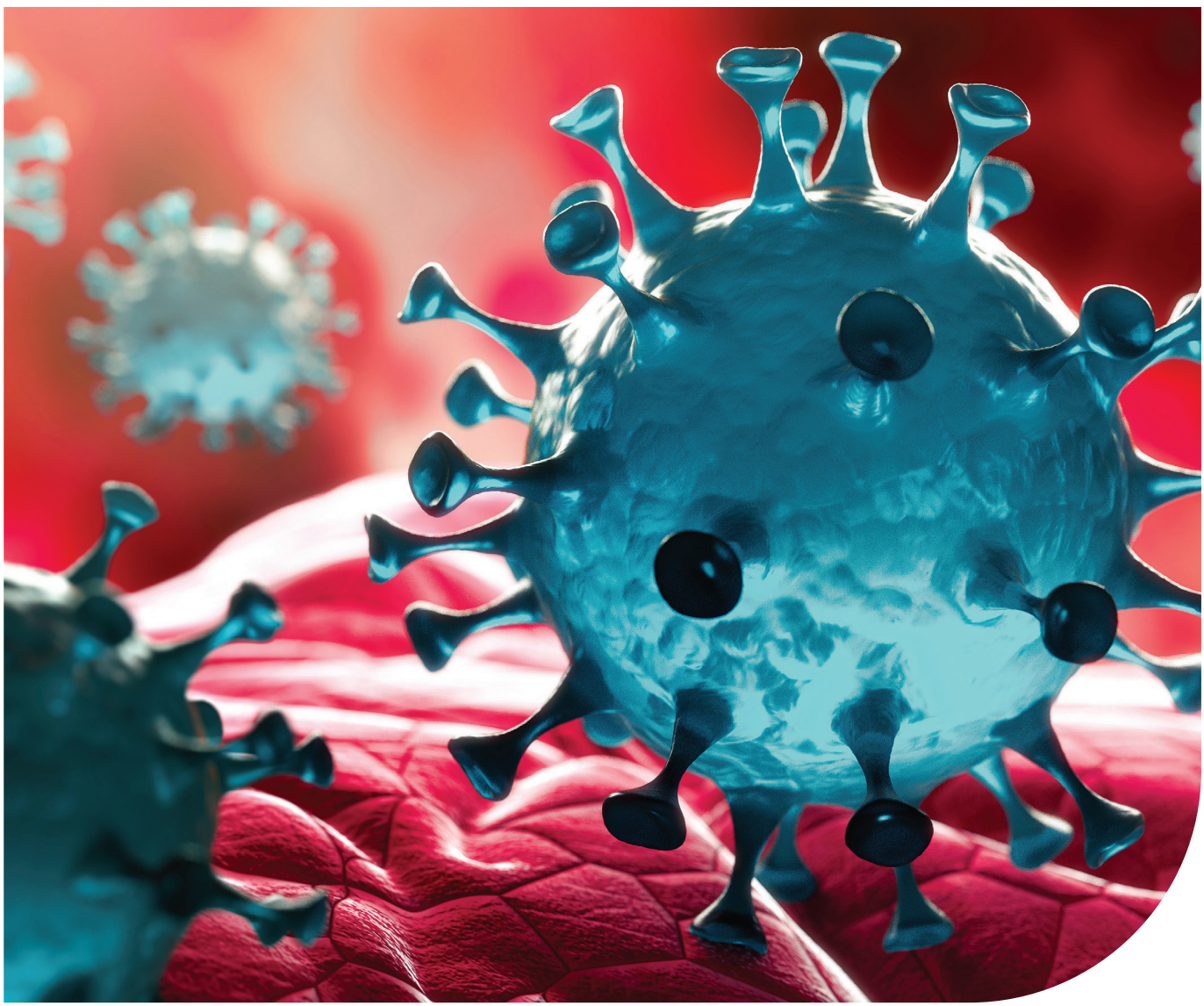
JUNE 2022 VOL 6 NO 1

A MEDICINE TODAY PUBLICATION

Dermatology Collection

PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS



Reprints in Dermatology

COVID-19 manifestations in the skin

Atopic dermatitis – an update on management in general practice

Viral exanthems: unravelling viral rashes

Skin lesions in darker skin phototypes

Recurrent, painful nodules on a girl's legs

A pregnant woman with a pruritic eruption

DERMATOLOGY COLLECTION
REPRINTS IN DERMATOLOGY
JUNE 2022 VOL 6 NO 1

ISSN 1443-430X

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A MEDICINE TODAY PUBLICATION

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PEER REVIEWED UPDATES FOR MEDICAL PRACTITIONERS

FOREWORD FROM THE EDITOR-IN-CHIEF, DERMATOLOGY COLLECTION

Our June 2022 *Dermatology Collection* covers a range of important dermatological issues, from the novel to the common and some in between.

The COVID-19 pandemic has wreaked global havoc, impacting the physical and mental health of those affected. Skin changes, including maculopapular eruptions, chilblain-like eruptions and urticaria, have been reported in up to 20% of patients with the disease. Such dermatological changes may indicate early infection, occur later in infection or be a sign of more severe disease.

With new treatments for severe atopic dermatitis recently available on the PBS, refresh your knowledge on diagnosing and managing this common, chronic and often debilitating condition.

Viral exanthems are another common presentation to the GP clinic. Read about the presentation, diagnosis and management of these diagnostically challenging rashes.

Although increased skin pigmentation is protective against UV radiation, the risk of developing certain skin conditions is higher, and prognostic outcomes of some skin cancers worse, for those with darker skin. This has particular relevance for improving outcomes for Indigenous patients.

Finally, test your diagnostic skills in two dermatology quizzes. What are the differential diagnoses and causes of the lesions in these case presentations?

Gayle Fischer OAM, *MB BS, FACD, MD*
Clinical Professor of Dermatology at Sydney Medical School – Northern, The University of Sydney, Royal North Shore Hospital, Sydney, NSW.

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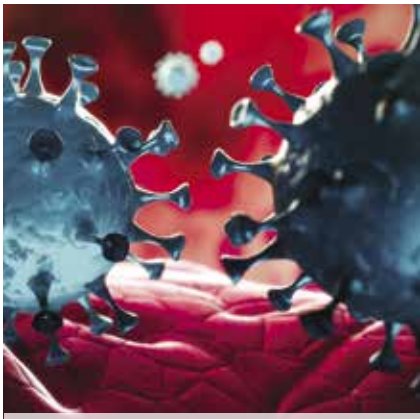

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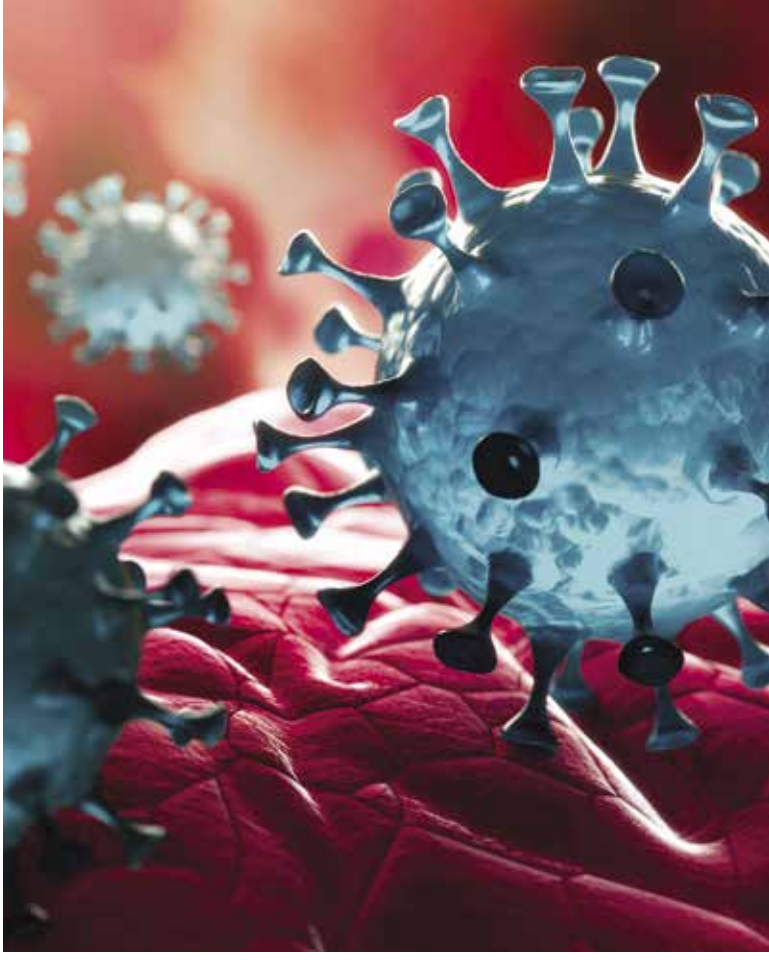
COVID-19 manifestations in the skin

PRUDENCE GRAMP MD, GCertIDI
MICHAEL FREEMAN MB BS, FRACGP, FACD

Skin changes are seen in up to 20% of patients with COVID-19 and vary widely in presentation. The most common include maculopapular eruptions, 'COVID toes', urticaria and most concerningly vaso-occlusive rashes, such as livedo reticularis and retiform purpura. Some of these skin signs are indicators of disease progression or severity.



The global pandemic of coronavirus disease 2019 (COVID-19) has now lasted more than two years, and more than 400 million cases of COVID-19 have been reported worldwide.[1] At the beginning of the pandemic, many different and unexpected skin changes were observed in association with COVID-19. It is now clear that skin changes occur in up to 20% of patients with COVID-19.[2,3] We know which skin signs are more common and which are related to disease severity. The range of possible dermatological changes is broad, including maculopapular eruptions, 'COVID toes', urticaria, nail and hair changes and vaso-occlusive rashes (Box).

This article reviews the most common skin changes associated with COVID-19, their course, relation with disease severity and management.

MedicineToday Dermatology Collection 2022; 6(1): 2-5
First published MEDICINE TODAY 2022; 23(3): 25-28

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KEY POINTS

- Skin changes are common in patients with COVID-19, seen in up to 20% of patients.
- Maculopapular eruptions and acral chilblain-like lesions are the most common skin changes seen in patients with COVID-19.
- Many skin changes have prognostic value and associations with severity of disease.
- Most skin changes do not need any specific treatment and resolve spontaneously over time.

Incidence of COVID-19 skin manifestations

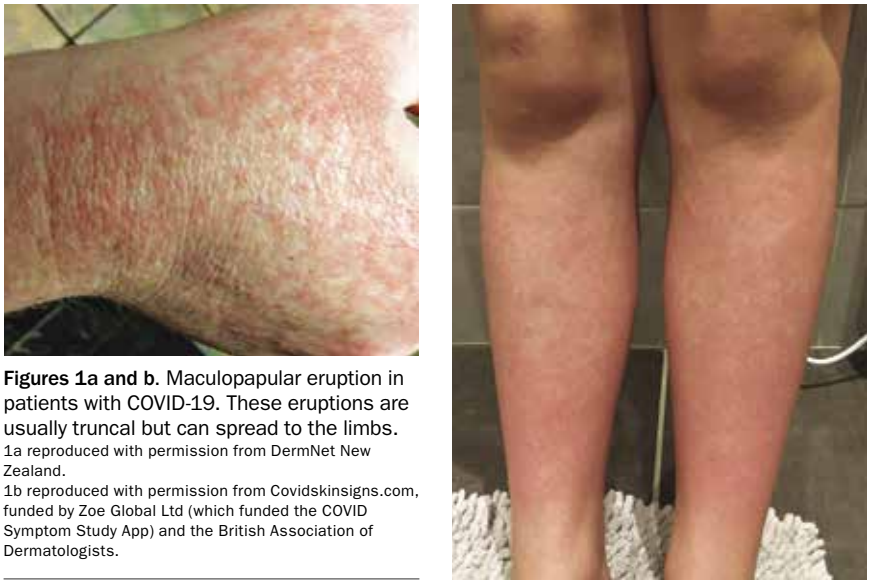
The online COVID-19 Dermatology Registry collates data about dermatological manifestations of COVID-19 on behalf of the American Academy of Dermatology and the International League of Dermatologic Societies. Any healthcare professional internationally is invited to contribute to the registry (www.aad.org/member/practice/coronavirus/registry).

The skin manifestations of COVID-19 most commonly reported to the Registry are:[3,4]

- maculopapular eruptions (22% of reported dermatological cases)
- chilblain-like or pernio-like acral lesions (18%)
- urticaria (16%)
- macular erythema (13%)
- papulosquamous eruptions (9%)
- retiform purpura (6%).

COMMON CUTANEOUS MANIFESTATIONS OF COVID-19

- Maculopapular eruption
- 'COVID toes' (pernio or acral chilblain-like lesions)
- Acute urticaria
- Livedo reticularis and retiform purpura
- Vesicular eruption
- Hair loss
- Nail signs
- Conjunctivitis
- Multisystem inflammatory syndrome in children (rare)



Figures 1a and b. Maculopapular eruption in patients with COVID-19. These eruptions are usually truncal but can spread to the limbs.
1a reproduced with permission from DermNet New Zealand.
1b reproduced with permission from Covidskinsigns.com, funded by Zoe Global Ltd (which funded the COVID Symptom Study App) and the British Association of Dermatologists.

In addition, COVID-19 has been associated with erythema multiforme, conjunctivitis, oral mucosal ulceration, petechiae, chronic urticaria and gangrene.[2,3] A multisystem inflammatory syndrome that includes skin changes has also been noted in children with COVID-19.[2,3]

Pathophysiology of COVID-19 skin changes

The dermatological signs of COVID-19 are believed to be due not to direct damage caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) itself, but rather to the elevated immune response to the virus. Overactivation of the complement system leads to microvascular damage, which is already increased in older people and may explain their higher rates of severe disease and mortality.[4] The vaso-occlusive (clotting) consequences of COVID-19 have been recognised to affect many organ systems and are thought to be also responsible for some of the skin changes.[4] Male-pattern baldness has been linked with increased risk of hospitalisation and severe disease.[5] This may be due to an increased level of the hormone dihydrotestosterone, which upregulates ACE2 receptors, the receptors that allow entry of SARS-CoV-2 into the cell.[5]

Common skin changes associated with COVID-19

Maculopapular eruptions

A maculopapular eruption is believed to be the most common skin sign associated with COVID-19 (Figures 1a and b). The rash is mostly truncal, comprising widespread small erythematous macules and papules. This type of eruption can occur at any time from the onset of illness to weeks later. Maculopapular eruptions have been associated with more severe COVID-19, with up to 2% mortality in patients with this rash.[4]

COVID toes

'COVID toes', or pernio or acral chilblain-like lesions (CLL) in the absence of cold exposure, are also very common and make up about 18% of reported dermatological manifestations of COVID-19.[3,4] COVID toes present as erythematous or violaceous itchy and painful macules over the hands or feet, with occasional vesicles or pustules (Figure 2).

