated by the presence of greasy scale in the nasolabial folds, external ear canals and central eyebrow region.[2]

Acne vulgaris

Acne vulgaris tends to occur in a younger age group and is characterised by the presence of open and closed comedones. It can also coexist with rosacea.[2]

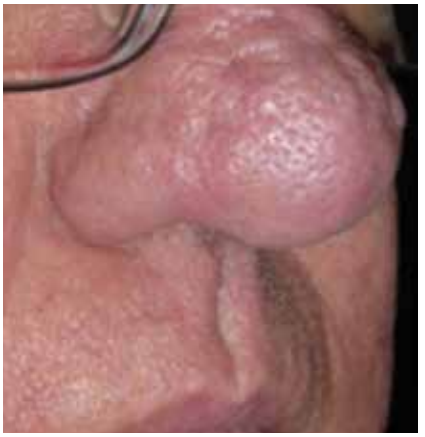


Figure 3. Phymatous rosacea – demonstrating rhinophyma.

Steroid-induced acneiform eruption

Steroid-induced acneiform eruption is an inflammatory response that can occur during or after chronic topical and systemic corticosteroid use.[12]

Perioral dermatitis

Perioral dermatitis is characterised by erythema, microvesicles and scaling around the mouth, nose or eyes.[12] It is commonly induced by topical corticosteroids or occlusive skincare products such as emollients, sunscreens and cosmetics.

Lupus erythematosus

The presence of pustules, papules or blepharitis favours a diagnosis of rosacea, whereas scaling, follicular plugging, pigmentary disturbance and scarring favour discoid lupus erythematosus (DLE) as the diagnosis. Histological examination may be necessary to make a distinction between the two. Both eruptions can be photoaggravated. Systemic lupus erythematosus (SLE) and subacute cutaneous lupus erythematosus (SCLE) are less common.[2]

Cutaneous sarcoidosis of the nose (lupus pernio)

This condition may resemble rhinophymatous rosacea; however, there is minimal skin surface change in patients with cutaneous sarcoidosis of the nose.[11]

Tinea faciei

Tinea faciei is an infection of the facial skin by dermatophyte fungi. Diagnosis is confirmed by microscopy and culture of skin scrapings.

Essential telangiectasia

Patients with essential telangiectasia will only have this condition and no other features of rosacea.

Carcinoid syndrome

In patients who present with severe or sudden-onset facial flushing, it is worth investigating for carcinoid syndrome. Gastrointestinal, cardiac and pulmonary symptoms may be present.

A list of differential diagnoses is provided in the box.

DIFFERENTIAL DIAGNOSES OF ROSACEA

- Acne vulgaris
- Seborrhoeic dermatitis
- Perioral dermatitis
- Steroid-induced acneiform eruption (steroid rosacea)
- Lupus erythematosus – discoid, systemic or subacute cutaneous
- Cutaneous sarcoidosis of the nose (lupus pernio)
- Tinea faciei
- Essential telangiectasia
- Carcinoid syndrome
- Drug reaction
- Polymorphous light eruption
- Atypical infections
- Contact dermatitis – irritant or allergic
- Lupus vulgaris (cutaneous tuberculosis)
- Acne agminata
- Dermatomyositis
- Polycythaemia rubra vera
- Superior vena cava obstruction

Investigations

Minimal investigations are required as the diagnosis of rosacea is usually based on history and clinical findings. Baseline blood test results including full blood count and kidney and liver function tests are necessary if the use of systemic therapy is being considered. A skin scraping is useful to exclude fungal infection. Autoimmune serology (antinuclear antibodies [ANA] and extractable nuclear antigens [ENA]) should be performed if a connective tissue disease such as lupus is suspected. Creatine kinase (CK) levels should be checked for dermatomyositis. Skin biopsy (for haematoxylin and eosin staining, immunofluorescence with or without culture) is worthwhile if symptoms are atypical, the diagnosis remains unclear or the condition is unresponsive to conventional therapy.[15]

Histological findings

Erythematotelangiectatic rosacea

Erythematotelangiectatic rosacea is characterised by the presence of enlarged dilated capillaries and venules in the upper dermis. These vessels may be unusually shaped (e.g. tortuous or geometric). *Demodex* mites are commonly present in affected patients. Other features include oedema in the upper dermis, lymphocytic inflammation and spongiosis.

The dermoepidermal junction appears normal in patients with rosacea, unlike in those with lupus erythematosus in which there are lichenoid changes at this junction.[15]

Papulopustular rosacea

Papulopustular rosacea is characterised by a mixed inflammatory cell infiltrate, with numerous plasma cells, neutrophils and sometimes eosinophils. *Demodex* mites are often present in affected patients, as are spongiosis and solar elastosis. Retentional elements, such as comedones and dermal infundibular cysts, are absent, helping to differentiate papulopustular rosacea from papulopustular acne.[15]

Phymatous rosacea

Phymatous rosacea commonly presents with rhinophyma, which is characterised by an increased volume of sebaceous glands and fibrosis. The sebaceous lobules are of normal structure but extremely large. The infundibula are also enlarged and filled with keratin, eosinophilic debris and organisms, commonly *Demodex* mites.[15]

Management

Education

It is important from the outset to explain to patients that rosacea is a chronic skin condition that can be controlled but not cured. Reassure them that it is generally responsive to treatment and rarely scars the skin. Improvement may be gradual, so patients need to persevere with treatment. Therapy should be trialled for at least three months to assess efficacy, and may be needed intermittently or continuously for years.[11]

Of course, if the patient is asymptomatic, no treatment is an option.

Avoid precipitants

In patients with mild rosacea, avoidance of triggers may be enough to improve the condition. Triggers to consider avoiding include extremes of temperature (hot or cold), ultraviolet (UV) radiation exposure, intake of spicy foods, hot or alcoholic beverages, wind, exercise and stress.[2,11]

Affected patients should avoid using topical corticosteroid agents. Although immediate improvement may be observed after application of a corticosteroid due to their vasoconstrictive and anti-inflammatory effects, in the long term topical corticosteroids worsen rosacea and may trigger acneiform eruptions.

Encourage patients to apply a cool, damp (tap water) soft cotton compress regularly to the facial skin for 10 minutes to reduce symptoms such as burning and stinging.

General skin care measures

Patients with rosacea should minimise their use of skin care products and cosmetics ('less is more'). Fragrance- and preservative-free cleansers and light emollient creams are usually all that are needed. Patients should use their fingers to apply the products (not foam pads or brushes) to minimise mechanical disruption of the skin barrier. Application of potential irritants, such as soap bars, toners and alcohol-based cleansers, should be avoided, as should products containing menthol, camphor and sodium lauryl sulphate.[16]

As sunlight is a common trigger for rosacea flare-ups, patients should wear a broad-spectrum low irritant SPF 50+ sunscreen daily, and limit sun exposure by wearing protective clothing and hats. Shade should be sought when outdoors, and patients should be encouraged to stay indoors during periods of high UV radiation. Sunscreens containing the physical blockers titanium dioxide and zinc oxide are well tolerated by most patients, and newer chemical agents are proving to be less irritant.[16]

Makeup may be used to conceal the signs of rosacea. Waterproof cosmetics and heavy foundations should be avoided, because these are difficult to remove without the use of irritating solvents and abrasive cloths. Green-tinted concealer helps camouflage erythema.[16]

Topical therapies

Fortunately a wide range of topical agents are effective as first-line therapy for patients with rosacea and a limited number of papules and pustules (Table). Careful consideration must be given to the vehicle used to deliver the active agent because this will affect tolerability (in view of altered skin barrier function), patient compliance and efficacy.[17] Formulations available include gels, lotions, creams, foams and ointments.

Metronidazole

Topical metronidazole 0.5 to 0.75% (available as a cream or gel) applied once or twice daily is effective in treating patients with papulopustular rosacea and has been used since the 1980s. It may also reduce

TABLE. THERAPIES DIRECTED AT THE ROSACEA SUBTYPE

Subtype of rosacea	Therapies
Erythematotelangiectatic	Topical brimonidine Vascular laser and intense pulsed light
Papulopustular	Topical metronidazole Topical azelaic acid Oral doxycycline or minocycline Isotretinoin
Phymatous	Isotretinoin Ablative laser Surgery

blanchable erythema (but not telangiectasia) in patients with erythematotelangiectatic rosacea. Anecdotally, patients with sensitive skin tolerate the cream formulation best, whereas men tend to prefer the gel base. Several weeks of application are required to see obvious improvement and it may be used on a long-term basis to maintain remission.

Patients should be advised that topical agents work best when applied to an entire affected area rather than as spot treatment.[2,14,16]

Alpha-adrenoreceptor agonists

Topical brimonidine 0.33% gel is a promising new therapy approved in Australia in 2014 for intermittent topical treatment of patients with the persistent facial erythema of rosacea. It targets the alpha-adrenoreceptors in the smooth muscle of superficial cutaneous blood vessel walls. Application reduces erythema within 30 minutes, with the peak effect lasting three to six hours, and gradual return to baseline 12 hours after application. Phase 3 trials showed no major adverse reactions besides occasional mild and transient skin irritation. Specifically, no significant tachyphylaxis or rebound erythema was noted.[5]

Azelaic acid

Topical azelaic acid (available as a 20% lotion or 15% gel) applied once or twice daily is an alternative to topical metronidazole in the treatment of patients with papulopustular rosacea. Although studies show it to be more efficacious than metronidazole, it can be more irritating, so patients should be advised to apply the preparation every second or third day initially.[14]

Other topical agents

Other topical agents such as compounded tacrolimus 0.03%, pimecrolimus 1%, compounded sodium sulfacetamide 10% with sulphur 5%, and clindamycin 1% (off-label use) may be useful in certain cases of rosacea.[16]

Oral therapies

Oral therapy is preferable when the skin lesions of rosacea are more extensive or when patients have not responded to topical therapy. Topical therapy may be added to the treatment regimen once the inflammation has begun to settle with the systemic agent; this minimises potential irritation. Once the rosacea improves, the systemic therapy may be discontinued and improvement maintained with topical treatment alone.[2,14]

Tetracyclines

Oral tetracyclines have anti-inflammatory properties and have been the mainstay of treatment for patients with rosacea for decades. They are particularly effective in treating patients with papulopustular rosacea.

With the loss of tetracycline hydrochloride from the Australian market, doxycycline (off-label use) has become the drug of choice. Doses of 50 to 100 mg/day have been used traditionally but recent studies show subantimicrobial doses of 40 mg/day are as effective (see novel therapies below).[18] Minocycline (off-label use; 50 to 100 mg/day) is also used to treat patients with papulopustular rosacea and is more lipophilic.

Chronic use of oral tetracyclines has been associated with the development of irreversible blue-grey pigmentation and drug-induced systemic lupus in a small percentage of patients. Response can be seen within four weeks. Intermittent use is preferable.

Metronidazole

Oral metronidazole (off-label use) 200 mg twice daily may be trialled in patients with rosacea in whom tetracyclines are contraindicated or ineffective. However, patients must abstain from alcohol intake during metronidazole therapy to avoid alcohol-induced headaches via disulfiram reactions.[16]

Other antibiotics

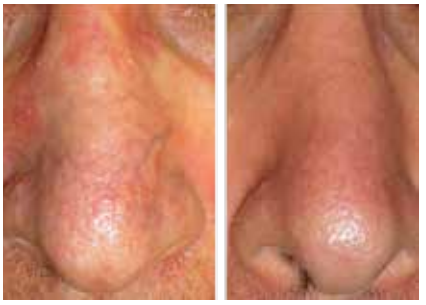
Studies have shown oral clarithromycin and azithromycin to be useful in the treatment of patients with rosacea (off-label uses).[16] Trimethoprim-sulfamethoxazole and ciprofloxacin are not generally used due to concerns of resistant bacterial populations. Penicillins and cephalosporins are generally ineffective in the treatment of patients with rosacea.[2]

Isotretinoin

Low-dose isotretinoin (off-label use) may be effective in patients with severe papulopustular or phymatous rosacea. Referral of these patients to a dermatologist is advised. Patients with refractory disease typically respond well to doses of 10 to 20 mg/day; long-term maintenance therapy may be required as the lasting response seen in acne does not often occur in rosacea.[2]

Other oral therapies

Other oral therapies reported to be



Figures 4a and b. Telangiectases. Before (a, left) and after (b, right) treatment with pulsed dye laser.

effective in patients with rosacea include clonidine, spironolactone, naloxone and ondansetron (all off-label use).[16] Single-dose oral ivermectin (off-label use) has been used in immunocompromised patients with rosacea-like demodicidosis with good effect.[18]

NSAIDs, such as diclofenac, may offer symptomatic relief in patients with rosacea.

Physical therapies

Laser and light

Vascular laser therapy, such as with the 595 nm pulsed dye laser, and intense pulsed light therapy can be used to remove refractory background erythema and clinically significant telangiectases (Figures 4a and b). The light in these devices is absorbed by oxyhaemoglobin and haemoglobin, leading to vessel destruction with minimal collateral tissue damage (Figure 5).[16] Ablative lasers can be used for the contouring of hypertrophied tissue in patients with phymatous rosacea.[2,14] Patients may be referred to a dermatologist for laser therapy.

Rhinophyma can be debulked by an ablative resurfacing laser (e.g. carbon dioxide) or radiofrequency electrosurgery devices. Treatment is aimed at debulking the excess tissue and then sculpting the disfigured nose. These devices are preferred for recontouring because there is little blood loss compared with scalpel excision.

Surgery

Scalpel excision has been used to debulk and sculpt the nose but is less precise than laser therapy.

Novel therapies

Subantimicrobial-dose tetracyclines

At higher doses the oral tetracyclines are antimicrobial; at lower doses they have anti-inflammatory actions without antibiotic activity. Doxycycline 40 mg once daily (delayed release) or 20 mg twice daily is effective in the treatment of patients with rosacea, without any development of antibiotic resistance or impact on skin flora. Efficacy is comparable with traditional dosing of doxycycline but there are fewer adverse effects.[18] A slow-release doxycycline preparation is not currently available in Australia.

Beta-blockers

Nonselective beta-blockers decrease sympathetic activity and produce vasoconstriction, which suppresses flushing. Oral propranolol 30 to 120 mg/day and carvedilol 15 to 25 mg/day have been shown to reduce the frequency and severity of flushing episodes (both off-label use). They may be used in normotensive patients as long as doses are gradually escalated and blood pressure monitored.[18]

Other antimicrobials

Topical 5% permethrin, 10% crotamiton and 1% ivermectin (all off-label use) have been reported to be useful in patients with rosacea. However, they should be used with caution as they may irritate sensitive skin.[18]

Prognosis

The duration of rosacea is highly variable, ranging from months to decades. Treatment of affected patients aims to suppress symptoms and prevent disease progression and complications; it does not appear to alter disease duration.

The course of rosacea fluctuates, characteristically waxing and waning in response to the various stimuli discussed above. When persistent, rosacea results in fixed facial erythema. Only a portion of patients, usually men, develop cutaneous hypertrophy, and this manifests most commonly as rhinophyma.[11]

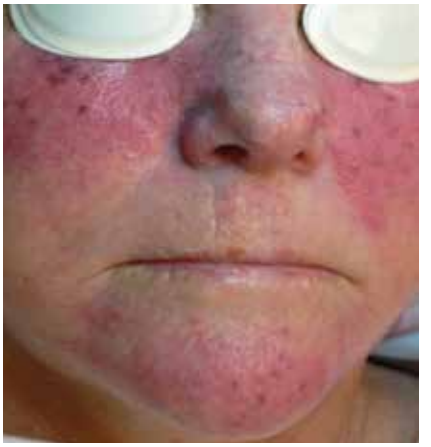


Figure 5. Erythema and spot purpura immediately after pulsed dye laser therapy.

Associations and complications

Psychosocial impact

Although rosacea is not a life-threatening disease, the impact on a patient's quality of life can be significant. Rosacea may cause embarrassment, anxiety, decreased self-esteem and social isolation. Patients may feel self-conscious of their 'alcoholic nose' or report disappointment that their disease cannot be cured.[19] These feelings should be taken into account when devising a treatment plan. Online support groups such as the Rosacea Support Group (http://rosacea-support.org/australia) can be useful.

Ocular rosacea

At least 70% of patients with rosacea experience ocular symptoms, with men and women being affected equally. Symptoms are often mild, so it is worth specifically asking about ocular involvement at the first consultation. Severe eye involvement may lead to ocular keratitis with subsequent scarring, corneal perforation and vision loss.[13]

Symptoms include tearing, conjunctival hyperaemia, foreign body sensation,

burning, stinging, dryness, itching, light sensitivity and blurred vision. When the cornea is involved, patients may report decreased visual acuity. Other signs include telangiectases of the conjunctiva and lid margin, lid and periocular erythema, blepharitis, conjunctivitis and styes.[13]

Early consultation with an ophthalmologist is recommended as slit lamp examination of the ocular surface is needed.[13,14] It is worth noting that ocular rosacea may occur in the absence of cutaneous manifestations, and the severity of ocular symptoms is not necessarily related to the severity of cutaneous findings.[13]

General measures to relieve ocular symptoms include application of warm compresses and lubricating eye drops. Mild rosacea can be treated with topical cyclosporin 0.05% (off-label use), which increases tear production and has mild anti-inflammatory effects, and antibiotic ointments to decrease eye flora. Metronidazole gel is useful in cases of rosacea-associated blepharitis. Topical corticosteroids may be used to settle inflammation; however, long-term use should be avoided because of increased risk of ocular infections and potential side effects such as glaucoma and cataracts. Moderate to severe ocular rosacea may require systemic therapies such as oral doxycycline or, as second-line, azithromycin.[13,14] Regular lubrication of eyes is essential when using oral isotretinoin for cutaneous rosacea.

Lymphoedema

Chronic inflammation in patients with long-standing rosacea damages local lymphatic vessels, resulting in a build-up of protein-rich lymphatic fluid in the skin (lymphoedema). Although an uncommon complication of rosacea, lymphoedema preferentially affects periorbital skin, resulting in eyelid swelling and even ectropion.[11] It can be acute or subacute in onset, and unilateral or bilateral in distribution.

Salivary gland involvement

Although rare, inflammation of the salivary glands as a consequence of rosacea can result in reduced salivary secretions and dry mouth.[11]

Conclusion

Rosacea is a common chronic inflammatory skin disease that often impacts significantly on the patient's quality of life. Referral to a dermatologist is recommended when the disease is not responding to conventional therapy or for consideration of laser or light therapies. Ophthalmology review is recommended if eye involvement is suspected. General measures such as avoidance of known precipitants and use of fragrance- and preservative-free skin care products are paramount to the management of the condition.

With the renewed interest in the pathogenesis of rosacea, particularly at both the microbiota[20] and immunological[6] levels, novel topical and systemic agents are under development. An exciting area of translational research is the inactivation of enzymes of the kallikrein family, which should reduce cathelicidin levels in patients with rosacea-prone skin and thus prevent aberrant activation of the innate immune response.[21] MT

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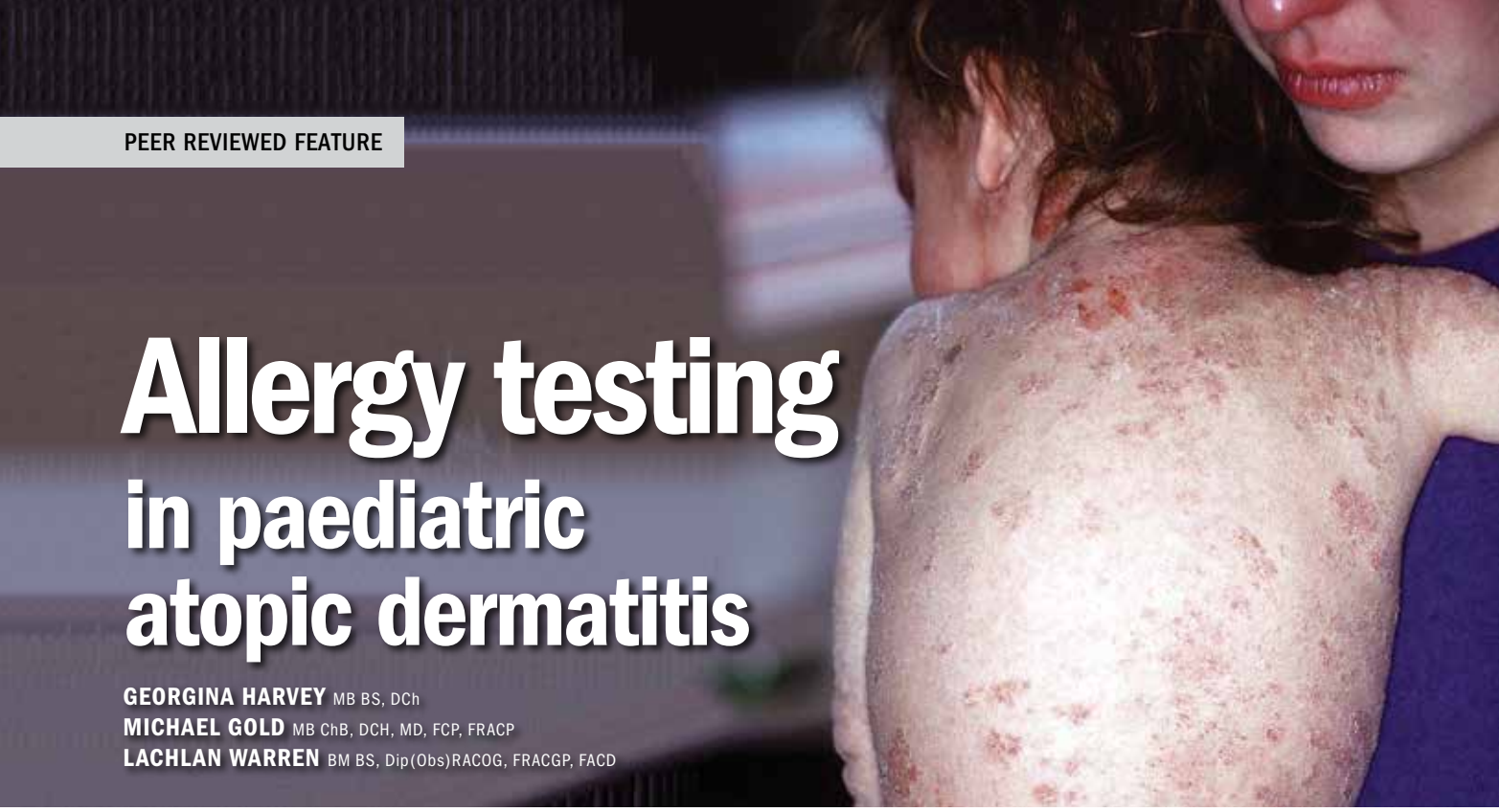

Allergy testing in paediatric atopic dermatitis

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In a child with atopic dermatitis, parents and the treating doctor may desire or need to consider the potential role of allergic triggers. The role of allergens in atopic dermatitis and the available and appropriate allergy testing methods are discussed in this article.