COVID toes occur later in the course of COVID-19 and are an indicator of mild disease.[4,6] The condition is most common in children and in patients with a lower body mass index and is more often documented in European and US populations than in Asian populations.[4,6] The pathophysiology is believed to involve a combination of vasospasm and a type I interferon immune response.[4,6]

Interestingly, patient presentations with CLL have increased significantly in the general population during the COVID-19 pandemic despite many of these patients having a negative PCR result for SARS-CoV-2. It is hypothesised that CLL may be a late sign of COVID-19, when SARS-CoV-2 can no longer be detected by nasal PCR tests. Alternatively, SARS-CoV-2 may cause isolated cutaneous effects, supported by the isolation of viral fragments from skin biopsy specimens of asymptomatic patients with a negative nasal PCR result.[6]

No specific management has been recommended for COVID toes, although some clinicians report a response to topical corticosteroids.[3]

Acute urticaria

Acute urticaria has been seen in COVID-19 patients, consisting of itchy erythematous raised oedematous wheals that resolve quickly (Figure 3). These wheals sometimes occur at the onset of fever and other symptoms, resolving within hours but reappearing in a different distribution. Urticarial eruptions have been noted to resolve completely in COVID-19 patients

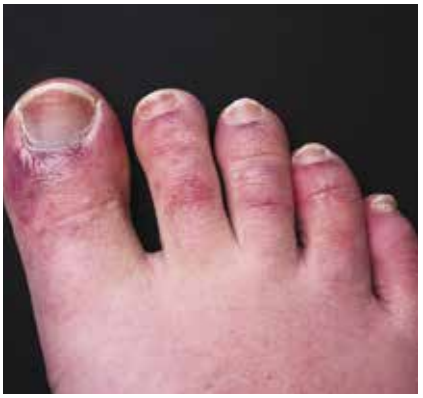


Figure 2. COVID toes showing violaceous macules.

usually within 24 hours to 10 days.[3,4] They are more common in middle-aged women and have been associated with mild or moderate disease.[4]

Acute urticaria does not require specific treatment unless it bothers the patient. The itch can be treated with a trial of nonsedating antihistamines or menthol cream.

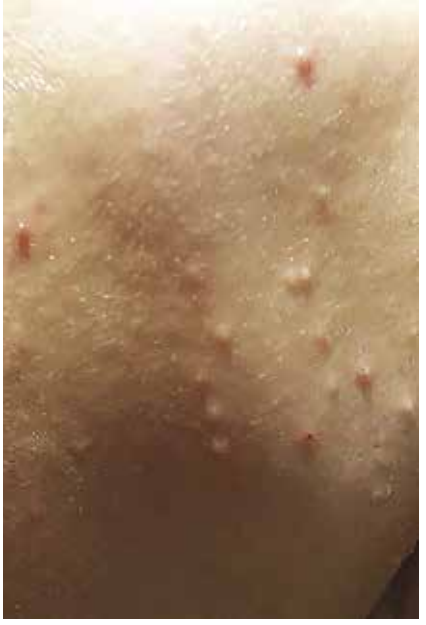


Figure 5. A vesicular eruption in a patient with COVID-19.
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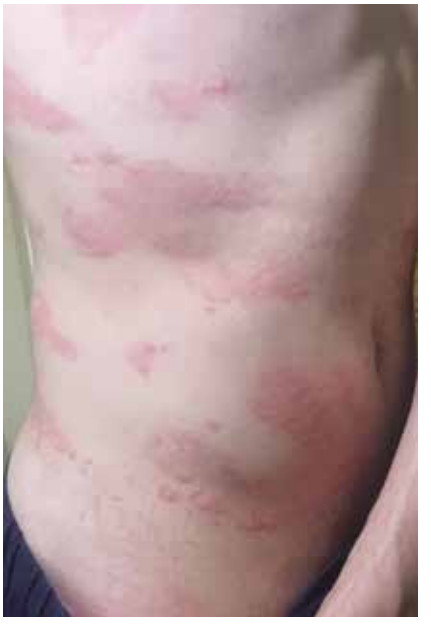

Figure 3. Urticarial eruption in a patient with COVID-19.
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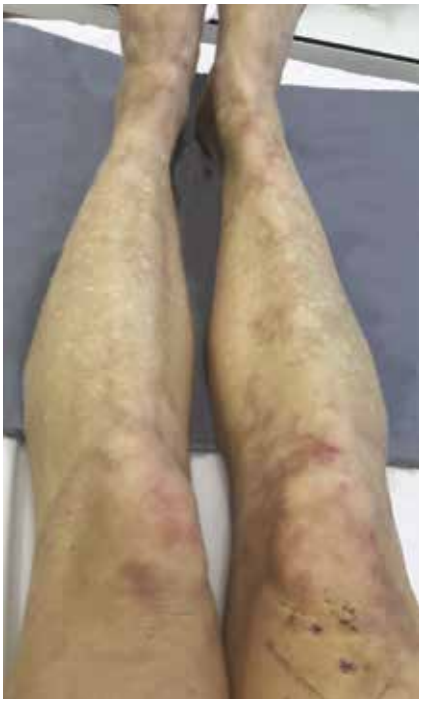

Figure 4. Livedo reticularis has been associated with severe COVID-19.

Livedo reticularis and retiform purpura

Livedo reticularis is a net-like purpuric eruption that is often described as bruise-like (Figure 4). Retiform purpura consists of stellate purpuric patches or plaques that can show necrosis or ulceration. Livedo reticularis and retiform purpura are believed to be due to thrombo-occlusion of blood vessels and complement-mediated microvascular damage.[4]

These skin signs have been associated with severe COVID-19, more commonly in older patients.[4,7] They are also associated with higher rates of intensive care admission and mortality.[4] In a case series of 11 patients with retiform purpura, all were hospitalised and nine had acute respiratory distress syndrome requiring intensive care admission.[8]

Vesicular eruption

A vesicular eruption has been seen in patients with COVID-19, consisting of small fluid-filled blisters most often on the trunk or hands (Figure 5). It occurs early in the disease course and has been associated with medium-severity COVID-19.[4] Middle-aged patients are more likely to be affected. The vesicular eruption commonly lasts about 10 days.[4]

Hair and nail changes

Hair loss (telogen effluvium and alopecia areata) can occur in many illnesses, including COVID-19, as a sign of a significant stressor on the body (Figure 6). Hair loss is usually a late sign or arises after COVID-19 illness has resolved.[9] Most hair loss resolves over time with minimal intervention. Ensuring patients' iron levels are optimised by correcting any deficiency assists with this process.

A range of nail signs have been seen in COVID-19 patients, including transverse ridges and red-violet lines (the red half-moon sign), distal onycholysis (nail plate separation) and an orange discolouration of the nail plate.[2,9] These signs

Figure 6. Alopecia areata can occur in patients after COVID-19.

Figure 7. Conjunctivitis can be a late complication of severe COVID-19.

usually appear late in the disease course or in the recovery stage and can persist for weeks to months.[9]

Conjunctivitis

Conjunctivitis has been seen in COVID-19 patients, most commonly later in disease progression and in patients with severe disease (Figure 7).

Multisystem inflammatory syndrome in children

A multisystem inflammatory syndrome in children (MIS-C) has also been associated with COVID-19, with a constellation of signs that include erythema and oedema of the hands and feet, oral mucositis, conjunctivitis and a polymorphic erythematous eruption.[3,10] This immune system 'overdrive' triggers inflammation of the heart and blood vessels similar to atypical Kawasaki disease, resulting in blood clots and symptoms of shock. Also termed paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), this is a rare complication that typically occurs two to six weeks after a child has had COVID-19.[10] Screening for vascular com plications should be considered for patients who present with other signs of this syndrome.

Cutaneous changes after COVID-19 vaccination

Some cutaneous changes have been associated with COVID-19 vaccines, the most common being injection-site reactions, angioedema and urticaria.[11] Maculopapular and morbilliform eruptions and pityriasis rosea have also been seen after vaccination. For some patients with dermatological conditions such as psoriasis or atopic dermatitis, flare ups have been reported after vaccination.[11]

Conclusion

Some dermatological signs of COVID-19 appear early in the disease, such as urticaria, maculopapular eruptions and vesicular eruptions. Testing for COVID-19 should be considered in patients with these rashes, if not already performed, to capture all positive cases. Other dermatological signs occur later in the disease course, such as COVID toes and conjunctivitis.

Vaso-occlusive skin signs such as livedo reticularis and retiform purpura and MIS-C are signs of more severe disease and can lead to severe complications. Patients with these skin signs require careful monitoring, referral and follow up. Most skin manifestations resolve within days to weeks and can be managed with simple measures, such as corticosteroid creams or antihistamines. MT

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COMPETING INTERESTS: None.

Atopic dermatitis

An update on management in general practice

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Atopic dermatitis is a common, chronic and often debilitating inflammatory skin disorder with a large burden of its diagnosis and management falling within primary care. New advancements and updates to management are significantly improving the outcomes for patients with this condition.

KEY POINTS

- Atopic dermatitis is a common condition and is largely managed in the primary care setting.
- Understanding and quantifying the impact of the condition on quality of life is important when tailoring therapy for patients.
- First-line therapy involves robust education around general measures and commencement of appropriate topical corticosteroid therapy.
- Should patients fail to respond to optimised general measures and topical corticosteroids after one month, they should be referred to a dermatologist.
- Dupilumab and upadacitinib are new advanced therapies that have profound benefits for patients with severe atopic dermatitis and have recently been added to the Pharmaceutical Benefits Scheme.

Atopic dermatitis is a common, chronic and often debilitating inflammatory skin disorder characterised by pruritis, erythema and excoriations. It affects between 15 and 20% of the Australian population, with the burden steadily increasing.[1] The highest incidence is associated with infancy and early childhood, with 20% of this age population being affected at some point. However, there is also a substantial prevalence of around 6% in adulthood.[1]

Atopic dermatitis is closely associated with other atopic diseases, including asthma, food allergies and rhinosinusitis. Its pathogenesis is complex and multifactorial, involving epidermal barrier abnormalities and immune dysregulation in genetically susceptible individuals, as well as environmental triggers, such as heat, infection and potential allergies.[2]

MedicineToday Dermatology Collection 2022; 6(1): 7-13
First published MEDICINE TODAY 2022; 23(4): 25-31

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Figure 1. Severe atopic dermatitis.

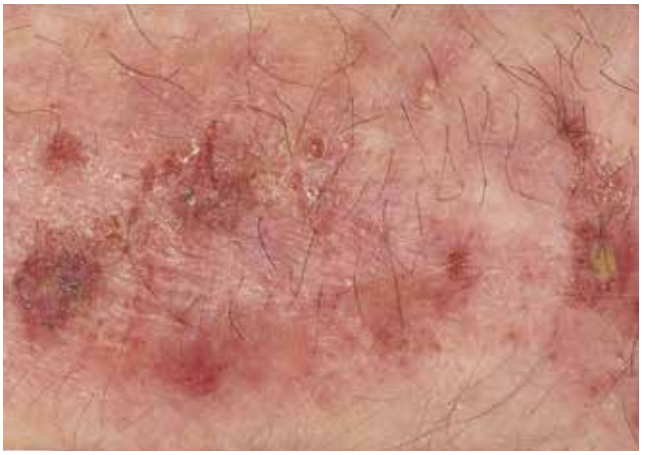


Figure 2. Close up of atopic dermatitis showing scaly erythematous plaques with excoriations.

Atopic dermatitis has a profound impact on quality of life, with associated mood and sleep disturbance.[3-5] Traditional treatment regimens are centred on symptomatic control through general measures, topical agents, light therapy and other immunosuppressants. Inadequate response to treatment and potential toxicity has previously limited treatment benefit.[6] The recent addition of advanced therapies, monoclonal antibodies and Janus kinase (JAK) inhibitors to the Australian Pharmaceutical Benefits Scheme (PBS) is significantly shaping the management of atopic dermatitis and improving the long-term outcomes for patients with severe disease.

Atopic dermatitis is consistently identified as the most frequent new dermatological consultation in general practice, and most patients with mild disease are managed in primary care.[7] This article provides a framework for the management of this highly prevalent condition, including new advances in therapy.

Pathogenesis

The pathogenesis of atopic dermatitis is complex, led by dysregulation of innate and adaptive immunity, as well as genetic risk factors and environmental triggers. It is driven by type 2 helper (Th2) cell inflammation, the key cytokines involved in this being interleukin (IL) 4 and IL-13.[2] Poor skin barrier function is associated with mutations in the epidermal protein filaggrin.[2] This predisposes patients to infection with micro-organisms, in particular bacteria and viruses, as there is greater penetration of these through the skin.[8] Environmental triggers include climate (low humidity), behaviours that increase skin dryness (e.g. soap use, hot showers, chlorinated swimming pools) and exposure to irritants and allergens.

Clinical appearance

Atopic dermatitis manifests as pruritic, poorly demarcated erythematous scaly lesions (Figures 1 and 2).[9] The distribution can vary, but is often flexural, affecting the antecubital fossae, popliteal fossae, face and neck. Over time, the skin becomes thickened due to chronic rubbing and scratching. Dyspigmentation can be seen, depending on skin phototype. The condition may be relapsing with acute flares and periods of remission, but in more severe cases there is continuous involvement.

Complications and psychological impact

Atopic dermatitis carries a large psychological burden and can have a significant detrimental impact on quality of life. There is greater prevalence of mood-related, sleep and behavioural disorders in patients with severe disease, generally driven by pruritus.[3-5] Additionally, there is a large cost burden relating to hospital admissions, treatments and potential time off school or work.[10]

Skin infections are common in patients with atopic dermatitis because of the deficient barrier function and antimicrobial activity.[8] *Staphylococcus aureus* colonisation is frequent, with infections exhibiting the characteristic features of honey-coloured crust and pustules. *S. aureus* can also be found in higher numbers in non-lesional skin, so antibiotics are not required on the basis of this finding on a swab result alone. Bleach baths are often recommended both as prevention (once or twice a week) and active treatment (daily) of infected eczema. The dilution is 12 mL bleach (e.g. plain, fragrance-free household bleach) per 10 L water, and the immersion time two to five minutes. No rinsing is required. This can minimise the need for oral antibiotics. In the case of severe bacterial infection, oral cephalexin (12.5 to 25 mg/kg, three times daily for seven to 10 days) may be necessary.