KEY POINTS

- Initial management of atopic dermatitis (AD) involves education, assessment of triggers and exacerbating factors, and topical therapy.
- Testing for food allergy may be considered if AD is severe or refractory, if skin flares follow specific exposures to foods or if there is a history of anaphylaxis.
- Serology and skin prick methods of IgE testing have high rates of false-positive results. Careful interpretation of results is required, with confirmation of suspected food allergy by oral food challenge.
- Inappropriate dietary restrictions can have severe nutritional consequences in children. Dietary restrictions should be reviewed regularly.
- Testing for aeroallergen allergies is available. Interpretation of results and recommendations for management are, however, contentious areas.
- Patch testing for delayed-type allergy is recommended if regional patterns of eczema suggest allergic contact dermatitis.

Atopic dermatitis (AD) is a common affliction of children and both its diagnosis and management provide concerns for patients and their medical advisors. Children with AD often have other atopic (immunoglobulin E [IgE]-mediated) disorders, such as asthma, food allergies and allergic rhinitis.[1] AD is also often referred to as 'eczema'; although AD is technically a subtype of eczema, in common practice the terms are used interchangeably. Allergic contact dermatitis, however, is different to AD, usually manifesting within days (rather than minutes or hours) of exposure in areas of skin directly in contact with the allergen.

The clinical manifestations of AD are skin changes characterised by erythema, scaling, weeping and pruritus. The distribution of skin lesions in AD varies with the patient's age: typically infantile AD involves the face, scalp, arms and legs, whereas in older children lesions are often prominent on flexor surfaces of the extremities.[2] Onset of AD is primarily before the age of 5 years, and often before 1 year of age. The impact of this condition can be severe, particularly because of the accompanying intense pruritus, which often has a significant impact on a child's functional ability and can cause major sleep disturbance.[3] The consequences of AD are not limited to the child as family members also suffer major effects and incur significant personal and financial costs.[4]

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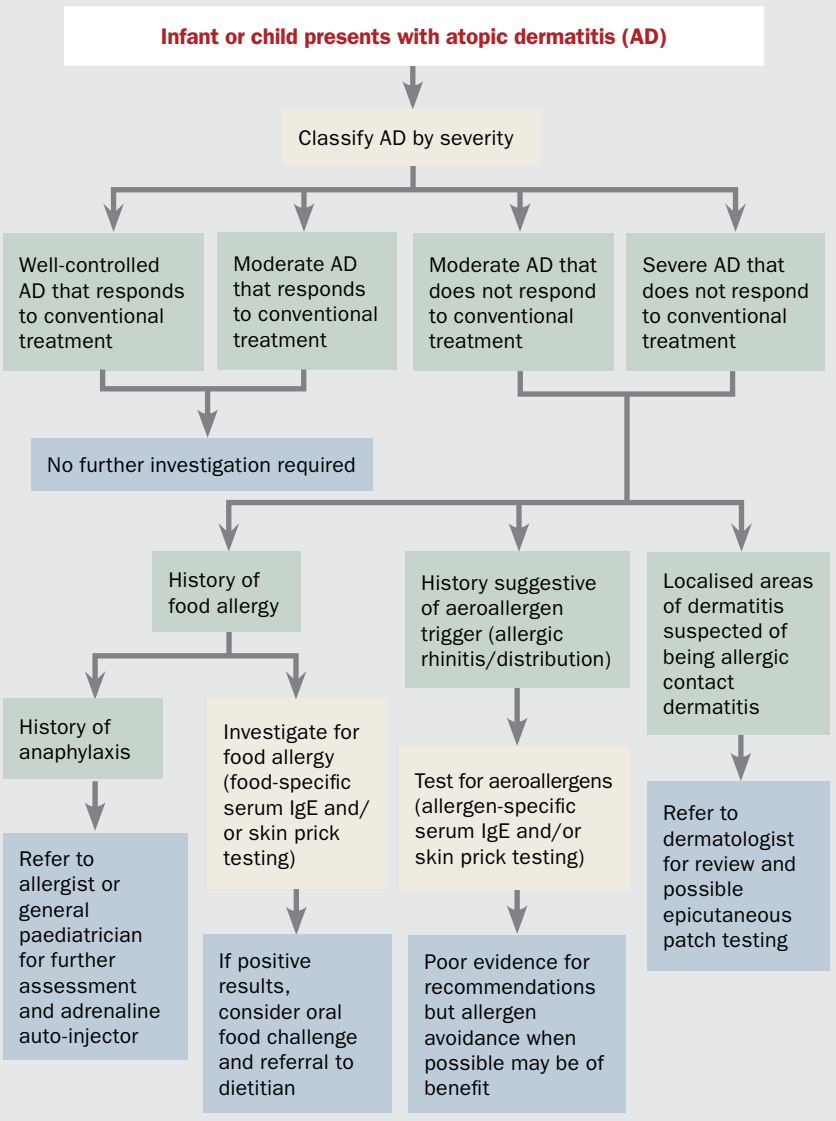
AN APPROACH TO INVESTIGATING PAEDIATRIC ATOPIC DERMATITIS



The aetiology of AD is related to an underlying defective skin barrier with altered immune responses to environmental allergens, skin irritants and microorganisms.[5] Multiple genetic abnormalities have been identified in patients with AD, with most evidence linking AD with a mutation in the *FLG* gene, which encodes for filaggrin (derived from 'filament-aggregating protein').[1,6] Filaggrin assists in the strength and structure of skin and aids in epidermal hydration. Defective filaggrin expression has been widely demonstrated in people with AD, asthma and allergic rhinitis, suggesting that impaired skin barrier function has a significant role in atopic diseases as a whole.[1,6]

The usual recommendations for treatment of AD can be summarised by the following steps:

- education regarding the aetiology and natural history of AD
- consideration of triggers and exacerbating factors (including a discussion of the possible partial and variable role of allergic triggers)
- reduction of irritant exposures
- maximising the barrier function of the skin by moisturising (i.e. appropriate use of emollients)
- appropriate use of topical corticosteroid and anti-inflammatory therapies
- consideration of antimicrobial or adjunctive modalities.

This article focuses on the assessment of the allergic triggers that can cause AD. A careful history of allergy should be obtained in children with exacerbations of AD, and children with severe or refractory AD should be further investigated. This investigation is discussed below, and the flowchart provides a useful pathway to guide this process.

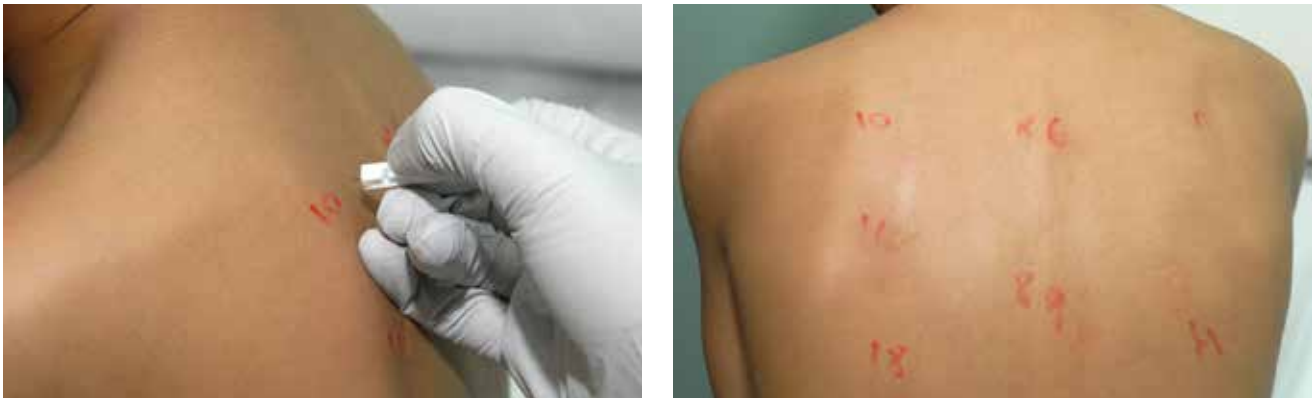
Allergic triggers in AD

The triggers that may exacerbate AD via an allergic (immune) mechanism include food proteins, aeroallergens and excipients contained in topical products. Testing for allergies involves serology or skin prick testing to detect allergen-specific IgE (in immediate-type hypersensitivities), epicutaneous patch testing (in delayed-type [type 4] hypersensitivities) and provocative oral challenges, usually to foods.

Any form of allergy testing, however, can only be correctly interpreted in conjunction with the clinical history. This is best illustrated by considering testing for food allergen-specific IgEs, which can determine sensitisation but not necessarily allergy. This is so because many children with AD are likely to be sensitised to a suspected food trigger (e.g. cow's milk), and therefore have raised levels of IgE specific to that food and yet are not allergic to it (i.e. they are able to tolerate the food when it is ingested).

Food allergens

The prevalences of both food allergy and AD continue to rise in developed countries. In addition, both food allergy and AD have their highest prevalence in preschool-aged children, and both conditions are often seen in the same child, with AD being an



Figures 1a and 1b. Skin prick testing. a (left). Allergen is enabled to enter the skin via a small prick made with a sterile lancet. b (right). Results should be read after 15 minutes.

important risk factor for the development of a food allergy.

Although exact mechanisms linking AD and food allergies are poorly defined, there is widespread belief that a late-phase IgE response may be the source of eczematous reactions to food.[7] Additionally, there is supporting evidence that transdermal sensitisation by environmental food allergens may be a contributing factor.[6]

The foods most commonly implicated in allergies and AD flares are hen's eggs, cow's milk, wheat, soy and peanuts. Because AD and food allergy frequently coexist in the same child, the issue of allergy testing in children with AD is often raised by parents and healthcare providers.

Aeroallergens

The aeroallergens most commonly implicated as triggers in AD are house dust mite, cockroach, pet dander and pollen. House dust mites and cockroaches produce airborne allergens that act as proteases, directly disrupting the skin barrier.[8] Pet danders and pollen both act via IgE-mediated allergy, resulting in the release of histamine from mast cells and stimulation of an inflammatory response.

Allergen-specific IgE tests

Serology

Measurement of allergen-specific IgE levels is very useful in assessing IgE-mediated allergy. The most commonly used method is Immunocap (also known as UniCap), which has replaced RAST (the radioallergosorbent test). The patient's serum is incubated with a known allergen and then enzyme- or fluorescent compound-labelled antibodies specific for human IgE are added, allowing detection of allergen-specific IgE.

Serological IgE testing should be reported with quantification of the level of specific IgE in International Units (IU) per litre, reflecting the level of sensitisations of the patient to each allergen. If an allergen-specific IgE is detected, this result must always be correlated with the history to assess the clinical relevance of the sensitisation. In general, the higher the level of specific IgE then the greater the positive predictive value will be for the child having an IgE-mediated food allergy. Predictive curves for common food allergens are available.

The nondetection of allergen-specific IgE on this test (the lower sensitivity of conventional assays is reported as less than 0.35 IU/L) carries a high negative predictive value. However, false-negative results can occur. Anaphylaxis may lead to a transient fall in specific IgE levels, or levels may decline to very low over time following exposure, despite the patient having an ongoing clinical allergy. Also, the allergens used for testing can break down (this is particularly so for food allergens), thus providing additional potential for false-negative results.

There is no indication to test for a food allergen mix as results are less sensitive than testing for single allergens and results are more difficult to classify. Considerable variability between allergen preparations leads to inconsistency with laboratory reporting. This variability is even higher with allergen mixes.[9,10]

Skin prick testing

Skin prick testing is another useful way of assessing IgE-mediated allergy, the wheal size indicating the response. Skin prick testing is usually performed on the forearm, and occasionally on the back. Allergen extract is placed on the skin, and a small prick in the skin is made with a sterile lancet through the allergen droplet, allowing the allergen to enter the skin (Figure 1a). The results are read after approximately 15 minutes, with a positive result indicated by the presence of a wheal greater than 3 mm at the test site (Figure 1b).[10]

The procedure is generally well tolerated by children and can be performed in infants if indicated. Local itch and swelling at the site usually subside within one to two hours after testing. Patients must not take antihistamines for three days before skin prick testing as mast cell histamine release is an integral part of the reaction in those with positive results.

The interpretation of skin prick testing results follows similar principles to that of serology; that is, a determination needs to be made of the positive and negative

predictive value of the test to each allergen. The particular benefit of skin prick testing is that it has high negative predictive value (more than 90%) for excluding IgE-mediated food allergies. Thus, in the setting of a positive serological test without a clinical history of food allergy, a negative skin prick test may play a role in excluding IgE-mediated food allergy.[11]

Skin prick testing in Australia is generally performed in allergy centres as part of a consultation, as it requires standardisation of technique and personalised interpretation of the results. Children in whom allergy testing is required therefore require specialist referral.

Using allergen-specific IgE tests for food-related allergies

Indications for food-specific IgE testing

When reviewing a child with AD, it is recommended that any suspected adverse reactions to food be investigated. The history should include whether the child has ever had a generalised allergic reaction to food, including an anaphylactic reaction (e.g. immediate skin rash, vomiting, cough, shortness of breath or collapse). If a history of anaphylaxis is present, referral to an allergist or general paediatrician is warranted for further evaluation, education about food avoidance and management such as the possible need for an adrenaline auto-injector.

Food-specific IgE testing (serological or skin prick testing) is not required for children with mild-to-moderate AD without a clear history of exacerbation by food. Testing should, however, be considered for all infants (less than 12 months of age) with severe eczema and in children with moderate-to-severe eczema that does not respond to standard topical treatment. A study on the epidemiology of food allergy and AD has reported that the relative risk of an infant with AD having an associated food allergy increased with the severity of the eczema.[12]

Interpretation of food-specific IgE tests

It is important for all practitioners to recognise that positive serum IgE titres or positive skin prick tests do not necessarily indicate a food allergy. Positive results obligate consideration of oral challenge tests and, if a food allergy is confirmed, involvement of a dietitian with expertise in paediatric food allergy. Restrictive diets based on serum IgE or skin prick test results alone may be unnecessary and can be harmful to children.[13] Furthermore, strict food avoidance may contribute to more severe anaphylactic reactions on subsequent exposure.[14] The role and risks of graded food exposure to induce tolerance is controversial and the subject of intense current research.

Decision cut-off points have been proposed for food-specific IgE levels to help interpret the significance of serum IgE results in symptomatic children and adolescents.[15] Individuals with food-specific IgE levels for the four major food allergens – eggs, cow's milk, peanuts and fish – above the values listed below were shown to have a 95% probability of reacting (immediate

hypersensitivity) to a food challenge:[15]

- eggs, 6 kUa/L
- cow's milk, 32 kUa/L
- peanuts, 15 kUa/L
- fish, 20 kUa/L.

In the same study, the positive predictive values for two other major allergens were 100% for wheat at a decision cut-off point of 100 kUa/L, and 86% for soy at a cut-off point of 65 kUa/L.[15]

Although these decision points are of great assistance in interpreting serum IgE test results, it must be noted that they were proposed for immediate skin reactions and not for delayed eczematous reactions to foods. The positive predictive value of food-specific IgE for late AD flares is significantly low, at 33%.[5] This low specificity reflects the large numbers of patients who are sensitised to certain foods but are asymptomatic. Furthermore, the above positive predictive values were based on a study performed in the USA and thus may not apply to all populations. Variations in the prevalence of different allergens in specific populations around the world have been well documented.

Confirming a food allergy – oral food challenge test

An oral food challenge test may be indicated to confirm a food allergy in any child. This test may be the only way to document a food allergy in a child who is sensitised to one or more foods. For some children, an oral food challenge will need to be done in a medical setting, usually in hospital, because of the risk of anaphylaxis.

A positive result on oral food challenge indicates the need for ongoing avoidance of the food. Patients with positive results should be referred to a dietitian for ongoing nutritional support, and have follow up by an allergist. Exclusion diets to investigate food allergy are recommended only under the supervision of both a medical practitioner and a dietitian.[10] Management of AD with an exclusion diet that is not based on a clear history and/or supportive testing is not recommended.

Using allergen-specific IgE tests for aeroallergen-related allergies

The role of aeroallergens in AD has been less studied than that of food allergens, but research has demonstrated a subset of patients with AD who have exacerbations of their disease secondary to exposure to aeroallergens. As mentioned earlier, the airborne proteins most commonly implicated are from house dust mites and cockroaches, and others include proteins from pet dander and pollen.[1,16]

Interventional studies have looked at the role of prevention of atopic disease in children through early avoidance of allergens. The Isle of Wight Allergy Prevention Study demonstrated a reduction in childhood atopic disease (to the age of 8 years) through the use of food allergen and house dust mite allergen avoidance in infancy.[17] This, however, has not been demonstrated in all studies: the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study showed an inverse relationship between house dust mite exposure and AD in infancy.[18] Given the conflicting results of existing research, further studies into the role of aeroallergens and AD are warranted.

Indications for aeroallergen-specific IgE testing

Aeroallergen-specific IgE testing with skin prick testing and serum IgE levels is indicated in children with AD unresponsive to conventional management and a concomitant diagnosis of asthma and/or allergic rhinitis. Infants rarely develop specific IgE to aeroallergens and thus testing in this age group is often negative. Testing is further supported by a history of seasonal exacerbations of AD and/or AD in an air-exposed skin distribution (face, neck, arms and lower legs, with sparing of the trunk).[16]

Interpretation of aeroallergen-specific IgE tests

The interpretation of aeroallergen testing results is a contentious area, with limited supporting evidence. Many children with eczema will have specific IgE to one or more aeroallergens.

Exposure to house dust mite can be reduced and a trial of reduction may be indicated in children with AD; a response to avoidance suggests a house dust mite allergy. Many children with AD have perennial allergic rhinitis triggered by house dust mite, and avoidance measures would be indicated for management of the rhinitis. Studies to support this are limited, with poor evidence for definitive recommendations, but there appears to be no adverse outcomes from a trial of house dust mite reduction.[19] Exposure to seasonal aeroallergens (pollen and moulds), however, cannot be avoided.

Allergic contact dermatitis

Allergic contact dermatitis may mimic or complicate AD. However, it usually manifests within days (rather than minutes or hours) of exposure in areas of skin directly in contact with the allergen, although in severe cases it can extend beyond the area of contact.[20] The delayed response of allergic contact dermatitis reflects its aetiology as a type 4 hypersensitivity reaction. Also, it may present with localised erythema, papules and vesicles on inflamed skin, as opposed to a generalised erythematous, pruritic reaction with AD.

The agents most commonly implicated in allergic contact dermatitis in children are nickel and cobalt, but reactions to topical therapies (especially to the preservative and fragrance components), plants, rubber chemicals, dressings and numerous other agents may be responsible.[21,22] Although allergic contact dermatitis has previously been thought to be uncommon in children, recent studies have shown an incidence of about 8% in adolescents in Denmark (diagnosis confirmed by clinically relevant patch testing).[23]

Testing for allergic contact dermatitis

Epicutaneous patch testing is useful in children with localised or regional dermatitis or suspected allergic contact dermatitis where the trigger is not obvious.