Viruses, including herpes simplex virus, herpes zoster virus and poxvirus

(molluscum contagiosum), are also common causes of cutaneous infection and flares of atopic dermatitis. Herpetic infection presents with crops of small, painful, punched-out ulcers or vesicles on an erythematous base. For suspected herpes infection, empirical oral aciclovir, famciclovir or valaciclovir is given for five days. If there are lesions around the eyes, urgent referral for ophthalmological assessment is required.

Diagnosis and scoring

Several scoring tools are available for the diagnosis of severity and to monitor patient progress against objective measures. The Dermatology Life Quality Index (DLQI) is a commonly used simple patient questionnaire for the clinical evaluation of the impact of eczema.[11] Table 1 shows the interpretation of the scoring involved in the DLQI; the full questionnaire can be found at https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index. The Eczema Area and Severity Index (EASI) is a validated scoring system that grades the physical signs of atopic dermatitis in each region of the body and gives a score equating to the percentage of total affected surface area.[12] Further information about the EASI can be found at https://dermnetnz.org/topics/easi-score.

These tools can form useful adjuncts in the management of atopic dermatitis. In the primary care setting however, where time may be limited, the emphasis should be on eliciting the severity of itch, impact on sleep and frequency of flares.[13]

Management of atopic dermatitis

General measures

Education and patient involvement are imperative in the management of atopic dermatitis, regardless of severity. It is important to listen to the patient's perspectives to identify any suspected triggers and discuss their treatment goals and potential limitations to adherence. Disease quiescence cannot be achieved without maintaining a constant background of general

TABLE 1. INTERPRETATION OF THE DERMATOLOGY LIFE QUALITY INDEX (DLQI)[11]

DLQI question	Answer	Score
1. Over the last week, how itchy, sore, painful, or stinging has your skin been?	• Very much • A lot • A little • Not at all	3 2 1 0
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?	• Very much • A lot • A little • Not at all	3 2 1 0
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	• Very much • A lot • A little • Not at all	3 2 1 0
4. Over the last week, how much has your skin influenced the clothes you wear?	• Very much • A lot • A little • Not at all	3 2 1 0
5. Over the last week, how much has your skin affected any social or leisure activities?	• Very much • A lot • A little • Not at all	3 2 1 0
6. Over the last week, how much has your skin made it difficult for you to do any sport?	• Very much • A lot • A little • Not at all	3 2 1 0
7. Over the last week, has your skin prevented you from working or studying? If 'No', over the last week how much has your skin been a problem at work or studying?	• Yes • No • A lot • A little • Not at all	3 2 1 0
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	• Very much • A lot • A little • Not at all	3 2 1 0
9. Over the last week, how much has your skin caused any sexual difficulties?	• Very much • A lot • A little • Not at all	3 2 1 0
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	• Very much • A lot • A little • Not at all	3 2 1 0
		TOTAL: /30

INTERPRETATION OF SCORE

0 to 1: No effect at all on patient's life

2 to 5: Small effect on patient's life

6 to 10: Moderate effect on patient's life

11 to 20: Very large effect on patient's life

21 to 30: Extremely large effect on patient's life

1. GENERAL MEASURES FOR MANAGEMENT OF ATOPIC DERMATITIS

Allergen identification and avoidance
- Identify external irritations and allergens, e.g. excessive hand washing or use of harsh detergents
- Recommend the use of soap-free washes, baths with oil and salt, and antimicrobial washes/bleach baths

Emollient use
- Recommend the use of simple emollients without added fragrances or allergens (e.g. essential oils) – emollients are the cornerstone of management to reduce xerosis and to restore the defunctive epidermal barrier
- Ceramide-containing moisturisers have the potential to repair the skin barrier more effectively than other emollients; adjust their texture and greasiness for the affected sites and patient preference

Heat avoidance
- Educate patients about the minimisation of too many layers of clothing, hot showers or baths, hot bedding and hot room temperatures

Oral antihistamine use
- Educate patients about the use of oral antihistamines – they are safe and can help manage symptoms of pruritus, and potentially sedating antihistamines can also help manage sleep disturbance

measures to restore barrier function and prevent infections.[13] All patients should be instructed to keep cool, moisturise twice daily (ideally with a ceramide-containing moisturiser) and avoid soaps and fragrances (Box 1).

Topical therapies

Mild atopic dermatitis is typically managed in the primary care setting. The basis of treatment is formed through the above general measures and the addition of topical corticosteroids (TCS) and/or topical calcineurin inhibitors.

Education, counselling and guidance for application of topical therapies are paramount. These therapies require patient motivation and can be time consuming and burdensome for both patients and their families.[10] Patients often underuse their topical treatments because of phobias and misunderstanding.[14] Lack of adherence leads to failure. It is important to encourage liberal use without strict time limits (which unfortunately only enhances their fears regarding these medications). Strategies to improve adherence include ensuring adequate quantities of topical medications are prescribed, arranging regular follow up and developing written action plans, including protocols for flares.

When used appropriately, TCS are safe and well tolerated.[15] Skin thinning (atrophy) is an overexaggerated side effect and is rarely seen. The most common side effect of the use of a potent TCS on the face is periorificial dermatitis, a form of steroid-induced rosacea that is treated with a tetracycline antibiotic. Striae are the most concerning side effect of potent TCS use in the groin or axillae as they are irreversible, unlike atrophy, which is minimally visible and reversible. Cataracts and glaucoma are the most concerning adverse effect of potent TCS use on the eyelids. For these reasons, a potent TCS should not be used on the face, and hydrocortisone 1% and topical calcineurin inhibitors are the treatments of choice for the face and genitalia. Pimecrolimus cream is safe and generally well tolerated, and is affordable as it is listed on the PBS. However, its use can be limited by stinging and lack of efficacy. Topical tacrolimus 0.1% is compounded as either ointment or cream in Australia and is significantly more effective then pimecrolimus, although more expensive. Topical calcineurin inhibitors should be avoided in the setting of herpetic infection and can also potentially trigger periorificial dermatitis.

The ideal duration of therapy for topical therapies is between two and four weeks, although ongoing low potency TCS use and intermittent long-term medium potency TCS use is considered safe.[13] Principles and strategies guiding choice of potency and vehicle of corticosteroid, based on severity, location and patient factors, are summarised in Box 2.

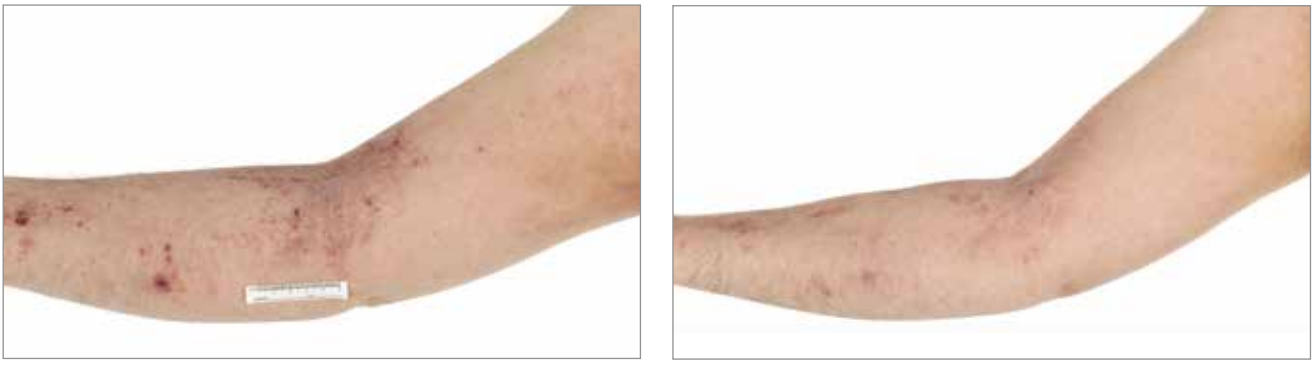
2. PRINCIPLES TO GUIDE TOPICAL CORTICOSTEROID USE

Potency of topical corticosteroids (TCS)
- Low potency TCS, such as 1% hydrocortisone, are preferred for use on large surface areas of skin or on sensitive areas including the face and groin, where there is thinner, more sensitive skin
- More potent agents can be used for thicker areas of skin:
  - mometasone furoate or methylprednisolone aceponate can be safely used on the torso and limbs
  - potent TCS such as betamethasone dipropionate are often warranted on the hands and feet

Vehicle choice
- Ointment formulations are more potent because of their enhanced penetration and moisturising ability, and are less likely to sting on broken skin; however, they are hotter and greasier, resulting in greater risk of folliculitis, periorificial dermatitis and lower acceptability in some patients
- Cream formulations are better tolerated in hairy or acne-prone areas of skin
- Lotion formulations should be prescribed for the scalp

Strategies to increase penetration
- Use under occlusion or in 'wet wraps' can increase penetration of TCS into the skin but this should generally only be for short durations (5 to 7 days) and with the lower potency agents
- TCS effectiveness is improved with hydrated skin, e.g. use immediately after baths or showers

Crisaborole is a topical phosphodiesterase-4 inhibitor that is a key regulator in the inflammatory cascade in atopic dermatitis. It has been shown to be a well-tolerated and efficacious, albeit expensive, alternative as it is not yet listed on the PBS. It can be used as a nonsteroidal



Figures 3a and b. Severe atopic dermatitis before (a, left) and six weeks after (b, right) commencement of dupilumab therapy.

option for patients in whom TCS are ineffective or contraindicated, or in patients who require a break from TCS therapy.[16]

Escalation of therapy

Treatment failure is guided by the patient's opinion of worsening of lesions after one to two weeks, or the physician's opinion of an unchanged clinical score four weeks after therapy (according to the DLQI or Physician Global Assessment [PGA] scores – a 5- or 6-point scoring system used to assess disease severity).[13] It is important to assess the factors relating to treatment response, including severity of disease, infection, compliance, and social and psychological factors. Dermatology referral should be made promptly for treatment failure, or in the setting of frequent number of flares, significant interference with quality-of-life, including sleep or ability to function at school or work, and recurrent bacterial or viral infections.

Phototherapy

Narrowband ultraviolet B (nbUVB) can be used as an adjunct in patients who fail to respond to topical therapies. In one recent large cohort study, it was found that 70% of patients received significantly less TCS in the 12 months following a course of nbUVB, and nearly 50% of patients were scored as clear or almost clear at the end of a two-month course of treatment.[17] Considerations before starting phototherapy include skin type (very fair skin and a history of skin cancer are relative contraindications), availability and logistics. Sessions ideally take place three times a week for around six to eight weeks, although this can vary depending on the patient and their response.[13] Phototherapy has a favourable safety profile and is well tolerated among most users. Risk of skin cancer is considered low, provided the number of treatments remains below 200 to 400.[13] Other possible adverse effects include burning, tanning and hyperpigmentation, depending on the patient's skin type.

Oral corticosteroid treatment

Systemic corticosteroid therapy should be reserved for patients with severe atopic dermatitis as rescue therapy for significant flares. A standard course for an acute flare of atopic dermatitis would be prednisolone 0.5 mg/kg (25 to 37.5 mg) for four days, 0.25 mg/kg (12.5 to 15 mg) for four days, 0.125 mg/kg (5 to 7.5 mg) for four days, then cease. Well described short- and long-term complications are involved with its use, and any patient requiring multiple courses per year needs to be assessed by a dermatologist.

Other immunosuppressant treatment

Other systemic therapies include immunosuppressants such as ciclosporin, azathioprine, methotrexate and mycophenolate mofetil. These have been important steroid-sparing agents for severe atopic dermatitis patients. However, there can be significant systemic toxic adverse effects and these should only be prescribed by a specialist; close clinical and laboratory monitoring is required.

Ciclosporin is the only oral immunosuppressant with an approved indication for use in atopic dermatitis. It is used in doses of 3 to 5 mg/kg. It is not recommended for continuous use of longer than two years because of the high risk of hypertension and renal impairment. Rebound flares are common on cessation. Close monitoring of blood pressure, renal function and for systemic infection is required.

Methotrexate in doses of 5 to 20 mg weekly has long been used as a steroid-sparing agent in atopic dermatitis as it is relatively low-risk and cost effective. It can be given either orally or as a subcutaneous injection (if there are compliance or absorption concerns). Nausea, liver toxicity and lack of efficacy are drawbacks to its use.

Azathioprine can be an effective treatment in a relatively small proportion of patients with atopic dermatitis. Nausea, infections and severe drug reactions can be seen, however, and regular monitoring of haematological parameters and liver function tests are required.

Mycophenolate mofetil has become more popular in the last few years as a treatment option for atopic dermatitis now it is more easily available and cheaper. The effective dose range is from 500 mg to 4 g per day. However, as with the other agents, many patients fail to achieve substantive improvement. Nausea, gastrointestinal upset and infections are the major side effects.

Biologic therapy

Dupilumab is a monoclonal antibody that specifically reduces the action of IL-4 and IL-13 cytokines by blocking their binding to their shared receptor. It is considered a targeted immunomodulator that addresses the type 2 inflammation without causing immunosuppression. It was listed on the PBS in April 2021 for use in patients aged 12 years and over with severe atopic dermatitis that has not responded to four weeks of moderate-potency TCS use. Large scale clinical trials have shown its efficacy and long-term safety.[18,19] Meaningful improvements in sleep, pruritus and overall quality of life can be experienced in as little as a few weeks and are sustained with long-term use.[12] 'Before and after' images of severe atopic dermatitis-affected skin treated with dupilumab for six weeks are shown in Figure 3.

Dupilumab is administered subcutaneously with an initial loading dose of 600 mg and then a 300 mg dose every two weeks. No blood test monitoring is required. The most common side effects of therapy are ocular symptoms, including dry eyes and conjunctivitis; these can usually be treated with topical therapies and rarely require cessation of therapy, although referral to an ophthalmologist may be required in some cases.

Other advanced therapies

The first of the JAK inhibitors, upadacitinib, was approved by the PBS in March 2022 for severe atopic dermatitis in patients aged 12 years and older. JAK inhibitors are small molecules that inhibit intracellular signalling. The initial dose is 15 mg daily, orally. Upadacitinib appears to be highly effective for atopic dermatitis, but not effective for atopic comorbidities, such as asthma. This class of medication requires monitoring of blood tests for anaemia, lymphopenia and hyperlipidaemia. Side effects include acne and an increase in infections, particularly herpes zoster, but no ocular issues as are seen with dupilumab. Patients are encouraged to be vaccinated against herpes zoster before starting upadacitinib.