Usually undertaken by dermatologists, patch testing assesses delayed type hypersensitivity, with allergens selected from a

large range of possible agents including metals, preservatives, plants, components of creams and environmental exposures. The usual procedure involves application to the individual's back of 20 to 40 known and standardised antigenic substances, which are retained with adhesive tape for 48 hours. Readings are required two and four days after initial application, and positive reactions (localised erythema, induration or vesicles) require careful and experienced interpretation. Specialised dermatology input is required if allergic contact dermatitis is suspected.

Patch testing may be considered or undertaken when the history suggests topical exposures or contacts aggravate eczema, or when the distribution of eczema is characteristic (examples of patterns include predominant hand dermatitis, rashes in areas of metal exposure, scalp and eyelid dermatitis and foot dermatitis).

Conclusion

There are numerous potential allergens involved in the exacerbation of atopic dermatitis in children. A careful history of allergy should be obtained, and children with severe or refractory AD should be further investigated. Specialist referral and assessment may be required for further management and investigation, based on interpretation of eczema flares after allergen exposure, clinical manifestations (including the pattern and regions affected) and response to treatments. MT

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COMPETING INTERESTS: None.

Treatment of actinic keratoses

Be sure first

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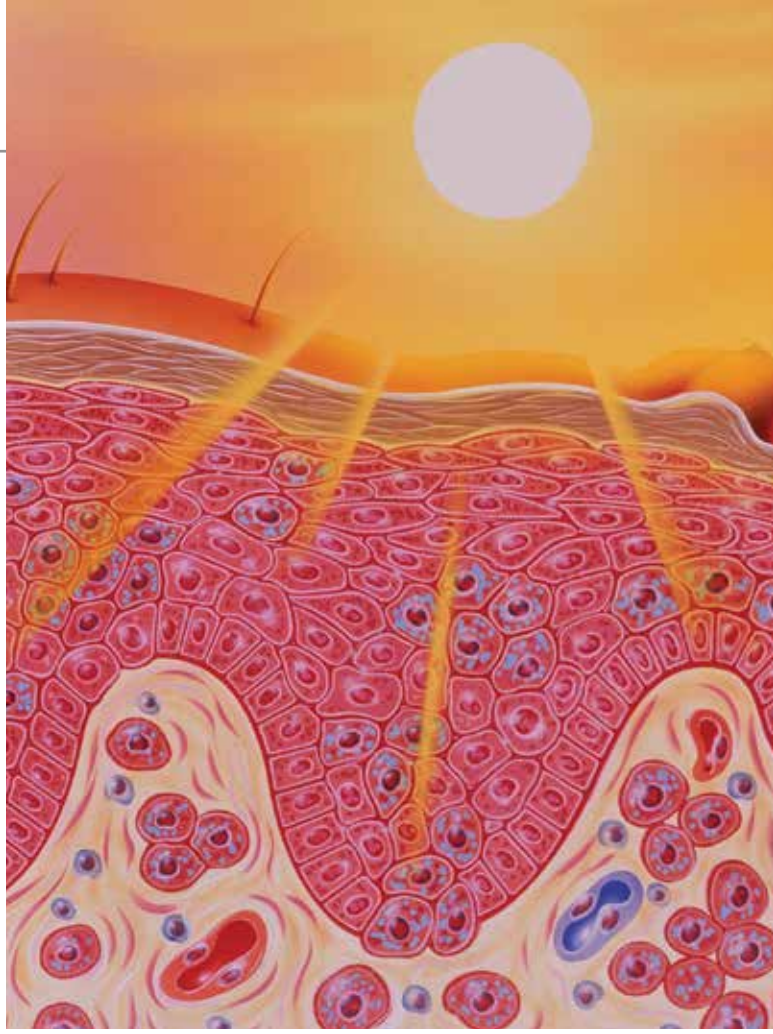
Actinic keratoses are clinically important because they have the potential to develop into squamous cell carcinomas. Treatment is aimed at preventing this transformation and at symptomatic and cosmetic improvement.



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KEY POINTS

- Actinic keratoses (AKs) are extremely common – about 40 to 60% of Caucasians in Australia will have at least one AK by the age of 40 years.
- AKs are localised proliferations of atypical epidermal keratinocytes that develop most often as a consequence of cumulative exposure to UV radiation but also as a result of immunosuppression, human papillomavirus infection and arsenic exposure.
- AKs are most commonly found on sun-exposed areas such as the scalp, face and forearms.
- AKs may develop into squamous cell carcinomas (SCCs), and therefore are strong predictors of the subsequent development of nonmelanoma skin cancers.
- If thickening, bleeding or tenderness are present in an AK, malignancy should be excluded before treatment is commenced.
- Patients at high risk of SCC should have their AKs biopsied if there is any doubt about the diagnosis.
- Traditional lesion-directed therapies such as cryotherapy are still popular; however, newer therapeutic options offering field therapy, such as photodynamic therapy, ingenol mebutate gel and imiquimod cream, provide more options for treatment of AK, including subclinical disease. They have similar efficacy but a superior adverse effect profile, albeit at a higher cost.

Actinic keratoses (AKs), which are also known as solar keratoses, are superficial cutaneous lesions consisting of localised proliferations of atypical epidermal keratinocytes. They develop most commonly as a consequence of prolonged exposure to ultraviolet (UV) radiation.

AKs are clinically important because they are considered premalignant lesions with the potential to develop into squamous cell carcinomas (SCCs). They therefore represent strong predictors of the subsequent development of nonmelanoma skin cancers. Treatment is aimed at achieving the highest cure rate without complication and with the best cosmetic outcome.[1] Currently, there are multiple modalities for treatment using lesion-directed or field therapy. The choice of treatment may be influenced by the location, thickness and number of lesions, the cost, convenience and compliance of the patient.[1]

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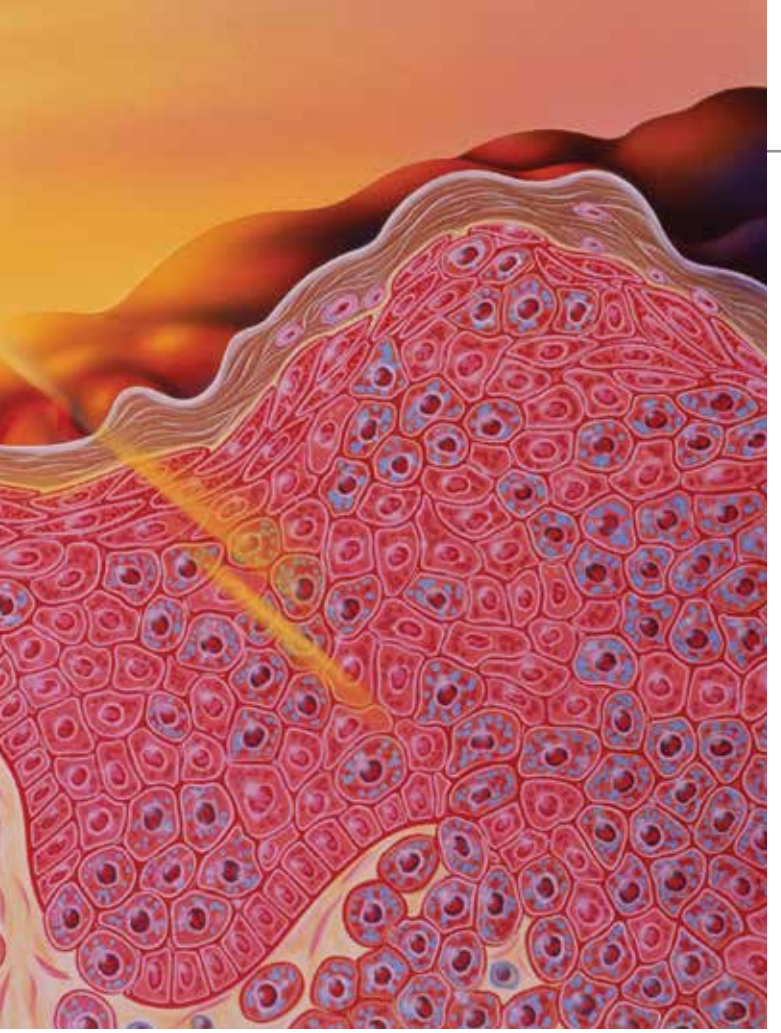

Epidemiology and natural history

The most important aetiological factors in the development of AKs are cumulative UV radiation exposure (including tanning bed use) and individual susceptibility. Individual susceptibility factors include advancing age and phenotypical characteristics, such as fair skin that burns easily and tans poorly, blue eyes and red or blond hair.[1]

UV radiation, in particular UVB, is the most important aetiological factor in the development of AK. UV radiation causes specific DNA mutations in the p53 tumour suppressor gene. Most AKs demonstrate this signature mutation. The same types of genetic mutations are seen in SCC, which supports the notion of the potentially malignant nature of AK.[1] As well as UV radiation, several other factors have been implicated in the aetiology of AK, such as immunosuppression, human papillomavirus (HPV) infection and exposure to arsenic.[1]

The prevalence of AKs in the Caucasian population in Australia is 40 to 60%, as compared with 11 to 25% in the USA and 6 to 15% in northern England.[1-4] In Australia, it has been estimated that 40 to 60% of Caucasian individuals aged 40 years or older will have at least one AK lesion.[1]

AKs are considered precancerous lesions because most SCCs are associated with adjacent or contiguous AKs.[5] Most SCCs developing in one monitored population arose within pre-existing AKs.[6] Some authors consider AKs to represent incipient intraepidermal carcinomas, but the potential for the malignant transformation of AKs to SCCs is not exactly known; reported rates range from 0.025% to 16% per year.[7,8] In addition, AKs may spontaneously regress at a rate reported to be from 15 to 25% over a one-year period.[9,10]

Clinical presentation

The presentation of AKs is typically that of erythematous scaly macules or papules that are 2 to 6 mm in diameter. The lesions may be discrete or confluent, forming plaques.

Classically, AKs are more easily felt than seen, but they may also present as variants that are thickened or hypertrophic, associated with a cutaneous horn, or pigmented. They occur predominantly on chronically sun-exposed skin, such as the head and neck, forearms and dorsa of hands (Figures 1 and 2). Although they are largely asymptomatic, they may be pruritic, burning or stinging and can also bleed or crust.

Diagnosis and differential diagnoses

Histopathologically, AKs are characterised by foci of atypical, pleomorphic keratinocytes along the basal layer of the epidermis,

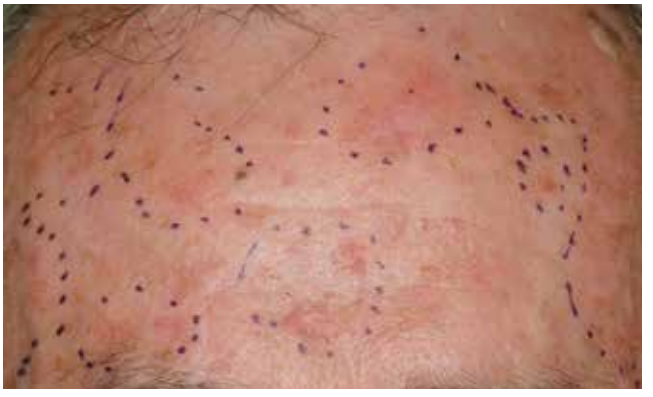

Figure 1. Actinic keratoses on the scalp. Prolonged sun exposure is the major cause of these superficial cutaneous lesions.

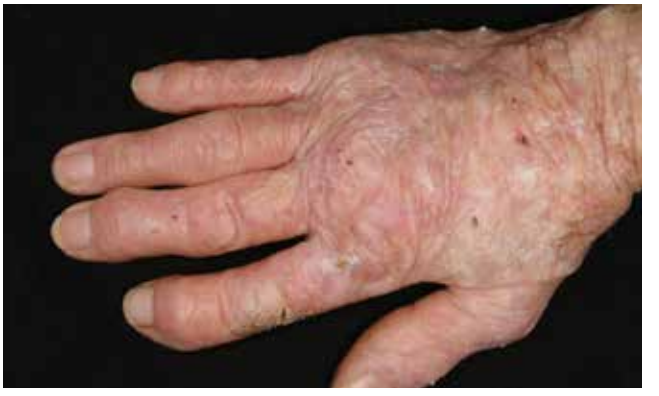

Figure 2. Actinic keratoses on the hand in a transplant recipient. Chronic immunosuppression is a risk factor for the development of these lesions.

1. THE DIFFERENTIAL DIAGNOSES OF ACTINIC KERATOSES

Erythematous actinic keratoses

- Irritated seborrhoeic keratosis
- Lichenoid keratosis
- Squamous cell carcinoma in situ (Bowen's disease, intraepidermal carcinoma)
- Superficial basal cell carcinoma
- Psoriasis

Hypertrophic actinic keratoses

- Squamous cell carcinoma
- Discoid lupus erythematosus
- Porokeratosis
- Verruca vulgaris

Pigmented actinic keratoses

- Solar lentigo
- Flat or macular seborrhoeic keratosis
- Lentigo maligna

with sparing over the adnexal structures. The diagnosis of AK is regularly made clinically without a biopsy. However, it is important to bear in mind that clinical diagnostic accuracy among dermatologists has been reported to be as low as 74% with most misdiagnosed lesions being some form of skin cancer.[6] In light of this, the threshold for biopsy should be lower in high-risk patients.

The differential diagnoses of classical erythematous AK, hypertrophic AK and pigmented AK are listed in Box 1. The clinical grading used to assess the severity of individual AK lesions is presented in Box 2.[11]

Management

Given that the rate of malignant transformation of AKs is not exactly known, some clinicians feel that definitive treatment of AKs is not universally required solely on the basis of preventing progression to SCCs. However, as 3 to 4% of SCCs will metastasise, other clinicians advocate early treatment of AKs to avoid the need for more extensive treatment in the future.[12]

Treatment should certainly be discussed if AKs are causing symptoms or disfigurement. If features such as thickening, bleeding or tenderness are present, a biopsy should be performed of the thickest area before treatment to exclude malignancy (Box 3). It is likely that repeated treatments would be required at intervals, because new AKs tend to develop over time.

Treatment options are discussed below and listed in Box 4 and the Table. Treatment is aimed at achieving the highest cure rate without complication and with the best cosmetic outcome. The choice of treatment may be affected by the site and size of the lesion, cost, convenience and compliance of the patient.[1]

Topical treatments

Emollients

In one study in which emollients were used as the placebo arm, resolution of AKs was seen in up to 34% of patients after 60 days of use.[13] It is likely, however, that emollients reduce the clinical manifestations of AKs rather than reverse the biological processes.

Sunscreens

Sunscreens have a combined emollient and photoprotective effect on AKs. Sunscreen use has been shown to decrease UVB-induced p53 mutations as well as UV-induced immunosuppressive effects.[14]

In a study carried out in Queensland, a single-daily application of sunscreen (sun protection factor 16) was associated with a 24% reduction in AK development over a two-year period, compared with discretionary use of the same sunscreen.[15] A shorter study found resolution of 24.6% of clinically diagnosed AKs over a six-month period with daily sunscreen application (sun protection factor 17).[16]

Salicylic acid

Salicylic acid preparations act primarily as emollients for mild AKs, but also provide a small additional benefit based on the keratolytic effects. A common formulation is 2 to 5% salicylic acid in sorbolene.

2. CLINICAL GRADING TO ASSESS THE SEVERITY OF SINGLE ACTINIC KERATOSES LESIONS[11]

- Grade 1 = Mild: slightly palpable, with lesion felt better than seen
- Grade 2 = Moderate: moderately thick actinic keratoses that are easily seen and felt
- Grade 3 = Severe: very thick hyperkeratotic lesions

3. CLINICAL INDICATIONS FOR BIOPSY

- Unclear clinical diagnosis
- Unresponsive lesion (no regression or early recurrence despite adequate therapy)
- Concerning clinical features:
  - ulceration
  - induration
  - bleeding
  - diameter >1 cm
  - rapid enlargement
  - pain
  - hyperkeratosis
  - pigmentation

Salicylic acid may also be used to prepare the treatment area before the application of topical 5-fluorouracil (5-FU) cream or photodynamic therapy (PDT) in order to reduce overlying keratin.

Diclofenac gel

Diclofenac 3% in 2.5% hyaluronan gel is considered to be a treatment with moderate efficacy and is used primarily to treat mild AKs. Topical diclofenac is generally well tolerated and side effects consist mainly of pruritus and rash.

The mechanism of action of diclofenac, an NSAID, in the treatment of AKs is not well understood but may be related to the countering of the increased prostaglandin levels in AK lesions through inhibition of inducible cyclo-oxygenase (COX; with preferential COX-2 selectivity over COX-1), and hence inhibition of prostaglandin

4. TREATMENT OPTIONS FOR ACTINIC KERATOSES

Topical treatments

- Emollients
- Sunscreens
- Salicylic acid 2 to 5%
- Diclofenac 3% in 2.5% hyaluronan gel
- 5-Fluorouracil 5% cream
- Imiquimod 5% cream
- Ingenol mebutate gel (0.015% or 0.05%)

Cryotherapy

Photodynamic therapy

Curettage and surgical excision

Other treatments

- Retinoids (oral and topical)
- Ablative lasers (carbon dioxide or erbium:YAG lasers)
- Dermabrasion
- Chemical peels (35% trichloroacetic acid)
- Nicotinamide

TABLE. SUMMARY OF SOME TREATMENT INTERVENTIONS AND MODE OF APPLICATION

Intervention	Mode of application
Curettage	Once, repeated up to two times
Cryotherapy	Once, for about 5 to 15 seconds per lesion, repeated up to several times
Carbon dioxide laser	Once, repeated up to several times
Er:YAG laser	Once, repeated up to several times
5-aminolevulinic acid	Conventional photodynamic therapy: single treatment. Incubation of at least one hour before illumination
Methylaminolevulinate	Conventional photodynamic therapy: single treatment. Incubation of two to three hours before illumination Daylight photodynamic therapy: single treatment. Incubation of up to 30 minutes before exposure to visible light for two hours
3% Diclofenac in 2.5% hyaluronic acid gel	Twice-daily application for 60 to 90 days
5-Fluorouracil	Once- or twice-daily application for two to four weeks
Imiquimod 5%	Once-daily application for two to three days per week for four to 16 weeks; continuously or intermittent
Ingenol mebutate 0.015% for lesions on the face or scalp	Once-daily application for three days
Ingenol mebutate 0.05% for lesions on the trunk or extremities	Once-daily application for two days

synthesis. Lipoxygenase is also inhibited. Diclofenac in hyaluronan gel induces apoptosis, inhibits cell proliferation and suppresses angiogenesis.

Two randomised, vehicle-controlled trials have demonstrated a significant difference in AK clearance following twice-daily treatment with diclofenac 3% gel. In one trial, there was resolution of 70% of target lesions in the active arm after 60 days of treatment compared with 34% in the control arm. In the other trial, 50% of patients in the active arm achieved a target lesion number score of zero after 90 days of treatment versus 20% in the control arm.[13,17]

It is recommended that diclofenac 3% in 2.5% hyaluronan gel be applied twice daily for 60 to 90 days.

Cost is a potential limitation for the use of topical diclofenac in the treatment of AKs because it is not listed under the Pharmaceutical Benefits Scheme (PBS) for subsidy for this indication unless patients are eligible under the Repatriation Pharmaceutical Benefits Scheme (RPBS). To qualify, the patient must be a candidate for topical field therapy for clinically visible and subclinical lesions where other standard treatments are inappropriate. A 25 g tube costs about A$57.

5-Fluorouracil

5-FU is a cytotoxic agent that is selective for dysplastic keratinocytes. It acts by inhibiting thymidylate synthetase (which is needed for DNA synthesis) and possibly also by interfering with the formation and function of RNA. Cytotoxic metabolites formed intracellularly from 5-FU induce cell cycle arrest and apoptosis.

5-FU therapy has been a mainstay of topical treatment for AKs for more than 30 years, with efficacy confirmed by a wide range of open trials and dose-ranging studies, as well as two randomised controlled trials. A trial of a three-week, twice-daily application of 5-FU in the currently available formulation of a 5% cream showed a mean reduction of 78% of lesions on the face at 12 months.[18] A similar trial showed a mean reduction of 70% of lesions on the hands at six months.[19] A more recent randomised clinical trial of 5% cream applied twice-daily to the face for four weeks showed a mean reduction of 73% at six months.[20]

Many different treatment regimens have been proposed for topical 5-FU, but the standard regimen usually consists of once- or twice-daily application to the entire affected region (field treatment) for two to four weeks. The total area of skin being treated should at any one time not exceed

500 cm^2. Larger areas should be treated a section at a time.

Treatment is usually ceased when the patient reaches certain clinical 'endpoints', such as change of skin colour to dusky red, widespread crust formation or increasing pruritus. Local adverse effects such as pruritus should be anticipated, with 90% of patients treated experiencing moderate to severe skin irritation.[21] Use of 5-FU may also uncover incipient AKs, and areas of skin where no AKs are visible can become inflamed during treatment.

To reduce the side effects of topical application of 5-FU, some clinicians reduce the frequency of dosing but increase the duration of application (for example, from daily application for three to four weeks to once- or twice-weekly application for three months). The evidence for the efficacy of such regimens is conflicting. A potential limitation in the use of 5-FU cream to treat AKs is cost, because it is not listed under the PBS for subsidy for this indication unless patients are eligible under the RPBS. The cost for a 20 g tube is about A$64.