Other novel therapies are being investigated and awaiting approval for use in Australia for the treatment of atopic dermatitis.[20,21]

Conclusion

Atopic dermatitis is a common condition that can range from mild to severe, and can have significant impacts on patients' quality of life. First-line therapy involves education around general measures and commencement of appropriate topical therapy with regular follow up. Dermatologist referral should be arranged for patients who have failed to respond to first-line measures, as there are now additional advanced treatments available for patients with severe disease. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Ross has received consulting, speaking and advisory board fees from Sanofi Genzyme, Abbvie and Leo, and meeting attendance support from Sanofi. Dr Arasu: None.

ONLINE CPD JOURNAL PROGRAM

List two non-corticosteroid topical treatments for atopic dermatitis on the face.

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Atopic dermatitis

An update on management in general practice

ALEXIS ARASU MB BS(Hons), BMedSc(Hons); **GAYLE ROSS** MB BS(Hons), FACD

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Viral exanthems

Unravelling viral rashes

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Common causes of viral exanthems in Australia include herpesviruses, enteroviruses, parvovirus B19, varicella, measles and rubella viruses and mosquito-borne alphaviruses. The cause can often be diagnosed clinically from the rash distribution and morphology, confirmed only when necessary with serological or PCR tests. Most viral exanthems are self-limiting, requiring supportive care alone.

Viral exanthems in children and adults are a common presentation to GPs. Viral exanthems can be triggered directly by an infectious pathogen (infectious exanthem) or indirectly by an immune response (parainfectious exanthem).[1] Although some viral exanthems are benign and self-limiting, early diagnosis is paramount in patients with severe systemic infection and in those who are pregnant, immunocompromised or require time off work or school, and before immunisation.[2] The diverse morphologies of viral exanthems can be a diagnostic challenge. Knowledge

KEY POINTS

- Viral exanthems are common, and detailed history taking and examination of the morphology and distribution of the rash are essential to determine the cause.
- Viral exanthems such as varicella and rubella can cause significant complications in pregnant women, so early diagnosis and treatment are key.
- Viral exanthems can be diagnosed clinically, and clinicians should think critically before ordering molecular and serological testing.
- Certain viral exanthems, such as Ross River virus disease, must be notified to the appropriate public health unit as per state or territory guidelines.
- High vaccination rates are crucial to reduce the incidence and morbidity of viral exanthems such as measles.

MedicineToday Dermatology Collection 2022; 6(1): 15-25
First published MEDICINE TODAY 2022; 23(1-2): 31-41

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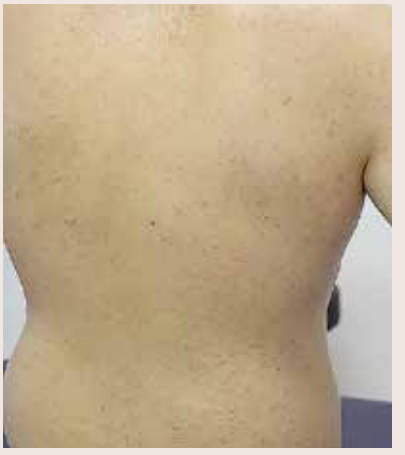
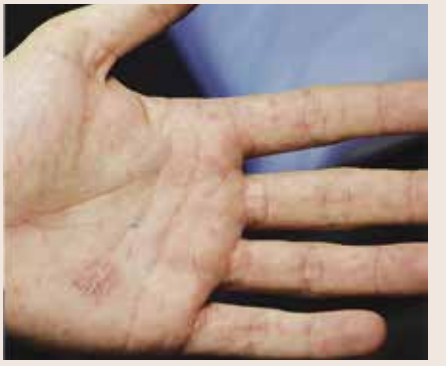
1. CASE STUDY: A 24-YEAR OLD MAN WITH AN ITCHY PAPULOPUSTULAR RASH

A 24-year-old man presented with a whole-body papulopustular pruritic rash (Figures 1a and b). He also had lethargy, myalgia and arthralgia and had returned from North Queensland a week before. Pathology testing showed mild thrombocytopenia and atypical lymphocytes. A skin biopsy showed vacuolar interface changes consistent with a viral exanthem. What are your differential diagnoses and how would you manage this patient?





Figures 1a and b. Papulopustular rash in a 24-year-old man.

of the different patterns of viral rashes and their epidemiology are crucial to identifying their aetiology.

In this article, we provide a diagnostic framework for viral exanthems based on the rash distribution and morphology (summarised in the Table). However, it should be noted that the different viral exanthems are not limited to any particular distribution or morphology. Further, presentations can be atypical, especially in patients who are vaccinated or immunocompromised. We also outline the common causes, investigations and management of viral exanthems. A case study of a viral exanthem is outlined in Box 1.

TABLE. COMMON VIRAL EXANTHEMS AND TYPICAL RASH PRESENTATION

Diagnosis	Typical rash presentation
Roseola infantum	Rash progresses from trunk to extremities
Hand, foot and mouth disease	Vesicles on mouth, palms, and soles
Papular-purpuric gloves and socks (PPGS) syndrome	Erythema in gloves and socks distribution
Gianotti-Crosti syndrome	Papules on extensor surfaces of limbs, buttocks and face
Herpes labialis and genitalis	Vesicles on the lips, mouth or genitals
Varicella (chickenpox)	Vesicles on the face, trunk and limbs
Zoster (shingles)	Vesicles in a dermatomal distribution
Measles	White lesions on the mucosa (Koplik spots)
Rubella	Maculopapular rash progresses cephalocaudally
Unilateral laterothoracic exanthem	Rash progresses centrifugally from axillae
Pityriasis rosea	Fir-tree distribution of rash on the trunk
Ross River virus disease, Barmah Forest virus disease	Maculopapular rash on limbs and trunk
Influenza	Maculopapular rash sparing face and palmoplantar surfaces or petechial exanthema
Coronavirus disease 2019 (COVID-19)	Morbillifom, vesicular, pityriasis rosea-like or erythema multiforme-like eruptions, chilblains or vasculopathies

How to differentiate viral and nonviral exanthems

Viral and nonviral exanthems have some distinguishing features. However, identifying the cause can be difficult as viral rashes can be a 'great imitator' for other diseases, and presentations can be atypical. Clues that suggest a rash is viral are listed in Box 2.[3] Differential diagnoses that should be considered include systemic adverse reactions to drugs, bacterial toxins, malignancy, allergic contact dermatitis and other diseases.[4]

Although many viral exanthems in children are accompanied by coryzal symptoms, the diagnosis can generally be made clinically. Before ordering respiratory viral tests, clinicians should critically assess the need for them, considering issues such as their clinical utility, accuracy and finite resources.[5] Similarly,

2. CLUES SUGGESTING A RASH IS DUE TO A VIRUS

Clinical history
- Abrupt onset
- Arthropod exposure
- Travel
- Sick contacts
- Vaccination

Symptoms
- Conjunctivitis, cough, diarrhoea, malaise, headache, insomnia, irritability, sore throat, vomiting
- No pruritus
- Viral rashes can also occur in children who are otherwise well

Morphology
- Bright macular or morbilliform rash
- Vesicles
- Petechiae

Distribution
- Symmetrical
- Starts on the face and acral sites and spreads to the trunk and buttocks
- Peripheral and central distribution

Other signs
- Fever
- Hepatomegaly
- Lymphadenopathy
- Rash on the mucous membranes (enanthem)[3]

Investigations
- Serology positive for specific virus
- PCR test positive for virus
- Lymphocyte count shows lymphocytosis

clinicians should think critically before ordering molecular and serological testing.

Rash progressing from trunk to extremities – roseola infantum

Roseola infantum (exanthema subitum, sixth disease) is a benign, febrile exanthem of childhood caused by human herpesviruses (HHV) 6 and 7. HHV-6 and HHV-7 are ubiquitous among humans, and nearly 100% of the population is infected by the age of 3 years. Primary infection often manifests as a mild illness, sometimes even asymptomatic. HHV-6 and HHV-7 are transmitted by salivary contact and via the placenta.[6]

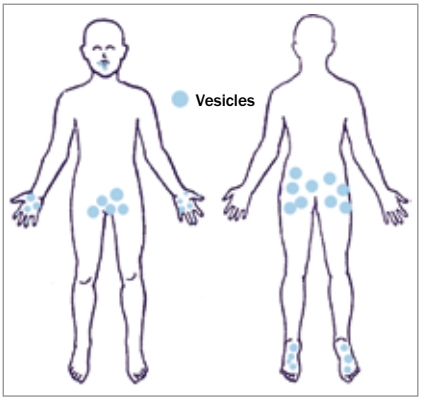
Roseola infantum starts with a high fever lasting three to seven days. After the fever subsides, a faint, rose pink, blanching skin eruption appears suddenly. Discrete, irregular, circular or elliptical macules or papules occur on the neck and trunk and can spread to the face and extremities (Figure 2). The rash lasts one to two days. Diarrhoea, upper respiratory symptoms and cervical lymphadenopathy can develop. Febrile seizures, hepatitis and encephalitis are rare sequelae.

Recognition of the distinctive clinical course is usually sufficient for diagnosis of roseola infantum. However, the gold standard for diagnosis is the detection of seroconversion and actively replicating HHV-6 or HHV-7 in peripheral blood through culture. PCR testing of body fluids and tissues can also be used to detect viral DNA and quantify viral load.

Roseola infantum is self-limiting, and supportive care involves antipyretics and maintenance of hydration. Antivirals can be effective in immunocompromised children.[4]

Vesicles on mouth, palms and soles – hand, foot and mouth disease

Hand, foot and mouth disease (HFMD) is the most common manifestation of human enterovirus infection. It is usually caused by coxsackievirus A6 or A16 or enterovirus 71. HFMD should not be confused with foot and mouth disease, which affects cattle, sheep and pigs. HFMD mostly affects children younger



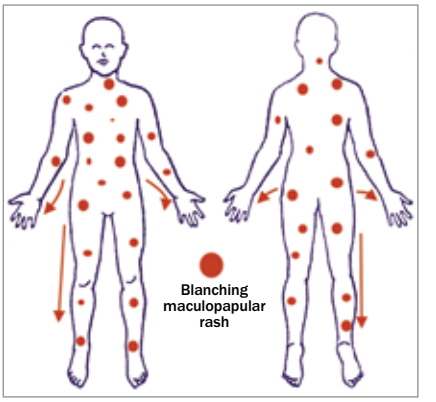
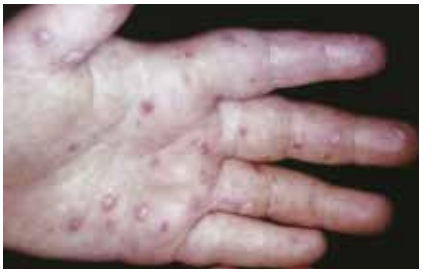


Figure 2. Typical distribution of the rash in roseola infantum (sixth disease).

than 5 years and has a peak incidence in summer. HFMD is spread by the faecal-oral or oral-oral routes, and outbreaks are common in childcare centres.

Patients with HFMD usually have a prodrome of fever, malaise, coryza, reduced appetite and sore mouth occurring one to two days before the rash. Classic HFMD presents as a localised eruption of vesicles and painful ulcerations in the oral cavity, followed by erythema and pruritic greyish vesicles on the digits, palms, soles, buttocks and genital area (Figures 3a and b). Atypical HFMD has been reported, with a widespread vesiculobullous and erosive eruption favouring the perioral, acral and buttock regions. Enterovirus infection with a fulminant course has also been noted to cause acute flaccid paralysis in South East Asia and Australia.[4]

Enteroviral exanthems can usually be diagnosed clinically, but the differential



Figures 3a and b. Hand, foot and mouth disease: typical distribution (a, left) and morphology (b, above) of the rash.

Figure 4. Erythema infectiosum (fifth disease, slapped cheek disease).

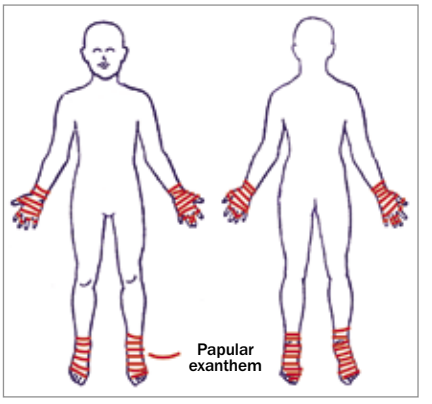


Figure 5. Typical distribution of the rash in papular-purpuric 'gloves and socks' syndrome.

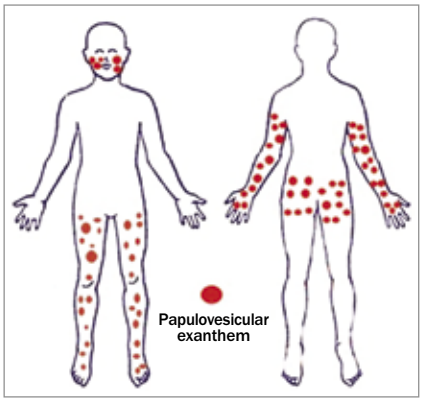


Figure 6. Typical distribution of the rash in Gianotti-Crosti syndrome.

diagnoses of erosive or bullous disorders and eczema herpeticum in children must be considered in atypical presentations. Diagnosis can be confirmed by PCR testing of blister fluid, throat swabs and stool samples.

The rash of HFMD can last days to weeks. Treatment is supportive, including rehydration and pain relief for sore throat, such as salt water gargles, mouthwashes or throat lozenges that do not contain benzocaine for children aged over 6 years.[7] Avoiding fruit juices high in acid such as orange juice and lemonade can minimise irritation of mouth sores.[8]

Erythema in gloves and socks distribution – papular-purpuric gloves and socks syndrome

Parvovirus B19 infection is associated with several exanthems, including erythema infectiosum (also known as fifth disease or slapped cheek disease, Figure 4) and papular-purpuric 'gloves and socks' syndrome (PPGSS). PPGSS mainly affects adolescent girls and young adults. It is contagious during the exanthem stage and can be transmitted via respiratory droplets, blood products and in utero.

The rash in PPGSS is typically a pruritic, burning, intensely erythematous, papular exanthem on the hands and feet that is sharply demarcated at the wrists and ankles (Figure 5).[9] Oedema can limit hand mobility. The oral mucosa can be involved, with vesicles, erosions and aphthous ulcers. Systemic manifestations include fever, lymphadenopathy and arthralgia.