Imiquimod

Imiquimod is an immune-response modifier that stimulates the innate immune response by inducing the synthesis and release of cytokines via binding to the cell surface Toll-like receptor 7 on immune cells, resulting in direct antitumour effects. It also indirectly stimulates cell-mediated immunity, leading to further cytokine production. In Australia, imiquimod has been approved by the Therapeutic Goods Administration (TGA) for the treatment of AK, superficial BCC, and genital and perianal warts.

The standard treatment regimen for AKs is imiquimod 5% cream applied on two to three days per week for up to 16 weeks (typically three to four weeks followed by a break from therapy). The maximum recommended dose per application is one sachet.

After one to two weeks of therapy, the treatment area may be expected to become erythematous, crusted or eroded. If the reaction is too severe, patients can interrupt treatment for one to two weeks before restarting therapy. Systemic adverse effects may occur with imiquimod use, including interferon-like side effects such as flu-like symptoms, headaches and myalgias.

Large multicentre randomised controlled trials have demonstrated imiquimod to be effective in clearing AKs in 48 to 57% of cases.[22,23] In addition, the clearance of AKs is more common in patients who develop intense application site reactions.[24] One study has reported treatment with imiquimod has a superior field effect and sustained 12-month clearance of a complete treatment field compared with treatment with cryotherapy or 5-FU (sustained clearance was 73% for imiquimod, compared with 4% for cryotherapy and 33% for 5-FU).[25] A potential limitation in the use of imiquimod cream to treat AKs is cost, as it is not listed under the PBS for subsidy for this indication unless patients are eligible under the RPBS. The cost for 12 x 250 mg sachets is approximately A$100 and A$105 for the more convenient pump.

Ingenol mebutate gel

Ingenol mebutate gel is a macrocylic diterpene ester, originally isolated from the sap of an indigenous Australian plant, *Euphorbia peplus*.[26] It has a dual mechanism of action involving rapid induction of primary necrosis followed by neutrophil-mediated, antibody-dependent cellular cytotoxicity of residual diseased cells mediated by protein kinase C activation.[27]

Large multicentre randomised controlled trials have demonstrated ingenol mebutate gel to be effective in clearing AKs after two to three days of field treatment. One study reported complete clearance in 42% of patients with treatment of the face and scalp and complete clearance in 34% with treatment of the trunk and extremities.[28]

Currently in Australia, the gel is available in two strengths for the treatment of AK (0.015% and 0.05%), the lower strength for the face and the higher for the extremities. Treatment is typically for two (trunk and limbs) or three (head and neck) consecutive days on a surface area of 25 cm^2.

Application site reactions such as pain, irritation, infection, periorbital oedema, nasopharyngitis and headache have been observed in clinical trials.[27-29] The most common local skin responses were dose-related erythema, flaking and dryness of skin, and crusting that resolved within four weeks.[27-29] Local reactions peaked at day four in most studies.[28]

The benefit of ingenol mebutate gel is the short treatment duration of two to three days, which may result in higher adherence to treatment. A limitation in the use of ingenol mebutate gel is cost, because it is not listed under the PBS for subsidy for this indication unless patients are eligible under the RPBS. The cost for either 0.015% or 0.05% gel is about A$138.

Cryotherapy

Cryotherapy with liquid nitrogen (boiling point, -195.8°C) is traditionally the most common treatment for AKs because of its low cost, ease of application and efficacy. Although clearance rates of as high as 98.8% have been described,[30] other randomised comparison studies have reported somewhat lower overall complete clearance rates of lesions, ranging from 68% (single freeze–thaw cycle) to 75% (double freeze–thaw cycle).[31,32]

The recommended freeze time for the treatment of AKs is about 5 to 15 seconds, depending on the lesion thickness. Cryotherapy can cause considerable localised pain, particular in sensitive areas such as the head and neck, both during and following treatment. Cryotherapy also nonselectively destroys healthy tissue within the treatment field, and treatment is followed by erythema, swelling and occasionally blistering. Another significant potential complication of cryotherapy is hypopigmentation, because melanocytes are exquisitely sensitive to cold temperatures. Hypopigmentation occurred in 29%

of cases in one report and appeared to be more likely with increasing freeze times.[33] Nevertheless, the cosmetic outcomes of cryotherapy are generally considered to be good to excellent.

Photodynamic therapy

PDT involves the application of a photosensitising agent to a selected treatment area before exposure to a red light-emitting diode lamp or, more recently, exposure to daylight.

Conventional PDT consists of the application of 5-aminolevulinic acid (5-ALA) or its methyl ester, methylaminolevulinate (MAL), which is converted intracellularly via the haem biosynthetic pathway to photoactive porphyrins (predominantly protoporphyrin IX), followed by irradiation with a dedicated light source of 405 to 635 nm wavelength. Application under occlusion must occur for one hour (5-ALA) or two to three hours (MAL) before illumination.

Daylight PDT involves application of MAL cream to a selected treatment area before exposure to daylight, using visible light as the photoactivating source. The irradiation of the photoactive porphyrins in the presence of oxygen results in the production of reactive oxygen species (such as singlet oxygen and hydroxyl radicals) that cause cell death. Selective destruction of neoplastic cells by apoptosis and necrosis is achieved through the increased absorption of the photosensitising agent within target cells compared with the absorption by normal keratinocytes.

Conventional PDT has been shown in randomised controlled trials to be as efficacious as cryotherapy in the treatment of AKs, with overall complete clearance rates ranging from 69 to 93% for PDT compared with 68% (single freeze–thaw cycle) to 75% (double freeze–thaw cycle) for cryotherapy.[25,31,32,34-36] The use of two MAL–PDT sessions one week apart compared with single treatment results in greater clearance rates for thicker lesions (84% *vs* 70%, respectively) but similar rates for thin lesions (89% *vs* 93%, respectively).[36] In these studies, cosmetic outcome was generally superior and patient preference was generally greater for PDT compared with cryotherapy.

When used on nonface or scalp areas, however, MAL-PDT was reportedly inferior in efficacy when compared with cryotherapy (the mean percentage reduction of lesion count being 78% for MAL-PDT and 88% for cryotherapy) but the cosmetic outcome was significantly better.[37] Although conventional PDT is efficacious, the common adverse effects of burning, stinging and associated pain are an impediment for patients with widespread lesions on the face and scalp. In addition, conventional PDT requires relatively long incubation periods of two to three hours, which can be inconvenient for patients.[38] It also requires dedicated equipment, which can limit availability and increase costs.[38]

Daylight PDT is a simple new treatment option for AK that offers advantages over conventional PDT, allowing large areas of actinic damage to be treated with reduced in-clinic treatment times, cost and improved tolerability.[38] The efficacy and safety of daylight PDT has been assessed in four randomised trials in Europe[39-42] and one in Australia.[43] The European trials demonstrated a greater than 70% response rate in grade I lesions.[38] The Australian study compared conventional PDT (c-PDT) and daylight PDT and demonstrated that daylight PDT was not inferior to conventional PDT with lesion response rates of 89% and 93%, respectively.[43] Participants reported significantly less pain with daylight PDT compared with c-PDT.[43]

Based on available data daylight PDT is recommended for treatment of grade I and II AKs on the face and scalp of patients who require field treatment. Daylight PDT is not recommended for treatment of grade III (hyperkeratotic) lesions.[38] Daylight PDT can be completed in all weather conditions with the exception of rain, dependent on patient's tolerability to heat, cold or humidity.[38] Patients are advised to apply a chemical-based sunscreen before treatment to avoid sunburn.[38] A physical-based sunscreen, such as a zinc oxide- or titanium oxide-based formula, is not recommended because it does not block out visible light.[38] Limitations of daylight PDT include restrictions in certain weather conditions, limited to areas that can be exposed to visible light, treatment time and cost.[38]

The use of PDT is potentially limited by cost because it is currently not listed on the PBS or Medicare Benefits Schedule for subsidy or reimbursement when used for the treatment of AK. Nevertheless, a recent study in Belgium showed that PDT was cost-effective in the treatment of AKs compared with cryotherapy over a one-year period (at 58 Euros [about A$85] per lesion), in line with previous economic modelling.[44]

Surgical treatments

Curettage and surgical excision are sometimes used in the treatment of AKs. No studies have examined the efficacy of these treatments but they are of particular value in determining the histopathological nature of atypical AKs unresponsive to other therapies, especially where invasive SCCs need to be excluded. Disadvantages of curettage and surgery include the need for a local anaesthetic injection and the possibility of infection and scarring.

Other treatments

Retinoids

Use of a retinoid normalises keratinisation and reduces the dysplasia of AKs. Oral retinoids (acitretin is used in Australia) are used in selected patients, such as organ transplant recipients, to reduce cutaneous carcinogenesis. However, their use may be limited by adverse effects such as cheilitis, excessive peeling, headaches and dyslipidaemia, as well as the potential for rebound flaring of carcinogenesis once treatment is ceased.

Topical retinoids such as adapalene and tretinoin have been shown to be effective in treating AKs in some patients but are not approved by the TGA for this use. A

regimen of tretinoin 0.1% applied twice daily for 15 months resulted in a lesion response rate of 73%, compared with 40% for placebo.[45] Topical retinoids are generally well tolerated but mild local reactions, such as photosensitivity, peeling, erythema and dryness, may occur.

Ablative lasers

Carbon dioxide or erbium: YAG (erbium-doped yttrium aluminium garnet) lasers may be used to treat AKs.[46,47]

Dermabrasion

Dermabrasion may be an effective treatment for AKs, with one study showing 96% of patients remaining free of AKs at one year.[48]

Chemical peels

In the treatment of widespread facial AKs, 35% trichloroacetic acid chemical peels have been found to have similar efficacy to 5% 5-FU with improvement sustained at 12 months.[18]

Nicotinamide

Nicotinamide is an amide form of vitamin B3, an essential water-soluble vitamin that is not stored in the body. It is maintained by dietary intake of vitamin B3 and tryptophan.[49] Nicotinamide is the precursor of nicotinamide adenine dinucleotide (NAD), a key coenzyme in the production of adenosine triphosphate (ATP), required for the transportation of chemical energy within cells.[49] Nicotinamide is also the sole substrate and inhibitor of the nuclear enzyme poly-ADP-ribose polymerase 1 (PARP-1), which is activated by UV radiation.[49] PARP-1 has several important cellular properties, such as DNA repair and genomic stability, as well as regulation of transcription factors in particular the expression of proinflammatory cytokines, chemokines and inflammatory mediators.[49] Adequate cellular energy and properly functioning PARP-1 appear to be necessary for nicotinamide to have a beneficial effect in the treatment of several skin conditions, such as AK.[49]

Two phase 2 double-blind randomised controlled trials comparing 500 mg of oral nicotinamide with placebo twice daily showed a 35% and 29% reduction in AK, relative to the placebo group, at four months.[50] Another double-blind randomised controlled trial compared the effect of twice daily topical 1% nicotinamide on AK. At three months, the nicotinamide group had a 22% reduction in AK compared with a 10% reduction in the placebo group. However, at six months the difference between the two groups was similar (25% in the nicotinamide group and 22% in the placebo group).[51] Nicotinamide is now included in some commercially made sunscreens in Australia.[50]

Conclusion

AKs are a common dermatological condition, particularly in Australia. Treatment is aimed at the prevention of transformation to SCCs, as well as symptomatic and cosmetic improvement. There are multiple treatment options, the most commonly used being cryotherapy and topical therapies (such as 5-FU cream). Other available effective treatments include PDT, diclofenac gel and imiquimod cream, but their use may be limited by cost. MT

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A list of references is included in the website version of this reprint collection (www.medicinetoday.com.au).

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Treatment of actinic keratoses

Be sure first

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Postadolescent acne in women

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Increasing numbers of women worldwide continue to have acne after adolescence or develop it when in their twenties to forties. It is important to recognise these patients because they may have underlying hormonal abnormalities and may benefit from hormonal therapy.

KEY POINTS

- Female postadolescent acne may be acne continuing past the teenage years or acne developing at or after the age of 20 years.
- Affected women may have normal or raised serum androgen levels.
- Polycystic ovary syndrome may be an underlying cause of female postadolescent acne.
- Assessment should include a menstrual history and examination for clinical signs of hyperandrogenism, such as hirsutism.
- Hormonal therapy (usually the combined oral contraceptive pill) is an effective adjunct in the management of these patients, including those with normal serum androgen profiles. Other antiandrogens, such as spironolactone or cyproterone acetate, may need to be taken in addition to the pill.

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Acne vulgaris is a common, self-limiting disorder affecting adolescents and teenagers. Acne may, however, continue or develop after the age of 20 years, and may even persist until menopause.

Women with acne fall into two subtypes: those with postadolescent acne that persists from teenage years into later life and those with late-onset acne who develop pimples at or after the age of 20 years and who have not had acne during their teens. It is important to recognise female patients with postadolescent acne as a distinct group because:

- the number of women affected worldwide is increasing
- the psychosocial effects of acne in this group may be profound and disproportionate to the severity of acne – many women find that their acne affects their working life or professional careers (such as when having to give office presentations or deal with clients)
- some women may have abnormal serum androgen levels that require further investigation
- these patients typically respond well to hormonal therapy alone or as an adjunct to other acne therapy, even in the presence of normal laboratory investigations.

Acne, hormones and the sebaceous gland

Acne is a complex multifactorial disorder. Its pathogenesis involves:

- abnormal keratinisation of the pilosebaceous opening
- increased sebum production by the sebaceous gland
- colonisation by *Propionibacterium acnes*
- inflammation.

Blockage of the sebaceous duct by abnormal keratinisation produces a microscopic plug (a microcomedo). Colonisation of pilosebaceous ducts by the bacterium *P. acnes* contributes to an inflammatory response that manifests as papules, pustules and inflammatory cysts. Effective acne management involves targeting these steps; often combination therapy is used to target as many pathogenic factors as possible.

Sebaceous glands are found throughout the body and are present in greatest quantity and density on the face. They secrete sebum in response to androgenic stimulation. In general, patients with acne produce more sebum than those without acne, and sebum production is greater in those with more severe acne.

Under normal conditions, the ovaries contribute about 50% of the circulating androgens in women. Overproduction of

androgens by the ovaries can occur in conditions such as polycystic ovary syndrome (PCOS) or ovarian tumours. The adrenal glands contribute the remaining 50% or so of circulating androgens in women. Stress may be a trigger by increasing adrenal androgen production that then stimulates increased sebum production.

Detailed discussion of PCOS[1] and other hormonal causes of acne, such as ovarian tumours or congenital adrenal hyperplasia, are beyond the scope of this article, as is also steroid ingestion as a cause.

Recognising postadolescent acne

History

The clinical history of a woman with acne should include enquiry about the factors discussed below and summarised in Box 1.

Age of onset

At what age did pimples start?

Some patients have acne that started with the onset of menstruation (i.e. when they were in their teens) while other patients develop acne when they are in their twenties or older.

Distribution of acne lesions

Where did the pimples start or spread to?

In some patients, the clinical pattern of postadolescent acne may look indistinguishable from teenage 'T zone' acne, which affects the forehead, nose and chin with or without upper chest and upper back involvement (Figure 1). In other patients, there is a more 'hormonal' distribution, with the lower third of the face being affected, particularly the lower cheeks, jawline, chin and neck (Figure 2). The trunk may also be affected and most patients will note seborrhoea or a greasy skin.

Duration of acne lesions

How long do the individual lesions last?

Patients may complain that their current acne lesions tend to last longer than lesions that occurred during adolescence – for weeks rather than days.

Characteristics of acne lesions

Do the pimples recur in the same area? Are there any symptoms?

Patients often report that their pimples are tender or feel 'blind'. Some describe their face as hurting. The lesions may last for weeks, heal and then recur weeks or months later in the same area. There may be post-inflammatory redness or pigmentation lasting for weeks or months as the lesions are resolving, and this is often very distressing for the patient. The inflammatory and chronic nature of these pimples may also lead to scarring (Figure 3).

Menstrual history

Is there any correlation of the pimples with the menstrual cycle?

It is common for the pimples to start a week prior to menses and continue for one to two weeks. Some patients will notice pimple activity at ovulation.

A careful menstrual history is

1. HISTORY CHECKLIST FOR POSTADOLESCENT ACNE

- Age of onset of acne – during teens or later?
- Distribution of acne lesions – 'T zone' or 'hormonal' (affecting lower face and neck)?
- Duration of acne lesions – weeks rather than days
- Characteristics of acne lesions – recurrence in same area, tenderness, greasy skin
- Menstrual history – irregular periods, premenstrual exacerbation of acne
- Symptoms of hyperandrogenism – deepening voice, increased libido, hirsutism, male-pattern baldness
- Family history
- Lifestyle factors – make-up, sports headgear
- General medical history, including medication use – e.g. phenytoin, lithium

Figure 1. Postadolescent acne. In this patient the distribution of the lesions is similar to that in adolescent acne although the forehead and nose parts of the 'T zone' are relatively spared and most of the lesions are on the cheek.

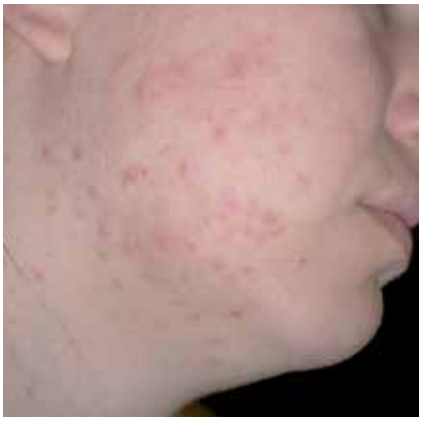

Figure 2. Postadolescent acne. Note the typical 'hormonal' distribution of lesions for late-onset acne: the lower cheeks, jawline, chin and neck.

important in the assessment of a woman who has late-onset acne. About 60 to 70% of women may complain of worsening of their acne on a cyclical basis, usually premenstrually. An irregular menstrual cycle may suggest underlying hyperandrogenism and the presence of PCOS. It may be worthwhile for the patient to chart her menstrual cycle because patients often assume their cycle is regular. Menstrual irregularity is defined as amenorrhoea for more than three months or irregularity of the menstrual cycle of greater than seven days from a standard 28-day cycle over three consecutive cycles.

Hyperandrogenism

Are there features of hyperandrogenism other than menstrual irregularity?

Features of hyperandrogenism other than menstrual irregularity may need specific enquiry; these features are listed in Box 2. Hirsutism may not be readily evident because patients may have had hair removed by a variety of means, such as waxing, electrolysis or laser. Mild hirsutism and irregular menstrual cycles have been reported in up to 29% and 14%, respectively, of these women.[2]

Obesity, hirsutism and irregular menstrual cycles are features of PCOS but are not always present in women with the syndrome. Data are conflicting regarding the number of women with postadolescent acne who have underlying PCOS; figures range between 10 and 50%.[3] Although it is beyond the scope of this article to discuss the diagnosis and management of PCOS, it should be noted that the diagnosis can be difficult in some cases because there are no universally accepted diagnostic criteria for PCOS.[4]

Family history

Do the patient's mother or sisters have acne?

One study has shown that 50% of patients had a first-degree relative who also had postadolescent acne.[2]

Lifestyle factors

Are there lifestyle factors that may promote or exacerbate acne?

Many patients report flares of acne when they are feeling increased stress.[5] Creamy or 'greasy' cosmetics may promote plugging of the pilosebaceous follicle opening and are comedogenic. Some patients may be in occupations where heat may play a role, such as working in kitchens.

Friction or trauma due to occlusive headgear (such as worn in cycling, rollerblading or softball) may rupture existing comedones and bring about inflammatory lesions.

General medical history

What is the general health of the patient?

Certain drugs taken for coexisting medical problems may exacerbate acne. Phenytoin and lithium are examples.

Examination

Postadolescent acne may be clinically indistinguishable from adolescent acne.[6] The examination should focus on:

- the distribution of lesions – lower cheeks, jawline, chin, neck, trunk
- the severity – nodules, cysts, scarring
- any psychological distress – how does the patient feel, does it stop her from doing any activity?
- features of hyperandrogenism – especially hirsutism or androgenic alopecia.

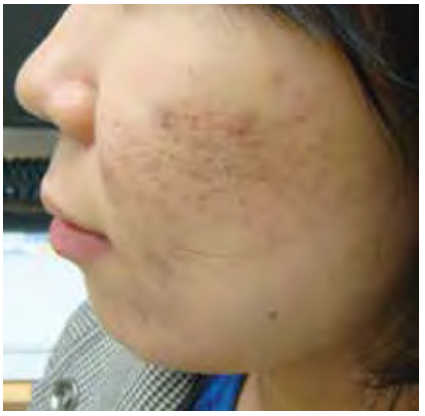

Figure 3. Acne scars from the inflammatory form of postadolescent acne.

Late-onset acne typically localises to the lower third of the face, especially the lower cheeks, jawline, chin and neck. This is in contrast to adolescent acne, which is often midfacial in distribution – in the 'T zone' (i.e. forehead, nose and cheeks). Features of hyperandrogenism should be looked for (Box 2). Although there is often a typical 'hormonal' distribution, the pattern may be the same as teenage acne so the two types cannot always be differentiated by the distribution of the lesions.

Investigations

Although laboratory investigations are not indicated for most patients with pimples, hormonal investigations are appropriate for women with postadolescent acne, irregular menstrual cycles or evidence of androgenism such as hirsutism.

A basic screening test for androgenic abnormalities should include serum free testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex-hormone binding globulin and the ratio of luteinising hormone (LH) to follicle-stimulating hormone (FSH). Elevated levels of free testosterone suggest hyperandrogenism but do not identify the source. Increased levels of DHEA-S suggest an adrenal cause and may be due to congenital adrenal hyperplasia or, rarely, an adrenal tumour.

Elevated levels of testosterone with an increased LH:FSH ratio (greater than 2:1) are consistent with PCOS. The interpretation of serum androgen profiles is summarised in the Table.

Frequently, both the ovaries and the adrenal glands are implicated in androgen overproduction in women with late-onset acne. Blood samples should be obtained in the early follicular phase (days one to seven) of the menstrual cycle where possible, and patients on oral contraceptives should discontinue their medication for at least two months before testing as the contraceptive may mask hyperandrogenism.

Depending on clinical circumstances, other investigations may be indicated. These include measurement of serum fasting glucose and lipids, prolactin, androstenedione and 17α-hydroxyprogesterone levels, and also pelvic ultrasound to detect polycystic ovaries. Patients with PCOS often have insulin resistance and are at increased risk of developing diabetes mellitus and cardiovascular disease. Referral to an endocrinologist or gynaecologist may be indicated. Patients may benefit from weight reduction or a low glycaemic index diet, and so a dietitian may also provide expert advice.

Compared with women of the same age without acne, women with postadolescent acne tend to have higher plasma levels of free androgens, often in the high normal range. It is important to appreciate, however, that the serum androgen measurements may be normal in many patients with postadolescent acne; this may reflect errors in sampling, contraceptive therapy or the end-organ response to androgens.

Sebaceous glands produce a range of enzymes capable of metabolising androgens to more potent forms. For example, dihydroxytestosterone is converted to testosterone by type 1 5α-reductase in acne-prone follicles. The local concentrations of androgen levels due to metabolism and/or end-organ hyper-responsiveness may be more significant in regulating sebum production than are the levels of circulating androgens. This is important to explain to patients because they often cannot understand why hormonal treatments are prescribed in the presence of a 'normal' hormonal assay.

Management

General advice and counselling

Excessive washing and the use of antibacterial soaps and scrubs are not necessary for the cleansing of acne-affected skin, and may irritate the skin. Gentle cleansing using an oil-free soapless cleanser is appropriate, particularly for those women who have sensitive skin, while a foaming cleanser may be more appealing to those who have very oily skin. General measures include using oil-free sunscreens, make-up and moisturisers.

Educating and counselling patients regarding their acne is vital. Myths regarding acne (such as 'poor hygiene' as a cause) should be dispelled. Patient expectations about treatments should be clarified because it may take three to six months before clinical improvement is observed. Patients may need reassurance because they may have had acne for a long time or be resistant to previously tried conventional treatments. They may therefore be quite frustrated by the time they seek your help. Encouragement during this period is helpful to promote compliance. Combination topical and oral therapy is often required.

2. FEATURES OF HYPERANDROGENISM

- Male-pattern baldness
- Hirsutism
- Increased libido
- Acanthosis nigricans
- Deepening of the voice
- Menstrual irregularities
- Insulin resistance

Women with PCOS may have abnormal lipid profiles and are at increased risk of type 2 diabetes. Lifestyle modifications, including weight reduction measures and exercise, are recommended for these patients.[7] As previously mentioned, a team approach involving also a dietitian, gynaecologist and/or endocrinologist may be required.

The therapeutic options for acne are summarised in Box 3.[8]

Topical agents

Topical salicylic acid (2% wash), glycolic acid, azelaic acid (15% gel) and benzoyl peroxide (2.5 to 10% gels and creams) preparations are keratolytic and reduce comedone formation. (Glycolic acid is an alpha hydroxy acid [AHA] that has beneficial effects on oily skin and acne. It is not TGA approved for use in treating acne but is contained, along with other AHAs [such as lactic and mandelic acids], in

TABLE. GUIDELINES FOR INTERPRETING SERUM ANDROGEN PROFILES

Test result	Possible diagnosis
DHEA-S	
• Above 20 μmol/L	• Adrenal tumour
• 10 to 20 μmol/L	• Congenital adrenal hyperplasia
Total testosterone	
• 5 to 7 nmol/L	• Ovarian tumour
• Mild elevations (below about 5 nmol/L)	• Polycystic ovary syndrome
LH:FSH greater than 2	• Polycystic ovary syndrome

Abbreviations: DHEA-S = dehydroepiandrosterone sulfate; LH:FSH = luteinising hormone to follicle-stimulating hormone ratio.

3. THERAPEUTIC OPTIONS IN POSTADOLESCENT ACNE[8]

Topical agents

Keratolytics

- Azelaic acid (gel)
- Benzoyl peroxide 2 to 10% (cream, gel)
- Glycolic acid
- Salicylic acid 2% (wash)

Topical antibiotics

- Clindamycin 1% (gel, lotion)
- Clindamycin 1% and benzoyl peroxide 5% combination (gel)

Topical retinoids

- Adapalene 0.1% (cream, gel)
- Adapalene 0.1% and benzoyl peroxide 2.5% combination (gel)
- Isotretinoin 0.05% (gel)
- Tazarotene 0.1% (cream)
- Tretinoin 0.01% (gel), 0.025%, 0.05%, 0.1% (cream)

Oral agents

Systemic antibiotics

First line

- Doxycycline 50 to 100 mg daily
- Minocycline 50 to 100 mg daily (if doxycycline not tolerated)

Second line

- Erythromycin 250 to 500 mg twice daily
- Trimethoprim 800 mg plus sulfamethoxazole 160 mg, once or twice daily

Systemic retinoid

- Isotretinoin

Hormonal agents

- Combined oral contraceptives:
  - ethinyloestradiol/cyproterone acetate
  - ethinyloestradiol/desogestrel
  - ethinyloestradiol/dienogest
  - ethinyloestradiol/drospirenone
  - ethinyloestradiol/gestodene
- Cyproterone acetate
- Glucocorticoids:
  - dexamethasone
  - prednisolone
- Spironolactone

many cosmetic products.)

The topical antibiotic preparations used in the treatment of acne include clindamycin 1% lotion or gel (available on prescription and compounded) and erythromycin 2% gel (available extemporaneously compounded). Both these agents may be used in pregnant women, but as they may be secreted in breast milk their use should be avoided during lactation. They are particularly helpful in inflammatory acne. The combination therapy of clindamycin 1% and benzoyl peroxide 5% is also effective.

Topical tretinoin, isotretinoin and tazarotene are vitamin A analogues (retinoids) that act mainly as keratolytic agents. Tretinoin is available as a 0.01% gel and as 0.025, 0.05 and 0.1% creams, isotretinoin as a 0.05% gel and tazarotene as a 0.1% cream. They should be applied at night. Patients should be advised about their side effects – irritation and photosensitivity (tazarotene has a higher irritant tendency than the others). These agents should be avoided in pregnancy.

Adapalene is a third-generation topical retinoid that is photostable and does not cause photosensitivity and therefore may be applied during the daytime; it is available as a 0.1% cream or gel. A newer combination topical retinoid – adapalene 0.1% and benzoyl peroxide 2.5% – is effective and applied once daily.

Systemic antibiotics

Oral antibiotic therapy is effective for inflammatory acne and suppresses acne until spontaneous clearing occurs. Doxycycline 50 to 100 mg daily and minocycline 50 to 100 mg daily are usually used as first-line antibiotics. Erythromycin 250 to 500 mg twice daily (or erythromycin ethyl succinate 400 to 800 mg twice daily) and trimethoprim 800 mg plus sulfamethoxazole 160 mg once or twice daily are considered second-line antibiotic choices.

Ideally, oral antibiotics should only be used for a maximum of three months at a time in order to minimise potential antibiotic resistance. If longer courses are required then the antibiotic should be used in combination with benzoyl peroxide or there should be a break of one to two weeks between three-month oral antibiotic courses during which benzoyl peroxide is used. Systemic antibiotics are, therefore, not an ideal option for long-term therapy, which is often needed for hormonal acne.

Oral isotretinoin

Women who have nodulocystic lesions or scarring acne should be referred to a dermatologist for consideration of oral isotretinoin treatment. Oral isotretinoin reduces comedogenesis, reduces sebum secretion and is anti-inflammatory.

Counselling is essential with respect to contraception and the risk of birth defects while on systemic retinoid medication. Pretreatment investigations include serum lipid levels, a serum pregnancy test and liver function tests; these tests should be monitored during therapy especially if an abnormal finding is noted.

Although patients with hormonal acne respond well to isotretinoin, they may relapse when their treatment courses are over because of the underlying hormonal stimulation of the oil glands. Although for some patients the use of low-dose or even intermittent oral isotretinoin will bring their pimples under control, oral isotretinoin should be considered a treatment option for refractory cases.

If acne tends to recur quickly after a course of isotretinoin then antiandrogen hormonal therapy such as the oral contraceptive should be considered as maintenance treatment.

Hormonal therapy

Hormonal therapy, usually with the combined oral contraceptive, is very effective in women who have postadolescent acne with or without elevated serum androgens.[9,10] Such therapy reduces sebum production by decreasing androgenic stimulation of the sebaceous gland. It may be used in combination with other antiacne therapies.

Hormonal therapy for postadolescent acne in women is indicated:

- in those with ovarian, adrenal or peripheral hyperandrogenism
- in those with PCOS
- for moderate to severe acne unresponsive to other therapy
- when there is relapse after multiple courses of antibiotics
- when there is quick relapse after a course of isotretinoin
- as an alternative to repeated courses of isotretinoin.

The therapeutic effect of hormonal therapy is slow, and patients should be warned not to expect noticeable improvement for three to six months. Therapy should be continued for at least 12 months. Relapses are not uncommon when hormonal therapy is ceased and patients should be advised of this before stopping the pill.

Combined oral contraceptives

The oestrogenic component of the combined oral contraceptive pill suppresses ovarian production of androgens and stimulates the production of sex-hormone binding globulin, thus reducing free testosterone levels. This has a benefit in acne because the oil glands are exposed to less androgenic stimulus.

Although all combined oral contraceptives are effective in acne because of the oestrogenic component, those containing androgenic progestins such as norgestrel and levonorgestrel are theoretically less effective.[11]

Preparations containing low-androgenic progestins such as desogestrel or gestodene are considered helpful antiacne contraceptives. For many years, the 'gold standard' has been the combination of ethinyloestradiol 35 μg and cyproterone acetate 2 mg. However, other antiacne pills have been introduced recently, such as the combinations ethinyloestradiol 30 μg and dienogest 2 mg, ethinyloestradiol 30 μg and drospirenone 3 mg, and ethinyloestradiol 20 μg and drospirenone 3 mg.

Side effects of hormonal therapy include nausea, breast tenderness, weight gain and headache. A small increase in the risk of breast cancer has been suggested by epidemiological studies and this should be discussed with the patient, along with other relative contraindications.

Mention should also be made of the several long-term benefits of oral contraceptive therapy, which include reduced risks of ovarian and uterine cancers.[12]

Appropriate patient selection and counselling are required with the use of the oral contraceptive. (Although this article is about postadolescent acne, hormonal therapy is also appropriate for female adolescents with acne; however, oral contraceptive therapy should be avoided before puberty because of the risk of accelerated epiphyseal closure.)

The efficacy of oral contraceptives in acne is due largely to the oestrogenic component. Progestin-only pills and implants are therefore unsuitable as antiacne therapies, and some patients using these have noted a worsening of their acne. Patients should be warned that acne improvement may be slow (taking at least three months) and that treatment is long term (at least one year). Combination treatment may give improved efficacy: if the acne has not improved significantly after three to six months of oral contraceptive therapy then an androgen receptor antagonist such as cyproterone acetate or spironolactone can be added.

Cyproterone acetate

Cyproterone acetate is an antiandrogenic progestin that acts by both inhibiting ovulation and blocking androgen receptors. The previously mentioned combination of cyproterone acetate 2 mg and ethinyloestradiol 35 μg is very effective for the treatment of acne in women with mild-to-moderate hyperandrogenism.

Cyproterone acetate is also available as a single agent 10 and 50 mg tablets, and can be prescribed in addition to a combined oral contraceptive preparation containing it, or indeed any other combined oral contraceptive. The dose of cyproterone acetate can therefore be increased if the acne is unresponsive to an ethinyloestradiol and cyproterone acetate oral contraceptive. For example, 50 mg of cyproterone acetate may be added to the first 10 days of a cycle of an ethinyloestradiol 35 μg and cyproterone acetate 2 mg combined oral contraceptive (or other combined oral contraceptive), starting with the first active pill. Alternatively, 10 mg of cyproterone acetate can be added to the first 15 days of the pill cycle. In postmenopausal women or those who have undergone hysterectomy, 50 mg of cyproterone acetate may be added to the entire active cycle (21 days) of therapy with an ethinyloestradiol and cyproterone acetate-containing oral contraceptive.

Improvement can be seen in 75 to 90% of women with acne who are treated with cyproterone acetate 50 to 100 mg per day. Oestrogen is necessary in these regimens because cyproterone acetate has strong antioestrogenic effects.

Side effects of cyproterone acetate therapy include menstrual abnormalities, breast tenderness and enlargement, mood changes, headache, nausea, melasma and fluid retention.

Glucocorticoids

If a woman's hyperandrogenism is due to an adrenal disorder, low-dose prednisolone (2.5 mg daily) or dexamethasone (0.25 mg daily) can be used to suppress adrenal production of androgens. Long-term use of these agents poses a risk of adrenal cortisol suppression, and patients should be monitored for this with periodic adrenocorticotropic hormone (ACTH) stimulation tests.

Spironolactone

Spironolactone is useful for women who are intolerant to oestrogens, have a contraindication to oestrogen therapy or do not wish to use oral contraceptives. Spironolactone acts as a competitive androgen receptor antagonist and as an inhibitor of 5α-reductase and is effective in doses of 50 to 200 mg daily. Using it as

monotherapy at low doses of 25 to 50 mg may improve acne and not alter the menstrual cycle. If higher daily doses are required, it is often combined with the oral contraceptive so that the menstrual cycle is kept regular. Treatment may be prolonged (six months or more), but dosages may be reduced once an adequate clinical response is achieved. A 30 to 50% reduction in sebum excretion is noted and some clinical improvement is seen after three months.

Dose-dependent side effects of spironolactone therapy include menstrual irregularities, breast tenderness, hyperkalaemia, headache, dizziness, drowsiness and hypotension. Side effects may be minimised if therapy is started with a low dose of 25 to 50 mg daily. As an antiandrogen, spironolactone may cause feminisation of a male fetus, and therefore patients should not become pregnant while on the medication. Although monitoring of blood pressure and serum electrolytes may be required in some patients, most young, healthy patients show no abnormalities in their blood pressure and do not require laboratory tests.

Conclusion

Women with postadolescent acne are a relatively common presentation in general practice. Assessment of such patients should include identifying the presence of hyperandrogenism and possible underlying causes. Hormonal agents such as the combined oral contraceptive are effective treatments and may be combined with other acne therapies such as topical agents and/or oral antibiotics. MT

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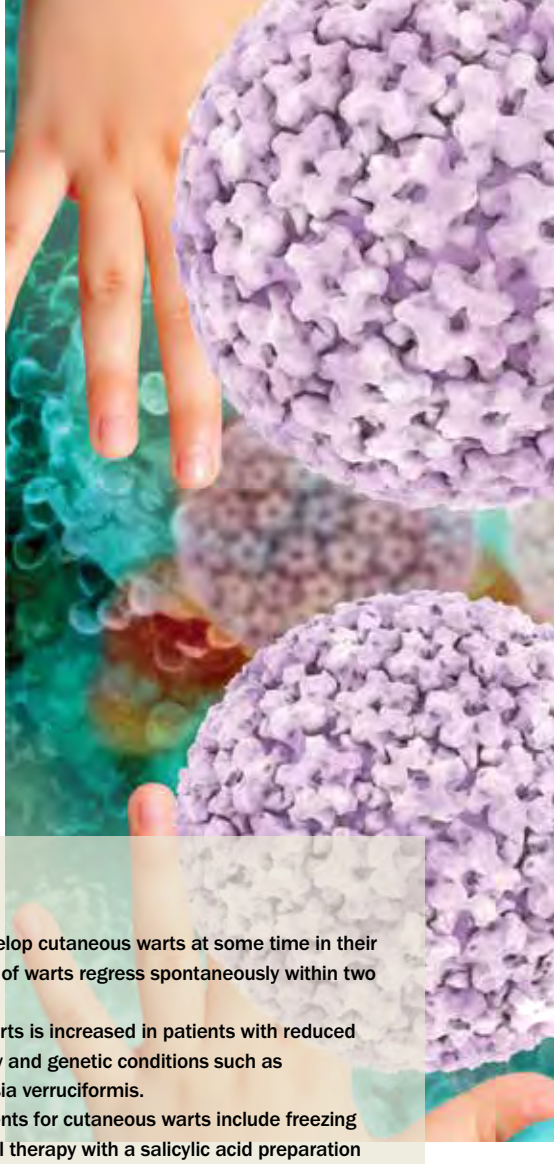
COMPETING INTERESTS: None.

Treating cutaneous warts
What are the options?



BRUCE TATE MB BS, PhD, FACD

First-line treatments for cutaneous warts include freezing and home topical therapy with a salicylic acid preparation plus heating, paring and zinc oxide cream. If prolonged use of these treatments fails or they are unsuitable then a wide range of chemical, immunological and physical treatment options are available.

Warts are caused by infection with a human papillomavirus (HPV). Most people develop cutaneous warts at some time in their life, with a point prevalence of 20% among Australian school children, slowly declining with increasing age.[1-3]

Papillomaviruses are closely related to nonenveloped DNA viruses and are highly species-specific. HPVs show considerable diversity; the complete DNA sequence is known for about 120 HPV genotypes, and partial DNA sequences for at least another 80 genotypes.[4] DNA sequencing reveals a phylogenetic tree where the virus groupings match their biological behaviours. The clinical subtypes of HPV infection and the commonly associated HPV genotypes are outlined in the Table.[5]

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KEY POINTS

- Most people develop cutaneous warts at some time in their life; around 65% of warts regress spontaneously within two years.
- Prevalence of warts is increased in patients with reduced cellular immunity and genetic conditions such as epidermodysplasia verruciformis.
- First-line treatments for cutaneous warts include freezing and home topical therapy with a salicylic acid preparation plus heating, paring and zinc oxide cream.
- When prolonged use of first-line treatments fails or is unsuitable, then treatment options include:
  - chemical therapies such as caustic agents, cantharidin
  - immune system modifiers such as diphencyprone, imiquimod, cimetidine
  - physical therapies such as duct tape occlusion, destructive treatments.

Clinical presentation

The clinical presentation of warts depends on the infecting HPV genotype and the site affected. Common warts (verruca vulgaris) occur on the hands, fingers, elbows and knees. These warts occur particularly on the fingers (including periungual or subungual sites) but also on the dorsal area of the hands (Figure 1).

Palmar and plantar warts may be solitary or multiple. On the soles, mosaic warts are more superficial plantar warts that have coalesced into larger plaques, usually on weight-bearing sites (Box 1, Figures 2a to c). Myrmecia (Latin for anthill) are thicker endophytic plaques of wart sloping to a central depression. Occasionally, large confluent plaques of plantar warts occur. Palmar and plantar warts are usually painless but can sometimes be surprisingly painful, particularly when on weight-bearing sites.

© XRENDER/SHUTTERSTOCK. HUMAN PAPILLOMAVIRUSES

Plane (flat) warts are more subtle than common warts, presenting usually with numerous, flesh-coloured to slightly red-brown papules or small plaques. They most often occur on the dorsum of the hands or nearby forearms and are also seen on the face and neck (Figure 3).

Rarely seen are epidermoid cysts of weight-bearing areas of the sole. These contain mainly HPV type 60 – one of a number of HPV genotypes that cause warts with inclusion bodies seen on histology.

Pathogenesis

Wart infection occurs:

- directly via skin-to-skin contact, either from person to person or through autoinoculation to adjacent skin
- indirectly via contaminated surfaces and objects such as showers in the home, at swimming pools or gymnasiums.

Infection is promoted by minor abrasions and maceration that allow HPV access to basal keratinocytes. The circular DNA of HPV becomes a replicon in the nuclei of epithelial basal cells, creating a long-term reservoir of viral DNA. The incubation period is up to 20 months for experimental HPV infections, but clinical experience suggests it may be considerably longer in some cases. Approximately 65% of warts regress spontaneously within two years.[6]

Warts can be persistent and have high recurrence rates. Furthermore, treatment may not prevent further HPV transmission (although the risk is low if the warts are not clinically apparent). Possible reasons include:

- the persistence of HPV DNA in normal-appearing skin surrounding the warts, as shown by polymerase chain reaction (PCR)
- the resistance of HPV to heat and desiccation
- the ability of HPV to evade the host's immune defences through mechanisms that include the absence of a viraemic phase in HPV infection, which minimises the systemic immune response; and low-level expression of viral proteins in the lower layers of the epidermis where antigen-presenting cells are most prevalent. Eventually, protective type-specific immunity does develop.