The diagnosis of PPGSS is based on the clinical presentation. Differential diagnoses include urticaria, Kawasaki disease, idiopathic palmoplantar hidradenitis and early stage vasculitis. PPGSS is generally self-limiting and resolves spontaneously in one to two weeks. Symptomatic treatment is recommended, such as adequate rest and maintenance of hydration.[7]

Papules on extensor surfaces of limbs, buttocks and face – Gianotti-Crosti syndrome

Gianotti-Crosti syndrome, also known as papular acrodermatitis of childhood, is a parainfectious exanthem. It is associated with a range of viruses, including hepatitis B virus, cytomegalovirus, Epstein-Barr virus, enterovirus, parvovirus B19 and HHV-6.[10] It has also been seen after hepatitis B vaccination.[11]

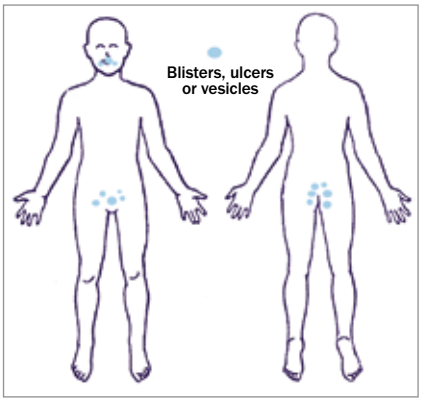
Gianotti-Crosti syndrome usually manifests in children aged between one and six years as an asymmetrical papular or papulovesicular exanthem on the cheeks, extensor surfaces of limbs and buttocks (Figure 6). Patients can also have a prodrome of fever and upper respiratory tract symptoms. There is no associated pruritus, hepatitis or lymphadenopathy.

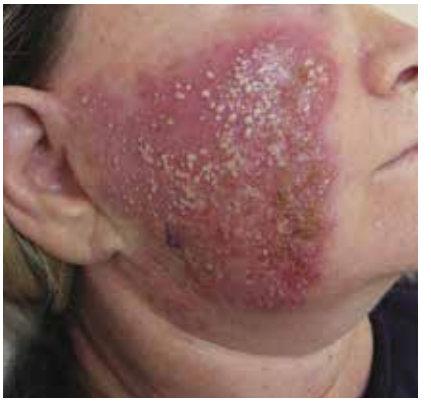
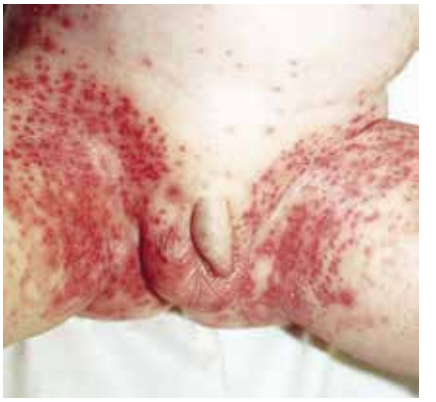
The diagnosis of Gianotti-Crosti syndrome is clinical, and many children do not require specific tests; however, a skin biopsy may be required in challenging cases. Differential diagnoses to be excluded include atopic dermatitis, drug-induced exanthem, lichen planus and Henoch-Schonlein purpura. Hepatitis serology should be assessed in patients who are not vaccinated against hepatitis B. A specific diagnosis is reassuring to parents, as the intensity of the rash in Gianotti-Crosti syndrome can be alarming.[12]

Gianotti-Crosti syndrome resolves over three to four weeks. Treatment is supportive.

Vesicles on lips, mouth or genitals – herpes labialis and genitalis

Herpes labialis and genitalis are caused by herpes simplex virus (HSV) type 1 and type 2. These viruses infect through direct contact of mucosal surfaces or abraded skin. The viruses become latent in the dorsal root ganglia for an indefinite period and can reactivate and multiply at the nerve root, then travel through the nerve to the skin or mucous membrane. HSV-1 usually causes herpes labialis, and primary infection occurs during childhood or adolescence.[13] Genital HSV is transmitted in most cases during periods of asymptomatic viral shedding.



Figures 7a to c. Herpes simplex virus infection: typical distribution of the rash in herpes labialis and genitalis (a, left); and complications in people with eczema: eczema herpeticum, also known as Kaposi varicelliform eruption (b and c, centre and right).

A prodrome of localised pain, tingling, burning, tenderness, paraesthesia, lymphadenopathy, headache, fever, anorexia or malaise precedes lesion formation by hours to days.

HSV-1 and HSV-2 typically cause blisters, ulcers or vesicular lesions on an erythematous base; these eventually erode and crust (Figure 7a). Vesicles can occur at a single site or affect multiple anatomical sites after autoinoculation or in disseminated disease, where oedema, fissures or pustules can develop. The duration of genital lesions ranges from less than one week for recurrences to up to three weeks for primary infection. HSV infection is associated with eczema herpeticum (also called Kaposi varicelliform eruption) in people with atopic dermatitis, herpes gladiatorum in athletes and erythema multiforme (Figures 7b and c).[14] Complications of genital HSV infection include enhanced HIV transmission, psychosexual morbidity, neuropathic bladder in the initial episode and neonatal herpes.

Herpes simplex recurrences vary in symptom severity and frequency, but most are asymptomatic or have minimal features. Local trauma and systemic stimuli such as immunosuppression or fever can trigger reactivation of latent HSV.[15]

Diagnosis of HSV infection usually relies on the history and physical examination findings; however, a PCR test of a swab of the base of the ulcer or deroofed vesicle can be useful to diagnose asymptomatic or subclinical cases.

Treatment should be commenced as soon as possible for an initial episode and for moderate-to-severe recurrences of HSV infection. Primary oral mucocutaneous herpes can be treated with a topical anaesthetic such as benzydamine 1% gel or lidocaine 2% viscous solution for minor cases. Patients with severe oral mucocutaneous herpes can be treated with oral valaciclovir 1 g twice daily for seven days. Minor recurrences of oral mucocutaneous herpes can be managed with episodic antiviral therapy comprising aciclovir 5% cream five times daily for five days. For severe recurrences, oral valaciclovir 2 g twice daily for one day can be used.

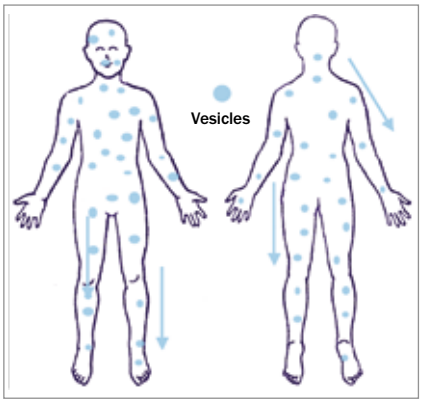
The recommended treatment of genital herpes primary infection is oral valaciclovir 500 mg twice daily for five to 10 days. Recurrent genital herpes can be treated with episodic therapy with valaciclovir 500 mg twice daily for three days, or suppressive therapy with valaciclovir 500 mg daily for six months. The choice between episodic or suppressive therapy depends on the frequency and severity of recurrences and psychosexual complications. Patients with frequent recurrences or immunosuppression may require higher doses of antiviral treatment. Antipyretics, saline baths and topical lignocaine can help relieve symptoms. Pregnant women, immunocompromised patients and patients with allergies to antiviral agents require specialist advice.[15]

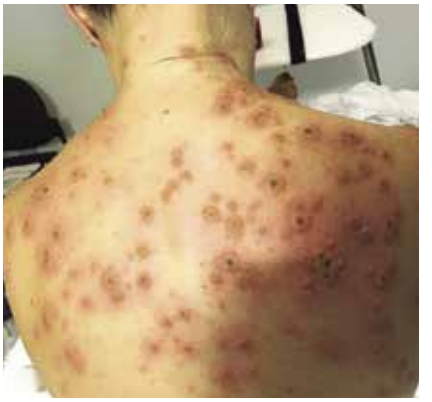
Exposure to HSV and varicella-zoster virus (see below) can cause viral keratitis, which is a medical emergency. Patients require urgent referral for sight-saving management.

Follow up of patients with genital herpes is recommended to complete sexual health screening, counsel about prevention and provide further sexual health education. This should cover the importance of abstaining from sexual activities when lesions or the prodrome are present and use of condoms. Herpes is not a notifiable condition.

Vesicles on the face, trunk and limbs – varicella (chickenpox)

Primary infection with the varicella-zoster virus (VZV) causes varicella (chickenpox), during which the virus becomes latent in ganglionic neurons. VZV is highly infectious and spreads by the airborne route, with skin vesicles the main infectious source. The incidence of varicella is highest among children aged 1 to 9 years, and during winter and spring. VZV vaccines have greatly reduced the incidence, morbidity and mortality of VZV infection; however, the rise of antivaccine movements and the increase in immunocompromise in the population means that ongoing efforts to prevent and treat VZV infection are essential.[16]





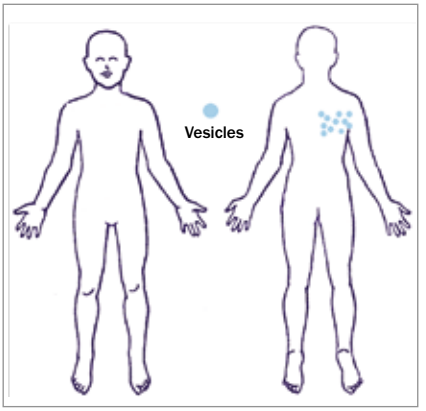
Figures 8a and b. Varicella: typical distribution (a, left) and appearance (b, right) of the rash.

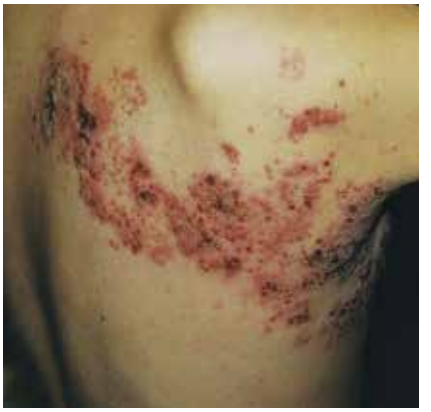
Cough, coryza, fatigue and fever can be experienced in the prodrome of VZV infection, which is followed by a generalised cropping, vesicular, pruritic rash. The rash spreads cranially to caudally, and can involve the scalp and oral mucosa (Figures 8a and b).[7] The vesicles can become haemorrhagic. Serious complications of VZV infection include bacterial sepsis, pneumonia and neurological and haematological complications.

Clinical diagnosis is the mainstay for VZV infection; however, PCR testing of swabs from skin vesicles, saliva and cerebrospinal fluid can confirm the diagnosis. Differential diagnoses include other herpesvirus or enterovirus infections or drug intolerance.

Varicella is usually self-limiting in otherwise healthy children. Treatment of uncomplicated cases of varicella in children is symptomatic, including taking lukewarm baths with baking soda or oatmeal, calamine lotion to reduce itch and paracetamol. Immunocompetent children with pre-existing skin disease should be treated with oral valaciclovir 20 mg/kg up to 1 g, eight-hourly for seven days.

Adults have a higher risk of adverse outcomes and should be treated with oral valaciclovir 1 g, eight-hourly for seven days. Antiviral therapy should also be started in people with severe varicella (intravenous aciclovir 10 mg/kg, eight-hourly), people who are immunocompromised, pregnant women and newborns with congenital varicella syndrome. Preventive measures include VZV vaccination and administration of VZV immunoglobulins in high-risk patients.[7]





Figures 9a and b. Herpes zoster: typical distribution (a, left) and appearance (b, right) of the rash.

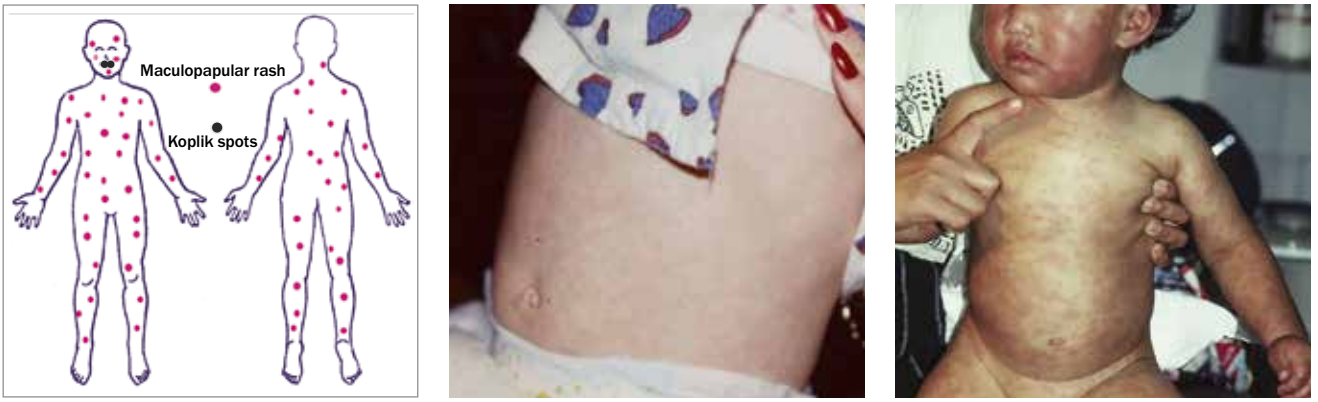
Vesicles in a dermatomal distribution – herpes zoster

Herpes zoster, also known as shingles, is caused by reactivation of VZV. Because of waning immunity, the incidence and severity of zoster rises with increasing age. By the age of 85 years, over half the population will experience at least one episode of zoster.

Zoster is characterised by a two to three-day history of burning pain, followed by a localised eruption of vesicular lesions in the dermatomal distribution of the infected sensory nerve.[17] The T1 to L2 dermatomes are those most affected (Figures 9a and b). Atypical presentations can occur, including a disseminated rash, minimal rash or no rash.[17] The rash heals over two to four weeks but can result in scarring and permanent pigmentation. The pain can be severe, and persistent postherpetic pain is common. Zoster paresis, neuralgia, meningoencephalitis and vasculopathy can be complications of zoster and may occur without a rash.[16]

Zoster can almost always be diagnosed clinically. Confirmatory tests include PCR, immunohistochemistry and viral culture of the vesicular fluid. Important differential diagnoses include contact dermatitis, herpes simplex and (for pain) cholecystitis, acute appendicitis and renal calculi.