Some conditions associated with an increased prevalence of warts are shown in Box 2. Warts are much more prevalent in people with reduced cellular immunity. Epidermodysplasia verruciformis is a rare genetic disease that involves infections with HPV genotypes that do not produce warts in normal individuals. The disease is mostly autosomal recessive (caused by mutations in the *TMC6* or *TMC8* genes, which encode transmembrane proteins involved in zinc transport). Onset is usually in childhood. Clinically, this condition is highly polymorphic with widespread lesions usually resembling plane warts or pityriasis versicolor.

HPV infection is responsible for the vast majority of cases of cervical carcinoma, and HPV vaccination will likely significantly reduce the incidence of this carcinoma in the future.[7,8] HPV infection is also strongly linked to anogenital squamous cell carcinoma (SCC) and some SCCs of the head and neck. Other HPV-associated conditions prone to transforming to invasive SCC are the higher-grade intraepithelial neoplasias of male or female genital sites (cervical warts, penile bowenoid papulosis and erythroplasia of Queyrat) and inverted papilloma (mostly seen in the nasal cavity).

Only some HPV genotypes are oncogenic, as they encode proteins that suppress known human tumour suppressor proteins. This mechanism allows proliferation of the viral genome in tissues that routinely 'turn off' cell proliferation as the epithelial cells differentiate. Nononcogenic HPV genotypes lack these proteins. The incidence of HPV-related malignancies is higher in people with a deficiency in cell-mediated immunity or epidermodysplasia verruciformis.[5]

Differential diagnoses

Corns or calluses

Corns or calluses are the main differential diagnosis but are uncommon in younger people. Repeated focal pressure or friction causes protective thickening of the skin, making that area firmer and more prominent, leading to a vicious cycle. Corns and calluses on the hands are mainly seen in manual workers and on the feet from poor fitting footwear, abnormally shaped feet or bony

TABLE 1. CLINICAL SUBTYPES OF HPV INFECTION AND THE COMMONLY ASSOCIATED HPV GENOTYPES

Infection type	HPV genotypes*
Skin	
Common warts (hands, fingers, elbows, knees)	1, 2, 4, 27, 57
Palmar and plantar warts	1, 2, 27, 57
Mosaic warts (soles)	2
Myrmecial warts (soles)	1
Plane (flat) warts	3, 10
Epidermoid cysts of the sole (with inclusion bodies)†	4, 57, 60, 63, 65
Butcher's warts (mainly seen in meat or fish workers)	7 (not animal sourced)
Digital squamous cell carcinoma and Bowen's disease	16
Epidermodysplasia verruciformis (EV)†	3, 5, 8 (and many others)
EV squamous cell carcinoma†	5, 8
Mucosa	
Anogenital warts (condylomata acuminata)	6, 11
Higher-grade intraepithelial neoplasias (cervical warts, penile bowenoid papulosis, erythroplasia of Queyrat)	16
Invasive cancers (cervix, vulval, penile, oral)	16, 18, 31, 45‡
Warty (condylomatous) squamous cell carcinoma	16
Oral warts	6, 11
Heck's disease (oral focal epithelial hyperplasia)†	13, 32 (only)
Conjunctival papillomas	6, 11
Nasal inverting papillomas†	11, 57
Recurrent respiratory papillomatosis	6, 11

Abbreviation: HPV = human papillomavirus.
* Many more HPV genotypes are less often linked to some of these clinical forms.[5]
† Occur rarely.
‡ These four genotypes account for around 80% of cervical cancers.

prominences on weight-bearing sites.

Corns are more focal with a hard keratinous seed; calluses are broader. Except for the central seed of a corn, paring with a surgical blade shows persistence of the normal skin markings, which are absent in the heart of a wart. Warts often also show black dots from thrombosed capillaries and bleeding from capillaries from more superficially located dermal papillae. These features may be clearer with dermoscopy. Macerated interdigital warts are difficult to distinguish from (soft) interdigital corns.

Neoplasms

Verrucous carcinoma (epithelioma cuniculatum type) is a rare low-grade, well-differentiated SCC on the soles of older adults. The term 'cuniculatum' refers to a rabbit burrow-like appearance with deep furrows. Verrucous carcinomas can gradually penetrate, destroying the subcutis, fascia or bone, and often recur after attempted removal but rarely metastasise. In the past, they were thought to result from HPV infection but stricter histopathological criteria suggest this is an uncommon factor.[9]

Rarely, in situ SCC (Bowen's disease) occurs between multiple toes or as periungual or subungual disease with warty change and/or granulating erosive change. HPV infection is probably a common aetiological factor.[10,11] This clinical presentation can also signify subungual melanoma, which is often amelanotic. If there is any doubt then biopsy is mandatory.

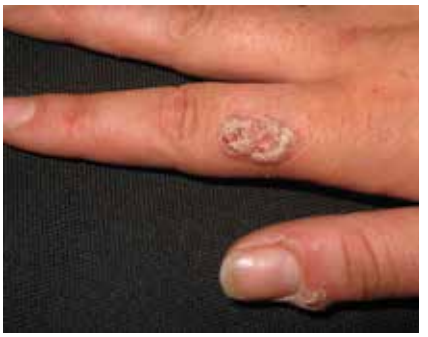


Figure 1. Moderate-sized common warts (verruca vulgaris) on the finger and subungual area of the thumb.

Psoriasis and tinea

Psoriasis purely of the palms and soles may be a distinct entity to psoriasis vulgaris, but the latter may include palms and soles as well as other sites. The plaques are well demarcated, red and scaly and vary from involving small, localised areas to confluent over most of the palms or soles. They can be thick and fissured. Sterile pustules may be present. Tinea should also be considered.

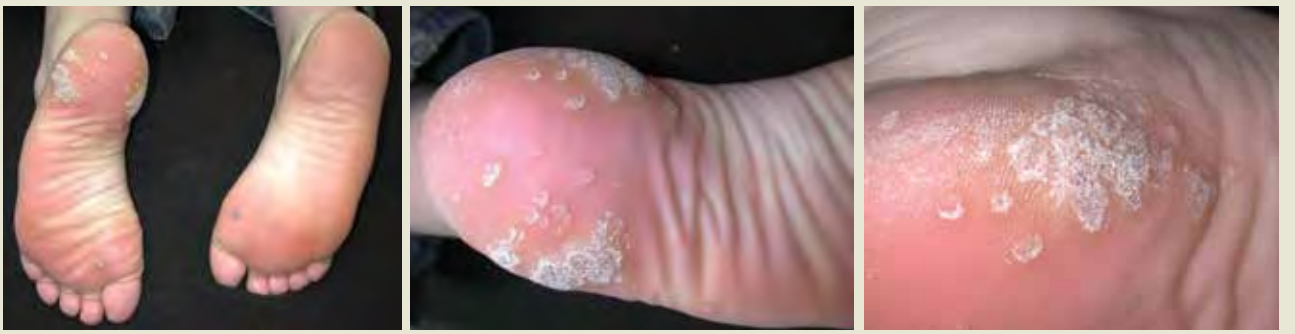
Hypertrophic lichen planus

Hypertrophic lichen planus most often occurs on the legs and dorsal area of the feet. The thickened scaly plaques have a

1. CASE: A YOUNG MAN WITH MOSAIC PLANTAR WARTS

Presentation
A 19-year-old man presented with mosaic warts on the left sole and smaller warts elsewhere on his soles, fingers and the dorsum of his hands (Figures 2a to c). He swam regularly and played soccer. He had used a proprietary wart paint daily for a month with no benefit. His GP froze the warts on two occasions two weeks apart. No blisters developed; some of the warts on the dorsum of his hand cleared but most persisted. The patient then used a wart home freezing device three times over three weeks with no benefit.

Treatment
I explained to the patient that warts of this type are often slow to respond to treatment and that he had not used the treatments for long enough to give them a fair trial. We elected to pare and solid freeze the warts, followed by combination home topical therapy. This comprised hot water soaks followed by application of 17% salicylic acid and 17% lactic acid in a collodion base at night and zinc oxide cream during the day, both under occlusion with a dressing tape. The patient did not return for follow up.



Figures 2a to c. Mosaic warts on the left heel and smaller warts elsewhere on the soles in a 19-year-old man.

livid hue and are usually itchy; the thickening results from repeated scratching.

Rare disorders

Punctate palmoplantar keratodermas include a number of rare inherited disorders, punctate porokeratosis and arsenical keratoses. The dorsal surfaces are usually spared.

Tuberculosis verrucosa cutis is rare in Australia but should be considered in immigrants from endemic areas. It occurs in individuals who have been previously infected with *Mycobacterium tuberculosis* after exogenous inoculation with this bacterium at sites prone to trauma. The lesion begins as a small, subtly inflamed wart-like papule, which gradually enlarges to a firm red-brown verrucous plaque.

Treatment of warts

There are few specific antiviral therapies to treat HPV infection. Most therapies aim:

- to physically remove visible warts
- to be cytotoxic to infected cells or
- to induce an immune response against the wart.

As warts are benign and self-limiting, patients – especially children – may not require treatment, and therapy likely to induce permanent scarring should be avoided. There is no evidence that aggressive removal of warts results in a better long-term outcome nor that temporary interruption of therapy is a problem.

The treatment recommendations below are based on personal experience and evidence from clinical trials. Using the strict criteria of evidence-based medicine, a recent Cochrane review concluded that of the treatment options for warts, only topical salicylic acid preparations are superior to placebo.[9] Another similar review concluded that 'significantly higher remission rates may be expected only with cryotherapy and salicylic acid used in combination'.[10] These

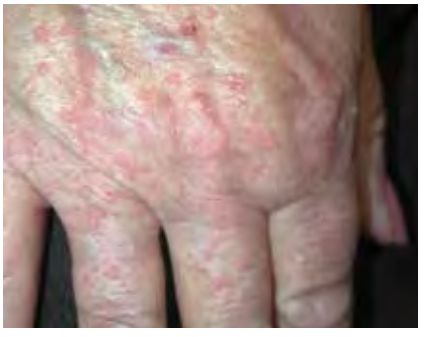


Figure 3. Multiple plane warts on the dorsum of the hand and fingers.

2. CONDITIONS ASSOCIATED WITH AN INCREASED PREVALENCE OF WARTS[5]

- Intravenous line infection
- Organ transplantation
- Some haematological malignancies (e.g. chronic lymphocytic leukaemia and Hodgkin's disease)
- Idiopathic CD4 lymphopenia
- Some rare genetic immunodeficiency syndromes (e.g. common variable immunodeficiency, severe combined immunodeficiencies, ataxia–telangiectasia, Fanconi's anaemia, Wiskott–Aldrich syndrome, DOCK-8 deficiency, WHIM syndrome, WILD syndrome)
- Epidermodysplasia verruciformis

3. SOME TREATMENT OPTIONS FOR CUTANEOUS WARTS

First-line treatments
- Cryotherapy (e.g. liquid nitrogen)
- Home topical therapy
  - heat (microwavable seed bags or hot water)
  - salicylic acid preparations
  - zinc oxide cream

Other treatments*
- Chemical therapies: cantharidin, caustic agents, formic acid, bleomycin, 5-fluorouracil, oral retinoids, adapalene, cidofovir
- Immune system modifiers: sensitising agents (e.g. diphencyprone), imiquimod, cimetidine, therapeutic vaccination, intralesional vaccines or antigens
- Physical therapies: home freezing with dimethyl ether plus propane, duct tape occlusion, destructive treatments such as surgery, electrosurgery, laser
- Others: photodynamic therapy, folk remedies

* Options when warts do not respond to prolonged use of first-line treatments or when first-line treatments are unsuitable.

conclusions are difficult to assess as there are few properly controlled, adequately sized trials to compare the range of available treatments. Despite this, many less adequately controlled trials report high response rates to the investigated treatments.

Treatment selection

Therapies may be divided into home therapies and those administered by a clinician. Combinations of therapies are often used. Some treatments are more suitable for anogenital warts than for plantar warts and vice versa. This article concentrates on therapies likely to be used by general practitioners, podiatrists and dermatologists for cutaneous warts. Treatment options for cutaneous warts are summarised in Box 3.

Important factors in deciding which modalities to use for a specific patient are:
- likely effectiveness
- cost of the product or of repeated visits to the practitioner
- which treatments have been tried previously and their adequacy (e.g. appropriateness for site, compliance, number of attempts and duration of treatment)
- likely compliance and issues that affect this (e.g. pain, particularly for children or people who are constantly on their feet, practicality and time constraints)
- side effects.

Advice to patients

It is important to explain to patients that all available wart treatments are slow to work and unreliable (prone to failure) and that warts are prone to recur after apparently successful treatment. No single treatment is much more effective than others. A rule of thumb is that the success rate for any individual treatment modality is approximately 70% after three months or longer of treatment. If a treatment appears to have had a partial effect by three months and is tolerated then I encourage patients to continue with that treatment for a few more months before abandoning it.

Preventive measures, such as wearing thongs when showering and not picking at warts, are also important (the latter may spread the HPV infection or allow periungual warts to develop).

An approach to treatment

After discussion of the treatment options with the patient, a useful approach is as follows. The use of this approach in a patient with mosaic warts is outlined in Box 1.[11-13]

Freezing

Solid freezing should be offered because a single freeze occasionally clears warts. Thick warts may be pared with a blade. With liquid nitrogen (boiling point -196°C), the freeze time needs to be long enough to induce blisters but not cause deep necrosis. Application is equally effective with cryosprays or thick cotton tip applicators but the latter often requires longer application times to achieve the same level of freezing.

Freezing is painful and most young children will not tolerate it. Topical local anaesthetics are not effective enough for the freeze times required. Various methods of distraction may allow braver children to tolerate it. I explain that freezing does not kill HPV but rather destroys the skin harbouring it, so hopefully exposes the virus to allow immune recognition. However, warts often re-appear in the healing skin.

I also instruct patients or their carers to snip off the roof of the resulting blister to reduce viral load and to apply povidone iodine ointment daily to the healing skin. Healing usually takes a week or two so the treatment is less suitable for physically active people.

If the warts do not clear or recur after a single freeze then the next main options are repeated cryotherapy or home topical therapy. Cryotherapy is usually repeated every two to three weeks until the warts clear, which may require many treatments. It is common for children not to be prepared to return for multiple treatments – a point that I emphasise to parents insisting on aggressive treatment. Studies have investigated more frequent freezing, with marginally improved results.

Clinicians should be aware that melanocytes are more sensitive to cryotherapy, so hypopigmentation (temporary or long-term) is a risk in darker skinned people. This is less of an issue on the feet than on the hands. Freezing is prone to lead to a 'donut' of recurrent warts around the freeze site.

A home freezing device that uses dimethyl ether and propane is claimed to be effective for treating warts. In my experience, this treatment often fails. A study found the achieved minimum temperature of 0°C at 40 seconds (compared with -20°C at 20 seconds for liquid nitrogen) was probably insufficient for therapeutic effect.[14] In addition, patients probably often do not adequately follow the instructions because of pain.

Home topical therapy

Home topical therapy is a good alternative or adjuvant to freezing. It is cheap, convenient and minimally painful. I recommend

that patients combine daily application of a compounded or proprietary salicylic acid preparation with physical treatments such as heating and paring of the wart and application of zinc oxide cream. Details of this strategy are shown in Box 4.

Products often claim to remove warts rapidly. I explain to patients that many months of treatment are required before the treatment should be abandoned as ineffective.

Other treatment options

If the warts fail to respond to prolonged use of the above treatments or there are issues with the treatments then a range of options exist.

Chemical therapies

Caustic agents. Repeat applications of caustic agents are reported to be effective. These include monochloroacetic acid or trichloroacetic acid, 35 to 80% in water or 80% phenol, each applied weekly with a salicylic acid preparation on the other days. The acids cause immediate quite painful stinging that lasts for a prolonged time so are less suitable for children. They also cause temporary frosting of the skin, which is prone to later pigment change. Another option is 10% silver nitrate in water, applied every second day for months.

Glutaraldehyde. Glutaraldehyde is a bacteriocidal and virucidal antiseptic. A 10% glutaraldehyde solution in a water-ethanol base is available as a wart treatment (Diswart). It is prone to causing allergic contact dermatitis so I do not recommend its use for warts. Treated skin hardens and turns a brown colour.

Cantharidin. Cantharidin is available from some dermatologists and some hospital dermatology outpatient clinics. It is a vesicle-forming terpenoid found in 'blister beetles'. It activates serine proteases that destroy epidermal desmosomal proteins, so the healing blisters do not scar.

The application of cantharidin is not painful. Blisters develop after hours to two days, usually with no or manageable pain, and heal within a week. Cantharidin is particularly useful in children who often do not associate any later pain with the treatment and so are usually prepared to return for repeat therapy.

Preparations include 0.7% cantharidin in a film-forming base and 1% cantharidin plus 20% salicylic acid and 2% podophyllum in a collodion base. They are not available from most pharmacies. Cantharidin is only for office use: a thin smear is applied to each wart and allowed to dry. Occlusion is not required but if used increases the intensity of the blister. Some recommend washing cantharidin off a few hours after application but removal is difficult and is not needed. Cantharidin is applied every one to two weeks until new warts stop appearing; usually many applications are needed. Zinc oxide cream can be applied on the days cantharidin is not applied.

Bleomycin. This chemotherapy agent is injected into each wart. It binds DNA causing single-strand breaks. It is used only for recalcitrant warts and is made up in syringes by hospital pharmacies so is available only through dermatology outpatient clinics. Protocols vary, but typically bleomycin sulphate 0.25 to 1 mg/mL is injected up to three times to a maximum total dose of 4 mg. The injections are very painful so prior local anaesthetic is used. The area may remain painful for a week or so after treatment. The warts develop haemorrhagic necrosis by two to three weeks, which can be removed by paring. Reported cure rates vary from 14 to 99%. Systemic toxicity does not occur with this method but it is not suitable in pregnant women. Local complications include nail loss or dystrophy for periungual injections, Raynaud's phenomenon in treated digits and local urticaria.

Methods harnessing the immune system

Diphencyprone (DCP). Also known as diphencyclopropenone, DCP is used for more treatment-resistant multiple warts and can be very effective. It is available from compounding pharmacies. Most patients develop a delayed hypersensitivity reaction

4. A HOME THERAPY STRATEGY FOR CUTANEOUS WARTS

1. Heat the warts for 15 to 30 minutes every evening
This is reported to be an effective stand alone modality. Heating can be achieved with microwavable flax-seed hot bags or by soaking the feet or hands in a baking dish or bowl of water at a temperature that is almost uncomfortable.

2. Dry the feet or hands and apply a wart paint under dressing tape overnight
I recommend 40% salicylic acid compounded in white soft paraffin as a cheap keratolytic wart paint (made up by the pharmacist on prescription). Over-the-counter proprietary alternatives are available with a similar formulation (17% salicylic acid and 17% lactic acid in a collodion base; including Dermatech, Duofilm Liquid and Wart Clear Solution). Collodion dries to form a rubbery film. Collodion also contains colophony, a common cause of allergic contact dermatitis (as seen with some brands of fabric adhesive tape). Another proprietary option (Wart-Off Paint) contains 20% salicylic acid, 12% lactic acid and 10% podophyllum resin in an ether–ethanol base.

Any of these paints should be applied moderately generously each night to each wart, and then occluded overnight with dressing tape (e.g. Micropore), which is removed the next morning.

3. Remove the soft surface of the warts each morning with a pumice stone or nail file and apply 36% zinc oxide cream generously, also under dressing tape
If daytime topical treatment is undesirable, such as for cosmetic or time reasons, then oral zinc sulphate is an alternative (10 mg/kg to a maximum dose of 600 mg daily for two months). There are trials suggesting that either form of zinc has efficacy.

If the warts become too sore then the night-time treatment is temporarily stopped and re-started once the discomfort settles, initially applied every second day and then daily if tolerated. The morning treatment is bland so is continued.

If the warts appear to clear then the treatment is stopped but if the warts recur it is recommenced. If time is limited then the heating step can be omitted.

(allergic contact dermatitis) to DCP and this immune attack is probably responsible for clearing warts. Squaric acid dibutyl ester is an alternative sensitising agent. Because these chemicals are used only for wart therapy, the allergy is of limited consequence.

The clinician applies 2% DCP to a small area of normal skin to induce sensitisation (dermatitis at the site) within 10 days. The patient then applies 0.1% DCP and 15% salicylic acid in white soft paraffin to the warts, initially a small amount every third day. The treated area must be carefully taped to ensure the DCP does not contaminate other sites as it will cause contact dermatitis wherever it touches the skin. If no reaction occurs by a week after DCP application then the frequency of application is slowly increased to each night, and then the amount applied is gradually increased, aiming to achieve a low to moderately active persistent local dermatitis.

Some patients need to apply DCP only every few days to maintain the dermatitis. Occasionally the concentration of the DCP must be increased to 0.2% to achieve the required reaction. It can also be used as a liquid, usually in acetone at a lower concentration (0.01 to 0.05%) and can be applied from daily to weekly to maintain the required moderate level of dermatitis. Some patients become exquisitely allergic to DCP and develop more severe local reactions or widespread urticarial or eczematous reactions. A marked reduction in DCP concentration will sometimes allow continued treatment in these situations. I also prescribe a potent topical corticosteroid so it is available to treat a too strong local reaction. DCP usually takes months (sometimes six to 12) to clear warts.

Imiquimod. Imiquimod activates the innate immune system via Toll-like receptor 7, causing mild to substantial inflammation. Available as sachets of 5% imiquimod cream, it is expensive, not covered by the PBS for this indication and is mainly used to treat genital warts, basal cell carcinomas and solar keratoses. It has poor penetration through keratin so is unlikely to work on areas with thick skin such as the palms and soles. Penetration may be enhanced by repeated paring of the warts, cryotherapy, occlusion and/or concurrent use of salicylic acid. An ideal treatment regimen has not been developed.

Oral cimetidine. Oral cimetidine (30 to 40 mg/kg daily in two divided doses to a maximum of 2400 mg daily for three to four months) stimulates production of some cytokines. Initial uncontrolled studies suggested efficacy, but two double-blind, placebo-controlled studies failed to confirm efficacy for recalcitrant common warts.[15,16]

Therapeutic vaccination. The commonly used HPV vaccine is effective against and specific to HPV types 6, 11, 16 and 18 and is effective in preventing most anogenital warts. The therapeutic use of HPV vaccines for already present anogenital and mucosal warts has not been reported as yet. Similarly, there are no trials on the therapeutic use of these vaccines for cutaneous warts, but one group has reported clearance of recalcitrant cutaneous warts in six patients.[17,18] Despite the vaccine being active against HPV genotypes not usually found in cutaneous warts, it may have an effect in some patients via epitopes shared by cutaneous and anogenital HPV genotypes. The ability of HPV vaccines to prevent the development of common cutaneous warts has not been investigated. Vaccine development is ongoing, raising the prospect of therapeutic vaccines against cutaneous warts.

Physical therapies

Duct tape. This occlusive plastic industrial adhesive tape is applied over the warts and left on for four to six days. The wart is then debrided with a blade or pumice stone and the duct tape reapplied in the same way. Early studies of its use for two months showed complete clearance rates in 60 to 85% of patients treated. However, later placebo-controlled studies found poor response rates.[19,20]

Destructive treatments. Destructive treatments such as excisional surgery, electrosurgery and carbon dioxide laser treatment are likely to cause scarring and should not be used for plantar warts on pressure-bearing sites as the firm scars become a nidus for equally troublesome and difficult to treat calluses or corns. These treatments can be used for recalcitrant warts on non-weight-bearing sites. However, permanent scarring is still an issue and warts not uncommonly recur, presumably as there may be wart virus in surrounding clinically normal skin. Excisional surgery is not practical for large or numerous warts. Carbon dioxide laser treatment is expensive. The smoke plume from electrosurgery and carbon dioxide laser treatment may carry infective virus so has a small risk of causing airway warts in the people in the room.

Less common treatments

Other treatments have been reported as successful in small series. They are used infrequently.

5-fluorouracil cream (5%). This is a chemotherapy agent used mainly to treat solar keratosis. Significant wart clearance rates have been shown in a number of trials of 5-fluorouracil used either alone with tape occlusion or mixed with 10% salicylic acid cream.[21,22]

Oral retinoids (acitretin or isotretinoin). These can help debulk warts by reducing epidermal proliferation. The infection usually persists, so relapse is likely on stopping treatment. Oral retinoids can be helpful in patients with extensive hyperkeratotic warts and immunosuppressed patients and to enhance the effectiveness of other treatments.[23,24]

Cidofovir. The antiviral agent cidofovir is a purine nucleotide analogue that can be extremely effective for plantar, anogenital, oral and laryngeal warts, even in patients with immunodeficiency.[25-27] It can be administered by systemic infusion (5 mg/kg once weekly), intralesional injection (2.5 mg/mL) or as a 1% gel or cream (available through compounding pharmacies). Side effects of systemic cidofovir include nephrotoxicity and bone marrow suppression, but topical treatment of skin lesions is usually well tolerated. Cidofovir is expensive and so is infrequently used.

Adapalene. Adapalene 0.1% gel is a vitamin A analogue used mainly as acne therapy.

85% formic acid solution. This is punctured into warts every second day up to 12 times.

Folk remedies. On the basis of scanty published literature and anecdotal reports, repeated direct applications of banana peel, milk weed thistle latex and fig tree latex have been recommended for the treatment of warts.[28,29]

Photodynamic therapy. This therapy involves a topical photosensitiser and a light source or pulsed-dye laser and is mainly used to treat vascular lesions.[30-32] These techniques have cleared a significant number of warts in small series. They are available from some dermatologists in private practice.

Intralesional injection. Injection of various vaccines or antigens into the largest wart can be successful. Antigens used include *Candida albicans*, *Trichophyton* spp., *Propionibacterium acnes* and mumps, measles and rubella vaccine or antiserum.

Conclusion

Warts are an unpleasant and embarrassing viral infection experienced by most people. On the more serious side, some genotypes have oncogenic potential, and a small number of patients with deficiencies in cell-mediated immunity can suffer overwhelming numbers or very large warts. Warts can be frustrating to treat and our enthusiasm to treat can be tempered by the fact that the majority resolve spontaneously in a few years. The many available treatments make treatment choice confusing, and their unreliability and potential side effects frustrating. There is a lack of large well-controlled trials to best guide treatment. The development of HPV vaccines against anogenital warts is exciting but these vaccines are considered to have a very limited role in controlling cutaneous warts. MT

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Biologics and psoriasis today

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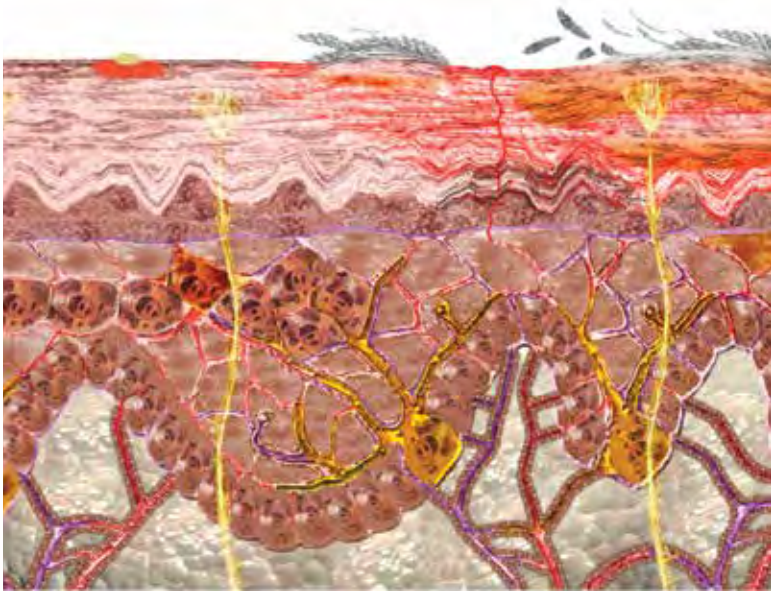
Biologic agents have emerged as alternative treatment options for patients with moderate-to-severe plaque psoriasis. These agents have shown good efficacy and are well tolerated.



Psoriasis is a chronic systemic immune-mediated inflammatory disease of unknown aetiology that manifests primarily in the skin. It affects approximately 2% of the Australian population and has a substantial negative impact on patients' quality of life. Patients with localised limited disease can usually be managed satisfactorily with topical agents, whereas those with moderate-to-severe disease often require systemic treatment.[1] Phototherapy and traditional systemic treatments, although often effective, can be associated with long-term cumulative toxicity. In addition, some patients have treatment-resistant disease, and patients themselves show high levels of dissatisfaction with standard approaches to treatment.[2]

Biologic agents are a significant breakthrough in the treatment of psoriasis, akin to the introduction of isotretinoin for acne or the discovery of the benefits of propranolol for infantile haemangiomas. They have higher efficacy rates and appear safer than the traditional treatment options, resulting in significant improvements in health-related quality of life for people with this potentially devastating condition. Some practice points regarding biologic agents and psoriasis are summarised in Box 1. The effects of biologic therapy in three patients with severe psoriasis are illustrated in Figures 1 to 3.

Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is a measure of overall disease severity in chronic plaque psoriasis. This score is calculated using the percentage of area coverage and the severity of the psoriatic plaques based on three clinical signs: erythema, thickness and scaling (each rated 0 to 4). Both the body surface area and the severity ratings are incorporated into a formula to calculate the PASI score on a nonlinear scale from 0 to 72. A score of 10 or more is considered moderate-to-severe psoriasis. A reduction in PASI score of at least 75% compared with baseline (termed a 'PASI 75' response) is considered the gold standard measure of treatment efficacy.[3,4]

Immunological basis of psoriasis

Psoriasis is a chronic, immune-mediated disorder that results from polygenic predisposition combined with environmental triggers. The underlying pathophysiology is mediated by T cells and involves the innate immune system stimulating the

1. BIOLOGICS AND PSORIASIS: PRACTICE POINTS

- Biologic agents are a recent advance in the treatment of patients with moderate-to-severe plaque psoriasis; they show good efficacy and are well tolerated.
- Pre-treatment screening for chronic infections is mandatory and age-appropriate screening for malignancy is recommended.
- Monitoring for infection and regular skin cancer surveillance are important during biologic therapy.
- The use of live vaccines is contraindicated while patients are receiving a biologic agent.
- The most common side effects that may prompt patients to seek GP advice include injection site reactions, nasopharyngitis and upper respiratory tract infections.
- The risks of biologic therapy during pregnancy and breastfeeding are not fully understood; current guidelines recommend ceasing therapy before conception and during pregnancy and breastfeeding.
- New promising biologic therapies are in development, offering more treatment options for patients with difficult to treat disease.

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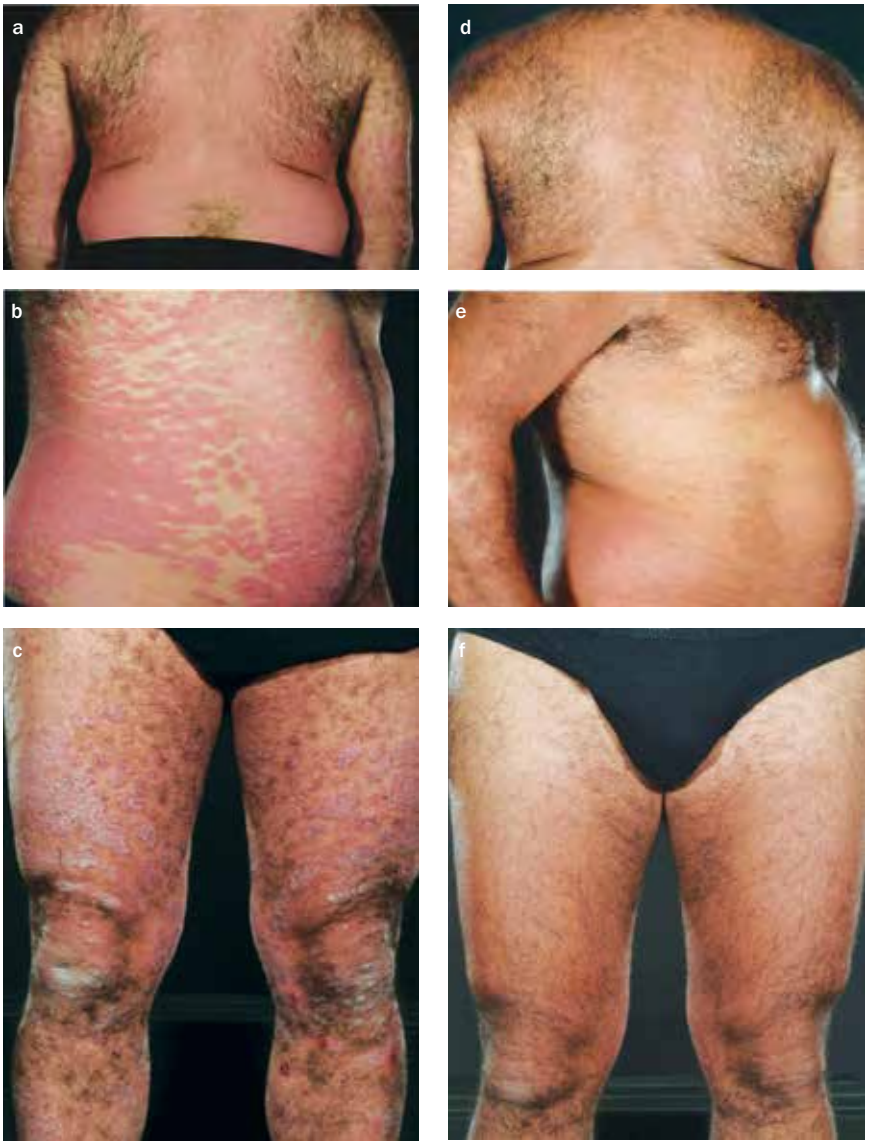


Figures 1a to f. A 39-year-old man with a 25-year history of severe psoriasis. a to c (left top, middle and bottom). Before treatment. d to f (right top, middle and bottom). After 24 weeks of biologic therapy, showing a decrease in the Psoriasis Area and Severity Index (PASI) from 25.3 to 1.8.

production of proinflammatory mediators, perpetuating an inflammatory loop.[5] Cellular components of the innate immune system that have been linked to the pathophysiology of psoriasis include dendritic cells, macrophages and neutrophils. Cytokines produced by immune cells that appear to play major roles in the development of psoriasis include interferon (IFN)-α, tumour necrosis factor (TNF)-α, interleukin (IL)-12, IL-17 and IL-23.[4-6]

When stressed (e.g. by trauma or infection), keratinocytes in the skin induce the production of IFN-α by plasmacytoid dendritic cells and release TNF-α. The latter activates dermal dendritic cells, which migrate and activate naïve T cells, promoting their differentiation into T helper (Th) cells.[5] IL-12 and IL-23 are key drivers of this T cell differentiation and the consequent production of chemokines and other inflammatory cytokines that act on the epithelium and epidermis. IL-12 and IL-23 are produced primarily by antigen-presenting dendritic cells and macrophages, and under their influence naïve T cells differentiate into Th1 and Th17 cells, respectively, the latter producing IL-17 and IL-22.[4-6] IL-17 was recently implicated as a central proinflammatory cytokine in the pathogenesis of psoriasis.[5,6]

Biologics and psoriasis

Biologic agents targeting specific immune mediators have emerged as alternative treatment options for patients with moderate-to-severe plaque psoriasis who are unresponsive to, intolerant of or have contraindications to nonbiologic systemic agents.[7] Unlike traditional systemic therapies (e.g. cyclosporin and methotrexate), biologics act in a targeted way, affecting various proinflammatory molecules involved in the immunopathogenesis of psoriasis.

Current biologics available for psoriasis in Australia include:

- monoclonal antibodies specific to TNF (infliximab, adalimumab)
- fusion proteins targeting TNF (etanercept)
- monoclonal antibodies to the p40 subunit of IL-12 and IL-23 (ustekinumab)
- monoclonal antibodies to IL-17 (secukinumab).[8]

Efalizumab, a humanised monoclonal antibody that inhibits activation of T cells, was withdrawn from global markets including Australia in 2009. This followed three confirmed and one suspected case of progressive multifocal leukoencephalopathy in patients with chronic plaque psoriasis who were continuously treated with efalizumab for three or more years.[8]

Current PBS-approved biologics

Five biologic agents are currently PBS-listed for the treatment of severe chronic plaque psoriasis (Table):

- three TNF-α inhibitors – adalimumab, etanercept, infliximab (etanercept also inhibits TNF-β)

- one IL-12 and IL-23 inhibitor – ustekinumab
- one IL-17 inhibitor – secukinumab.

These biologic agents are subsidised only for patients with severe chronic plaque psoriasis who have had lesions present for at least six months from the time of initial diagnosis and have failed to achieve an adequate response (i.e. have a PASI score of 15 or higher) after a minimum of six weeks of therapy with at least three of four conventional therapies: phototherapy, cyclosporin, methotrexate and acitretin, unless contraindicated or a toxicity develops to treatment (Box 2).

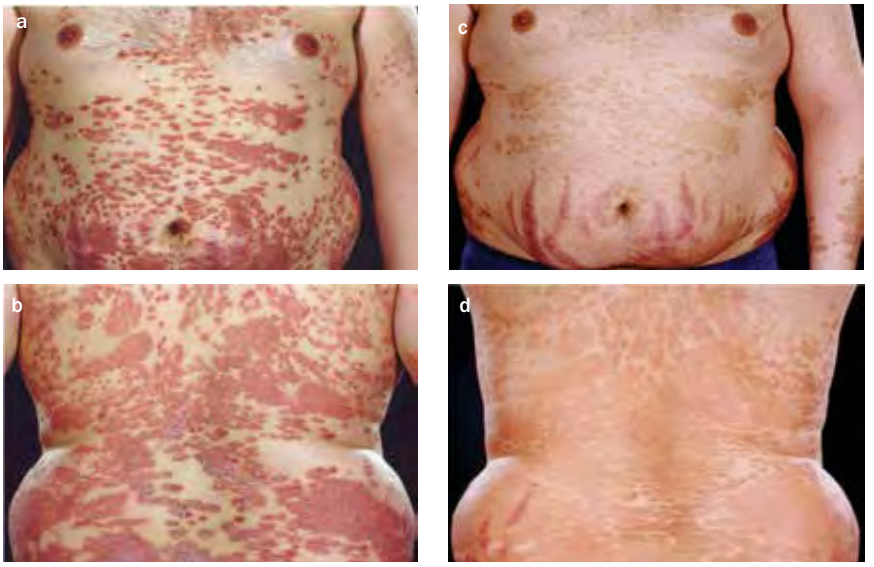
In addition, adalimumab, etanercept, infliximab and ustekinumab are PBS-listed for the treatment of severe active psoriatic arthritis. Recently published trial data have shown secukinumab to also be effective in patients with psoriatic arthritis.[9] Secukinumab is not yet PBS listed for psoriatic arthritis but recently received a positive PBAC recommendation for this indication.

The PBS listing for the biologic therapies requires that patients be treated by a dermatologist and does not permit variation in dosing schedule. The choice of biologic is individualised for the patient. Over time, all the biologics may decrease in efficacy. This may manifest as a worsening of residual psoriasis or some return of clinical disease in the lead up to the next dose. The managing dermatologist may choose any of a number of options, including increasing the dose, shortening the dose interval (neither are possible on the PBS), adding additional therapy (topical agents, phototherapy or methotrexate) or switching agents.

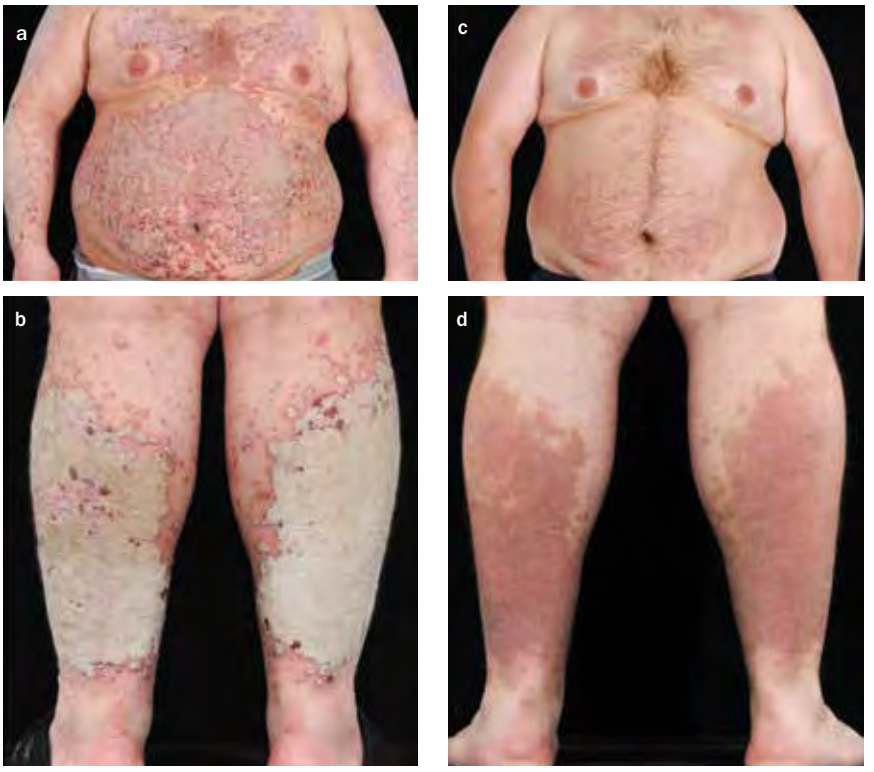
All companies that market biologics in Australia provide nursing support programs to educate and instruct patients how to self inject. They also provide support websites.