A seven to 10-day course of oral antiviral therapy is recommended for patients with zoster, especially those who are immunocompromised, aged over 50 years and have lesions involving the face and eye. Treatment is most effective when started within 72 hours of rash onset. Patients should be advised to keep the rash clean and dry and avoid irritating products to prevent delayed healing and superimposed bacterial infection.[18] Additionally, patients should cover the rash and maintain hand hygiene to prevent VZV transmission, and avoid contact with pregnant women, children who have not had varicella or VZV vaccine and people who are immunocompromised. Patients who have eye involvement or who are immunocompromised should be referred to a specialist.



Figures 10a to c. Measles: typical distribution (a, left) and appearance (b and c, centre and right) of the rash.

White lesions on the mucosa (Koplik spots) – measles

Measles is a highly contagious disease caused by measles virus and was the first immunosuppressive infection to be discovered. Measles was the leading cause of child morbidity and mortality before the development of measles vaccines in the 1960s. Measles typically begins with a fever and at least one of the three Cs: cough, coryza and conjunctivitis.[12] Small white papules, known as Koplik spots, can appear on the buccal mucosa one to two days before the rash. A confluent maculopapular nonitchy rash first appears on the face and behind the ears and then spreads to the trunk and extremities (Figures 10a to c). The rash may be diminished in vaccinated children. The infectious period begins a few days before onset of the rash and lasts for several days. In uncomplicated cases, recovery can take one week. Possible complications include pneumonia, laryngotracheobronchitis, otitis media and keratoconjunctivitis.

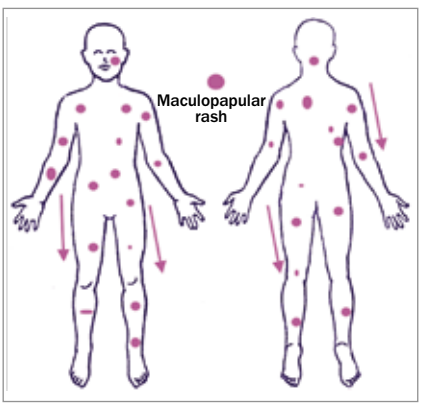


Figure 11. Typical distribution of the rash in rubella.

Measles can be recognised clinically; however, diagnosis can be challenging in the early stages of the disease and in immunocompromised and poorly nourished children. Testing for measles virus-specific serum IgM antibody can be confirmatory; however, antibodies are not detectable until at least four days after rash onset. Detection of viral RNA through PCR testing of throat, nasal, nasopharyngeal and urine samples is a more reliable diagnostic test. Other diseases that may be confused with measles include rubella and human parvovirus B19, enterovirus and HIV infection.

Management of patients with measles includes supportive therapy, correction of dehydration and nutritional deficiencies and monitoring for secondary bacterial infection.[19] It is crucial to follow local communicable disease guidelines on notification and contact management.

Maculopapular rash with cephalocaudal progression – rubella

Rubella, also known as 'three day' or 'German' measles, is caused by rubella virus. This virus spreads through the respiratory route and is a candidate for global eradication because humans are the only known host. Rubella outbreaks occur in spring, and the mean age for rubella among unvaccinated children is 5 to 9 years.

The clinical manifestations of rubella are mild and appear in only 50% of infected cases. A five-day prodrome of fever, headache and upper respiratory tract symptoms is associated with a cephalocaudal progression of a rose-pink coalescing maculopapular eruption (Figure 11). The rash disappears in one to three days. Symmetrical lymphadenopathy mainly affecting occipital and postauricular lymph nodes is also a prominent feature.[1] Severe complications include haemolytic anaemia, thrombocytopenia, pericarditis, myocarditis and encephalitis.[2] Rubella just before conception or during early pregnancy causes fetal defects in up to 90% of cases.[20]

Acute rubella can be diagnosed by a positive PCR test for rubella virus or demonstration of rubella-specific IgM seven to 10 days after onset of the rash (in the absence of recent rubella vaccination), or a fourfold rise in rubella IgG antibody concentrations between paired acute and convalescent sera spaced at least a fortnight apart (in the absence of recent rubella vaccination). It should be noted that a high proportion of IgM-positive results will likely be false positives given the low incidence of rubella in Australia. Differential diagnoses include adenovirus and parainfluenza

virus infection and drug-induced exanthems.[21] Treatment of rubella is supportive, including bed rest and maintenance of oral fluid intake.

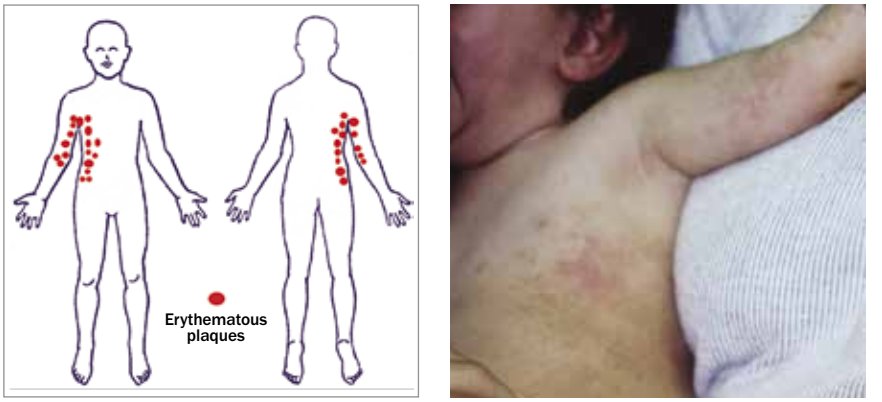
Women planning pregnancy should be tested serologically for rubella immunity, so they can be vaccinated before conception if necessary. The detection of rubella-specific IgM in pregnant women needs to be confirmed in a reference laboratory, and repeat testing for IgG seroconversion may be required. Women diagnosed with rubella during pregnancy should be referred promptly to an obstetrician for counselling about the risks of intrauterine rubella infection and follow up. Prenatal rubella can be diagnosed by detection of viral RNA in a chorionic villi biopsy specimen, amniotic fluid or fetal blood.[1]

Rash with centrifugal progression from axillae – unilateral laterothoracic exanthem

Unilateral laterothoracic exanthem (asymmetric periflexural exanthem of childhood) is presumed to be caused by a virus, although the aetiology has not been proven. It typically affects children of European background aged one to five years. There is a female preponderance, and the condition occurs more frequently in the winter and spring.[22]

The eruption starts around the axilla or inside of the elbow and spreads along the affected side. The rash is usually limited to one side of the body (Figures 12a and b). The lesions coalesce to form large erythematous oedematous plaques accompanied by itching. There can be a surrounding pale halo in the early stages of the eruption, which later becomes scaly. A prodrome or concomitant gastrointestinal or upper respiratory symptoms may develop. Unilateral laterothoracic exanthem is a self-limiting disease with no sequelae and resolves over three to six weeks.

The diagnosis of unilateral laterothoracic exanthem is fundamentally clinical, and a skin biopsy is not usually required. Differential diagnoses include Gianotti-Crosti syndrome, miliaria, scabies, fungal infection and atypical pityriasis rosea. Supportive treatments include oral antihistamines and topical bland emollients and soothing lotions.[23] Topical corticosteroids are not effective.[12]



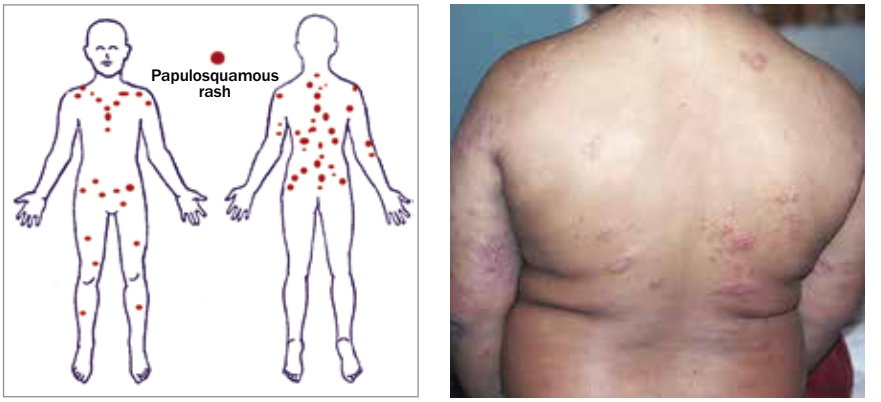
Figures 12a and b. Unilateral laterothoracic exanthem: typical distribution (a, left) and appearance (b, right) of the rash.

Fir-tree rash on the trunk – pityriasis rosea

Pityriasis rosea is an acute self-limiting exanthem with an unknown aetiology, although possibly caused by HHV-6 and HHV-7. It commonly affects adolescents and young adults. Pityriasis rosea typically starts with a single erythematous, scaly plaque, known as the herald patch. This is followed by a secondary eruption consisting of smaller papulosquamous lesions along the cleavage lines of the trunk in a 'Christmas tree' or 'fir-tree' pattern, which last for days to weeks (Figures 13a and b).[2] Atypical presentations include unilateral, inverse, lichenoid, vesicular, papular, purpuric, erythema multiforme-like and urticarial rashes.[24] Postinflammatory hyper- or hypopigmentation may result. Up to 60% of patients experience prodromal symptoms or pruritus.

The diagnosis of pityriasis rosea is clinically challenging, and skin biopsy shows nonspecific changes. A pityriasis rosea-like eruption has been linked to certain medications, including lamotrigine, metronidazole, terbinafine, isotretinoin, ACE inhibitors and clonidine. Differential diagnoses such as guttate psoriasis and secondary syphilis should be considered.[9]

Treatment is symptomatic, and patients



Figures 13a and b. Pityriasis rosea: typical distribution (a, left) and appearance (b, right) of the rash.

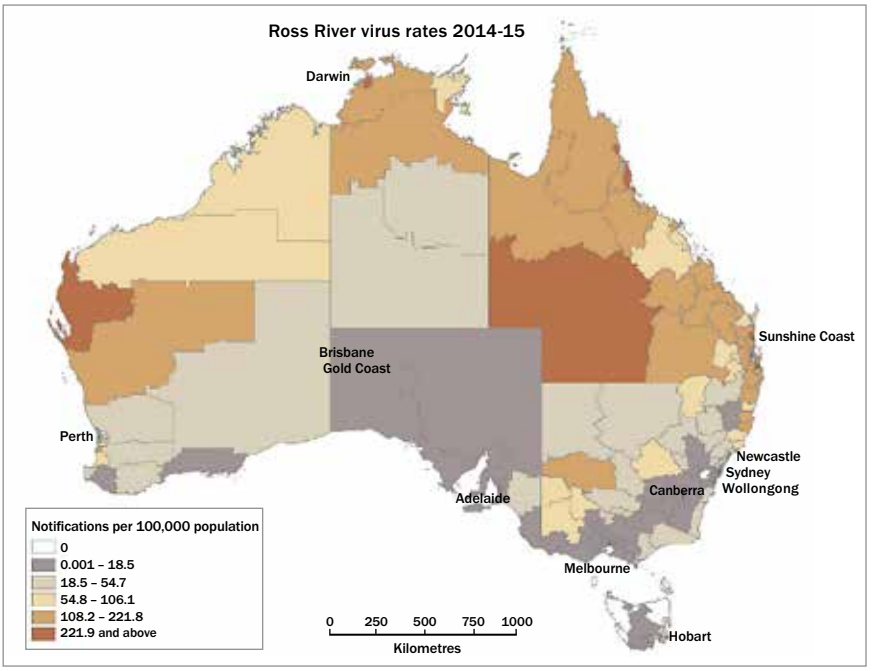


Figure 14. Notification rates for Ross River virus infection, 2014 to 2015, by ABS statistical area, level 3.

should be reassured that the condition is not contagious. If symptoms are severe, topical menthol or a corticosteroid can be trialled. If the rash persists for more than three months, or if symptoms are severe or diagnosis is uncertain, referral to a dermatologist is recommended.

Other viral exanthems

Ross River virus disease

Ross River virus (RRV) is a mosquito-transmitted alphavirus that causes epidemic polyarthritis and arthralgia, known as RRV disease. RRV is endemic in Australia, particularly northern Australia (Figure 14) and Papua New Guinea and has caused epidemics in the Pacific Islands.[25] Risk factors for outbreaks are increased rainfall and high maximum tides.

RRV disease commonly affects adults aged 25 to 44 years, with men and women equally affected. The incubation period is generally seven to nine days, and infection is subclinical in 30% of cases.[26] Symmetrical joint pain and lethargy are common complaints, with other symptoms including myalgia and headaches. A rash appears in 40% of patients, which is generally maculopapular affecting the limbs and trunk.[14] There are also case reports of associated splenomegaly, haematuria, glomerulonephritis, meningitis and encephalitis. Arthralgia can take five to seven months to resolve.

Differential diagnoses include infectious mononucleosis, Barmah Forest virus disease, rubella, Q fever and other rheumatic conditions. Diagnosis is confirmed by seroconversion, with a change in paired serology results (IgM and IgG) consistent with transient IgM followed by long-term IgG (see the case study in Box 3).[27]

Management of RRV disease is supportive, including rest, NSAIDs and physical interventions such as massage and physiotherapy.[1] In the acute phase, patients' functional ability may be significantly impaired, and many require support with activities of daily living. RRV cases require notification to the appropriate public health unit as per state or territory guidelines.[25]

Barmah Forest virus disease

Barmah Forest virus (BFV) is another alphavirus endemic in Australia. It causes BFV disease, characterised by epidemic polyarthritis and myalgia. It is the second most common mosquito-borne disease after RRV disease.[28]

The incubation period of BFV disease is five to 15 days. BFV causes a rash in 90% of cases; the rash is more florid than that in RRV disease. It appears with the onset of illness and spreads cephalocaudally. The rash may be maculopapular, purpuric or vesicular.[14] Patients with BFV disease tend to have less joint swelling than those with RRV disease. BFV infection can also be asymptomatic.

Because of the overlap in symptoms with RRV disease, patients are generally tested for both BFV and RRV. BFV disease is confirmed in the same way as RRV disease and is also notifiable. Clinically appropriate symptomatic treatment such as NSAIDs or paracetamol should be administered while waiting for confirmation.[27]

Influenza

Influenza is a common respiratory disease caused mostly by influenza A and B viruses. It is transmitted from human to human. The health impact of influenza is generally mild in healthy individuals. However, certain groups are at higher risk of developing severe disease and complications, including people of advanced age, infants, those of Aboriginal and Torres Strait Islander origin or patients who are immunocompromised, have a chronic condition, are obese or pregnant and those who smoke.