TNF inhibitors

TNF is a proinflammatory cytokine produced by a wide variety of cell types, including keratinocytes and T lymphocytes.[10]



Figures 2a to d. A 32-year-old man with a 14-year history of severe psoriasis. a and b (left top and bottom). Before treatment. c and d (right top and bottom). After 10 weeks of biologic therapy, showing a decrease in erythema score from 4 to 0. After therapy there was only post-inflammatory pigmentation and striae, the latter caused by long-term topical corticosteroid use.



Figures 3a to d. A 25-year-old man with a five-year history of severe psoriasis. a and b (left top and bottom). Before treatment, with a PASI of 43.3 and a scale score of 4. c and d (right top and bottom). After 24 weeks of biologic therapy, there was an 85% reduction in PASI and a decrease in the scale score to 0 (trunk) and 1 (lower limbs).

TABLE. PBS-APPROVED BIOLOGICS FOR THE TREATMENT OF SEVERE CHRONIC PLAQUE PSORIASIS

Drug	Class	Dosing schedule	Common side effects	Contraindications	Warnings	Pregnancy and breastfeeding	PBS approval date	Doses per script
Adalimumab	Anti-TNF-α	Adults 80 mg (2 x 40 mg injections) initial dose, then 40 mg fortnightly (subcutaneous)	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection	• TGA pregnancy category C • Caution in breastfeeding (insufficient data)	June 2009	2
Etanercept	Anti-TNF-α and β	Adults 50 mg weekly (subcutaneous)	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy • Cyclophosphamide	• Serious infection	• TGA pregnancy category B2 • Caution in breastfeeding (insufficient data)	August 2006	4
Infliximab	Anti-TNF-α	Adults 5 mg/kg at weeks 0, 2, 6, then every 8 weeks (intravenous)	• Infection • Infusion reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection	• TGA pregnancy category C • Compatible with breastfeeding	December 2007	1
Ustekinumab	IL-12 and IL-23 inhibitor	Adults 45 mg at weeks 0, 4, then every 12 weeks If >100 kg, 90 mg (2 x 45 mg) may be prescribed (subcutaneous)	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection	• TGA pregnancy category B1 • Caution in breastfeeding (insufficient data)	March 2010	1
Secukinumab	IL-17 inhibitor	Adults 300 mg at weeks 0, 1, 2, 3, then every month from week 4	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection • Active Crohn's disease	• TGA pregnancy category C • Caution in breastfeeding (insufficient data)	September 2015	1

Abbreviations: IL = interleukin; TNF = tumour necrosis factor.

TNF inhibitors are a class of systemic biologic agents used to treat patients with a range of inflammatory autoimmune diseases, including psoriasis, rheumatoid arthritis, ankylosing spondylitis and Crohn's disease.[8] In chronic psoriasis, TNF inhibition can reverse epidermal hyperplasia and cutaneous inflammation. Three anti-TNF therapies are approved in Australia for the treatment of chronic plaque psoriasis: adalimumab, etanercept and infliximab.

Etanercept

Etanercept was the first TNF antagonist approved for use in Australia in patients with psoriasis. Etanercept is a genetically engineered fusion protein composed of a dimer of the extracellular portions of human TNF receptor 2 fused to the Fc domain of human immunoglobulin G subclass IgG1.[4] Etanercept binds both soluble and transmembrane forms of TNF and also binds lymphotoxin (TNF-β). Etanercept is administered subcutaneously as a weekly fixed dose. About 34% of patients achieve a PASI 75 response at week 12.[2,3,11] The maximal effect may take up to 24 weeks of therapy with etanercept. At this time point, at least 50% of people will have achieved a PASI 75 response.[10] Etanercept is the only biologic that is PBS-listed for patients with psoriasis younger than 18 years.

Adalimumab

Adalimumab is a fully human monoclonal antibody that binds to TNF-α, preventing it from activating TNF receptors.[10] It is administered subcutaneously at weeks zero and one, and fortnightly thereafter. Onset of action is rapid, with significant improvement seen within four weeks and maximum disease response between weeks 12 and 16. About 70% of patients achieve a PASI 75 response by week 16.[11] Efficacy data show long-term responses for up to three years, with no evidence of significant loss of

2. PBS CRITERIA FOR USE OF BIOLOGIC THERAPY IN PATIENTS WITH PSORIASIS (INITIAL TREATMENT)*

To qualify for PBS authority approval for the initial treatment of chronic plaque psoriasis, the following conditions must be met:

- Patients must have a diagnosis of chronic plaque psoriasis where lesions have been present for at least six months from the time of initial diagnosis with a baseline PASI score greater than 15

OR

- Severe chronic plaque psoriasis of the face, palm or sole of the foot where lesions have been present for at least six months from the time of initial diagnosis **AND**
  EITHER
  - Two of the three PASI symptom subscores are rated severe (3) or very severe (4)

  OR
  - The affected skin is 30% or more of the face, palm of a hand or sole of a foot

AND

- The patient must have failed to achieve an adequate response, as indicated by PASI assessment (PASI score greater than 15) or the development of contraindications or intolerance, following at least six weeks' treatment with at least three of the following four treatments:
  - Phototherapy consisting of a minimum three treatments per week
  - Methotrexate at a dose of at least 10 mg weekly
  - Cyclosporin at a dose of at least 2mg per kg per day
  - Acitretin at a dose of at least 0.4 mg per kg per day

* Note: Patients must be aged 18 years or older (except in the case of etanercept) and must be treated by a dermatologist.

response over that time.[10] Interrupted therapy may result in loss of treatment response because of the formation of antibodies.[8,11]

Infliximab

Infliximab is a chimeric human–murine monoclonal antibody and the only intravenously administered biologic agent approved for psoriasis.[10] It is infused at weeks 0, 2 and 6, and then every eight weeks thereafter. Onset of action is rapid, with evidence of significant improvement within the first two weeks of treatment and maximum benefit by week 10, with 79% of patients achieving PASI 75.[11] Loss of efficacy correlates with development of antibodies to infliximab, which occurs in approximately 28% of patients treated.[10]

Interleukin inhibitors

IL-12 and IL-23 are inflammatory cytokines that play a crucial role in T cell differentiation and production of chemokines and other inflammatory cytokines that act on the epithelium and epidermis. In addition, IL-17 has recently been implicated as a central proinflammatory cytokine in the pathogenesis of psoriasis.[5,6] IL-17 stimulates keratinocytes to secrete chemokines and other proinflammatory mediators that recruit additional inflammatory cells.[12]

Ustekinumab

Ustekinumab is the only PBS-approved IL-12/IL-23 inhibitor for the treatment of chronic plaque psoriasis. Meta-analyses of clinical trial data have shown ustekinumab response rates of over 70% after 12 to 28 weeks of treatment.[3] Ustekinumab is a human monoclonal antibody that inhibits IL-12 and IL-23 by binding with high affinity to the p40 protein subunit.[10] It is administered subcutaneously at weeks 0 and 4 and then every 12 weeks thereafter. Onset of action is within two weeks, with 72% of patients achieving a PASI 75 response by week 12.[11] Disease responses are maintained long-term with continued therapy. On cessation of therapy, median time to relapse is 15 weeks.

Secukinumab

Secukinumab is the only PBS approved IL-17 inhibitor for the treatment of chronic plaque psoriasis.[12] It is a human monoclonal antibody that binds to and inhibits IL-17. Secukinumab is administered subcutaneously at weeks 0, 1, 2 and 3, and then monthly thereafter from week 4. Onset of action is within two weeks, with 81% of patients achieving a PASI 75 response by week 12.[12] This agent has only been commercially available since early 2015, but response is maintained at least to 12 months, based on published data.[12]

3. PRE-THERAPY SCREENING FOR PATIENTS COMMENCING BIOLOGIC THERAPY

Blood tests

- Full blood count, urea, electrolytes and creatinine levels, liver function tests, antinuclear antibody
- Hepatitis B and C screening
- HIV serology
- Interferon gamma release assay (for tuberculosis)

Imaging

- Chest x-ray

Other

- Age-related cancer screening (e.g. prostate specific antigen testing, mammography)

Pre-therapy screening

Patients should be thoroughly screened and fully vaccinated before commencing biologic therapy. All patients starting a biologic should be screened for serious infections, malignancy and a history of chronic illness.[7,10] Recommended pre-therapy screening includes baseline blood tests and hepatitis and HIV serology (Box 3). Pre-treatment screening for tuberculosis is mandatory. A pre-treatment chest x-ray and interferon gamma release assay currently remain the preferred screening tests.[10] Patients with signs to suggest tuberculosis, a history of previous treatment for tuberculosis or positive screening test results should be referred to a physician specialising in tuberculosis.

Biologics should be used with caution in patients with chronic infection or a history of recurrent infection. Additional baseline investigations may include lipid and

4. VACCINES CONTRAINDICATED IN PATIENTS RECEIVING BIOLOGIC THERAPY

Live attenuated bacterial vaccines

- Bacille Calmette–Guérin (BCG)
- Oral typhoid

Live attenuated viral vaccines

- Japanese encephalitis
- Poliomyelitis (oral)
- Rotavirus
- Rubella (measles–mumps–rubella, measles–mumps–rubella–varicella)
- Varicella
- Yellow fever
- Zoster

glucose levels (as people with moderate-to-severe psoriasis have higher rates of hyperlipidaemia and diabetes) and syphilis, strongyloides and varicella serology.

Treating clinicians must ensure patients are fully vaccinated before starting biologic therapy. Recommended vaccines include influenza, hepatitis A, hepatitis B, pneumococcal, diptheria, pertussis and tetanus vaccines.[10]

Drug interactions

Biologic agents have few drug interactions and concerns are mainly to prevent excessive immunosuppression. The use of other immunosuppressive agents should be considered carefully. Concurrent use of cyclophosphamide with etanercept is not recommended.

The use of live vaccines with any biologic agent is contraindicated (Box 4).[10] Patients should not receive live or live attenuated vaccinations less than two weeks before, during or less than five drug half-lives after discontinuation of biologic therapy.[10] Inactivated vaccines are safe to administer concurrently with biologic therapy. However, where possible, inactivated vaccines should be administered at least two weeks before starting biologic therapy to ensure an optimal immune response. Patients should be advised to receive pneumococcal vaccine and annual influenza vaccine while receiving biologic therapy.[10]

Monitoring

Access to ongoing PBS reimbursement requires formal specialist monitoring of response (Box 5). After the initiation period, patients need to see their dermatologist approximately every 24 weeks for assessment of PASI response and monitoring of side effects. Because biologics inhibit cellular immune responses, there is a possibility that these agents can impair defences against infections and increase the risk of malignancies.

All treating doctors should be aware of the possibility of infection. In the case of serious infections, biologic treatment should be suspended until the infection resolves. Patients with latent or previous serious infection should be carefully monitored. Regular liver function tests and full blood examination are recommended.

Side effects

Biologics are generally well tolerated with no cumulative end-organ toxicity. The most common side effects that may prompt patients to seek GP advice include injection site reactions, pruritus, rash, gastrointestinal symptoms and infections such as nasopharyngitis and upper respiratory tract infections.[7] Unless there is a suggestion of significant infection, biologic therapy can be continued.

Injection site reactions

Injection site reactions are localised areas of erythema, induration, pruritus and tenderness at the sites of subcutaneous injections of biologics, considered to be immunological in nature. Most frequently they occur a day or two after an injection and tend to last three to five days. They are usually mild and can be treated with cool compresses, topical corticosteroids, antihistamines and/or paracetamol. They usually do not require cessation of therapy and typically decrease in frequency over time, although a persistent or worsening reaction has been described. Patients are advised to rotate the site of injection. It is important to explain to patients that injection site reactions will resolve and are not related to the disease process.

5. PBS CRITERIA FOR USE OF BIOLOGIC THERAPY IN PATIENTS WITH PSORIASIS (CONTINUING TREATMENT)*

To qualify for PBS authority approval for the continuing treatment of chronic plaque psoriasis, the following conditions must be met:

- Patient must have a documented history of severe chronic plaque psoriasis

AND

- Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biologic agent for this condition in the treatment cycle

AND

- Patient must have demonstrated an adequate response to their most recent course of treatment with this drug (PASI score reduced by 75%)

AND

- The treatment must be as systemic monotherapy (other than methotrexate)

AND

- Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction

* Note: Patients must be aged 18 years or older (except in the case of etanercept) and must be treated by a dermatologist.

Paradoxical psoriasis

Paradoxically, new-onset psoriasis may appear for the first time, primarily when biologic therapy is used for indications other than psoriasis. This is an uncommon side effect, and the pathophysiology is poorly understood. The clinical appearance may be of typical plaque psoriasis or an atypical form such as pustular psoriasis, particularly involving palms and soles. Paradoxical psoriasis is an indication for dermatological review.

Serious infections

Serious infections and reactivation of latent infections such as tuberculosis have been reported in clinical trials of biologic agents. The most common infections about which patients may seek GP advice include nasopharyngitis and upper respiratory tract infections.[6] There are no known interactions between biologics and antibiotics used to treat infections. Choice of antibiotic is determined by the clinical situation, not the biologic the patient is taking. For mild infections, the biologic should be continued. For more significant infections or infections slow to respond to antibiotics, consideration should be given to temporarily suspending biologic administration.

Patients receiving biologic therapy should be monitored for early symptoms and signs of infection throughout treatment. Each review should include a detailed systems review, asking about symptoms such as fevers, night sweats and prolonged cough, prompting investigation where indicated. In addition, at each review clinicians should re-emphasise the risk of infection and the need for patients to have a lower threshold for seeking medical attention if they develop symptoms or signs of infection.

Hepatitis B

Reactivation of hepatitis B infection has been reported with anti-TNF therapy.[7] Current guidelines recommend that, in general, anti-TNF therapy should not be used in patients who are chronic carriers of hepatitis B virus.

Hepatitis C

TNF plays a role in hepatitis C-induced hepatocyte injury and treatment resistance to IFN-α2b. TNF antagonists have been used in the treatment of rheumatological disease and psoriasis in hepatitis C-positive patients with no increase in rates of hepatotoxicity or viral replication.[7,13]

Human immunodeficiency virus

The safety of biologic therapy in patients with HIV infection is unknown. Particular caution should be exercised in this group given the risk of opportunistic infections.[7]

Candida

In trials, rates of candida infection were higher in participants receiving secukinumab than in those receiving placebo or etanercept.[12] All reported cases of candida infection were mild to moderate, involving skin or mucosal surfaces, and responded to topical or oral therapies. No participants withdrew from the trials because of candida infection.[12] Any patients who develop thrush during biologic therapy should be treated with topical or oral agents as indicated, in the same manner as patients not receiving biologic therapy.

Malignancy

Any immunosuppressant agent has the potential to increase the risk of malignancy. However, to date there is no robust evidence of increased risk of malignancy with TNF inhibitors in patients with psoriasis. Data from clinical trials of their long-term use in rheumatology populations show no increased risk of solid tumours and lymphoma compared with traditional disease-modifying antirheumatic drug (DMARD) therapy.[10]

Nevertheless, all patients should be fully assessed before and during biologic therapy regarding their past or current history of malignancy and future risk of malignancy. Age-appropriate malignancy screening should be undertaken as per national guidelines for the general population.

Biologic therapy should be used with caution in patients with a history or a high risk of malignancy. It should be avoided in patients with current malignancy or a recent past history of malignancy unless the malignancy was diagnosed and treated more than five years previously and the likelihood of cure is high.[10]

Regular comprehensive dermatological assessment for skin cancer, including melanoma, is recommended before and at regular intervals during therapy, especially in patients who have an increased risk of skin cancer at baseline.[10] This monitoring is typically undertaken by the prescribing dermatologist.

Cardiovascular disease

TNF antagonist therapy should be avoided in patients with severe cardiac failure (NYHA class III or IV). Patients with well-compensated cardiac failure (NYHA class I or II) should have a screening echocardiogram, and those with an ejection fraction less than 50% of normal should not commence TNF antagonist therapy.[10] Furthermore, treatment should be withdrawn at the onset of new symptoms or worsening of pre-existing heart failure.[10]

Long-term safety

Biologic agents have shown good efficacy for the treatment of moderate-to-severe plaque psoriasis and are well tolerated in short-term trials.[7] In contrast, conventional therapies for moderate-to-severe plaque psoriasis can be associated with long-term side effects.[7] Cyclosporin has been shown to increase blood pressure, induce renal toxicity and increase the risk of non-melanoma skin cancer. Long-term treatment with methotrexate may lead to hepatotoxicity. Retinoids have been linked to teratogenicity.[7]

A review of long-term safety data (one year or longer) on etanercept, infliximab, adalimumab and ustekinumab from randomised controlled trials, open-label extension studies and meta-analyses found no long-term safety concerns. However, the data are limited and further ongoing evaluation of the long-term safety profile of these drugs is required.[7] Infusion reactions, demyelination and a lupus-like syndrome are rare side effects of anti-TNF therapy.[10] Injection site reactions are frequent but generally mild.[10]

Secukinumab was well tolerated in phase 3 trials over 52 weeks.[12] The most common adverse events reported were nasopharyngitis, headache and upper respiratory tract infection.[12] Candida infections were more common in patients receiving secukinumab but resolved on

their own or with standard therapy.[12] Crohn's disease exacerbations were observed in clinical trials; caution is required when prescribing secukinumab to patients with active Crohn's disease.[14]

Use in pregnancy and breastfeeding

No studies have assessed the safety of biologic treatments for moderate-to-severe plaque psoriasis during pregnancy. According to manufacturers' guidelines, women should discontinue biologics for five drug half-lives before conceiving.[7] Drug half-lives vary from 2.9 days for etanercept up to 21 days for ustekinumab.

Pregnancy should be avoided in patients with psoriasis receiving biologic therapy. The drugs are not thought to be teratogenic; however, patients who become pregnant while receiving biologic treatment should be referred to a specialist obstetrician for further assessment, and consideration should be given to stopping biologic therapy.[10]

Biologic agents are excreted in breast milk but are not orally absorbed; currently there is no evidence about the risk they pose. Current guidelines advise that breastfeeding should be avoided in patients receiving biologic therapy.[15]

Use of biologics before surgery

Although there is no conclusive evidence that biologics increase the risks associated with surgery, the known increase in risk of infections associated with biologics has prompted caution in the lead up to surgery. Current guidelines recommend discontinuation of therapy before surgery based on each agent's half-life and dosing interval. It is also recommended that biologic therapy is restarted postoperatively, provided that wound healing is satisfactory and there is no evidence of infection.[7]

Biologics and travel

Patients treated with systemic biologic therapy can easily travel provided there is adequate planning and preparation. Patients should ensure they have sufficient supplies of the drug to last the duration of the trip. Patients receiving intravenous therapy may find it more difficult to travel for long periods because of the need to attend an infusion centre regularly but benefit from the eight-week interval between doses.

All biologic medications must be packed in carry-on luggage to avoid extreme temperatures. Airlines will generally have a policy about how injectable medications can be carried and stored in flight. Patients need to understand that, in general, systemic biologics must be stored at 2 to 8°C to maintain their efficacy. The rules around taking medical supplies into other countries vary widely. Patients must check well in advance with the relevant authorities. Documentation including an explanatory letter from a medical professional is generally required.

Before international travel, patients should receive all necessary inactivated vaccinations. Live vaccines must not be administered. As yellow fever vaccine is a requirement for entry to some countries, patients receiving biologic therapy are precluded from travel to these countries unless they have received the vaccine before starting treatment. If patients wish to take a break from treatment during a holiday, the treating doctor must assess their PASI and document the response so that they can recommence treatment on their return.

Indications for stopping therapy

Biologic therapy should be discontinued when patients fail to achieve an adequate response after an adequate duration of therapy or when treatment response is not maintained. Withdrawal of therapy is also indicated in response to the following events:

- a serious adverse event, including malignancy (excluding nonmelanoma skin cancer)
- severe drug-related toxicity
- severe infection (temporary withdrawal)
- pregnancy (temporary withdrawal)
- elective surgical procedures (temporary withdrawal).[10]

Future for biologics

Despite the progress made to date with targeted therapies for psoriasis, not all will be effective for every patient.[16] New promising therapies for psoriasis are in development that offer treatment options for patients with difficult to treat disease and those who have failed previous biologic therapy. The advances to date have revealed new information on the immunopathogenesis of psoriasis, with a specific focus on Th17 cells and the central role of IL-17A as an effector cytokine.[5,16] These new biologics include an IL-17 antagonist (ixekizumab) and IL-23 antagonists (guselkumab and tildrakizumab).[16]

Conclusion

Psoriasis is a chronic systemic immune-mediated inflammatory disease. Biologic therapy has emerged as a safe and efficacious alternative treatment for patients with moderate-to-severe psoriasis. Patients receiving biologic therapy need monitoring for infection and regular skin cancer surveillance. The most common side effects that may prompt patients to seek GP advice include injection site reactions, nasopharyngitis and upper respiratory tract infections. New promising biologic therapies are in development, offering more treatment options for patients with difficult to treat disease. MT

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A list of references is included in the website version of this reprint collection (www.medicinetoday.com.au).

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