An exanthem is uncommon in influenza, found in only 2% of cases, but is more likely in children. A confluent maculopapular rash sparing the face and palmoplantar surfaces was detected in patients infected with the novel influenza A (H1N1) 2009 pandemic strain (influenza A [H1N1]pdm09). Petechial exanthems can also occur, and influenza A can trigger Gianotti-Crosti syndrome.[12]

Influenza should be considered in children who present with a fever and rash, especially if they have respiratory

3. CASE STUDY CONTINUED FROM BOX 1

The patient's serological test results were negative for Q fever, brucellosis, toxoplasmosis and infection with Barmah Forest virus and parvovirus B19. A test was positive for Chikungunya IgM, but no seroconversion to IgG was demonstrated. The patient tested positive for Ross River virus IgM with subsequent IgG seroconversion, which was reported to the relevant state health department. He was treated conservatively, and his symptoms gradually resolved.

symptoms during the 'flu season'.[14] Administration of the latest influenza vaccine around March or April every year confers the best protection against influenza.[29]

Coronavirus disease 2019 (COVID-19)

Since December 2019, coronavirus disease 2019 (COVID-19) has caused significant morbidity, mortality and financial impact worldwide. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and transmission is via respiratory droplets and potentially aerosols. SARS-CoV-2 enters cells by binding to angiotensin-converting enzyme-2 (ACE-2) receptors, which are found in many parts of the body, including mucosal sites, the endothelium of dermal blood vessels and epithelial cells in eccrine glands. This distribution possibly explains the cutaneous manifestations observed in patients with COVID-19.[30] Skin involvement has been reported in 0.2 to 24% of cases, although the true prevalence is difficult to ascertain.[31]

There is great heterogeneity in COVID-19 cutaneous presentations, possibly because of different immune responses to the virus. Cutaneous presentations include morbilliform, vesicular, pityriasis rosea-like and erythema multiforme-like eruptions, chilblains and Kawasaki-like disease in children.[32] Vasculopathy-related lesions such as livedo reticularis, retiform purpura, ulcerations and necrosis have been seen in hospitalised patients with COVID-19. These lesions are hypothesised to be caused by the increased clotting tendency from complement activation.[31] Herpes zoster is also increased in patients with COVID-19.[33] Vesicular eruptions can be an early cutaneous sign, whereas chilblains can be a late sign.

It is important to include skin eruptions as clinical features of COVID-19 and to perform a full skin examination when evaluating patients with suspected COVID-19.[30]

Conclusion

Viral exanthems are polymorphous in their clinical presentations. Diagnosis can be challenging, especially in patients with unusual presentations or in those who are vaccinated, with potential for the vaccine to contribute to cross-reactivity or complement activation protection, or immunocompromised. Clinical diagnosis of viral exanthems depends on the distribution and morphology of the rash, geographic location of the case and exposures. Most exanthems are self-limiting and are treated with supportive care. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Associate Professor Shumack is an investigator and advisory board member for Leo Pharma and Sanofi.
Dr Lai, Dr Phan and Dr Dawes-Higgs: None.

Acknowledgement

The authors wish to thank Professor Gayle Fischer, Royal North Shore Hospital, Sydney, for providing the clinical photographs in Figures 3 to 13.

Viral exanthems

Unravelling viral rashes

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Skin lesions in darker skin phototypes

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Pigmented skin is protected against UV damage and the development of certain skin cancers. However, some skin conditions are more prevalent in darker skinned communities, particularly Indigenous Australian communities. GPs should be aware that such patients are still at risk of developing skin cancer and early diagnosis and considered management are key to improving patient outcomes.

KEY POINTS

- Increased skin pigmentation is protective against UV radiation and development of skin cancers. There is, however, increased significance for trauma and chronic inflammation in the development of skin cancers.
- Although less common, skin cancers such as melanoma do occur in Indigenous populations but are diagnosed at a later stage. This results in significant hospitalisation and reduced survival.
- The risk of hyperpigmentation should be considered in the presentation and treatment of common skin conditions in pigmented skin.
- The prevalence of certain skin conditions, including infectious diseases, systemic lupus erythematosus and discoid lupus erythematosus, is higher in Indigenous Australians.
- Awareness by GPs and patients of the risks of these skin lesions and conditions is important to improving outcomes for Indigenous patients.

Skin can be categorised into different phototypes based on richness of pigmentation. These are the Fitzpatrick skin types, ranging from type I fair skin (which always burns and never tans) to type VI darkly pigmented skin (Table 1).[1] Darker skin phototypes (Fitzpatrick skin types IV to VI) display differences in incidence, presentation and management of many dermatological diseases compared with lighter skin phototypes.[2] This article will discuss common skin conditions and how they present in darker skin phototypes, and the skin conditions that are more prevalent in the Australian Indigenous population.

Skin cancers in darker skin phototypes

Increased levels of melanin and larger melanosomes in darker skin phototypes provide greater photoprotection that results in a lower overall incidence of skin cancers.[2,3] The combined burden of melanoma and nonmelanoma skin cancers is thus lower in Australian and Torres Strait Islander peoples than the general Australian population, although it is still a very common cause for hospitalisation.[4] In Indigenous patients, skin cancers account for 1% of deaths compared with 4% in the non-Indigenous population.[4] A summary of the most common skin cancers in pigmented skin and their management is outlined in Table 2.

Basal cell carcinomas

Basal cell carcinomas (BCCs) are the most common cancer overall in people with fair skin. In people with pigmented skin, increased levels of melanin offer UV protection, which results in a lower prevalence of BCC; however, this means that scarring, radiation and trauma have a greater role in carcinogenesis.[2,5,6]

MedicineToday Dermatology Collection 2022; 6(1): 27-30
First published MEDICINE TODAY 2021; 22(4): 23-26

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TABLE 1. FITZPATRICK SKIN PHOTOTYPE CLASSIFICATION[1]

Skin phototype	Defining factor
I	Always burns, never tans
II	Usually burns, tans with difficulty
III	Sometimes burns, usually tans
IV	Rarely burns, always tans
V	Moderately pigmented skin
VI	Darkly pigmented skin

BCCs classically present as single, discrete lesions with a pearly appearance, rolled border and telangiectasia. In darker skin phototypes, they are often translucent with central ulceration.[5] Half of BCCs that present in darker skin types may be pigmented (Figure 1) compared with 6% in lighter skin.[5] It holds true that BCCs most commonly occur on sun-exposed areas.[2]

Diagnosis is made via histopathology. Treatment modality is the same as with lighter skin types and includes topical imiquimod, topical fluorouracil, photodynamic therapy, cautery and curettage or excision.[2] Exact treatment options depend on BCC site and histological subtype.

Squamous cell carcinomas

Squamous cell carcinomas (SCCs) are the most common skin cancer in dark skin phototypes.[5] Classically, SCCs appear in areas exposed to UV light; however, in darker skin, up to 65% occur in non-sun-exposed areas.[7,8] The most important risk factors for formation of SCCs are chronic inflammation and scarring.[2,5]

SCCs present as erythematous lesions with scale and crust in darker skin.[7] Treatment modalities are the same as for lighter skin types and include topical imiquimod or fluorouracil for suitable in situ lesions, depending on site and other risk factors such as immune suppression, or excision for invasive lesions.[2] Risk factors for metastasis in darker skin are cancers associated with scarring, discoid lupus erythematosus, non-sun-exposed areas or involvement of the mucous membranes.[2,9,10]

Melanomas

Melanomas occur less commonly in pigmented skin; the incidence of melanoma in Indigenous Australians is lower compared with non-Indigenous Australians. However, survival rates for melanomas directly relate to disease extent at time of diagnosis, and thus early diagnosis is crucial. Unfortunately, melanoma is often diagnosed at a later stage in darker skin, resulting in reduced survival.[2,11] This is attributed to less education around skin cancer in Indigenous and darker skinned communities, in contrast to the increased awareness across the population more broadly.[2]

Melanoma typically presents as an isolated, rapidly evolving pigmented lesion, although it may be hypomelanotic or amelanotic. It arises de novo or from an existing naevus. The most common sites in darker skin are non-sun-exposed sites, especially the palms and plantar or subungual surfaces (acral lentiginous melanoma).[12] A clinical pearl is to look for the presence of Hutchinson's sign – the extension of pigment into the proximal nail fold (Figure 2) – which occurs in a subungual melanoma and helps distinguish malignancy from benign melanonychia.[5] Melanonychia is also more likely to involve multiple nails.

Confirmation of diagnosis is via histopathology, with excision being the mainstay of treatment. Further management depends on the staging. There are many targeted molecular therapies and immunotherapies for advanced melanoma. Testing for *BRAF* gene mutation guides the decision-making.

TABLE 2. SUMMARY OF COMMON SKIN CANCERS IN PIGMENTED SKIN

Skin cancer	Appearance on darker skin phototypes	Prevalence	Differential diagnoses	Confirmation of diagnosis	Treatment
Basal cell carcinoma	Classically a single lesion with a pearly appearance and telangiectasia, 50% are pigmented	• Most common skin cancer overall • Second most common in darker skin	• Pigmented lesions may appear to be a melanoma	Histopathology	• Excision is the preferred treatment • Superficial lesions can be treated with topical imiquimod or photodynamic therapy • Cautery and curettage is another option
Squamous cell carcinoma	Erythematous lesions with scale and crust	• Most common skin cancer in people with pigmented skin, especially in sites with chronic inflammation • Up to 65% occur in non-sun-exposed areas	• Hyperkeratotic actinic keratosis	Histopathology	For in situ lesions: • topical imiquimod • fluorouracil For deeper lesions: • excision
Melanoma	Isolated, rapidly evolving lesion	• Far less common • More likely to occur on non-sun-exposed areas	• Melanonychia	Histopathology	• Excision • Metastatic disease can be managed via BRAF/MEK inhibitors or other immunotherapies

If positive, BRAF/MEK inhibitors are an effective treatment. Other therapies for advanced melanoma include immune checkpoint inhibitors but these have unpredictable toxicity.[13]

Acne

Acne is one of the most common skin conditions seen in outpatient clinics. Darker skin is more predisposed to postinflammatory hyperpigmentation, keloids and scarring than lighter skin, and hence acne warrants a discussion here.[2]

Acne presents similarly with open and closed comedones, papules, pustules, nodules and cysts.[2] Initial acne therapies are the same for all skin phototypes, and include benzoyl peroxide, topical antibiotics and retinoids. Oral antibiotics can be used in moderate to severe acne. Isotretinoin is used for resistant nodular cystic acne. To help avoid postinflammatory hyperpigmentation, treatments that cause irritation or inflammation should be avoided in the treatment of pigmented skin.[2] Retinoids can be commenced at lower doses and less frequent intervals (such as every second day). Benzoyl peroxide can be drying and irritating, therefore, using concentrations less than 5% can limit subsequent hyperpigmentation.[2]

For presentations of both acne and post-inflammatory hyperpigmentation, treatment with azelaic acid 15% or 20%, topical retinoids and chemical peels may be helpful.[14-16] Last-line therapies include oral antibiotics, hormonal therapies (spironolactone, oral contraceptives) or isotretinoin.[2]

Postinflammatory hyperpigmentation

Post-inflammatory hyperpigmentation is more common in people with darker skin.[17] It results from inflammation from a condition (such as eczema or acne) or from medication. Clinically, it presents as ill-defined hyperpigmented macules and patches in the distribution and shape of the original lesions (Figure 3). The exact colour of the hyperpigmentation depends on its depth in the skin, and can range from tan and brown to dark brown and then blue-grey as the pigmentation extends deeper.[2]

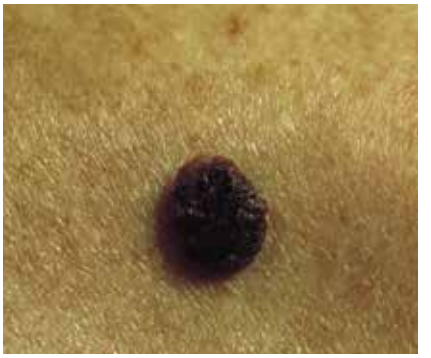

Figure 1. Pigmented basal cell carcinoma.

The mainstay of treatment is control of the underlying disorder to prevent further inflammation. Hyperpigmentation will fade over six to 12 months, although this can take longer. Avoidance of sun exposure and the use of sunscreen to prevent darkening of hyperpigmented areas, as well as avoiding irritants such as medications, alcohol, fragrances and cosmeceuticals is also recommended.[2,17]

Optimal medical therapy involves hydroquinone 4%,[17] although it has been linked to ochronosis (darkening of the skin).[18] Other treatment options include retinoids, azelaic acid, chemical peels, corticosteroids, or a combination of these. There is also emerging evidence for topical tranexamic acid in improving hyperpigmentation.[19]

Common skin conditions affecting Indigenous Australians

It is well known that Indigenous Australians bear a disproportionately high burden of disease compared with non-Indigenous Australians. Skin disease contributes to this high burden, constituting roughly 15% of consultations between Indigenous Australians and primary healthcare practitioners.[3,20] Skin problems in Indigenous communities predominantly result from infectious diseases. More common noninfectious skin diseases include vitamin D deficiency, systemic lupus erythematosus and discoid lupus erythematosus, whereas psoriasis and type I hypersensitivity disorders are less common.[3]

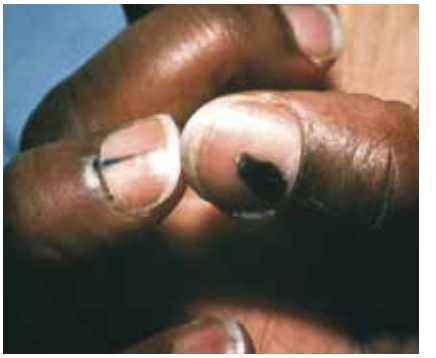

Figure 2. Nail bed pigmented lesions of the thumb and middle finger indicative of Hutchinson's sign.

Image reproduced from the Centres for Disease Control and Prevention (CDC) Public Health Library (PHL). Content provider: CDC/Carl Washington, MD, Emory University School of Medicine; Mona Saraiya, MD, MPH. ID: 13433.

Infectious diseases

Infectious diseases make up a higher burden of disease in the Indigenous population, which is likely due to socioeconomic determinants of health such as economic inequities, living conditions and overcrowding and access to healthcare in remote communities.[21,22] One study of Indigenous patients attending dermatology clinics found that fungal infections were the most common type of skin infection, followed by viral, parasitic and bacterial infections.[20]

The most common dermatophyte in central and northern Australian communities is *Trichophyton rubrum*.[21] Other *Trichophyton* species and *Malassezia furfur*, which causes pityriasis versicolor, are also

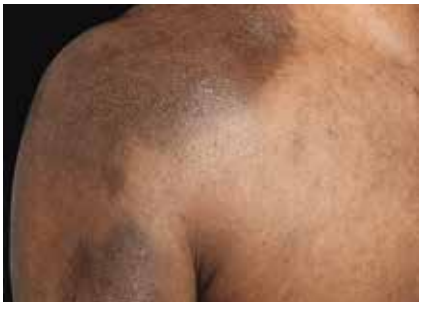

Figure 3. Postinflammatory hyperpigmentation in eczema.

FIGURE 1 © SDIGITAL/ISTOCKPHOTO.COM
FIGURE 3 © DR P. MARAZZI/SPL

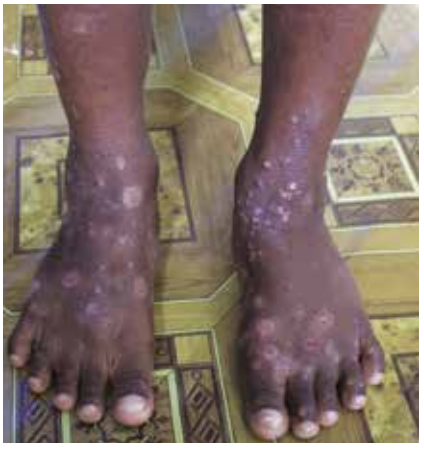

Figure 4. Papular rash of scabies.
Image courtesy of Murdoch Children's Research Institute. Reproduced with permission.

common.[21,22] Pityriasis versicolor responds to topical selenium sulphide or imidazoles such as clotrimazole or miconazole.[21,22] Tinea corporis or unguium, or simply more widespread disease may require oral griseofulvin or terbinafine.[21]

Sarcoptes scabiei is endemic in many remote Aboriginal communities with scabies and is prevalent in up to 50% of children and 25% of adults (Figure 4).[21] In these communities, scabies may be associated with 50 to 70% of streptococcal pyoderma.[23] Treatment with 5% permethrin is highly effective and has been used effectively in public health settings for whole communities.[21] Whole-community treatment has the additional benefit of halving the prevalence of pyoderma.[21] Crusted scabies may require oral ivermectin.[24]

Streptococcal pyoderma affects up to 70% of children in Indigenous communities and has the sequelae of post-streptococcal glomerulonephritis and acute rheumatic fever.[21] *Streptococcus pyogenes*, a Group A streptococcus, is the primary pathogen in up to 80% of cases.[21] Streptococcal pyoderma has an excellent response to treatment with benzathine penicillin.[21,22]

Common viral infections are *Herpes simplex*, which may require treatment with aciclovir, and *Molluscum contagiosum*, which is likely to resolve spontaneously with no need for treatment.[20,22]

Systemic lupus erythematosus and discoid lupus erythematosus

The prevalence of systemic lupus erythematosus in Indigenous patients is 2.1 to 3.8 times higher than in non-Indigenous patients.[3,25,26] Indigenous people also tend to have a higher morbidity and mortality, which may relate to later presentation.[26]

Discoid lupus erythematosus has also been reported to have a higher prevalence in Indigenous communities compared with non-Indigenous communities.[27] The cause for this higher prevalence is uncertain, although it has been postulated that it may be due to higher rates of infections through the induction of cross-reactive anti-double stranded DNA antibodies, via the super antigen effect, or the result of increased environmental UV light exposure leading to exacerbation of subclinical lupus.[25,28]

Discoid lupus erythematosus presents as sharply demarcated circular hyperpigmented plaques with peripheral erythema and scale (Figure 5). There is a propensity for it to occur on the lips, and there is an association with SCCs at this site.[3,29]

Vitamin D deficiency

Although the increased melanin content of pigmented skin may be protective against skin cancer, it unfortunately results in enhanced susceptibility to vitamin D deficiency. Vitamin D is obtained through UVB exposure, and deeper skin pigmentation requires longer exposure of UVB to synthesise adequate amounts of vitamin D.[30] Average levels of 25-hydroxy vitamin D levels have been found to be low in Indigenous populations.[31]

Vitamin D deficiency has been associated with chronic diseases such as diabetes and heart disease.[32] There is also some evidence to suggest a link between low vitamin D levels and high body mass index.[33,34] Maintaining adequate vitamin D levels, particularly in remote Indigenous communities where access to emergency health services may be lacking, is therefore important to not only prevent falls and risk of fracture,

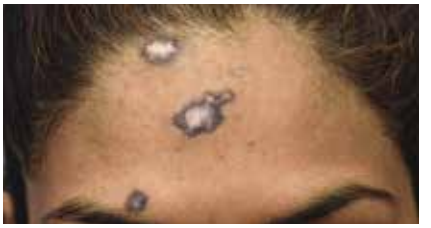

Figure 5. Lupus erythematosus lesions on the forehead in circular hyperpigmented plaques with areas of hypopigmentation.

but also to reduce the risk of chronic and cardiometabolic disease.

Psoriasis and eczematous conditions

Although less common in Indigenous patients, it is instructive to note the appearance of these disorders on darker skin phototypes. Psoriasis tends to form violaceous rather than red/pink plaques, with grey rather than white scale. There is more pronounced postinflammatory hyper- and hypopigmentation.[35] As for eczematous conditions, erythema may present as subtle hyperpigmentation. There is also increased prominence of postinflammatory hyper- and hypopigmentation. Follicular papules may be more common.[36] The correct diagnosis may rely on nonpigmentary aspects of the lesions.

Conclusion

Darker skin phototypes are protective against the development of skin cancers. However, dark skinned populations, in particular Indigenous Australians, are still at risk of developing skin cancers and other skin conditions. Greater awareness and recognition of the risks to Indigenous populations and implementation of preventative strategies are required to improve early diagnosis in these communities. Certain diseases have a higher prevalence in Indigenous Australians, and requires careful consideration of diagnosis and management. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

Skin lesions in darker skin phototypes

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Recurrent, painful nodules on a girl's legs

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

Case presentation

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

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

Differential diagnoses

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

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

MedicineToday Dermatology Collection 2022; 6(1): 32-33
First published MEDICINE TODAY 2020; 21(1): 54-55

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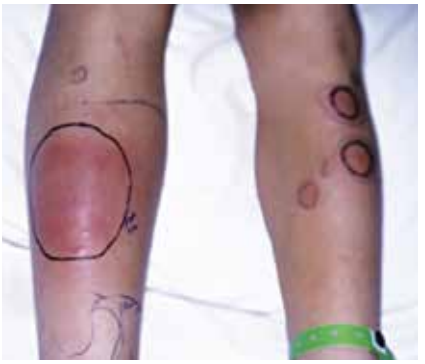

Figure 2. Cellulitis.

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

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

Management

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

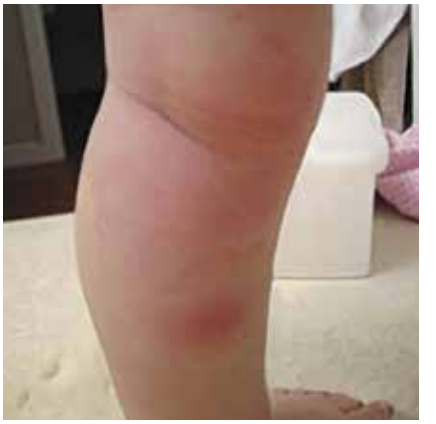

Figure 3. Insect bite reaction.

Outcome

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

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COMPETING INTERESTS: None.

A pregnant woman with a pruritic eruption

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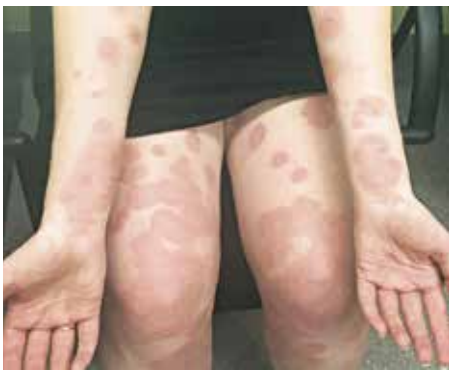
Test your diagnostic skills in our regular dermatology quiz. What has caused this rash on the trunk and limbs of a pregnant woman who is otherwise well?

Case presentation

A 34-year-old woman presents at 30 weeks' gestation in her first pregnancy with an intensely pruritic eruption (Figures 1a and b). It has been present for three weeks and is unresponsive to antihistamines. The rash started at her umbilicus and progressed to involve her trunk, arms and legs. Her face, scalp and palmar surfaces are not involved. The rash is characterised by fixed, oedematous, annular lesions that have coalesced on her trunk and limbs. Vesicles have appeared on some lesions.

The patient is otherwise well and her pregnancy is progressing normally.



Figures 1a and b. The itchy rash on the patient's arms and legs (not palms) at presentation. The rash started at the umbilicus.

Differential diagnoses

Conditions to consider among the differential diagnoses include the following:

- **Urticaria.** This is a common immunoglobulin (Ig) E-mediated reaction to drugs, viruses or foods. It is characterised by pruritic evanescent oedematous wheals that 'move' around the body over hours. Urticaria can be quite extensive (Figure 2). It is not the correct diagnosis in this patient because her lesions are fixed and not responsive to antihistamines.
- **Erythema multiforme (EM).** This classic skin eruption is usually precipitated by infections, most commonly herpes simplex virus (HSV), although some drug reactions can have the same appearance. It presents with lesions that develop extensively over 24 hours. The rash is often associated with a prodrome of flu-like symptoms. The lesions may be typical or atypical targets – the former have three distinct colour zones creating a target, whereas the latter are annular lesions with only two colours; both have a central vesicle (Figure 3). The lesions may have an itching or burning sensation and they can occur anywhere on the body, including the palms and soles. EM is divided into a minor form, which does not have mucosal involvement and often is a mild disease, and a major form, which has extensive mucosal involvement. EM is not the correct diagnosis in this case, as the patient had no preceding infection on history or serological investigation, there have been no new drugs, the rash does not involve the palms and there is no mucosal involvement despite extensive cutaneous disease. In addition, the annular lesions in this patient do not have a central vesicle typical of EM.

MedicineToday Dermatology Collection 2022; 6(1): 35-36
First published MEDICINE TODAY 2019; 20(7): 43-44

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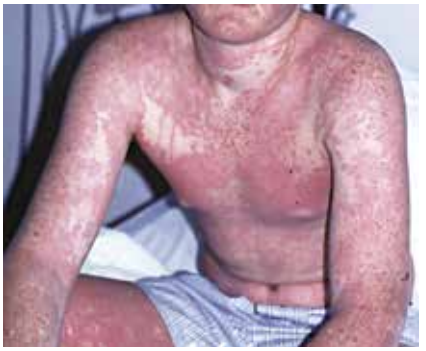

Figure 2. Urticaria

- **Polymorphic eruption of pregnancy (PEP).** PEP is a relatively common pregnancy dermatosis that occurs in the last three months of gestation. It is also known as pruritic urticarial papules and plaques of pregnancy (PUPPP). The condition is thought to be an immune response to the stretching of the skin. It is characterised by red to brown pruritic papules and plaques over the abdomen, especially the striae. Atypical variants may demonstrate annular or vesicular lesions. PEP only occurs in first pregnancies. It resolves soon after delivery.
- **Pemphigoid gestationis (PG).** This is the correct diagnosis. PG is an uncommon dermatosis of pregnancy characterised by intensely pruritic annular and vesiculobullous lesions. It is an autoimmune condition in which IgG attacks bullous pemphigoid antigen 180 (BP180), which is located in the basement membrane. As the inflammation progresses, it causes cleavage of the epidermis from the dermis, resulting in tense vesicles and bullae. PG typically develops after 13 weeks' gestation but can also occur in the first week postpartum. The rash is first noticed in or around the umbilicus but progresses over days to weeks to involve the trunk and limbs. The lesions are initially characterised by urticarial oedematous lesions; these lesions then develop vesicles and bullae, which are very characteristic of PG. The rash usually resolves within days of delivery but can occasionally last for many months. Relapses can occur with the return of menstruation or use of the combined oral contraceptive pill.

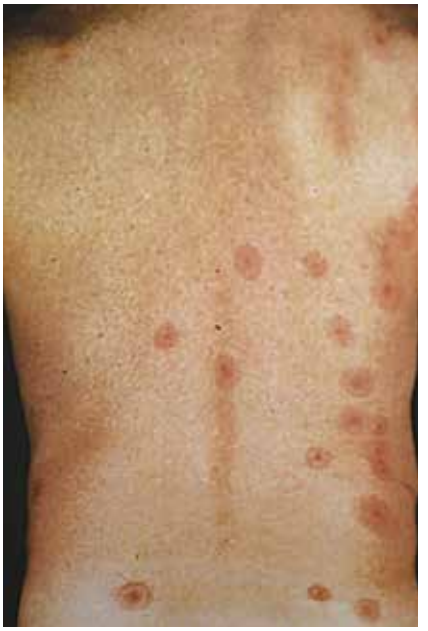

Figure 3. Erythema multiforme.

Diagnosis and investigations

The diagnosis of PG is made through a combination of history, examination and biopsy. Two biopsy specimens should be obtained for histology and direct immunofluorescence, which shows linear IgG and/or C3 at the basement membrane. Polymerase chain reaction testing for herpes simplex virus and *Mycoplasma pneumoniae* is needed if biopsy results are consistent with EM.

Ongoing routine investigations and ultrasounds for the rest of the pregnancy are important because there is an increased risk of small-for-gestational-age and premature neonates.

PEP has considerable overlap for presentation with PG. However, for this patient PEP can be excluded because the rash involved the umbilicus, did not primarily involve stretch marks and was characterised only by annular lesions.

Management

The priority of treatment is to reduce the patient's pruritus. The rash is rarely responsive to treatment with a topical corticosteroid, and oral prednisone is almost always required at the minimum dose required to reduce symptoms. Steroid- sparing agents such as azathioprine may be needed to reduce the prednisone dose.

Secondary bacterial infection of the lesions should be treated with an oral antibiotic that has been shown to be sensitive and is safe during pregnancy. Cephalexin is Category A for use in pregnancy.

Outcome

This patient was commenced on prednisone 50 mg daily and improved rapidly. The dose was titrated down to 30 mg daily and, after the birth of a healthy infant, prednisone was withdrawn over the following two weeks without relapse.

The patient was counselled that PG would recur and would probably do so earlier in the next pregnancy. There have been cases where patients who have a subsequent pregnancy with a different partner did not experience recurrence. MT

COMPETING INTERESTS: None.